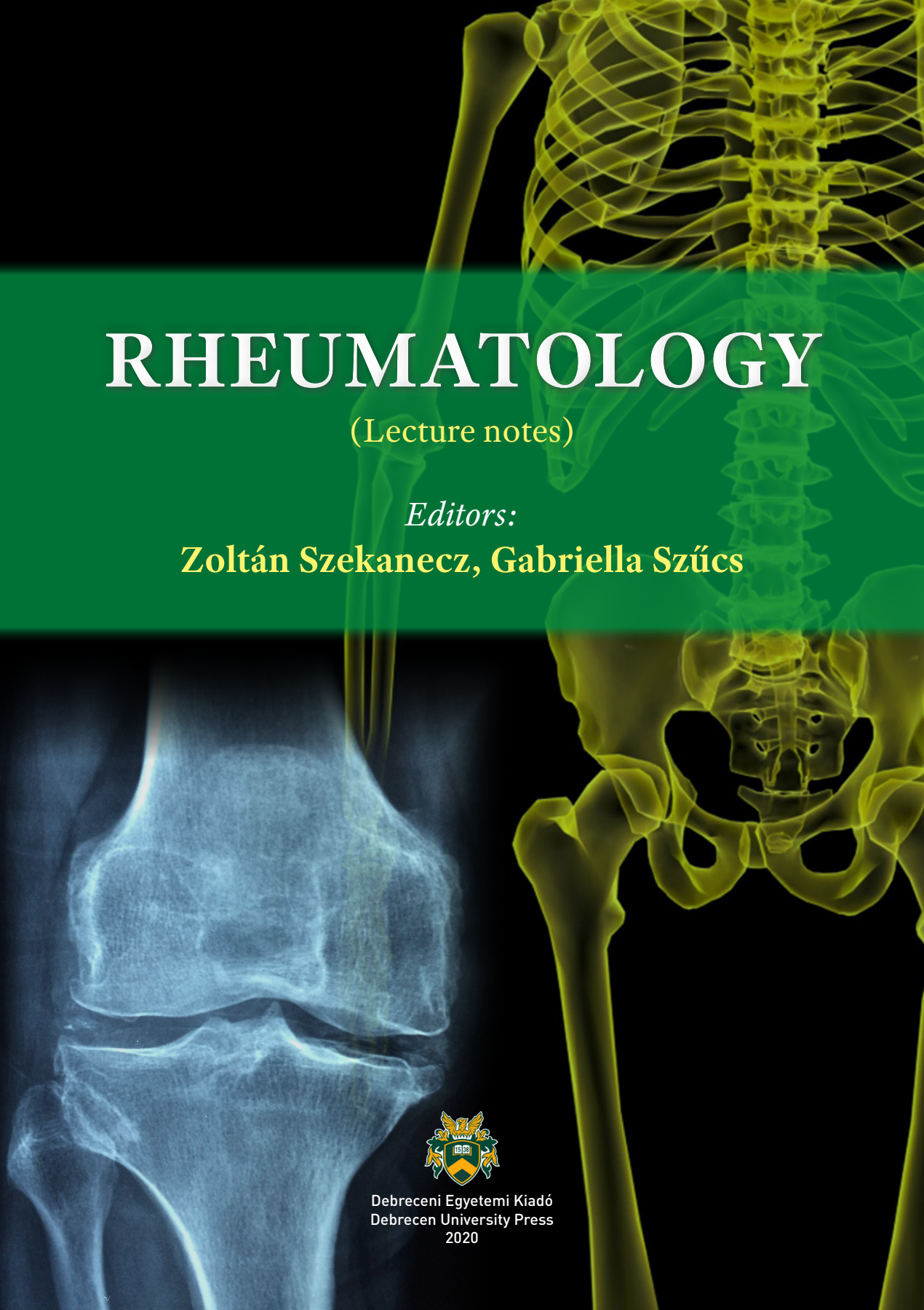

RHEUMATOLOGY

(Lecture notes)

Editors:

Zoltán Szekanecz, Gabriella Szűcs

Debreceni Egyetemi Kiadó
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Table of contents

1. Propaedeutics

Zoltán Szekanecz

1.1. Introduction

The musculoskeletal system includes joints, ligaments, tendons and tendon sheaths, bursae, muscles and bones. The patient's musculoskeletal examination is carried out according to the following order:

1. musculoskeletal history;
2. physical examination;
3. laboratory tests;
4. imaging and other diagnostic procedures;
5. biopsies and histological examinations;
6. consultations.

1.2. Taking a history

Primarily *the characteristic aspects of musculoskeletal diseases* are being described. However, we have to emphasize that the musculoskeletal examination is part of the general (internal medicine) examination, therefore we should always try to make at least a brief assessment of other organ systems (e.g. cardiovascular system, gastrointestinal system, etc.) as well. Musculoskeletal diseases are often associated with other illnesses and may have systemic symptoms affecting other organ systems (for more information see Consultations).

When *taking a history,* we follow the general approach of medical history: *1. present complaints; 2. preceding events triggering present complaints; 3. previous illnesses; 4. family and social history.* (Attention! The patient presents with complaints, so always ask for the current complaints, do not bother the patient immediately with a long discussion about previous illnesses!)

Taking the musculoskeletal history should be targeted, so, in addition to the general questioning, some characteristic features should be in all cases explicitly questioned (e.g. trauma; recent surgery; other diseases associated with musculoskeletal diseases, such as psoriasis, inflammatory bowel disease, ocular inflammation, diabetes, endocrine diseases).

When investigating *present complaints* and the events triggering them, some specific aspects that may help the diagnosis should be taken into consideration:

1. How have the complaints started? Did the complaints have an acute (e.g. gout) or an insidious (e.g. rheumatoid arthritis; RA) onset?
2. Is the involvement of the joints symmetrical (e.g. RA) or asymmetrical (e.g. spondylarthritides; SpA)?
3. Is the joint pain of a wandering nature (e.g. rheumatic fever) or not?
4. The number of joints involved (1: monoarticular, e.g. gout; 2–4: oligoarticular, e.g. AS; >4: polyarticular, e.g. RA)?
5. Are there any signs of arthritis (inflammation) (e.g. pain, joint swelling, heat, redness, functional impairment)?
6. Are there any musculoskeletal complaints other than joint involvement (e.g. low back pain, muscle pain, tissue disorders, etc.)?
7. Are there any non-musculoskeletal complaints that can be associated with rheumatologic disorders (e.g. skin: psoriasis; gastrointestinal system: inflammatory bowel disease; eyes: uveitis, iritis; metabolic-endocrine: diabetes, thyroid disease, hyperparathyroidism; kidney: lupus nephritis; lung: pneumonitis)?
8. How serious are the symptoms? Is there a disability? Does the patient use any device? Have there already been a hospitalization because of this?
9. How is the patient's functional ability? Is the patient able to do their job? Is the patient self-supporting at home? Are there any limitations in the day to day life?
10. What previous treatment(s) did the patient receive and what is the current treatment the patient is receiving for the present disease? Has the patient been treated with any medication for the disease? Have there been any that had to be discontinued for some reason?
11. Does the patient know, understand their disease?
12. Are there any psychosocial, financial considerations that can influence diagnosis and treatment (e.g. ordering expensive drugs) (family circumstances, social, financial conditions)?
13. Any pathogenic factors:
    - was there a workplace distress (e.g. chemicals: scleroderma; administrative work: nerve compression syndrome),
    - had there been a trip to an exotic or underdeveloped geographic region (e.g. TB, hepatitis: reactive arthritis),
    - sexual history (sexually transmitted diseases: reactive arthritis),
    - quality of life (crowded home: rheumatic fever; living in an endemic area: Lyme disease),

– was there a recent infectious disease among family members,
– has the patient experienced extensive emotional or physical stress?

Among the specific complaints, *pain* is the complaint that commonly and the earliest propels the patient to visit a doctor. Detailed analysis of the pain is important. The nature of the pain may be dull, spasmodic, sharp, hurting, stinging, burning; duration and course may be short-term or persistent, constant or of variable strength, occurring (even) at rest or increasing by load, occurring rather at night. We need to know the place of origin of the pain and possible its radiation: whether it occurs more in the joint, bone or muscle. We need to find out if it alleviates with movement or rest, cold or heat.

All in all, we distinguish two major groups of musculoskeletal pain:

- mechanical pain (e.g. herniated dics): occurs / exacerbates with movement, alleviates with rest;
- inflammatory pain (e.g. arthritis): occurs at rest, even at night.

Less often, pain can be neuropathic (sharp, radiant), bone-derived as well.

The degree of pain can be recorded by more precise methods. The so called Visual Analogue Scale (VAS) is a generally 10 cm long line, where 0 indicates no pain, and 10 the maximum pain. The patient may also indicate the degree of the pain by giving it a value 1–10.

The place of pain is not always easy to determine. Lumbar herniated disc may occur in the form of knee pain, cervical herniated disc, shoulder pain, and knee osteoarthritis may radiate to the hip or ankle. In case of long-term headache cervical spine disease should be considered. Patients can locate the same disease condition in different locations. There are also great individual differences in the perception of pain, including the threshold of pain. The patient's description of pain depends largely on tolerance, mental attitude, stress, mood, intelligence and expression. Therefore, in addition to the spontaneous history, the patient should be given the appropriate targeted questions. Finally, it is very important to be able to obtain information about the patient's state of mind and behaviour immediately.

1.3. Physical examination

Physical examination can be done by a variety of logical steps: it is essential to cover all body regions. Due to content limitations, the examination is not de-

scribed in full detail here, but there is a reference to the more detailed manuals listed in the Literature.

Based on a region strategy, we can perform the Doherty-screening. This screening method is the easy-to-remember GALS (Gait, Arms, Legs, Spine). According to this, we observe the characteristics of walking at the patient's arrival: smoothness, symmetry, harmony. Are the steps of equal length? Are the phases of the steps physiological? Examine the arch, the heel strike and the swing through of the stride. Examine walking on toes, heels and with closed eyes. After this a detailed examination of the arms, lower limbs and spine is carried out, which can be recorded on an examination sheet.

According to the *classic strategy,* we may follow the inspection-touch-function examination order.

Inspection from the back: Inspect for scoliosis. Inspect the head position. Inspect the level of shoulders and iliac crests. Inspect for muscle atrophy in the region of the shoulders, gluteal region, region of the thighs and legs. Inspect the lower limb's angulation: valgus or varus? The patient brings one then the other thigh to his stomach (Trendelenburg's-sign). Ask the patient to lean sideways with straightened arms (spine-deformities).

Inspection from the side: Inspect the arches of the spine. Inspect the inclination of the pelvis. Inspect for a pelvic or knee joint contracture. Ask the patient to bend forward and tilt back with extended arms (finger-to-floor distance).

Inspection from the front: Ask the patient to lean their head sideways towards the right and left shoulder. Inspect the position and shape of the shoulders. Inspect the position of the elbows – are they fully extended? Inspect the wrists and finger for swelling or any deformities. Ask the patient to make a fist with both hands. Ask the patient to touch each fingertip to the thumb on the same hand. Ask the patient to lift both arms to the side then place them on the back of the head. Ask the patient to squad down, then stand up. Inspect the legs and the muscle bulk of the tights. Inspect the knees for swelling and any deformities. Inspect the position of the feet. Inspect the ankles, toes for swelling and any deformities.

Feel: Can be used to detect any joint swelling, other soft tissue swelling (e.g. bursa, Baker's cyst), bone growth or fluid accumulation in small joint due to synovitis *(Figure 1.1.)*. The consistency and pressure sensitivity of the muscles is examined by palpation. Joint pain can be induced by pressing the gap in a given joint, or by squeezing the small joints of the hands or feet laterally. Skin pain can be triggered by pinched skin folds; enthesitic pain (due to inflammation of the tendon or ligament adhesion site) by pressing the point of adhesion; nerve pain

by pressing the nerve (e.g. Tinel's sign); bone pain by pressing or tapping the bone region. In certain diseases (e.g. fibromyalgia) special pressure points (so-called tender points) are known. Special maneuvers are required, for example in case of disc herniation the Lasègue test *(Figure 1.2.)* or in case of sacroiliitis Mennel's test *(Figure 1.3.),* which causes the patient to report pain.

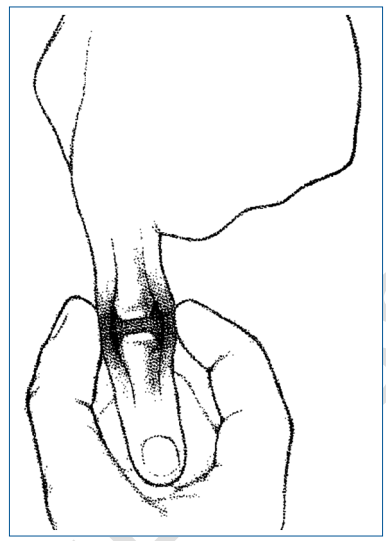

Figure 1.1. Palpation of joint fluid in small joint arthritis of hand

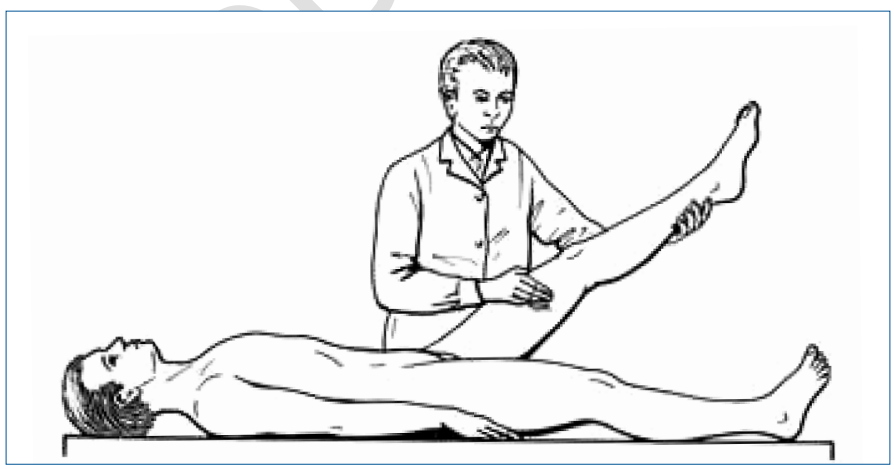

Figure 1.2. Lasègue's test

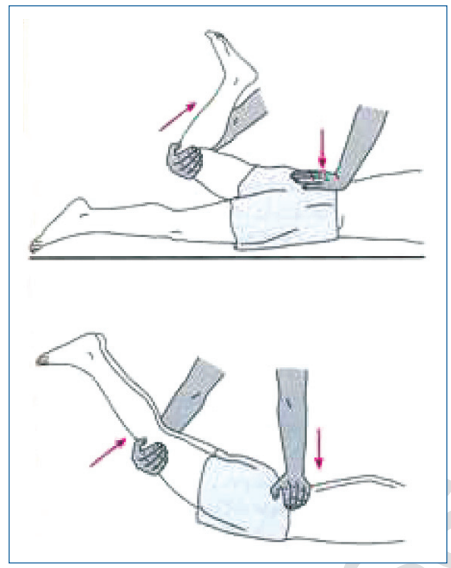

Figure 1.3. Mennel's test

Function tests: The accurate knowledge of the anatomy of the given musculoskeletal region, the structure (1-2-3-axes joints) and function (the maximum extent of each movement in degrees) of joints is indispensable. *Active movements* may be impaired or absent in acute inflammation due to intense pain; in subacute processes due to muscle spasm; in chronic conditions due to contractures, ankylosis. In addition to musculoskeletal disorders, active movement is restricted in cases of paralysis, myasthenia. *At passive movement* the patient is instructed to completely loosen their limbs. Passive mobility is reduced or absent in case of severe pain, joint contracture, joint shrinkage, ankylosis. Movement is also hindered by connective tissue diseases (e.g. Scleroderma, dermatomyositis, Dupuytren's contracture). When examining passive movement, it should be kept in mind that only the examined joint's movement is being assessed: in case of complex joints (e.g. the shoulder) in order to assess the mobility of just one joint (e.g. glenohumeral joint) adjacent joints must be immobilized. When examining joint movement, it is advisable to follow the active movement with the hand placed on the joint. If the movement is narrowed, it is recommended to determine the range of joint movement by passively moving it. If no abnormality is found during the examination of the joint marked as painful by the patient, the so-called resistance test should be applied. If pain still occurs, the site of the lesion can be localized by touch (e.g. in case of tendinitis around the shoulder joint).

During the examination *functional stages* are also determined on a semi-quantitative scale:

I. (early stage): various joint swellings, but uninterrupted function;
II. narrowing of joint movements, but satisfactory mobility, no deformities;
III. pronounced joint deformities, muscle atrophy, movement and ability to work are significantly impaired, the patient is often in need of help;
IV. in addition to the elements of the previous stage: fibrosis, bony ankyloses, disability of varying degrees.

In case of a patient with musculoskeletal disease physical examination must not be exhausting. Therefore, instead of the continuous changes in body position (standing, laying down, sitting, standing up) examination of the musculoskeletal system is carried out according to the given body position. Accordingly, first we observe the walking, posture, lower extremities and inspect the spine movements of the patient in a standing position. The patient is then directed to take a seat on a chair and head and neck movements, chewing joints, thoracic amplitude and upper limbs are observed, after which the patient is directed to lie down for the examination of the abdomen, lower spine and lower limbs, and screening of the nervous system. (It is not appropriate to "boss around" a patient with musculoskeletal disorder often in pain.)

Finally, measurement and documentation are also important in rheumatology. The VAS scale for pain measurement has already been discussed. Special questionnaries can also be used to express functional ability (e.g. Health Assessment Questionnaire – HAQ) and quality of life (e.g. SF-36, EuroQoL) numerically. All of these tools can be used to track changes in the patient's condition and in the effects of treatment.

1.4. Laboratory tests

Generally speaking, the range of laboratory tests used in musculoskeletal diagnostics is rather poor. Only a few tests have a clear *diagnostic value* (e.g. serum uric acid level, crystal detection, auto-antibodies, while others (e.g. erythrocyte sedimentation rate: ESR, C-reactive protein: CRP, hematology, HLA-B27, parathyroid hormone) are important from a *differential diagnostic* point of view. The most common rheumatic diseases (e.g. osteoarthritis, discopathy, spondylosis, osteoporosis) show virtually no laboratory abnormalities. (The laboratory values of systemic autoimmune disorders are discussed in another chapter.)

General quantitative blood test is mandatory among *blood tests.* Anemia can be observed in chronic inflammatory diseases (e.g. RA, AS). (The differentiation can and should be further investigated by serum iron, transferrin saturation, ferritin, MCV, MCH: chronic inflammation is characterized by saturated iron storages at a normal or low serum iron level; megaloblastic anemia, with folate deficiency, may occur in case of methotrexate treatment.) True iron deficiency should be distinguished from inflammatory normocytic anemia. (In the latter case, iron supplementation can be particularly harmful.) Leukocytosis is common in inflammatory diseases, leukopenia is characteristic for Felty's syndrome and SLE, but may also indicate non-steroidal anti-inflammatory drug (NSAID) toxicity. Thrombocytosis may indicate inflammatory activity, while thrombocytopenia is more likely to occur in autoimmune diseases.

Qualitative blood count is of differential diagnostic significance. Numerous arthritis and immunosuppressive treatments are accompanied by an increased risk of infection. In bacterial infections neutrophilia, left shift may occur. Chronic inflammation may be accompanied by monocytosis. Lymphocytosis may occur due to viral infections. In RA, the frequency of lymphomas can also increase. Evaluation of the *bone marrow smear* may be important to rule out malignant hematologic disease (mainly myeloma, lymphoma), tumor metastasis and haemochromatosis.

Among the *serum proteins* the albumin fraction is reduced while the immunoglobulins increase in number in arthritis. In case of elevated total protein, myeloma multiplex should be ruled out (determination of serum paraprotein). Elevated serum proteins, namely CRP, ferritin, ceruloplasmin, amyloid-A (SAA), haptoglobin and fibrinogen as well as elevated ESR indicate acute phase reaction. The latter is the screening test for inflammation. However, its determination alone is of no diagnostic value since ESR can be elevated in case of infections, tumors, pregnancy and (normally) in older age. (Normal value: men under 50 years old: <15 mm/h, women under 50 years old: <20 mm/h; men over 50 years old <20 mm/h, women over 50 years old: <30 mm/h.) ESR in arthritis is elevated most of the time, but is not characteristic in one third of SpA patients or in case of inactive RA. The elevation of ESR is relatively slow, beginning around 24 hours after the onset of inflammation, with a half-life of 4–5 days after the reaction has stopped. In contrast, CRP rises within 6 hours and decline rapidly, within 20–48 hours. Therefore, CRP is a more sensitive (although more expensive) method to screen for inflammation. Both the ESR and CRP are capable of monitoring the inflammatory activity and the efficacy of therapy.

Routine blood chemistry is of limited significance. Serum potassium levels should be monitored while on steroid treatment; monitoring kidney and liver function is related to the monitoring of drug treatment (e.g. NSAID, paracetamol, DMARDs). Elevated CK, GOT and LDH may indicate myositis. Alkaline phosphatase levels increase in Paget's disease, osteomalacia and bone metastases. Determination of serum uric acid levels is important in gout. Measurement of serum calcium and phosphate levels may be of importance for the discrimination among metabolic bone diseases (osteoporosis, osteomalacia, hyperparathyroidism).

Among other blood tests, the determination of *specific auto-antibodies* is of prime importance in polysystemic autoimmune disorders, which are discussed in the immunological chapter of this book. The most well-known auto-antibody in RA is rheumatoid factor (RF), of which the IgM isotype determination is widely used in practice. IgM RF is determined by latex test, Waaler-Rose test, more recently by nephelometry or immunoturbidimetry. RF determination is very sensitive (over 80%), but not specific at all: 70–90% of RA patients are RF positive (seropositive), but may be detectable in systemic autoimmune diseases, sarcoidosis, pulmonary fibrosis, infections, tumors and even in old age. (The significance of IgA RF is not yet clear.) In recent years, the role of anti-citrullinated protein autoantibodies (ACPA) has been revealed. ACPA against various proteins (vimentin, fibrinogen, collagen) and peptides (cyclic citrullinated peptide: CCP) can be detected by ELISA, which is very specific (>90%) and quite sensitive to RA. The determination of antinuclear antibodies (ANA) may also be of major importance in systemic autoimmune diseases. In rheumatology, juvenile idiopathic arthritis (JIA) may be of importance in the oligoarticular form, where ocular complication (uveitis) occurs more frequently in case of ANA positivity.

Procalcitonin (PCT) is the prohormone of calcitonin, with increased production in sepsis, severe bacterial, fungal or parasitic infections. However, in sterile inflammation (e.g. chronic arthritis) serum PCT levels are normal. Therefore, it is of paramount importance in distinguishing between inflammatory and infectious processes.

Determination of markers of *bone and cartilage degradation* have become more prevalent in recent years. For the differential diagnosis of metabolic bone diseases, the determination of osteoporosis (bone loss) "turnover" (thus measuring the effectiveness of the therapy) the markers for bone breakdown (e.g. collagen crosslinks) and bone formation (e.g. osteocalcin, bone-specific alkaline phosphatase, acid phosphatase) are important. The biochemical marker of

cartilage degradation and joint destruction is – among others – the cartilage oligomeric matrix protein (COMP).

Microbiological serology may be important for differential diagnosis. In this regard, the serological detection of antibodies against Yersinia, Klebsiella, Chlamydia, Epstein-Barr virus (reactive arthritis, Reiter's disease), Borrelia burgdorferi (Lyme arthritis), hepatitis B and C (vasculitis, cryoglobulinemia) may be important. Anti-streptolysin O titer (AST, ASO) may be important for ruling out rheumatic fever and streptococcal focus. With the introduction of biological therapy there is a growing need for advanced tuberculosis (TB) tests (skin test, test based on interferon production). Molecular genetic techniques are now used to detect viruses, Mycobacteria and Borrelia.

The scientific value of *genetic testing* is clear, but its practical benefit is controversial. The HLA-B27 antigen can be detected on the white blood cells of a large proportion of patients with spondylarthritis (90% of SpA patients). Its cytofluorimetric determination is relatively inexpensive, in addition to clinic and X-ray it aids in the diagnosis of the disease group. However, HLA-DR4 (shared epitope), which means susceptibility to RA, is determined by molecular genetic (PCR) technique and its cost-effectiveness is unclear.

The first morning *urine* sample is examined by macroscopical, microscopical, biochemical and possible by microbiological methods. In certain autoimmune disorders associated with renal involvement proteinuria, hematuria, cilinduria may occur but this may also indicate paracetamol, NSAID toxicity. Bence-Jones protein appears in urine in case of myeloma multiplex. During the examination of the urine sediment white blood cells may indicate infection, but urine crystals may also be seen in the sediment (gout).

Synovial fluid testing is of diagnostic importance only in a few cases (e.g. crystal arthropathy, infectious arthritis).

Quantity: Under normal conditions varies from joint to joint, but lesser quantity does not rule out the possibility of inflammation. (E.g. in gout it is customary to needle the "dry joint" to detect the crystal.)

Color: Normally, it is of light straw-yellow color, transparent. It is greenish and xanthochrome in arthritis; dense and lacteous in septic (pyrogenic) arthritis; and red (bloody) in villonodular synovitis and hemophilia. Its transparency changes inversely with the leukocyte count.

Viscosity: Depends on the hyaluronic acid count. The non-inflammatory synovium drips "gooey". At the time of the instillation the length of the "tail" may be observed. Viscosity decreases in inflammatory processes.

Mucin test: The large molecule proteoglycans ("mucin") are depolymerized in inflammation. 1% acetic acid normally produces a strongly positive (+++) mucin test, in active inflammation loose, fluffy precipitate (+) forms.

Protein content: Physiologically, the synovial membrane is impermeable to larger proteins. Protein concentrations increase in inflammation (>30–40 g/l). When the inflammatory synovium coagulates it indicates the presence of fibrinogen.

Glucose: Normally, the sugar concentration is approx. 0.5 mmol/l less than the values measured in parallel serum samples. The difference in case of inflammation can be up to 2.2 mmol/l.

Cell count: Physiologically, the cell count is <0.2 G/l. In inflammations there may be a couple of tens of G/l, cell numbers above 60 G/l absolutely indicate infection.

Crystal examination: The detection of crystal by polarized microscope is essential in the diagnosis of gout. In the synovial fluid sample urate crystals can be detected in about 85% of patients. These give a strong, thin, needle-shaped, polarized light negative double refraction. On the other hand, in calcium pyrophosphate (CPPD) arthropathy (pseudogout) the crystals are rhomboidal and give a positive double refraction.

Cultivation: Bacteriological examination should be carried out at the slightest suspicion of infectious (septic) arthritis. Aerobic, anaerobic cultivation and Gram staining are also performed. The most common pathogens are Staphylococcus aureus, Streptococcus pyogenes and pneumoniae, Haemophilus influenzae.

1.5. Imaging and other diagnostic procedures

1.5.1. Conventional X-ray

Decades ago, X-rays were the only weapon in musculoskeletal imaging. In most diseases (e.g. osteoarthritis, spondylosis, RA, SpA) we still consider this as the basis, and the finer (but usually more expensive) examinations are only used in case of differential diagnostic problems. It is essential that not only the case report is read, but that the rheumatologist take a look at the film. This is the only way to reconcile the clinical picture, laboratory findings (which the radiologist often known little about) and imaging results.

Generally, in bidirectional symmetrical disease (e.g. RA) *limbs* are examined by a comparative imaging. In addition of bidirectional images of the *spine*

additional images are often required. For example, foramen imaging of vertebral openings in the cervical spine; functional imaging is required to verify subtle abnormalities (e.g. subluxation) of vertebrae, small joints. Dittmar-image is indicative of vertebral rupture associated with lumbar spondylolisthesis.

The images show several *characteristic abnormalities* of bones and joints. This requires well-adjusted good quality X-rays. There are two ways in which the bone structure can change: osteolysis or sclerosis can occur as a result of increased osteoclast and osteoblast activity. Osteolysis can be sharp-edged with peripheral sclerosis (e.g. cyst, fibroma); sharply contoured, without sclerosis (e.g. giant cell tumor); blurred boundary osteolysis (e.g. acute inflammation or malignancy); moth-eaten osteolysis (e.g. RA) or penetrating hole (e.g. sarcoma, metastasis). Sclerosis may occur in the form of calcareous, tumorous stroma (e.g. compact island, osteosarcoma); bone necrosis (infarct). It is very important to judge the surrounding periosteal reaction, which can be triggered by blood, pus and tumor. This is when the bone that becomes radiant in the periosteum is formed. The periosteal reaction may be homogeneous, lamellar, bulbous and may come with spicular formation. The picture may indicate an inflammatory, tumorous (benign or malignant) origin.

1.5.2. Musculoskeletal ultrasound

Recently, ultrasound has approached the level of conventional X-ray, becoming a routine examination that is performed by rheumatologists in several places. The advantage of ultrasound is that it is inexpensive, easily accessible, well repeatable, dynamic, and can help with intervention (e.g. joint puncture). Primarily ultrasound is a method for evaluating joints and soft parts. It is examiner and device dependent. In experienced hands the use of a high-resolution device can be employed instead of CT or MRI. Changes around the joints (e.g. synovitis, bursitis, erosions), (e.g. heel), soft tissue abnormalities (e.g. tendons, ligaments) can be well evaluated. The knees, shoulders and hips can be particularly well-examined, but an experienced examiner can also detect abnormalities of the smaller joints (e.g. wrists, ankles, small joints). Power Doppler ultrasound also specifically detects inflammation through increased blood flow.

1.5.3. Computed tomography (CT)

CT scans also use X-rays, but have a much higher contrast resolution. It can be used to eliminate the summation-shadow detected during X-ray examination. First and foremost, it is useful for a more accurate assessment of the bone structures and the abnormalities within. It is well suited for the representation of the

spine (especially the lumbar region). It has a featured role in the analysis of the sacroiliac region. It is useful in the evaluation of bone tumors and periosteal abnormalities. However, neither CT nor MRI can be evaluated independently without prior conventional radiography. Recently, special CT techniques (e.g. dual energy CT: DECT) have been used, e.g. smaller gouty tophi can also be detected. In addition to bone density peripheral quantitative CT (pQCT) is also useful for assessing bone structure.

1.5.4. Magnetic resonance imaging (MRI)

The advantage of MRI over other imaging techniques is that it allows direct imaging in all directions. Its contrast resolution is very high, it shows the soft parts perfectly, but it does not see lime-containing structures directly. The conventional T1 sequence provides an initial picture of the anatomy. T2 images are sensitive to pathological changes in water content (e.g. inflammation). A number of special sequences are used. For example, the lipid depression (STIR) sequence indicates pathological changes in the bone marrow (e.g. in early sacroiliitis SpA). Intravenous gadolinium complex (Gd DTPA) administration can also be used to make functional images so that the inflamed, vascular synovium can be well distinguished from the non-inflammatory, fibrous pannus. MRI is well suited for imaging synovitis, haemarthrosis, synovial cyst and bone marrow processes. It is nearly the first examination for early detection of arthritis and sacroiliitis with no X-ray abnormalities, and to detect cervical spine herniation.

1.5.5. Isotope diagnostics

With the spread of ultrasound, CR and MRI scintigraphy techniques are now being overshadowed. Radiopharmaceuticals used in musculoskeletal diagnostics include bone-seeking compounds (osteoarthritis, tumor), labeled leukocytes and antibodies (inflammation), tumor-seeking isotopes and positron emission tomography (PET). The advantage of the isotope technique is that the whole body can be imaged and its sensitivity is high, but it is not specific. Of the bone-seeking isotopes, technetium (^{99m}Tc) -labelled bisphosphonates are the most commonly used. This maps the skeletal system by incorporation into hydroxyapatite crystals of the bone with a changed metabolism. Three-phase scintigraphy is suitable for imaging inflammatory bone and joint abnormalities, algodystrophy. Normally enrichment is seen on both sides of the front of the skull, in the shoulder joints, in the sternoclavicular and sacroiliac joints. Severe pathological enrichment occurs in cases of benign and malignant bone tumors, arthritis, traumatic abnormalities, Paget's disease and osteonecrosis. Inflamma-

tory abnormalities can be detected with indium (^{111}In) -labeled white blood cells or gallium citrate (^{67}Ga), although inflammation can be better visualized by ultrasound and MRI. 2-fluoro-2-deoxy-D-glucose (FDG) used for PET is a glucose analogue that is specific for the detection of tumors and inflammation. It is currently used mainly in malignant processes, but is also spreading in the field of inflammatory diseases (e.g. giant cell vasculitis). Nowadays PET-CT and PET-MRI examinations are also available. They use the combined benefits of the two imaging techniques.

1.5.6. Other diagnostic procedures

Bone densitometry (DEXA or DXA) based on dual energy X-ray absorptiometry determines bone mineral density, BMD and compares it to a young healthy population. The deviation is given in standard deviation (SD) called the T-score. If the measured value is one SD smaller than the control, the T-score is –1. Normal bone density is characterised by a T-score between 0 and –1; osteopenia by a T-score between –1 and –2.5, and a T-score lower than –2.5 describes osteoporosis. Bone densitometry findings can only be evaluated along with clinical and laboratory findings. Conventional X-rays are also important since DEXA can give a false-negative result in advanced spondylarthritis.

Capillary microscopic examination visualizes the capillaries of the nail bed. In certain inflammatory and vascular diseases (e.g. systemic sclerosis, Raynaud's disease) avascularity and giant capillary formation can be observed due to the death of the small vessels.

Electromyography (EMG) is a great help in discrimination among muscle diseases. Pathological abnormalities of the nerve conduction (e.g. polyneuropathy, nerve compression syndrome) can be confirmed by *electroneurography* (ENG).

Arthroscopy can be of diagnostic and therapeutic nature as well. Looking into joints, bone surfaces and ligaments can be brought into the field of view and biopsies can be performed. On the other hand, smaller abnormalities can be operated this way.

1.6. Biopsies and histological examinations

Histological sampling (biopsy) can be carried out blindly (by pricking the knee) or by the aforementioned arthroscopy. Histological examination of the synovial specimen only rarely results in specific findings. Histological examination may be of diagnostic value in TB (granuloma formation, detection of mycobacteria),

sarcoidosis (characteristic granuloma formation), gout (detection of crystals in synovium), haemochromatosis (iron detection with Berlin blue staining), multicentric reticulo-histiocytosis and pigmented villonodular synovitis (characteristic histopathology). Otherwise, most chronic synovitis (e.g. RA, AS, psoriatic arthritis) has a similar histological pattern. Pathologist can only determine the presence of the chronic synovitis, not the exact diagnosis.

In rheumatology, especially in systemic diseases, biopsies of other tissues and organs (e.g. muscle, kidney, salivary gland, lung, liver, sural nerve, abdominal adipose tissue) are also performed.

1.7. Consultations

Rheumatology is connected with most medical professions. Therefore, it is essential that the patient is occasionally referred for *consultation* for diagnostic and differential diagnostic purposes. A *dermatologist* can help distinguish between psoriasis (psoriatic arthritis), SLE (distinctive skin symptoms) and vasculitis. An *ophthalmologist* can detect uveitis, scleritis or keratoconjunctivitis sicca associated with arthritis, and also they are the one to control chloroquine therapy. In case of focal examination (reactive arthritis, rheumatic fever) the help of an *ear-nose-throat specialist, dentist, urologist and gynecologist* may be needed as well. A *neurologist* can help distinguish between polyneuropathies, nerve compression syndromes and myopathies, while a *psychiatrist* can help distinguish between chronic pain syndromes (e.g. fibromyalgia). In systemic autoimmune rheumatological disorders the involvement of a *nephrologist* (e.g. lupus nephritis), *pulmonologist* (e.g. pneumonitis, pulmonary fibrosis), *cardiologist* (e.g. pulmonary hypertension, secondary atherosclerosis), *oncologist* (e.g. secondary tumors) and *orthopedic* and *neurosurgeon* (recommendation for musculoskeletal surgery) can also be needed.

The scope of this chapter is not sufficient to review further details of musculoskeletal history taking and physical examination, so it is important to review the following literature for further details.

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2. Pathogenesis of rheumatologic diseases

György Nagy

2.1. Introduction

The immune system's multiple functions include distinguishing between the body's own antigen and others, actively protecting of its own structures, eliminating pathogens as needed, creating immunological memory and preventing the growth of tumors. Loss of tolerance to the body's own antigens may lead to autoimmune disease. The regulation of innate and adaptive immunity can also change in autoimmune diseases. The first line of defense against infections is the phylogenetically older, not pathogen specific innate immune system with no immunological memory. Dendritic cells, monocytes, macrophages and eosinophil granulocytes are the cells of natural immunity. The adaptive immune system's activation is more time-consuming; its pathogen specific and has immunological memory. B and T lymphocytes are the cells of adaptive immune response. To our current understanding, the following factors have a fundamental role in autoimmune diseases:

1. genetic factors;
2. environmental factors, such as smoking or infections;
3. immunoregulatory dysfunction originating based on genetic and environmental factors implying autoimmunity years before the onset of the disease.

Reaching a threshold, the sum of the predisposing factors leads to a disease *(Figure 2.1.)*. In this chapter we review the pathomechanism of autoimmune-rheumatologic disorders. (Other pathogenic mechanisms [pain, biomechanics, etc.] involved in rheumatologic diseases are not discussed in this chapter due to chapter limitations. More detailed information can be obtained from more detailed rheumatology textbooks and manuals.)

2.2. Genetics of autoimmune rheumatologic diseases

The role of genetic factors in autoimmune diseases is well known, however, the presence of genes predisposing autoimmunity on its own does not lead to disease. Clear evidence of this is that in identical twins the concordance of autoimmune diseases in most cases is around 15–50%, significantly differ in certain diseases. In the world of comprehensive genome-wide genetic studies our knowledge is growing almost day by day. Among genetic factors predisposing autoimmune diseases MHC genes play a prominent role.

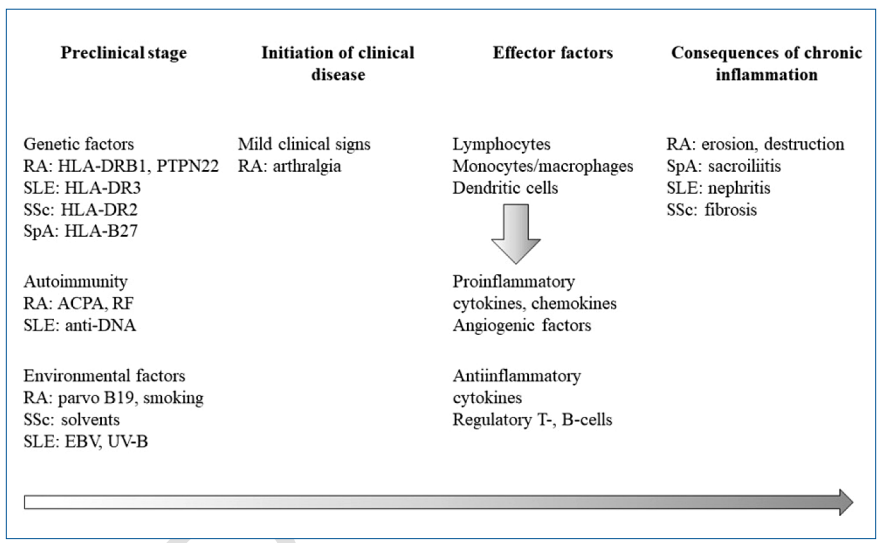

Figure 2.1. Complex pathogenesis of autoimmune rheumatologic diseases

2.2.1. MHC genes

More than half a century ago, MHC proteins involved in the regulation of transplant rejection were the first MHC proteins identified. According to various animal models, in addition to their role in organ transplantation, MHC proteins also regulate the immune response to antigens. MHC class I proteins (HLA-A; -B; -C) are present on the surface of all nucleated cells, while MHC II proteins (HLA-DP, -DQ and -DR) are present on the surface of antigen presenting cells. The main function of MHC proteins is to present peptides formed during the body's own and foreign protein degradation to T lymphocytes. Thus, potentially all nucleated cells are able to present the body's own antigen with MHC I molecule, while the antigen presenting cells can also present foreign antigens with the help of MHC II.

Rheumatoid arthritis (RA) is a multifactorial disease, in addition to genetic factors, the role of environmental factors and infections are also known in the development of the disease. The concordance of RNA in identical twins is 30–50% indicating a significant role of genetic factors. The relationship between certain MHC genes and RNA has been known since the 1970s and is the subject of intensive research. The HLA-DRB1 allele is one of the best known and most studied genes predisposing to RA. HLA-DRB1 alleles share a so-called shared epitope (SE) sequence, which is the 70–74. amino acid in the DR beta-chain's third hypervariability region (QKRAA, QRRAA, or RRRAA sequence). In addition to SE, the association of several other genes with RA has been confirmed. The association of SE with RA has been known for more than two decades, but the reason why it predisposes to RA is still unknown.

Although *ankylosing spondylitis* (AS) is not a typical autoimmune disease, immune-mediated processes play a central role in the development of the disease. In identical twins, the disease concordance is estimated to be 60–70%. The close association of the disease with HLA-B27 positivity has been known for about four decades, but the role of HLA-B27 in the development of the disease is still unknown. Interestingly, while most systemic autoimmune diseases are associated with MHC II genes, MHC class I HLA-B27 represents one of the most important genetic risks in SpA. HLA-B is one of the most polymorphic genes, more than 700 HLA-B protein has been identified, including more than thirty HLA-B27 proteins. Only 1–2% of HLA-B27 positive individuals develop SpA. HLA-B27 transgenic animal develops spontaneous spondyloarthropathy, similar to human SpA, thus HLA-B27 may contribute to the development of the disease. The most common types of HLA-B27 are HLA-B2705, HLA-B2704 and HLA-B2702. All three types predispose to SpA, on the other hand HLA-B2706 and HLA-B2709 are not associated with SpA. HLA-B2706 differs from HLA-B2704 by only 2 amino acids, which are located at positions 114 and 116, both in the F pocket of the peptide binding site. HLA-B2709 differs from HLA-B2705 by only one amino acid at position 116. These examples show that a single amino acid change in the affected MHC region can have a crucial influence on the disease association.

Systemic lupus erythematosus (SLE) has a concordance of 40–60% in identical twins, while 2–5% in dizygotic twins. HLA DRB1*1501 (DR2), DRB1*0301 (DR3) predispose to SLE, but the role of MHC genes in SLE formation is lower than in non-MHC genes compared with RA or SpA formation.

Genetics are less important in *systemic sclerosis* (SSc, scleroderma). In identical twins, the disease concordance is around 5–8%. The association of HLA-A1, HLA-B8, HLA-DR2 and HLA-DR3 with SSc has been proven.

According to the literature, in polymyositis HLA-B8 and HLA-DR3, while in Sjögren syndrome (Ss), among others, HLA-A24 is more common.

2.2.2. Other genetic factors

In addition to MHC genes, the polymorphism of *protein tyrosine phosphatase* (PTP) enzyme is one of the most studied and most important polymorphism predisposing to autoimmunity. PTP is an enzyme involved in the activation of B and T lymphocytes, in which the arginine / tryptophan exchange at position 620 may lead to increased activation of T lymphocytes. PTPN22 polymorphism is characteristic of many autoimmune diseases, including inflammatory rheumatic diseases (RA, SLE, juvenile idiopathic arthritis), type 1 diabetes mellitus and Graves- Basedow's disease, while this polymorphism does not predispose to SSc and Sjögren's syndrome. Thus, this polymorphism is not specific for an autoimmune disease, rather predisposes to autoimmunity in general, and development of the disease is dependent on the present genetic and environmental factors and the presence of PTPN22. The PTPN22 polymorphism is a good example that a single nucleotide exchange can lead to a modified function of a protein and thereby predispose to autoimmunity.

In some patients with active lupus elevated ESR is often observed alongside normal C-reactive protein (CRP) levels. The CRP gene is located in region 1q23-24 of chromosome 1. Some CRP haplotypes with low basal and inducible CRP production are characteristic for SLE.

The *immunoglobulin* gene superfamily includes receptors for IgG-containing immune complexes (FcgRIIa, FcgRIIb, FcgRIIIa, FcgRIIIb), and their genes are located in the Iq23 region. Deposition of immune complexes in various organs is characteristic of SLE. Genetic polymorphisms of receptors of the immune complex, particularly those that may have functional consequences, may contribute to the development of the disease. Weaker immune complex binding of the FcgRII receptor results in the histidine / arginine exchange of amino acid 131 (FcgRIIa-R131), which may contribute to the elimination of the reduced immune complex and thus to the development of the disease. Interestingly, the FcgRIIa-R131 receptor binds CRP with very high affinity, and thus may play a role in the appearance of proinflammatory cytokines at the site of immune complex deposition. The association of lupus nephritis with the FrgRIIa-R131 polymorphism has been confirmed. Similarly, replacement of FcgRIIa 176. amino acid from valine to phenylalanine leads to weaker immune complex binding, which is also more common in SLE.

The *poly-ADP ribosyl-transferase* (PARP) enzyme plays a central role in repairing DNA damage and breakage as well as in apoptosis. Its gene it also located in the 1q41-42 region. PARP mRNA levels and PARP activity are lower in SLE patient compared to healthy controls. CA dinucleotide repeat located in the PARP promoter region may influence transcription of the gene. CA dinucleotide repeat polymorphism is characteristic to SLE. TNF plays a key role in the pathomechanism of systemic autoimmune diseases, with its gene located on chromosome 6 near the HLA genes. Several polymorphisms have been identified in the TNF-α promoter region regulating gene transcription. TNF promoter polymorphism has also been described in RA, SpA, SLE and scleroderma. Both examples show that a polymorphism in a promoter region of a gene can influence gene transcription and thus predispose to disease.

Complement system is part if the innate immune response. Several complement abnormalities have been described in autoimmune diseases. The complement system activation plays a central role, especially in SLE. The complement system can be activated through three pathways:

1. classical pathway – directly by pathogens or by the antibodies binding to pathogens;
2. lectin pathway – activated by carbohydrates on the surface of pathogens;
3. alternative pathway – activated by the surface antigens of the pathogens.

Some of the complement genes are located on the short arm of chromosome 6 (C2; C4 and B factor genes), on the long arm of chromosome 1 (e.g. CR1; DAF and C4b binding protein), while the membrane damaging complex genes are located on chromosome 5. Genetic differences in complement components predispose to SLE. Very rarely, a complete C1q deficiency can occur, which is 90% likely to lead to the onset of SLE (approximately 50 cases have been reported so far). Deficiency of C2 and C4 factor is more common and leads to SLE in approximately 33–75% of cases.

Nowadays, millions of *polymorphisms* examination is available, and even the entire genome can be sequenced, so the genetic risk of certain autoimmune diseases can be quite accurately declared. Detailed analysis of genetic data, environmental factors, clinical and serological data will allow accurate assessment of the likelihood of developing the disease, assessment of prognosis and personalized treatment may also be possible.

2.3. Environmental factors, infections

In addition to genetic background predisposing to autoimmune diseases, environmental factors such as infections, chemicals and smoking can also contribute to the development of the diseases.

The association between *smoking* and RA has been known for decades, and interesting new data have emerged about its pathomechanism in recent years. Two of the most important genetic risk factors for RA are HLA-DRB1 and PTPN22. Carrying both of them and smoking predispose to anti-citrullinated protein antibody (ACPA) positive RA (see also the following chapter for more information about ACPA). Components of tobacco smoke may induce peptidyl arginine deiminase type 2 (PAD, see also below) in the lungs; PAD enzymes can case proteins to citrullinate. HLA-DRB1 encoding the shared epitope may contribute to the production of antibodies against citrullinated proteins. The causative role of smoking in RA can be considered to be proven and currently it provides one of the best examples of how genetic and environmental factors combined can influence the development of the disease *(Figure 2.2.)*.

Infections can also contribute to the development of autoimmune diseases. Epstein-Barr infection is thought to play a role in lupus and RA, parvovirus B19, lentiviruses or rubella in RA. The role of sunlight in activating SLE is well known, especially UV-B radiation can activate or induce the disease. Apoptosis of keratinocytes can be caused by UV radiation, during which intracellular antigens can enter the surrounding tissues and trigger an immune response. The role of organic solvents in provoking SSc is also known.

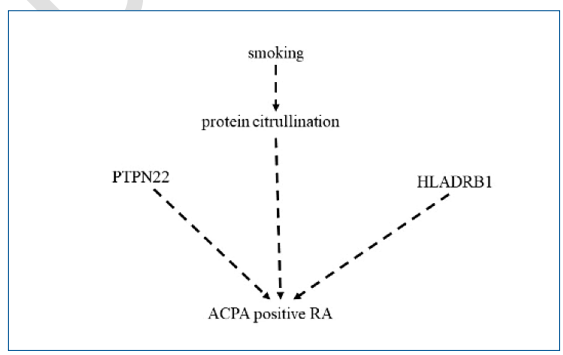

Figure 2.2. The association between genetic factors (HLA-DRB1, PTPN22) and smoking in RA

2.4. Immune dysregulation and autoimmunity preceding clinical symptoms

In the functioning of immune system, disease specific abnormalities indicative of autoimmunity may develop years, sometimes decades prior to the disease. Even in this early stage, there is the potential for drug treatment for prophylactic purposes. There is no adequate clinical evidence in any inflammatory rheumatic disease yet.

2.4.1. Anti-DNA antibodies

Experimental evidence supports the role of increased apoptosis and necrosis in SLE. Anti-DNA antibody specific in SLE was first described in 1957. In a significant number of patients anti-DNA antibody levels are elevated years before the SLE diagnosis, and serum levels of the antibody usually change with disease activity.

2.4.2. Auto-antibodies and autoreactive T cells in RA

Rheumatoid factor (RF) is an antibody produced against the Fc part of antibodies. RF can also occur in other autoimmune diseases besides RA. The identification of RF was the first argument in favor of the autoimmune nature of the disease. RF may appear years before the onset of the disease, it is a poor prognostic factor and its level does not change with disease activity.

The presence of *anti-citrullinated protein antibodies* (ACPAs) is highly specific for RA, their appearance can forego the development of the disease by years. The brief history of ACPA discovery: In 1967, the anti-perinuclear factor (APF) an antibody against keratohyalin granules of differentiating oral mucosa, detectable in the serum of RA patients, was described. The detection of immunofluorescence-detectable APF antibody was not widespread into daily practice due to the difficult accessibility of buccal mucosa. A few years later, another antibody (AKA) recognizing the esophageal keratinous structures was described. Later, it was confirmed that both APF and AKA antibodies are produced against the epithelial protein, filaggrin. Filaggrin is a protein expressed in epithelial cells, mainly involved in the movement of cytoskeletal structures; and under normal conditions is not found in the joints. Only filaggrin isolated from mature epithelial cells reacts with the patient's serum sample. This is explained by the fact that during cell differentiation, profilaggrin is cleaved to 10–12 filaggrin protein, than about 20% of their arginine amino acids convert into peptidylarginine deiminase (PAD) to citrulline. In both APF and AKA assays these cit-

rullinated polypeptides are the antigens, so the citrullination of filaggrin is required for its antigenicity. Citrulline is synthetized by modification of peptides, by a so-called post-translational modification (citrulline tRNA is not known), not by de novo synthesis. Synovial B lymphocytes of ACPA positive RA patients spontaneously produce anti-CCP antibodies. Citrulline-containing proteins can be detected in synovitis, but due to the absence of filaggrin in joints, other citrullinated proteins can be expressed in case of RA. Among citrullinated fibrin and intracellular proteins, citrullinated vimentin and citrullinated alpha-enolase can initiate and maintain ACPA production. Fibrin is likely to be citrullinated by cell-derived PAD enzymes, while citrullinated intracellular proteins released from cells may also act as triggers for ACPA production.

Auto-reactive T cells may also appear before the onset of the disease. Among others, the presence of T cell clones specific for GP39 cartilage proteins, type 2 collagen and citrullinated protein has been confirmed.

2.5. Onset of clinical symptoms, causes of disease

Little is known about what triggers the disease in the presence of existing predisposing factors (genetic background, environmental factors, immune dysregulation). The aforementioned environmental factors and infections are likely to play a role not only in predisposing to the disease but also in triggering it. Thus, an infection, or even smoking, may contribute to the immune dysregulation mentioned in the previous section; under different circumstances may also trigger the disease. Accordingly, the outcome of an environmental factor (e.g. an infection) may be of three types, depending on the presence of other factors predisposing to the disease:

1. "disappears without a trace;"
2. causes immunoregulatory disorder and may contribute to a subsequent illness;
3. triggers the disease.

Psychological factors and hormonal changes can also play a role in triggering illnesses.

2.6. Effector mechanisms in the maintenance and regulation of the inflammatory process

The diagnosis requires the presence of the clinical symptoms. The presence of the aforementioned genetic and environmental factors, as well as auto-antibodies, auto-reactive T-cells (typically for years, up to more than 10 years) can be considered as a pre-disease state. However, it is important to emphasize that some anti-DNA, ACPA, or RF positive individuals do not develop disease. Here, we review the characteristics of certain cell types and cytokines that are critical in autoimmune diseases.

2.6.1. Activation of T-lymphocytes and T-cell subpopulations in autoimmune diseases

T lymphocytes play a central role in the adaptive immune response; and carry a *T cell receptor* (TCR) on their surface. TCR exhibits a high degree of diversity, with approximately 10^{11} different TCRs being expressed. TCR recognizes a peptide (not an intact antigen) processed by an antigen presenting cell and presented by an MHC I or MHC II molecule.

T-lymphocytes play a fundamental role in the pathomechanism of most of the known autoimmune diseases; and of course, they represent a therapeutic target. A distinction is made between helper T-lymphocytes (Th), which play a central role in the regulation of immunological processes, and cytotoxic T-lymphocytes with primarily effector function. T-lymphocytes develop in the thymus. During the selection process, cells that are unable to cooperate with their own MHC (cell that cannot be physiologically activated; positive selection), or those reacting with their own antigen with too high affinity (potentially auto-reactive cells; negative selection) cease to exist. About 95% of T-lymphocytes die during the positive and negative selection process in the thymus. Our immune system tolerates its own antigens. A decrease or loss of tolerance can lead to autoimmune disease. As a result of selection processes in the thymus, T-cell reactive to self are introduces to the periphery. This is called central tolerance. Functioning of regulatory T cells results in peripheral tolerance (see below).

Based on the structure of the TCR, we distinguish αβ and γδ T cell. About 98% of peripheral T-lymphocytes are αβ T-cells, the remaining 2–3% are γδ T-cells. The exact function and role of γδ T-cells in autoimmunity is not fully known yet. Two thirds of αβ T-cells are CD4+ and the remaining one third is CD8+ T-lymphocyte. CD8+ T-cells recognize self peptides presented by MHC I molecule, while CD4+ T-cells recognize foreign antigens presented by class II

MHC molecule. CD8+ lymphocytes efficiently recognize and eliminate virus-infected or tumor cells, mainly through their production of cytotoxic perforin. The importance of CD4+ Th-cells is shown by the fact that the decreasing number of these cells causes severe immunodeficiency in HIV infection.

Our knowledge about the functions and group of CD4+ Th-cells has increased significantly in recent years *(Figure 2.3.)*. Most CD4+ types have a characteristic transcription factor. Th1 cells predominantly produce IL-2, IFN-γ, IL-12 and tumor necrosis factor alpha (TNF-α); their characteristic transcription factor is STAT4 (signal transducer and activator of transcription 4). Typical cytokine of Th2 cells: IL-4; IL-5; IL-6; IL-9; IL-10 and IL-13; and their transcription factor is STAT 6. Th9 is a newly described subtype of Th-cells. It plays an essential role in the defense against worm infections; and produces IL-9. Th17 cells produce the potent pro-inflammatory cytokines IL-17 and IL-22. Intensified IL-17 is also important in the pathogenesis of psoriasis, psoriatic arthritis (a disease associated with psoriasis with diverse clinical picture), AS, SLE and RA. IL-17 is an important potential therapeutic target.

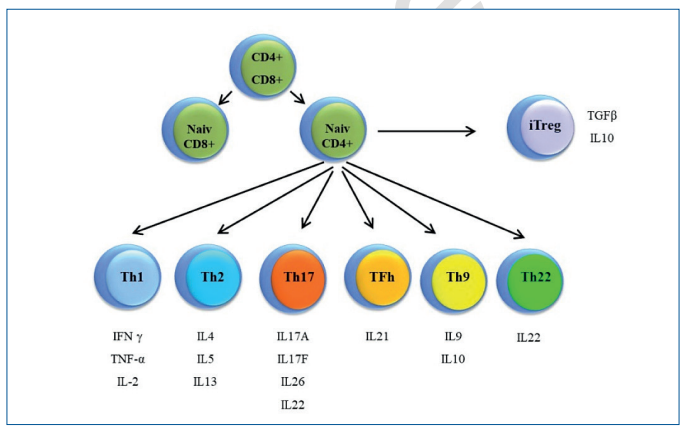

Figure 2.3. T-lymphocyte subtypes and their characteristics
(Figure by Prof.Edit Buzás, MD.)

The role of Th22 cells in skin is know; their characteristic cytokine is IL-22. Follicular Th cells play an essential role in B-lymphocyte activation *(Figure 2.4.)*.

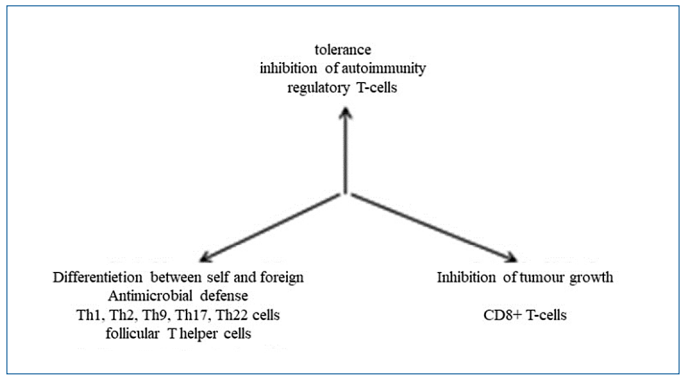

Figure 2.4. Complex functions of T cells

The fate of peripheral T-lymphocytes may be activation, anergy, apoptosis or necrosis. Connection of TCR and peptide presented by antigen presenting cell (APC) / MHC complex can lead to T lymphocyte activation. The binding site of TCR / peptide / MHC is the immunological synapse. Additional stimulatory signals are also required for complete T-lymphocyte activation, these are referred to as *co-stimulatory signals*. The best known and most studied of these is the co-stimulation resulting from the connection of CD28 T-lymphocyte and CD80 / CD86 APC. In case of excessive activation, T-lymphocytes express a cytotoxic T-lymphocyte antigen (CTLA4) protein that binds with much greater affinity to CD80 / CD86 than CD28, and has an inhibitory effect on cell activation (co-inhibition, *Figure 2.5.*). CTLA4 immunoglobulin fusion protein (abatacept) occupying the binding site of CD80 / CD86 APC, inhibits T-cell activation, and has a potent immunosuppressive effect. Another drug that inhibits T-lymphocyte activation is cyclosporin A (CsA), which is and immunosuppressive agent used in e.g. rheumatoid arthritis, psoriatic arthritis and nephrosis syndrome. CsA binds to cytoplasmic cyclophylin; the CsA-cyclophylin complex inhibits calcineurin, the regulator of NFκB-activation and interleukin-2 transcription. Thus, CsA inhibits interleukin-2 production and lymphocyte proliferation.

Regulatory T-cells (Treg) inhibit the immune response by several mechanisms. Major anti-inflammatory cytokines produced by Treg cells: IL-10, IL-35, TGF-β, their characteristic transcriptional factor is FoxP3. Regulatory T-cells continuously express CTLA-4. Treg cells inhibit T-cell proliferation, and are characterised by CD25 expression in addition to CD4 expression. 5–10% of CD4+ T-cells are Treg cells. As mentioned earlier, Treg cells are responsible for peripheral tolerance. Functional dysfunction of CD4 / CD25 Treg cells has been described in several autoimmune diseases. In RA, the function of Treg cells is

impaired, which is partially restored after TNF blockade. Functional dysfunction of Treg cells is also known in SLE and SSc. The regulation of the function and differentiation of regulatory T-cells is one of the most interesting research areas in immunology and rheumatology. Treg cells represent therapeutic target.

Both αβ and γδ TCR have a very short intracellular part; the non-covalently bounding CD3 is responsible for signal transduction. CD3 and the ζ-chain contains *sections responsible for activation of the cytoplasmatic domain* (Immunoreceptor Tyrosine-based Activation Motif – ITAM). Activation of TCR results in the phosphorylation of several intracellular proteins through the activation of protein tyrosine kinases and serine kinases, leading to cytoplasmic Ca^{2+} signal, and finally to T cell activation and clonal expansion *(Figure 2.5.)*. Defects in several sub-processes of T cell activation have been described in systemic autoimmune disorders. Most data on altered T cell function are available in SLE and RA.

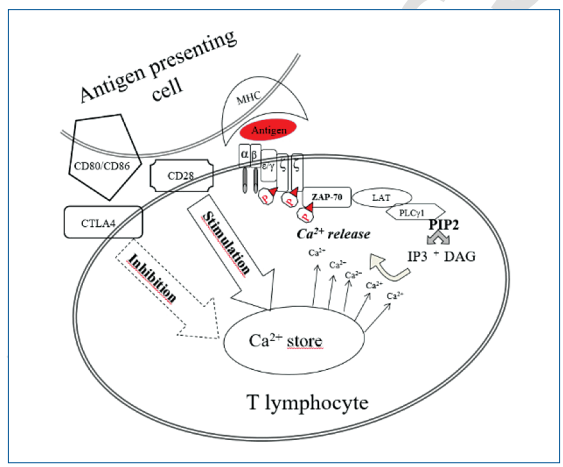

Figure 2.5. T cell activation. The earliest event after T cell receptor activation is the activation of protein tyrosine kinases. During TCR activation, the interaction of CD4 or CD8 molecules with P56lck kinase leads to the autophosphorylation of P56lck, followed by phosphorylation of ITAM motifs. CD45 tyrosine phosphatase is responsible for the phosphorylation of tyrosine of P56lck at position 505. Activated P56lck then phosphorylated ZAP-70 protein (ζ associated protein), and then the phospholipase C-γ1 (PLC-γ1) activates via LAT adapter protein. The active PLC-γ1 cleaves phosphatidyl-inositol 4,5 bisphosphate into inositol 1,4,5 trisphosphate (IP3) and diacylglycerol (DAG). DAG activates protein kinase C (PKC). IP3 liberates Ca^{2+} from the internal stores. After emptying the internal stores, extracellular Ca^{2+} enters the cell through Ca^{2+} channels of the cell membrane during Ca^{2+} influx. Ca^{2+} signal can be measured within seconds after cell activation.

According to several experimental and clinical observations, T-lymphocytes play a central role in inflammation in RA. The efficacy of the abatacept, mentioned above, in RA supports the central role of T cells in this disease. Spontaneous point mutation of ZAP-70, involved in T cell signaling, leads to arthritis in mice, which is serologically, histologically and clinically very similar to human RA. Synovial T-lymphocytes in RA patients are less stimulated than control cells, with reduced interleukin-2 (IL-2) and interferon-γ (IFN-γ) production measured upon stimulation. The expression of the ζ chain regulating the intracellular signaling of the TCR / CD3 complex is reduced in synovial T cells of RA patients, which may explain the reduced activation of these cells. Control T lymphocytes undergoing TNF-α treatment show similar signaling defects as synovial T cells in RA: TNF-α reduces the Ca^{2+} signal that can be measured upon activation. Interestingly, TNF-inhibition restores synovial T-cell activation in RA patients.

The role of T-lymphocyte signaling defects in SLE is also well known. It is noteworthy that in T lymphocytes of SLE patients resting Ca^{2+}-levels are higher, upon activation a faster and greater Ca^{2+} signal can be measured in the minutes after the activation, while the retained Ca^{2+} signal is smaller. The cause of the most studied abnormality in SLE, the significantly reduced ζ- chain-expression is unknown. ζ-chain expression can be influenced by glucocorticoid treatment, but the reduced ζ-chain-expression observed in SLE is probably not solely due to steroid treatment.

2.6.2. Functions of B-lymphocytes and their role in autoimmune diseases

In addition to T-lymphocytes, B-lymphocytes are also cells of the adaptive immune response and play a fundamental role in the pathogen-specific immune response. B cells play a central role in the pathogenesis of RA, one of the best evidence of which is the efficacy of the monoclonal antibody (rituximab) against CD20 in RA. B-cell activation takes place in peripheral lymphoid organs following the meeting of an antigen and a B-cell. Receptor (BCR) on the surface of B-lymphocytes is an IgD and IgM surface immunoglobulin to which an antigen (e.g. bacterium) bound specifically. The cell then takes up and processes the antigen, and presents it on the surface of MHC II molecules to T lymphocytes (see also description of MHC genes). Binding of T- and B-cell results in the aforementioned immunological synapse; T-lymphocytes are required for specific B-cell division.

In case of certain antigens (thymic independent antigens), T-cell independent B-cell activation is also possible, thus e.g. bacterial lipopolysaccharide (LPS)

endotoxins result in polyclonal B cell activation. Unlike monocytes and dendritic cells, B-lymphocytes only take up and present antigens that are specific for their cell surface immunoglobulin receptor. Due to the constant expression of MHC-II and specific antigen binding, B-lymphocyte antigen uptake and presentation occurs even at a very low antigen concentration. Recently, a group of B-lymphocytes very similar to regulatory T cells, regulatory B cells, have been identified. They are characterized by inhibition of the immune response, and IL-10 production; their role in systemic autoimmune diseases is not yet known.

CD5 + B1 cells produce low affinity natural antibodies that recognize self antigens. B2 cells, which account for over 90% of the B cell pool, produce high affinity immunoglobulins. In addition to antigen presentation and antibody production, B cells also produce cytokines. ITAM motifs are also found in the cytoplasmic sections of BCR, similar to CD3. BRC binding induces tyrosine phosphorylation of several proteins. The most important protein tyrosine kinases (PTKs) are Syk, Btk, Lyn, Lck and Fyn enzymes. Syk activates the phospholipase C, enzyme which, like T cells, leads to Ca^{2+} signaling and PKC activation. Several PTKs involved in B cell activation are potential therapeutic targets. Like TCR, immunoglobulins also show tremendous variability, which may result in the production of approximately 1011 immunoglobulins of different antigen specificity due to rearrangement of immunoglobulin genes and other molecular mechanisms. During the first encounter with the antigen predominantly IgM is produced, whereas the repeated encounter leads to a faster and much larger production of IgM and IgG.

The presence of pathological *autoantibodies* is characteristic of many autoimmune diseases; SLE having the most variable antibodies. In Lupus, in addition to higher levels of antibodies against proteins, the levels of antibodies against nucleic acids, carbohydrates, and lipids are also higher, which is a consequence of polyclonal B-cell activation characteristic of the disease. Recent data suggest that the levels of the above-mentioned natural antibodies may also differ in autoimmune diseases. The *B lymphocyte stimulator* (BLyS, also known as BAFF) is a transmembrane protein of 285 amino acids with a structure similar to that of the TNF receptor. BLyS is cleaved by proteases, resulting in the cleavage of a 17kDa soluble protein. BLyS plays a vital role in the survival of B lymphocytes. Serum immunoglobulin levels and B lymphocytes numbers are significantly lower in BLyS-deficient (gene knockout) mice. BLyS transgenic animals develop high levels of anti-DNA, high levels of immune complexes and polyclonal hypergammaglobulinemia, which may lead to a lupus-like disease. In SLE and RA patients, BLyS levels are significantly higher than in control samples. Serum

BLyS levels correlate with SLE activity and anti-DNA levels. BLyS / BAFF inhibition is a therapeutic option in SLE (belimumab).

Soluble antigens and antibodies form immune complexes that are rapidly eliminated from the body under physiological conditions; red blood cells carrying complement receptors are essential for the elimination of immune complexes. Immune complexes play a central role in the pathomechanism of lupus (see also the section on genetics).

2.6.3. Monocytes and macrophages

The cells of the natural immune response are monocytes and their differentiated forms in tissues, macrophages. Their main roles are phagocytosis, cytokine production and antigen presentation. Macrophages are activated during synovitis and can differentiate into osteoclasts and dendritic cells (see below). Activation of synovial macrophages in RA is thought to occur via toll-like receptors (TLRs); primarily via TLR2, TLR3, TLR4 and TLR6 receptors. Increased TLR expression has been confirmed in chronic synovitis. Immune complexes can also activate macrophages via their FCGR receptors. Activated macrophages in RA are a major source of proinflammatory and bone destruction cytokines, thus IL-1, IL-6, IL-15, IL-18, IL-32, TNF-α, BLys, VEGF (vascular endothelial growth factor) and RANKL (receptor activator of nuclear factor κB ligand) are produced in significant amounts in macrophages. All of these cytokines represent potential therapeutic targets; IL-1, IL-6, TNFα and RANKL blocking are currently available.

2.6.4. Dendritic cells

Dendritic cells (DCs), the most effective antigen presenting cells, are part of the natural immune system, named after their dendritic projections. Their growth factor is IL-12. As mentioned earlier, monocytes can differentiate into dendritic cells in the presence of GM-CSF and IL-4. Epithelial dendritic cells or Langerhans cells are $CD11c^{+}$-cells, requiring TGFβ for their maturation. As a medical student, Paul Langerhans is the first to mention these neuron-resembling cells in a study contest entitled *"Nerve Cells in the Human Skin"*. After Langerhans's discovery in 1868, more than a century went by before learning about the functions of the cells he described.

Follicular dendritic cells (FDCs) are similar in appearance only to the aforementioned dendritic cells, and are located in the germinal center of lymphoid tissues. Their main function is to bind antigens and present them in intact form to B lymphocytes.

Interferon alfa (IFN-α) serum levels are higher in SLE patients than in healthy controls. Serum from SLE patients increased the differentiation of monocytes into dendritic cells, which is mainly attributed to high IFN-α levels. Differentiating dendritic cells may present autoantigens and this process plays a central role in the pathomechanism of SLE. Higher expression of IFN-α-regulated genes is observed in the majority of SLE patients. IFN-α is a potential therapeutic target in SLE.

2.6.5. Cytokines and chemokines

Cytokines and chemokines play a major role in the communication of the cells of the immune system. Many cytokines have already been discussed in this chapter, and further information can be found in the books detailed section on the role of cytokines in certain diseases. Cytokines can be pro-inflammatory (IL-1, IL-6, IL-15, IL-17, IL-18, IL-32, TNF-α) and anti-inflammatory (IL-10, IL-35). In systemic autoimmune disorders, the dysregulation of the immune system is complex. A change in the production of a single cytokine or a change in the cellular function does not explain the pathomechanism of these diseases. The operation of the network of pro-inflammatory and anti-inflammatory cytokines regulates the degree of the inflammation. Most cytokines exert their effect on a variety of cell types via cell surface receptors; cytokines can enhance or inhibit production and/or effect of other cytokines. Blockage of a single cytokine can affect the effects of several other cytokines, thus even the functioning of the network as a whole. The network of the participants involved in immune regulation and inflammation can be intervened with the currently available immunomodulatory agents. Apart from the function of the target cells and targeted cytokines, immunomodulation may affect the function of other cells and organ systems as well. The side effects of cytokine blocking are partly explained by their various physiological effects.

Chemokines, 8–10 kDa proteins, play an essential role in the exit of lymphoid cells from the vasculature, also in their migration to the site of the inflammation and their activation. According to the position of the cysteine, CC, CXC, XC and CX3C chemokines can be distinguished. CCL2, CCL5, CCL21 and CXCL13 regulate lymphocyte organization and the formation of synovial germinal centers. Therapeutic attempts targeting chemokines have yet to fulfill the hopes.

2.6.6. Immune cell migration and angiogenesis

Recognition of antigens entering the body in different ways (respiratory tract, intestinal tract, skin, etc.) and the development of an effective immune response

are provided by the constantly moving cells of the immune system. The cell migration process is finely regulated, in addition to cytokines and chemokines, integrins, selectins, cadherins and the hyaluronic acid receptor, CD44, direct the leukocyte migration. The leukocytes exit the circulation and get into to the surrounding tissues primarily through high-endothelial venule (HEV), producing adhesion receptors, with the steps of *rolling, adhesion* and *transmigration*. During rolling, the cells come into contact with endothelial cells, their movement is slowed, and the process is primarily regulated by selectins (E-, P-, and L-selectin). This is followed by adhesion, during which leukocyte integrins are tightly bound to their endothelial partner molecules (e.g., ICAM-1; VCAM-1). Finally, during transmigration, the leukocyte passes through between the endothelial cells *(Figure 2.6.)*.

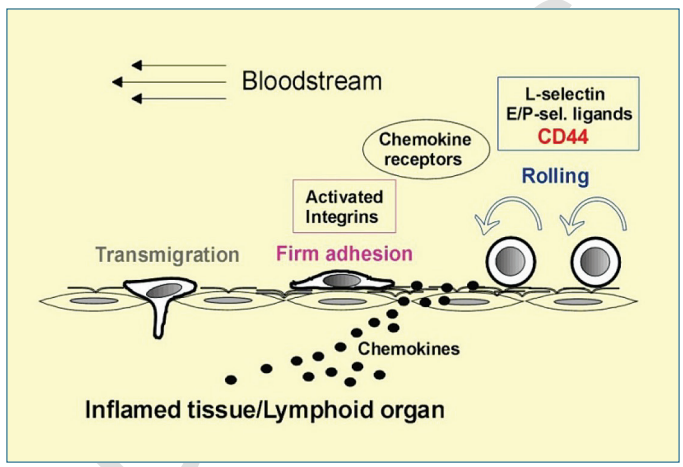

Figure 2.6. Leukocyte-endothelial interactions during inflammation: rolling, adhesion, and transmigration.
The role of chemokines and adhesion molecules.

In RA, during synovitis, synovial endothelial cells become structured similar to HEV, allowing leukocytes to migrate into the synovial space. Proinflammatory cytokines increase endothelial cell expression of E- and P-selectin, ICAM-1 and CD44. In RA, increased expression of E- and P-selectin and CD44, as well as higher levels of soluble E-selectin and CD44, have been confirmed.

Angiogenesis (neovascularization) may also be observed during synovial inflammation. During this process, the activated endothelial cells produce proteases, digest the basal membrane and migrate to the surrounding tissue where they proliferate under the influence of angiogenic mediators. The forming vessel

is connected to the original vessel. VEGF is of angiogenic effect, but angiogenic effect of proinflammatory cytokines, chemokines and hypoxia has also been proven in RA.

Thus, during synovitis, leukocyte exit from the vasculature and neovascularization can also be observed, and contribute to the inflammatory process. Medically influencing both cell migration and angiogenesis is a potential therapeutic option in RA.

2.7. Late consequences of chronic inflammation: tissue destruction

In autoimmune rheumatic diseases, persistent inflammation can lead to structural and functional damage of the target organs *(Figure 2.1.)*. Synovial inflammation developing during RA leads to the damage of the articular cartilage and of the bone in close proximity, followed by joint deformity. Osteoclasts are responsible for the formation of erosions, so the regulation of their differentiation is essential in RA. RANKL, a member of the TNF superfamily, is required for osteoclast differentiation; it is expressed on synovial T cells and fibroblasts, and its production is regulated by proinflammatory cytokines (IL-1, IL-6, IL-17, TNF-α). Binding of RANKL and RANK expressed on dendritic cells, macrophages and osteoclasts results in differentiation and activation of osteoclasts. On the other hand, soluble RANK receptor osteoprotegerin (OPG) inhibits bone resorption. Thus, we see that chronic inflammation (activation of immune-competent cells, production of numerous cytokines and chemokines and "permeability" of synovial vessels) ultimately leads to osteoclast activation and thus erosions in RA. According to recent data, anti-citrullinated protein antibodies also increase the differentiation and activation of osteoclasts. Less is known about the details, e.g. of the molecular pathomechanism of fibrosis in SSc, the mechanism of glomerulonephritis in SLE, or the mechanism of necrotizing inflammation of the upper airways in granulomatosis with polyangiitis (GPA; Wegener's). These processes might also lead to structural and functional impairment.

The exact reason why certain diseases affect only specific organs or organ systems is still unknown. Despite significant advances in recent years, we are only beginning to understand the pathomechanism of systemic autoimmune diseases, and fortunately this process is leading to the introduction of newer and newer drugs.

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3. Infectological approach in rheumatology

Éva Rákóczi

3.1. Introduction

Finding out the origin of infections in autoimmune rheumatological diseases (AIRD) is often not easy. Infections in patients with immuno-suppressed AIRD are often of non-ordinary course and they treatment require careful consideration. Defense against multidrug-resistant pathogens is becoming increasingly difficult in the medical field. Rheumatologic care, as all other specialties, require to have a generic approach to infectology that helps the patient's holistic approach.

3.2. Associations of infections with rheumatologic disorders

3.2.1. Risk of infection

In AIRD, the risk of infections is different from the risk in the average population. The most common infections are septic arthritis, pneumonia, skin infections, herpes zoster, bloodstream infections and sepsis. The increased susceptibility to infection is due, in part, to the underlying disease (functional asplenia, decreased immunoglobulin / complement levels) and partly to the treatment of the underlying disease; in many cases it may be explained with the combination of immunosuppressive therapies.

Among the disease modifying antirheumatic drugs (DMARDs), patient treated with leflunomide has been reported to be more prone to pneumonia; and the rate of infections in SLE patients increased with cyclophosphamide treatment. The results of a large case studies confirmed that the number of serious infections occurring with biological therapy was higher than with conventional disease modifying agents. Patients with AIRD treated with biological therapy are exposed to varicella zoster viruses (herpes zoster) and opportunistic infections such as Mycobacterium tuberculosis, Histoplasmosis, Legionella infection and Pneumocystis jiroveci infection. The risk of bloodstream infections and pneumonia is significantly higher with steroid therapy. Rheumatoid arthritis

(RA), lupus and gout are associated with an increased risk of infectious arthritis; this risk is further increased in patients with other comorbidities, as diabetes mellitus, liver cirrhosis or renal failure.

3.2.2. Pathogen spectrum in rheumatologic disorders

If an infection is suspected, one should be aware of the most common pathogens that may be responsible for the disease process. From an infectological point of view, the role of the following two pathogens can be highlighted:

3.2.2.1. Staphylococcus aureus

In general, in septic arthritis Staphylococcus aureus is the most common Gram-positive bacterium, which is a leading pathological background in rheumatoid arthritis patients as well. Immunosuppressive therapy is a major risk factor in septic arthritis; in RA, the risk of septic arthritis doubles in the presence of tumor necrosis factor alpha (TNF-α) inhibitors. Recent studies have shown that staphylococcal bacteremia has a severe course in RA, and is an independent risk factor for osteoarthritis and early death. The role of Staphylococcus in spondylodiscitis cannot be neglected either. The methicillin-resistant form of the bacterium should be considered when the response to conventional Gram-positive antimicrobial therapy is inadequate.

3.2.2.2. Streptococcus pneumoniae

A Streptococcus pneumoniae (Gram positive bacterium, pneumococcus in short) is the leading pathogenic factor behind pneumonia. Respiratory tract infections are common in AIRD here the risk of pneumonia should be highlighted. Deaths due to respiratory infections are 2.5 times more common in RA than in the general population. The risk of pneumonia is significantly higher with steroid treatment, regardless of the dose. Effective vaccines against pathogens, which protects immuno-suppressed patients from serious infections (bacteremia, pneumonia, meningitis and arthritis), are available.

3.3. Application of antibiotics in rheumatological practice

One of the most difficult steps in treating a patient suffering from an infectious disease is antibiotic selection. Effective antibiotic treatment is achieved when the pathogen is susceptible to the agent, the agent reaches the site of infection, and is administered at the appropriate dose and for the appropriate duration.

Knowing the underlying disease, risk factors, comorbidities, the nature and extent of immunosuppression and the origin of the focal point one should follow a "pathogen thinking" approach. Precise identification of the pathogen is important, therefore targeted microbiological sampling of the infectious site, and a supplemental hemoculture is recommended. Not all antibiotics reach the joints and bones. A recent review, evaluating more than 30 antibiotics, concluded that amoxicillin, piperacillin / tazobactam, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, doxycycline, vancomycin, linezolid, daptomycin, clindamycin, trimethoprim / sulfamethoxazole, fosfomycin and rifampicin penetrates properly into bones and joints. The exceptions are penicillin and metronidazole bone penetration, and flucloxacillin joint penetration, which have not been found to be adequate. Joint infections usually require 2–4 weeks of treatment, while treatment of osteomyelitis requires a much longer, 6 weeks of antibiotic treatment.

3.4. Role of pathogens in autoimmune rheumatological disorders

There are many points in common between infectology and rheumatology. The role of certain pathogens in autoimmune diseases is based on increasing evidence. Trigger mechanisms of autoimmune diseases include e.g. environmental factors. Although bacterial and viral trigger effects require further scientific confirmation, their inducing role is indisputable. Trigger mechanisms of pathogens include molecular mimicry, bystander activation, and immunity-mediated effects (persistence) of antiviral antibodies.

Among the viruses, the trigger effect of Epstein-Barr virus (EBV) is primarily based on molecular mimicry. The effect between viral antigens and patient's antigens has been described in RA, SLE and also in systemic sclerosis. The pathomechanisms of parvovirus B19's RA-inducing trigger function include virus-induced apoptosis and antibody cross-reaction.

The role of the hepatitis C virus, EBV, and human T cell leukemia virus (HTLV-1) has been demonstrated in numerous studies to have a triggering role in Sjögren's syndrome (SS). The role of microbiome in autoimmunity in both SS and SLE has been the subject of recent studies.

There is also increasing evidence of the trigger role of Gram-negative bacteria. High levels of antibody against *Proteus mirabilis* have been detected in RA patients. A high degree of chemical similarity between the bacterium and ACPA has also been found. Similarly, molecular homology has been demonstrated between *Kleb-*

siella pneumoniae and ankylosing spondylitis (AS). Diagnostic criteria for early AS include the presence of high anti-Klebsiella nitrogenase and pullulanase antibodies.

3.5. Infection prevention: vaccination

3.5.1. Vaccinations in general

Vaccination is the safest way to prevent infectious diseases. The compulsory childhood vaccination program is regulated by country. Adults' immunity to vaccination depend on childhood vaccination; the vaccination rate is crucial in the spread of infections. Adulthood reflects a different state of protection, as a significant proportion of adults have not received the newly introduced vaccines, and, due to failure to administer the recommended vaccines in adulthood, there is an inadequate vaccination rate in immuno-suppressed patients and / or patients suffering from advanced chronic diseases.

3.5.2. Vaccinations in immuno-suppressed – AIRD patients

Vaccines can be categorized according to their live pathogen content (containing live pathogen e.g. mycobacterium, yellow fever, chicken pox, herpes zoster-HZ; not containing live pathogen e.g. hepatitis, flu, HPV). The ideal vaccine elicits an appropriate antibody response (protective effect) and its protective effect is sustained (immunogenicity). The antibody response and immunogenicity in an immunosuppressed individual differs from the response of a healthy individual to vaccination. Establishing an appropriate vaccination program in these patients is essential.

It is recommended that patients with AIRD receive vaccines that protect against common, major infectious diseases (flu, pneumococcus), and against special infections that may develop (HBV, HPV, HZ) along the underlying disease and the given immuno-suppressive therapy. The aim of the vaccination program is to try to administer the vaccines before adjusting the immuno-suppressive regimen; the antibody response requires at least 2 weeks (4 weeks in case of a live pathogen). Vaccination program for AIRD patients is recommended to be set up with the help of a vaccination consultant.

Vaccination containing live pathogen is not allowed to be given during biological therapy. Among the immuno-suppressive agents, B-cell inhibition should be highlighted, during which the vaccines do not induce antibody production, so an appropriate interval should be kept before and after treatment. The se-

quential (not simultaneous) administration of pneumococcal vaccines (higher immunogenicity, conjugated vaccine containing 13 serotypes and polysaccharide vaccine containing 23 serotypes) is complementary. Pneumococcal vaccines given during biological therapy (except for B-cell inhibitors), DMARDs given in lower than "high immunosuppressive doses" or during steroid therapy, can elicit an appropriate antibody response. It is essential to administer the seasonal flu vaccination every year. Herpes zoster vaccination (live virus!) in RA can shorten the severe, prolonged shingles pain, but is only recommended to be given to patients who went through chickenpox. Due to the high incidence of HPV infections, vaccination against HPV is strongly recommended in SLE, preferably before the underlying disease is immuno-suppressed.

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4. Differential diagnosis of arthritides and autoimmune disorders

Gabriella Szűcs

4.1. Basic questions to consider

Analyzing the reasons why patients seek medical attention, every 6th visit occurs due to some musculoskeletal problems. The first encounter, the anamnestic data, and status differences determine a series of differential diagnostic steps to make the correct diagnosis. Properly recorded medical history and the physical examination can provide approx. 80% of the diagnosis. In the case of musculoskeletal complaints, the following questions should be considered:

1. Limited / systemic process?
2. Articular / non-articular?
3. Monoarticular / polyarticular?
4. Acute / chronic?
5. Inflammatory / non-inflammatory?
6. Arthritis: axial / peripheral / both?
7. Symmetric / asymmetric?
8. Pain: intermittent / persistent?
9. Are there any signs of muscle or neurological dysfunction?
10. Has there been a similar process in the family?

Knowing the symptoms, the answers to the questions above confirm or exclude certain diseases.

4.2. Basic aspects of joint process

Arthritis in terms of the number joints involved, may be monoarthritis, involving one joint, oligoarthritis, involving 2–4 joints, or polyarthritis, involving 5 or more joints.

Most common forms of *monoarthritis* are infectious arthritis (pyogenic bacterium, mycobacterium) and crystal arthropathies (gout, CPPD).

The most common examples of *oligoarthritis* are spondylarthritides, which include ankylosing spondylitis, reactive arthritis, arthritis associated with inflammatory bowel disease, and psoriatic arthritis. In rheumatoid arthritis (RA), oligoarthritis can occur rarely, predominantly in the elderly; 2–4 joints may be involved in chronic gout, and osteoarthritis may involve more joints at the same time.

The background of *polyarthritides* is much more diverse. Polyarthritis may be a symptom of non-differentiated polyarthritis (NDP; undifferentiated polyarthritis (UDP), non-differentiated connective tissue disease (NDC; undifferentiated connective tissue disease – UCTD). Definitive systemic autoimmune disease (systemic lupus erythematosus – SLE, systemic sclerosis – SSc, IIM, mixed connective tissue disease [MCTD], Sjögren's syndrome, vasculitis) can be the underlying cause. The classic representative of polyarthritis is RA. Less frequently, some members of the spondyloarthritides may exhibit polyarthritic activity (e.g. psoriatic arthritis), but osteoarthritis may also have involved more than 5 joints. Finally, various infections (viruses: CMV, EBV, HCV, HBV, HSV etc. and bacteria) or other internal medicine diseases (e.g. endocrine disorders, hyperthyroidism, sarcoidosis, malignancies, including, in particular, lymphomas and multiple myeloma) associated with polyarthritis make up a fairly significant group. Regarding the outcome of UDP, symptoms may resolve spontaneously or in response to asymptomatic treatment (approx. 60%); may be chronic non-erosive (approx. 15–16%) or erosive form requiring early treatment, most often resulting in definitive RA.

Some aspects of *differential diagnosis of polyarthritides* to be clarified:

- What is the chronology of the symptoms?
- Is there an actual inflammation?
- What is its scope?
- What is the course of the disease?
- Are there specific demographics?
- Are there extraarticular manifestations present?

In terms of the *chronological* nature of the symptoms and changing of the symptoms with time, complaints present up to 6 weeks is considered acute polyarthritis. These are most commonly viral or bacterial infections associated with acute, so-called self-limited (self-healing) polyarthritis, but it also may be the onset of a chronic illness. In the latter, the symptoms persist for more than 6 weeks and do not improve without treatment.

An important aspect is the *inflammation,* the presence of arthritis that we must distinguish from non-inflammatory arthralgia. Inflammation is associated with actual joint swelling (palpation!), prolonged joint stiffness, pain at rest, and other general symptoms (e.g. fever, weight loss, lymphadenomegaly). When determining the *extent* of polyarthritis, localization, symmetry, spinal and sacroiliac joint (axial) involvement should be considered. RA with symmetric MCP-PIP involvement, usually in a destroying form, SLE, DM / PM, SS, polyarteritis nodosa (PAN) in a non-destroying form cases hand-foot arthritis of the small joints. Asymmetrically, DIP joints are involved in psoriatic arthritis (dactylitis, arthritis mutilans form). Among osteoarthritis, Heberden-osteoarthritis (DIP) and Bouchard-osteoarthritis (PIP) also affect small joints of the hand, which may be accompanied by signs of inflammation. Metabolic or endocrine disorders can also cause abnormalities of the small joints of the hands and feet. Inflammatory lesions of the spine are characteristic of spondylarthritis, with ankylosing spondylitis being the characteristic disease. In addition to spinal involvement, sacroiliitis is also present. Cervical spine abnormalities may also occur in RA in the form of atlantoaxial subluxation.

The nature of the *diseases course* may provide a basis for diagnosis. Intermittent arthritis occurs in crystal arthropathies, palindromic rheumatism. Gonococcal arthritis, rheumatic fever, sarcoidosis, SLE and bacterial endocarditis is characterized by migrating arthritis.

Demographics can also be used to screen for different disorders. Pre-menopausal women are 9 times more likely to have SLE and 3 times more likely to have RA than men (the difference is less significant over 50 years), parvovirus arthritis is more common in women, but ankylosing spondylitis (AS) and gout show male dominance. Regarding age groups, SLE, RA, reactive arthritis, spondyloarthritis and rheumatic fever occur at a younger age, whereas osteoarthritis, polymyalgia rheumatica and giant cell arteritis are diseases of the elderly. Races can also be determining: Caucasian people are more likely to have granulomatosis polyangiitis from the ANCA-associated vasculitis, and polymyalgia rheumatica, while SLE and sarcoidosis is more common and severe in African Americans. AS, RA and Heberden's osteoarthritis show family aggregation.

4.3. Extra-articular manifestations

In addition to clarifying the joint process, the next, most important question is whether the patient has any extra-articular manifestation that may indicate certain diseases.

The following symptoms and abnormalities may indicate the presence of *connective tissue disease:* Raynaud's phenomenon, sicca syndrome, skin symptoms, proteinuria, hematuria, polyneuropathy, symptoms indicating antiphospholipid syndrome (APS), recurrent serosa, leukopenia, interstitial lung disease (alveolitis, pulmonary fibrosis) or pulmonary hypertension. Detailed questioning and full physical examination of the patient, from head to toe, is required to consider and assess these symptoms and abnormalities.

General symptoms are not specific, but can certainly help the diagnostic process. Fever may occur in any systemic autoimmune disease, but may be most common in SLE, Still's disease, and arthritis following an acute viral or bacterial infection, or malignant disease (primarily hematological disease). Lymphadenomegaly is characteristic of SLE, polyarthritis associated tumor and vasculitis.

Some of the *skin symptoms* that can stand alone to support diagnosis of certain disorders are disease-specific skin symptoms: the butterfly rash on the face is indicative of SLE, Gottron's papule, Gottron's sign is indicative of idiopathic inflammatory myopathy (IIM), sclerodactyly, perioral sclerosis indicate systemic sclerosis, and erythema migrans indicate Lyme disease. There are less specific skin symptoms that can occur in more diseases, but their presence narrows the range of possible conditions, e.g. photosensitivity (SLE), shawl sign (dermatomyositis), purpura characteristic of lower limb vasculitis, are those more common in autoimmune diseases, and livedo reticularis in APS. Subcutaneous nodules may be indicative of RA, and tophus of the presence of gout. Hypo- or hyperpigmentation is predominantly observed in scleroderma, subcutaneous calcinosis is common in scleroderma and in myositis. Hair loss can be a common accompanying symptom of any chronic disease, but it is also a symptom of activity in SLE.

The next easy area for questioning and examining is the mapping of *ophthalmic abnormalities*. Uveitis is primarily the extra-articular manifestation of spondyloarthritis. Conjunctivitis sicca occurs in Sjögren's syndrome or as a co-symptom in other systemic autoimmune disorders. Scleritis may accompany RA. Ischemic optic neuritis is characteristic of giant cell arthritis and different ophthalmic symptoms may occur in granulomatosis with polyangiitis.

Examination of *ear-nose-throat / larynx* may reveal oral ulcers, aphtha which may occur in SLE, Behçet's disease and reactive arthritis. Swelling of the parotid is characteristic of Sjögren's syndrome, sensitivity to forehead pressure of giant cell arteritis, inflammation of the auricle of polychondritis, and sinusitis of ANCA-associated vasculitis (primarily granulomatosis with polyangiitis).

Examination of *nail* in polyarthritis is essential. Typical dots, onycholysis can be observed, which supports the diagnosis of psoriatic arthritis.

When *examining the internal organ manifestations,* it is necessary to examine each organ symptoms (pulmonary, cardiac, gastrointestinal, urogenital, nervous, etc.), the abnormalities of which may be characteristic of certain disorders. Pulmonary fibrosis in present in scleroderma, pleuritis, pericarditis is often found in SLE, myocardial abnormalities may be present in scleroderma and polymyositis, glomerulonephritis is present in SLE and vasculitis, esophageal dysmotility is present in scleroderma, diffuse abdominal pain due to bowel ischemia is present in polyarteritis nodosa, and central nervous symptoms are present in SLE and vasculitis.

Based on patient's history and physical examination, a *diagnostic plan* is established. During this process, various laboratory and imaging tests may be requested to support the suspected diagnosis.

4.4. Laboratory and imaging tests

Laboratory tests can be divided into general and specific sections. During the *general tests,* we examine erythrocyte sedimentation (ESR) and C-reactive protein (CRP) as common markers of inflammation. If certain diseases are suspected, ferritin levels (e.g. Still's disease) or serum amyloid A (SAA) levels (e.g. giant cell arteritis and polyarthritis) should be checked from the inflammatory markers. During routine examination, blood work, liver and kidney function parameters, serum uric acid levels and a general urine test for proteinuria and hematuria should be checked. If needed, different viral and bacterial serological tests may be required.

Then can be moved on to more *specific tests*. Rheumatoid factor (RF) and anti-CCP antibody may support the suspicion of RA; HLA-B27 positivity is characteristic of spondyloarthritides, including ankylosing spondylitis. In case of suspicion of systemic autoimmune disease, it is important to test the antinuclear factor: homogeneous antinuclear antibody (ANA) positivity can be observed in SLE, granular in Sjögren's syndrome, polymyositis / dermatomyositis, scleroder-

ma, and nucleolar pattern may be present in scleroderma as well. If the symptoms are well established, specific autoantibody tests are required (anti-DNA, anti-Sm – SLE; anti-SSA, anti-SSB, anti-alpha-fodrin antibody – Sjögren's syndrome; anti-U1RNP – MCTD; anti-Scl70, anticentromere, anti-RNA polymerase III – SSc; anti-Jo-1 – polymyositis; antineutrophil cytoplasmatic antibody [ANCA] – vasculitis; antiphospholipid antibodies – APL). In diseases with immune pathomechanisms, low levels of complement can be observed due to the utilization of complement factors (SLE and vasculitis). Immunoglobulin levels (IgG, IgA and IgM levels) should be considered as a starting point when examining patients for autoimmune disease, as it is known that, for example, in case of immunodeficiency (most commonly common variable immunodeficiency – CVID) there is an increased incidence of autoimmune disorders.

Imaging tests examinations (conventional X-ray, ultrasound, CT, MRI, angiography, isotope examinations, PET / CT, etc.) can be used to assess joint status and internal organ manifestations, and to clarify the background of internal organ abnormalities. The erosions seen in the comparative hand-foot images may be characteristic of RA and gout (different character and localization of erosions). Joint or spinal X-rays show degenerative abnormalities, fractures, compression, abnormalities characteristic of metastasis, and sacroiliitis on sacroiliac image. In case of an inflammatory process, a targeted ultrasound or MRI scan may provide a more detailed picture of the joints, soft tissues, while CT scan provide information on bones. Partially the chest X-ray, but more precisely pulmonary high-resolution CT scan of the lungs may reveal pulmonary processes associated with systemic disease; cardiac ultrasound, cardiac MRI is needed to clarify the cardiac background. Special CT or MRI-angio, PET-CT can be used in case of suspected vasculitis.

In most cases, during the diagnostic process, there is time to schedule examinations and wait for the results, but there are situations where taking an immediate action and making an early therapeutic decision is needed. These situations include high fever, acute pain of one or only a few joints (infection and exclusion of crystal arthropathy), suspected renal, cardiac and pulmonary manifestations that can progress rapidly, trauma, neurological complications and vasculitis, which can cause irreversible damage. In such cases, starting treatment appropriate for the most likely diagnosis is needed, and gathering evidence already during the treatment there is a need to support the diagnosis.

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5. Drug therapy in rheumatology

Zoltán Szekanecz

5.1. Introduction

Rheumatological disorders are divided as predominantly autoimmune / inflammatory (arthritis, systemic disorders) and predominantly degenerative (osteoarthritis, backache, osteoporosis) disorders (although osteoarthritis is now more commonly referred to as osteoarthritis). The analgesia and inhibition of inflammation, which is achieved primarily with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), is important in all rheumatological diseases. Immunosuppressive therapy and, more recently, biological therapy are important in the treatment of immune-mediated inflammatory diseases (RA, AS, juvenile idiopathic arthritis: JIA). In osteoarthritis, they are also trying to preserve cartilage with restorative drugs and treating osteoporosis with special medicines. In this chapter, we will review the main classes of medications only in general terms; practical application and therapeutic methods will be discussed in later chapters discussing the given disease.

5.2. Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to reduce inflammation in rheumatic diseases and other disorders. They are also known to have analgesic and antipyretic properties, however, in the first instance, simple analgesics and antipyretics are recommended for these indication *(Table 5.1.)*. Among the musculoskeletal disorders, it is used for the treatment of arthritis, osteoarthritis, low back pain, soft-tissue rheumatism, and injuries. It is also commonly used in non-rheumatic indications to relieve dysmenorrhea, headaches and migraines. They are also available in oral, injectable, suppository, and topical (ointment, cream, gel, patch, spray) applications.

It is no coincidence, therefore, that this is a very popular and widespread class of drugs, which, as we have seen, is highly effective in many indications. In other respects, the widespread use and the fact that some products are available

over-the-counter also carry the risk of side effects. Most side effects of NSAIDs are due to their primary mechanism of action, which is inhibition of prostaglandin synthesis.

In terms of *mechanism of action,* it is known that cyclooxygenase (COX) and lipoxygenase (LOX) synthesize prostaglandins and leukotrienes from arachidonic acid released from phospholipids of the cell membrane by phospholipase A2.

Prostanoids, in addition to their other biological effects (e.g. regulation of platelet function and coagulation, protection of the stomach mucosa, regulation of renal blood flow and renal function), generate inflammation from inflammatory leukocytes. This results in increased permeability of the blood vessel wall, formation of edema, pain and fever.

NSAIDs inhibit both COX and LOX enzyme. COX has three isoenzymes, of which COX-1 and COX-2 are essential. The former inhibits inflammatory processes, the latter is involved in homeostasis. Due to content limitations, we cannot go into detail, but the side effects of NSAIDs (e.g. gastrointestinal, cardiovascular) are mainly based on the COX-1 / COX-2 balance and whether the particular NSAID preparation preferably inhibits COX-1 or COX-2 enzyme.

This *drug group has many members.* It should be noted that there is no significant difference in their efficacy, and the same anti-inflammatory and analgesic effect can be achieved with essentially any of these drugs *(Table 5.1.).* However, due to the side effect profile, half-life and a few differences, we often have to choose from a large number of formulations. Different application modes also offer a choice.

Table 5.1. Daily doses of commonly used NSAIDs (in arthritis)

Compound	Daily dose
Aceclofenac	200 mg
Acemetacin	200–600 mg
Acetylsalicylic acid	500–1500 mg
Celecoxib	200–400 mg
Dexibuprofen	600–1200 mg
Dexketoprofen	75 mg
Diclofenac	75–225 mg
Etoricoxib	60–120 mg
Ibuprofen	1200–3200 mg

Compound	Daily dose
Indomethacin	150–200 mg
Ketoprofen	150–300 mg
Meloxicam	7.5–15 mg
Naproxen	550–1100 mg
Niflumínsav	250–750 mg
Nimesulid	100–200 mg
Phenylbutazon	100 mg*
Piroxicam	10–20 mg
Tenoxicam	20 mg

**can be given up to 7–10 days at most*

Historically, salicylic acid was first used to relieve pain and reduce fever, and at the beginning of this century it was synthesized and marketed as aspirin. Today, several compounds are available in hundreds of names and packagings. Analgesics, antipyretics and anti-inflammatory drugs may be classified according to their structural relationship or half-life. We will not go into further details here. In practice, compounds with short(er) half-lives have to be administered 3–4 times daily; and as the effects of long-lived compounds last up to 12–24 hours, they are usually administered 1–2 times daily. Although 1–2 times daily dosing is more convenient for the patient, in the case of longer half-life formulations there is a greater risk of cumulation and toxicity. Regarding method of administration, systemic anti-inflammatory effect can be achieved with oral medication (e.g. tablets, capsules) or suppositories, whereas when the inflammation and pain is localized to a particular area (e.g. a single joint or body region) external drug forms (patch, ointment, gel and spray) are the ones to show success.

As far as the *practical implementation* of the utilization is concerned, the choice between agents should be based on the indication, the expected treatment duration and the risks. Although, as mentioned above, the same effect can be achieved with virtually any formulation, if we seek short-term, effective treatment, e.g. in case of acute arthritis, gout-like seizure, we choose the very potent, but often more toxic preparations, with only a short-term use allowed. Relief of chronic pain, e.g. in the case of OA, we may be compelled to administer NSAIDs for several weeks or months, in which cases often less potent but safer formulations, in particular selective COX-2 inhibitors are administered. Nowadays several com-

binations are available in which the NSAID is combined with a simple or opioid analgesic. Systemic use of two NSAIDs is contraindicated! (Oral agent should be combined with external drug.)

In terms of *risk and side effects,* more or less all NSAIDs damage the gastrointestinal mucosa (including the small and large intestines!), can worsen blood count, and can cause kidney and liver damage, and high blood pressure. In recent years, it has become apparent that both COX-2 inhibitors and conventional NSAIDs may increase cardiovascular risk. NSAIDs should be used with caution and in reduced dose in patients with chronic heart, liver or kidney diseases. Special caution is important particularly in the elderly, who may have a pre-existing heart disease, and whose kidney and liver function are already impaired. In the elderly, as drug elimination worsens, NSAIDs may accumulate, therefore increased caution is advised and preparations with long half-life should be avoided.

The most common side effects of NSAIDs are gastric mucosal damage, dyspepsia, erosive gastritis, ulcers and their complications, bleeding and perforation. Unfortunately, there is usually no correlation between NSAID-induced gastric complaints and the severity of the adverse reaction: in individuals presenting with no complaints endoscopy often detects erosion, ulceration, and the NSAID-induced gastric bleeding may occur suddenly and asymptomatically. At other times, morphological abnormalities cannot be found in the background of persistent heartburn and dyspepsia by endoscopy. The underlying cause of gastric mucosal injury is the inhibition of the cytoprotective role of prostaglandins. There is an even greater risk in case drug with enterohepatic circulation (e.g. indomethacin, piroxicam). Helicobacter pylori infection does not enhance the ulcerogenic effect of NSAIDs, but slows the healing of established ulcers. Patients with a history of ulcers, and those taking steroids or anticoagulants, are at high risk for gastrointestinal side effects. Since H2 blockers alone are not sufficient to prevent gastric damage, proton pump inhibitors should be given with NSAIDs. In this respect, the development of safer, selective COX-2 inhibitors meant major breakthrough in regards to the gastrointestinal tract. It is also important that in addition to gastric and duodenal ulcers, the small intestine (NSAID enteropathy) and the large intestine (colonopathy) can also be damaged, resulting in diarrhea, protein loss, and bleeding.

Other important side effects of NSAIDs are the kidney damage and the hypertension partly related to this kidney damage. Since prostaglandins play a role in regulating renal blood flow, this side effect is also common to the entire class of drugs. The risk is even greater with concomitant ACE inhibitors or diuretics. NSAIDs increase both systolic and diastolic blood pressure, thereby contribut-

ing to increased cardiovascular risk. NSAIDs usually do not cause severe hepatic impairment, but some preparations (e.g. nimesulide) have been reported to cause increased hepatotoxicity. Moderate elevations of serum transaminases may occur with all NSAIDs, thus periodic monitoring of liver and renal function is strongly recommended. Inhibition of platelet function does not usually cause manifestation of hemophilia, but may exacerbate bleeding from other causes (e.g. ulcers). In some susceptible patients, NSAIDs may provoke bronchial asthma. Since NSAIDs are most commonly prescribed for OA, it is important that these agents can have cartilage-damaging properties. Since the pain in OA is mechanical and not primarily of inflammatory origin, it is preferable to administer simple analgesics (e.g. paracetamol) in the first line and order NSAIDs only in case for inflammation (inflammatory OA). Of the rare, drug-specific side effects, phenylbutazone can cause severe aplastic anemia, so it should only be used in highly justified cases and for a short period (up to 7–10 days). In higher doses, salicylates can cause tinnitus, acetylsalicylic acid and indomethacin dizziness, headache, and confusion.

As we have already mentioned, the identification of *isoenzymes of COX enzyme* (COX-1 and COX-2) and better understanding of their functions have yielded considerable scientific results. The COX-1 isoenzyme is found in virtually every tissue cells and is involved in the constitutive synthesis of prostaglandins, serving physiological functions. COX-2, on the other hand, is predominantly found in white blood cells; and is an isoenzyme induced by inflammation. COX-2 inhibition is responsible for the anti-inflammatory and analgesic effects of NSAIDs, while concomitant inhibition of COX-1 is an adverse event responsible for gastrointestinal and renal side effects, and hemorrhage. Based on this, selective COX-2 inhibitors (celecoxib, etoricoxib) have been developed, which predominantly exert their anti-inflammatory effects by COX-2-inhibition, while barely having an effect on COX-1 enzyme, therefore having a more favorable side effect profile. These extensive studies have shown significantly less gastrointestinal damage, but other side effects (such as cardiovascular side effects) are more prevalent.

In addition to side effects, risks also include *drug interactions.* Elderly patients with musculoskeletal diseases often take other medications. NSAIDs can compete with anticoagulant coumarins and oral antidiabetics for binding to plasma proteins, thereby increasing INR and lowering blood glucose levels. In contrast, NSAIDs may reduce the efficacy of certain antihypertensive agents, particularly ACE inhibitors and beta blockers.

5.3. Replacement of articular cartilage with drugs

Systemic or local administration of the organic constituents of articular cartilage (glucosamine, chondroitin sulfate and hyaluronic acid), either in a therapy-like or continuous manner, in addition to a moderate analgesic effect, can also result in a structure-preserving effect. In the latter respect, larger analyzes and metaanalyzes have yielded contradictory data.

Of the licensed glucosamines, crystalline glucosamine sulfate (1500 mg/day) is the only one proven to be effective in both clinical and real-life studies. Both glucosamine sulfate and chondroitin sulfate are rapidly absorbed and have been shown to be effective in the treatment of patients with OA.

Several hyaluronic acid formulations are available, the main difference being in their molecular weight. The highest molecular weight product should be used. Topically, intraarticularly, administered hyaluronic acid treatment is recommended for middle-aged patients with moderate knee OA having an active work. When administering an injection into the joint, maximum efforts should be made to comply with the rules of asepsis and antisepsis. Various hyaluronic acid formulations should not be used in case of inflamed or infected joints or in patients who have skin infections at or near the injection site. Orally administered hyaluronic acid is well-liked among patients for its ease of application and good tolerability. It is proven to be absorbed from the small intestine and reaches the joints. It reduces pain and inflammation on OA, and has a cartilage regenerating effect. Data on the use of oral collagen are also available.

5.4. Corticosteroids

The basics and details of corticosteroid treatment can be found in theoretical pharmacology books. Only the main guidelines of corticosteroid treatment for inflammatory rheumatic diseases are described here. There are several formulations to choose from, but to assess the expected effect, we need to know the equivalent doses of the various corticosteroid compounds *(Table 5.2.)*.

Table 5.2. Main properties of corticosteroid compounds

	Equivalent doses (mg)	Glucocorticoid activity	Mineralocorticoid activity	Biological half-life (hours)
Short duration of action				
Cortisone	25	0.8	0.8	8–12
Cortisol (hydrocortisone)	20	1	1	8–12
Medium duration of action				
Prednisone	5	4	0.6	16–36
Prednisolone	5	4	0.6	16–36
Methylprednisolone	4	5	0.5	18–40
Triamcinolone	4	5	0	12–36
Long duration of action				
Dexamethasone	0.75	20–30	0	36–54
Betamethasone	0.6	20–30	0	36–54

In the past, arthritis was treated much more frequently with steroid formulations, especially before the highly effective disease-modifying antirheumatic drugs and biological therapies were used. Again, it is important to note that despite the several available compounds (e.g. prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone) there is no clear difference between the formulations. The main side effects seen with each product are fluid retention, edema formation, hypertension, osteoporosis, gastropathy, glaucoma, cataract, diabetes mellitus, myopathy, psychosis. Considering the effect / side effect ratio methylprednisolone is probably the optimal choice today. Common side effects of triamcinolone are myopathy, while dexamethasone is associated with hypertension and diabetogenic side effects.

The route of administration of corticosteroids is also important. In the case of transient synovitis of one or two joints, good results can be achieved by topical (intraarticular) administration, while in polyarthritis, in case of systemic symptoms and organ involvement, systemic administration (oral or iv injection) is preferable.

Knowing all this, corticosteroids may be administered in the following indications in rheumatic inflammatory disorders *(Table 5.3.):*

Table 5.3. Dosage of corticosteroids

Low dose	≤7.5 mg prednisolone or equivalent dose daily
Medium dose	>7.5 mg but ≤30 mg prednisolone or equivalent dose daily
High dose	>30 mg but ≤100 mg prednisolone or equivalent dose daily
Very high dose	>100 mg prednisolone or equivalent dose daily
Bolus therapy	≥250 mg prednisolone or equivalent dose daily for one or several days

- Clinical and radiological progression can be slowed down in the early stages of arthritis (within the first 3–6 months; irrespective of a definite diagnosis), with initially 0.5–1 mg/kg body weight, followed by a tapered dose (5–7.5 mg prednisolone equivalent per day) of steroid therapy. Therefore, after excluding infectious arthritis and gout, corticosteroids should be given in early cases of RA, SpA and JIA;
- Bridging therapy (bridging or bridge therapy): steroids may be used for a few days or weeks, until the new drug introduced after disease-modifying anti-rheumatic therapy or switching;
- Local (intraarticular) treatment: when the activity of one or two joints occurs during the otherwise polyarticular process; in such case, local injection is more effective and safer than systemic application. A maximum of three depot-steroid injections per joint may be given in one year. Enthesitis may also be treated by local corticosteroids;
- In addition, systemic steroid treatment may be required in case of marked or persistent activity. In this case, the strategy for systemic autoimmune disorders should be chosen: slowly tapering the dose after administering a medium to high dose for a few days. A maximum of 7.5–10 mg of prednisolone equivalent (6–8 mg methylprednisolone) may be given permanently;
- In systemic autoimmune rheumatic diseases (SLE and myositis), depending on the severity of the symptoms, moderate (50–100 mg), high (100–250 mg) or bolus dose (500–1000 mg) corticosteroid treatment may be given in a specialized center.

5.5. Conventional immunosuppressive drugs

Years ago, it became evident that NSAIDs and / or corticosteroids, while temporarily significantly reducing inflammation and thus providing rapid success for physicians and patients, have no long-term effect on the outcome of chronic

arthritis and autoimmune diseases. Disease-modifying agents (DMARDs, disease-modifying antirheumatic drugs) are formulations that have been shown to slow down the progression of chronic arthritis. Conventional DMARDs *(Table 5.4.)* and targeted therapies (biological agents and tyrosine kinase inhibitors) (*Table 5.5.;* see below) are known.

Table 5.4. Conventional immunosuppressive agents

Drug subgroup	Molecule
Cytotoxic agents	azathioprine cyclophosphamide methotrexate leflunomide mycophenolate mofetil
Non-cytotoxic immunosuppressive agents	corticosteroids chloroquine/hydroxychloroquine cyclosporin A tacrolimus sirolimus (rapamycin) sulfasalazine thalidomide

The *main purpose* of immunosuppressive therapy is to inhibit self-sustaining immunological activation, neovascularization and synovial proliferation; and consequently to inhibit inflammatory mediators (cytokines, chemokines, metalloproteinase enzymes, etc.) that damage articular cartilage and subchondral bone, leading to joint destruction. Most importantly, however, disease-modifying antirheumatic therapy slows down the rate of joint destruction and organ damage. Nowadays, we do not always wait for a final diagnosis, preferring early, aggressive treatment and giving DMARD therapy in the early stages of non-differentiated arthritis or non-differentiated collagenosis (NDC). The acceleration of the process of arthritis and the onset of structural damage, and organ damage in autoimmune diseases occurs 3–6 months after the onset of the disease; thus, the therapeutic window, within which effective immunosuppressive treatment must be started, must not be more than half a year.

In principle several immunosuppressive agents are widely used for the treatment of arthritides and systemic autoimmune disorders, however, based on a risk-effectiveness assessment, only four-five DMARDs are used nowadays, while other, previously used agents (e.g. gold salts, penicillamine) have been discarded from the day to day practice. *Methotrexate* is the "gold standard" for the treatment of RA and other peripheral arthritis (SPA, PsA, JIA) as it is highly effec-

tive, relatively safe and very inexpensive. It is also used in SLE, scleroderma and dermatopolymyositis, primarily for the relief of joint and skin symptoms. The starting dose is 7.5 mg per week, which is recommended to be titrated every 2–3 weeks to a maximum of 20–25 mg per week. Importantly, underdosing is disappointing for both the patient and the doctor, so be sure to administer the required effective dose! All of this is done under close control of blood count and liver function. Side effects can be prevented by administration of folic acid or folinic acid. In case of gastrointestinal intolerance, injectable preparations may be recommended instead of oral administration.

The efficacy and side effect profile of *leflunomide* is similar to that of methotrexate, however leflunomide is slightly more expensive. Its indications are RA and PsA. Nowadays, leflunomide is preferred in cases where methotrexate is contraindicated for some reason, but in some cases it may be the first DMARD therapy choice. The dose is 20 mg daily. Compared to other drugs, its effects develop very rapidly, in 2–3 weeks. Common side effects are hair loss and nausea, which do not account for stopping the drug; it can be reduced to a dose of 10 mg daily. However, as a side effect, deterioration of the blood count or liver function may occur, and in these cases treatment should be discontinued. Laboratory parameters should therefore be checked very frequently.

Nowadays, the treatment of RA is practically based on methotrexate and leflunomide, but in mild, early cases and in combination, *chloroquine and hydroxychloroquine* are still in use. These originally antimalarial agents are among the less effective but relatively safe formulations. However, they exert their effect after a longer period (3–4 months). The initial dose of chloroquine is 2×250 mg for 1–2 weeks, which is to be tapered to 1×250 mg every second day. The dose of hydroxychloroquine is 200–400 mg daily. The formation of cornea deposits should be considered in particular with the administration of chloroquine. For this reason, the patient should go to an ophthalmologist for the first 3 months of the treatment, and afterwards every six months. Regular blood count monitoring is recommended. Now, these agents are the gold standard for SLE, and almost every patient has to be given these. In addition, it is mainly used in combination in other autoimmune inflammatory disorders.

Sulfasalazine is a complex of 5-aminosalicylic acid and sulphonamide, and accordingly its anti-inflammatory effect has long been recognized. Its effect in arthritis is weaker than that of methotrexate, so it is used in early, mild cases and in combination. It exerts its effect very quickly, within 3–4 weeks, and together with methotrexate is considered to be the best profiled drug in terms of the effect / side effect relationship. Each tablet contains 500 mg of the active agent.

The dose used to treat RA is usually 2000 mg (2×2 tablets), less frequently it can be 3000 mg (3×2 tablets). The main side effects of sulfasalazine are leukopenia and thrombocytopenia and therefore blood count monitoring is required. Rarely, gastrointestinal intolerance can also occur.

Of the less commonly used DMARDs, the use of *cyclosporine* A is nowadays overshadowed, since its less effective than the aforementioned formulations, yet its expensive and its several side effects are known. However, it is occasionally used, in addition to organ transplantation, in RA, psoriasis, PsA and systemic autoimmune disorders (SLE and myositis). The starting dose is 2.5 mg/kg; and doses higher than 4 mg/kg are rarely required in RA. Most of the side effects (bone marrow suppression, proteinuria, nephrotoxicity, gingival hyperplasia) occur above the 5 mg/kg threshold, so the standard dose (2.5 mg/kg) can be safely administered.

In systemic autoimmune rheumatic diseases (SLE, myositis, MCTD and vasculitis) *cyclophosphamide* and *azathioprine* are more common. It can be administered orally at a dose of 100–150 mg daily. Cyclophosphamide can also be administered intravenously in the form of infusion. Due to their likely oncogenicity and teratogenicity, prolonged use (more than 6–12 months) is unlikely, and blood count, liver and kidney function should be monitored closely.

Mycophenolate mofetil is an ester of mycophenolic acid isolated from *Penicillium* species. When administered, the mycophenolic acid released inhibits lymphocyte proliferation and B-cell antibody production, as well as leukocyte accumulation at the site of inflammation. In addition to transplantation, it has gained ground in the treatment of autoimmune disorders, primarily in SLE (lupus nephritis) and ANCA-associated vasculitis. The dose in these disorders is 2.5 mg/kg daily. The treatment may cause gastrointestinal side effects and neutropenia.

Tacrolimus, a macrolide antibiotic, is produced by species of fungi, Streptomyces. Binding to immunophilin-like FKBP (FK506-binding protein), like cyclosporin A bound to cyclophilin, it inhibits the production of cytokines; it is one hundred times more potent than cyclosporin. Among the immunopathological diseases it can be used in focal glomerulosclerosis, chronic active hepatitis, psoriasis, and atopic dermatitis. Among its side effects are neuro- and nephrotoxicity can be highlighted.

Thalidomide is primarily an inhibitor of angiogenesis, but has several other immunosuppressive effects. Thalidomide inhibits TNF-α, and stimulates IL-10 production. It also inhibits phagocytic functions of neutrophils. Although primarily registered for the treatment of multiple myeloma, it is also used for

the treatment of SLE and there are also promising attempts in the treatment of other autoimmune disorders. The most well-known side effect is teratogenicity, which led to its withdrawal from the market in the 1960s. Today, it is used with great care in these indications, especially in patients of with no childbearing potential. Other side effects include increased peripheral neuropathy, constipation, rash and increased risk of thromboembolism.

Combination therapy is becoming more common. Nowadays, combinations of anti-TNF therapy (biological therapy, see below) and conventional DMARDs (primarily methotrexate) is common. However, in case monotherapy is ineffective and / or biological therapy cannot be given, it may still be possible to increase the effectiveness of DMARD therapy by co-administration of two or three agents, preferably with a complementary side effect profile. Among the two-component strategies, the combination of methotrexate + sulfasalazine has become common nowadays, but cyclosporin A may also be incorporated. Antimalarial agents are also readily used in combination.

5.6. Targeted therapy

The essence of targeted therapy is that while the first application of the above-mentioned classical immunosuppressive agents is usually experimental and the exact mechanism of action of the agents is only later known, the agents used in targeted therapy exert their effect at a single well-defined point of inflammation (e.g. on the level of a particular cytokine or intracellular kinase). Within the context of targeted therapeutic drugs, only protein-like molecules (monoclonal antibodies and soluble cytokine receptors), which are administered by injection or infusion, are actually referred to as biological agents (biologics). In addition, specific low-molecular-weight synthetic chemical compounds (e.g. tyrosine kinase inhibitors) are also available which are administered orally *(Table 5.5.)*.

Table 5.5. Targeted therapeutic agents

Drug group	Drug subgroup	Molecules
Biologics	TNF-α inhibitors	adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
	IL-6 inhibitors	tocilizumab, sarilumab
	IL-1 inhibitors	canakinumab, anakinra
	IL-17 inhibitors	secukinumab, ixekizumab, bimekizumab
	IL-12/23 inhibitors	ustekinumab
	T-cell inhibitors	abatacept
	B-cell inhibitors	rituximab, belimumab
	Integrin inhibitors	natalizumab, vedolizumab, alefacept
	RANKL inhibitors	denosumab
	IgE inhibitors	omalizumab
Synthetic tyrosine kinase inhibitors	JAK inhibitors	tofacitinib, baricitinib

Nowadays, targeted therapy can be used in most countries, including Hungary, in case of classical DMARDs inefficacy and or toxicity of and a persistent disease activity. In addition to the outstanding RA, in which is now more than ten agents available, biologics are also used in AS, PsA, JIA, gout and systemic autoimmune diseases (e.g. SLE, myositis and systemic sclerosis). In Hungary, biological therapy is possible in designated centers. Prior to initiation of the therapy, screening (laboratory, TB screening, cardiologic examination, exclusion of other autoimmune diseases, demyelinating disease, hepatitis and other infections) should be performed according to the professional protocol, and then therapy may be initiated. During the application, close monitoring (medical evaluation, therapeutic efficacy and side effects) is required every 3 months.

Biological therapy mainly involves the use of antibodies (immunoglobulins). These can be mouse, mouse-human chimeric (human part 60–70%), humanized (human part 90–96%) or fully human (100%) antibodies. In this order, the names of the molecules include the "-omab", "-ximab" (e.g. infliximab), "-zumab" (e.g. certolizumab), and "-umab" (e.g. adalimumab) suffixes *(Figure 5.1.)*.

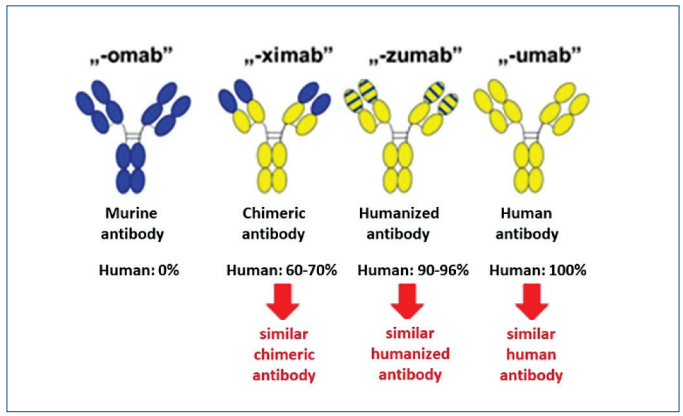

Figure 5.1. Structure and nomenclature of antibodies used as biological therapy

Nowadays, the first line of biological therapy is attempts to inhibit tumor necrosis factor-α (TNF-α), a cytokine that plays a central role in inflammation. There are currently five types of anti-TNF formulations available. The human mouse chimeric anti-TNF-α monoclonal antibody, *infliximab,* the human anti-TNF antibodies, *adalimumab* and *golimumab,* the Fab fragment of the anti-TNF antibody linked to polyethylene glycol, thereby having a more favorable pharmacokinetics, *certolizumab pegol* and the recombinant form of the IgG-linked TNF-α receptor, *etanercept* are available. The efficacy of these agents is roughly the same, with minor differences in the side effect profiles. Infliximab is given by infusion and the other four agents are administered by subcutaneous injection. The efficacy of each TNF inhibitor can be increased by co-administration with methotrexate. As for risks, milder side effects (rash, fever and nausea) are well tolerated by patients and do not require discontinuation of the treatment. The main problem is opportunistic infections, especially TB; in some cases reactivation of hepatitis has been described. Therefore, detailed screening should be performed prior to treatment to exclude TB, hepatitis B and C, and other latent infections. Some patients have developed secondary autoimmune events, possibly due to the disruption of immune regulation, such as anti-DNA autoantibodies (in 0.2% of cases with clinical symptoms of SLE) and demyelinating states. In terms of side effects, screening and monitoring, guidelines of anti-TNF agents are standard for the other non-TNF inhibitors targeting agents as well (see below).

Among other cytokine inhibitors, *tocilizumab,* an antibody against the IL-6 proinflammatory cytokine receptor, is an alternative to anti-TNF treatment.

This drug is administered monthly, in infusion or weekly in subcutaneous injection. IL-1 cytokine is implicated in autoinflammatory diseases such as gout, and childhood, congenital fever syndromes. The therapeutic inhibition includes anti-IL-1 antibody, *canakinumab* and IL-1 receptor antagonist, *anakinra*. The IL-23/IL-17 axis also plays an important role in inflammation. The IL-23 inhibitor, *ustekinumab* is primarily used in psoriasis, but also has a modest effect in PsA. The two anti-IL-17 antibodies, *secukinumab* and *ixekizumab,* can be used in the form of sc. injection in PsA and AS.

B-cell inhibitor, *rituximab,* is also used in RA administered in form of infusion, inhibiting B-cell autoantibody production. *Belimumab,* the antibody against B cell activating factor (BAFF) can be used to treat SLE. Antigen response, antigen-presenting cell-T cell interaction and, indirectly, inflammation outcome are highly dependent on the CD28/CTLA4-B7.1/B7.2 and CD40-CD40L (CD40 ligand) costimulation pairs. In the absence of costimulation, it is tolerance that develops instead of an immune response. CTLA-4 antigen present on cytotoxic T cells mediates a negative costimulation signal, thereby inducing tolerance rather than an immune response. *Abatacept,* CTLA-4-IgG fusion protein is administered in a monthly infusion for the treatment of RA.

Among non-biological, small molecule kinase inhibitors, *tofacitinib* and *baricitinib* act by inhibiting Janus kinases (JAKs). By inhibiting JAK and then STAT proteins, these drugs inhibit the production of multiple inflammatory cytokines and cytokine receptors involved in lymphocyte activation and proliferation. Tofacitinib has been approved for RA, PsA, and ulcerative colitis, while baricitinib has been approved for the treatment of RA. Tofacitinib can be taken as a tablet at a daily dose of 2×5 mg or 1×11 mg (retard), while baricitinib can be taken as a tablet at a daily dose of 1×4 mg. Side effects may include an increased risk of infection, liver function abnormalities, bone marrow depression, changes in lipid levels, and hypertension.

In addition to the above named, hundreds of new molecules (other cytokine inhibitors, chemokine inhibitors, inhibitors of cell adhesion and angiogenesis, etc.) are under development.

5.7. Medicines for osteoporosis

Osteoporosis (OP) is a generalized, progressive disease of the skeleton in which the loss of bone mass, the damage to the microarchitecture and the deterioration of bone quality leads to increased fragility. Various classes of drugs are used in the therapeutic strategies.

Recent data clearly indicate that adequate *calcium* and *vitamin D* intake is essential for the effectiveness of anti-resorptive therapy. Proper calcium intake is essential for normal growth, i.e. to maximize peak bone mass development and maintain the balance of adult bone metabolism. In Hungary, too, it is noticeable that in most cases supplementation is needed because of the intake is less than required (daily 1500 mg in children, 1000 mg in premenopausal women, 1500 mg in case of pregnancy, 1500 mg in postmenopausal, 1200 mg in men). It is advisable to take in the recommended amount mainly in the form of food, therefore it would be desirable to increase the consumption of milk and dairy products, calcium-enriched foods and mineral waters. If needed, intake should be supplemented with medication. In doing so, preference should be given to calcium citrate, which has the advantage of pH-independent absorption, improved bioavailability and reduced risk of kidney stones over carbonate salt. The calcium carbonate preparations available in Hungary are suitable for calcium supplementation. Several preparations contain both calcium and vitamin D. With the exception of active vitamin D, in case of insufficient natural intake calcium supplementation is required in addition to anti-OP medications.

Recent data have been published on *vitamin D (hormone)*. According to Hungarian surveys, the elderly, especially those living in social homes, have a particular vitamin D deficiency; but the daily intake of vitamin D is also lower in the average population (around 550 IU) than desired (2000 IU per day). Vitamin D deficiency results in bone loss due to secondary hyperparathyroidism. In addition, vitamin D also has extraosseal effects: it has been shown to have immunomodulatory-immunosuppressive (treatment of autoimmune diseases!), antitumor, anti-diabetogenic, and vasoprotective effect. Interestingly, vitamin D has an immunomodulatory effect, and most inflammatory rheumatic disorders are associated with low vitamin D levels. Therefore, in rheumatology, vitamin D supplementation is important not only for the prevention of OP but also for the treatment of the underlying disease! 2000 IU daily is recommended for the treatment of OP. Alternatively, it may take an occasional treatment with approximately 50–100 thousand IU e.g. every 2–3 months. For appropriate indications (e.g. in the elderly and in case of renal or hepatic dysfunction), active vitamin D_3 derivatives such as alphacalcidol (1-hydroxy-D3) or calcitriol (1,25-dihydroxy-D3) may be used. As we will see, formulations combined with bisphosphonates are marketed to facilitate proper intake for better compliance. Serum calcium and urinary calcium should be monitored regularly during vitamin D therapy.

Antiresorptive drugs primarily inhibit bone breakdown. These include bisphosphonates, the aforementioned anti-RANKL antibody, denosumab, and the

recently overshadowed selective estrogen receptor modulators (SERMs), calcitonin, female sex hormones, and thiazides.

Bisphosphonates are first line treatment for most of OP forms nowadays. This group of compounds contains synthetic derivatives of natural pyrophosphate. Among their effects, their direct anti-resorption effect should be highlighted. The new generation of aminobisphosphonates suppress osteoclasts 3–4 orders of magnitude more than mineralization, thus the difference between therapeutic and toxic doses is very large. While the former bisphosphonates were administered cyclically, the newer formulations come with a continuous treatment. In favour of better compliance, bisphosphonates are now being used weekly, monthly, or once a year. In Hungary, risedronate and alendronate administered once a week, and ibandronate, administered once a month, have been marketed in tablet form. The latter is also available in intravenous form, which is administered every 3 months. Parenteral zoledronate is given as an infusion once a year to treat OP, and once every two years for Paget's disease. Bisphosphonates, as proven by extensive studies in thousands of patients, significantly increase bone mineral content and reduce the risk of fracture, both in the lumbar spine and in the hip region. As mentioned, bisphosphonates are "packaged" with calcium and vitamin D3 for better compliance. The use of oral bisphosphonates requires attention as they may cause hyperacidity and esophagitis, thus should be taken with plenty of water in the morning on an empty stomach. Parenteral formulations do not have such a problem. Based on this information, bisphosphonates are first-line preparations for involutional OP, and are also recommended for high-risk patients (e.g. steroid users) and in cases of male OP. Bisphosphonates are contraindicated in patients with renal impairment where GFR <30 ml/min/1.73 m^2. In recent years, it has been shown that bisphosphonates, especially in cancer patients, may increase the risk of osteonecrosis of the jaw (ONJ). This is rare with the doses used in osteoporosis, however periodic dental examination is recommended before and during long-term bisphosphonate treatment.

The first biological therapy for the treatment of osteoporosis, antibody against *RANK ligand (denosumab)* was registered a couple of years ago. Should be administered every six months in the form of subcutaneous injections. Denosumab can also be used in patients with impaired renal function. Very rarely, ONJ may occur with denosumab as well.

Exerting estrogen-like effect in bone and anti-estrogen effect in other tissues, one of the long-known members of *selective estrogen modulators* (SERM), tamoxifen, is not used in OP therapy. One of its variants, raloxifene, reduced bone loss and prevented vertebral fractures in a several studies. It is nowadays under-utilized.

We refer to gynecological books on the basic effects of *menopausal hormone therapy* (MHT). Here is a brief outline of the basic information about MHT, with particular reference to the doubts that have arisen in recent years. Several clinical trials (e.g. HERS, ERA, WHI, Million Women study) have shown in the population of 65 years old an increase in invasive breast cancer, coronary artery disease, stroke, pulmonary embolism, and cholelithiasis after an average of 5.2 years of therapy, compared to placebo control group, although the previously proven beneficial bone effect was maintained, and the risk of colon cancer was also reduced. The advantage-disadvantage analysis also significantly increased overall morbidity. It is hypothesized that gestagen used in combination with estrogen plays a major role in increasing the risk of breast tumors and cardiovascular complications. Until the issue is clarified, given the MHT's reduced risk of fracture, it is recommended to use MHT for a controlled period of time to a maximum of 5 years and at the lowest effective dose, primarily to reduce the symptoms of menopause. It can only be used in the short term for OP treatment as a second line agent, only in postmenopausal OP.

Calcitonin, produced by thyroid C cells, was discovered in 1961. Its main effects are reversible inhibition of osteoclast function, reduction of their proliferation and reduction of serum calcium levels. In the kidney, calcitonin increases calcium excretion. 200 U daily nasal sprays are recommended for OP treatment. Injection of calcitonin is indicated for the relief of acute pain associated with fracture, mainly with vertebral compression; and as an adjuvant in the treatment of hypercalcemic crisis. The use of calcitonin has been reduced in recent years. Nowadays, it is recommended for elderly patients with osteoporosis who cannot be given bisphosphonates, denosumab or raloxifene due to a contraindication or side effect.

Of *bone-building agents,* daily administered 20 μg of oligopeptide injection of human recombinant parathyroid hormone (PTH-1-34; *teriparatide*) increases bone formation and bone density without inducing hypercalcemia. It also significantly reduces the risk of fracture in both the spine and the hip region. Therapy with teriparatide should therefore be recommended for up to 18 months in patients with severe multiple fractures due to osteoporosis or in patients who suffered multiple osteoporotic fractures alongside one-year anti-resorptive therapy.

New drugs (cathepsin and sclerostin inhibitors) are also under investigation.

As far as the *practical algorithm* is concerned, adequate calcium and vitamin D supplementation is the basis of the treatment of osteoporosis. For patients over 65 years with reduced kidney function or those who do not respond well to cholecalciferol, hydroxylated vitamin D may be more beneficial. During

early menopause, especially when symptoms of menopause are present, MHT is recommended. However, nowadays, bisphosphonates are generally the first line of therapy. It is recommended to supplement the bisphosphonate treatment with calcium and vitamin D, for which combination bisphosphonate-calcium-vitamin D formulations are particularly suitable. In case of contraindications or side effects of *oral* formulations, *intravenous formulations may be given*. Denosumab is very useful in the treatment of primary OP, it only needs to be given twice a year. It is recommended that teriparatide be used for 18 months in patients with very severe osteoporosis or who have experienced multiple fractures while receiving antiresorptive therapy. Thereafter, antiresorptive therapy or denosumab is recommended to maintain bone mass.

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6. Physiotherapy, balneotherapy

Györgyi Cserháti

6.1. Fundamental concepts

Physiotherapy is the oldest form of healing that utilizes the energy of nature, such as water, air, sun and climate. The term itself is derived from the Greek word "phusio". Initially based on purely natural energies, physiotherapy, like everything else, has been and continues to evolve, so in addition to the possibilities offered by nature, artificial energies have appeared, replacing the natural. Nowadays, physiotherapy has become an independent discipline. *Physicotherapy* uses only physical energies, while physiotherapy uses physical and chemical energies as well. Physiotherapy is therefore a broader concept that includes physicotherapy. The basic principle of physiotherapy is that only the energy that is absorbed affects the body. The reflected or penetrated energy is ineffective. The purpose of physiotherapy is to achieve a local effect. In addition, its overall biological effect is the neurohumoral response. The tasks of physiotherapy are prevention, treatment, rehabilitation and research.

Mineral water is drinking water from the depths of the earth that contains more than 1000 mg/liter of solutes or higher than the average amount of an element (in ionic form), which gives it a specific taste and often a curative power. The mineral water comes from the same source that drinking water does: from a protected artesian well or a spring.

Medicinal water is a mineral water that has physical properties and chemical composition that has been proven to be curative by objective testing methods.

Thermal water is water that has a surface temperature of 30 °C or higher.

Hydrotherapy refers to treatment with water using the physical properties of water. These are:

- hydrostatic pressure: increases venous backflow, relieves muscle tension, reduces edema development
- buoyant force: facilitates movement and exercise for patients with difficulty moving on land
- drag: suitable for muscle strengthening

- temperature: may have a biological effect on blood vessels. Indifferent water is 31–35 °C; cool water is 28–31 °C; cold water has a temperature of less than 28 °C; warm water is 36–39 °C; and the hot water is 40 °C or warmer. Indifferent water has no biological effect on blood vessels. Cold water causes vasoconstriction and hypertension, while warmer water has analgesic and muscle relaxant effects.

Balneotherapy means treating with medicinal water.

The essence of bath reaction is that during the spa treatment, after about 4–6 treatments, the patient's symptoms may temporarily increase. Feeling unwell, tiredness, headaches, possibly tachycardia, and subfebrility can sometimes occur. It will pass in a few days.

Bath fatigue usually occurs after improperly applied long-term spa treatment and it does not run its course in a few days. Prolonged fatigue and increased pain may occur.

6.2. Division, indications and contraindications of physiotherapy

The Hungarian division is based on the energy input *(Table 6.1.):*

- Electrotherapy, mechanotherapy, hydrotherapy, thermotherapy and phototherapy work with *physical* energies.
- Balneotherapy, climate therapy, inhalation and diet work with *physical and chemical* energies.

Of course, there are overlaps between the various treatments (e.g. climate therapy and balneotherapy).

General *contraindications* of physiotherapy are damaged, inflamed skin; untreated hypertension; osteomyelitis; infection, fever; malignant tumors (TENS treatment allowed); thrombophlebitis, deep vein thrombosis (for 6 months); loss of sensation (in case of local treatments); increased bleeding; pregnancy; cardiac arrhythmia; pacemaker; metal implants in the area to be treated (except for magnetotherapy).

Table 6.1. Classification and methods of physiotherapy

Electrotherapy • *low frequency treatment* – stable galvanic – selective electric stimulus – four-compartment galvanic – diadinamia – iontophoresis – TENS • *medium frequency treatment* – interference • *high frequency treatment* – short wave – decimeter wave – micro wave • *magnetotherapy*
Mechanotherapy • *physiotherapy* – individual – group – underwater • *massage* • *manual therapy* • *traction* – extension – weight bath • *ultrasound therapy* • *shockwave therapy*
Hydrotherapy • *tangentor* • *hydroxeur* • *effervescent bath* • *weight bath* • *mofetta* • *underwater physiotherapy* • *packings*
Thermotherapy
Phototherapy
Balneotherapy • *mud*
Climate therapy
Inhalation
Diet

6.3. Electrotherapy

6.3.1. Introduction

The conscious application of electrotherapy started in the 18th century. In 1720 Gray discovered that the human body was conducting electric current; later Rezső Deutchh discovered that chemical solutions could be taken into the body through the skin by electric current.

Biological responses are generated by frequency. Based on this, a distinction is made between low-frequency (0–1000 Hz), medium-frequency (1000–100 000 Hz) and high-frequency (above 100 000 Hz) treatments. The current is applied to the body part to be treated by electrodes. It is important that the electrode should not have direct contact with the skin, since it would cause electric burns. To prevent this, so-called intermediates are used. Typically, sheet, dot, or vacuum electrodes are used. The electrode may be of lead, metal or plastic saturated with carbon powder. It is important for the edges to be rounded because of the so-called peak effect. Similarly, complete anti-crease is required. Intermediate material is disinfected linen, sponge or other durable material, which should be 1 cm bigger in all directions compared to the electrode and should be 0.5–1 cm thick. Before application, moisten with 34–35 °C tap water (distilled water is not appropriate, because it does not conduct electricity).

The most serious adverse effect of electrotherapy is electrolysis (electric burn). Typically, it recovers much slower than heat burns, though less painful.

6.3.2. Low frequency treatments

6.3.2.1. Stable galvanic (constant direct current)

The analgesic effect is based on the "gate control" principle, which means that electrical stimulation reaches substance gelatinosa on the fast conducting fibers, thus preventing the pain stimulation entering the spinothalamic pathway. In addition, galvanic current also causes vasodilatation, which results in local hyperemia, thus reducing the pain caused by anemia. Localized hyperemia opens up local capillaries, enhances their lumen, increases metabolism, and thus absorption of inflammatory tissue can increase.

In the case of descending galvanic treatment, the anode is located proximally and the cathode is distally. Its effect is analgesic, vasodilator, circulation enhancer. During ascending galvanic treatment, the cathode is located proximal, while the anode distally. All of this exerts an exciting effect. In case of transversal treatment, the cathode and the anode encompass the part to be treated.

Indications for galvanic treatment: neuralgia, myalgia, tendinitis, tendovaginitis, periarthritis, discopathy, epicondylitis, OA pain, arthritis and algodystrophy.

Special galvanic treatments include Bourgignon treatment. During this involves positive electrode is placed on the supraorbital region and the negative electrode on the nape. Its indications include migraine and supraorbital neuralgia. During Bergonier treatment, a mask is applied to the affected cheek, which corresponds to the positive electrode, and the negative electrode is placed to the nape. The indication of the treatment is trigeminal neuralgia. During Kowarschik's galvanic treatment, large electrodes (corresponding to the length of the lower and upper limbs) are used. Indications for the treatment include cervicobrachialgia, brachialgia, lumboischialgia, ischialgia and n. femoral neuralgia. In Riesz's calcium electrostasis, calcium should be administered intravenously 10 minutes or intramuscularly 20 minutes prior to electrotherapy. Its indications are algodystrophy, osteoporosis and in conditions after suffering fractures.

6.3.2.2. Selective current treatment

During the treatment, muscle contractions are induced by electrical stimulation. It can be by direct muscle stimulation or indirectly by nerve stimulation. Its indications are muscle atrophy, reversible paralysis and nerve injury.

6.3.2.3. Partial electric bath (4-compartment galvanic treatment)

The device used to work with galvanic current, while nowadays they tend to use an electric stimulus. The treatment is carried out at 34–35 °C in indifferent water. It is possible to use four or two compartments, but always symmetrically. Indications for the treatment involve diseases of limbs (e.g. arthritis of small joints and OA).

6.3.2.4. Diadynamic treatment (Bernard current)

Impulse current consisting of sinus half waves is applied to a direct current (base current) of 1–3 mA. The impulse current can be one-way (10 ms impulse pack followed by 10 ms pause) or two-way (no pulse pause). A combination of these gives the different current forms:

- MF (monophasic, 50 Hz): stimulating
- DF (diphasic, 100 Hz): muscle relaxant
- CP (Court Period, MF and DF alternation per second): helps to absorb fluid, abnormal metabolites by increasing blood circulation and metabolism
- LP (slow change of Long Period, MF and DF): analgesic effect.

6.3.2.5. Iontophoresis
It is a combined form of treatment during which drug ions are delivered into the body through skin by current. This process is called electro-osmosis. The type of current can be galvanic, stimulus, diadynamic or interference. The solutions used have a concentration of 1–3%. Iontophoresis has local and general effect as well.

The most commonly used solutions are:

- may be introduced from the anode (+): lidocaine, procaine, dionine, calcium, potassium chloride, magnesium chloride and vitamin B1,
- may be introduced from the cathode (–): Na-salicylate, sulfur and NSAIDs.

In practice, lidocaine and dionine are used for analgesia, sulfur solution for cartilage regeneration and joint pain relief and NSAID solutions and gels for anti-inflammatory and analgesic purposes.

6.3.2.6. TENS (Transcutaneous Electronic Nerve Stimulation)
It operates on the basis of the "gate principle" mentioned earlier. Its main indication is pain relief. The device is small, easy to use, relatively inexpensive, and its use is allowed several times a day. Its great advantage is that it can be applied at home. It is the only treatment that is safe even for cancer patients and is deliberately recommended for home pain management, to spare medicine.

6.3.3. Medium frequency treatments

6.3.3.1. Interference
Interference treatment is performed at 3900–5000 Hz alternating current (AC). Interference currents are created by crossing two circuits; at which the so-called floating current is generated. When applied, it causes less discomfort than low-frequency treatment and has a deeper effect. Indications: muscle stimulation, neuralgia, hematoma and edema.

6.3.4. High frequency treatments

They are deep-acting treatments that warm the tissues. It includes shortwave treatment (frequency: 27 MHz, wavelength: 1–30 m), decimeter wave treatment (frequency: 433 MHz, wavelength: 69 cm) and microwave treatment (frequency: 2400 MHz, wavelength: 12.5 cm). Indication include degenerative joint diseases, myalgia, sinusitis and pelvic inflammation.

6.3.5. Magnetotherapy

The magnetic field can be continuous or impulse. The electromagnetic field increases muscle contraction, reduces inflammation, assists in the absorption of sweat, facilitates the incorporation of Ca into the bones and improves microcirculation. Indications involve peripheral circulatory disorders, osteoporosis, conditions after suffering bone fractures, promotion of wound healing, promotion of ossification around prostheses, ischemic pain, algodystrophy, ulcers, angiopathy, sprains, joint swelling, enhancement of performance and dyssomnia. A great advantage over all other physiotherapeutic treatments is that it can be applied over metal.

Nowadays BEMER treatment is widespread. It is actually a magnetic sheet controlled by a computer. Its mechanism of action and indication is the same as that of magnetotherapy. There are also local applicators.

6.4. Mechanotherapy

6.4.1. Exercise and gymnastics

This is the most important element of physiotherapy. There is no indication where it cannot and should not be applied. Exercise can be done individually, in groups, and in a relaxed form subaqually. This modality is discussed in Chapter 7.

6.4.2. Massage

Massage is the oldest used therapy. It can be refreshing, curative, sport or diagnostic massage. Massage enhances muscle metabolism and stimulates venous backflow. Indications involve myalgia, connective tissue diseases and muscular dystrophy / atrophy.

6.4.3. Manual therapy, chiropractic and taping

Manual therapy and chiropractic use special grips, pulls, and pressures. Indications involve spinal pain, small joint block and sprains. In addition to the general contraindications, osteoporosis, spondylolisthesis, osteolysis and habitual sprain are also considered contraindications.

The kinesiological tape is a skin-adhesive elastic material under which tissues become loose and blood and lymph circulation is improved. It stabilizes the muscles and relieves tissues, reduces the likelihood of inflammation. Indications involve spinal and limb pain, bruising and sprains. Contraindicated if the skin is damaged or the patient is allergic to the adhesive.

6.4.4. Traction

6.4.4.1. Weight bath
The most effective and gentle traction treatment. It was developed by Károly Moll, who was the chief rheumatologist in Hévíz in the 1930's. Weight bath combines stretching and pulling mechanical effects with the physical and chemical effects of water. The purpose is to release the areas under pressure during treatment and to dissolve the contractures. It can happen with neck suspension or armpit support. To increase the effect, weights can be applied to the waist or ankles. The strain is up to 10 kg for neck suspension, up to 20 kg for armpit support, and up to 4 kg for hip and knee complaints. Indications involve discopathy, hip and knee osteoarthritis and contractures of lower limb joints. It is not used in patients with spondylolisthesis, spondylolysis or AS!

6.4.4.2. Extension-traction device
A digitally controlled device that can be used for continuous, intermittent or harmonic intermittent traction.

6.4.4.3. Gravity inversion table
Hungarian invention, related to Attila Bujdák. Actually, it is the land-locked form of weight bath. The table can be tilted up to 180°. During the treatment the angle at which the complaints are relieved should be set. The pulling force on the spine causes the spine to stretch, the vertebra to move further apart, the muscles to relax and the tension to decrease. A vacuum is created inside the cartilage discs, the discs become hydrated, and the compressed nerve is released from pressure. Following the principle of graduality is important! Indications are the same as those mentioned at the weight bath.

6.4.5. Ultrasound treatment

The principle of ultrasound (US) treatment is the piezoelectric effect, which is the conversion of electrical energy into mechanical energy by means of crystals in the operator. US penetrating into the tissues creates a so-called micro massage (mechanical effect). It is based on the fact that the elements of a cell vibrate at the same frequency but with different amplitudes. The absorbed kinetic energy is converted into heat (thermal effect), increasing blood and lymphatic circulation (biological effect), and improving oxygen supply (chemical effect). Mention must also be made of the adverse effects of US, cavitation.

Underwater US is used when treatment would be difficult with direct application of the device's head (e.g. hand and foot misalignments).

During sonophoresis, a drug is injected transdermally in the course of the US treatment.

Indications for US treatment include myalgia, osteoarthritis, enthesitis, bursitis, panniculitis, periarthritis, synovitis contractures, exostosis and nerve compression syndromes. In addition to the general contraindications, osteoporosis is also a contraindication to US treatment.

6.4.6. Shock wave therapy

During therapy, piezoelectric pressure pulses are generated. These shock waves penetrate the tissues through various applicators, and relieve pain and reduce inflammation. Nowadays radial shock wave therapy is used. Indications include enthesitis, bursitis, tendinitis and exostosis. Contraindications include coagulation disorders, thrombosis, tumors, pregnancy, diabetes, nerve damage, purulent node, acute inflammation, steroid treatment and growing children. Should not be applied above the thoracic and abdominal cavities, in the area of the cerebral and spinal cord, and along large nerves-veins.

6.5. Hydrotherapy

6.5.1. Tangentor (underwater jet massage)

The treatment is done in indifferent water. The water jet used has a pressure of 1 atm. During treatment, the muscle tone is reduced in the water, affecting deeper tissues as well. The jet of water pushes in the skin, causing transient ischemia. When the tissue is released from pressure, hyperemia develops, increasing blood flow and metabolism. Indications involve myalgia and lymphatic circulation disorders.

6.5.2. Hydroxeur treatment (Jacuzzi)

During the treatment, artificially circulating air bubbles massage the entire body. Indications involve myalgia, fibromyalgia and relaxation.

6.5.3. Carbonated bath

The treatment is carried out in 32–34 °C water with a CO_2 content of 1000 mg/l. It can be done with natural or artificial carbonic acid gas. The main effect of carbonic acid is that the gas bubbles floating in the water adhere to the surface of the body, reducing the feeling of cold, causing the capillaries to expand (skin redness appears). Indications involve osteoporosis, peripheral circulatory dis-

orders, coronary artery disease, postoperative treatment of heart and other surgeries, venous insufficiency, diabetic vascular disease, Raynaud-syndrome and algodystrophy.

6.5.4. Mofetta

Mofetta is a gas related to volcanic activity, upwelling from the soil about 1000 meters deep. The word mofetta originates from the Italian word "mephitis", which means "stinky evaporation", referring to the composition of the gas and its volcanic origin. The gas has a high concentration of carbon dioxide and radon, also containing oxygen, nitrogen and methane. Indications are the same as for carbonated bath.

6.5.5. Weight bath

See traction.

6.6. Phototherapy

6.6.1. Ultraviolet radiation

Vitamin D formation is the most important biological effect of ultraviolet (UV) radiation. Indications involve psoriasis, osteoporosis and increased callus formation. Cannot be applied in case of allergic photosensitivity.

6.6.2. Blue light

Used to treat neonatal icterus.

6.6.3. Bioptron lamp

It is a polarized light similar to natural light, which includes visible light and part of the infrared spectrum but does not contain UV rays. Bioptron lamp stimulates photosensitive structures. Indications involve pain relief, inflammation reduction in degenerative diseases, tendinitis, bursitis, enthesitis, wound healing, sprains, muscle injuries and skin diseases.

6.6.4. Infrared radiation

As a result, erythema develops within minutes, which increases metabolism. Indications involve osteoarthritic pain and inflammatory diseases of ear, nose and throat. Should not be used in feverish conditions.

6.6.5. Soft laser therapy

Soft laser (0.5–500 mW) is used in rheumatology. Improves cellular oxygenation, increases circulation, reduces inflammation and edema, and accelerates wound healing. Indications involve degenerative disorders, enthesitis, tendinitis, lumbago, neuralgia, muscle spasm, herpes, sinusitis, wound healing and scar release. Contraindications involve mycosis, tumor, and fever. In addition, not applicable in the areas of a mole, the thyroid and the chest.

6.7. Balneotherapy

6.7.1. Introduction

Balneotherapy is hydrotherapy carried out with medicinal water. The effects of both hydrotherapy and medicinal water should be taken into account in case of balneotherapy. During treatment, the minerals exert their effect in solute form absorbed through the skin or inhaled.

6.7.2. Bathing water types and their main effects

- salt bath: anti-inflammatory, horn-forming effect. Indications involve chronic inflammation, psoriasis, gynecological inflammation and muscle spasm.
- carbonated bath: opens the capillary network. Indications involve venous circulatory disorders, Raynaud-syndrome, osteoporosis and poorly healing wounds.
- sulfur bath: anti-inflammatory, antimicrobial and cartilage regenerative effects. Indications involve degenerative joint disorders, chronic phase of inflammatory diseases (RA), and certain skin disorders.
- radon bath: anti-inflammatory and analgesic effect. Indications involve neuralgia, AS and RA.
- iodine-bromide bath: enhances vascular permeability. Indications involve degenerative diseases and gynecological inflammation.
- Ca-Mg hydrocarbonate bath: anti-inflammatory effect. Indications involve degenerative disorders and stomach problems in which drinking cure can be applied.
- sulphate water: recommended for drinking cure for patient with stomach and liver problems.

6.7.3. Mud spa treatment

The mud used in the treatment is a naturally occurring fine-grained substance with a high mineral content. Due to their good water binding and heat storage capacity they are suitable for making wraps out of them. The temperature used is 42 °C, but it can be lukewarm mud at 30–32 °C or cold mud at 8–10 °C. Indications involve degenerative diseases, soft-tissue rheumatism, AS, psoriasis and gynecological inflammatory diseases.

6.7.4. Other treatments

Inhalation and diet will not be discussed in this chapter, but are part of pulmonary and gastroenterological rehabilitation.

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7. Therapeutic exercise

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7.1. Introduction

An important part of the treatment of rheumatic diseases of different etiologies is targeted, complex therapeutic exercise, which takes into account functional and structural changes caused by inflammation, degeneration and other pathomechanisms. The purpose of early diagnosis and timely therapy is to prevent the consequences, deformities, axial misalignments and improve functions. After permanent deformity develops, exercise has a role of maintaining the given condition, reducing the degree of further progression, and aims rehabilitation, while following the rules of joint protection.

Exercises should initially be designed from the perspective of prevention, and at later stages the exercises are intended to restore function or to adapt to the permanent damage. The choice of therapeutic practice should take into account the extent of cartilage damage, the intensity of pain, the range and quality of joint movement, actual muscle strength, dysfunction, and the degree and quality of deformity correction. Movement and manual movement are used as therapeutic stimuli to repair various tissue changes.

7.2. General aspects of movement therapy

- Joint components require a special, adapted stimulus to achieve regeneration, which stretching for ligaments and capsules, stretching and strengthening for muscles, stretching and compression forces for trabecular structure of the bones, and healthy compression for cartilages.
- The task of the physiotherapist is to perform a detailed physical examination of the musculoskeletal system based on the given diagnosis, to select appropriate forms of movement and treatment techniques. An important factor in the design of the therapeutic plan is the stage of articular damage and the extent of the cartilage damage. Physiotherapy should take into account the extent of joint damage determined by the degree and quality of pain, range of motion,

muscle strength, and correction of deformities. Knowledge of the structure, biomechanics and mobility of the joint is very important when selecting the forms of movement, as these factors determine the damage.

- Abnormal movement forms and processes easily fixate, they should be interrupted by the opportunities offered by physiotherapy and attempts should be made to restore the physiological function. If this is not possible, compensatory movements should be provided and, if necessary, patient should be provided with a medical equipment. In case of an established form of internal compensatory movement, the physiotherapist needs to assess whether the compensation is harmful to the joints.
- Concentric and excentric muscle strengthening and parallel stretching can ensure restoration of muscle balance, improvement of proprioception and coordination. Muscle work should never support or favor any potentially dangerous deformity.
- The purpose of physiotherapy is to maintain joint protection, motion track, muscular strength, manipulation, functional capacity and aerobic capacity if possible, to reduce pain and inflammation.
- Joint protection is the economical use of the strength of the muscles surrounding the joint during work flow processes (workplace, home tasks) and relaxation, taking into account the current state of the patient – acute or chronic state –, structure, mechanics, stabilization system of the affected joint(s) with special regards to the bearing capacity of articular cartilage.

7.3. Therapeutic exercise for arthritis affecting peripheral joints

7.3.1. Exercise therapy methods of acute phase and aspects of physiotherapy

Positioning should be aimed to prevent possible contractures and reducing pain. During exercise, painful and high-amplitude movements and excessive strain should be avoided. For the local reduction of inflammation, it is recommended to use ice gel for 10–15 minutes several times a day. Grade I joint traction combined with oscillation reduces pain and compression of joint surfaces. In addition to isometric muscle activity, isotonic exercises with short load arms can be performed, but only to the limit of pain.

7.3.2. Roles of chronic phase and aims of physiotherapy in the context of pain, cartilage damage, and movement.

The determining factor of physiotherapy is Seyfried's stage and classification, which is shown *Table 7.1.* Seyfried's classification is based on subjective (presence of pain during movement) and objective values (extent and quality of movement) experienced during examination. Contraindications are summarized in *Table 7.2.*

Table 7.1. Seyfried's stages in arthritis

Large joints (shoulders, elbows, hip and knees)	I. The patient's joint can be moved continuously and painlessly within the existing range of motion. II. The movement is painless and continuous, without resistance. III. Turning off gravity, the movement happens in an unburdened state of. Movement under straining of limbs cannot be carried out either; a so-called cogwheel rigidity occurs. IV. Movement involves considerable pain and is difficult / impossible to perform even when unburdened.
Wrist, hand	I. The patient can actively correct the deformities. II. The deformities can be passively corrected which patients can actively maintain. III. The deformities can be passively corrected which patients can not actively maintain. IV. Deformities cannot be corrected passively either.
Ankle, leg	I. Dysfunction that patients can correct with active muscular strain (standing). II. Dysfunction, which patients can correct with active muscular unburdened of strain or passively during straining. III. Fixed deformity.

Table 7.2. Contraindications in arthritis

The shoulder – giving up of compensated exercises, and charge weight in III–IV stadium – combine motion of the head-neck-shoulder – large arm circling	**The elbow** – flexion in supinated position against the resistance – giving up of compensated exercises, and charge weight in III–IV stadium – exercises in weight-bearing
The wrist and hand – inversion of sequence of the correction – overworking of the joints – complete clenched hand (rolling dough or grasp of the sponge ball) – extension of the wrist and fingers over neutral position – palm cup / on hands and knees – giving up of the orthesis, if it is needful	**The hip** – to practice the crouch and stepping off / up overworking the joint because extend of the gluteal maximus muscle overloads the cartilage with compression – palm cup / on hands and knees – elevating of the lower extremity (lying supine), because extend of the iliopsoas muscle is a greater extent for the joint surface – running, because this activity is eightfold weight-bearing for the hip
The knee – to practice the crouch and stepping off / up overworking the patellofemoral joint – palm cup / on hands and knees – giving up of the orthesis in ligamentous insufficiency – exercises in weight-bearing	**The ankle and foot** – to practice the scratch with fingers, which develops more deformities – standing on tiptoe – giving up of the arch-support – wearing of the sharp-nosed shoes

7.4. Exercise therapy for disorders with spinal inflammation

In addition to the spine, conventional exercise focuses on moving the larger joints and stretching and strengthening the muscles around the shoulders and hips. Developing analytical and complex movements of upper and lower limbs, and increasing the elasticity and strength of the muscles serve to develop physiological synergisms.

Breathing exercises are primarily used to mobilize spine and chest joints and their connections, as well as to develop proper breathing mechanics. Learning elongated breathing, widening the superoanterior and basal thorax, coordinating controlled and coordinated movements of the torso, upper and lower limbs with breathing, and strengthening the diaphragm ensure the harmony of the musculoskeletal and respiratory system. Breathing exercises are complemented by manual mobilization of the chest, which means manual support for the

movement of the ribs, which contributes to an increase in chest deflection and the development of cost-effective breathing.

The concept of global posture re-education was built on the basis of exercise therapy, the biomechanical analysis of the typical joint and muscular changes characteristic of AS. It is intended to strengthen antigravity muscles, combining exercise with stretching elements. Elongation of the trunk, sensation of antigravity muscle function, learning antero-posterior direction of the pelvis tilt, and execution of independent and complex movements of different spinal sections determine this closed-loop complex movement material. The practice of global posture re-education is based on the functioning of the entire musculoskeletal system in addition to scapulo-thoracic and pelvico-lumbar synergisms.

7.5. Background, consequences and treatment of specific and non-specific low back pain

Low back pain occurs for a variety of reasons, which can be divided into two broad categories. The suspicion for specific low back pain is the so-called red flags, which require effective disease-specific treatment. Non-specific low back pain is all low back pain that does not show any red flags; in these cases, pain and inflammation should be reduced quickly, effectively. Management considerations are summarized in *Table 7.3.*

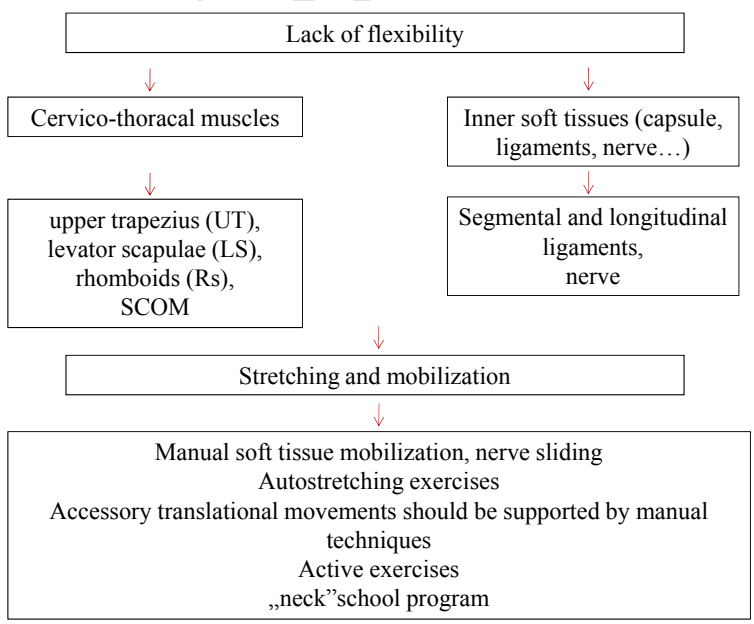
Table 7.3. Priorities in case of different spine diseases

	Aim	
	To increase mobility (in joint and muscle dysfunction)	**To increase stability (neurological dysfunction)**
	muscle imbalance (tight agonist, weak antagonist) protective muscle spasm Discopathy Spondylosis Scoliosis (functional and structural) Ankylosing Spondylitis	Herniated disc Spinalis stenosis Spondylolysis Spondylolisthesis Instability with arthritis (sacroiliitis) Osteoporosis
	Indication	**Contraindication**
Mechanical pain	all movements should be practiced	–
Facet compression	elongation, complex movements flexion, lateral flexion and rotation	extension over pain, combining with rotation and lateral bending at the affected side

	Indication	Contraindication
Radiculopathy	elongation combining with flexion, lateral flexion and rotation, till radicular pain	extension what can provoke pain, combining with rotation and lateral bending at the affected side
Herniated disc	elongation combining with flexion, lateral flexion and rotation, till radicular pain pain should be centralized	overflexion what can provoke local or radicular pain, combining with rotation and lateral bending at the affected side (depending on the level of herniation)
Spondylolysis, spondylolisthesis	all movements are free till pain, stabilization has priority	all movements what could provoke pain

7.6. Background and treatment of cervical and thoracic problems

A major factor in the background of these problems is the limited extensibility of the soft parts (capsule, ligament and muscle). Decreased flexibility, and possibly adhesive alteration of the articular capsule, segmental and longitudinal ligaments can result in increased joint compression and reduced and painful range of motion. Pre-positioned head and neck posture and contracture of the extensor muscles can cause local, later radiating pain. In case of reduced flexibility, manual mobilization techniques should be applied specifically to the tissue



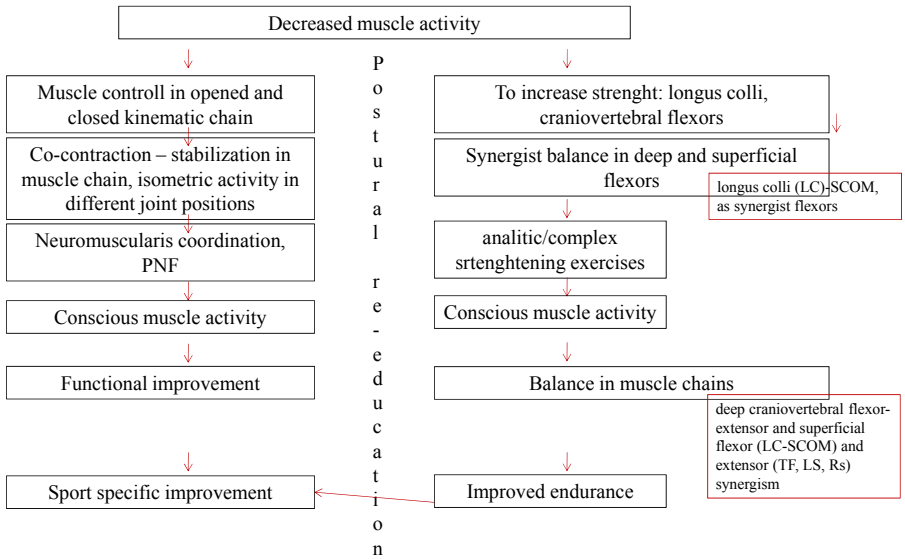


Figure 7.1. Algorithm for the treatment of cervico-thoracic problems

(joint mobilization, soft tissue mobilization, nerve sliding and stretching). In order to increase muscle activity, cervical-thoracic synergism is built by analytical (open kinematic chain) and later complex (closed kinematic chain) exercises; the treatment algorithm is summarized in *Figure 7.1.*

7.7. Background and treatment of scapulo-humeral problems

The problem is also due to the limited elasticity of the soft tissues (glenohumeral (GH) capsule and ligament system and scapulohumeral muscles). Shrinkage of the posterior part of the GH joint capsule, reduced ligament flexibility, and possibly adhesive alteration of ligaments cause increased joint compression in the shoulder and can result in reduced and painful movement. In the background of the change in muscle synergism resulting from contracture, the m. pectoralis minor, m. levator scapulae and rhomboid muscles cause the anterior tilt of scapula, which can also cause impingement syndrome in the shoulder joint. In order to increase muscle activity, scapulo-humeral synergism is built by analytical (open kinematic chain) and then complex (closed kinematic chain) exercises. Postural control is a prerequisite for shoulder-shoulder girdle muscle balance, as scapular muscles are stabilized by the erector spinae group during activity, and m. latissimus dorsi-trunk muscle connection should be monitored.

7.8. Problems and treatment of cervicobrachialgia

Functional and structural abnormalities of the cervical spine can result in local and radiation pain to the upper limb as well. It is important to distinguish cervical joint / local dysfunction from nerve problems, nerve compression syndromes and other soft tissue disorders. Based on the physiotherapy examination, the affected nerve can be differentiated and then mobilized to complement the upper quadrant physiotherapy.

7.9. Tendinitis, bursitis, capsulitis

It is important to distinguish, based on Cyriax principles, what tissue damage (capsular-non-contractile or muscle / myogenic-contractile) causes movement constriction. Common soft tissue lesions, major symptoms and treatment are summarized in *Table 7.4.*

Table 7.4. Exercise therapy of tendinitis and bursitis

Tasks of acute phase
- positioning, resting to relieve pain due to tension and compression of soft parts,
- by reduction of pain and inflammation with medication and use of and cryotherapy. Ice jelly can be used for a period of at least 15 to 20 minutes, even several times a day,
- careful passive movement, taking care not to increase pain,
- isometric exercises

Tasks of subacute phase
- application of joint traction and glide, with slight oscillation
- passive stretching of soft parts – using pendulum / swing exercises, gravity and limb weight for traction
- US treatment on soft parts
- guided active movement with short strain arms
- mobilization techniques: massage, soft part mobilization and stretching

Tasks of chronic phase:
- passive joint mobilization as long as the capsular factor is present and influences the movement pathway and the end position of sensation
- mud packing, US treatment
- movement in water
- targeted physiotherapy: initially developing analytical, then complex synergistic functions around the affected joint, teaching auto stretching exercises
- improving coordination, posture correction

7.10. Osteoporosis

General aspects of exercise therapy:

- pelvic adjustment, preservation, restoration of physiological curves, posture correction,
- correction of deformities if possible,
- preventing or correcting muscle imbalance,
- developing harmonious musculature to prevent fractures,
- balance and coordination exercises to prevent falls,
- body weight exercises and weight training exercises to increase bone mass,
- improving endurance (Nordic walking, swimming and cycling),
- breathing exercises,
- supply with medicinal equipment: hip protecting trousers, corset, walking frame and cane.

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8. Principles and practice of rehabilitation in rheumatic disorders

Zsuzsanna Vekerdy-Nagy

8.1. General concepts of rehabilitation

Rehabilitation, which is a comprehensive activity and has several interdependent dimensions, aims to help the person with disability or the person at risk of disability achieve the most optimal activity for their environment. It is extremely important to understand that rehabilitation activities are fundamentally related to the characteristics of the dysfunction(s) and not to the underlying diseases. In all cases, the aim is to achieve maximum possibly mobility and autonomy, thus achieving optimum activity in the community, which also improves the individual's quality of life.

The system of comprehensive rehabilitation therefore includes medical, vocational, pedagogical and social elements. The purpose of this note is to focus primarily and almost exclusively on healthcare aspects, including a narrower area of rehabilitation related to dysfunctions due to rheumatic diseases. However, in order to understand these, it is essential to acquire some general knowledge and concepts, which are described below.

Medicinal rehabilitation refers to the activity that medical science provides to persons with disabilities by their own means (diagnostics, therapy, prevention and care) in order to regain some or all of their independence by developing their existing abilities and enabling them to integrate into family, workplace, and society. The main point, therefore, is to accurately assess existing functions and performance (health assessment), their compensatory development and training, and to provide the individual with devices if any of these assist the individual in carrying out independent activities.

Rehabilitation medicine is an independent, interdisciplinary clinical specialty of medicine. Its activities are aimed at optimizing the functional capacity of individuals who are physically disabled or at increased risk of disability. The development of abilities takes into account the interaction with the environment, using specific methods, in the form of multiprofessional teamwork, to achieve a realistic goal(s) of rehabilitation, building on the active involvement of the patient during the rehabilitation process. From hospital to GP care, rehabilitation

can be provided at all levels of the medical care system. It also comes in the form of subspecialties.

8.2. Expected rehabilitation needs in rheumatic diseases

Rehabilitation needs related to rheumatic diseases are usually caused by complaints of patients and dysfunctions caused by the diseases. Pain and restricted range of motion impede lives, meaning not only do they have difficulties in their daily activities, but their participation in society is also hindered, thus impairing the quality of life. Rehabilitation in health care is a multidisciplinary team activity in which the active participation of the patient is essential. Throughout the process, patient education is emphasized, as all activities are aimed at patients to understand what they can do to remedy his or her complaints, symptoms, and resulting problems. Thus, active therapies and the learning process have priority in the rehabilitation process, and the role of (passive) physiotherapy, which is popular among rheumatology patients, complements the therapeutic palette.

During rehabilitation, one must strive to help optimize activity. The timing of the rehabilitation process tailored to disease activity is very important. Clinical studies published in recent decades have shown that multidisciplinary teamwork programs have a measurable benefit on dysfunction caused by several rheumatic diseases. Patient education programs help raise awareness of the most important tasks. The spread of problem-oriented learning methods is typical in higher education, but also pervades patient education. It is essential for patients with chronic diseases to learn how to live together with their illness and limitations the most optimally, and how to avoid worsening of their condition. This is important because, whether patients receive rehabilitation in hospital settings (in-patient care) or during out-patient care, they must learn the tasks they need to perform in their homes on a continuous basis. In addition to forms, rhythm and frequency of exercise, this also includes the rate of rest and daily activity, the knowledge of proper (ergonomic) equipment, the use of assistive technologies and rails or orthesis, and the specifics of nutrition and weight control. A key moment in rehabilitation is a learning process that is personalized and empowers patients to apply what they have learned.

Dysfunction on the base of rheumatic diseases mainly affect physical activity, and very rarely affect speech or cognitive function. However, diseases can be very painful, most are progressive, some are systemic. Distortions develop over the years, which can gradually narrow the patient's life space. Many people find

it difficult to cope with the difficulties of chronic illness. During rehabilitation activities providing psychological help is not dispensable. Psychotherapy can also play an important role in winning patient collaboration. There is often a need for vocational consulting advice, preparation for retraining, and various social helper activities.

It is important for both patients and rehabilitation team members to measure the results of rehabilitation as objectively as possible. Changes need to be monitored in three areas: 1. functional status; 2. mental health; 3. disease activity.

Functional status: with the help of global and specific functional scales. The most comprehensive system for describing functional status is the ICF (International Classification of Functioning, Disability and Health issued by the World Health Organization [WHO]). In ICF, it is possible to describe body structures (s), body functions (b), activities and participation (d), as well as environmental factors (e). In addition to the letters listed, problems can be specified with scales, just like in the ICF system. However, ICF is also able to judge severity based on 5-grade ratings, which can also be used to adjudicate the degree of loss of a particular function / activity. In the case of environmental factors, auxiliary factors are indicated with a positive sign. WHO workgroups have compiled a list of the most common conditions for the so-called core sets from typical ICF items. There are musculoskeletal (general), OA, rheumatoid arthritis, low back pain, ankylosing spondylitis, osteoporosis, chronic pain syndrome and acute arthritis core set in the context of the diseases covered by this note there is a short and extended version (http://www.icf-core-sets.org). The rating system is used in everyday rehabilitation practice for inpatient care. Typical ICF items can be described in rehabilitation program systems by partly mandatory, partly optional, qualifying ICF items specific to the individual patient at the beginning and end of the rehabilitation program. This will be discussed in detail with each individual disease.

Among the global scales, FIM (Functional Independent Measure) and the Barthel Index are the most widely used. FIM has a total of 18 theses, the first 13 of which are so-called motor while the 14–18. theses compose the so-called cognitive group. In the rehabilitation program system, both are required when administering and discharging patients in rehabilitation in-patient care. Walking tests widely used to assess mobility include 3-minute and 10-meter walking tests used to assess walking ability, in addition to the 6-minute walk test. In elderly, the Timed Up and Go (TUG) test is used. Specific scales describe typical dysfunctions due to the underlying disease, so different scales are used e.g. in RA and AS. In general, however, the measurement of Range Of Motion (ROM),

muscle strength (BMC – based on British Medical Council recommendation), muscle tone (Ashworth scale, or its modified version – MAS), and examination of coordination is informative for all diseases. Although, the Visual Assessment Scale – VAS is a subjective measurement, it is widely used for the assessment of the level of pain, as well as for monitor changes, and it reflects well the pain level of patients.

Mental health is assessed through psychological questionnaires, disease burden indices, and methods assessing quality of life (health status) related to mental health items. Of the eight most commonly used item types of the SF-36 scale, four deal with mental and four with physical health.

Laboratory and imaging techniques and other methods of rheumatology are used to monitor disease activity.

8.3. Inflammatory diseases: rheumatoid arthritis

A typical type of inflammatory diseases is rheumatoid arthritis (RA), so the fundamentals are presented through this disease. In the ICF system, the items describing the functional state of RA patients are: in addition to b280 (sensation of pain), b710 (mobility of joint functions), b780 (sensations related to muscles and movement funtions), walking (d450) and dressing (d540) activities must be declared about. In addition, several other areas can be described, both in terms of body functions, activities and participation. In addition to the FIM scale, disease-specific tests, DAS28, HAQ, WOMAC, or Roland-Morris questionnaire for back involvement can also be used. In addition to the b280 ICF item, VAS is also suitable for monitoring pain.

Special emphasis is given to patient education during treatment. Resting / relaxing and saving energy is extremely important, especially when active inflammation is present in the joints – in this case, it is primarily important to relax and cool the joints, however any treatment enhances inflammation is not allowed. A prolonged resting state should be avoided as well due to the harmful consequences of inactivity. Some studies have shown that more than two weeks of bed-rest reduces the strength of patients by 1–1.5% daily. On the other hand, resting for at least 30 minutes a day can avoid complications due to extreme fatigue. Therefore, all patients should be educated to find the optimal level of daily activity for them to conserve their energy. Throughout this process, the entire rehabilitation team assists the patient, but it is the patient who must sense and understand the concept of relative rest.

Among physiotherapeutic methods, the patient's active physiotherapy is the primary one. Activating physiotherapy, both in dry and aqueous media, are also effective in improving aerobic capacity, especially when combined with muscle strengthening exercises. There is less clarity in the literature regarding the effectiveness of hand exercises. Dynamic, activating home exercise (e.g. stationary bicycle) has proven to be beneficial for fatigue and quality of life.

Among passive physiotherapeutic methods, ultrasound, low-frequency laser treatment and paraffin wrap may be effective for hand functions, whereas cold / warm treatments do not significantly alter pain or function.

Pain relief and function improvement has been described in connection with balneotherapy (mud and sulfur wrap).

As far as assisstive devices are concerned, deformities of the hands, feet and shoulders are most common in RA patients. Careful consideration should be given to the patient's need for orthesis, e.g. prevention of foot plantar flexion ‚falling' or pain relieve. Patients' independence depends on preserving range of motion. Physiotherapist, orthopedic technician and the patient assisted by a rehabilitation specialist selects the appropriate orthesis.

Upper limb: The most characteristic deformities of the hands located on the fingers, are the so-called buttonhole and swan neck deformities, special rails can be used for prevention, correction and pain relief, although there are differences of opinion regarding their effectiveness. They can help to increase the patient's sense of comfort and avoid forced, strained use.

Lower limb: the deformities of the legs can be variable; especially orthopedic special shoes relieve pain and maintain the ability of walking despite the present deformities. Occasionally, special plastic rails and insoles may be put in the shoe. Orthoses are stiffer and provide a better biomechanical effect, but are often poorly tolerated by patients due to their discomfort. However, they indication include pain prevention / reduction. Occasionally, insoles are sufficient – this should be considered individually.

RA patient similarly to other patient with joint deformities may need help during rehabilitation in learning or maintaining activities such as driving a car. Gripping, manipulation, reduction of handgrip strength, weakening of general fitness, and constriction of spinal movement (reversing!) may require placement of special adaptive devices in the vehicle, which may be selected and assisted by an ergotherapist, a member of the rehabilitation team to in carrying out the appropriate car adaptations. The healthcare team can advise on transfers (getting in and out of a vehicle, wheelchair transfer), positioning the wheelchair in the vehicle, developing vehicle steering and opening / closing systems, and practicing movements with patients.

Different diets are widespread among RA patients, but there is no evidence of any efficacy in either mode. At the same time, conscious weight control helps to prevent excessive weight loss or gain, which is beneficial for daily activity.

8.4. Characteristics of inflammatory diseases of other origin

8.4.1. Psoriatic arthritis (PsA)

Due to the presence of skin lesions, some hydrotherapeutic treatments cannot be used in this disease; physiotherapy, in simultaneous treatment of psoriasis should be supplemented, e.g. with special balneotherapy and phototherapy. In PsA, the tendency to depression is more common, there is a greater likelihood that a psychiatrist will be required and vigorous antidepressant treatment may be required.

8.4.2. Ankylosing spondylitis (AS)

BASFI and BASDAI questionnaires were specifically designed for the functional examination of patients; otherwise acting as described for RA. The introduction of biological therapy, a breakthrough in the treatment of AS, has dramatically changed the course of the disease – providing patients with a lasting asymptomatic period from discovery. Previously, only exercises played some role in reducing total spinal stiffness. Following the introduction of anti-TNF therapy, the importance of physical training did not diminish, as it is shown by EULAR and ASAS recommendations.

The new approach to learning body weight control and mastering global posture re-education techniques primarily prepares patients to practice at home and learn body schema through a specialized, individualized approach to patient education. This therapeutic modality is most consistently supported in the literature. Progression of pain and narrowing of the spine movement is less improved, while physical activity is more improved. For AS patients, underwater exercises are particularly effective, balneotherapy can provide a good complementary treatment option, but there is no clear recommendation for the latter.

8.5. Degenerative diseases

Degenerative joint diseases or OA, whether primary or secondary, cause similar dysfunctions, so the rehabilitation process is the same. Contrary to what is described in RA, degenerative diseases mainly affect large joints. Given that

there may be differences in the involvement of individual joints, there may be differences in utilized rehabilitation equipment, the main directions required for physiotherapy and ergotherapy, thus the rehabilitation characteristics of OA patients will be discussed separately for the three major joints (hips, knees, and shoulders) and spine.

The main complaint of an OA patient is mechanical pain, which occurs during movement, walking, longer period of standing, so occurs during increased physical activities, and is almost immediately relieved or disappears due to rest. The other major problem is caused by gradually developing deformities. Among the deformities of the spine, information is given by antalgic posture and changes in curvature of the spine. Bone deformities, differences in limb lengths, muscle tension and atrophy also cause anatomical changes. These two symptoms and impairements together lead to dysfunctions that already affect patients' daily lives, their ability to work and thus their overall well-being is adversely affected.

In OA patients, function assessment is similar to that described in RA. In the ICF system, lower limb dysfunction is characterized by pain b280 (sensation of pain), b710 (mobility of joint functions), muscle strength (b760) and walking (d450) and dressing (d540) and hand and arm use (d445). Measuring FIM (especially motor), gait tests, TUG, and pain with a VA scale, and evaluating ROM in problematic joints are part of routine testing both at the start of a rehabilitation and during follow-up.

Patient education and active physiotherapy play a prominent role among therapeutic options. Individualized form of physiotherapy (selective muscle strengthening, scheduling, rate) is the most effective form of physiotherapy, subaqual exercises for patients with OA have a pronounced analgesic effect (knees and hips). Balneotherapy has been described as more advantageous. Dry aerobic capacity improving training can result in the improvement of function by strengthening muscles.

Among the passive methods, traction, with reducing connective tissue adhesions, together with the effects of water (mineral water), has good analgesic properties regardless of the body area affected by OA. Opinion is divided on the effects of thermal treatments – paraffin wraps are good for pain relief in the case of hand involvement, icy wraps are suitable for knee OA, while the effectiveness of US treatment and magnetic treatment is questionable. Among the low- and mid-frequency procedures, the analgesic effect of stable galvanic is widespread in practice, especially for the administration of drugs for analgesia (knee joint).

Kneejoint has a particularly important feature in rehabilitation, namely that relatively small axial malignment (flexion position greater than 15 degrees or val-

gus more than 10 degrees) significantly increases gait-related energy expenditure and poses additional gait complications due to an incorrect load axis.

Patient education: The most important factor for protecting knee joint is to avoid excessive body weight, and in case of obesity, to increase the load capacity, it is necessary to eliminate the excess weight. Understanding the relationship and initiating weight loss and strength training requires serious collaboration from the patient. In addition, learning knee joint-friendly postures is the basis of a successful rehabilitation.

Selective physiotherapy (especially for quadriceps) for the knee joint is beneficial in improving function, while balneotherapy, direct-contact mud therapy and iontophoresis / wrap administering drugs are beneficial mainly in pain reduction. There is reliable literature on the analgesic effect of TENS treatment, a stable galvanic, although the placebo effect is also important. The advantage of TENS is that it can be used at home.

Ergotherapy: This involves teaching the patient the rules of joint protection in patient education. Choosing the most appropriate ergonomic sitting and lying (avoiding low chair, bed), using long-handled appliances (avoiding kneeling and crouching), proper posture during daily activities (e.g. avoiding cross-legged sitting and permanent static positions, such as standing or sitting with bent knees), wearing appropriate shoes (avoiding high and thin heels).

Orthoses and assistive technologies: help gait and self-care for patients with knee OA and patient with rigid knee. Among these insoles, orthoses, raised toilet seat, bath seat, and cane are to be highlighted. Rollators are primarily used for indoor and smaller distance transport (within 200–300 meters), the load carrying capacity of the two-handed support better distributes. Rollator also provides for sitting, so support resting. Longer distances can be reached by car or street electric moped.

The hip joint is a very stable joint, but due to the biomechanical changes of the upright position, the role of soil forces conducted from the leg (ankle) to the spine is very specific. Therefore, the majority of secondary OA is not traumatic in origin, but is caused by poor posture and improper strain (fatigue and over-exertion). Consequential dysfunctions affect daily activities very uncomfortably: walking (especially walking longer distances), climbing stairs (mainly uphill), putting on socks / stockings / shoes, bathing (getting in and out of the bathtub) and can be accompanied by significant pain. When designing a rehabilitation plan, it is important to clarify:

– What is the origin of OA and how long has it persisted? Is it only the hip joint (one or both sides) or the spine, knee are also affected, or are other areas affected by the process as well?

– Is there limb shortening, asymmetry?
– What are the leading consequential dysfunctions?

Patient education: understanding and modifying patients' lifestyles and habits can also prevent the development of hip OA when considered on presentation of potential causes and onset of diseases. Especially childhood onset of hip dislocation, dysplasia, Perthes disease, epiphyseolysis, and in the course of childhood rehabilitation due to these diseases, prevention of secondary hip OA at a later age may be established. Weight control, avoiding physical activity straining the hips is recommended for anyone who, in any age group, for a variety of reasons, is exposed to abnormal hip strain. Even after the first symptoms of OA appear, there is a lot that patients can do to slow down the progression. In the case of advanced OA, a timely performed endoprosthesis is essential. Before and after surgery, the patient should be aware of a number of lifestyle and movement rules to avoid further complications, including surgical complications associated with patient behavior.

Ergotherapy and health care equipment. In ergotherapy, the primary aim is to recommend and practice the use of devices to help patients with dysfunction in their daily lives. During ergotherapy sessions, the patient can learn the most appropriate way to sit down, stand up, and other changes in position, also reaching for and picking up objects. The patient can get advice on assistive devices (raised toilet seats, devices used for dressing, etc.) and ergonomic seating at home or at the workplace. Under the guidance of rehabilitation and other specialists, appropriate devices, such as orthopedic special shoes, various orthoses. For mobility, the rehabilitation team, together with the patient, can select the appropriate devices for indoor and outdoor use. The cane or rollator is usually sufficient for indoors, for short distances. An electric moped may be needed for longer distances.

Individualized physiotherapy and underwater exercises in case of hip OA strengthening the muscles around the joints improves function and relieves pain. Hip joints are more difficult to access with physical procedures than knees, especially in patients with a higher body weight. Tensile treatment can be effective in preventing contractures. There is no conclusive data on ultrasound and laser treatment. There is a positive experience with the analgesic effect of balneotherapy.

In the *shoulder joint,* degeneration is most commonly secondary to shoulder microtraumas, direct and indirect injuries, and inflammatory processes. Injuries to the joints and heat effects can trigger a synovial reaction, which can quickly

become painful due to adhesions, and can cause significant limited mobility, resulting in a frozen shoulder. Working over the head permanently, e.g. ceiling painting, car repair in the inspection pit, etc. causes a heavy strain on the shoulder joint. Most often, strain is formed in the shoulder joint. Shoulder OA leading to severe and significant deformity is usually traumatic or possibly hormonal in origin. Aseptic necrosis of different etiologies of the humerus head may play a role in the development. It occurs predominantly in old age and no significant side difference can be detected. More often than not, irradiating pain due to degenerative cervical discus causes shoulder joint antalgic, which is fixates with time. Immobilization also plays a role in adhesive capsulitis in patients with hemiplegia and infarction. Excessive shoulder movement limited in all directions can cause severe dysfunction for the patient and can sometimes lead to disability. It limits self-care, dressing, hygiene and eating.

Patient education: The primary goal is to understand the characteristics of the shoulder joint, and to teach already at a young age to spare the joint (primary prevention). Patients with shoulder joint OA should be advised to do other activities instead of hazardous occupations when the degenerative process is not yet extensive, but is developing. In severe cases, further complications can be prevented.

Physiotherapy involves intensive movement therapy, always starting from a relaxed position. The most important thing in ergotherapy is teaching the so-called self-stretching (stretching, moving the body while stabilizing the arm) and mastering shoulder relaxation among mobilization techniques (elbow support while lying on the abdomen, putting the weight between the arms or sitting by a desk with the affected arm on the desk and slowly sliding the arms forward).

Among physiotherapeutic methods, interference current treatment can reduce pain in the soft tissues of the shoulder. Observations on ultrasound treatment and laser radiation are controversial.

Psychological and other support: Shoulder joint pain can significantly impair patients' quality of life, which may require an assistance of a psychologist. Many people have to change professions or workplaces because of the illness. This change can be prepared with the help of the rehabilitation team.

Spondylosis and spondylarthrosis are disorders of the *spine* associated with pain, decreased range of motion, reactive inflammation, and calcification. Intervertebral disc degeneration can cause disc herniation and neurological symptoms. In spondylosis, the functional integrity of the spine is disrupted. Changes in any parts of the vertebrae, intervertebral discs, small joints, ligaments and

musculoskeletal system cause a change in all other body parts, which worsens the stability of the segment and hence of the spine. Disease rarely leads to disability, but its economic and social impact is significant. In addition to the cost of health care services, particularly being absent from work and the amount of various benefits paid out are significant.

Patient education: The spine plays a special role in adjusting to vertical position. Structural abnormalities (scoliosis and kyphosis), which propose a risk of developing spondylosis in adulthood, are present from early childhood. The importance of prevention, which is based on the knowledge of correct sitting, standing and correct posture in these static situations, cannot be overemphasized. Sedentary lifestyle, ergonomically unsuitable school benches and workplace chairs increase the risk of developing secondary degenerative spinal impairment as a civilization hazard. It is in the patients' best interest to learn proper posture and to incorporate daily movement into their lives. The key task of each member of the spinal rehabilitation team is to help patients acquire this knowledge.

Ergotherapy: refers to the theoretical and practical application of the spinal school. Patients must learn all the knowledge that will help them avoid pain and cope with the disease. Main elements:

- a clear description of the anatomical-pathological background of degenerative spinal disease;
- posture correction in various body positions and in everyday situations;
- explaining the difference between correct and incorrect posture, developing self-correction;
- introduction to the role of psychological stress and teaching of simple relaxation techniques;
- doing sports and developing daily routine;
- introduction and selection of suitable furniture.

In addition to individualized physiotherapy, spine exercises are performed in groups primarily for preventative purposes – pain can be reduced and posture improved with targeted strengthening of the paravertebral muscle. Regular spine exercises in group settings are more effective than exercises done at home. In addition to traction treatment, the thermal and chemical effects of medicinal waters also help with analgesia – in case of the spine the efficacy of the therapy is supported by evidence. In addition to practical experience, the effectiveness of massage (a traditional Swedish massage) in reducing pain is well documented in the literature. The same cannot be said about the effectiveness of various manual therapies.

Medical equipment: Patients should be aware that these are not a substitute for regular exercise, however their daily use makes life easier. The following aids, devices are particularly recommended: elastic corsets, waist belts (recommended for static loads only), bolster under the neck or waist for lying, bolster cushion for sitting, Schanz foam collar for neck problems, ankle foot brace or splint for peroneal nerve paresis. The support of a cane is only rarely and temporarily required.

Psychological and social rehabilitation: It is important to accept the patient's complaints while motivating the patient to participate in the rehabilitation program. It is advisable for the patient to acquire one of the relaxation techniques: autogenous training, progressive relaxation.

8.6. Systemic autoimmune rheumatic disorders

SLE, scleroderma, myositis, MCTD, systemic vasculitis, Sjögren's syndrome and antiphospholipid syndrome (APS) are autoimmune diseases affecting multiple organs. Their common characteristics are the involvement of the blood vessels, heart, lungs, kidneys, gastrointestinal system, and the musculoskeletal system, which leads to the malfunctioning of certain organ systems and eventually to permanent impairment and disability.

The most important issues in rehabilitation are:

- Skin lesions: skin rash of varying extents, persistent skin ulcers, scleroderma-like skin thickening, including face and other body parts, joint contractures;
- Dysfunctions of the musculoskeletal system: decreased range of joint movement (contractures) and pain in the upper and lower limbs, especially in the hand joints, chronic muscular weakness, especially in the trunk muscles (core muscles), in severe cases in the pharynx and accessory respiratory muscles;
- General symptoms: chronic fatigue, subfebrility;
- Cardio-respiratory involvement: chronic myocarditis, endocarditis, coronary heart disease, cardiac conduction disorders, pulmonary arterial hypertension, pneumonia, pulmonary fibrosis;
- Gastrointestinal involvement: persistent dry mouth, slowing of bowel movement, reflux disease, chronic constipation;
- Chronic renal failure;
- Central or peripheral nervous system symptoms: paralyses, epilepsy, psychiatric disorders, depression and cognitive impairment.

In the functional examination of patients, the previously listed ICF items are complemented with gait functions (b770) and sensation related muscles and movement functions (b780) items, as well as with characteristics of specific organ system abnormalities. Activities include emphasis on treatment of fine hand use (d440), doing housework (d640), and handling stress and other psychological demands (d240).

In addition to the general principles described in RA (physiotherapy, patient education, ergotherapy, assistive technologies and physicotherapy), the specific symptoms of a given systemic disease determine the course of action for each disease; the most important ones are highlighted.

In case of *scleroderma,* in addition to physiotherapy (aerobic training and subaqual exercise) aimed at improving cardiorespiratory function, therapies aimed at reducing skin lesions are also emphasized. These include connective tissue massage techniques, manual stretching, treatment / prevention of lymphoedema if required, paraffin warm treatments (combined with physiotherapy) and special facial muscle relaxations (various proprioceptive stimulation therapies) in case of face involvement should be performed.

In the case of systemic lupus erythematosus (SLE), less specialized procedure literature is available. Because of the general weakness of the disease, strengthening exercise (within tolerance) to maintain physical fitness can be beneficial.

In inflammatory muscle diseases, the role of gradually built individual physiotherapy (from passive treatments to training-like strengthening) is emphasized.

In addition to those described for scleroderma and SLE, systemic vasculitis also requires attention to reduction in lung and respiratory capacity.

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9. Rheumatoid arthritis and related diseases

Péter Surányi

9.1. Definition

Rheumatoid arthritis (RA) is a chronic inflammatory disease with an immune pathology affecting 0.5–1.0% of the adult population, with a 2–3:1 rate affecting women population. RA primarily attacks the joints and leads to their slow damage, but can also occasionally affect other organ systems.

9.2. Etiology

9.2.1. Predisposing factors

To the best of our knowledge, the onset of the disease cannot be explained by one well-defined cause. Like other inflammatory diseases of unknown origin, a multifactorial origin – a combination of genetic and environmental factors – leads to its development. A clear association has been found between smoking and the development of the disease. Surprisingly, rheumatoid arthritis has also been shown to be more common in people with chronic periodontitis. Obesity also predisposes to RA.

9.2.2. Genetic predisposition

HLA-DR1 and certain carriers of HLA-DR4 cell surface antigens have a higher incidence of rheumatoid arthritis. A common feature of the various HLA-DR antigens that predispose to the development of the disease is a sequence of 5 amino acids called a shared epitope (SE). The HLA-DR molecules are class II histocompatibility (MHC-II) antigens, present on the surface of antigen presenting cell, and play an essential role in triggering the immune response.

Genome-wide association studies have also identified additional loci predisposing to RA. As common feature, they encode proteins necessary for the immune system to function (see also Chapter 2.2).

9.2.3. Autoimmunity

In RA, the autoimmune reaction is directed against primarily citrullinated, and to a lesser extent against carbamylated and acetylated proteins that have undergone posttranslational modifications. Citrulline is an amino acid that is formed after translation, that is, after synthesis of the primary protein, from arginine by the catalytic activity of the protein arginine deiminase (PAD). Citrullination also changes the antigenicity of the protein. The presence of anti-citrullinated protein antibodies (ACPA) is strongly correlated with SE carrying. A study of stored serum from blood donors with later diagnosed with rheumatoid arthritis has shown that ACPA antibodies appear up to 10 years before the clinical manifestation of the disease. Thus, the development of RA is a decades-long process that begins with the inheritance of predisposing genes at conception, and continues with harmful predisposing factors (smoking, periodontitis and obesity) until the development of autoimmunity. This completes the preclinical period. The clinical stage begins with the onset of arthralgia and then develops nonspecific arthritis and later on classic RA.

9.2.4. Model of the multifactorial origin of RA

How do seemingly distant factors, such as shared epitope carrying, smoking, and periodontitis, fit into the process leading to arthritis? Smoking has been shown to increase the citrullination of proteins in the lungs. Porphyromonas gingivalis, a pathogen of periodontitis, among bacteria is uniquely constitutively producing and secreting PAD into its environment, thus promoting the citrullination of proteins. The SE carrying MHC class II antigens are capable of binding peptides derived from citrullinated proteins and presenting them to specific helper T cells. Thus, an immune response leading to the formation of an ACPA antibody is initiated. The link between the immune process starting in the lung and arthritis may be citrullinated proteins found at both sites. Although there is normally little citrullinated protein in the synovium, but it can increase by any subclinical inflammation or trauma (second hit). (Of course, this "model" is greatly simplified, since RA occurs in non-smokers, in case of healthy teeth, non-carriers of shared epitope, and there is seronegative disease as well.)

9.3. Pathology and pathomechanism

The main, though not exclusive, area of inflammation is the synovium. In healthy individuals, the synovial membrane of only 2–3 cell layers thickens up to 10–12 cell layers in the initial stages of rheumatoid inflammation. Through the walls of newly formed capillaries, which are richly located in the inflamed tissue, monocytes, T and B lymphocytes exit the bloodstream and settle in the synovial membrane (see details in Chapter 2.6). The developing tissue image is non-specific for rheumatoid arthritis, similar to many other synovitis of various origins. Most lymphocytes are T cells, including CD4 positive helper cells. Although T lymphocytes have traditionally been attributed a critical role in the development of the disease; the facts are contradictory. In the synovial tissue, much less detectable B lymphocytes and plasma cells have previously been implicated in the pathomechanism in a subordinate role, while rituximab monoclonal antibody depleting B lymphocytes has not been shown to be an effective drug in RA beyond lymphomas. In addition to T-cells, macrophages are the most abundant cells in the rheumatoid infiltrate.

The effects of the produced pro-inflammatory cytokines can be used to explain virtually all pathological and clinical manifestations of rheumatoid arthritis. The proinflammatory cytokines known in animal models are, from their discovery, obvious targets for targeted therapies with monoclonal antibodies or with solubilized receptors or possibly natural counter-regulators. In the late stages of the disease, the tissue image is altered: fewer infiltrating inflammatory cells, fibroblasts showing signs of activation – increased protein synthesis – and fibrosis dominate. This almost tumor-like proliferating tissue, called pannus erodes the articular cartilage and the bone beneath or the bone at the cartilage-bone border. Under the influence of proinflammatory cytokines, synovial fibroblasts produce matrix metalloproteinase enzymes capable of breaking down various macromolecular constituents of the cartilage. Cathepsins released from the granulocytes of the synovial fluid have a similar, but less significant role. The same osteoclasts are responsible for bone periarticular erosion that are otherwise responsible for bone resorption in physiological bone turnover. The local activation of osteoclast progenitor cells results from interaction with synovial fibroblasts and T cells: RANK (receptor activator of nuclear factor kappa) expressed on the surface of osteoclast progenitor cells binds to complementary RANK ligand (RANKL) on the surface of fibroblasts and T cells.

9.4. Initial clinical picture, musculoskeletal abnormalities

RA is characterized by a latent, polyarticular onset, but rarely, the disease may start in acute form, or in the form of mono- or oligoarthritis. First, the PIP, MCP joints and joints of the wrists usually become symmetrically painful and swollen. DIP joints are spared. In the legs, inflammation of the MTP joints is indicated by pain during walking. In physical examination, the complaint can be provoked by laterally compression of the MTP row (MTP compression test). A typical complaint is morning joint stiffness that lasts for several hours. Patients may also report fatigue and muscle pain. Larger joint complaints usually occur later. Swelling and tenderness can be observed, above them the skin may be slightly warmer. Pronounced hyperemia rather refers to septic complication. Passive movement of the affected joints can provoke pain.

In long-term disease, the joint capsule shrinks, the position of the tendons relative to the joints – and hence the direction of the force they transmit – changes, and subluxations develop. The joints are typically distorted, based on this, advanced cases can usually be diagnosed at a glance. Swan neck deformity of a hand is typical: PIP hyperextension and DIP joint flexion contracture. Buttonhole deformity is just the opposite: PIP joint flexion contracture, DIP joints are extended. MCP joints develop ulnar deviation, and the dorsal interosseous muscles atrophy. The wrist is subliminal relative to the forearm, resembling a bayonet attached to a rifle in side view. The destruction of the radioulnar ligament leads to the mobility of the processus styloideus ulnae, similar to a piano key. Inflammation of the wrist is usually accompanied by tenosynovitis of the extensor tendons, and its prolonged existence can cause rupture of the tendons of the IV–V. fingers. Tendonitis of the palmar flexor tendons can lead to nodule formation, which results in an extension disorder called a "trigger finger" *(Figure 9.1)*.

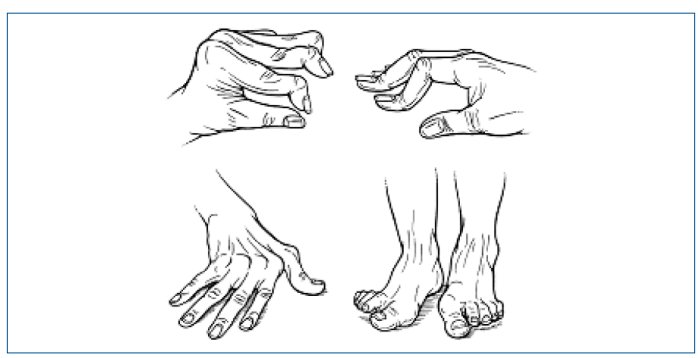

Figure 9.1. Hand and foot joint lesions in rheumatoid arthritis

Swelling of the elbow joint between the olecranon and the radius head is palpable, flexural contracture may develop relatively early. The inflammation of the olecranon bursa is palpable as a soft swelling fluctuating on the extensor surface. The synovial fluid accumulated in the glenohumoral joint produces a visible and palpable swelling on the anterior surface of the shoulder or following the rupture of the rotator jacket.

Hip involvement in RA is relatively rare. Acetabular protrusion and flexion contracture may be a late consequence. The most common form of large joint involvement is inflammation of the knees. The accumulated synovial fluid is pressed through a valve-like opening into the semimembranous and semitendinous bursae. The resulting Baker-cyst can be palpable in the popliteal fossa, and in case of doubt, can be detected by US examination. Its rupture causes a syndrome that can be mistaken for acute deep vein thrombosis, but must be distinguished from it by US examination and, if necessary, by arthrography, as incorrectly initiated anticoagulant treatment can cause severe hematoma. In long-standing disease, the mobility of the knee joint is limited and the joint becomes unstable. More often, the ankle joint is inflamed and the inversion-eversion is painful, and later valgus deformity develops. In the foot, the metatarsal head subluxate in the plantar direction, hallux valgus can be observed, the other toes also deviate in the fibular direction, and hammer toes are visible.

Temporomandibular joint injury may be indicated by chewing pain. Synovitis can also occur in the small joints of cervical spine (however, involvement of the lower spine is not characteristic in RA). Subluxation of the atlantoaxial joint may be a serious consequence of the disease. After the destruction of the ligament attached to the anterior arch of the atlas, the dens shifts backward toward the spinal canal and upward toward the foramen magnum, compromising vital nerve structures and vessels. Neck and nape pain, dizziness, and "drop attacks" can draw attention to this dangerous complication. The increase in the distance between the anterior surface of the dens and the posterior surface of the anterior arch of the atlas on functional X-ray (lateral view of the cervical spine with the head bent forward) indicates atlantoaxial subluxation. An MRI scan is needed to clarify the anatomical conditions. If spinal cord compression is present and / or neurological abnormalities suggestive of spinal cord compression is observed, surgery is recommended to prevent fatal outcome. Radiological examination of the cervical spine is essential prior to any intervention requiring intratracheal narcosis.

9.5. Extraarticular manifestations

RA can not only affect the joints, but can also lead to extraarticular complications that worsen the prognosis. On the extensor surface of the limbs, above the bony base, most commonly at the elbow, 20–30% of patients have palpable so-called rheumatoid nodules. Vasculitic lesion may appear on the fingers around the nail bed. Vasculitis can also be the cause of purpura usually seen on the leg. Cutaneous ulcer are most commonly found in patients with rheumatoid arthritis due to venous insufficiency, but may also be of vasculitic origin. It may be equally problematic to clarify the cause of foot ischemia or gangrene: is it due to obliterative endarteritis or other arterial occlusion – arteriosclerosis or embolism? The fortunately rare, vasculitis of medium size arteries, like polyarteritis nodosa, can lead to ischemic damage of the gut, brain, heart, and kidneys.

Patients may develop severe generalized osteoporosis even without steroid therapy, partly due to inactivity and partly to the effect of proinflammatory cytokines on osteoclasts.

In addition to atlantoaxial subluxation nervous system complications may occur in the form of compression syndromes and polyneuropathy. Most commonly, synovitis of the wrist accompanying carpal tunnel syndrome is observed. The milder sensory form of neuropathy causes glove-like and sock-like numbness and pain in the hands and feet. Severe, generalized vasculitis is indicated by mononeuritis multiplex caused by vasculitis of the vasa nervorum: a sudden sensory and motor damage in the nerve (most commonly in the radial nerve and peroneal nerve).

Lung involvement can be manifested in a variety of clinical syndromes. The most common is dry pleuritis. Chest X-rays may show round shaped shadows of tissue structure similar to subcutaneous rheumatoid nodules. During a physical examination, the crepitation above the lung base points to pulmonary fibrosis. Severe, progressive interstitial lung disease can affect 10–15% of patients. Serositis can affect not only the pleura but also the pericardium. Severe tamponade is not characteristic, it rarely causes other clinical symptoms, it is revealed as an echocardiographic finding. The association of seropositive rheumatoid arthritis and pneumoconiosis (silicosis, asbestosis) is called Caplan syndrome.

As an ophthalmic complication, keratoconjunctivitis sicca is most commonly seen as part of the secondary Sjögren's syndrome. Episcleritis with painful, but benign red eye is also common, fortunately scleritis and vision-compromising scleromalacia performans is rare.

Patients are most likely to experience axillary enlarged lymph nodes. Prolonged and inadequately treated inflammation can lead to generalized secondary AA amyloidosis.

Although not considered as extraarticular manifestation, it is very important for prognosis that cardiovascular diseases are more common and appear earlier in patients with rheumatoid arthritis. In addition to known traditional risk factors, systemic inflammation plays a prominent role. In RA, as in other inflammatory rheumatological diseases, the morbidity and mortality of myocardial infarction, stroke, and peripheral arterial disease increases. Rheumatological comorbidities will be discussed in Chapter 19.

A special association of extraarticular manifestations is characteristic of Felty's syndrome, a rare, special form of RA. In addition to severe, destroying arthritis, rheumatoid nodules and cutaneous ulcers of lower limbs may be observed; hepatosplenomegaly may be palpable on examination of the abdomen. The sine qua non of the diagnosis is leukopenia, which is often predisposed to severe, cumulative infections. RF titer is high. This variant is treatable with disease modifying anti-rheumatic drugs, including those that induce bone marrow depression on their own, such as methotrexate. Splenectomy is recommended in refractory cases. Temporarily, the critically low white blood cell count can be increased by a colony stimulating factor.

9.6. Diagnosis

The most important laboratory tests for diagnosis and assessment of the prognosis are disease-specific autoantibodies, rheumatoid factor (RF) and ACPA. Unfortunately, in the early stages of the disease, both can be detected only in 50–60% of cases and may be absent in 10–20% of advanced diseases. However, RF, although usually in lower titers, also occurs in a number of diseases with symptoms similar to RA: in other systemic autoimmune diseases (Sjögren's syndrome, SLE), chronic inflammatory diseases (sarcoidosis), chronic bacterial infections (infective endocarditis), during acute viral infections, and in lymphoproliferative disorders. RF can also be detected in healthy individuals and up to 10–15% in the elderly. In contrast, the recently recognized ACPA autoantibody reacting with citrullinated proteins is almost one hundred percent specific for RA. Prognostic value of the ACPA autoantibody, like RF, is significant for early prediction of progressive, destructive arthritis.

The activity of the disease (or inflammation) is indicated by accelerated erythrocyte sedimentation rate and elevated CRP levels, leukocytosis and thrombocytosis. Unfortunately, examination of synovial fluid does not show specific signs of inflammation for rheumatoid arthritis. Histological examination of the synovial membrane is of no diagnostic value either.

Imaging procedures are another important tool of diagnosis. Comparative posterior-anterior view of the hands and feet show erosions. The disease is characterized by marginal erosion with blurred margins. Initially, it can be detected only about 40% of patients, but can be detected in an additional 30–40% within two years. For MCP, PIP, MTP joints, processus styloideus ulnae should first be examined. The very first erosions are often seen on the head of V. metatarsus on the X-ray of a complaint free leg. MRI examination of hand and foot joints not only reveals erosions earlier, but synovitis and pannus formation, and even bone marrow edema prior to bone destruction can also be detected. However, the specificity of the procedure is still questionable. Ultrasonography (ultrasound) also detects erosion earlier than conventional X-ray. In addition, it is suitable for examination of tendons and bursae, and a power Doppler device can detect increased blood flow characteristic of active synovitis.

Numerous studies have shown that the chances of achieving a drug-free, long-term remission are greater when treatment is started within the first 3 months of the disease (window of opportunity). However, latent onset and low sensitivity of our diagnostic procedures make early diagnosis difficult. Classification criteria developed for classification purposes can also be useful as diagnostic criteria *(Table 9.1.)*.

Table 9.1. Diagnostic criteria for RA – scoring system

Joint involvement		**Serology**		**Duration**		**Acute phase reaction**	
2–10 medium or large joint	1	RF- or ACPA-positivity (<3× ULN)	2	>6 weeks	1	Abnormal We or CRP	1
1–3 small joint	2	RF- or ACPA-positivity (>3× ULN)	3				
4–10 small joint	3						
>10 small joint	5						

Definitive diagnosis requires at least 6 points. Within each category, only the highest point counts. ULN: upper limit of normal value. For other abbreviations see the text.

9.7. Therapy

Life-long treatment, requiring sacrifices on the part of the patient, is only possible in close cooperation between the patient and the doctor. This requires the patient to be aware of their illness, their prognosis, the opportunities and risks of therapy. Time should not be spared on the initial and follow-up education of the patient. The patient should be thought the gentle use of their joints, and later the regular physiotherapy.

Long-term medications, such as corticosteroids, small molecule disease modifying anti-rheumatic drugs (DMARDs), and targeted biological therapies alleviating inflammatory symptoms and preventing joint destruction are described in detail in Chapter 5.5 and 5.6. (Non-steroidal anti-inflammatory drugs (NSAIDs) are only symptomatic drugs, they cannot stop progression, and are not recommended for long-term use because of their toxicity.)

Regularly updated therapeutic guidelines of major professional organizations (European League Against Rheumatism, American College of Rheumatology) provides advice on which of the many medications to use for the current situation.

Treatment should be started immediately after diagnosis of rheumatoid arthritis. It is agreed that treatment should begin with the most effective, most tolerated and inexpensive methotrexate. In case of contraindication or intolerance, sulfasalazine or leflunomide may be a substitute. It is also widely accepted that patients should take corticosteroids initially but for 6 months at longest. (Unless absolutely necessary and no risk factors for known corticosteroid side effects, particularly atherosclerosis, exist, 5 mg/day of prednisolone equivalents corticosteroid may be given permanently.) Initial medication should be adjusted if there is no improvement within 3 months, or no remission or at least low inflammatory activity has been achieved within 6 months. Measurement of polyarthritis activity is essential for this. Disease activity score (DAS) originally used in clinical drug trials is the best for this purpose. At first glance, it seems complicated, but with a proper pocket calculator or an application now available on the Internet (www.das-score.nl), an index ranging from 0 to 10 can be calculated in seconds based on the number of swollen and tender joints, erythrocyte sedimentation rate or CRP value and the patient's own condition as measured by the VAS scale. Below 3.2, the disease is moderately active, and below 2.6 is in remission.

If initial methotrexate monotherapy fails to achieve remission or at least low disease activity, the European League Against Rheumatism (EULAR) recom-

mends that in case of a favorable prognosis conventional DMARD combination (MTX or leflunomide + sulphasalazine or antimalarial agent) can be used, and in case of an unfavourable prognosis (a high number of swollen joints, moderate to high disease activity, elevated inflammatory laboratory parameters, RF and ACPA positivity, early erosions) DMARD treatment should be supplemented with biological therapy or similarly effective JAK inhibitors. Due to the high cost of biological therapy, Hungarian practice is determined not by the guidelines above, but by the financing protocol for health care social insurance. Biological therapy may be initiated if despite combined conventional DMARD therapy for at least 3 months, DAS28 is higher than 5.1, and the therapy may be continued beyond 3 months if the decrease of DAS28 is higher than 1.2. Medication should be modified until remission or at least low inflammatory activity is achieved (treat-to-target). If sustained remission is achieved, attempts may be made to first discontinue corticosteroids, followed by tapering and discontinuation of biological therapy.

If only one joint inflammation dominates the clinical picture, long-term depot glucocorticoid formulations administered into the inflamed joint may reduce the patient's symptoms for months. We hope for a more lasting result from the intraarticular application of radioactive isotopes (synoviorthesis). It is not a definitive solution, but for active synovitis lasting more than half a year, synovectomy through an arthroscope is recommended to alleviate complaints and slow down progression.

If the joints have been permanently damaged, the purpose of treatment and rehabilitation is to restore joint function and compensate for the loss of function. The exercises taught and periodically reviewed and strengthened by a physiotherapist should be continued at home on a regular basis. Medical aids, orthoses, and especially wrist splints are available to relieve weakened joints.

The destruction of large lower limb joints causing significant pain and limited mobility necessitates endoprosthesis implantation. Correctional arthroplasty, partly by implantation, is possible even in the case of destruction and deformation of the small joints of hands and feet most affected by rheumatoid arthritis. Surgery is the only safe solution for a life-threatening atlantoaxial subluxation due to spinal cord compression. Although less well-established, procedures can replace nowadays almost any joint if needed.

9.8. Measurement of progression

Quantitative assessment of anatomical damage is provided by standardized measurement of erosions and joint space narrowing seen on radiographs of hands and feet. The original evaluation was developed for scientific purposes, to measure the effectiveness of drug treatments, even simplified versions are too time consuming to be easily applied in everyday clinical practice.

For the monitoring of changes in the functional state, questionnaires, such as *Health Assessment Questionnaire* (HAQ), which can be quickly filled out by patients during consulting hours, have become widespread and validated in Hungary. The HAQ questionnaire includes questions related to activities in 8 categories that are important in everyday life – dressing, arising, eating, walking, hygiene, reach, grip, and activities. Based on the weighted responses, the functional state score can be calculated.

9.9. Can rheumatoid arthritis be prevented?

Examination of earlier samples of RA patients stored in blood banks revealed that the patients had already had ACPA autoantibody on average 5 years before the onset of arthritis. 40% of patients with seropositive arthralgia develop rheumatoid arthritis within 4 years. Thus, there is a preclinical phase of an autoantibody positivity in the disease, which may provide an opportunity for prevention. In this case, elimination of known risk factors is obvious: quitting smoking, losing weight and proper oral hygiene. In addition to lifestyle changes, prevention with medication may be effective: 1000 mg rituximab once a day has been shown to delay the clinical manifestation of arthritis in patients with ACPA-positivity, arthralgia, and elevated CRP or in patient with subclinical synovitis showed by imaging tests. Yet, rituximab was unable to prevent the onset of RA. Perhaps the time will come when this disease causing so much suffering, will not only be effectively cured but also prevented.

9.10. Adult onset Still's disease

A systemic form of juvenile idiopathic arthritis, also called Still's disease, may also occur in adulthood. Its etiology is unknown. Generalized activation of the monocyte / macrophage system plays a major role in its pathomechanism and is therefore more recently classified as an autoinflammatory syndrome.

The disease is characterized by high intermittent fever, sore throat, mild polyarthralgia / polyarthritis, pale pink rashes, lymphadenomegaly and hepatosplenomegaly, and serositis. Patients have significant leukocytosis and high levels of acute phase proteins such as CRP. Although serum ferritin acts as an acute phase protein, its levels in Still's disease is extremely elevated compared to other inflammations. GPT activity may also be increased. In severe cases, life-threatening reactive hemophagocytic lymphohistiocytosis may accompany the disease: in addition, cytopenia, DIC and neurological symptoms can be observed. Decreasing white blood cell count and hypofibrogenemia may raise awareness of this life-threatening complication. The detection of hemophagocytic macrophages in the bone marrow is of diagnostic value. (There is also an opinion that Still's disease is considered to be a milder form of reactive hemophagocytic lymphohistiocytosis; these are two ends of a spectrum.) Based on the clinical picture, patients can be divided into two groups, one with dominant systemic manifestations and the other with musculoskeletal symptoms. The two groups also have different cytokine profiles: the former is characterized by elevated IL-1, IL-18 and IFN, while the latter is characterized by TNF, IL-6, IL-17 and IL-23. It is still questionable whether this is a disease with two different pathomechanisms or the disease has a biphasic course.

Unfortunately, we do not know any examination with a diagnostic value for this disease, therefore the diagnosis is based on the exclusion of diseases with similar symptoms. Initial throat pain usually makes one think of feverish angina. Symptoms and laboratory abnormalities are very similar to sepsis, and it is very important to exclude this by repeated hemocultures and echocardiography due to the different therapies. The determination of procalcitonin levels is informative: it increases in bacterial diseases but not in sterile inflammations. Due to occasionally very high white blood cells, leukemia is also a possibility. Generalized vasculitis, such as polyarteritis nodosa, can also cause similar symptoms. Diagnostic criteria are set out in *Table 9.2.*

Table 9.2. Diagnostic criteria for Adult onset Still's disease

Major criteria	Minor criteria
Arthralgia / arthritis	Sore throat
Intermittent fever	Lymphadenopathy and / or splenomegaly
Typical rash	Liver function abnormalities
Leukocytosis	Negative ANA and RF

A minimum of 5 criteria is required, of which at least 2 criteria should be major.

Although NSAIDs (e.g. 150–200 mg/day indomethacin) may be sufficient in 20% of cases, most patients require corticosteroid treatment. The dosage is 0.5–1.0 mg/kg/day. Dose reduction may be initiated after 4–6 weeks if systemic symptoms have resolved and laboratory abnormalities have also resolved. In case corticosteroid therapy fails or the dose cannot be reduced, treatment should be supplemented by methotrexate. Further therapy for refractory cases depends on which of the above described group was the patient categorized into. In case of predominate systemic symptoms, the IL-1 inhibitor, anakinra, and secondary tocilizumab should be administered. If arthritis dominates the clinical picture, the TNF inhibitor or tocilizumab is the agent of choice. Therapy for life-threatening reactive hemophagocytic lymphohistiocytosis is not yet developed. There have been successful attempts at corticosteroid pulse therapy, administration of intravenous immunoglobulin, and anakinra given in higher dose than usual.

Adult onset Still's disease can resolve in a few weeks-months, but tends to recur in relapses. In some cases, a condition similar to rheumatoid arthritis with permanent joint damage develops later. In long-term patients with untreated disease, secondary amyloidosis has been observed in the past.

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10. Spondyloarthritides

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10.1. Introduction

Spondyloarthritides represent a group of diseases which share similar clinical characteristics, genetic background and radiological abnormalities. Spondyloarthritides include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease associated SpA and non-differentiated SpAs (nd-SpA). Depending on the leading manifestations two major SpA groups are defined: axial SpA and peripheral SpA. Axial SpA is characterized by inflammation of the sacroiliac joints and / or spine, while in peripheral SpA the typical manifestations are arthritis, enthesitis and dactylitis *(Figure 10.1.)*.

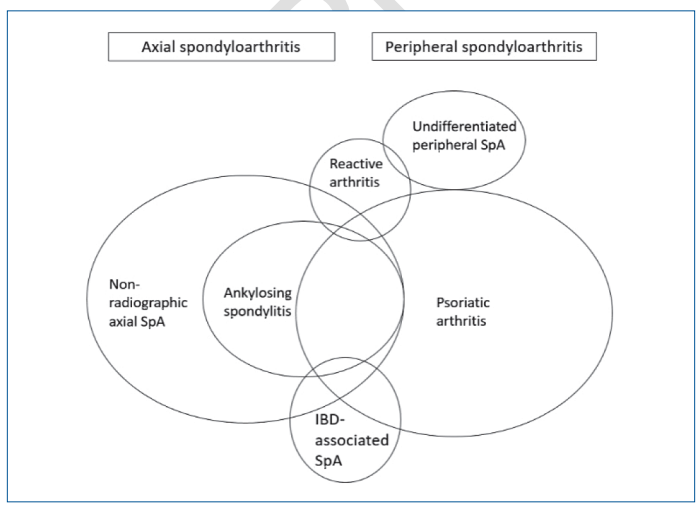

Figure 10.1. Family of spondyloarthritides

SpAs show strong correlation with HLA-B27 (especially the axial forms) and are accompanied with disease-specific extra-articular manifestations such as acute anterior uveitis, inflammatory bowel disease and psoriasis in a variety of scenarios.

10.2. Ankylosing spondylitis (AS)

10.2.1. Epidemiology, pathomechanism and pathology of ankylosing spondylitis

The prevalence of AS in Central-Europe is approximately 0.2–0.5%. The disease is 2–3 times more common among males than in females. HLA-B27 is present in 95% of AS patients. In the family of HLA-B27 positive AS patients the risk of onset of the disease is 10–30% in HLA-B27 positive first-degree relatives, while this risk is only 1–2% among HLA-B27 negative ones.

Although the role of HLA-B27 is obvious in the pathogenesis of the disease the precise mechanism is unclear. The first theory proposes that a self-peptide from joint tissue, which is similar to a bacterial peptide („molecular mimicry") is presented by HLA-B27 to $CD8^+$ T-cells inducing pathological auto-reactivity. The other hypothesis suggests that the unique structure of HLA-B27 often leads to misfolding of this peptide in the endoplasmic reticulum and the accumulation of these unfolded proteins stimulates production of proinflammatory cytokines (e.g. TNFα) and transcription factors (e.g. NFκB). The third hypothesis proposes that HLA-B27 heavy chain homodimers express on the surface of antigen presenting cells which results in the activation of NK-, T- and B-cells by presenting antigenic peptides.

In human-HLA-B27 transgenic rat model spondylitis / arthritis do not develop if the animals are maintained in sterile condition supporting the common role of HLA-B27 and bacterial antigens in the pathogenesis of AS.

In AS pathologic abnormalities typically occur in the sacroiliac joints at the attachment sites of ligaments to the bones. Later the inflammation ascends to the lumbar, thoracic and cervical parts of the spine. Chronic inflammation is followed by cartilage metaplasia and new bone formation leading to the ossification of ligaments, bony bridges between vertebrae and the ankylosis of the spine at late stage of the disease.

10.2.2. Clinical manifestations of ankylosing spondylitis

The initial and most typical symptom of AS is low back pain felt in the gluteal and lumbar region in young adulthood. Low back pain is very common in the population, so it is important to know the features of inflammatory back pain. AS usually starts at the age of 15–40, the onset of AS after the age of 45 is very rare, back pain occurring after this age is rather mechanical origin due to degenerative spine diseases (e.g. spondylosis). The inflammatory low back pain is usually dull in character, alternates from side to side and starts at gluteal region.

At the beginning it can be unilateral, but in a few weeks or months it becomes bilateral, persistent and accompanied with lumbar spine pain. The pain is usually worse at the second half of the night waking patients up. The stiffness associated with the pain lasts for hours, improves during movement and worsens after rest especially in the morning *(Table 10.1.)*. Non-steroidal anti-inflammatory drugs (NSAID) are effective in these symptoms, reducing pain in hours.

Table 10.1. ASAS („Assessment of SpondyloArthritis international Society") inflammatory back pain criteria by experts

• Age at onset < 40 years • Insidious onset • Improvement with exercise • No improvement with rest • Pain at night (with improvement upon getting up Inflammatory back pain presents if at least 4 out of 5 parameters are fulfilled.

Over the progression of the disease it affects the lumbar, thoracic and cervical spine with ascending pattern. This period can last for years. At the sites of inflammation calcification occurs leading to complete fusion of adjacent vertebrae and finally the ankylosis the entire spine. The loss of lumbar lordosis, increased thoracic kyphosis with forward position of head and neck result in the hunchback posture limiting the horizontal fields of vision sometimes. The involvement of thoracic spine, including the costovertebral and costotransversal joints and the sternocostal joints gradually leads to the limited chest expansion. Due to the rigidity of the ribcage, patients with advanced AS are not able to expand the chest fully on inspiration, and therefore most of them breathe primarily by using their diaphragms.

In AS the attachment sites of tendons and ligaments to the bone can also be inflamed. The enthesitis of Achilles-tendon and plantar fascia at the calcaneus are rather common and contribute to the difficulty in walking. The involvement of peripheral joints is not frequent in AS, the root joints like shoulders and hips can be affected, sometimes the swelling and tenderness of knee and ankle joints are present.

The most typical extra-articular manifestation is the uveitis, mainly the acute anterior uveitis occurs in the front of the eye (iris and ciliary body). The inflammation is usually unilateral, but may alternate as well, tends to flare up and characterized by redness of eye, pain, blurred vision and photophobia. If it is not

treated properly posterior synechiae and glaucoma occur and it may lead to loss of vision. The less common complications of the disease are the compression vertebral fracture in association with accelerated osteoporosis, the inflammation of ascending aorta and subsequent aortic valve regurgitation, conduction defects of heart, the fibrosis of upper lobes of lungs and amyloidosis of kidneys.

10.2.3. Diagnosis of ankylosing spondylitis

The diagnosis of AS is based on patients' history, physical examination, laboratory and radiological findings. Tenderness above the sacroiliac joints, flattening of the lumbar lordosis, and the limitation of the range of motions of lumbar spine are often the first signs. Schober test is easy to perform and useful to detect the reduced lumbar anteflexion. At the beginning of Schober test the patient is in a standing position and the physician makes a mark at the level of posterior superior iliac spines on the skin and 10 cm above. Then the patient is asked to bend forward as much as possible while keeping the knees straight. If the distance of the two marks do not increase by at least 4–5 cm, then this is a sign of restriction in the lumbar flexion. In the case of advanced AS this increase is below 2 cm. The reduction of chest expansion implies the thoracic spine involvement. It should be measured at the level of 4th rib (at the level of nipples in males and just below the breasts in females) at the end of maximal expiration and maximal inspiration. Normally the increase of circumference is approximately 5 cm. Although there is not normal value as it depends on age and gender, reduction below 5 cm –with other typical complaints and findings – suggests AS. The limitation of neck movement is usually associated with the ankylosis of thoracic and lumbar spine and patients are not able to touch the wall with their occiput. To determine the limitation and follow the progression the measurement of wall-to-occiput or wall-to-tragus distances can be used. The inspection and palpation of the most common sites of enthesitis (plantar surface of the heel, attachment site of Achilles-tendon, ischial tuberosities, greater trochanters) help us to find the presence of enthesitis.

There are no specific laboratory tests to identify AS. Determination of HLA-B27 helps to set up the diagnosis, but the presence does not mean AS for sure, so the result should be evaluated with symptoms, physical and imaging findings. The acute phase-reactants (ESR, CRP) are elevated in some of the patients, but their levels do not correlate with the activity of the disease necessarily.

Pelvic X-ray reveals blurred sacroiliac joints in the early stage of the disease, later irregularity of joint surfaces due to erosions and subchondral sclerosis followed by the partial or complete bony ankylosis in advanced AS. The grading

of sacroiliitis: normal (grade 0), suspicious (grade 1), minimal sacroiliitis: small localized areas with erosion and sclerosis without alteration in the joint width (grade 2), moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis: (grade 3), severe: total ankylosis (grade 4). Erosions of corners of vertebral bodies, later new bone formation of the adjacent ligaments can be frequently seen on spinal X-ray. This ossification results in the formation of syndesmophytes and later the complete ankylosis of vertebral column (bamboo spine). As the development of obvious abnormalities takes months or sometimes years, pelvic X-ray is often normal, particularly in the early stages of the disease, so it is not valuable in the early diagnosis as well as the modified New York Criteria based on clinical and X-ray findings *(Table 10.2.)*. MRI examination is very useful to detect early inflammatory signs of sacroiliac joints and vertebrae. Bone marrow edema at sacroiliac joints appearing as hyperintense signal on STIR sequence is the earliest sign of inflammation of sacroiliac joint, while T1-weighted sequences shows the structural abnormalities of sacroiliac joints and vertebrae. The role of scintigraphy in the diagnosis of sacroiliitis is very limited, as there are many false positive results. CT is superior to MRI in the detection of bony changes, and it can be used in the diagnosis of spinal stenosis and vertebral fractures, but there is a significant radiation exposure associated with it.

Table 10.2. Modified New York Criteria

1. Clinical criteria: *a)* Low back pain ≥ 3 months, improved by exercise and not relieved by rest *b)* Limitation of lumbar spine in sagittal and frontal planes *c)* Limitation of chest expansion (relative to normal values corrected for age and sex)
2. Radiological criteria: Bilateral grade 2–4 sacroiliitis, or unilateral 3–4 sacroiliitis Requirements: bilateral grade 2–4 or unilateral grade 3–4 sacroiliitis AND any clinical criteria (see X-Ray grading of SI joints).

10.2.4. Treatment of ankylosing spondylitis

Various treatment choices (pharmacological and non-pharmacological) supplement each other, even the most effective biologic treatment cannot replace the regular exercises and physical therapy *(Figure 10.2.)*.

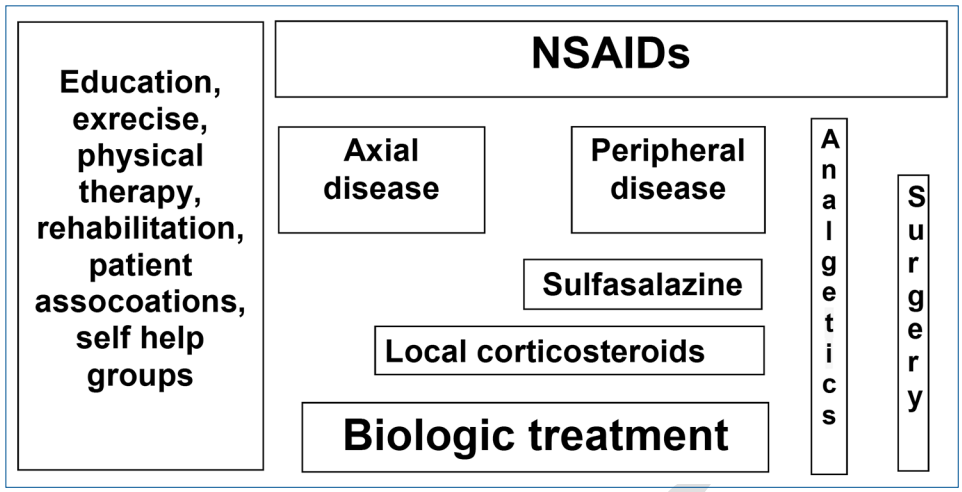

Figure 10.2. ASAS/EULAR recommendations for the management of ankylosing spondylitis

Regular exercise (either home-based or supervised exercise program) is the most important non-pharmacological treatment, which can relieve pain and improve physical function. Supervised group physiotherapy is more effective than home exercises supposedly due to psychic factors, and this type of exercise may provide the optimal balance of mobility, stretching, strengthening, cardiopulmonary and functional fitness components. As Hungary is rich in thermal water, it is important to point out that balneotherapy is effective in amelioration of musculoskeletal function, but it may cause the flare of the disease especially in acute phase.

NSAIDs are the first line drugs in the pharmacological treatment of AS patients with pain and stiffness. Both traditional NSAIDs and coxibs can effectively relieve pain and improve physical functions. In AS – in contrast with other rheumatic diseases – continuous NSAID treatment is preferred at the maximal recommended dose. The long-lasting treatment with NSAIDs may retard the radiologic progression of the disease, but the benefit and the potential side effects of these drugs should be taken into account. If a patient failed to respond to a NSAID, switch to another NSAID should be considered. Analgetics (paracetamol, tramadol etc.) can be administered to relieve residual pain. There is no evidence for efficacy of traditional DMARDs (e.g. methotrexate) and corticosteroids in axial form of AS, DMARDs (preferably sulfasalazine) should be administered in peripheral arthritis, as well as corticosteroid for local intraarticular treatment. Local corticosteroid may also be an option for the treat-

ment of enthesitis, but its anti-inflammatory effect and rupture of the tendon as a potential side effect has to be balanced.

Biologic treatments represent the second-line drugs in AS. Patients who has active disease and failed to respond to conventional drugs (NSAIDs in axial-, sulfasalazine in peripheral disease, local corticosteroid in enthesitis) and physical therapy should be treated with biologic treatment. The use of biologics in AS is regulated by the ASAS (Assessment in SpondyloArthritis international Society) recommendations which usually serves as a basis for national protocols. On the basis of ASAS guideline those AS patients are eligible for biologic therapy who has active disease as determined by BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and do not respond to at least two NSAIDs. Biological therapy provides significant improvement in disease activity, functional capacity and disease-related quality of life for most of AS patients in a long-term period.

TNF-α inhibitors are usually chosen as first-line biologic drug according to recommendations and current practice, as there is an extensive experience with this drug. According to the meta-analysis of randomized-controlled trials, it became evident that all available TNFi-s (adalimumab, certolizumab-pegol, etanercept, infliximab and golimumab) exert similar effects on signs and symptoms of the axial components of the disease. They can delay the ossification if it is started in the early stage of the disease. The anti-TNF monoclonal antibodies (adalimumab, certolizumab-pegol, infliximab and golimumab) can be used successfully in the treatment of most common extra-articular manifestations of the disease, while etanercept has milder effect on uveitis and inflammatory bowel diseases. If a patient with AS do not respond properly to the initial TNF-inhibitor or their symptoms worsen over time or any side effect related to the drug interfere the continuation of the treatment switch to another drug is needed. TNF inhibitors are structurally different and they have different mechanism of action, an unsuccessful treatment with a THF-inhibitor does not preclude response to another one.

A second class of biologic treatment has been approved recently, the interleukin-17 inhibitors (ixekizumab and secukinumab). They have been proved to be effective among AS patient who failed to TNF-inhibitors as well as first line biologic drug. It seems to be rational to switch to another drug with different mechanism of action. Extra-articular manifestations should also be considered as IL-17 inhibitors has favorable effect in psoriasis but not efficacious in inflammatory bowel diseases.

Tapering of dose of biologic treatment is possible in a significant proportion of patients whose disease is in sustained remission. Increasing the interval

between two doses of subcutaneous drugs or decrease the dose of intravenous drug seem to be reasonable way for dose tapering. The high cost of biologic drugs also supports this method of treatment. Disease activity has to be checked regularly and the recommended maximal dose should be restarted in the case of increasing disease activity. Complete discontinuation of biologic drugs is usually not possible, as flare can be detected in most of the cases in a few months.

Biologic treatment increase risk of infectious diseases, therefore appropriate screening is needed before starting these drugs. As TNF-α plays an important role in the formation and maintenance of tuberculotic granulomas the presence of latent tuberculosis has to be excluded. Case reports have been published about demyelinating diseases of central nervous system, lupus-like syndrome, worsening of heart failure etc., but safety profile of biologic agents is favorable.

Vertebral osteotomy as surgical procedure should be considered if the spine deformity limits the horizontal field of view. It improves the posture of AS patient, but do not restore the flexibility of the spine. AS is associated with accelerated osteoporosis, so vertebral fracture is more common than in general population. Fracture causing segmental immobility of the spine may require fixation.

10.3. Psoriatic arthritis (PsA)

10.3.1. Epidemiology, pathomechanism and clinical forms of psoriatic arthritis

PsA can be defined as arthritis / spondylitis associated with psoriasis. Psoriasis affects approximately 2% of the population, and 10–40% of psoriatic patients suffer from inflammatory joint disease. The most common form of psoriasis is the plaque psoriasis, which usually presents on scalp, sacral region, and the extensor surfaces of elbow and knee as red skin lesions covered with silvery scales. Other patterns of skin involvement such as guttate, pustular, erythrodermic may be detected on any other skin regions, and psoriasis may affect nails as pitting, thickening, discoloration and sometimes with separation from the nail bed. Arthritis more often develops after the onset of psoriasis, but in approximately 15% the rheumatological manifestations precede the onset of the cutaneous lesions. Sometimes psoriasis occurs in skin folds and hidden areas of the skin (inside or around the ear, gluteal fold etc.), so if the patient is admitted with classical form of psoriatic arthritis but without obvious skin lesions, it is important to search for psoriasis.

In the pathogenesis of PsA genetic and environmental factors play crucial role. Among genetic factors the class I HLA alleles and non-HLA genes (e.g. genes of

IL12/23 pathway) are associated with differing clinical manifestations of skin and musculoskeletal system, and stress, bacterial infections and trauma of the skin (so called Koebner phenomenon) can trigger skin and joint diseases. In the synovial tissue of PsA joints there are more prominent vascular changes, such as bushy, tortuous, elongated vessels compared to those ones in found in rheumatoid arthritis, and a large amount of proinflammatory cytokines (e.g. TNF-α and IL-1).

According to the classification criteria of Moll and Wright five different forms of PsA can be distinguished, these subtypes can change and transform into another pattern during the course of disease:

- Asymmetric oligoarthritis
- Symmetric polyarthritis
- Predominant distal interphalangeal joint involvement
- Predominant spondyloarthritis
- Destructive (mutilans) arthritis

The most common form of PsA is symmetric polyarthritis followed by asymmetric oligoarthritis. The frequency of distal interphalangeal joint involvement is about 10%, clinically significant spondyloarthritis is present in less than 5% of psoriatic patients. Destructive (mutilans) form is rare and occurs in patients not treated properly for a long time. Other typical symptoms in PsA are enthesitis and sausage-like swelling of one or more fingers or toes called dactylitis. Extra-articular manifestations such as uveitis or inflammatory bowel disease may also be accompanied with PsA, although their frequencies are lower than in AS.

10.3.2. Diagnosis of PsA

Definitive test for psoriatic arthritis is currently unavailable, elevation of acute-phase reactants (ESR, CRP) can be detected in polyarthritis rather than other forms. Plain X-ray reveals joint-space narrowing, erosions and resorptions accompanied by new bone formation at periosteal and entheseal sites. Pencil-in-cup deformity sometimes occurs in interphalangeal joints results from periarticular erosions and bone resorption at the head of bone (pencil) and new bone formation on the opposite site of joint (cup). Ultrasound is very sensitive in detecting thickening, vascularity, erosions and enthesophytes of tendons and bones at their attachment sites. MRI allows detailed assessment of synovitis and enthesitis associated bone marrow edema, as well as detection of early inflammatory signs of sacroiliac and spine joints in spondylarthritis form of PsA.

10.3.3. Treatment of PsA

Successful treatment of PsA is based on the cooperation of rheumatologist and dermatologist. Regular exercises and physical therapy are essential in non-pharmacological treatment, especially in spondylarthritis form in order to prevent the stiffness and ankylosis of spine. Non-steroidal anti-inflammatory drugs provide symptomatic effect. Administration of systemic glucocorticosteroids should be avoided as withdrawal of this drug results in the flare of skin symptoms. Steroid injections are sometimes recommended intra-articularly or around the inflamed tendons or entheses. In patients with peripheral arhritis, especially with polyarthritis, elevated acute phase reactants and structural damages of affected joints conventional synthetic disease modifying anti-rheumatic drugs (DMARD) should be started as early as it is possible to achieve remission or low disease activity. Methotrexate is preferred as first choice drug at a weekly dose of 15–25 mg with folic acid supplementation, but leflunomide (10–20 mg daily) can also be administered. These drugs have favorable effect on skin and joint symptoms as well. The efficacy of conventional synthetic DMARDs is lacking in spondylitis and equivocal is dactylitis and enthesitis. In PsA patients with peripheral arthritis and inadequate response to at least one conventional synthetic DMARD or with spondylitis failed to respond to two different NSAIDs biologic DMARD, usually a TNF-α blocker should be administered. TNF inhibitors significantly improve joint, spine and skin symptoms, functional capacity and quality of life of PsA patients. In patients who failed to respond to a TNF-α inhibitor or have active disease after an initial favorable effect of this drug, another TNF-α blocker or biologic DMARD targeting interleukin-17 or 12/23 pathways, as well as JAK inhibitors should be considered. Biologic DMARDs have been proved to be effective in enthesitis and dactylitis.

10.4. Enteropathic arthritis

10.4.1. Epidemiology and symptoms of enteropathic arthritis

Inflammatory bowel diseases are associated with spondylitis or arthritis in 5–20% of cases. Spondylitis occurs in 10–20% of IBD patients, but symptoms are often mild and the axial manifestation remains silent. In contrast to AS the male: female ratio is close to 1:1. The prevalence of HLA-B27 among entheropathic spondylitis patients is somehow less (50–70%) than in classical AS. Radiographic findings at sacroiliac joints and vertebrae are similar to that found in AS, but usually less severe. Intestinal symptoms do not correlate with spondylitis.

Peripheral arthritis occurs in 5–15% of patients suffering from IBD. This ratio is slightly higher in Crohn's disease than in ulcerative colitis. The synovitis is usually transient and does not result in erosions but the IBD associated arthritis can be destructive as well. Activity of joint and gut symptoms change parallel, which is especially true in ulcerative colitis associated arthritis. Metacarpophalangeal, proximal interphalangeal, knee and ankle joints are affected primarily. There are typically 2 patterns of arthritis: pauciarticular (less than 5 joints involved), which is milder as it tends to improve spontaneously and polyarticular (5 or more joints affected) accompanied with erosions and joint destructions.

Skin manifestations can be observed sometimes in enteropathic arthritis. Erythema nodosum develops slightly more common in patients with ulcerative colitis and tends to regress spontaneously. In contrast to that pyoderma gangraenosum is a more severe ulcerative skin disease. As an extra-articular manifestation uveitis appears in a few percent of patients.

10.4.2. Diagnosis of enteropathic arthritis

Endoscopy combined with biopsy are essential in the diagnosis of inflammatory bowel disease underlying enteropathic arthritis. There is no typical laboratory marker of enteropathic arthritis. Acute phase reactants elevate in line with activity of inflammatory bowel disease.

10.4.3. Treatment of enteropathic arthritis

Treatment of IBD is the primary strategy, as the improvement of bowel symptoms is followed by amelioration of the arthritis and less evidently the spondylitis. Systemic corticosteroid treatment is effective in Crohn's disease and ulcerative colitis, but it can be used to achieve remission, as long-term administration is associated with side effects. Sulfasalazine and its derivative 5-ASA is effective in ulcerative colitis and peripheral arthritis but not in Crohn's disease and axial involvement. Azathioprine is useable to maintain remission in both forms of IBD, and has favorable effect on peripheral arthritis. Monoclonal antibodies against TNF-α (e.g. infliximab and adalimumab) often result in remission in both forms of IBD as well as in arthritis and spondylitis associated with bowel inflammation. On the other hand, the receptor fusion protein etanercept and the IL-17 inhibitors have not shown to be helpful with IBD. It has to point out that long-term administration of NSAID in maximal recommended dose may lead to flare of IBD, therefore their use in IBD associated arthritis or spondylitis in not recommended.

10.5. Reactive arthritis (ReA)

10.5.1. Definition, epidemiology and pathogenesis of reactive arthritis (ReA)

ReA can be defined as an arthritis followed by an extra-articular infection within a few weeks. Synovial culture is negative suggesting that ReA is caused by a pathologic immune reaction. ReA is usually triggered by Gram-negative, intracellular aerobic bacteria with a lipopolysaccharide containing outer membrane. The infectious agents responsible for ReA can be classified according to the primary site of infection: Chlamydia trachomatis, Neisseria gonorrheae, Mycoplasma genitalium, Ureaplasma urealyticum causing urogenital and Salmonella, Shigella, Yersinia, Campylobacter strains causing gastrointestinal tract infections. The incidence of ReA after urogenital infection is 2–4%, and up to 15% after gastrointestinal infections. The association with HLA-B27 in ReA is lower than in AS, 30–80% of ReA patients are HLA-B27 positive.

10.5.2. Symptoms of ReA

The primary infection is often symptomless but may cause dysuria and pollakisuria especially in men and diarrhea depending on the infectious agent. The clinical symptoms of ReA develop with a delay of 1–4 weeks. ReA usually occurs in young adulthood between the ages of 20–40 and affects both sexes equally after gastrointestinal infections, while Chlamydia infection induced ReA is more frequent among men. The most typical clinical symptoms are asymmetric oligoarthritis of lower extremity (knees, ankles), while sometimes arthritis occurs in the joints of upper extremity. Other manifestations may include mild polyarthritis, inflammatory low back pain or dactylitis. Extra-articular symptoms may also be present such as conjunctivitis frequently or acute anterior uveitis rarely as well as various skin rashes.

10.5.3. Diagnosis of ReA

The only specific laboratory test in ReA is identification of triggering infectious agent. Isolation of bacteria from stool is often unsuccessful as the patient recovers from gastrointestinal infection till onset of ReA. Chlamydia trachomatis infection can be proved by PCR from the first proportion of morning urine sample or by urogenital swab but the infection is commonly asymptomatic especially in women. Diagnostic value of detection of antibodies against bacteria is limited as there is a cross reactivity between Chlamydia trachomatis and Chlamydia pneumoniae. Salmonella and Yersinia induce a strong antibody response but repeated tests are needed to prove actual infection.

10.5.4. Treatment of ReA

Approximately half of the ReA patients recover spontaneously, although mild arthritis, spondylitis or enthesitis can persist causing episodic complaints. The presence of HLA-B27, the positive family history for SpA and chronic infection increase the risk of developing chronic diseases. The main aim of treatment is to cure the primary infection and prevent patient from chronic complications. If the triggering infection is still present, antimicrobial therapy should be started without delay. In the case of Chlamydia trachomatis infection, the patient and his / her partner have to be treated.

Administration of antibiotics in uncomplicated enteritis does not improve the outcome of ReA. NSAIDs as well as intra-articular or perientheseal corticosteroids have symptomatic effects and represent first choice treatment in the acute phase of the disease. DMARDs such as sulfasalazine should be given in acute and chronic polyarthritis. Methotrexate is recommended in more severe, chronic phase of ReA.

10.6. Undifferentiated spondyloarthritis (USpA)

USpA is originally a member of SpA family which can be characterized by typical symptoms, physical findings, imaging and laboratory abnormalities of SpA but does not meet the criteria of the other members of SpA (e.g. AS, PsA etc.). Some of the patients with USpA later develop other symptoms and can be classified into a more specific form of SpA, so USpA is considered as preceding stage of AS, PsA, enteropathic arthritis etc., while others will remain in chronic USpA with usually mild symptoms.

The possibility of the detection of early inflammatory signs with MRI at sacroiliac and peripheral joints and the introduction of highly effective biologic agents in the treatment of SpA led ASAS to develop a new classification criteria for axial and peripheral SpA *(Figure 10.3.)*. This can also be used as diagnostic criteria by rheumatologist, so it allows to diagnose and treat patients suffering from USpA earlier instead of waiting for progression into a more specific disease. According to the ASAS criteria peripheral SpA may be applied for those patients suffering from arthritis, enthesitis or dactylitis and at least 1 or 2 SpA features defined by the ASAS experts. Axial SpA is an umbrella term for non-radiographic axSpA and AS, so those patients can be classified into axial form of SpA who are suffering from chronic low back pain with an onset before the age of 45 accompanied with one or more SpA features. Nowadays USpA should

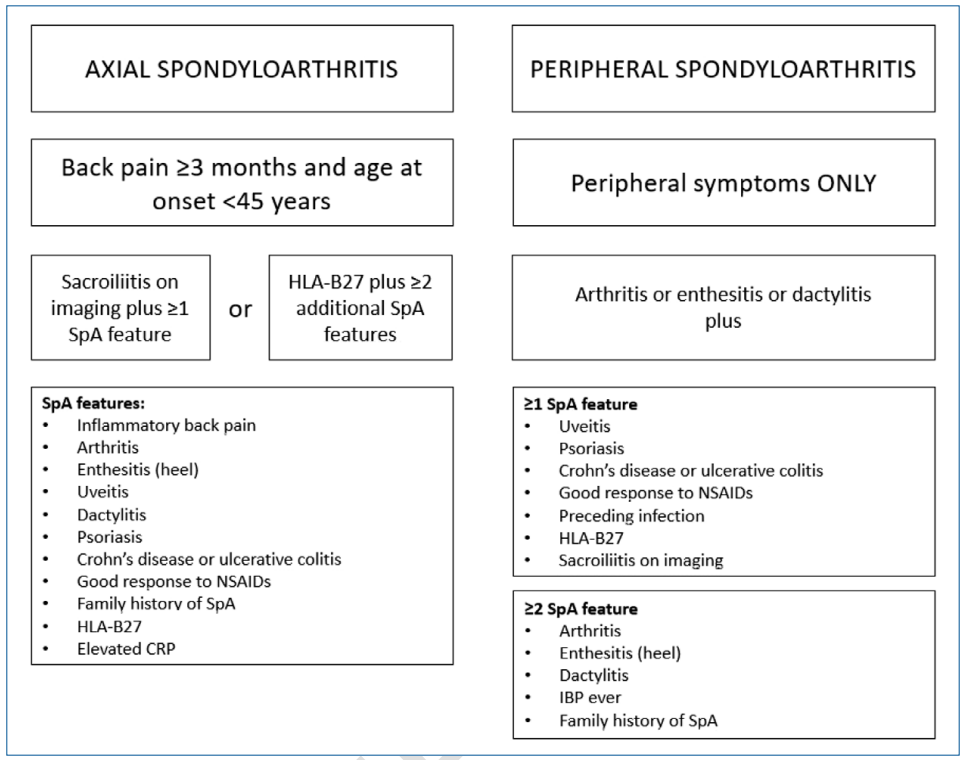

Figure 10.3. Classification criteria for axial and peripheral spondyloarthritis

be used as term for those patients who are suspicious SpA but does not fit into a specific category of ASAS criteria. For example, someone may have long lasting low back pain in young adulthood, HLA-B27 positivity but no more SpA feature (axial form of USpA) or dactylitis and positive family history for SpA (peripheral form of USpA).

First choice drugs in treatment of USpA are NSAIDs. Most of the patients respond well to these drugs but flare is quite common after withdrawal (this feature can be used in diagnosis). NSAIDs should be administered at the highest recommended dose to achieve required effect paying attention to the potential side effects. DMARD, especially sulfasalazine is recommended at a dose of 2–3 g/day in long lasting peripheral arthritis. TNF-α inhibitors – although proved to be effective in the treatment of USpA patients – are not approved in this indication. However, IL-17 inhibitors may be utilized in these patients.

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11. Infectious arthritis

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11.1. Bacterial arthritis

11.1.1. Definition

Bacterial arthritis is defined as bacterium-induced arthritis, in which the pathogen can be breed from synovial fluid or synovial membrane. The significance of the disease is that it is extremely destructive; its course is very fast without therapy; mortality is relatively high, despite the gradual increase in the antibiotic arsenal available to us.

11.1.2. Pathophysiology-pathogenesis

A special feature of the synovial membrane is that it can be considered a hypervascularized, relatively closed space without a basal membrane where bacteria can colonize and proliferate relatively easily. The mode of bacterial transmission is predominantly hematogenous, the pathogen enters the blood stream from a bacterial focus located elsewhere in the body, then, the pathogen reaches the joint. 90–95% of cases develop this way. The importance of direct inoculation (surgery, penetrating injury, „thorn synovitis") and spreading from a surrounding bone / soft parts is significantly lower.

11.1.3. Clinical symptoms

The most common symptom is the sudden, acute pain and swelling of a joint or joints, accompanied by a decreasing of the joints' range of motion. The affected joint is usually warm, and the patient reacts with intense pain to touch and movement. Typically, the disease, with the exception of severely immunocompromised patients, is also accompanied by general symptoms (fever, fatigue, cold shakes in case of bacteremia). Laboratory parameters characteristic of acute inflammation (increased erythrocyte sedimentation rate, leukocytosis, elevated CRP and procalcitonin levels) are usually easily detectable. Frequency of the affected joints: knees (55%), hips (11%), ankles (11%), shoulders (8%), wrists (7%), elbows (6%), and the other joints (5%). The disease is polyarticular in 10–20% of cases.

11.1.4. Diagnosis

The diagnosis is based on the detection of the pathogen in the synovial fluid or synovial membrane. This requires synovial fluid or biopsy specimen, the basic method of sample taking is puncture of the joint, which in most cases can be done blindly. However, in the case of hard-to-reach joints (hip and sacroiliac joint), ultrasound or CT-guided puncture is also possible. Bacteriological culture and Gram staining are performed from the taken sample as well. During cultivation, if aerobic and anaerobic Neisseria / Hemophilus infections are suspected the sample should be inoculated on chocolate agar medium. Hemoculture detects the pathogen in 50% of the cases, but the sensitivity of the articular sample culture is nearly 100%. Positive Gram staining confirms the suspicion based on clinical symptoms, and during cultivation it is possible to make the definitive diagnosis by identifying the pathogen and determining its antibiotic sensitivity. In rare cases, when other pathogens causing arthritis have been excluded with negative cultures, and the clinical picture is characteristic, the PCR (polymerase chain reaction) may be used to test the synovial fluid. This test may be used to detect the specific DNA of the suspected pathogen.

The role *of imaging diagnostic methods* is not limited primarily to diagnosis, it includes monitoring the progress and determining the extent of structural damage. In the early stage, conventional radiography shows only widening of the articular gap, increased soft-tissue shadow, and an examination after weeks-months can detect periarticular lime-deficiency, narrowing of the articular gap, erosion and secondary degenerative abnormalities. However, in an early stage, certain special symptoms (gas formation, epiphyseal destruction, osteolysis and metaphyseal periostitis) may orient towards an infectious origin. CT and MRI examinations are reserved for joints that are difficult to judge by X-rays. The extent of synovitis, intraarticular fluid and cartilage destruction can be assessed by ultrasound. In case of uncertain, targeted puncture / biopsy hard-to-reach sites (eg around the prosthesis) or suspected vertebral infections, more accurate localization of the infectious foci can be performed by various inflammatory scintigraphic methods (3-phase bone scan, TC99m HMPAO labeled leukocyte scan, Tc99m antigranulocyte scan, Ga67 citrate scan) can help the diagnosis.

11.1.5. Predisposing factors

It is extremely important to know that infectious arthritis is extremely rare among perfectly healthy individuals. Certain predisposing factors are required for its development, which largely contribute to the formation of infectious foci, intra-articular colonization of the bacterium, and their proliferation by reduc-

ing the effectiveness of antibacterial protection. Such factors include the use of immunosuppressive drugs, alcoholism, uremia, diabetes mellitus, malignancies, extensive burn, recurrent arthrocentesis, intraarticular steroid injection, arthroscopy, intravenous drug use, sickle cell anemia, HIV infection, and various associated arthritides (RA, crystalline arthropathies, advanced osteoarthritis, neurogenic arthropathy, hemarthrosis, SLE).

11.1.6. Bacterial spectrum

The most common pathogens by age are listed in *Table 11.1.*

Table 11.1. Frequency of certain pathogen in bacterial arthritis

	Adult (%)	Children (%)
Gram-positive cocci		
Staphylococcus aureus	35	27
Streptococcus (pyogenes, pneumonia, viridians)	10	16
Gram-negative cocci		
Neisseria (meningitidis and gonorrheae)	50	8
Hemophilus influenzae	<1	40
Gram-negative rods		
E. coli, Salmonella and Pseudomonas species	5	9
Mycobacteria	<1	<1

11.1.7. Treatment

In the case of clinical suspicion of bacterial arthritis, immediate puncture of the affected joint and bacteriological examination of the aspiration sample (culture and Gram staining) are the most important. If the aspiration sample does not appear to be macroscopically purulent, or if the Gram staining does not confirm a pathogen, immediate antibiotic administration is not required, the decision may be postponed until the final result of the culture and, if the bacterium can be cultivated, an antibiotic corresponding to the antibiotic sensitivity may be given. If Gram staining detects a pathogen, the criteria for so-called empirical antibiotic selection based on experience prevail. Methicillin, cephazolin or fluoroquinolone should be given in the case of a Gram-positive pathogen and vancomycin, nafcillin or rifampicin in case of an immunosuppressed patient. In case of Gram-negative pathogens, aminoglycoside and penicillin or aminoglycoside and 3rd generation cephalosporin are the appropriate choices, while in the case of beta-lactam allergic patients fluoroquinolone antibiotic is the appropriate choice.

In order to maintain adequate blood levels, the antibiotic should always be administered intravenously for at least two weeks, followed by oral antibiotic treatment (sequential treatment) for at least two weeks. In case of readily accessible joints (knees, ankles, and wrists), closed needle aspiration should be attempted daily or every two days to achieve a reduction in joint capsule tension, removal of inflammatory products and proteases, and monitoring of the efficacy of the therapy (white blood cell count of the aspiration sample, culture, and Gram staining). Open surgical drainage is required in case needle aspiration is unsuccessful, in hip / sacroiliac infections, in case of no responds to antibiotic treatment within 48 hours, if dense pus is emitted during puncture, and when there is concurrent osteomyelitis / soft tissue progression.

11.1.8. Prognosis

Even nowadays, bacterial arthritis is one of the diseases with a high mortality rate (5–15%); chronic joint damage remains in 25–60% of cases. Effectiveness of treatment depends on the duration of the infection, virulence of the pathogen, the affected joint (worse outcome is expected in the case of hip involvement), the age of the patient, the presence of co-morbidities and the patient's immunity.

11.1.9. Spondylodiscitis

Infection of the intervertebral discs can be a potentially very serious condition, as the infection can cause the adjacent vertebral bodies to burst, extend vertically below the ligament system of the spine, and may lead to abscess formation, which, spreading to the thoracic / abdominal cavity, may lead to life-threatening sepsis. The disease most often develops in the lower dorsal and lumbar regions. The mode of transmission is predominantly hematogenous at all ages. After non-invasive interventions, the probability of spondylodiscitis is up to 20%, and after invasive interventions and major spinal surgeries it may be up to 5%. After operations or even without operation, clinically worsening spinal pain localized to a vertebra, spinous processus tenderness, pain in the affected area of the spine, subsequent persistent nocturnal spontaneous pain, decreased range of motion of the spine, muscle spasm and fever is characteristic. Important new data is that CRP, ESR, and procalcitonin levels are significantly less useful in diagnosis and therapy monitoring. In addition to the typical clinical picture, the diagnosis is based on the increased inflammatory laboratory parameters, and the characteristic radiological picture (articular gap narrowing, later erosions on vertebral plates). Unfortunately, the disease must be present for at least 2–3 weeks before

the conventional X-ray can detect any abnormalities. The most reliable imaging technique is MRI of the spine, which not only provides excellent morphological picture, but also reliably illustrates the extent of the inflammation. MRI is specific and sensitive, and efficacy can be further enhanced by administration of a gadolinium contrast agent, which, when administered results in a strong accumulation in vertebral bodies and discs. In questionable cases, scintigraphy techniques (Tc99m HMPAO-labeled leukocytes, human polyclonal immunoglobulin, antigranulocyte scintigraphy, Ga^{67} citrate scintigraphy) which can be positive after 2-3 days, may be used to visualize leukocyte accumulation. Although MRI is the gold standard in diagnostics, PET-CT may be a step forward in cases where MRI and / or contrast agent cannot be used (allergy, metal implant and kidney failure). The diagnostic value of PET-CT is the same as that of an MRI, although due to its expenses, it will probably not spread in everyday practice.

Definitive diagnosis can be obtained by cultivation / Gram staining, which can be obtained by aspiration or surgery. The most common pathogens are Staphylococcus aureus, Gram-positive cocci, but E. coli, Proteus, Pseudomonas, Salmonella, fungi and Mycobacterium tuberculosis is also frequent. Hemoculture in feverish conditions is less reliable in this regard. If the clinical picture is clear but cultivation has not confirmed a pathogen, PCR (polymerase chain reaction) may help to detect the pathogen, although antibiotic susceptibility testing is not possible in this case.

The therapy is based on at least 6 weeks of an effective antibiotic treatment with CRP monitoring. The aspects of antibiotic selection do not differ from those of peripheral arthritis. The effectiveness of the antibiotic is indicated by a reduction in pain and laboratory parameters of inflammation (e.g. CRP). The appearance of abscesses near the spine may be an important complication, but not necessarily an indication of an ineffective therapy. It is important to immobilize the spine for 2-3 weeks using corset or lumbar plaster. Neurosurgery is indicated for resistant cases, repeated sampling, vertebral compression or abscesses formation, and in case of unstable spine section.

Changes affecting the vertebral plates and the bone marrow of the adjacent vertebrae, abnormalities (Modic-type degeneration) have been described decades ago by a special MRI picture. The results of recent years have shown that these abnormalities are caused by slowly growing pathogens (mainly Propionibacterium acnes). This finding has led to the attempt to use long-term antibiotic therapy (90-100 days) in these types of lesions. The results have been contradictory so far.

11.1.10. Osteomyelitis (bone marrow inflammation)

Osteomyelitis is an inflammation of bone caused by bacteria, more rarely fungi. Most commonly osteomyelitis is caused by hematogenous spreading of the pathogens, less frequently by direct transmission to the bone from the environment, however forms based on sterile circulatory problem are also known. Basically, we distinguish the following forms: 1. acute hematogenous osteomyelitis; 2. osteomyelitis of the vertebrae 3. osteomyelitis transmitted from the environment with or without circulatory problem 4. chronic osteomyelitis.

Acute hematogenous osteomyelitis is primarily a disease of childhood, mainly because increased blood supply of the growing bones creates the opportunity for pathogens to adhere. The most important moment in pathogenesis is the proliferation of pathogens in the small vessels of the metaphysis, which trigger an inflammatory response, accompanied by increased bone resorption and bone remodeling. If the process is left untreated, the infection will continue to spread to the direction of the epiphyses and the joint, causing bacterial arthritis, and, following a pyogenic periostitis, the resulting pus may empty into the outside world. Over time, the process may become subacute then chronic, with the formation of sequestrum within the dead bone, which is in most cases surrounded by a sheath of live bone (involucrum) (Brodie's abscess).

Osteomyelitis may be caused by a variety of pyogenic bacterial pathogens, the most common being Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus pneumoniae and Kingella kingae; the latter two being particularly common in children under 3 years of age. Rarely, coagulase negative Staphylococci (CoNS), anaerobic bacteria, and Gram-negative enterobacteria, and fungi cause osteomyelitis only in immunocompromised individuals.

Acute hematogenous osteomyelitis typically begins with fever, bone pain, general symptoms (loss of appetite, weight loss, nausea, fatigue). The affected area is swollen, erythema is present on the skin above the affected joint, and the affected limb is visibly spared. Occasionally, fistulae formation and less frequently deforming joint swelling may be seen at the first examination; the latter making pyogenic arthritis likely. In a small number of cases, the disease is indolent, has a subacute course, and in some cases the patient may be referred to a physician with an established Brodie's abscess. Vertebral osteomyelitis develops in the elderly, often following spinal surgery or trauma, in which case the spread from the environment also plays an important pathological role. It is important to know that osteomyelitis of the pelvis can cause abdominal-pelvic pain, which is often embarrassingly mimicking the symptoms of acute abdominal or gyneco-

logic inflammation. Some other diseases, like cardiovascular disorders, diabetes, immunosuppressed conditions and hemoglobinopathies in childhood also predispose for osteomyelitis.

Osteomyelitis following surgery (craniotomy, otologic and dental surgery, sternotomy, prosthesis implantation, open fracture reconstruction) is a major concern; intraoperative contamination being the most likely cause. There is a serious risk of ear-nose-throat and dental pus spreading to the surrounding bones. Long-term bedridden patient, ulcers that develop on pressurized sites may become superinfected and spread to the surrounding bone.

A particular area of limb surgery is osteomyelitis that develops on the basis of blood vessel stenosis and / or diabetes. Neuropathy and impaired circulation make it difficult to detect injuries, and diabetes increases the chance of bacterial colonization, a special form of which is the so-called diabetic foot. Inadequately treated or already indolent, subacute-onset osteomyelitis can become chronic, and in many cases it is difficult to distinguish it from recurrent osteomyelitis, especially if factors that impair the healing of the primary process (diabetes, malnutrition, kidney disease, blood vessel stenosis, neuropathy, and immunosuppressed state) are present. Chronic osteomyelitis causing persistent septic state, chronic bone pain, difficult to heal fistulae, bone deformities, or even pathological fractures sours the patient's (and the doctor's) life.

The diagnosis is based on the clinical picture, increased inflammatory parameters, left shift in blood work and bacteriological examination of the specimen obtained by aspiration or surgery, and in questionable cases based on PCR test. Radiological examinations are also important. Conventional X-ray shows lytic lesions with sclerotic margins and subperiosteal abscess formation in the bone, while inflammation scintigraphy (3-phase bone scintigraphy, Tc99m HMPAO-labeled leukocyte scintigraphy, antigranulocyte scintigraphy, Ga67, and In111 scintigraphy) can also visualize leukocyte inflammation in addition to local inflammation. MRI can also visualize the anatomical limits of the process and the spread to the soft tissue (psoas abscess in osteomyelitis of the spine).

Treatment of osteomyelitis is basically an orthopedic surgical task, in which the main task is to empty the intramedullary cavities and soft tissue abscesses filled with pus, as well as to eliminate the fistula passages. In addition, long-term antibiotic treatment of at least 3–6 weeks is required, ideally, followed by sequential oral suppressive therapy. The treatment is based on the susceptibility of the pathogen, bacterium, thus giving a product which penetrates well into the bone. Most β-lactams, clindamycin, vancomycin and fluoroquinolones penetrate the bone well, although the latter are not recommended for children. It is

advisable to start the empirical therapy as soon as possible (before the final antibiotic susceptibility result is obtained). First choice for the most likely pathogen (S. aureus) nafcillin, clindamycin or first-generation cephalosporin therapy is recommended; in case of suspected methicillin-resistant Staphylococcus infection, vancomycin may be a step forward. In the case of osteomyelitis in children not immunized against Hemophilus influenzae; and vancomycin is to be supplemented with third generation cephalosporins (cefoperazone, cefotaxime, and ceftriaxone). If there is no clinical improvement, switching to an antibiotic that the pathogen is susceptible, may be successful. It is advisable to seek the help of an infectologist, especially if there is a therapy resistant case, in which case newer, but very expensive antibiotics (linezolid and daptomycin) may be given.

Sterile osteomyelitis (SAPHO, PAPA, CRMO, etc.) is basically not a group of infectious diseases, but an autoinflammatory disease, the discussion of which would expand the framework of this chapter.

11.2. Special bacterial arthritides

11.2.1 Neisseria gonorrheae infection

Disseminated Neisseria gonorrheae infection is associated with joint involvement in 0.5–3% of the cases. Its importance is due in part to the fact that Neisseria gonorrheae is the most common infectious arthritis agent in the reproductive age and, on the other hand, the disease has an excellent healing propensity. The clinical picture is extremely characteristic: migratory polyarthritis (25–50% purulent), tenosynovitis, and dermatitis (maculo-papules, vesicles, and gunmetal pustules) is characteristic, which dissolves within 4–7 days but may reappear several times. The latency of the disease varies from 1–60 days. It is extremely important that only a quarter of the cases have urogenital symptoms (urethritis and vulvovaginitis).

The *diagnosis* is based on bacteriological examination (in addition to the typical clinical picture). The urogenital tract culture (rectum or throat secretion in a homosexual individual) is positive in 80–90% of cases, while articular sample culture is positive in 25–70% of cases; the accuracy of the hemoculture is significantly worse (25–30%). It is essential that the material is inoculated onto chocolate agar medium and cultured in a carbon dioxide-rich medium. If Gram staining of a smear taken with a typical clinical picture confirms Gram-negative cocci, the diagnosis is almost certain before the arrival of results. If a bacteriological test is negative with a typical clinical picture, it is advisable to send the sample for PCR (polymerase chain reaction).

The disease generally responds well to *antibiotic therapy:* oral treatment for 7 days is sufficient using 4×500 mg ampicillin, 2 g erythromycin, or 2 g ciprofloxacin, but parenteral formulations such as 1 g ceftriaxone daily, or 2×2 g spectinomycin may also be administered. In case of purulent arthritis, daily puncture of the joints is essential. A majority of patients also have concomitant Chlamydia infection, thus patients should be investigated in this direction. If Chlamydia positivity is confirmed, 200 mg of doxycycline daily (2 g of erythromycin in pregnant women) or 1 g of azithromycin should be given in one dose. The same treatment should be given to the asymptomatic sexual partner. Due to non-negligible co-infections, all patients should be tested for both syphilis and HIV.

11.2.2. Lyme-disease

Lyme disease a tick-borne infectious disease was discovered in 1975 in connection with an increase in arthritis in city of Lyme of Connecticut. Among the three human pathogenic Borrelia species (B. burgdorferi sensu lato, B. grani and B. afzelii) introduced into the skin by biting of Ixodes ticks, B. burgdorferi is most closely associated with arthritic involvement.

The *patomechanism* of the disease is slightly different from that of arthritis due to infection. Rapid dissemination after direct bacterial infection leads to colonization in the joints, which however never becomes purulent, despite the fact that the protective immune response develops slowly. It is likely that direct infection is only involved in the onset of the disease, and persistent synovitis is maintained by immunological mechanisms. It is also a unique feature that the pathogen can be detected in the joints over many years, often cultivated without showing any marked inflammatory activity. Lyme borreliosis itself occurs in three stages, with joint symptoms typically occurring in the third stage, with an average of 60% (!) 6 months after the onset of the disease.

Intermittent arthritis involving especially the large joints is characteristic, becoming chronic in 10–20% of cases. In addition, enthesitis, periostitis, chronic soft tissue pain and secondary fibromyalgia syndrome may occur. The *diagnosis* is based on the clinical picture, characteristic patient history (tick bite in an endemic area), and antibody response to B. burgdorferi (increased within 4 weeks). Due to the rare false positivity, confirmation of the latter by Western blotting should also be considered. Seropositivity persisting despite appropriate therapy, which may in many cases lead to unnecessary therapeutic courses, may be a problem, therefore alternative diagnostic tools may be available to confirm the presence of the pathogen (PCR, T cell proliferation assay with specific Borrelia antigens).

Treatment of arthritis usually involves 30–60 days of oral therapy (doxycycline 100 mg daily; amoxycillin 4×500 mg; cefuroxime 2×500 mg; erythromycin 4×250 mg). In refractory cases, 30 days of intravenous treatment is recommended in the form of 2 g of ceftriaxone or 6×3–4 million U of penicillin G daily. Prevention basically means preventing tick bites (in endemic areas wearing long pants tucked into socks). If tick bites occur in an endemic area, prophylaxis with oral doxycycline for 10 days should be considered, using penicillin V for children. Vaccination in endemic areas may be warranted; vaccines against certain proteins (OspA, OspB) of the pathogen are being tested. So far, the experience has shown an efficacy of about 90%.

11.2.3. Tuberculosis

In the developed countries, the prevalence of tuberculosis (TB) has declined since the 1940s, but this trend seems to be reversing over the last 20 years, probably due to significant population movements, HIV infection and widespread intravenous drug use. The proportion of osteoarticular TB among extrapulmonary cases is 10%. More than half of them affect the spine (spondylitis), mainly in the dorsal lumbar region.

Spreading of the pathogen is haematogenous, the progress is slow, insidious and can cause vertebral collapse, with complications of paravertebral-prevertebral abscess (cold abscess). The development of localized spinal pain, fever-subfebrility, weakness, weight loss, kyphosis, neurological symptoms in patients at high risk for TB should be suspected of TB spondylitis, which can be confirmed by imaging studies, PPD test or interferon γ based assays, Ziehl-Neelsen's staining, cultivation, histology, biopsy, sputum cultivation, and PCR if necessary. TB spondylitis requires 18 months of combined inhibitor therapy; in case of 6 weeks of unsuccessful conservative treatment and in case of neurological progression, surgical debridement can be effective. 30–40% of osteoarticular TB cases are arthritis and 20% are osteomyelitis cases. The former is typically associated with large joint pain, swelling, slow progression, the latter with pain and swelling of metaphysis of tubular bones, abscess and fistula formation.

The basic *diagnostic* tools are no different from the above mentioned. Arthritis therapy involves a minimum of 9 months of combined treatment, where 6 weeks of unsuccessful conservative treatment require surgical intervention.

In a broader sense, *Poncet disease,* a latent onset of sterile febrile polyarthritis that is associated mainly with lymph node and bone TB and is cured over months with antituberculotic therapy, is associated with TB infection. Probably considered reactive arthritis. Even after BCG vaccination, granulomatous

osteoarthritis lesions and typical self-limiting seronegative spondylarthritis, which respond well to NSAIDs, have been reported rarely.

11.3. Viral arthritis

Arthritis following viral infection is by no means a rarity, joint pain / swelling is a typical accompanying phenomenon of various viral infections and often occur as the only clinical manifestation. In most cases, spontaneous transient non-destructive polyarthritis develops, with little clinical significance, but occasionally, viral infections play a role in the induction of various autoimmune syndromes / diseases.

Possible pathomechanisms of viral infection associated with the development of arthritis are shown in *Table 11.2.*

Table 11.2. Pathomechanisms of viral arthritis

• Direct synovial destruction with inflammation (rubella, and varicella)
• Persistent or latent infection with prolonged immune response (altered synovial membrane antigenicity or viral products in the joint)
• Immune complex mechanism
• Molecular mimicry
• Autoantibody production, polyclonal B cell activation

Diagnosis of viral arthritis is basically based on the characteristic clinical picture and the positivity of the virus serological tests, and their therapy is essentially symptomatic, involving resting and transient NSAID administration.

Concerning certain viral infections, in *hepatitis B* infection, polyarthritis / polyarthralgia develops before the icteric phase, with symmetrical, sometimes migratory nature (hands, knees, ankles, wrists), significant joint stiffness that persists after the development of icterus in 5% of cases. Other rheumatologic manifestations such as polyarteritis nodosa, mixed cryoglobulinemia, immune complex glomerulonephritis, may also occur, the treatment of which is fundamentally different from the treatment of uncomplicated cases and goes beyond the scope of this chapter.

Rubella virus, of the togavirus family, associated with arthritis is essentially an occupational (nurses, nursing staff, pediatricians) disease. The incubation phase of about 2 weeks is followed by a prodromal period of 1–5 days, then by the appearance of typical maculopapular rashes on the neck, trunk, limbs, and lymphadenopathy. The incidence of arthritis ranges from 30% (women) to 6%

(men), has a sudden onset, usually before the rash, is symmetrical, sometimes of a migrant nature, with the involvement of hands, wrists, elbows, and ankles, and typically involves prolonged morning joint stiffness. Periarthritis, tenosynovitis, and carpal tunnel syndrome are not uncommon either. The disease runs its course within 3–4 weeks on average, with good prognosis, although prolonged or shorter arthralgia may remain. Interestingly, even after rubella vaccination, 1–5 days of arthralgia or arthritis may develop, highlighting the role of immunological mechanisms.

Human parvovirus B19 (HPV B19), DNA virus, isolated in 1975, is the "fifth childhood disease", the cause of erythema infectiosum, with headache, fever and rash ("slapped cheek") in children aged 4–10 years. In adults, 48% (!) of those infected may develop acute, symmetrical polyarthritis with small join involvement and significant morning joint stiffness. Less frequent manifestations include systemic (necrotizing) vasculitis, adult onset Still's disease, and SLE-like syndrome.

The population is highly transinfected (95% of adults are seropositive) with *Epstein–Barr-virus* (EBV), ubiquitous DNA virus. It is very often suspected of provoking autoimmune syndromes. This is because EBV DNA is common in the serum / synovium of RA patients, and chronic virus or carrying antigen causes periodic polyclonal B cell activation by chronic synovial cell proliferation or inhibition of B cell apoptosis. True arthritis is rare, but mono-oligoarticular arthralgia is more common.

Mumps virus of the Paramyxovirus family is an RNA virus. Arthritis caused by mumps virus is rare, less than 50 cases have been reported. Migrant large joint arthritis following characteristic clinical picture (generalized symptoms, swelling of the parotid, epididymic-orchitis, rarely oophoritis, mastitis, prostatitis, thyroiditis, meningitis, and encephalitis).

Arthritis associated with *varicella-zoster virus* infection is even rarer than mumps virus arthritis (there have been only 20 reported cases). Arthritis is a predominantly monoarticular affecting the large joints, less often small joint polyarthritis, with the appearance before of the rashes. Because of the immunosuppression associated with infection, it is important to exclude joint superinfections!

Hepatitis C virus (HCV) infection is suspected to be in connection with associated with a number of rheumatic immunological disorders (membranoproliferative glomerulonephritis, Sjögren's syndrome, RA, neuropathies, cryoglobulinemia, and vasculitis). This is not primarily due to direct viral effects but an abnormal response of the immune system to the viral infection (excess immune complex production, cryoglobulin and autoantibody production). HCV infection may be

associated with multiple rheumatic syndromes with different frequencies: arthralgia (9%), polyarthritis (4%), myalgia (24%), Raynaud's syndrome (44%), and fibromyalgia (16%) with anti-HCV positivity is of diagnostic value. The treatment of chronic HCV infection / HCV carrying is primarily a hepatological task.

Human immunodeficiency virus (HIV) infection is almost immediately associated with various musculoskeletal pain and inflammatory syndromes. Arthralgias, early painful joint syndrome, develops in 30% of patients within a few months of HIV infection. Reactive arthritis and mono-oligo-polyarticular HIV-associated arthropathy are not considered to be rare either. More and more reports have emerged of new-onset psoriatic arthritis, polymyositis / dermatomyositis, Sjögren's syndrome, necrotizing vasculitis, and RA-like, SLE-like syndromes, which are considered to be the consequence of the pathological direction of autoimmunity. Acquired immune deficiency may be a direct consequence of septic arthritis, especially in hemophiliac patients. Reference is made to the relevant books on the diagnosis and treatment of HIV infection.

An important feature of our modern world is the increased mobility of the population. In addition to its several advantages, the disadvantage is the possibility of encountering and infecting with exotic pathogens and thus the possibility of epidemics that are difficult to manage. Alpha viruses (Ross River virus, Barmah Forest virus, O'nyong-nyong virus, Sindbis virus, Mayaro virus, and Chikungunya virus) transmitting with bites of mosquitoes, native to Africa, Asia, South America, and Australia, are basically accompanied by spontaneous transient symmetrical feverish polyarthritis. There are no fundamental differences in the clinical picture, except joint pain causing extreme limited mobility in case of Chikungunya virus infection. Clinical picture of Flaviviruses (Dengue, Zika virus), native to Africa, are similar. Zika virus has appeared in Europe in the last few years, which, in addition to mild course general symptoms, also causes symmetrical polyarthritis. Recognition of exotic viral infections with a misleading clinical picture is far from simple. Traveling to exotic places, in patient's history, serology and PCR (RT-PCR) plays a significant role in this disease.

11.4. Fungal arthritis

Fungal osteoarthritis is characterized by latent onset, significant destruction with minimal inflammatory symptoms, and a tendency to osteomyelitis. Diagnosis is based on symptoms, serological and histological examination, positive cultivation result and coccidioidine positive skin test. Treatment is basically conserva-

tive, surgical intervention is considered only in the case of progression while under treatment, spread to the adjacent bone, or in case of extraarticular dissemination. In non-HIV infected individuals, 6 months of treatment with ketoconazole, fluconazole, and itraconazole is sufficient, and amphotericin B can be given in case of inefficacy. HIV infected patients require a lifelong suppressive therapy after eradication.

Coccidioides immitis and *Blastomyces dermatitidis* essentially cause lung infections (coccidiomycosis and blastomycosis), from which pathogens enter the joints by hematogenous pathways. They cause arthritis of the large joints and osteomyelitis, which is accompanied by progressively worsening pain, joint stiffness and early radiological destruction with minimal joint swelling.

Aspergillus nidulans, Cryptococcus neoformans and *Candida albicans* are pathogenic only in immunosuppressed patients. Causes lung infection (aspergillosis, cryptococcosis or torulosis, candidiasis), which directly spreads to the vertebrae, discs, and ribs; hematogenous transmission is less frequent.

Soil parasitic *Histoplasma capsulatum* causes primary pulmonary infection (histoplasmosis) as well, from which polyarthritis develops by hematogenous dispersion (most commonly involving the knees, joints, and ankles) and the development of accompanying erythema nodosum is common.

Sporothrichum schenckii is the saprophyte of earth and roots. Primary infection is caused by direct inoculation of the skin, less frequently by inhalation. Disseminated infection (sporotrichosis) occurs essentially only in immunocompromised individuals. Bone and joint infections are rare, polyarticular forms are common; hand and wrist involvement are unique, often resulting in fistulae and gross destruction.

11.5. Reactive arthritis

Post-bacterial arthritis (reactive arthritis) has been discussed in more detail with spondyloarthropathies (see chapter 10).

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12. Crystal arthropathies

Szilvia Szamosi

12.1. Gout

12.1.1. Definition

Gout is characterized by recurrent flares of inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in joints and other tissues. Chronic gouty arthritis is usually associated with tophi formation, other extra-articular manifestations and comorbid states. Hyperuricemia is a necessary but not sufficient precondition for the development of urate crystal deposition, thus it should be distinguished from gout, the clinical syndrome.

12.1.2. Epidemiology

Both the incidence and prevalence of the disease has been increasing for the last few decades; hazards to civilization and comorbid conditions predisposing for hyperuricemia (obesity, hypertension, diabetes, chronic renal failure) gives explanation for this rise. It mainly affects men by their fourth or fifth decades of life, but the prevalence also increases in women after menopause. Other notable influencing factors are genetic polymorphisms and mutations in different enzymes. Estimates of the average prevalence in adult population is about 2–5%, being the highest in Taiwan (10%).

12.1.3. Pathogenesis: uric acid metabolism

New advances have revealed that gouty arthritis is an autoinflammatory disease involving the activation of innate immune responses and inflammasome activation. An acute inflammatory response to MSU crystals in and around the joints is in the center of pathogenesis of gout.

Uric acid (UA, 2,6,8-triohydroxy-purine) is the final metabolite of purine metabolism in humans *(Figure 12.1.)*. Daily production of UA is appr. 1–1.5 grams. The levels of serum uric acid depend on the balance between purine ingestion, synthesis and degradation. The main source of purine is from the turnover of cellular nucleic acids (80%) endogenously and a minority (20%) originates from the dietary intake. Purine degradation involves the breakdown of the purine

mononucleotides, guanylic acid (GMP), inosinic acid (IMP), and adenylic acid (AMP) into the purine bases, guanine and hypoxanthine. These latter two compounds are then metabolized to xanthine. In the final step, catalyzed by the enzyme xanthine oxidase (XO), xanthine is irreversibly oxidized to produce uric acid. In most mammalian species uric acid is further metabolized by the enzyme uricase to the more soluble allantoin, which is subsequently excreted in the urine. However, humans lack a functional uricase enzyme and therefore uric acid is the final breakdown product of the pathway. Purine bases can be synthesized de novo or recycled by salvage pathways. During de novo biosynthesis ribose-5-phosphate converts to phosphoribosyl-pyrophosphate (PRPP), which further transforms into inosine-5-monophosphate (IMP). Two salvage enzymes with different specificities recover purine bases. Adenine phosphoribosyl transferase catalyzes the formation of adenylate, whereas hypoxanthine-guanine phosphoribosyl transferase (HGPRT) catalyzes the formation of guanylate as well as IMP, a precursor of guanylate and adenylate. Details of purine metabolism is shown on *Figure 12.1.*

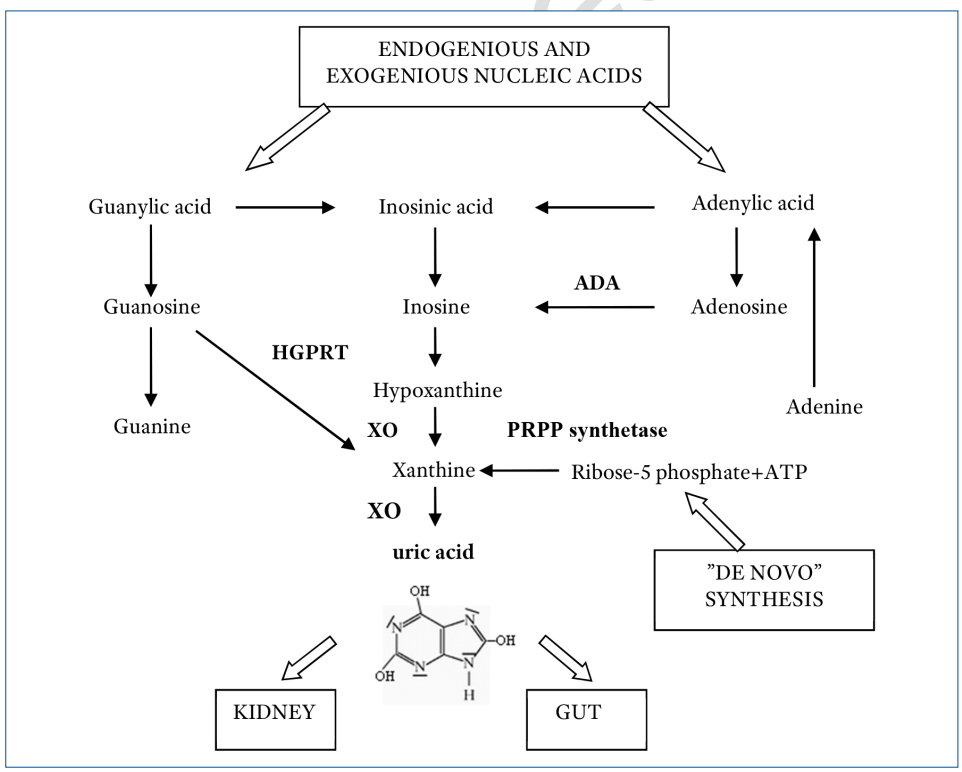

Figure 12.1. Purine metabolism

To maintain homeostasis, urate elimination from humans occurs via two main routes; approximately two-thirds being excreted in urine, while the remainder is thought to be largely excreted via the gastrointestinal (GI) tract. Renally excreted and filtered urate is reabsorbed in the proximal tubule in 90–95%, but then secreted as well. These processes are mediated by several urate transporters. Normal humans have serum urate concentrations approaching the theoretical limit of solubility of urate in serum (6.8 mg/dL) and regularly excrete urine that is supersaturated with respect to uric acid. Uric acid is a diprotic acid with pKa of about 5.75 in blood (5.35 in urine), thus at physiological pH, it predominately exists as the monoionic urate ion. Under normal steady state conditions, daily turnover of about 60 percent of the urate pool is achieved by balanced production and elimination of uric acid.

Table 12.1. Different forms of hyperuricemia

		Primary	Secondary
Increased renal urate overload	*Increased urate production*	Increased function of PRPP-synthetase, decreased function of HGPRT and / or APRT Urinary urate excretion >600 mg / day / 1.73 m^2 and fractional urate excretion ≥ 5.5%	Increased turnover of nucleic acids, myelo- and lymphoproliferative diseases, cytostatic therapy, obesity, hypertriglyceridemia, psoriasis, sarcoidosis
	Decreased extrarenal urate excretion	Decreased intestinal excretion (mainly ABCG2 urate transporter deficiency), consequently increased urate level and renal urate excretion Urinary urate excretion >600 mg / day / 1.73 m^2 and fractional urate excretion ≥ 5.5%	Extensive gastrointestinal involvement
Decreased renal urate excretion		Functional deficiency of kidney-specific urate transporters Urinary urate excretion ≤ 600 mg / day / 1.73m^2 and fractional urate excretion < 5.5%	Severe kidney failure, hypertension, drug related effect (thiazide diuretics, cyclosporine, PZA, salicylic acid), lead toxicity, alcoholic ketoacidosis, diabetes, etc.
Combined form		Urinary urate excretion > 600 mg / day / 1.73 m^2 and fractional urate excretion < 5.5%	Deficiency of glucose-6-phosphate dehydrogenase (von Gierke disease) and deficiency of fructose-1- aldolase

Not in all hyperuricemic individuals develop gout, but hyperuricemia is definitely a risk factor for crystal deposition. Hyperuricemia originates from either increased renal urate overload (as a result of increased urate production

or decreased extrarenal excretion), or decreased renal urate excretion, or even a combination of the two. Primary and secondary factors might be both associated with these cases *(Table 12.1.)*.

Presence of different enzyme deficiencies give the background of *primary forms* in most cases. HGPRT deficiency causes a rare, inherited disorder, Lesch–Nyhan syndrome. The enzyme activity is decreased beyond 0.5–1% of normal level in 1–2% of gout patients. Increased activity of PRPP synthetase and xanthine-oxidase also increases urine production. Decreased renal urate excretion without significantly affected renal function might be caused by functional impairment of organic anion transporters due to structural changes in the channel protein member. An ATP-driven efflux pump, ABCG2 is expressed both in the proximal tubule epithelial cells and in the intestine. Genetic variation in human ABCG2 transporter thus contributes to clinical hyperuricemia resulting in renal overload (ROL).

Secondary hyperuricemia might develop as a result of other metabolic or renal diseases. Increased cell turnover and nucleic acid production is associated with certain hematologic disorders (myelo- and lymphoproliferative diseases and hemolytic anemia), cytostatic drug administration or psoriasis. Dietary exposures are important modifiable risk factors for gout. Alcohol containing beverages, sweetened soft drinks with high fructose content, red meats and seafood are the most common high-purine foods. Decreased renal urate excretion is associated with other medical conditions including chronic renal insuffiency, diabetic or starvation ketoacidosis, lactic acidosis and usage of certain drugs (e.g. salicylic acid, thiazide diuretics, cyclosporin) interacting with renal urate transporters. Decreased extrarenal urate excretion is the consequence of extensive GI tract involvement.

The central event of gouty inflammation is the activation of leukocytes by MSU crystals. Native or protein coated crystals act as danger-associated molecular patterns (DAMPs) and may be recognized by TLRs on dendritic cells, namely TLR2 and TLR4. This will initiate assembly and activation of the cytosolic macromolecular NLRP3 inflammasome complex, and the release of multiple cytokines. The activation of NLRP3 inflammasome requires two signals. During priming, there is an increased expression of inflammasome components initiated by TLR ligands, such as crystal particles or free fatty acids. The second or „activating" signal results in the formation of the inflammasome complex and the subsequent activation of caspase-1. The activated caspase-1 cleaves pro-IL-1β and pro-IL-18 leading to the maturation and secretion of these pro-inflammatory cytokines. Besides DC and macrophage activation, recruitment and

activation of neutrophil granulocytes, mast cells and synovial fibroblasts end in an increased production of proinflammatory cytokines (IL-1, Il-6, IL-8, TNF-α) and other mediators like matrix metalloproteinases (MMPs), prostaglandins, leukotrienes, lysosomal enzymes and reactive oxygen species (ROS). These cells also contribute to the development of cartilage and bone erosions associated with long-standing inflammation. After the perpetuation of this inflammatory cascade, there is also a counter regulatory, anti-inflammatory network that attenuates gouty inflammation and attacks.

Anti-inflammatory cytokines (TGF-ß, IL-10, PPAR-γ, Apo-B, Apo-E) and increased clearance of apoptotic cells and pro-inflammatory mediators, as well as neutrophil extracellular traps (NET) are involved in the resolution of gouty inflammation.

Hyperuricemia is not the only factor influencing the solubility and crystallization of MSU. Lower temperature (peripheral arthritis of the toe), lowering of the pH value, dehydration and traumatic injury induces nucleation and increases the probability of crystal formation. The above mentioned inflammatory process is mainly related to acute gouty inflammation. Chronic tophi formation is also induced by crystals, but this inflammation is rather characterized by foreign body giant cell accumulation and granulation tissue formation with secondary calcification.

12.1.4. Clinical manifestations

The clinical manifestations of gout may include a wide variety of disease spectrum; asymptomatic hyperuricemia, acute gouty arthritis and chronic tophaceous gout. Special attention is needed to diagnose and take care of comorbidities.

Asymptomatic hyperuricemia: serum urate level is increased, but defining an exact threshold is difficult to establish. A persistent urate level of > 8 mg / dL (480 μmol / L) is used as the threshold for initiating evaluation and, where warranted, lifestyle and / or pharmacologic intervention for management of asymptomatic hyperuricemia.

Acute gouty inflammation (monoarthritis): sudden onset of severe pain, redness, warmth, swelling and disability occurs most frequently overnight, with a predilection site at the base of the great toe, at the I.MTP joint. Involvement of the ankles, knees, small hand joints, elbows may also occur initially. Associated general symptoms, malaise, fever are frequently present as well. Certain provoking factors of gouty flares can be identified; most frequently alcohol consumption, diet change or use of diuretics. The first attack usually resolves in a few days or in a week, which is not associated with limited joint function.

Recurrent gout flares (intercritical gout): a second episode usually occurs within 2 years. Intercritical periods early in the course of gout are most often entirely asymptomatic. Most untreated patients experience polyarticular symptoms with multiple recurrences with short or absent symptom-free intervals.

Chronic gout: it is characterized by a low-grade inflammation and often destructive changes in the surrounding connective tissue. Joint involvement on the upper extremity is more frequent, and accompanied deformities, tophi formation and destructive changes are seen. Predilection sites of tophi formation are the external ear, the olecranon, knee and Achilles tendon. They may cause skin ulceration, bony erosions and the mutilation of the fingers.

In addition, multiple comorbid conditions, including hypertension, obesity, type 2 diabetes, hyperlipidemia and ischemic heart disease have significant effect on mortality of gout patients. Presence of hyperinsulinemia and insulin resistance are characteristic for all of them. Insulin and increased renal vascular resistance with decreased glomerular filtration rate (GFR) have been shown to reduce renal excretion of urate. There are three major renal complications of chronic hyperuricemia: acute tubular nephropathy, nephrolithiasis and chronic urate nephropathy. Acute uric acid nephropathy is characterized by acute renal failure due to uric acid precipitation within the tubules. This disorder is usually due to overproduction and accompanying excessive excretion of uric acid in patients with lymphoma, leukemia, or a myeloproliferative disease, particularly after chemotherapy that has induced rapid cell lysis. Chronic urate nephropathy is a form of chronic kidney disease induced by the deposition of sodium urate crystals in the medullary interstitium resulting in renal functional impairment. Uric acid stone formation is facilitated by high urine uric acid concentration, an acid urine pH and decreased amount of urine. Urate crystals may provoke renal hypertension through direct toxicity to renal vascular endothelium. Lesch–Nyhan syndrome is associated with severe neurological disturbances (spasticity, mental impairment, extrapyramidal symptoms) besides tophaceous gout.

12.1.5. Diagnosis

The new 2015 ACR / EULAR classification criteria for gout is a scoring system enabling clinicians in classifying patients with the help of clinical, laboratory and imaging modalities *(Table 12.2.)*.

Table 12.2. The ACR/EULAR classification criteria

			Score
Step 1: **Entry criterion** Entry criterion (only apply criteria below to those meeting this entry criterion)		At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2: **Sufficient criterion (if met, can classify as gout without applying criteria below)**		Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	
Step 3: **Criteria (to be used if sufficient criterion not met)**			
Clinical criteria	Pattern of joint / bursa involvement during symptomatic episode(s) ever	Ankle or midfoot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint	1
		Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
	Characteristics of symptomatic episode(s) ever • Erythema overlying affected joint (patient- reported or physician-observed) • Can't bear touch or pressure to affected joint • Great difficulty with walking or inability to use affected joint)	One characteristic Two characteristics Three characteristics	1 2 3
	Time course of episode(s) ever Presence (ever) of >2, irrespective of antiinflammatory treatment: • Time to maximal pain <24 hours • Resolution of symptoms in ≤14 days • Complete resolution (to baseline level) between symptomatic episode	One typical episode Recurrent typical episodes	1 2
	Clinical evidence of tophus: Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Present	4

			Score
Laboratory criteria	Serum urate: Measured by uricase method. Ideally should be scored at a time when the patient was not receiving urate-lowering treatment and it was. 4 weeks from the start of an episode (i.e., during intercritical period); if practicable, retest under those conditions. The highest value irrespective of timing should be scored Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)	<4 mg/dL (<240 μmol/L) 6–<8 mg/dL (360–<480 μmol/L) 8–<10 mg/dL (480–<600μmol/L) ≥10 mg/dL (≥600 μmol/L) MSU negative	–4 2 3 4 –2
Imaging criteria	Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign or DECT demonstrating urate deposition Imaging evidence of gout-related joint damage: conventional radiography of the hands and / or feet demonstrates at least 1 erosion	Present (either modality) Present	4 4

Before embarking upon classification criteria, entry criteria should be used to identify the relevant patient population to whom the classification criteria would be applied. The entry criterion was defined as the occurrence of at least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa. Sufficient criteria could classify gout without further need to apply the classification criteria scoring system that is defined as the presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus. While this gold standard method has high specificity, its feasibility and sensitivity may be inadequate, because of difficulty with aspiration of joints and / or examination of the sample under polarizing microscopy. Further domains of the new classification criteria include clinical (pattern of joint / bursa involvement, characteristics and time course of symptomatic episodes), laboratory (serum urate, MSU negative synovial fluid aspirate), and imaging (double contour sign on ultrasound or urate on dual-energy computed tomography, radiographic gout-related erosion). Serum urate was considered a mandatory element of the classification criteria scoring system with a threshold of 6 mg/dL (360 μmol/L). However increased inflammatory markers and neutrophilia are frequently seen they are not included in the laboratory panel. Imaging modalities allowing sufficient identification of

urate deposition are ultrasound and dual-energy CT (DECT). Gout-related joint damage, erosions can be scored on the basis of conventional radiography. The maximum possible score in the final criteria is 23. A threshold score of ≥8 classifies an individual as having gout.

12.1.6. Differential diagnosis

Acute inflammatory gouty arthritis must be differentiated from septic arthritis, erysipelas, other crystal induced arthritides, osteoarthritis (OA), reactive arhritis, and psoriatic arthritis. Culture, X-ray, crystal analysis and the presence of extraarticular symptoms might be helpful to exclude other conditions. In case of chronic tophaceous gout further consideration is needed to exclude rheumatoid arthritis and OA.

12.1.7. Management

Different treatment strategies are used to control an acute gouty attack, for the prevention of new attacks, lowering urate level and to manage comorbidities. Both pharmacological and non-pharmacological (dietary, lifestyle-related) remedies are important in this regard. Treatment is based on the 2016 EULAR and „treat-to-target" (T2T) recommendations.

Acute flares of gout should be treated as early as possible. Recommended first-line options for acute flare are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed by 0.5 mg per hour till 4 mg on day 1 and / or an NSAID (plus a proton pump inhibitor if appropriate), oral corticosteroids (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine inhibits microtubule polymerization, inhibits activation and migration of neutrophils *to sites of inflammation* and interferes with inflammasome complex that mediate IL-1β activation. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroids (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers and high cost also sets a limit to their usage.

Urate lowering therapy (ULT) should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flare (≥2/year), tophi, urate arthropathy and / or renal stones. All ULTs should be started at a low dose and then titrated upward until the serum uric acid (SUA) target is reached. SUA <6 mg/dL (360 μmol/L) should be maintained lifelong. In patients with normal kidney

function, allopurinol, a xanthine oxidase inhibitor (XOI) is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricemic target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or an uricosuric, or combined with an uricosuric. Febuxostat is a potent non-purine selective XOI approved at daily doses of 80 and 120 mg in Europe. It is metabolized in the liver and renal excretion is not a major route of elimination, which allows for its use in patients with mild-to-moderate kidney failure. In patients with crystal-proven severe debilitating chronic tophaceous gout and poor quality of life, in whom the SUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated. Pegloticase is a pegylated uricase, that catalyzes the oxidation of uric acid into allantoin, a more soluble end product.

Every person with gout should receive advice regarding *lifestyle:* weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.

Every person with gout should be systematically screened for associated *comorbidities and cardiovascular risk factors,* including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout. When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension, consider losartan or calcium channel blockers; for hyperlipidemia, consider a statin or fenofibrate.

12.2. Calcium-pyrophosphate-dihydrate (CPPD) arthropathy

12.2.1. Definition

Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease is an umbrella term encompassing all instances of calcium pyrophosphate dihydrate (CPP) crystal precipitation in connective tissues seen in asymptomatic patients or associated with several clinical syndromes. These include acute CPP crystal arthritis (formerly called „pseudo-gout"), osteoarthritis (OA) with CPPD (formerly „pseudo-OA") and chronic CPP crystal inflammatory arthritis (formerly „pseudo-RA").

12.2.2. Epidemiology

CPPD is mainly a disease of the elderly. Prevalence of radiological chondrocalcinosis (CC) subsequently increases with age and about 30–40% in those aged 85 years or more. There is a female predominance in younger ages but later balanced sex distribution is seen with ageing.

12.2.3. Etiopathogenesis

CPPD may manifest as a primary sporadic (idiopathic) or familial (autosomal dominant) disease, or it can also be secondary to a number of metabolic diseases, including primary hyperparathyroidism, haemochromatosis and hypomagnesemia.

Pyrophosphate (PPi) is a structural component of bone hydroxyapatite crystals and acts as a potent inhibitor of calcification. Pyrophosphate (PPi) is generated from extracellular ATP and forms complexes with calcium to create CPP crystals. CPP crystals induce acute inflammation follows patterns similar to MSU crystal induced inflammation. CPP crystals could also interact with synovial fibroblasts leading to the release of matrix metalloproteinases and other mediators involved in joint destruction.

12.2.4. Clinical presentation

Chondrocalcinosis is most frequently asymptomatic, recognized incidentally on radiographs of elderly individuals. It is also a frequent cause of acute arthritis in the elderly, involving both knees less frequently the wrists, shoulders, ankles or elbows. Severe inflammation of a large joint may be accompanied by fever. Chronic CCPD arthritis may mimic rheumatoid arthritis by long standing bilateral and symmetrical synovitis, involving the wrists, finger joints and tendon sheaths. OA with CPPD is more common at some sites, such as ankles, elbows, wrists and shoulders. Severe osteolysis, destruction and secondary hypertrophic osteophyte formation may also occur.

12.2.5. Diagnosis

Diagnosis is based on the evaluation of crystals from the synovial fluid or joint biopsy. CPP crystals are poorly birefringent and are better seen by regular light microscopy. They have characteristic rhomboid shape with a length of 2–10 mm. The demonstration of typical CC by radiographs of knees is of good diagnostic value. Fine subchondral bone sclerosis is evident in line with the articular surface, moreover affecting soft tissues and the joint capsule as well. Elevated inflammatory markers (ESR, CRP) may be also present.

12.2.6. Differential diagnosis

It should be differentiated from septic arthritis, gout, rheumatoid arthritis, OA and neuropathic arthropathies with the help of the above mentioned diagnostic tools.

12.2.7. Treatment

Acute CPP crystal arthritis is best treated by rest, local ice packs, synovial fluid aspiration and anti-inflammatory drugs. Colchicine or NSAIDs can be used but may be poorly tolerated by the elderly, thus intraarticular steroid injection may be helpful.

In the management of chronic arthropathy, physiotherapy and radiation therapy or radiation synovectomy may be beneficial, but joint replacement must be considered in case of end-stage joint destruction. Magnesium supplementation and chondroprotective agents can be advised in certain situations.

12.3. Basic calcium phosphate (hydroxyapatite) arthropathy

12.3.1. Definition

Acute or chronic inflammation induced by peri- and intraarticular basic calcium phosphate (BCP) crystals deposits.

12.3.2. Epidemiology

There is no accurate data about the prevalence since crystal deposition is usually clinically silent. Calcification can arise in context of various connective tissue diseases (systemic sclerosis, dermato / polymyositis), primary hyperparathyroidism and terminal renal failure.

12.3.3. Etiopathogenesis

Calcification are frequently multiple leading to a hypothesis that systemic factors may play a role in the pathophysiology. Local factors have been incriminated at the shoulder. Traumatic injury, critical ischemia, paresis and metabolic disorders (e.g. diabetes) may be associated with ectopic calcification. Crystals induce metalloproteinases and prostaglandins that will cause destructive inflammatory arthritis.

12.3.4. Clinical presentation

BCP crystals can cause acute tendinitis or bursitis. Periarticular calcification is most frequently found around the shoulder. Pain is of abrupt onset and very

intense leading to severe restriction of movements. Untreated, chronic "frozen shoulder" syndrome may develop. Crystal deposition is more frequent in the knee joint in younger patients while in the middle-aged women small hand joints are involved. Destructive arthropathy affecting the shoulders is called "Milwaukee shoulder" in elderly women.

12.3.5. Diagnosis

Besides clinical symptoms, the diagnosis of periarticular calcifications relies on imaging techniques using X-rays and ultrasound (US). Plain radiographs show homogeneous ovoid opacities especially at the rotator cuff. Joint destruction, erosions and subluxations may be also seen. Definite diagnosis is based on the crystal analyses and in this context, US has been found to be helpful at guiding needle aspiration of the deposit.

12.3.6. Differential diagnosis

Infective arthritis, traumatic injury and synovial tumor need to be excluded.

12.3.7. Treatment

No specific therapy is available, but the aspiration of synovial fluid, and corticosteroid injections are usually helpful with resting position of the joint. Oral analgesics, NSAIDs and colchicine can be used in the acute phase. For chronic illness, physiotherapy, radiation therapy and chondroprotective agents are recommended. In case of Milwaukee-shoulder, arthroscopy or shoulder replacement might be needed.

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13. Systemic autoimmune rheumatic disorders

Gabriella Szűcs

13.1. Introduction

Systemic autoimmune rheumatic disorders (also known as connective tissue diseases) are a group of diseases in which the pathological immune response is directed against a general component of the cell and can cause damage to any organ. Disorders are multifactorial in origin, with genetic, environmental (infections, chemical effects, etc.) and hormonal factors (female dominance) contributing to their development. As a result of various pathological factors, immune dysregulation develops, which leads to the loss of auto-tolerance, and processes led by autoreactive cells and autoantibodies result in organ damage. In addition to the basic similarities, disorders are very diverse, with unique features in terms of pathomechanism and clinical symptoms. In the early stages of the development of systemic autoimmune disorders, immunological abnormalities can be observed without clinical symptoms. It is important that immunoserological abnormalities without clinical symptoms should not be considered as a disease, nor should they be treated, only monitored. The next stage in the development of the disease is the undifferentiated autoimmune disease, followed by the definitive systemic autoimmune disease, with distinctive immunological abnormalities and specific clinical symptoms.

13.2. Undifferentiated connective tissue disease

13.2.1. Definition

Undifferentiated connective tissue disease (UCTD) is when a patient develops some of the symptoms of systemic autoimmune diseases with immuno-serological abnormalities, but these do not exhaust the diagnostic criteria for a definitive systemic autoimmune disease. The development of the disease can be a long-term process, where the immunological abnormalities can precede the onset of symptoms by years.

13.2.2. Clinical picture, diagnosis, course of disease and treatment

The disease often begins with general symptoms, subfebrility, recurrent fever, weight loss, general weakness and fatigue. Common underlying symptoms are arthralgia, arthritis, usually symmetrically affecting the MCP and PIP joints of the hands, wrists, ankles, and knees. Raynaud's phenomenon is characteristic of autoimmune diseases. It is caused by small vessel vasospasm of the fingers, which can cause discoloration of the fingers: after initial whitening, lividness, and after the disappearance of the vasoconstriction, hyperemia occurs (3 phases of Raynaud's phenomenon). Patients may also develop sicca symptoms early, but skin symptoms, recurrent serositis, myositis, abnormalities characteristic of interstitial lung disease, and nervous system symptoms (e.g. neuropathy) may occur as well. Laboratory tests can generally detect higher levels of erythrocyte sedimentation rate and C-reactive protein (CRP) indicative of inflammation. Symptoms characteristic for antiphospholipid syndrome (APS; e.g. habitual miscarriages and thromboembolic events) or proteinuria, hematuria observed in urine samples may also indicate autoimmune disease. Immunserology reveals antinuclear antibody (ANA) positivity, autoantibodies produced against nuclear and cytoplasmic components. Diagnosis of UCTD can be made when at least 2 typical clinical symptoms and a non-organ specific antibody are present.

The *outcome* of UCTD can vary: in 10–15% of patient the symptoms regress, permanently disappear, in 30–35% remain in the NDC stage and in 50–60% of the symptoms complemented and the disease develops into a definitive systemic autoimmune disease.

Treatment of UCTD is largely symptomatic. It is advisable to choose a therapy adapted to the clinical symptoms and organ involvement. Non-steroidal anti-inflammatory drugs may be selected for anti-inflammatory therapy, and in case of more severe symptoms, corticosteroid treatment may be required, and antimalarial agents for joint activity. In case of certain organ manifestations, the therapy also includes complementary immunosuppressive therapy (e.g. interstitial lung disease, etc.), which therapeutic choice is consistent with the therapies used for each definitive disease.

13.3. Systemic lupus erythematosus

13.3.1. Definition and epidemiology

Systemic lupus erythematosus (SLE) is a prototype of systemic autoimmune diseases, a disease affecting multiple organs, with varied clinical and laboratory

findings. It occurs primarily in young women of childbearing potential, aged 16–40 (female: male ratio: 7:1–15:1). Its occurrence is determined by geographical, ethnic, demographic and social factors. Its prevalence is 20–150/100 000 and the incidence is 1–25/100 000. It is more common in African American and Asian populations. The clinical picture is variable, its course is wavering, exacerbations and remission alternate. Within the disease subgroups are distinguished, with different disease course and prognosis. Prognosis depends on gender, age, localization of organ symptoms, inflammatory activity, development of irreversible organ damage, comorbidities and complications.

13.3.2. Etiopathogenesis

The disease is multifactorial, its development is influenced not only by genetic susceptibility but also by the provocative effect of hormonal and environmental factors. The *genetic susceptibility* is partly due to MHC and partly to non-MHC genes, their role has been confirmed in SLE animal models and observed in humans. It is known that the incidence of the disease or other autoimmune diseases is higher in patients with SLE in the family history. The concordance is 24–50% in identical twins. Predisposing genes include genes encoding molecules that regulate lymphocyte signaling and apoptosis, and molecules that regulate apoptotic cell function. Probable susceptibility factors are genetic complement defects.

The role of *hormonal factors* is supported by female dominance. The disease rarely occurs before puberty, relapses are common during pregnancy or in the post-partum period. In addition to genetic and hormonal factors, the development of the disease requires the provocative effect of certain environmental factors (sunlight, UV radiation, medication, infections, etc.).

The *pathogenesis* of the disease is characterized by a complex disruption of immune regulation. As a basic process, the "breakthrough" of autotolerance is primary, with autoreactive T and B cells being activated and persistent. Disruption of increased apoptosis, mechanisms that clear apoptotic debris and pathological immune complexes, damage of DNA repair, and not adequate epigenetic changes, e.g. the disruption of DNA methylation, result in an increased and continuous supply of autoantigens. Activated autoreactive B cells produce pathogenic autoantibodies. Most of them exert their effect by activating complement by classical immune complex mechanism, but also by antibody-dependent cytotoxic processes (e.g. immunocytopenia associated with SLE). In contrast, antiphospholipid antibodies act directly. Enhanced B-cell activity is predominantly T-cell dependent, influenced by increased CD4+ T-helper activity and

decreased regulatory CD4+/CD25+ T-cell activity. In addition to the pathological adaptive immune response, the innate immune response is also affected: pathological macrophage and dendritic cell activation, apoptosis characteristic of neutrophilic granulocytes, and NETosis (neutrophilic extracellular trap) is also enhanced, maintaining a supply of autoantigens. In conclusion, during the immune-complex (IC) process, which is most characteristic of pathogenesis, pathological ICs are deposited in various tissues, where they activate humoral and cellular factors, leading to the release of inflammatory mediators, followed by complement activation, fibroid deposition, and attraction and activation of mononuclear cells, leading to tissue damage. The leading cytokines of the process are B-lymphocyte activating factor (BAFF) and interferon-α, which are also therapeutic targets.

13.3.3. Clinical symptoms

The clinical picture is very diverse, usually characterized by alternating remissions and exacerbations. Initially, clinical symptoms are most commonly *general / constitutional symptoms:* fever, weight loss, weakness, fatigue, and hair loss. It rarely starts in a hyper-acute form with the full spectrum of symptoms, rather it starts with a form that does not have spectacular symptoms.

Skin symptoms occur in the majority of patients. Some of the skin symptoms are lupus-specific: butterfly rash on the face (vespertilio), photosensitivity, acute malar erythema in the form of spots or plaques, and chronic discoid lesions. Non-lupus-specific skin symptoms may include panniculitis, ophiasis or diffuse alopecia, urticaria, various vasculitic skin symptoms, livedo reticularis and Raynaud's phenomenon. In addition to superficial skin symptoms, oral mucosa abnormalities, ulcerations, and nasal septal erosions are characteristic.

Musculoskeletal symptoms are common; occurring in approximately 90% of patients. Arthralgia, symmetrical, non-erosive, and non-deforming polyarthritis is characteristic. In about 5% of cases, deforming polyarthritis (Jaccoud arthropathy) may also occur with ulnar deviation of the fingers. Myalgia and muscle weakness occur mainly as general symptoms and as side effects of corticosteroid treatment; true myositis is rare. Aseptic bone necrosis and osteoporosis may also occur as a side effect of steroid therapy.

Among *pulmonary symptoms,* pleuritis with or without pericarditis may occur. Less common is the development of interstitial lung disease with restrictive ventilation. Bronchiolitis obliterans and alveolitis may occur. Hemorrhagic alveolitis, a serious life-threatening condition, is a very rare manifestation of SLE. Pulmonary hypertension is also a rare and serious symptom. Secondary

antiphospholipid syndrome associated with SLE may result in pulmonary embolism.

Cardiovascular symptoms are characteristic in 50–60% of patients. Pericarditis is common, with myocarditis occurring in half of the patients, but disturbances in stimulus generation and signal conduction, and valvulopathy also occur. Non-infectious, verrucous Libman-Sacks endocarditis is typical in SLE. Accelerated arteriosclerosis and its complication, coronary artery disease, must be taken into account during a long-term disease.

Renal involvement is a negative prognostic factor for patient survival. Clinically, it may occur in any kidney syndrome: may include minimal proteinuria and hematuria, nephrosis syndrome, progressive renal disease with hypertension, impaired renal function, and eventually renal failure. Renal biopsy should be performed if clinical symptoms and urinary examination suggest renal involvement. From the biopsy sample, localization, activity and chronic nature of the process can be reported based on International Society of Neurology / Renal Pathology Society (ISN / RPS) classification *(Table 13.1.)*. Planning of the treatment can also be adapted to this.

The appearance of *neuropsychiatric* (NP) symptoms in addition to renal involvement is another poor prognostic factor. It also affects the central, peripheral and vegetative nervous systems. Symptoms are varied, usually not specific to SLE; other illnesses can cause similar symptoms. The classification of lupus NP symptoms according to the American College of Rheumatology (ACR) is described in *Table 13.2.*

Other organ manifestations may include hepatosplenomegaly, lymphadenomegaly (generalized and reactive), sicca symptoms, especially keratoconjunctivitis sicca and ophthalmic symptoms (retinal vasculopathy, chorioretinitis and optic neuritis). Gastrointestinal symptoms are rare in SLE, however are more likely to be side effects of long-term medication, in rare cases vasculitis or thrombotic processes affecting the visceral vessels may be the cause.

Table 13.1. ISN/RPS classification of lupus nephritis based on histopathological signs

Class	Type	Characteristics
I.	Minimal mesangial nephritis	Negative light microscope image, but mesangial deposits may be shown by electron microscopy or immunofluorescence
II.	Mesangial proliferative lupus nephritis	Mesangial hypercellularity or widening of the mesangial matrix by immunodeposits

Class	Type	Characteristics
III.	Focal lupus nephritis (involving <50% of glomeruli)	*a)* Active lesions: focal proliferative GN *b)* Active and chronic lesions: focal proliferative and sclerosing GN *c)* Chronic inactive lesions with glome rular scarring: Focal sclerosing GN
IV.	Diffuse lupus nephritis (involving >50% of glomeruli)	Active or inactive, segmental or global endo- or exocapillary GN, with or without subendothelial immunodeposit and mesangial involvement. This group can be further divided into diffuse segmental (IV-S) type, when only a portion of the involved glomeruli is affected, and diffuse global (IV-G) type, in which the whole glomerulus is involved. Each can be active or chronic.
V.	Membranous lupus nephritis	Global or segmental subepithelial immunodeposit detectable with light, electron or immunofluorescence micro-scope, with or without mesangial variations It may occur with Class III or Class IV variations.
VI.	Sclerosing glomerulonephritis	Sclerosis and scarring can be observed in at least 90% or more of glomeruli, without active tissue inflammation

Table 13.2. Classification (ACR) of neuropsychiatric symptoms of SLE

Central nervous system symptoms	Peripheral nervous system symptoms
Aseptic meningitis Cerebrovascular lesion Demyelination syndrome Headache (including migraine) Chorea Myelopathy Epilepsy Psychosis Acute confusional state Cognitive dysfunction Behavior disorders Anxiety	Guillain-Barré syndrome Disorders of the autonomic nervous system Mononeuritis simplex / multiplex Myasthenia gravis Cranial neuropathy Polyneuropathy Plexopathy

Hematological abnormalities, normocytic anemia, autoimmune hemolytic anemia (with direct Coombs positivity), leukopenia, including lymphopenia and thrombocytopenia may accompany the disease. SLE can be associated

with secondary antiphospholipid syndrome (APS), where the diverse vascular symptoms of SLE are accompanied by the characteristic vascular symptoms of antiphospholipid syndrome.

Immunological abnormalities: The disease is characterized by the presence of a variety of autoantibodies, among those used in day-to-day diagnostics include ANA: anti-dsDNA (anti-double-stranded DNA antibody), anti-Sm (autoantibodies against Smith antigen), anti-SSA, anti-SSB, and antiphospholipid antibodies such as anti-CL (cardiolipin), anti-β2-glycoprotein (B2GP) and LA (lupus anticoagulant). Anti-nucleosome antibody and anti-C1q is characteristic in lupus nephritis. Due to the complement utilization of the immune complex mechanism, low total complement activity (CH50), and decreased C3 and C4 levels are observed. High B cell activity usually results in high polyclonal immunoglobulin levels. In active disease, general signs of inflammation, such as elevated Westergren values, can be detected. Importantly, an increase in C-reactive protein (CRP) is not typical of SLE activity, but high levels suggest an infectious process.

13.3.4. Diagnosis

The most important is the recognition of autoimmune system disorders and the exclusion of other diseases causing systemic symptoms (malignant diseases, infection, other inflammatory rheumatic-immunological disorders). Diagnosis is supported by the 2012 SLICC (Systemic Lupus International Collaborating Clinics) revised criteria system for classification *(Table 13.3.)*. In order to establish a treatment plan, it is absolutely necessary to clarify SLE activity, to assess organ manifestations and the damage with appropriate diagnostic tests.

13.3.5. SLE subgroups

Within the disease subgroups are distinguished, with different course of disease and prognosis.

Subacute cutan lupus erythematosus (SCLE): characterized with predominant skin symptoms, good prognosis, symmetrical, non-fixated, non-scarred exacerbating-remitting subacute cutan lesions on the face, neck and upper torso. Skin symptoms may include maculosquamosus, psoriasiform or annular symptoms. May be accompanied by polyarthritis and marked photosensitivity. Anti-SSA positivity is characteristic.

Table 13.3. SLE classification criteria (EULAR/ARC, 2019)

Inclusion criterium: ANA≥1:80 (HEP-2 on the cell or with an equivalent test)			
Clinical domains and criteria	**Score**	**Immunological domains and criteria**	**Score**
Constitutional		**Antiphospholipid antibody**	
Fever	2	Anti-cardiolipin or	
		Anti-ß2GP1 or	
Hematological		Lupus anticoagulant	2
Leukopenia	3		
Thrombocytopenia	4	**Complement proteins**	
Autoimmune hemolysis	4	Low C3 or low C4	3
		Low C3 and low C4	4
Neuropsychiatric			
Delirium	2	**SLE-specific antibodies**	
Psychosis	3	Anti-dsDNA or	
Convulsion	5	Anti-Smith	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulceration	2		
Subacute cutan or discoid lupus	4		
Acute cutan lupus	6		
Serositis		*Required:*	
Pleural or pericardial liquid	5	*inclusion criterium*	
Acute pericarditis	6	*+ ≥10 score*	
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5 g / 24 h	4		
Kidney biopsy: Class II or V lupus nephritis	8		
Kidney biopsy: Class III or IV lupus nephritis	10		

Drug-induced lupus: develops mainly in the elderly, among the so-called slow acetylators; shows HLA-DR4 association and affects the genders almost equally. It is usually triggered by drugs containing hydrazine, amino and sulfhydryl groups (hydralazine, procainamide, penicillamine, captopril, hydantoin derivatives, quinidine, etc.). Respiratory abnormalities, renal and central nervous system manifestations may occur. Antihistone antibody positivity is common. It is usually a reversible disease, the symptoms disappear after the drug ceases to work.

Neonatal lupus develops rarely in newborns of pregnant women with anti-SSA / Ro positive, less frequently anti-SSB / La positive SLE, due to autoantibodies crossing the placenta. Newborns are characterized by diffuse maculopapular skin rashes at birth, which disappear in weeks or months as maternal antibodies clear from their bodies. Hepatosplenomegaly, hemolytic anemia and thrombocytopenia can also be observed. The most important but rare complication of maternal anti-SSA positivity is congenital heart block in the fetus, which occurs between 18 and 28 weeks of gestation. Increased, frequent fetal ultrasound monitoring is required in these cases.

Lupus in the elderly usually occurs above 60 years of age with predominant musculoskeletal symptoms. It is a benign disease with a milder course, serositis, skin symptoms, pulmonary fibrosis and sicca symptoms.

13.3.6. Treatment

Treatment of SLE is a multidisciplinary task, with the goal of bringing the disease to an inactive stage and maintaining it, ensuring long-term patient survival, preventing irreversible organ damage, and ensuring an appropriate quality of life. The choice of the optimal therapeutic combination depends on the present organ manifestations, the activity of the disease, and the presence of irreversible organ damage. In the therapeutic decision, a distinction should be made between mild disease not involving major organ manifestation and moderate / severe disease with major organ involvement.

Generally, it is recommended that, unless contraindicated, all SLE patients be treated with an antimalarial agent (primarily hydroxychloroquine, or chloroquine) with appropriate ophthalmic control. In addition, all patients should receive vitamin D3 substitution.

In the treatment of mild SLE, patient education, providing information and lifestyle tips, appropriate sun protection, avoiding UV radiation and using sunscreens is paramount. The treatment of musculoskeletal disorders may include analgesics and nonsteroidal anti-inflammatory drugs. Antimalarial agents are suitable for the treatment of skin and joint symptoms. In many cases, mild disease may require low-dose corticosteroid (CS) treatment (<15 mg prednisolone or equivalent), which in some cases may be omitted during the inactive phase.

Intensive immunosuppressive therapy is the basis of *moderate / severe SLE treatment.* In practice, the treatment of severely ill patients consists of two phases: the purpose of induction treatment is to prevent and stop organ damage, and, if possible, restore organ function. This is followed by less intensive main-

tenance therapy aimed at maintaining remission and preventing relapses. The dose of CS treatment and the mode of administration depends on the nature and severity of the process – low, medium, high dose, and pulse steroid treatment. Additional immunosuppressive agents is also required if the process is unresponsive to the primary treatment; the steroid dose cannot be reduced to the appropriate maintenance dose in lupus nephritis (Class III, IV and V), and severe thrombocytopenia, severe hemolytic or aplastic anemia, steroid nonresponsive immune neutropenia, hemorrhagic alveolitis, abdominal vasculitis and in case of severe nervous system involvement. Cyclophosphamide (CYC) is recommended for induction therapy and azathioprine (AZA) is recommended for maintenance therapy. Mycophenolate mofetil (MMF) is effective in lupus nephritis, while methotrexate (MTX) treatment can be considered in polyarthritis. Cyclosporin A (CSA) is recommended primarily for membranous glomerulonephritis but may also be used for hematological abnormalities such as thrombocytopenia and aplastic anemia. Multitarget therapy, co-administration of MMF + calcineurin inhibitor, may be appropriate for severe nephrotic syndrome and incomplete renal response. The dose of CS maintenance treatment is optimally <7.5 mg / day prednisolone equivalent, which in case of persistent remission should be completely omitted. If the patient does not respond well to standard treatment, targeted biological therapy, such as anti-B cell therapy (anti-BAFF – belimumab, anti-CD20 – rituximab), may be considered.

Other options: high dose intravenous immunoglobulin (IVIG) is recommended for refractory thrombocytopenia and autoimmune hemolytic anemia. Plasmapheresis may be warranted for cytopenia, in case of associated cryoglobulinemia, severe CNS manifestation, and thrombotic thrombocytopenic purpura. Chronic dialysis is required for end-stage renal disease and kidney transplantation is also considered. Finally, based on strict criteria system, autologous stem cell transplantation is recommended for severe, refractory SLE patients.

In SLE, besides treating the underlying disease, it is also important to treat co-morbidities. Antiphospholipid antibody screening and thrombocyte aggregation inhibitor therapy initiation is required in case of high thrombotic risk. Prevention and treatment of osteoporosis, screening and prevention of cardiovascular disease are recommended in accordance with international recommendations. Due to the underlying disease and immunosuppressive treatment, patients are at increased risk of infections, therefore, it is recommended that all patients be given the specified vaccines (primarily against influenza and Pneumococcal vaccines) on the basis of appropriate criteria.

13.3.7. SLE and pregnancy

In SLE, the outcome of pregnancy is less favorable than in the normal population, with a higher risk of miscarriage and premature delivery; during pregnancy the underlying disease may flare up, the risk of thrombosis may increase, and neonatal lupus may develop in newborns. For these reasons, choosing the date of pregnancy is essential; the best outcome of pregnancy is associated with 6–12 months long remission and stable renal function. Pregnancy is not recommended in case of active lupus nephritis and neuropsychiatric symptoms.

Corticosteroids, azathioprine, hydroxychloroquine, low-dose aspirin and, if necessary, LMWH (low molecular weight heparin) or IVIG may be used to treat patients with SLE during pregnancy. Based on the evidence so far, CYC, MTX and MMF cannot be given. To prevent pregnancy, the use of oral estrogen contraceptives is recommended for patients who are inactive or have only mild disease activity. Not recommended in case of patients with moderate / severe illness or who have antiphospholipid antibody positivity, which may increase the risk of developing APS when taken with contraceptives.

13.3.8. Prognosis

Along with early diagnosis and differentiated therapy, SLE survival has improved in recent decades. The most common cause of death in the first 5 years is renal or central nervous system manifestation, and in the late stages cardiovascular and cerebrovascular diseases and thromboembolic complications, tumors, and infections in both stages. In addition to screening for co-morbidities, monitoring of side effects of long-term medication is warranted.

13.4. Antiphospholipid syndrome

13.4.1. Definition and epidemiology

Antiphospholipid syndrome (APS) is a systemic autoimmune disease induced by anti-phospholipid autoantibodies with the development of clinically thrombotic events (arterial or venous thrombosis and / or pregnancy morbidity). Its primary form is an independent disease without underlying disease, and its secondary form is associated with some other disease (e.g. systemic autoimmune diseases, primarily SLE, malignant diseases, infections, hematological disorders, drug-induced forms, chronic renal failure, and dialysis). The frequency of APS is not known. The anti-phospholipid antibody is detectable in 2% of the average population.

13.4.2. Etiopathogenesis

The exact mechanism by which the disease develops is not known. It is influenced by genetic factors in the background, and the provocative role of environmental factors such as infections is known. Antiphospholipid antibodies (APAs) are IgG, IgA or IgM immunoglobulins that react with neutral or negatively charged phospholipid structures (cardiolipin, phosphatidyl inositol, phosphatidyl serine, phosphatidyl ethanolamine, phosphatidyl choline, etc.) and / or glycoprotein antigens (β2-glycoprotein 1, annexin V, prothrombin, protein C and S, and heparan sulfate). The pathomechanism is complex, antibodies are prothrombotic, proatherogenic, inhibit endogenous anticoagulants (activated protein C, antithrombin III, etc.), binding to endothelium activate endothelial cells, and directly activate lymphocytes. Together, these factors lead to thrombosis in the blood vessels.

13.4.3. Clinical symptoms and diagnosis

Leading symptoms of APS include thrombosis (venous and arterial) in various organs and pregnancy morbidity (repeated miscarriages, late fetal death, premature birth, placental detachment, intrauterine retardation, etc.). The most common symptom is peripheral arterial or venous thrombosis (lower limb deep vein thrombosis with or without pulmonary embolism, lower limb arterial, venous subclavian or jugular vein thrombosis), but can affect the central nervous system, pulmonary arteries or abdominal organs (kidney, spleen, liver, gastrointestinal tract). Skin symptoms (livedo reticularis, gangrenes and ulcers) and musculoskeletal symptoms (arthralgia, arthritis, and avascular bone necrosis) are also common in this disease.

Hematological abnormalities predominantly occur in the forms of thrombocytopenia or hemolytic anemia. Overall, the clinical picture is always influenced by the symptoms of the organ damage. Catastrophic APS (CAPS) is a severe form of APS that affects at least 3 vital organs simultaneously (most commonly the brain, lung, kidney, and gastrointestinal tract), with half of the cases being fatal.

Diagnosis of APS requires repeated anti-cardiolipin (CL) or anti-β2-glycoprotein (B2GP) or lupus anticoagulant (LA) positivity in medium or high titer repeatedly twice with 3 months apart, in addition to a thrombotic clinical symptom *(Table 13.4.)*.

Table 13.4. Classification criteria for antiphospholipid syndrome (Sydney criteria revised in 2006)

Clinical criteria	Laboratory criteria
1. *Vascular thrombosis* Thrombosis of one or more arteries, veins or small vessels of in any organ, tissue (should be confirmed by imaging or histology) 2. *Pregnancy-related pathology* *a)* Repeated spontaneous abortion: ≥3 times before the 10th week of pregnancy *b)* Premature birth: On week 34 or before with symptoms of morphologically normal fetus, placental failure, severe preeclampsia, and eclampsia *c)* Stillbirth: morphologically intact fetus at or after 10 weeks of gestation *d)* Other complications: eclampsia, placental abruption and intrauterine fetal retardation	1. Lupus anticoagulant (LA) 1 or 2 times, at least 12 weeks apart 2. Anticardiolipin IgG or IgM antibody at medium or high titers at least 2 times 12 weeks apart 3. Anti-β2-glycoprotein 1 IgG or IgM antibody more than once at least 12 weeks apart

13.4.4. Treatment

In primary APS, treatment of the thromboembolic process is essential, while in secondary APS, adequate treatment of the underlying disease is also required. No treatment is required for asymptomatic APA positivity; results on primary prophylaxis of thrombosis are ambiguous. (However, due to the higher risk associated with persistent presence of 3 APAs, consideration should be given to low-dose acetylsalicylic acid treatment). If venous thromboembolism occurs, initial heparin administration is recommended, followed by oral anticoagulant therapy (target INR: 2–3). Warfarin / coumarin treatment is usually recommended to be a life-long treatment in primary APS. For recurrent venous thrombosis, INR should be adjusted to 3–4. Arterial thromboses primarily affect the cerebrovascular system and warfarin or low-dose aspirin treatment is equally recommended, according to the Antiphospholipid Antibody in Stroke Study. There are several options for recurrent arterial thrombosis in a properly anticoagulated patient: adjusting warfarin / coumarin therapy to a higher INR 3–4), switching to LMWH therapy or adding thrombocyte aggregation inhibitor (aspirin, ticlopidine) to warfarin / coumarin therapy. Corticosteroid treatment alone has no proven efficacy in APS, but it is absolutely necessary to monitor the underlying disease in secondary APS when it is active. The therapeutic

efficacy of the new type direct oral anticoagulant is unclear, therefore, they are currently not recommended for the prevention of secondary thrombosis in primary APS or in case of SLE-APS. In the treatment of difficult-to-treat APS and recurrent thromboses may also include hydroxychloroquine, statin, IVIG, plasmapheresis or rituximab, which are aimed at reducing thrombotic risk.

In pregnancy, the treatment of APS is based on specific criteria. Prophylactic LMWH and low-dose aspirin therapy are recommended for APA-positive pregnant women who have not had thrombosis, but have a history of one or more miscarriages after the 10th week of pregnancy. Aspirin is recommended to be started at conception, and LMWH is sufficient to be started after the confirmation of pregnancy. Pregnant women who have had thrombosis during pregnancy in association with APS require full-dose treatment with LMWH in addition to aspirin. Due to increased risk of thrombosis in the post-partum period, continuing treatment is recommended until post-partum week 8–12th, then tapering the dose till omitting. If the pregnant patient was on warfarin / coumarin therapy even before pregnancy or had thrombosis during pregnancy, oral anticoagulant therapy should be reinstated in the post-partum period.

In case of CAPS, early diagnosis and initiating adequate treatment, including elimination of the underlying cause (e.g. infection), anticoagulant therapy, CS therapy complemented with plasmapheresis and / or IVIG, as soon as possible is critical. In case of resistant CAPS, therapy may also include rituximab or anti-C5 monoclonal antibody and eculizumab therapy.

13.5. Systemic sclerosis (scleroderma)

13.5.1. Definition and epidemiology

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by connective tissue proliferation and fibrosis. Systemic sclerosis affects the skin, peripheral and visceral vessels and internal organs. The disease mainly occurs in women, usually between the ages of 45 and 65. SSc is a rare disease prevalence of 1.4–5.6 / 100 000 and an incidence 0.6–2.3 / 100 000 / year.

13.5.2. Etiopathogenesis

The role of genetic abnormalities (both HLA and non-HLA genes) in the development of the disease is considered. Mutation of the fibrillin gene has been confirmed among Choctaw Indians, where scleroderma is more common. There is a clear association between scleroderma-specific autoantibodies and certain

HLA haplotypes. The provocative role of environmental factors, such as prolonged exposure to chemicals and organic solvents or physical causes (e.g. exposure to vibration), viral infections and certain medications, has been proven. In addition, persistent microchimerism (the persistence of fetal cells that made it into the maternal circulation during pregnancy) may be implicated in the development of the disease.

Pathogenesis is characterized by three factors side by side: 1. abnormalities of the microvasculature and microcirculation with endothelial damage; 2. immunopathological changes; 3. pronounced collagen and extracellular matrix accumulation in the skin and internal organs.

The damage to the vasculature is primary, where microcirculatory dysfunction is due to pathological endothelial cell activation, endothelial degeneration, basal membrane injury, and increased vasoconstrictive tendency of small vessels. These together lead to vascular obstruction, obliterative vasculopathy, decrease in the number of capillaries, dilation of the remaining capillaries (giant capillaries), resulting in hypoperfusion and nutritive disorder of the given organ. The cytokine responsible for increased vasoconstriction is endothelin-1. Vascular lesion is also crucial for fibroblast activation.

In the process of pathological fibrosis, the proliferation capacity of activated fibroblasts and myofibroblasts is increased, their extracellular matrix and collagen production is increased, while the activity of the enzymes and metalloproteinases involved in their degradation decreases. TGF-β plays a crucial role in the development of fibrosis, but the production of several cytokines and growth factors (IL-2, IL-4, IL-6, IL-8, TNFα, PDGF, etc.) differs from normal during the pathomechanism.

Changes in humoral immunity are characterized by the appearance of ANA, anti-Scl70 (anti-DNA topoisomerase-1 antibody), anti-centromere (ACA), anti-RNA polymerase I and III, and anti-fibrillarin antibodies. Cellular immune processes also change in the disease. In the skin, a higher proportion of CD4-positive cells, including Th2 cells, and in the lungs, a higher proportion of CD8-positive cells can be observed.

13.5.3. Clinical symptoms

SSc is a chronic disease that progresses without spectacular remission or exacerbations. The appearance of clinical symptoms and their severity differ between the two major groups of scleroderma. In diffuse cutaneous systemic sclerosis (dcSSc), within one year after the onset of Raynaud's syndrome, internal organ manifestations appear, which are more severe than those seen in the lim-

ited form of the disease. Skin symptoms also involve the skin of the torso. In limited cutaneous systemic sclerosis (lcSSc), the Raynaud's phenomenon precedes the development of other scleroderma symptoms by years. Severe pulmonary, cardiac or renal disease is rarely observed in patients, however, pulmonary arterial hypertension (PAH) is more common. Skin symptoms affect the acral areas. CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome is a variant of the limited form with characteristic symptoms, accompanied by ACA positivity in 80% of the cases. As a rare form scleroderma-specific fibrosis of the internal organs without skin symptoms – scleroderma sine scleroderma – can occur. SSc can also occur with other systemic autoimmune disease, in the form of a SSc-overlap.

Skin symptoms: almost 100% of patients experience Raynaud's phenomenon. Thickening and tightening of the skin of the fingers (sclerodactyly), perioral sclerosis and reduced aperture of the mouth is characteristic. Proximal scleroderma is a condition where the scleroderma skin symptom also affects areas proximal to the metacarpo-phalangeal joints. Hypo- and hyperpigmentation, telangiectasia, subcutaneous calcinosis, digital ulcers, and digital pitting scars may also occur.

Musculoskeletal symptoms: common initial symptoms include polyarthralgia, myalgia, and muscle weakness, and muscle atrophy develops in a later stage. In some cases, scleroderma polymyositis overlap occurs. Due to circulatory dysfunction, acral osteolysis of the fingers, absorption of the distal phalanx and surrounding soft tissues can be observed.

Pulmonary symptoms are common in scleroderma. Pulmonary fibrosis usually occurs in more severe forms of dcSSc, particularly in cases of anti-Scl70 antibody-positivity, while pulmonary vascular disease and consequent PAH is more common in the limited form. Respiratory function tests indicate restrictive ventilation defect in nearly 80% of patients and also reduce the diffusion capacity (DLCO). Pulmonary fibrosis is usually preceded by fibrotic alveolitis, which can be confirmed by high resolution CT or bronchoalveolar lavage.

Cardiac involvement is also common, with underlying myocardial microcirculation disorder and fibrosis. It is manifested in the form of pericarditis, congestive heart failure, impulse generation, and signal transduction disorders. Firstly, left ventricular diastolic dysfunction can be observed, and later on, systolic function declines with symptoms of cardiac decompensation.

Renal involvement: kidney manifestation with clinically poor prognosis occurs in the first years of dcSSc. The most important symptom is the development of accelerated hypertension and rapid progressive renal failure, the so-called

scleroderma renal crisis, which is caused by obliterative renal vasculopathy. In rare cases, renal crisis may also occur in normotensive form.

Gastrointestinal symptoms: Gastrointestinal problems affect 80–90% of patients. The most common is esophageal dysfunction (primarily in the lower third of the esophagus), with dysphagia, dyspepsia, and symptoms of gastroesophageal reflux. The motility disorder can also affect the stomach, small intestine and large intestine, which manifests in the form of nausea, vomiting, obstipation and malnutrition. Gastrointestinal hemorrhage rarely occurs, primarily from erosions, rarely from the antrum, due to vascular ectasia (watermelon stomach). Broad-based diverticula are characteristic of the colon. Fibrosis can lead to anorectal dysfunction with fecal incontinence.

Other symptoms include sicca syndrome (due to the fibrotic process of salivary and lacrimal glands), peripheral neuropathy, carpal tunnel syndrome and trigeminal neuralgia. Fertility problems, spontaneous abortion, premature birth, or low birth weight newborns are more common in scleroderma patients.

Serological symptoms: ACA positivity is more common in mild cases, but pulmonary hypertension, digital amputation and biliary cirrhosis may also develop as well. Anti-Scl70 and anti-RNA polymerase III is associated with a more severe cardiac and renal involvement characteristic of dcSSc; anti-RNA polymerase III antibody is also associated with a higher risk of malignancy. Anti-PM-Scl and anti-Ku antibody are characteristic of scleroderma- polymyositis overlap syndrome.

13.5.4. Diagnosis

Early diagnosis of SSc is essential for early treatment. Very early SSc is considered when a patient has a combination of Raynaud's phenomenon, puffy fingers, and nailfold capillary abnormalities examined with capillary microscopy, and at least one scleroderma-specific antibody (ACA, anti- Scl70 or anti-RNA polymerase III) positivity. The ACR / EULAR classification criteria established in 2013 help to identify SSc patients *(Table 13.5)*.

Table 13.5. ACR / EULAR classification criteria 2013 for systemic sclerosis*

Criteria	Subcriteria	Score**
Thickening of the skin on the fingers and hands on both sides proximal to the metacarpophalangeal joints	–	9
Thickening of the skin on the fingers (only the highest score is counted)	Puffy fingers Sclerodactyly	2 4
Digital lesion (only the highest score is counted)	Digital ulcers Digital pitting scars	2 3
Telangiectasia	–	2
Abnormal nailfold capillary pattern	–	2
Pulmonary arterial hypertension and / or interstitial lung disease (maximum score 2)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's ' phenomenon	–	3
SSc-dependent autoantibody (anticentromere, anti-topoisomerase I-Scl70, anti-RNA polymerase III (maximum score 3)	Anticentromere, Anti-topoisomerase I, Anti-RNA polymerase III	3

* *These criteria can be used for patient enrollment in SSc. It should not be used in patients whose symptoms could be explained by other diseases better (e.g. scleromyxedema, scleroderma diabeticorum, eosinophilic fasciitis, generalized morphea, porphyria, lichen sclerosis, nephrogenic systemic fibrosis, etc.).*

** *The total score is the sum of the points in each category. Definitive SSc can be classified if the patient has a score of ≥9.*

From a differential diagnostic point of view, the disease should be differentiated from any disorder with scleroderma-like symptoms: e.g. amyloidosis, sclerosis / scleromyxedema, eosinophilic fasciitis, hypothyroidism, chronic graft versus host disease, porphyria cutanea tarda, phenylketonuria, progeria, carcinoid syndrome, localized lipoatrophy, etc.

13.5.5. Treatment

The preparation of the treatment plan requires proper diagnosis of SSc, determination of its duration, subgroup classification, determination of the severity of each organ manifestation, assessment of the risk of disease progression, patient education, and psychological guidance.

The purpose of the drug treatment is to alleviate the patient's symptoms, to prevent possible complications or to slow the progression of the developed abnormalities. Real, disease modifying therapy is unknown. The three targets of

the therapy are immunomodulation / immunosuppression, reduction of vascular ischemia and slowing down of fibrosis. There is no evidence-based therapy for the latter in clinical practice.

Immunomodulation / immunosuppression: The efficacy of *cyclophosphamide* has been confirmed in pulmonary fibrosis, fibrotic alveolitis, or in case of rapidly progressing diffuse skin symptoms. *Methotrexate* treatment is indicated for SSc patients with early diffuse skin symptoms where no other immunosuppressive therapy (e.g. CYC) is required based on other organ involvement in case of overlap myositis, polyarthritis or RA. *Azathioprine* is considered as maintenance treatment after CYC therapy in pulmonary manifestation, fibrosis or alveolitis. *Mycophenolate mofetil* is as effective as CYC in the treatment of pulmonary fibrosis. Immunosuppressive treatment with *corticosteroids* is required for certain symptoms of scleroderma – e.g. fibrotic alveolitis, polyarthritis, pericarditis, associated myositis. In these cases, only low-dose, short-term steroid treatment is recommended as higher doses (>20 mg / day prednisolone) of long-term CS treatment can provoke scleroderma renal crisis (SRC). Therefore, if steroid therapy is used in patients with scleroderma, close monitoring of blood pressure and renal function is strongly recommended.

Other immunosuppressive / immunomodulatory therapy: in early dcSSc, where the risk of disease progression is extremely high, and, therefore, the patient's life expectancy is poor, based on strict criteria autologous hematopoietic stem cell transplantation can be recommended. There is increasing evidence on the use of certain biological therapies, e.g. anti-IL6R tocilizumab or anti-CD20 rituximab treatment may be effective in lung manifestation. There are results for photopheresis, plasmapheresis and IVIG therapy, however there are not widespread.

Vascular therapy: the purpose of treatment is to treat circulatory dysfunction (of the skin and internal organs) and Raynaud's phenomenon caused by microvascular abnormalities, and to improve symptoms. Non-pharmacological part of vascular therapy includes quitting smoking, protecting from the cold, and keeping one's hands warm. *Calcium channel blockers* may be used as first-line treatment (dihydropyridine-type agents), which are the basis for the treatment of peripheral ischemic symptoms in addition to pulmonary hypertension. *Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB)* can be chosen. The beneficial effect of ACE inhibitors in case of SRC is clear. Other vasodilator treatments are also possible: alpha-blockers, nitric oxide donors (isosorbide mononitrate, glycerol trinitrate) and nitroglycerin. *Prostanoids and prostacyclin analogues* are available for treatment of severe Raynaud's phenomenon, digital ulcers and NYHA stage III-IV PAH, while

phosphodiesterase inhibitors (e.g. sildenafil, tadalafil) and endothelin-1 receptor antagonists (e.g. bosentan, macitentan, ambrisentan) are recommended in SSc-PAH treatment. Other drugs already used in the treatment of idiopathic PAH (e.g. riociguat, prostacyclin receptor agonist) may be introduced to the treatment of SSc. Other treatments to improve vascular symptoms include pentoxifylline, which increases the flexibility of red blood cells; the pleiotropic effects of statins can be exploited through their improving effects on endothelial dysfunction.

As an *inhibition for fibrosis,* in 2019, the FDA registered tyrosine kinase inhibitor nintedanib in SSc-associated interstitial lung disease (SSc-ILD).

Proton pump inhibitors, H2 receptor blockers, and motility enhancers may be used *to treat organ symptoms.* Malabsorption requires adequate energy, protein and vitamin supplementation. Appropriate antibiotic treatment is recommended for symptoms of small and large intestine hypomotility, bacterial overgrowth and pseudoobstruction.

Supportive therapy: cold prevention, proper physiotherapy, massage to soften the skin and prevent contractures. In case of digital ulcers, in addition to the aforementioned medical treatment, local treatment of ulcers and treatment of infections is necessary.

13.5.6. Prognosis

Patients' survival is primarily determined by the severity of organ manifestations and the degree of damage, including lung, kidney and heart involvement. Diffuse form, late disease onset, and male gender mean worse prognosis. Survival can be improved by early detection and early treatment of organ symptoms of the disease, which clearly requires close and regular monitoring of patients.

13.6. Inflammatory muscle diseases (idiopathic inflammatory myopathies; myositis)

13.6.1. Definition and epidemiology

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune diseases that share a common feature of chronic, immune-mediated inflammation of striated muscles, leading to progressive muscle weakness. They are rare diseases with an incidence of 0.1–1 / 100,000 / year and a prevalence of 1–6 / 100,000. The male to female ratio is 1:2. IIM has several clinical subgroups with different frequency, histology, syndromes, course, and prognosis *(Table 13.6.)*.

Table 13.6. Clinicopathological classification of inflammatory muscle diseases

Group	Type
I.	Adult onset polymyositis (PM)
II.	Adult onset dermatomyositis (DM)
III.	Juvenile PM / DM
IV.	PM / DM in association with other autoimmune diseases (overlap – OM)
V.	Inclusion body myositis (IBM)
VI.	Necrotizing autoimmune myopathy (NAM) • Cancer-associated myositis (CAM) • Statin-induced myopathy • Infection-induced myopathy

13.6.2. Etiopathogenesis

Genetic and environmental factors both play a role in the disease development. Immunological processes are different for polymyositis (PM) and dermatomyositis (DM). PM is primarily mediated by cell-mediated processes. Initially, an increased expression of MHC-1 occurs in muscle fibers, followed by macrophage and CD8+ cytotoxic T-cell infiltration, which develops endomysially. The latter are responsible for the development of muscle damage. In DM, the humoral immune response dominated by the involvement CD4+ T cells and B cells. During the immune process, inflammatory infiltration can be detected perivascular in the muscles. During endothelial damage, IgG and IgM deposition occurs in the capillary wall, leading to damage of the capillaries through complement activation. In IBM, muscle fiber degeneration and variable degree of inflammatory infiltration, while in NAM, muscle fiber necrosis is the leading pathologic abnormality.

13.6.3. Clinical symptoms

General symptoms, fever, weight loss, and weakness may occur in the acute phase. Clinical symptoms suspected of myositis are primarily led by proximal limb muscle weakness and pain with difficulty in lifting arms, standing up, and going up stairs. In case of pharyngeal and respiratory muscle involvement, speech and breathing become difficult. Besides muscle symptoms, characteristic skin symptoms can also be seen in DM. Pathognomy symptoms include Gottron papule (reddish papules over the MCP and PIP joints) and Gottron's sign (purple macula on the stretching surface of the joints due to vasculitis, e.g. knee), and characteristic symptoms include heliotrope rash (purple discoloration of the eyelids), and cervical erythema (shawl symptom). Calcinosis can develop in the

skin, but can also affect the muscles in the form of myositis ossificans. Other organ manifestations may include arthritis, myocarditis with arrhythmias, pulmonary fibrosis, fibrotic alveolitis with dyspnea and dry cough, gastrointestinal symptoms, especially dysphagia due to the muscles involved in swallowing, which can also cause pneumonia due to aspiration. Symptoms of inclusion body myositis occur primarily in males over 50 years of age and, in addition to proximal muscles, affect distal muscles as well.

13.6.4. Diagnosis

Diagnosis is based on the recognition of characteristic clinical symptoms. Among laboratory examinations, elevated levels of serum creatinine kinase (CK) and lactate dehydrogenase (LDH) are characteristic. (Note that GOT and GPT may also be elevated in myositis, therefore testing for liver disease may be omitted in case of muscle pain and muscle weakness.) Diagnosis can be supported by distinctive electromyographic (EMG) abnormalities and histological findings in muscle biopsy. The Bohan-Peter criteria system is used in DM / PM diagnosis *(Table 13.7.)*. The criteria system allows for making a reliable, probable and possible diagnosis. As the results of EMG and muscle biopsy are altered by steroid treatment, if myositis is suspected, tests should be performed prior to initiating treatment, taking into account that treatment should be initiated as soon as possible.

The autoantibodies present in the disease may be myositis-associated (MAA) and myositis-specific antibodies (MSA). Based on specificity several subgroups of the disease can be distinguished, all of which have different treatment strategies. The most important of these is the anti-Jo1 antibody (20–30% of adult patients), which indicates the presence of antisynthetase syndrome (fever, Raynaud's phenomenon, polyarthritis, interstitial lung disease) with a less favorable prognosis. Anti-SRP (signal recognition particle) syndrome (<5%), associated with severe myositis, cardiac symptoms, and poor prognosis is rare. Anti-Mi2 syndrome is typically associated with DM with good prognosis.

Table 13.7. Bohan and Peter's diagnostic criteria for inflammatory muscle diseases (DM / PM)

1. Symmetrical weakness of proximal limb muscles 2. Positive muscle biopsy (mononuclear infiltration, necrosis, muscle fiber degeneration, regeneration) 3. Elevation of isoenzymes (CK, LDH, aldolases) 4. EMG-specific triad: low amplitude polyphase waves, high frequency spikes, spontaneous fibrillation, and steep waves 5. Characteristic skin symptoms: Gottron's sign/Gottron papule, heliotrope rash, shawl erythema Definitive PM: at least 2 symptoms of 1–4 are present Definitive DM: 3 symptoms of 1–4 are present and any skin symptoms of the 5th point

13.6.5. Treatment

The treatment strategy depends on the severity of the muscular weakness (is there a threat of respiratory failure, difficulty in swallowing, aspiration), whether there are symptoms of organ manifestation or malignancy. A key issue is *early* therapy to stop, slow down or reduce the rate of permanent muscle damage.

During immunosuppressive therapy, the basic strategy is administration of corticosteroids. Two-third of patients respond well. Ideally, therapy should be started within 3 months of the first symptoms, depending on the activity of the symptoms, at a dose of 0.5–3 mg / kg / day. Dose tapering may occur after 3–4 weeks, achieving maintenance therapy within approx. 10–12 weeks. In the case of inadequate improvement, CS refractory cases or systemic symptoms, supplementing treatment with a second-line immunosuppressive agent is warranted. These include methotrexate, azathioprine, cyclophosphamide (iv. or p.o.), cyclosporin A. In severe conditions, IVIG or plasmapheresis (especially DM) may be used as complementary therapy. Anti-malarial agents (hydroxychloroquine) are effective primarily in the initial stages of DM, the treatment improves mainly skin symptoms. In case of resistant disease, high doses of IVIG, rituximab, mycophenolate mofetil, tacrolimus may also be effective. In addition to the medication, physiotherapy is a very important complementary therapy. Active movement in the active phase is not recommended, but it is still necessary to maintain movement range of the joints by passive movement, and to perform respiratory physiotherapy to maintain the function of respiratory muscles. In long-term inactive phase isotonic exercises are recommended to prevent and reduce muscle atrophy and contracture, and improve muscle strength.

13.7. Sjögren's syndrome

13.7.1. Definition ad epidemiology

Sjögren's syndrome (SS) is a slowly progressive systemic autoimmune disease, which is primarily characterized by impaired function of exocrine glands. Antibodies to SS-A (Ro) and SS-B (La) autoantigens are characteristic of SS. In addition to the involvement of the exocrine glands, SS may cause a number of extraglandular symptoms. SS is one of the most common systemic autoimmune diseases with a prevalence of 0.5–3%. Female dominance, with a female:male ratio of 9:1 is typical. SS mainly occurs in the 40–50 age group. Its primary form is an independent autoimmune disease with characteristic criteria symptoms, while the secondary form may be associated with other autoimmune diseases.

13.7.2. Etiopathogenesis

The disease is triggered by environmental factors in genetically susceptible individuals (showing close association with HLA-B8 and -DR3 antigens). These triggers can be viruses, drugs or UV radiation. Among the viruses EBV, CMV, HSV, HIV, HTLV-1 are suspected to play a role: they persist in the epithelial cells of salivary glands and lead to increased HLA-DR expression. As a result, epithelial cells will have antigen presenting capacity, which initiates an inflammatory process with autoreactive CD4+ T cell and polyclonal B cell activation. Lymphocytic foci develop in the salivary glands, leading to damage to the glands (epithelitis). In addition, increased apoptosis of salivary gland epithelial cells can be observed, during which the continuously released autoantigens provide additional sustained autoantigenic stimulation for lymphocytes. Prolonged polyclonal B cell activation is characteristic, which may lead to the development of persistent lymphoma in some cases.

13.7.3. Clinical symptoms

The leading symptoms of SS are glandular ophthalmic and stomatological symptoms: reduced tear production, keratoconjunctivitis sicca and xerophthalmia develops, which in severe cases can lead to corneal ulcer and scleromalacia perforans. Dry mouth and xerostomia are common, which can lead to rapid tooth decay and oral candidiasis. Swelling of the salivary glands, sicca symptoms of other organs may also occur e.g. bronchitis sicca, vaginal dryness and pancreatic dysfunction. In addition to glandular symptoms, extraglandular symptoms may also accompany the disease, two groups of which being periepithelial and extraepithelial organ involvement. In connection with the former we encounter

interstitial nephritis, hepatitis and bronchiolitis due to lymphocytic infiltration of epithelial cells. The latter is characterized by cutaneous vasculitis (palpable purpura), glomerulonephritis, polyarthritis (non-erosive) and interstitial lung disease (usually lymphocytic interstitial pneumonitis). Not classified into the groups above, however neuromuscular symptoms, sensory neuropathies, motor neuropathies on the basis of vasculitis may also develop.

SS is often associated with other systemic (e.g. SLE, RA, SSc, PM, MCTD) or organ-specific autoimmune diseases (e.g. Hashimoto's thyroiditis, autoimmune liver diseases). During SS treatment, special attention should be paid to the higher risk of developing lymphoma. Persistent parotid gland swelling, lymphadenopathy, splenomegaly, cryoglobulinemia, neuropathy and vasculitis (e.g. purpura) also present an increased risk.

13.7.4. Diagnosis

The diagnosis is based on clinical symptoms, salivary gland biopsy, and autoantibody positivity. This requires ophthalmic and dental examination and salivary gland biopsy. The most recent classification criteria for Sjögren's syndrome are the ACR / EULAR 2016 criteria *(Table 13.8.)*.

Table 13.8. ACR / EULAR classification criteria for Sjögren's syndrome, 2016.

Criterium	Score
Focal lymphocytic sialadenitis during small salivary gland biopsy, ≥1 focus / 4 mm^2	3
Anti-SSA / Ro positivity	3
Ocular staining score ≥5 on at least one eye	1
Schirmer test ≤5 mm / 5 min on at least one eye	1
Unstimulated saliva secretion ≤0.1 ml / min	1

A patient who meets the inclusion criteria, meets no exclusion criteria, and has a score of ≥4 based on the 5 criteria can be classified with primary SS.

Inclusion criteria: At least one of the symptoms of ocular or oral sicca: (1) Persistent dry eye for more than 3 months; (2) Recurrent foreign body sensation in the eye; (3) Use of artificial tear more than 3 times a day; (4) Daily occurring dry mouth for more than 3 months; (5) Frequent liquid intake in case of dry foods

Exclusion criteria: previous head and neck irradiation; active hepatitis C infection (positive HCV-PCR); AIDS; sarcoidosis; amyloidosis; Graft-versus-host disease; IgG4-related disease

13.7.5. Treatment

There are three pillars to SS management. The first is the treatment of exocrinopathic symptoms with appropriate substitution. The second is the enhancement of secretion, if possible, with effective therapy existing to reduce xerostomia. The third part is treating systemic symptoms according to the organ manifestations.

Artificial tear or autologous serum eye drop may be used to treat xerophthalmia; the artificial tear may contain retinol palmitate, polyethylene glycol, polypropylene glycol, dextran, hypromellose or be preservative-free. Soft contact lenses can protect the corneal surface, but can sometimes lead to local infection. In severe cases, blocking the punctum can bring improvement. For secondary infection, topical antibiotics are required. In case of cornea perforation corneal transplantation is the solution. There are data available on the efficacy of pilocarpine, cevimeline and topical cyclosporin A used to enhance secretion. Treatment of xerostomia is difficult, artificial saliva is available for substitution treatment. The use of glucose-free lozenges and chewing gums may reduce subjective symptoms. It is important to quit smoking, treat candidiasis, improve oral hygiene, avoid dry air-conditioned rooms, and avoid anticholinergics. Therapy-like application of N-acetylcysteine helps to reduce viscosity. In case of severe symptoms, muscarinic agonists, such as pilocarpine or bethanechol, which stimulate secretion are considered. Different lotions can be used for dry skin, and local gels for vaginal dryness.

Immunomodulatory therapy may be required for extraglandular systemic symptoms. In cases of mild joint complaints, nonsteroidal anti-inflammatory drugs (NSAIDs), while in polyarthritis transient corticosteroid treatment or DMARD therapy (hydroxychloroquine, methotrexate, sulfasalazine, leflunomide) may be used. In rare, severe systemic symptoms (pneumonitis, glomerulonephritis, vasculitis and peripheral neuropathy) a higher dose of CS is required in combination with another immunosuppressive therapy (cyclophosphamide, azathioprine). In cryoglobulinemic vasculitis, plasmapheresis may be chosen for unresponsive patients. There is data available on the effectiveness of biological therapies (anti-B cell therapy, anticytokine therapy).

13.8. Mixed connective tissue disease

13.8.1. Definition and epidemiology

Mixed connective tissue disease (MCTD) is a systemic autoimmune disease with symptoms characteristic of multiple autoimmune diseases (SLE, PM, SSc,

RA) and anti-U1-RNP autoantibody positivity. MCTD begins in the thirties with female dominance; the female to male ratio being 9:1.

13.8.2. Etiopathogenesis

Genetic susceptibility, as well as endogenous and exogenous provoking factors both play a role in the development of the disease. There are two basic processes involved in its pathomechanism: obliterative vasculopathy of the small and medium arteries, and immune complex-mediated tissue damage. Enhanced endothelial activation and activation of the coagulation cascade can both be observed in the vascular process. Its immunological feature is the anti-U1 RNP antibody, the antigen of which belongs to the so-called small nuclear (sn) RNPs. Among the three protein components of U1 RNP, the antibody binds to the protein of 70kDa.

13.8.3. Clinical symptoms and diagnosis

Initial symptoms are often general, with weakness, fatigue, Raynaud's phenomenon of the fingers, arthralgia, and myalgia. Approximately two thirds of patients have polyarthritis (MCP, PIP). Swelling of the back of the hand and fingers is a typical symptom of MCTD. Mucocutaneous symptoms, malar rash, discoidal skin symptoms, erythema, buccal ulcerations, sicca symptoms, livedo vasculitis and subcutaneous nodules are also common. Myalgia is often caused by focal myositis with elevated CK and LDH values. However, in some cases, characteristic signs of myositis cannot be found with either enzyme assays or EMG, probably due to the focal nature of the process. Similarly, to other autoimmune diseases, organ manifestations are also present in MCTD. The most common and sometimes the most serious complications are pulmonary abnormalities in the form of interstitial pneumonitis / fibrotic alveolitis, but PAH due to obliterative vasculopathy of the lungs may also occur. Sometimes PAH is just transient, unlike in scleroderma. Cardiac manifestations are differences due to pericarditis, myocarditis or right ventricular pressure load. Common gastrointestinal symptoms are gastroesophageal reflux and esophageal dysmotility. Kidney disease rarely and only mildly affects patients with MCTD. Mostly membranous GN, extremely rarely proliferative GN is found. Alarcon-Segovia or Kahn diagnostic criteria helps diagnosing MCTD *(Table 13.9.)*.

Table 13.9. Diagnostic criteria for MCTD

	Alarcon-Segovia criteria	Kahn criteria
Serological	Anti-U1-RNP antibody Titer ≥1:1600	Anti-U1-RNP antibody Titer ^{3}1:1200
Clinical	1. Swelling of the back of the hand 2. Synovitis 3. Myositis (confirmed) 4. Raynaud's phenomenon 5. Acrosclerosis	1. Swelling of the fingers 2. Synovitis 3. Myositis 4. Raynaud's phenomenon
Confirmed MCTD:	Serological positivity + 3 or more clinical signs (of which one must be myositis or synovitis)	Serological positivity + Raynaud's phenomenon + 2 of three other clinical signs

13.8.4. Treatment

In MCTD, the treatment strategy always depends on which autoimmune disease-specific symptoms are the leading symptoms; following their treatment protocol is required. In case of arthralgia and mild arthritis, NSAIDs, antimalarial agents, or low dose CS may be recommended. In the case of persistent polyarthritis, DMARD therapy used in RA, especially MTX, may be chosen. The treatment of Raynaud's phenomenon is the same as the treatment used in scleroderma. Pericarditis, pleuritis, myositis, myocarditis, aseptic meningitis requires low to medium dose CS treatment, more severe cases require a high dose CS treatment supplemented with other immunosuppressive drugs (e.g. MTX, AZA). Cyclophosphamide is recommended for interstitial pneumonitis / alveolitis. The major cause of death in MCTD is pulmonary hypertension; its detection and early treatment is required to achieve adequate improvement. During the inactive phase of MCTD, CS can be tapered or sometimes discontinued, but in some patient long-term steroid treatment is required. In addition to the basic treatments, we should also pay attention to the supplementary treatment of complications, e.g. osteoporosis and cardiomyopathy.

13.9. Overlap syndromes

Overlap syndrome is when the diagnostic criteria for two or more systemic autoimmune disorders are met in one patient. Classical diseases such as SLE, SSc, PM / DM, RA, are primarily involved in this. Sjögren's syndrome occupies a special place, which may be associated as a primary form as well, e.g. with SLE, but sicca syndromes may also be present in secondary form, e.g. in RA,

SSc, etc. A relatively common combination is the SSc-PM overlap, of which the PM-Scl antibody is specific. Myositis is also combined with SLE, SS or RA. Co-occurrence of SSc-RA with erosive arthritic process and SLE-RA combination (RHUPUS) are also observed. In contrast, the SLE-SSc combination is very rare, which may have very serious therapeutic difficulties, given that steroid as a primary therapy in SLE increases the risk of SRC in SSc.

The clinical picture is very diverse, the symptoms are present together, but they also influence each other development and severity. In diagnosis, the diagnostic criteria for each disease should be used.

The treatment of overlap syndromes is based on the most serious disease, and organ manifestation. According to this, the treatment should always individualize, and common points in the treatment of the various diseases should be chosen when designing the therapeutic plan, avoiding drugs that can worsen the comorbidities.

13.10. Systemic vasculitides

13.10.1. Definition and classification

Vasculitis is an inflammation of various sized and localized blood vessels in the body caused by immunological reactions; the inflammation can affect arteries, arterioles, capillaries, venules and veins. The process can be segmental, organ-specific vasculitis, or extensive, generalized systemic vasculitis involving multiple organs. Systemic vasculitis is a heterogeneous disease. The disease may be primary vasculitis without any other underlying disease, or alternatively secondary vasculitis associated with other underlying diseases, e.g. systemic autoimmune diseases, infections, malignancies and transplantation. Recommendation of the Chapel Hill Conference are applied for the classification of primary systemic vasculitides. The classification was based on clinical and histological features, size of the affected blood vessels, presence of serological and other immunological parameters, and immuno-histochemical characteristics of affected tissues *(Table 13.10.)*.

Table 13.10. Nomenclature of vasculitis
(International Chapel Hill Consensus Conference, 2012)

Large vessel vasculitis	Takayasu's arteritis Giant cell arteritis
Medium vessel vasculitis	Polyarteritis nodosa Kawasaki disease
Small vessel vasculitis	ANCA-associated vasculitis • Granulomatosis with polyangiitis • Microscopic polyangiitis • Eosinophil granulomatosis with polyangiitis Immune complex small vessel vasculitis • Anti-glomerular basal membrane disease • Cryoglobulinemic vasculitis • IgA vasculitis (Henoch-Schönlein) • Hypocomplementemic uritcarial vasculitis (anti-C1q vasculitis)
Variable-vessel vasculitis	Behçet syndrome Cogan's syndrome
Single organ vasculitis	Cutaneous leukocytoclastic vasculitis Cutaneous arteritis Primary central nervous system vasculitis Isolated aortitis
Vasculitis associated with systemic disease	Lupus vasculitis Rheumatoid vasculitis Sarcoidosis vasculitis Other
Vasculitis associated with suspected etiology	Hepatitis C virus associated cryoglobulinemic vasculitis Hepatitis B virus associated vasculitis Syphilitic aortitis Drug-associated immune complex vasculitis Drug-induced ANCA-associated vasculitis Vasculitis associated with malignancy Other

13.10.2. Etiopathogenesis

Systemic vasculitides are multicausal diseases with an appropriate genetic background, the role of external factors (primarily infections) is likely. Antibody-dependent cellular cytotoxicity (type II immunoreaction), immune complex mechanism (III), and late type T cell-mediated granuloma formation (IV) are involved in the pathogenesis of vasculitides.

13.10.3. Symptoms and diagnosis

Clinical symptoms are partly generalized symptoms (fever, weight loss, anorexia, weakness, and fatigue) and partly related to the disease in question and characteristic of the affected organs. Diagnosis of vasculitides is based on a combination of clinical, serological, histological and imaging findings.

Each disease will be further described.

13.10.4. Giant cell arteritis and polymyalgia rheumatica

Giant cell arteritis (GCA) is a type of vasculitis affecting the large vessels, most commonly affecting the temporal artery (arteritis temporalis). GCA and polymyalgia rheumatica (PMR) are discussed together, as the two disease often coexists. GCA occurs primarily over 50 years of age, and is characterized by recent headache, mandibular claudication, visual disturbances, and irreversible blindness as the most severe symptom. Cerebrovascular symptoms are rare. PMR is common, also occurring predominantly in women over the age of 50. The disease is characterized by symmetrical shoulder girdle and pelvic girdle pain, muscle weakness, stiffness, accelerated erythrocyte sedimentation rate, and occasionally symmetrical arthritis; and associated with GCA in approx. 22–55% (*Table 13.11.:* PMR classification criteria, *Table 13.12.:* GCA classification criteria). Symptoms of PMR may be similar to those of elderly RA, which can make differentiation difficult. Moreover, the two diseases can occur together.

Table 13.11. Classification criteria for polymyalgia rheumatica (ACR/EULAR, 2012)

	Score without ultrasound (0–6)	**Score with ultrasound† (0–8)**
Morning stiffness >45 minutes	2	2
Hip pain, decreased morning stiffness	1	1
RF or ACPA deficiency	2	2
Lack of other joint involvement	1	1
Subdeltoid bursitis of at least one shoulder and / or biceps tenosynovitis and / or glenohumeral synovitis (posterior or axillary) and at least one iliac synovitis and / or trochanteric bursitis	–	1
Bilateral shoulder subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	–	1

Score ≥4 (without ultrasound examination) or ≥5 (with ultrasound examination)

Table 13.12. Classification criteria for giant cell arteritis, ACR 1990

• Age over 50 • Recent headache • A. temporalis pain or weakened pulse • ESR above 50 mm/h • Presence of vasculitis with giant cells, mononuclear cells, granulomas with a. temporalis biopsy

Diagnosis: In case 3 or more criteria are present

In PMR diagnosis, apart from clinical symptoms, joint ultrasound (confirmation of shoulder and / or hip bursitis) is crucial. In GCA diagnosis, temporal artery ultrasound is essential, but only approx. 50% of cases have a positive temporal artery biopsy. The most accepted examinations, depending on the localization, are CT-angio or MR-angio or PET / CT.

Treatment of PMR and GCA is based on similar therapies. Due to the risk of vision loss in the GCA, immunosuppressive therapy with CS (usually 1 mg/kg/day) should be started as soon as possible. In case of refractory CS, or the dose of CS cannot be optimally reduced, MTX or AZA can be chosen as complementary therapy. In case of visual impairment iv. steroid therapy is needed. In case of poorly responsive GCA, targeted biological therapy with anti-IL6R blocker may be selected. PMR generally requires a lower dose of CS, which, in addition to rapidly improving clinical symptoms, also means a rapid reduction in ESR. Maintenance therapy is often required for 1–2 years as relapses are common after CS discontinuation.

13.10.5. Takayasu's arteritis

Takayasu's arteritis is a type of vasculitis affecting the aorta and its main branches, a disease called pulse-free disease. Giant cell granulomatous inflammation in the artery walls causes vasoconstriction and obstruction with ischemic consequences. The disease most often begins under the age of 40, with ischemic symptoms of the affected area (upper and lower extremity claudication, cerebral symptoms, musculoskeletal disorders and arthralgia), accompanied by accelerated erythrocyte sedimentation rate and generalized symptoms (*Table 13.13.* classification criteria for Takayasu's arteritis). Diagnosis is based on symptoms and imaging tests (angiography, MR-angio, CT-angio, PET / CT). The treatment of the disease depends on the duration of the disease and its stage. Treatment of the early, active inflammatory phase, where complete arterial obstruction has not yet occurred, CS therapy is recommended (1 mg/kg/day on average, and tapering). In relapse or severe cases, other immunosuppressive agents (MTX,

AZA, CYC, and MMF) are required in addition to CS. According to case reports, TNF-α inhibitor and IL6 inhibitor therapy appear to be effective in the disease. In case of definitive arterial stenosis or occlusion, vascular surgery may also be necessary, as medication does not solve existing constrictions or obstruction.

Table 13.13. Classification criteria for Takayasu's arteritis, ACR 1990

• Onset of disease under 40 years of age
• Limb claudication
• Decreased brachial artery pulsation
• The difference in blood pressure in the upper limbs is more than 10 mmHg
• Murmur over a. subclavia or the aorta
• Stenosis and occlusion on the arteriography

Diagnosis: In case 3 or more criteria are present

13.10.6. Polyarteritis nodosa

Polyarteritis nodosa (PAN) is necrotizing vasculitis affecting medium vessels segmentally. In addition to the immune complex mechanism, cytotoxic T-cell response also plays a role in the pathomechanism. It is characterized by frequent hepatitis B virus association. The disease mainly manifests by skin symptoms (purpura, skin necrotizing vasculitis), mononeuritis multiplex, symptoms of mesenteric ischemia and renal manifestation. Typically, no immunodeposit can be detected in the histological samples, and usually ANCA is negative.

Clinically, different forms may occur: mild, moderate, and from rapid with fatal outcome. As the vasculitic process can affect all areas of the body, symptoms of any organ or organ system may be at the forefront of the disease. Often, direct organ symptoms can be accompanied by general symptoms (subfebrility, fever, weight loss, arthralgia, etc.). The PAN classification criteria are set out in *Table 13.14.*

In the treatment of PAN, CS administration is primary. In mild disease, this may be sufficient, in the case of moderate or severe disease, concomitant administration of aggressive immunosuppressive therapy, corticosteroids and cyclophosphamide is required. Alternative therapies may include azathioprine, methotrexate, mycophenolate mofetil, and in very severe cases, plasmapheresis and rituximab therapy among biological therapies. In case of PAN associated with hepatitis B infection, the infection should also be treated.

Table 13.14. Classification criteria for polyarteritis nodosa (ACR, 1990)

• Weight loss >4 kg • Livedo reticularis • Testicular pain or tenderness • Myalgia and weakness • Mono- or polyneuropathy • Diastolic blood pressure >90 mmHg • Increased urea nitrogen or creatinine levels • Hepatitis B-positivity • Arteriographic abnormalities: segmental abnormalities, constrictions, obstruction, aneurysms • Histological abnormalities: granulocytic, mononuclear infiltration of small or medium arteries

Diagnosis: In case 3 or more criteria are present

13.10.7. Kawasaki disease

Kawasaki disease is the inflammation of medium-sized arteries that occurs primarily in children. The disease is characterized by fever, mucosal and skin symptoms, lymphadenomegaly, eye and joint complaints, myocarditis and myocardial damage due to typical coronary vasculitis. There are two main steps to treating the disease: 1. administration of aspirin, initially at an anti-inflammatory dose (100 mg/kg/day) followed by a thrombocyte aggregation inhibiting dose (5 mg/kg/day); 2. IVIG treatment. Usually a single dose of 1-2 g/kg is sufficient, in case the treatment is within the first 10 days of the disease. CS is usually contraindicated as it increases the likelihood of coronary aneurysm. However, it may be used if the disease recurrences, in case severe myocarditis is confirmed, or the process is refractory to IVIG. Thrombolytic therapy may be warranted in acute coronary thrombosis. There is available data on the efficacy of infliximab in Kawasaki disease.

13.10.8. ANCA-associated vasculitis

ANCA-associated vasculitis (AAV) is a group of diseases associated with inflammation and necrosis of the small vessels, which is due to the pathogenetic role of the antineutrophilic cytoplasmic antibody (ANCA). External trigger (infection) activates neutrophils, resulting in the appearance of other cytoplasmic antigens (e.g. proteinase 3, myeloperoxidase, elastase, etc. enzymes) on their surface. These are specifically bound by ANCA, activating the chronic inflammatory process. The AAV group includes granulomatosis with polyangiitis (GPA, formerly known as the Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as the Churg-Strauss syndrome).

Granulomatosis with polyangiitis: GPA is necrotizing granulomatous vasculitis of the upper and lower respiratory tract and kidneys. It is characterized by the closest association with ANCA, including cytoplasmic c-ANCA positivity (proteinase 3-, PR3-ANCA). In addition to the general symptoms, rhinitis, sinusitis, tracheobronchitis, infiltrations in the lungs, cavities and nodules occur. Besides the respiratory tract, kidney involvement is the most common in the form of rapid glomerulonephritis. Rarely, eye (scleritis, episcleritis, uveitis, retinal vasculitis, etc.), skin, cardiac and neurological symptoms may also occur. The GPA classification criteria are set out in *Table 13.15*.

Table 13.15. Classification criteria for granulomatosis with polyangiitis (ACR, 1990)

• Nasal or oral inflammation (ulceration, purulent, bloody discharge)
• Chest X-ray abnormalities (fixed infiltrates, nodules, cavitation)
• Microhematuria (>5 erythrocytes or erythrocyte-cylinder per visual field)
• Characteristic histology: granulomatous inflammation in the arterial wall or perivascular

Diagnosis: In case 2 or more criteria are present

Microscopic polyangiitis: MPA is necrotizing vasculitis affecting small vessels, with little or no immune deposit at the site of inflammation (pauci-immune vasculitis). MPA occurs over the age of 50, mainly affecting men. It is often manifested as pulmonary-renal syndrome with pulmonary capillaritis, life-threatening alveolar hemorrhage and glomerulonephritis, but may be restricted to the kidneys or systemic (respiratory, kidney, lung, skin, nervous system, gastrointestinal tract, muscle, and eye manifestations). MPA is primarily characterized by p-ANCA and anti-myeloperoxidase (anti-MPO) positivity.

Eosinophilic granulomatosis with polyangiitis: EGPA primarily affects the respiratory system; the process is characterized by pre-existing asthma or allergic rhinitis, eosinophilia, associated with other manifestations of systemic vasculitis. ANCA is positive in approx. 50% of patients, mainly p-ANCA and anti-MPO. EGPA classification criteria are set out in *Table 13.16*.

Table 13.16. Classification criteria for eosinophilic granulomatosis with polyangiitis (ACR, 1990)

• Asthma bronchiale in the patient's anamnesis • 10% eosinophilia of peripheral blood • Mono- or polyneuropathy • Pulmonary infiltrates • Paranasal sinus abnormalities • Characteristic histology: granulomatous inflammation in the arterial wall or perivascular with eosinophils

Diagnosis: in case of the presence of at least 4 criteria

Treatment of ANCA-associated vasculitis: due to the similar course and prognostic factors of AAV disorders, the therapeutic protocol considers the AAV group together. Definitive diagnosis is required before initiating treatment. There are two basic phases of the treatment: induction treatment aimed at disease remission, followed by maintenance therapy to preserve remission and prevent relapses. It is important to assess the severity and extent of the disease when developing a treatment strategy.

In generalized AVV with severe organ involvement, the induction treatment is a combination of corticosteroid and cyclophosphamide treatment. In addition to CS, azathioprine, methotrexate or mycophenolate mofetil should be selected for maintenance treatment, which should be continued for at least 2 years. In addition to maintenance therapy, trimethoprim / sulphomethoxazole (2×2 tablets of Sumetrolim weekly) is also used, primarily to prevent infection.

In localized or early systemic disease, also the combination of CS and CYC is to be chosen, but remission is usually reached sooner and maintenance treatment can be started sooner. Localized, limited forms, may be treated with MTX alongside CS instead of CYC.

In the treatment of severe life-threatening conditions, high-dose CS with CYC is recommended and, if necessary, the treatment can be supplemented with IVIG and plasmapheresis.

In case of serious illness, anti-CD-20 rituximab has the same affects as CYC in induction treatment; and in case of relapse or refractory disease, rituximab is clearly more effective than CYC.

13.10.9. Anti-glomerular basement membrane disease

In the pathogenesis of anti-glomerular basement membrane disease (Goodpasture syndrome), anti-glomerular basement membrane (anti-GBM) antibody is involved. Binding to the basement membrane primarily induces an inflamma-

tory response in the glomeruli and alveoli. Clinically, it is usually manifested as lung-kidney syndrome in the form of rapidly progressive glomerulonephritis and / or alveolar hemorrhage. It is usually an acute life-threatening condition that requires aggressive immunosuppressive therapy with CS and CYC supplemented with intensive plasmapheresis. Rituximab is an option in unresponsive cases or when contraindicated is CYC. As a maintenance treatment, AZA, MTX, or MMF may be used to reduce CS dose.

13.10.10. Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis develops due to cold-precipitated cryoglobulins. According to their composition, cryoglobulins are divided into 3 groups:

Type I: composed of monoclonal IgM (less frequently IgG). Occurs in myeloproliferative disorders (multiple myeloma, Waldenström macroglobulinemia)

Type II: consists of IgM with monoclonal RF activity and polyclonal IgG (mixed II)

Type III: composed of polyclonal IgM and IgG (mixed III)

Vasculitis most often occurs in the III. mixed form. The disease with an immune complex pathomechanism is often associated with hepatitis C virus (HCV). Characteristic clinical symptoms include palpable purpura, Raynaud's phenomenon, digital gangrene, ulcers of the lower limb, and glomerulonephritis. The prognosis is primarily determined by kidney disease. In case of HCV association, treatment of active infection is the primary consideration. In case of severe manifestations (renal disease, gangrene) immunosuppressive treatment with corticosteroids, cytostatic drugs and occasionally plasmapheresis is required; and in case of refractory disease rituximab has to be chosen.

13.10.11. Henoch–Schönlein-purpura

Henoch-Schönlein purpura (HSP) is the most common vasculitis syndrome in childhood. It is usually a benign process that often occurs after intercurrent disease (especially after upper respiratory tract infection). Leading symptoms include purpura, arthritis, abdominal pain with occult bleeding in the stool, and microscopic hematuria. Very rarely, systemic involvement and life-threatening condition is observed. It is characterized by small vessel vasculitis, with deposition and complement activation of IgA-containing immune complexes in the vascular wall.

Diagnosis of HSP is primarily based on clinical symptoms; diagnostic criteria, 2010 are used *(Table 13.17.).*

Treatment of HSP is primarily symptomatic, and in most cases heals spontaneously. NSAIDs can be given in arthritis, while CS can be used for severe edema, joint and abdominal pain. In the treatment of rare, acute, severe renal failure, immunosuppressive therapy is recommended, either intravenous steroid treatment alone or in combination with other immunosuppressive agents (cyclophosphamide, azathioprine). In severe cases or in case of inadequate response, plasmapheresis or IVIG may be recommended.

Table 13.17. Diagnostic criteria for Henoch-Schönlein purpura (EULAR/PRINTO/PRES, 2010)

Criteria	Description
Mandatory criterium Minimum 1 out of 4	Palpable purpura or petechia with lower limb dominance Acute diffuse abdominal pain Histologically confirmed leukocytoclastic vasculitis or proliferative glomerulonephritis with predominantly IgA deposits Acute arthritis/arthralgia Renal involvement with proteinuria or hematuria

13.10.12. Other vasculitis

Cutaneous leukocytoclastic vasculitis: Cutaneous leukocytoclastic vasculitis, according to previous nomenclature, can be considered hypersensitive vasculitis, where type III. immune response plays a role. In order to make a diagnosis, it is necessary to exclude vasculitis affecting organs other than the skin. Drug exposure is primary in the background of the disease, but it may also develop after certain infections. Most often, the disease manifests in the form of purpura of the lower limb. Often, it is enough to eliminate cause of the disease, and sometimes corticosteroid treatment may also be required.

Isolated vasculitis of the central nervous system is an inflammatory process affecting small and medium vessels. A characteristic symptom is transitorial ischemic attack (TIA) after 1–3 months of headache, followed by focal symptoms. Some patients may develop confusion and progressive dementia. Cerebral angiography is the most sensitive part of the diagnosis. Treatment requires a combination of CS and CYC, similarly to PAN treatment.

Behçet syndrome is immune vasculitis characterized by urogenital aphetas, arthritis, ophthalmic, nervous system, cardiopulmonary, and renal manifestations. Its diagnostic criteria are also based on clinical symptoms *(Table 13.18.)*. The treatment depends on the given symptoms. Local steroid preparation or tacrolimus may be sufficient for the treatment of mild mucocutaneous symp-

toms. Colchicine, dimethyl sulfone (Dapsone), and thalidomide for severe mucocutaneous symptoms may be used. Another option is MTX, or low dose CS. In severe systemic diseases, combined immunosuppressive therapy is warranted.

Table 13.18. Diagnostic criteria for Behçet syndrome (ISG, 1990)

A symptom: recurrent (>3 / year) aphthas in the mouth
B symptoms:
• Recurring genital ulcers
• Eye symptoms (uveitis, retinal vasculitis)
• Skin symptoms (erythema nodosum, pseudofollicilitis, papulopustular lesions, acneiform nodules)
• Positive pathergy test (papular / pustular reaction after needle prick)

Diagnosis: A + 2B symptoms (with the exclusion of other pathologies)

Cogan syndrome is a very rare vasculitis with interstitial keratitis and vestibuloauditoric dysfunction (tinnitus, vertigo, hypoacusis), described in detail in Section 16.4.

Buerger's disease or thrombangiitis obliterans is not included in the latest nomenclature of vasculitis, but should be mentioned due to the inflammatory process of the vessels. It is a disease occurring primary in male young smokers, with leading symptoms of obliterative vasculitis, affecting medium vessels of lower limbs and recurrent superficial thrombophlebitis. The diagnosis is based on anamnesis and a characteristic angiographic image. Smoking cessation, vasodilator treatment and thrombocyte aggregation inhibitor therapy are primary in treatment. The efficacy of immunosuppressive therapy has not been established.

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14. Pediatric rheumatology

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14.1. Introduction

Rheumatic diseases may have acute or chronic course. In the absence of specific diagnostic tests, sometimes diagnosis only becomes clear by monitoring the disease. Most of them are associated with muscular weakness, joint contracture and consequent dysfunction that affects the child's psychosocial development, school performance and the life of the whole family. The most common pediatric rheumatologic disease, juvenile idiopathic arthritis (JIA), is defined by the age of the patient, although there is no known age at which the symptoms of the disease change abruptly. Certain rheumatologic diseases are more common in young children (e.g. oligoarthritis associated with uveitis, Kawasaki disease), while others occur almost exclusively in adults (e.g. gout, osteoarthritis). Some diseases (e.g. vasculitis) have similar clinical symptoms and laboratory abnormalities at all ages. The following factors may be responsible for different age characteristics:

- genetically determined disorders usually appear in childhood (e.g. inherited bone dysplasia, metabolic disorders, hemophilia, periodic fever syndromes),
- maturation of the immune system,
- growth, development of the musculoskeletal system,
- maturation and involution of the endocrine system, changes in hormone production
- exposure time of environmental damage,
- lifestyle: physical activity, injuries, nutrition.

14.2. Physical examination of the organs of the musculoskeletal system

Physical examination of the ill child is time consuming and normal variants of each stage of life must be known to distinguish them from pathological abnormalities. The so-called pGALS (pediatric gait, arms, legs, and spine) (www.ar-

thrirtisresearchuk.org), can be used as a screening test, and in case of a deviation, a more detailed examination of the affected and adjacent joints is required.

14.2.1. Regional examination of the musculoskeletal system:

- Inspection: pain symptoms, skin symptoms, limb length and muscle mass, deformity, swelling, asymmetry
- Touch: sensitivity to pressure, heat, swelling
- Examination of movement: observing range of motion, symmetry and pain-inducing movement during active and passive movement.
- Functional examination: walking, fist formation.

14.3. Normal variations of posture

The following differences are common and pass without treatment, but in severe, progressive cases, with pain, dysfunction, or asymmetry are considered to be abnormal.

1. *Genu varum (bowlegs):* toddlers' gait is wide, with the front of the leg turned inwards, keeping their knees apart. Most noticeable when standing with touching ankles.
2. *Genu valgum (knock-knee):* standing with touching knees, the ankles far apart, the intermalleolar distance normally not exceeding 8 cm.
3. *Pes planus (flat feet):* The feet of toddlers learning to walk are flat, due to the presence of the later disappearing roll of fat and the medial longitudinal curvature. It is most noticeable when standing on tiptoe or with passive extension of the first finger. Hypermobility leads to pronounced flat feet, in older children it may indicate contracture of the Achilles tendon or inflammatory arthritis.
4. *In-toeing:* the feet points inward when walking or running; three variations are known.
   - Inward rotation of the foot (metatarsus varus): adductive deformity of the highly mobile foreleg, which usually occurs in newborns is spontaneously corrected at 5 years of age.
   - Internal tibial torsion: is the rotation of the tibia excessively inwards relative to the femur. Common in infants, usually associated with genu varus, resolves by age 5.
   - Hip / femoral anteversion: an inward rotation in the femur. It may be associated with hypermobility of the joints and usually resolves spontaneously by age 8.

5. *Toe-walking:* common in young children and may become permanent if getting used to. Habitual tip-toeing should be distinguished from mild cerebral palsy, Achilles tendon shortening, or arthritis of the leg. In older boys, Duchenne muscular dystrophy should be ruled out.

14.4. Classification according to musculoskeletal symptoms

The pediatric rheumatologist is most often referred to for lower limb or spinal complaints due to gait disturbance, and should therefore be aware of the orthopedic, hematological, and oncological differences with symptoms similar to inflammatory conditions.

14.4.1. Causes of lower limb and back pain

1. *Growing pain:* Generalized, symmetrical lower limb pain occurring at night in children aged 3–12 years; which pain often wakes the child from their sleep but never occurs during the day. Physical examination can detect at most joint hypermobility in some cases.
2. *Hypermobility:* mild hypermobility is common and asymptomatic in young girls. Most of them utilize their flexibility as a dancer, a gymnast, but the increased load can cause joint and muscle pain. Hypermobility may be a symptom of some chromosomal abnormalities (e.g. Down syndrome) and congenital collagen defects (e.g. Marfan and Ehlers-Danlos syndrome).
3. *Acute-onset lower limb pain* is most often caused by trauma; less frequent osteomyelitis, malignant disease, and septic arthritis also require urgent treatment. Acute lymphoblastic leukemia can occur with both bone pain and arthritis, the pain is strong, more pronounced at night. Neuroblastoma can mimic the symptoms of pelvic inflammation, and its metastases causes difficult to localize bone pain. Malignant bone tumors (e.g. Ewing's sarcoma) are rare, occurring with pain, swelling, and sometimes pathological fractures. Osteoid osteoma is a benign tumor usually developing in teenage boys, usually affecting the femur, tibia, and vertebrae. The pain is stronger at night, which is well alleviated by nonsteroidal anti-inflammatory drugs (NSAIDs).
4. *Knee pain:* hip pain often radiates to the knees, so it should always be examined in case of knee complaints.
   – Osgood-Schlatter disease: is the apophysitis of tibial tuberosity, which is associated with pressure-sensitive swelling, sometimes free fragment formation, of the knee, mainly in adolescent athletes (football, handball) or

overweight boys. It is characterized by anterior knee pain during physical exertion (running, jumping, kneeling, stair climbing), which ceases at rest.
- Chondromalacia patellae: thinning of the cartilage surface of the patella, which mainly affects adolescent girls. Standing up and stair climbing causes pain as the patella is in close contact with the femoral condyle. Rest and physical therapy can help, but in more severe cases arthroscopic intervention is required.
- Osteochondritis dissecans (subchondral segmental avascular bone necrosis): local circulatory disorders and trauma are likely to play a role in its development. Most commonly affects femoral condyle, characterized by sudden pain, swelling, and later occurring recurrent blockages. Joint movement becomes restricted, accompanied by painful crepitation, and finally, moving away from the body of the dead piece, permanently damages the articular surface as a free joint body.
- Patellar subluxation and dislocation: in case of generalized hypermobility, subluxation is common, sometimes dislocation of the lateral part can occur, which is accompanied by sudden sharp pain. It can be resolved by mild extensions of the knee may or spontaneously.
- Injuries: most often contact sports cause acute knee injury, but other sports can also cause chronic or overexertion injury.

5. *Back pain:* the cause of which is often recognizable compared to adults. The younger the child, the more likely there is a significant problem in the background. High fever may indicate infection, osteoid osteoma or malignant bone cancer may be the cause of persistent pain which wakes up the patient up. Root / spinal cord compression may be associated with focal neurologic symptoms. Weight loss, general weakness and fatigue are symptoms of malignancy.
   - Mechanical causes: symptoms are usually muscle spasm and soft tissue pain, which are most often the result of sport injuries, postural disturbances, or increased strain (e.g. carrying a heavy school bag).
   - Tumors: osteoid osteoma often develops in vertebrae, but other primary tumors or metastases may also occur.
   - Spinal osteomyelitis or discitis: it is characterized by localized pressure sensitivity, avoidance of pain, gait, and heavy lifting when bending the spine, accompanied by fever and malaise.
   - Spinal cord or nerve root compression: caused by tumor or disc prolapse, which may be develop by trauma or lifting a heavy object.
   - Scheuermann's disease: is the osteochondrosis of the vertebral body, which leads to kyphosis of the thoracic spine, is usually accompanied by back pain.

- Spondylosis / spondylolisthesis: spondylolysis can be unilateral, congenital. It can also be caused by bilateral stress fracture of the vertebral arch. The latter causes spondylolisthesis, i.e., sliding of the vertebral body forward, which can result in root or spinal cord compression. Spondylolisthesis can occur without lysis.
- Complex regional pain syndrome: can be diagnosed if there is no physical abnormality, it can be provoked by mental stress.

14.4.2. Limping

1. Transient synovitis (transitory coxitis): is the most common cause of acute limping and hip pain in children aged 2–12 years. It is often associated with a viral infection without a fever, and the symptoms of the infection are also usually very mild. The pain occurs when moving, especially when the hips rotate inward and usually radiates to the knees. Transient synovitis should be distinguished from incipient septic arthritis, and Perthes disease.
2. Perthes disease: avascular necrosis due to dysfunction of femoral head blood supply, which heals in 18–36 months due to revascularization or reosification. It is more common in boys aged 5–10 years, and is bilateral in 10–20%. Its prognosis is the best in children under 6 years of age, especially if less than half of the epiphysis has been affected. Subsequent femoral head deformity may lead to degenerative arthritis.
3. Juvenile epiphysiolysis of femur head (adolescent femur head shift): the femoral head's epiphyses turn backwards and down on the femoral neck and slip gradually or suddenly. Among the causes, predominance of growth hormone overweighs sex hormones. Growth hormone widens the growth cartilage and causes the epiphysis to rotate around the neck as a result of the shear force. It occurs at the time of fastest growing in the prepubertal period, in boys aged 10–15 and girls aged 11–13. The child complains of thigh, knee and hip pain, falls, is unable to stand, and the lower limb turns outwards in the acute form. The affected children are usually overweight, associated with hypothyroidism and hypogonadism, and it is twice as common in boys. In case of suspected epiphyseolysis, comparative X-rays in anterior-posterior and Lauenstein positions are needed to confirm the presence of the disease and assess the degree of the shift. Treatment: surgical.

14.5. Arthritides

Symptoms of acute arthritis include pain, swelling, redness, warmth and limited mobility. The division of polyarthritis is shown in *Table 14.1.*

Table 14.1. Etiological classification of polyarthritis

Bacterial infection	*Mycoplasma, Chlamydia, Campylobacter, Yersinia, Salmonella, Shigella, Borrelia*
Viral infection	rubella, mumps, herpes, hepatitis, adenovirus, coxsackie B, parvovirus
Inflammatory bowel disease	Crohn's disease, ulcerative colitis
Vasculitis	Schönlein-Henoch purpura, Kawasaki disease
Systemic autoimmune disease	Juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), polyarteritis nodosa, mixed connective tissue disease (MCTD)
Hematological disorder	hemophilia, sickle cell anemia
Malignant diseases	leukemia, neuroblastoma
Other	cystic fibrosis

14.5.1. Reactive arthritis

Reactive arthritis is the most common transient synovitis in children affecting mainly the hips, knees and ankles, which heals spontaneously or with NSAID treatment within a few days without any remnant. It may be a symptom of a viral infection, but may develop following extraarticular bacterial infection *(Mycoplasma, Chlamydia, Campylobacter, Yersinia, Salmonella, and Shigella)*. Nowadays, post-streptococcal reactive arthritis and rheumatic fever are scarce in developed countries due to the proper use of antibiotics.

14.5.2. Septic arthritis

Septic arthritis in children younger than 2 years of age is more common with hematogenous scattering or direct spread from infected skin lesions or osteomyelitis. Usually, the hip is affected, the most common pathogen is Staphylococcus aureus. In newborns, due to heavy subcutaneous adipose tissue, it is difficult to recognize septic hip arthritis. It should be thought about when a feverish infant does not move the lower limbs, keeps them flexed and rotated inwards to reduce intraarticular pressure and cries when the limb is moved. Inflammatory laboratory parameters are elevated, with X-rays initially indicating only a widened joint

and soft-tissue edema. Hip ultrasound helps to confirm fluid retention. Hemoculture is required, based on which it is possible to narrow down the empirical antibiotic therapy started immediately in order to prevent destruction.

14.5.3. Juvenile idiopathic arthritis

14.5.3.1. Definition and epidemiology
Juvenile idiopathic arthritis (JIA) is the leading cause of chronic arthritis and musculoskeletal disorder in childhood. JIA is defined as joint swelling that cannot be explained by any other cause occurring before the age of 16, persisting at least 6 weeks. Its prevalence is approx. 1:1000 (similar to e.g. epilepsy). It differs clinically in approx. 95% from adult rheumatoid arthritis.

14.5.3.2. Classification of JIA
Classification of JIA is based on clinical symptoms. It considers the number of joints affected during the first six months of the disease. JIA has seven subtypes.

- *Oligoarthritis* is responsible for half of the cases. It occurs before the age of 6 and is 5 times more common in girls. Generally, the knee, ankle and wrist joints are affected; prolonged oligoarthritis affecting more than 4 joints after 6 months, while up to 4 joints are inflamed in the persistent form.
- 25–30% of JIA is *polyarthritis* affecting at least 5 joints. Rheumatoid factor (RF) negative form is more common in girls younger than 6 years of age, usually affecting large and small joints symmetrically, and affecting the cervical spine and temporomandibular joints, too. RF positive polyarthritis affects approx. 5% of patients, mainly adolescent girls; inflammation can quickly become progressive and destructive.
- *Psoriatic arthritis* affects the large and small joints asymmetrically and can precede characteristic skin symptoms by years. The presence of nail symptoms, dactylitis and first-degree relatives with psoriasis helps to recognize the disease.
- *Enthesopathic arthritis* affects HLA-B27 positive children older than 6 years of age; and is 4× more common in boys. It starts with arthritis of the lower limbs, often accompanied by plantar fascia and Achilles tendon enthesitis (local inflammation of the tendon or ligament that attaches the muscle to the bone). Later on, inflammation of the lumbar spine and sacroiliac joint, which corresponds to the juvenile form of ankylosing spondylitis may occur.
- *Systemic JIA* (Still's disease) is more common in infants, with predominant extraarticular symptoms: fatigue, lymphadenopathy, daily high fever, faint

rashes, joint and muscle pain. Initially, the symptoms of arthritis are not obvious, later either oligoarthritis or polyarthritis may develop.
- *Undifferentiated arthritis* can either be classified into no subtype or fit into at least 2 subtypes at the same time.

14.5.3.3. Clinical presentation and diagnosis

In the absence of a specific diagnostic test, JIA can be recognized by relying on clinical symptoms. Joint stiffness after rest, moderated by movement or warmth, intermittent limp alluding suggestive of pain, or avoidance of previously favorite activities are warning signs because the infant is not yet able to determine his or her complaints. The onset is usually slow, non-characteristic, laboratory tests show no significant difference except for systemic form, where anemia and increased inflammatory parameters can be observed. Antinuclear antibody (ANA) positivity can be observed in healthy children and in infection as well. In case systemic symptoms are present, sepsis and malignancy should be excluded.

14.5.3.4. Complications of JIA

- *Chronic anterior uveitis* develops in 10–20% of patients, it is asymptomatic for a long time, but causes severe vision loss in 30–40% due to the development of cataracts or glaucoma. Regular ophthalmic screening with a slit lamp recognizes early stage of the disease; ANA positive oligoarthritis poses an increased risk.
- *Flexion contracture* develops when the patient rests the joint permanently in a position that minimizes intraarticular pressure. In the long run, it can lead to severe destruction or ankylosis.
- *Growth failure* may be caused by systemic corticosteroid treatment, or anorexia due to chronic disease. Protracted inflammation may cause local growth disturbances; in case of knee involvement, overgrowth leads to a difference in limb length, and in case of temporomandibular joints, due to early fusion of the epiphysis, micrognathia can be observed.
- *Osteoporosis* can be the result of calcium or vitamin D deficient nutrition, systemic corticosteroid treatment, decreased physical activity or late adolescence.
- *Amyloidosis* is a very rare, high-mortality disease, the initial symptom of which is proteinuria, followed by renal failure.

14.5.3.5. JIA therapy

The goal is to achieve remission as soon as possible through complex treatment, where in addition to medication, physiotherapy has an important role; and ophthalmologists, orthopedic surgeons, oral surgeons and psychologists often need to be involved. Cooperation of the patient and the family can be strengthened with giving sufficient information and support. Despite a significant improvement in prognosis, approximately one third of patients require continued treatment in adulthood to maintain remission.

Drug treatment:

- NSAIDs and analgesics do not affect the course of the disease, but reduce symptoms.
- Intraarticular steroid can be used in oligoarticular JIA, while in polyarticular form multiple injections can be given as a bridging therapy until the effect of methotrexate develops.
- Methotrexate can be given with regular monitoring of liver function and blood count, and it is effective in approx. 70% of polyarticular JIA.
- Systemic corticosteroid use should be minimized to prevent growth retardation and osteoporosis. High-dose intravenous methylprednisolone can be life-saving in severe systemic arthritis.
- Cytokine modulators (biological therapy) and other immunosuppressive agents may be effective in severe methotrexate refractory processes. Currently, anti-TNF alpha, anti-IL-1, anti-CTLA-4, and anti-IL-6 can be administered in JIA if the appropriate criteria are met. Autologous bone marrow transplantation combined with T-cell depletion may be curative in refractory disease.

14.6. Autoimmune diseases in childhood

14.6.1. Henoch-Schönlein purpura

It is the most common vasculitis in childhood. It is twice as common in boys, mainly affecting those aged 3–10. It accumulates in the winter months, and is often preceded by upper respiratory tract infection. Joint pain and periarticular edema occur in two thirds of patients, mainly in the knees and ankles, and heal without complications. Henoch-Schönlein purpura is recognized by the presence of characteristic hemorrhages mostly on the extensor surface of the lower limbs. It is often associated with abdominal pain, in the presence of glomerulonephritis, long-term immunosuppressive treatment is required.

14.6.2. Juvenile dermatomyositis

It usually starts insidiously with fatigue, weakness of the muscles of the shoulder and pelvis. A characteristic rash appears on the cheeks, which also spreads to the nasal bridge, with livid discoloration of the eyelids and periorbital edema. The rash appears on the extensor surface of the joints (Gottron's papule) as well, and as the disease progresses, subcutaneous calcinosis may develop. Muscle pain is common and arthritis occurs in 30% of cases.

14.6.3. Systemic lupus erythematosus (SLE)

SLE is rare in childhood, but may occur in adolescent girls with fatigue, joint pain, photosensitivity, and butterfly rash. The disease involving the kidneys, the central nervous system and the lungs has a serious course.

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15. Osteoarthritis and spinal pain

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15.1. Osteoarthritis

15.1.1. Introduction

Osteoarthritis (OA) is the most common degenerative joint disease characterized by damage to the articular cartilage and subchondral bone. It imposes pain and, in severe cases, reduced mobility on the individuals and a considerable financial burden on society. The incidence of the disease increases with age and increasing prevalence of obesity, causing problems to a third-quarter of the 65 plus age group.

Knee OA has the highest incidence of 240 / 100 000. In case of hand and hip OA, this value is 100 and 88 / 100 000, respectively. All three types of OA are becoming more common with aging, and over 50 years of age, overall more women are affected than men. However, knee and small joint hand OA are more common in women, and hip OA is more common in men.

15.1.2. Etiology and risk factors

The disease mainly affects the load-bearing joints of the lower limb, the knees and hips, and the joints of the hand, including predominantly distal interphalangeal joints. The most important etiological factor of OA is age, usually occurs in the ages of 50–60. The course of the disease is progressive. Although the disease is degenerative in nature, but secondary inflammatory processes can occur as complications, in which case the pain increases and the joint deformity may be accompanied by inflammatory swelling. Morphological changes associated with age, such as thinning and softening of articular cartilage, are caused by cartilage structural protein (primarily proteoglycans) damage due to the reduced regenerative capacity of chondrocytes.

There are several risk factors that can increase joint degeneration. They could be 'modifiable' (e.g. obesity, nutrition, workplace injury, and repetitive strain) or 'non-modifiable' (e.g. genetics, gender, age, and previous trauma) factors.

Predisposing anatomical abnormalities (e.g. hip dysplasia, genu varum) increase the predisposition even under normal strain, but the risk is even greater

in e.g. obesity. On the one hand, body weight has a direct physical effect on the joint and, on the other hand, increases bone mass, which leads to stiffness of the subchondral bone and stimulation of cartilage destruction. *Age* is a clear risk factor that can be further exacerbated by age-related factors (e.g. obesity, joint laxity). In women, hand, knee, and generalized OA are more common. This difference does not occur in hip OA. The role of *sex hormones* is also suggested by the fact that OA is more common in women, it may be related to chondrocyte estrogen receptors. In terms of *ethnicity,* OA is more common in the USA, and less common in the Asian population than in the Caucasian ethnicity. *Physical overload* can also predispose, and in the case of work involving kneeling (e.g. parquetage), the frequency of knee OA increases. Hip OA is also associated with endurance and weight lifting. Prolonged repetitive overuse of the hands leads to damage; carpometacarpal (CMC) OA is known to cause repetitive overuse of the thumb. Previous hip or knee injuries are independent risk factors for OA. The effect is twofold: in addition to injury, altered biomechanics is also a risk factor.

The genetic background of the disease is indicated by the familial incidence of OA, but the inheritance is not as clear as in other rheumatic diseases (e.g. AS). To date, almost 40 genes or gene polymorphisms have been associated with OA, most of which involve genes encoding proteins involved in inflammation and matrix metabolism. To name a few examples: mutations in the genes responsible for the production of collagens, IL-1, and insulin-like growth factor-1 (IGF-1) were detected in case of higher susceptibility to OA.

A number of other conditions can lead to secondary OA *(Table 15.1.)*.

15.1.3. Pathology

OA was considered a predominantly degenerative, age-related wear and tear disease developing due to physical factors. Nowadays, it is known that in addition to mechanical factors, inflammatory and even immuno-inflammatory phenomena play a role.

The pathology of OA is characterized by damage to articular cartilage, consequent joint space narrowing, formation of osteophytes at the joint edges, subchondral bone sclerosis, and thickening of the synovial membrane and joint capsule.

Normally, the cartilage is rich in fluid and forms a soft covering on the bone, which allows movements and shift. Over time, it becomes damaged, cracks and erosions appear on the cartilage surface; this can progress to the uncovering of the bone surface. There is increased remodeling, including sclerosis and thickening, in the subchondral bone.

Table 15.1. Main causes of secondary OA

Trauma	Fractures and sprains penetrating the joints Trauma distant to the joint Microtraumas (vibration, overload)
Metabolic disorders	Ochronosois Hemochromatosis Storage diseases
Endocrine disorders	Diabetes mellitus Hypothyroidism Obesity Acromegaly
Crystalline arthropathies	Chronic gout CPPD, BCP arthropathies
Malformations, static deviations	Hip dysplasia Coxa valga, coxa vara, genu valgum, genu varum Perthes disease Hypermobility syndrome
Other	Secondarily after arthritis Osteochondritis dissecans Osteonecrosis Paget's disease Chondromatosis Hemophilia Neurogenic arthropathy (Charcot joint)

In the cartilage, chondrocytes are surrounded by ECM, the main elements of which are collagen type II, to which type IX. and type XI. collagen is attached. Collagen is connected to proteoglycans (PGs), among which aggrecan is notable, containing a central core protein and glycosaminoglycan (GAG) side chains (chondroitin sulfate and keratin sulfate). GAG side chains bind water molecules. Aggrecans bind to hyaluronic acid (HA) through a linker protein. HA can form a complex with up to 100 aggrecans.

Overall, OA is a complex disease involving articular cartilage, bone, synovium, ligaments, and muscles. In addition to ECM degradation and bone formation, inflammation and general phenomena (e.g. metabolic processes) also play an important role in the pathogenesis of the disease.

Molecular changes in cartilage in early OA are characterized by an increase in water content and consequent edema, which is accompanied by a decrease in collagen type II synthesis and a relative increase of collagen type I. PG content also decreases and short-chain GAG molecules appear. These changes, which otherwise occur with age, result in decreased water-binding capacity of ECM and abnormal biomechanical abnormalities.

Several matrix degrading enzymes e.g. MMPs and aggrecans are known. At the onset of OA, increasingly detached cartilage particles induce inflammation, and the inflamed synovium produces pro-inflammatory mediators (cytokines such as TNF-α, IL-1, and proteases), which stimulate the production of matrix-degrading enzymes (e.g. MPMs, aggrecans), thus enhancing the degradation of the cartilage matrix, forming a vicious circle.

Adipose tissue (the role of obesity) produces a number of mediators, of which the role of adipokines is primary, correlating with the development of OA.

15.1.4. Symptoms of osteoarthritis

The most important symptom of OA is *pain,* mainly following load, which initially only occurs from time to time and then becomes permanent. The pain increases with movement and exertion, decreases with rest, but may persist for hours after increased physical activity. Nocturnal pain is not typical, but may occur in severe, advanced cases or when associated with secondary inflammation.

Joint stiffness can occur in the morning or after a period of a longer rest. Morning joint stiffness, unlike inflammatory diseases, can resolve within 15 minutes. Initial pain and stiffness are characteristic, which disappears after a few minutes. Pain may not always occur only around the affected joint, may also radiate to other areas (e.g. hip OA often manifests as knee pain).

Pronounced OA leads to the narrowing of musculoskeletal function, physical activity, where even daily activities (putting on socks or stockings), walking a few hundred meters, longer standing, stair climbing, kneeling (hip or knee OA), and use of hands, e.g. cooking, cleaning (Heberden OA in the DIP joints of the hand) is difficult and painful. Chronic pain can even lead to depression and sleep disturbances.

In summary, OA is typically associated with pain and limited mobility, which significantly affects quality of life.

15.1.5. Diagnosis of OA

The reasons leading to secondary OA should be clarified during medical history taking.

Physical examination reveals deformity in the affected joints (knee, small joints of the hand), the contours of the joints are blurred. It is usually of bony origin and can be well distinguished from possible secondary inflammation by palpation. Pain occurs on movement of the affected joint. During passive movement decreased range of motion may be one of the first physical signs of OA. The 'cracking', crepitation observed on the displacement of uneven joint

surfaces due to cartilage damage, is usually palpable, less frequently audible. The joint examination must include examination of the load-bearing joints with exercise stress test as well. The varus or valgus position of the knees indicates an increased load on the lateral and medial joint surfaces, respectively. Loose joints also predispose to rapid-onset OA. Examination of the surrounding muscles of the joints and other soft tissues (e.g. bursae) suggests secondary muscle atrophy and associated inflammatory abnormalities (bursitis and synovitis).

Among the imaging techniques, X-ray examination is the most useful to confirm the diagnosis of OA. X-rays of the load-bearing joints (hips and knees) should be taken upright. In addition to clarifying the diagnosis, the examination also shows the extent of disease progression and can be used to rule out other diseases causing similar complaints (e.g. algoneurodystrophy, Paget's disease). The most common radiological signs are joint space narrowing due to cartilage death, osteophyte formation and subchondral sclerosis as a result of bone remodeling. However, it should be emphasized that X-ray abnormalities and patient complaints do not always correlate with each other. Other imaging techniques (MRI and UH) may be used only in case of differential diagnostic issues and to detect the signs of inflammation.

Most *routine blood tests* are not warranted in OA. The acute phase reaction (ESR, CRP) shows normal values for the given age. Laboratory tests are performed to differentiate OA from other diseases (e.g. gout, hemochromatosis, arthritis).

ACR criteria help to diagnose hip and knee OA *(Table 15.2.)*. ACR classification criteria help the recognition of knee, hand, and hip OA. Nevertheless, since radiological abnormalities are more common, using the aforementioned ACR criteria the incidence of OA can be underestimated compared to that according to imaging criteria.

Table 15.2. Diagnostic criteria for hip and knee OA (ACR)

Hip OA	Knee OA
A) Hip pain + at least two of the following symptoms: • We <20 mm/h • femur or acetabulum arthrophyte on X-ray • narrower articular gap on X-ray Or *B)* Hip pain + one of the following: • femur or acetabulum arthrophyte on X-ray • narrower articular gap + We <20 mm/h	*A)* Knee pain + arthrophyte on X-ray + at least one of the following: • age >50 years • morning joint stiffness <30 minutes • crepitation during examination Or *B)* Knee pain + one of the following: • arthrophyte on X-ray • age >40 years + morning joint stiffness <30 minutes + crepitation

In case of knee and hand OA, diagnosis is based on risk factors, clinical symptoms, and physical signs according to the diagnostic criteria established by EULAR. Conventional X-rays do not pose a condition, are rather of additional importance. Therefore, based on only three clinical symptoms (pain, short-term morning joint stiffness, and functional limitations) and three physical signs (crepitation, bone growth, and decreased range of motion) the diagnosis can be made with great certainty. Thus, this method is easy to apply in primary care.

15.1.6. Treatment of OA

When treating OA patients, it is essential to educate and inform the patient about the important role of healthy eating and weight control, joint protection and reduction of load, regular physiotherapy and physical activity, pain relief and the use of aids if necessary is also important.

A complex therapeutic approach using an appropriate proportion of pharmacological and non-pharmacological therapies is optimal.

As a first step of *non-pharmacological treatment,* it should be emphasized that the disease itself is very common, however, in most cases it causes only a temporary complaint, can be well treated with non-pharmacological treatment, and generally does not lead to severe functional impairment. Weight reduction alone significantly reduces the complaints of patients with knee and hip OA. Heat treatment is often used in the form of hot water packs, hot wraps, paraffin when inflammation is mild or absent, and cold treatment in the form of wraps or icing in inflamed OA. It is listed in several recommendations as a supplementary, safe analgesic treatment. Within electrotherapy, TENS can be used even at home providing effective and safe pain relief. Previous European recommendations included ultrasound therapy in combination with warm treatment in hand OA. The role of physiotherapy is very important. Two types of movement are recommended: aerobic exercise and strengthening the muscles around the affected joint (e.g. quadriceps muscle in case of knee OA), which also relieves pain and increases joint stability, thereby slowing the progression of the disease.

During complex treatments used in spas, patients can receive a combination of the abovementioned treatments (electrical treatments, mud packs, underwater physiotherapy in case of wear of large weight-bearing joints).

Among the pharmacological methods, topical NSAIDs and capsaicin-containing patches, gels and creams are over-the-counter medicines. Their use is only suitable for OA of superficial joints (e.g. knees).

Among the systemic medications that can be used as simple analgesics, paracetamol-containing agents are the first choice. Their recommended daily dose

is 1.5–3 grams, divided into 3 portions. Prolonged use may be hepatotoxic and toxic to the kidneys. In case of ineffectiveness of paracetamol or if OA is accompanied by secondary inflammation, the use of NSAIDs may be considered. It is important to consider the patient's co-morbidities, as COX-1 inhibitors predominantly increase the risk of gastrointestinal and COX-2 inhibitors increase the risk of cardio- and cerebrovascular adverse events. The preparations can only be taken for a few days as a cure. Given the over-the-counter drug arsenal, patients should be made aware of the possible dangers of using multiple NSAIDs together, as in this case the effect does not increase, only the risk of side effects. They are available in different forms, tablets, granulates, drops, and suppositories. Milder opioids such as tramadol can be used as the next step in pain relief. The dose can be increased up to 300–400 mg daily, with nausea and vomiting as possible side effects, in which case the dose should be increased slowly. If the pain is still uncontrollable, stronger opiates, transdermal fentanyl, may be required. In the elderly, side effects (nausea, constipation, dizziness, confusion, and itching) may limit their use, and addiction may also develop.

In the treatment of OA corticosteroid and hyaluronic acid derivatives can be used intraarticularly. Although corticosteroids significantly reduce patient complaints and improve the movement of the affected joint, their effects last only temporarily, for a few weeks and may be more likely to damage the cartilage surface in the long-term use. Therefore, its use is recommended only 3–4 times a year in cases of acute inflammation. Hyaluronic acid derivatives are recommended to be applied to the affected joint weekly, altogether 3–5 times. In addition to its "lubricating" function, which improves joint movement, the high-molecular-weight protein also has a moderate analgesic and anti-inflammatory effect.

Glucosamine and chondroitin sulfate, physiological cartilage constituents, can also be taken orally or administered parenterally. The formulations are in part over-the-counter medication and are also available in combination. The use of glucosamine 1500 mg daily or chondroitin sulfate 1200 mg daily may result in pain relief and function improvement. Although the "cartilage-building" effect of the products can be assumed, it is not clear from clinical trials. The existence of disease-modifying (structure-preserving) therapy in OA, similar to other arthritis, is the subject of ongoing research. Several studies have been performed with different components of the matrix described in detail earlier: hyaluronic acid, proteoglycans, doxycycline, risedronate, strontium ranelate, platelet-rich plasma (PRP), vitamin D, hydroxychloroquine, methotrexate, antibody against NGF (tanezumab), anti-IL-1 therapy, TNF inhibitor, nitric oxide, protease inhibitors, and intracellular cytokine signaling molecule inhibitors are under in-

vestigation, but these are generally minor, short-term studies and have not been successful yet. At present, therefore, it can be said that disease-modifying therapy for OA has not been resolved yet.

In case of severe, advanced knee and hip OA, *surgical interventions* are considered. Surgical indication is persistent pain, joint stiffness and limited mobility despite conservative treatments. There is little evidence for the frequently used arthroscopic lavage and debridement; these are more likely to be considered in structural abnormalities resulting from a previous injury. Osteotomies are used to correct joint axis deviations or to delay prosthetic surgery by relieving the damaged surface. Implanting a prosthesis reduces pain, thereby improving quality of life, but postoperative rehabilitation is not negligible, it ensures the fullest possible musculoskeletal function.

Medical aids can help with anatomical correction, improving biomechanical condition, and reducing load. Canes and other walking aids, walking frame, rollator reduce joint load and pain in knee and hip OA. It is important to draw the patient's attention to the fact that the applied cane should be used in the opposite hand. Assistive devices that facilitate daily activities (for example, in the case of hip and knee OA, raised toilet seat, shower instead of a tub, and rail, and jar opener devices in case of hand OA) can improve the patients' quality of life.

15.2. Low back pain

15.2.1. Introduction

Low back pain is one of the most common musculoskeletal complaint, with 84% of people suffering from low back pain in their lifetime, mostly between the ages of 45 and 65. Altogether 90% of acute low back pain heals without treatment within 4–12 weeks, but within a year, 73% of patients complain of low back pain again.

Degenerative diseases of the spine include abrasion abnormalities of the discs, vertebral bodies, ligaments, and joint protrusions, as well as consequent functional impairments.

Abnormalities leading to low back pain may include congenital factors (such as LV vertebral sacralization in lumbosacral transition and SI vertebral lumbarization), scoliosis, spinal stenosis, discopathy, Schmorl's nodes, and ligament calcification, pseudoarthrosis and osteitis condensans ilii between spinous process. In addition to which external factors (such as a high degree of unilateral exertion, physical work), and obesity also play a role.

In the pathology of the disease, in addition to the cartilage damage observed in OA, the peculiarities resulting from the special structure of the intervertebral discs must also take into account.

15.2.2. Clinical presentation and diagnosis

Low back pain often has a sudden onset, however persistent low back pain is common, especially in old age, mainly due to degenerative abnormalities. However, in a few percent of cases, a serious illness (tumor, inflammation, or vertebral fracture) may be the underlying cause; screening these patients is the biggest challenge in diagnosing low back pain.

When taking the medical history, targeted questions should be asked to find out whether such a serious disease (e.g. tumor, infection) may be the cause of the illness, or whether there are any complaints indicating neurological complications (e.g. sensory or motor disturbances suggestive of root involvement, sensory deficit, and so-called cauda equina syndrome with sudden urinary of fecal incontinence).

During physical examination high pressure sensitivity at one point above the spine may indicate a tumor or infection, while bilateral comparative, sensory, muscle strength, and reflex examinations are required to elucidate root involvement.

Among the imaging techniques, the conventional X-ray examination should be performed after 2–4 weeks in case of non-improving or increasing complaints. Ultrasound examination may help to detect soft tissue changes, and bursitis. EMG, ENG can help identify root and peripheral nerve origin and carpal tunnel syndrome. CT and MR examination can be used to find specific cause, and support surgical indication (tumor or severe discus hernia) *(Table 15.3.)*.

Table 15.3. Characteristics of specific and non-specific low back pain

Specific origin
• pathological diagnosis is possible, necessary
• red flags
• pain at night, at dawn
• morning stiffness of spine: 30–60 min.
• pain is relieved by movement
• stagnant progressive course
• laboratory and imaging is required
• causal therapy

Not specific
- cause is unknown, only symptomatic diagnosis is possible
- no warning signs
- pain during the day
- triggered by movement, work, and load
- relieved by rest and unburdening
- morning stiffness of spine: 5–10 minutes
- laboratory, imaging not required
- improvement by conservative therapy
- surgery is not required

15.2.3. Causes of low back pain

Lumbago is the most common cause of low back pain, which usually occurs suddenly after a bad movement or physical strain. Its exact location is often undetectable, and the nerve irritation that causes pain can come from the muscles and fascia of the area, and small joints or ligaments of the spine. The pain usually does not radiate; and can be both unilateral, or bilateral. The pain is pronounced, it can even cause limited mobility; almost every movement intensifies the pain, it is difficult to find a less painful position. It resolves by a few days of local heat treatment, use of painkillers, NSAIDs and bed rest, but not in case the patient is bedridden. Initially, due to the pain is very strong, pain relief is paramount, and then spinal exercise, started in parallel with the reduction of complaints, reduces the risk of recurrence of the complaints.

In the case of *discopathy and discus hernia,* the anulus fibrosis of the intervertebral discs' ruptures, the nuclear pulp protrudes into the spinal canal and can cause pain by compromitting the nerve root. It most often develops between the ages of 35 and 45, and the disc between L IV-V and L V-S I is affected. The pain usually occurs suddenly, it is a stabbing pain. Depending on the affected roots, pain may radiate on the anterior-lateral surface of the thigh and lower leg to the dorsum pedis and I. toe (L5 root involvement) and through the lateral surface of the thigh and lower leg to the V. finger (S1 root irritation). Coughing and sit-ups increase the symptoms. Determination of the Lasegue signal during physical examination can be used to verify root involvement. By lifting the outstretched lower limb, the patient may suddenly report severe pain in the lumbar region and lower limb. Pain on the affected side can often be provoked by raising the contralateral limb as well. Accurate diagnosis of discus hernia requires CT or even more so MRI examination, since the diagnostic value of conventional X-rays is small. Imaging tests should be performed urgently only in the case of physically detectable complications requiring surgery (e.g. cauda equina syndrome, paresis presenting as a complication), since most disc hernia-

tion can improve with non-surgical treatment. Prolonged, severe pain lasting for months also requires precise clarification of the lesion and, if necessary, surgical intervention. The non-surgical treatment options for disc herniation are practically the same as that of lumbago, however, the mobilization of patients should be slower and more gradual.

Spinal stenosis is a disease affecting people over 60 years of age and men, in which degenerative abnormalities of the lumbar spine can cause spinal stenosis and root compression symptoms. The narrowing most often occurs at the height of the L IV-V and L III-IV discs, which can be considered severe at a spinal canal diameter of less than 7 mm. Cauda fiber dysfunction causes intermittent limping (vertebrogenic claudication), numbness, cramps, pain, and weakness in the lower extremities after walking a certain distance. Straightening worsens while short resting and leaning forward improve complaints. Results of physical examination are poor, with pressure sensitivity above the lumbar spine the Lasegue signal is usually negative. CT is the most appropriate method for diagnosing a bone lesion. If complaints do not decrease with conservative treatment, surgery is required.

Inflammatory low back pain most commonly occurs in spondylarthritides (e.g. ankylosing spondylitis) primarily in young adulthood. In contrast to degenerative low back pain, the pain occurs at dawn, disturbs the patients rest, is accompanied by a feeling of stiffness, and is relieved by movement.

In rare cases, low back pain can be caused by *cancer,* metastasis to the vertebrae, or, less commonly, by primary tumor or epidural metastasis. The processes that cause metastasis can be of prostate, lung, breast, kidney, gynecological, or lymphoma origin. It is very important to screen for as soon as possible, as a late diagnosis can worsen a patient's chances of survival. Anamnestic data are important, the history of the cancer, the age, the insidious onset of pain, which persists and does not decrease with bed rest and pain relief, raises the possibility of cancer origin. Complaints and symptoms commonly associated with cancer, such as loss of appetite, weakness, and weight loss, may also aid in diagnosis. Imaging techniques (X-ray, CT and MRI) and, less commonly, laboratory examinations (e.g. detection of paraprotein from serum in case of suspected multiple myeloma) can help to confirm the underlying disease. Pharmacological analgesic treatment is less effective, the primary goal is causal treatment.

Epidural abscesses are a rare, but may even be a life-threatening cause of low back pain. The pathogen can usually be transmitted hematogenously, predisposing factors being diabetes mellitus, renal failure, impaired condition caused by alcoholism, previous surgical or rheumatological intervention. Intolerable

sharp low back pain is usually followed by fever and pain radiating to the gluteal region, and lower limbs, accompanied by movement disorders. Among laboratory tests, the significantly elevated inflammatory parameters (ESR and CRP levels) and the presence of bacteria that can be cultured from the bloodstream may indicate an abscess, the exact localization of which can be detected by MRI. The disease has a significant mortality, requires urgent surgical intervention, and long-term intravenous antibiotic treatment.

Acute organ disease – such as appendicitis, kidney stones, intestinal perforation, rectum tumor, ectopic pregnancy, pancreatitis, aortic aneurysm, incipient Herpes zoster infection, or a slowly progressing specific cause such as spinal tuberculosis or benign conus-cauda tumor – may be the underlying cause of radiating pain requiring urgent internal medicine treatment, sometimes surgical intervention.

15.2.4. Treatment of low back pain

While in the more developed countries the recognition and treatment of low back pain and osteoporosis, i.e. degenerative musculoskeletal diseases in general, takes place mainly in primary care (i.e. competence of a general practitioner), in Hungary and the surrounding countries the majority of patients are treated by specialists. Accordingly, the majority of patients with low back pain should be treated by a GP and only in complicated cases or in cases showing no improvement within 4–6 weeks, help of appropriate specialist (rheumatologist, orthopedist, traumatologist, neurologist, neurosurgeon, and rehabilitator) is needed.

The algorithm of investigation, treatment, and care should go hand in hand. One possible algorithm is illustrated in the figure below *(Figure 15.1.).* (A similar algorithm can be used for neck and back pain)

First-line treatment of low back pain is classically started with analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants.

In most cases, however, either no pharmacological treatment is required or, other procedures (lifestyle, relaxation, exercise) used alongside NSAIDs help. Analgesics (paracetamol, acetaminophen) have almost the same effect as NSAIDs, but are much safer and cheaper. In terms of comorbidities in elderly, it is very important to consider the gastrointestinal damaging effect of traditional NSAIDs and the increased cardiovascular risk of selective COX-2 inhibitors. The classic "sciatic infusion" used to treat acute low back pain contains a corticosteroid in addition to the analgesic and muscle relaxant to eliminate radiculitis and local edema. Infusion of diclofenac content may be effective in inflammatory spinal pain. In

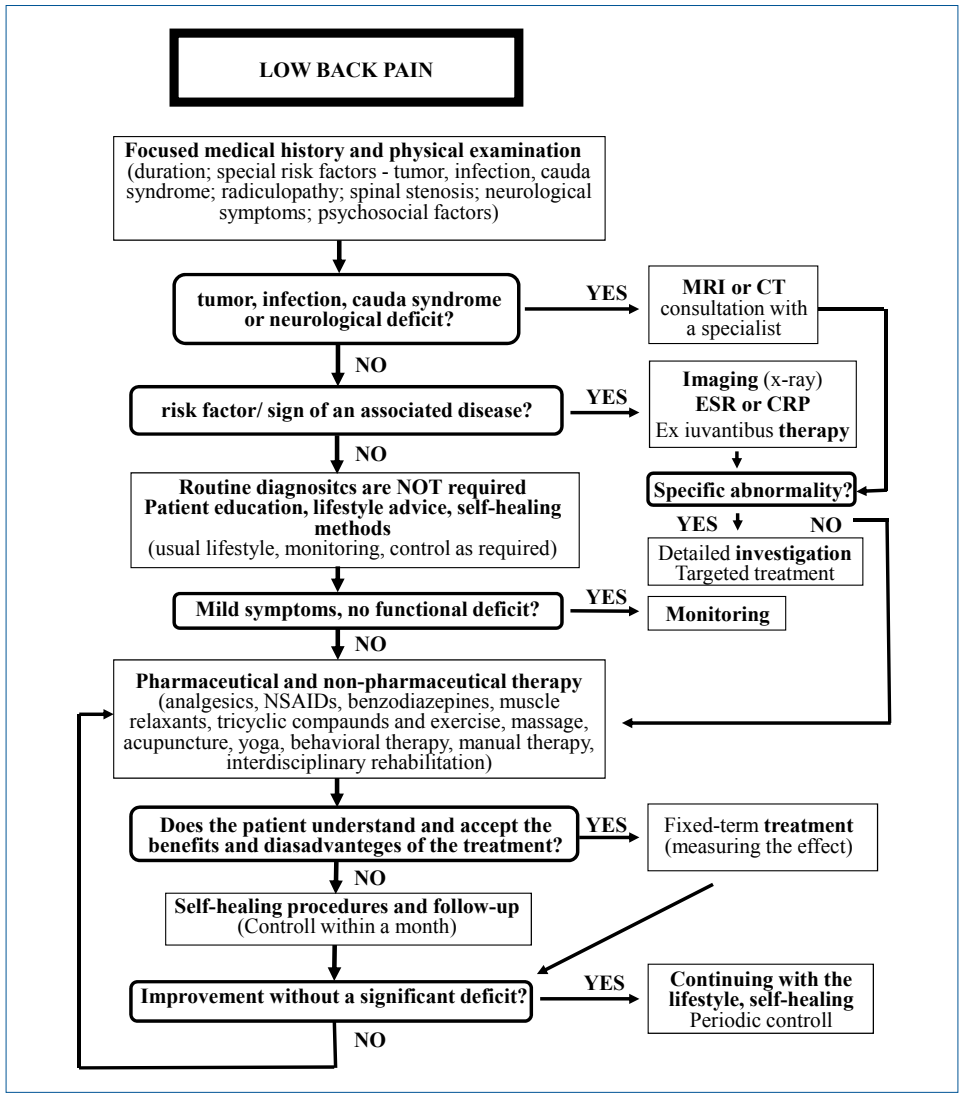

Figure 15.1. Algorithm for investigating and treating low back pain (spine pain)

more severe cases, opiate analgesics (tramadol, fentanyl) can also be used transdermally. As for local treatment, corticosteroid is administered paravertebrally by local depot injection in combination with lidocaine.

One of the most difficult things is to persuade a patient with frequent severe pain to continue *physical activity*. In contrast to the old recommendations of previous decades recommending several days' of strict bed rest (lumbago, lumboischialgia), now, gradual physical activity is required for acute low back pain.

Any form of *physiotherapy* helps maintain daily activity. In addition, the analgesic effect of endorphins produced during exercise, the effect of maintaining mobility, and a positive attitude helps a lot in overcoming low back pain. There are several exercise programs known: scoliosis exercises, in case of discopathy McKenzie exercises, osteoporosis exercises. Physiotherapy methods (massage, manual therapy, TENS, other electrotherapy, ultrasound) often used instead of exercises (!), have only a complementary effect; among the several physiotherapy techniques, exercise is the primary.

As for the principle of *complex treatment,* in large studies, the combined use of medication and physiotherapy has been shown to be more effective than medication alone. The goal is a more durable, complex program to restore function. This combines initial medication with physiotherapy.

When low back pain occurs, especially in acute cases, setting up a *surgical indication* is a common problem. The decision is made based on the joint decision of the patient, GP, rheumatologist and neurosurgeon. It is often really difficult to draw the line beyond which surgery is absolutely necessary. Many methods are used, from injections through neuroablative techniques to open surgeries.

It is important to highlight the importance of *rehabilitation,* which unfortunately is often partial or even completely missed. This complex movement-physiotherapy exercise program should be continued after surgery (even more intensively if necessary), otherwise the symptoms often return (scarring at the site of surgery, *failed back syndrome*).

15.3. Neck pain

Neck pain can result from a variety of anatomical structures, including soft tissues along the spine, intervertebral discs and joints, the spinal cord, and the roots and nerves exiting it, and internal organs located at the neck. The causes of pain can be degenerative and inflammatory rheumatic disease, trauma, infection, or tumor, although the exact cause and location of the common neck pain lasting for a few days often remains unknown. The pain may be localized to the neck itself, or it may cause radiating pain in case of root, spinal cord compression; the latter occurring primarily in case of involvement of the four lower root (C5-8), since these provide nerve supply to the upper limbs.

15.3.1. Neck pain localized to the neck

Pain from degenerative abnormalities of the cervical spine usually presents in the neck and nape of the neck. The symptoms in the back of the neck can be so severe that the patient's leading complaint is a headache. X-ray examination can confirm the abnormalities characteristic of cervical spondylosis, but there is no close correlation between the patient's complaints and symptoms, and the detectable radiological signs. Since high blood pressure can also cause headaches at the back of the head, the values of blood pressure should always be asked.

Herniated cervical disc can only cause pain localized to the neck in the case of injury to the richly innervated annulus fibrosis, in case the hernia causes neither root nor myelin compression. If the neck pain is of myofascial origin, the pain is caused by the spasticity of the trapezius and periscapular muscles. In these cases, the pain can be provoked by cold, drafts, bad movements or stress. Complaints can be persistent, and pathological reflex muscle spasm can persist even after the cause of the muscle spasm has ceased.

Atlanto-axial joint arthritis associated with rheumatoid arthritis may also be the underlying cause of neck pain. The pain can be provoked by rotation of the neck, while arthritis of the atlanto-occipital joint causes severe pain during flexion and extension of the neck. Functional cervical radiographs can be used in the diagnosis, while MRI gives a more precise picture.

In rare and advanced cases *ankylosing spondylitis* can cause inflammatory pain in the cervical spine, which increases at rest and decreases with movement. Considering the upward spread of the disease, stiffness of the lumbar and thoracic spinal segments can already be observed in cervical spine pain.

Infections and tumors rarely cause neck pain. In this case, the source of pain is the destruction of vertebral bodies and irritation of the nerve endings of the periosteum, and the altered biomechanics of discs and spinal joints. History of cancerous disease or bacteremia, immunosuppressed condition, fever, chills, unexplained weight loss or weakness, and persistence or exacerbation of pain during the night may also be indicative of underlying cancerous or infectious disease. Early diagnosis and early treatment are very important.

15.3.2. Diagnosis

Adequate medical history and physical examination are sufficient in the vast majority of cases to make an appropriate diagnosis for adequate treatment; imaging and laboratory tests are required in case of certain warning signs (data suggestive of infectious or cancerous underlying disease, persistent, therapy-resistant complaints). Acute neck pain is often caused by bad neck position

during sleeping, bad movement, or computer neck syndrome in those sitting in front of a computer. This is when the spasticity of the paravertebral muscle develops, there are palpable, painful lumps in the muscle, accompanied by a temporary decreased range of motion. Persistent pain, accompanied by limited range of motion, is most often caused by degenerative abnormalities, but AS involving the cervical spine can lead to severely decreased range of motion. Radiculopathy can also be caused by disc herniation or degenerative changes in the joints and consequent bone growth (osteophyte). In the case of very severe neck pain, when the patient tries to reduce their complaints by supporting their head, even a small pressure exerted on the head can significantly increase the pain. In addition to disc herniation, there is the possibility of sterile or infectious spinal inflammation (spondylitis, spondylodiscitis or osteomyelitis), malignant vertebral process and bleeding or inflammation accompanying meninx irritation, which requires urgent diagnostic and therapeutic progress.

15.3.3. Treatment

In acute cases, it is recommended to rest the neck in a lying position or by a so-called Schanz collar, and as for the medication painkillers and muscle relaxants should be used. Since degenerative lesions are often associated with a secondary inflammatory process, the use of NSAIDs or topical steroid injections may be attempted. In addition to medication, physiotherapy is very important.

15.4. Back pain

Bad posture is most often responsible for the development of back pain. Unilateral, static loading of the spine, sedentary lifestyle, and poor posture lead to weakening and shrinking of the muscles adjacent to the spine, which is usually accompanied by deep, unpleasant pain. Later, the perpetuating postural defect increases the risk of developing degenerative abnormalities, therefore it is important to master and perform the exercises that ensure the proper posture.

Scheuermann's disease developing in adolescence and having an incidence of over 10%, can also contribute to back pain in the future. The essence of the disease is a vertebral growth disturbance, as a result of which vertebral end plate becomes uneven, impressions are formed on it, and the vertebrae can become wedge-shaped in side view. As a result of the disease, the physiological kyphosis of the dorsal spine increases or, less frequently, flattens, which may initially manifest itself only in a decrease in static load capacity, and later in persistent

back pain. The development of deformities can be slowed down or stopped by regular spinal exercises and swimming.

In the elderly, in the background of back and low back pain following minor trauma osteoporotic *vertebral compression fracture* is considered. The vertebral compression fracture in addition to acute pain, may also predispose to the development of increased dorsal kyphosis causing chronic pain and consequent degenerative lesions. It is important to clarify the freshness of the process, if the process is fresh, vertebroplasty, filling the collapsed vertebral body with cement is possible in some cases.

In case, the back pain presents relatively quickly, does not decrease at night, or is associated with fever or unexplained deterioration, the possibility of inflammatory or cancerous origin also arises, necessitating urgent diagnostic progression. However, organ disease, infection, or abnormalities that require surgery, such as herpes zoster infection, tuberculosis, heart attack, pancreatitis, tumor and cholangitis should also be considered. In the case of degenerative back pain, in addition to analgesics, physiotherapy, proper posture and therapeutic swimming should dominate.

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16. Metabolic bone diseases

Ágnes Molnár

16.1. Introduction: definition

Disrupted balance of bone resorption and formation is basic feature of generalized metabolic diseases. Among the diseases in this group, postmenopausal osteoporosis, Paget's disease of the bones and primary hyperparathyroidism are primarily associated with accelerated bone resorption, while rachitis and osteomalacia are present in reduced formation, and both processes play a role in the development of renal osteodystrophy.

16.2. Osteoporosis

16.2.1. Epidemiology and etiopathogenesis

The most common bone disease in civilized societies is osteoporosis. According to the WHO osteoporosis is the third most common disease after cardiovascular diseases and cancer in the world. The disease can remain asymptomatic for a long time, does not cause a complaint, that is why it is also called the silent epidemic.

According to estimations, 200 million people worldwide have osteoporosis, 9 million of whom suffer from low-energy bone fractures each year. On average, 10% of the population is affected; the incidence of the disease being higher in the northern countries. In Hungary, 600 000 women and 300 000 men over the age of 50 are affected. 15 000 new hip, 40 000 vertebral, 27 000 wrist and 9 000 upper arm fractures are registered annually. Vertebral fractures need to be treated with particular care due to their frequency and hip fractures due to their severe consequences, as the latter most often require hospitalization and surgery, and a third of patients die within a year, with an additional 50% becoming permanently disabled, 66% of the patients will require help.

Osteoporosis is defined as a decrease in bone mass, a damage to their microstructure, the clinical manifestation of which is low force fracture. Osteoporosis is considered a multifactorial disease where the role of genetic factors is very

significant, according to some data it is more than 60%. Various risk factors are responsible for the development of the disease, some of which cannot be influenced (female gender, age over 65, Caucasian race, history of osteoporosis in first-degree relatives, thin physique, early menopause), others can be influenced (low physical activity, sedentary lifestyle, calcium deficient diet, significant alcohol consumption, smoking, certain medications). Low physical activity and age over the age of 65 predispose to both osteoporosis and fracture, in addition, previous fracture, hip fracture in the family history, low bone mass, visual and balance disorders leading to frequent falls, medicines that increases this and an environment that is dangerous for fall is also predisposing to fracture.

Continuous bone metabolism, modeling and remodeling is based on the continuous communication of osteocytes, osteoblasts and osteoclasts. Remodeling is controlled by mechanostat; the essence of which is that the bone mass and bone strength is adapts to the mechanical stress. Lack of physical activity leads to bone loss, negative bone balance. Increased physical activity increases bone mass, size, and strength. Forces affecting on bone are perceived by osteocytes. Several factors play a role in the pathogenesis of involutional osteoporosis. These factors involve cells (osteoclast, osteoblast / osteocyte, T-cells, dendritic cells), cytokines (RANKL, TNF-α, IL-17), mediators (PG), hormones (D3, PTH) and proteins. TNF-α and IL-17 play a key role in the development of osteoporosis. TNF-α induces RANKL expression and cytokine production (IL-1, 6, PG), causes direct preosteoclast activation and osteoblast inhibition, while IL-17 directly activates preosteoclasts, mediates PTH effect by osteoblasts and stimulates osteoblast / osteocytes to RANKL expression.

RANK-RANKL-OPG system imbalance is responsible for the development of osteoporosis. Normal osteoblast and osteoclast balance ("coupling") are disrupted and OPG (osteoprotegerin) -regulated bone formation decreases, while RANKL-regulated bone resorption increases.

Osteoporosis can be primary or secondary. In involutional osteoporosis, the increase in bone resorption is triggered by a decrease in the estrogen levels; the estrogen inhibiting bone resorptive cells and cytokines that activate these cells. In women, hormone levels fall abruptly as the ovary loses its function. In men, estrogen forms from testosterone by aromatase enzyme; the decrease in hormone levels is gradual due to a gradual decrease in testosterone production in the testes.

In the absence of estrogen, T and B lymphocytes are activated along with mononuclear cells, leading to the accumulation of cytokines. Increased production of RANKL, TNF-α, IL-1, IL-6, IL-7, IL-11, IL-17 leads to increased bone

resorption. In the absence of estrogen, the amount of OPG and TGF-ß also decreases, which also causes a decrease in bone mass. In old age, in addition to the lack of vitamin D and calcium and developed secondary hyperparathyroidism, the aging of bone-building cells and the decrease of their synthetic activity lead to the development of osteoporosis.

In *secondary osteoporosis* there are some detectable causes or disease(s) underlying osteoporosis *(Table 16.1.)*. Causes may include endocrine causes, e.g. diabetes mellitus, thyroid and hypophysis dysfunction, and increased parathyroid and adrenal gland function. Hematological disorders (multiple myeloma, leukemia), gastrointestinal disorders with impaired absorption, and chronic liver diseases can also lead to secondary osteoporosis. Chronic lung, neurological and renal diseases, chronic inflammatory rheumatic diseases (rheumatoid arthritis, SLE) and certain drugs (glucocorticoids, anticoagulants, antiepileptics, thyroxine, proton pump inhibitors) can also cause secondary osteoporosis.

Table 16.1. Major conditions leading to secondary osteoporosis

Endocrine disorders	Hyperthyroidism, Cushing's disease, hypogonadism, diabetes mellitus, hypopituitarism, hyperprolactinemia
Tumors	Multiple myeloma, hematological malignancies, mastocytosis
Gastrointestinal diseases	Malabsorption, celiac disease, alcoholism, inflammatory bowel disease, chronic liver disease
Rheumatic disorders	Arthritides, SLE and other autoimmune diseases
Respiratory diseases	COPD
Immobilization	E.g. after a stroke
Kidney diseases	Renal failure, renal hypercalciuria
Medication	Corticosteroids, thyroxine, cytostatic drugs, cyclosporin, methotrexate, anticoagulants, antiepileptics, GnRH analogs

Peak bone mass is reached at the age of 25–35; the bone mass is higher in men than in women. Then, bone mass begins to decrease, the process progresses gradually in women for about 5 years after menopause. This period is characterized by rapid trabecular bone loss, therefore mainly wrist and vertebral fractures are common, and later in the elderly the trabecular and cortical bone mass also decreases and the number of hip fractures increases. For the above-mentioned reasons, women are expected to develop osteoporosis at a younger age.

16.2.2. Clinic picture and diagnosis

The clinical picture is characterized by the fact that the disease may remain asymptomatic for a long time and does not cause a complaint. Osteoporosis is also called a silent epidemic, therefore it is difficult to recognize at an early stage. Warning signs of asymptomatic decrease in the height of the vertebral bodies are rib, back and low back pain, which occur when standing longer and when there is a decrease in the patient's height. In some cases, back pain is associated with a consequent increase in dorsal kyphosis and a decrease in lumbar lordosis.

Diagnosis of osteoporosis can be suspected based on the anamnesis and clinical picture, and diagnosis can be made with the help of osteodensitometry, radiological and laboratory tests. When taking a medical history, it is important to ask about previous fractures, family history, previous falls and medication, as well as risk factors.

Physical examination reveals increased dorsal kyphosis, decreased height, shortened spine, and flattened Michaelis' rhomboid. Measuring and comparing body height with juvenile body height is particularly important, since its 4 cm decrease raises suspicions of vertebral body fracture. The posture changes, the crista-rib distance decreases, the skin of the trunk wrinkles symmetrically, which is called a Christmas tree syndrome. Pain at one point that can be provoked by percussion, and fixed retroflexion of the thoracolumbar spine may also be indicative of vertebral fracture.

Patient examination is followed by determination of the bone density, for which *densitometric examination* performed by photon absorption osteodensitometry is used. In clinical practice, the dual energy X-ray absorptiometry (DEXA) method is widespread. DEXA can be used to examine both peripheral and axial bone regions. The measured bone mineral density (BMD; g/cm^2) is compared to the mean, peak bone mass (PBM) of healthy young individuals, and is given as a T-score, which is the deviation of the measured bone density from the average peak bone mass in youth -expressed in standard deviation. According to the 1994 WHO definition, if the T-score is between –1.0 and –2.5, it means osteopenia, if the T-score is below –2.5, osteoporosis, and in case there is also a low-energy fracture, it is severe osteoporosis. Each unit decrease in T-score doubles the risk of fracture.

Measurement of bone density is warranted for women over 65 and men over 70, for women and men aged 50–69 in case of osteoporosis and / or present fracture risk factors or fractures, and in case of diseases or medications predisposing to low bone mass or bone loss, and before a long-term steroid treatment.

An axial DEXA that includes both the spine and the hip region is best suited for measuring bone mass. In special cases, peripheral (forearm) DEXA should be requested for diseases affecting cortical bone (hyperthyroidism, hyperparathyroidism, diabetes mellitus, and chronic renal failure). Other examination methods (quantitative computed tomography and magnetic resonance imaging) are also suitable for measuring the quantity and quality of bone, but these have not become widespread in routine practice due to their cost.

Decreased bone mass does not automatically mean osteoporosis, as it can be caused by many diseases, i.e. the diagnosis of osteoporosis is based on the exclusion of other diseases (mainly hyperparathyroidism, osteomalacia, cancer, renal osteodystrophy), therefore, in case of abnormally low bone density further examinations need to be performed.

Classical X-ray plays an important role in recognizing fractures and assessing the severity of the disease. A lateral spinal image is taken to detect possible vertebral compression. The vertebral bodies are translucent, with longitudinal striation and sclerotic end plates. Vertebral compression occurs in the dorsal and lumbar sections (wedge vertebra or biconcave vertebra), but it is not uncommon to see collapse in several other vertebrae. A 20% or 5 mm reduction in the height of the vertebral body is indicative of vertebral compression fracture. Fresh vertebral compression (instability of the end plates) can be diagnosed by comparing X-rays performed in standing and lying position, and in the case of an inpatient, by hypomochlion image, or by MRI. Severe scoliosis, kyphoscoliosis, and M. Scheuermann can also cause X-ray changes similar to vertebral compression. Conventional X-rays can also help diagnose other metabolic bone diseases.

Routine laboratory tests (measurement of serum calcium, phosphorus, creatinine, alkaline phosphatase, urinary calcium and phosphatase excretion in collected 24-hour urine, calcium / creatinine ratio from morning urine, tubular phosphate reabsorption) help identify osteoporosis, osteomalacia, hyperparathyroidism, Paget's disease of the bones, and other metabolic bone diseases *(Table 16.2.)*.

Table 16.2. Laboratory differential diagnosis of metabolic bone diseases

	Serum calcium	Serum phosphate	Alkaline phosphatase	Urine calcium	Urine phosphate	TRP (%)
Osteoporosis	=	=	=	= or↑	=	=
Osteomalacia	= or↓	↓	↑	↓	↓or =	= or ↓
Primer hyperparathyroidism	↑	↓	↑	↑	↑	↓

	Serum calcium	Serum phosphate	Alkaline phos-phatase	Urine calcium	Urine phosphate	TRP (%)
Seconder hyperpara-thyroidism	= or↑	↓	↑	= or↓	= or↑	↓
Paget-disease	=	=	↑	=	=	=

=: no change; ↓: decrease, ↑: increase, TRP: tubular reabsorption of phosphate

Tests to be performed at first appearance should include serum calcium, phosphorus, alkaline phosphatase, PTH, TSH, liver and kidney function parameters, erythrocyte sedimentation rate, blood count, and urinary calcium excretion. These are not abnormal in patients with osteoporosis. Vitamin D deficiency is often found in the background of calcipenia, therefore measuring serum 25-OH-D3 levels is also an important laboratory parameter in the differential diagnosis.

With the help of *special bone metabolism tests,* substances produced by osteoblasts and osteoclasts are introduced into the blood and urine in connection with bone turnover. These are biochemical markers of bone formation and bone resorption, the clinical significance of which is that they predict the risk of fracture regardless of ODM outcome, and the effectiveness of therapy can be examined as early as 3 months after starting treatment. Markers of bone formation in serum include the use of bone-specific alkaline phosphatase, C- and N-terminal propeptides, and osteocalcin. The most accepted markers of bone resorption are examination of serum amino- and carboxy-terminal telopeptide levels of collagen type I, tartrate-resistant acid phosphatase isoenzyme (TRAP-5, TRAP-6) and urinary hydroxyproline and type I collagen pyridinoline (PYD) and measurement of the amount of deoxypyridinoline (DPYD) crosslinks *(Table 16.3).*

Table 16.3. Biochemical bone markers

Bone resorption	• C-terminal telopeptide (β-crosslaps) (serum) • N-terminal telopeptide (serum) • tartrate-resistant acid phosphatase isoenzyme (TRAP-5, TRAP-6) (serum) • pyridinoline (PYD) and deoxypyridinoline (DPYD) crosslinks (urine) • C-terminal (CTX) and N-terminal (NTX) cross-linked polypeptides (urine) • – hydroxyproline (urine)
Bone formation	• bone-specific alkaline phosphatase (serum) • osteocalcin (serum) • – C-terminal (PICP) and N-terminal (PINP) collagen extension propeptides (serum)

16.2.3. Therapy

The results of the DEXA and the calculation of the 10-year probability of fracture (FRAX score; https://www.sheffield.ac.uk/FRAX/tool.aspx) are important in the selection of patients to be treated. Patients who have undergone hip, vertebral, wrist, or upper arm fracture and suffer from osteoporosis, or who have >3% ten-year absolute risk of fracture of hip or >20% major osteoporotic fractures, should be treated. In patients who have not yet undergone a fracture, a T-score in the osteoporotic range (below –2.5) and a high risk of fracture are indications for special antiporotic treatment.

Accurate examination and diagnosis are essential for effective treatment. In order to monitor the effectiveness of the treatment, depending on the density, DEXA is performed every 1, 2 or 3 years, laboratory tests every 3–6 months and a spine X-ray every 3 years. If the patient falls or hits his or her spine, lateral thoracolumbar spine X-ray should always be performed to rule out possible vertebral compression.

Treatment of patients with osteoporosis is based on *adequate calcium and vitamin D supplementation and physical activity*. Special antiporotic drugs are given as monotherapy and are supplemented with calcium and vitamin D. The average calcium intake of the Hungarian population does not exceed 400–500 mg per day. This should always be supplemented with medication as needed. In children, during pregnancy and after menopause, the daily intake of 1500 mg of calcium, before menopause 1000 mg, and in men 1200 mg of calcium compensates urinary and fecal calcium loss. Vitamin D can be given in the form of a native or activated form. The daily dose of the native preparation over 50 years is 800–2000 IU, in case of pregnant and lactating women 2000–3000 IU. Obese patients may require 2–3 times the amount. Serum 25-OH-D3 levels reflect the body's vitamin D3 supply, the target value is a minimum of 75 nmol/l, in pregnant women 100 nmol/l. The daily dose of the activated derivative is 0.25–1 μg. Activated vitamin D3 (alpha-calcidol, calcitriol) are effective in the elderly, in osteoporosis complicated by autoimmune diseases, in impaired renal function and in vitamin D3-resistant osteomalacia. Active metabolite administration is contraindicated in patients with kidney stone.

Based on their mechanism of action, formulations used in the treatment of osteoporosis are divided into three groups. *Antiresorptive drugs* include oral and parenteral bisphosphonates, selective estrogen receptor modulators, various forms of female hormone replacement therapy, and a semi-subcutaneous monoclonal antibody against RANKL administered every six months. *Bone formation is aided by* subcutaneous parathyroid hormone analogues, including

teriparatide and abaloparatide, the former has been available for years, and the latter will be introduced in Hungary shortly. There are *multitarget agents,* that simultaneously inhibit bone resorption and stimulate bone formation. These include strontium ranelate (already withdrawn from the market in Hungary) and activated forms of vitamin D (alpha-calcidol, calcitriol). In addition to the above-mentioned, in daily practice, thiazide diuretics have been shown to be effective in patients with abnormally high urinary calcium excretion. There is also evidence that statins used to lower cholesterol also have a beneficial effect on bone mass. (See chapter 4 for a detailed description of medicines.)

If a drug belonging to one group is needed to be switched to another drug, the efficacy is optimal if the bone formation enhancer is given first to the patient and is followed by an inhibitor of bone resorption.

In addition to medication, *physiotherapy,* which increases muscle strength and coordination, and improves posture, also plays an important role. In case of an acute vertebral fracture, in addition to temporarily strict bed rest and the use of a corset, strong analgesic can provide relief. If the patient's pain does not decrease with conservative treatment, surgical intervention may be the next step. Filling the vertebral body with bone cement (vertebroplasty or hypoplasty) resolves the pain in a few days and the patient can be mobilized quickly after surgery. In secondary prevention, having a proper diet and reducing the risk of falling with medical aids for walking and properly adapting the living environment (fitting handrails, skid-proofing). Wearing hip protector pants during the autumn-winter period is excellent for preventing hip fractures.

16.3. Osteomalacia and rickets

16.3.1. Development of vitamin D deficiency

Vitamin D3 plays an extremely important role in the metabolism of calcium and phosphor: enhances intestinal absorption of calcium and phosphor, enhances osteoblast differentiation, proliferation and function, inhibits osteoblast apoptosis, reduces renal calcium excretion, suppresses PTH secretion, enhances the stimulatory effect of PTH on osteoclasts. As a result, bone formation and remodeling increase, and serum calcium and phosphate levels increase.

Osteomalacia is a generalized, partially reversible bone disease based on functional or true vitamin D deficiency. This results in a quality disorder of bone structure with a decrease in inorganic components. The mineral content of the bone is small, the osteoid tissue formed in sufficient quantity is insufficiently

mineralized. In osteomalacia, the bone is deformed and becomes increasingly fragile.

Rickets is the childhood equivalent of the process. In rickets the enchondral mineralization along the growth cartilage is disturbed, therefore children lag behind in growth and the bones are deformed. In adulthood only osteomalacia develops due to the ossification of the growth cartilage.

Disruption of bone mineralization can be caused by vitamin D deficiency of a variety of reasons or a lack of vitamin D effect *(Table 16.4.)*. Vitamin D and its active metabolite calcitriol are required to maintain normocalcemia. Deficiency can be caused by the absence of vitamin D, calcium, and phosphate, although these causes are usually present at the same time. In the absence of vitamin D, the absorption of calcium and phosphor and then the ionic calcium content of the serum decreases, which causes secondary hyperparathyroidism. In case calcium deficiency leads to osteomalacia, either the dietary calcium intake is low or the diet has a high phytate or oxalate content, this is why less calcium is absorbed than necessary, which only leads to secondary hyperparathyroidism and is associated with increased osteoclast activity, increasing bone resorption.

Vitamin D deficiency due to insufficient intake is common *in elderly malnourished people, living closed off, not exposed to sunlight. In this case, oral intake or lack of sunlight* leads to the disease. The effect of vitamin D may be lacking in case of malabsorption, diseases of the stomach and small intestine of various origins (Crohn's disease, gastric resection) and severe alcoholism. Chronic kidney disease or severe parenchymal liver disease, and childhood-onset, severe, autosomal, recessively inherited vitamin D-dependent rickets type I may cause vitamin D activation disorder and lack of effect. Vitamin D receptor dysfunction is responsible for the development of vitamin D-dependent rickets type II. Phosphate deficiency, inherited hypophosphatasia and renal tubular acidosis may also be pathogenic factors. Disorders of vitamin D metabolism and thus mineralization disorders can also be caused by certain drugs, e.g. fluorides, etidronate, cadmium and some iron oxides, aluminum-containing antacids, antiepileptics and cholestyramine. It should not be forgotten that phosphatonin (cytokine lowering phosphate levels) -producing tumors can also cause osteomalacia *(Table 16.4.)*.

Table 16.4. Causes of osteomalacia and rickets

Lack of vitamin D effect	• decreased intake (lack of sunlight, decreased oral intake) • malabsorption (resection, inflammatory bowel disease, alcoholism) • activation disorder (chronic liver and kidney disease, vitamin D-dependent rickets type I) • vitamin D receptor disorder (vitamin D-dependent rickets type II)
Phosphate deficiency	• decreased intake and absorption • increased tubular loss (Fanconi syndrome, vitamin D-resistant rickets, Wilson's disease, glycogenosis, tumors)
Renal tubular acidosis	• loss of bicarbonate
Hypophosphatasia	• familial forms
Medication (mineralization disorder)	• fluorides, aluminum salts, hydantoin, barbiturates, cholestyramine, rifampicin

16.3.2. Clinical picture and diagnosis

The clinical symptoms of pediatric osteomalacia (rickets) are more severe than those of adult osteomalacia. The skull is deformed, craniotabes form, the fonticulus anterior does not close, and the os frontale and parietale bulge. The chest is also deformed, funnel chest develops. Long tubular bones are bent and painful.

In adulthood, mild osteomalacia does not cause complaints, only laboratory parameters indicate the disease. The most important *clinical symptoms,* are bone pressure sensitivity, pain, and muscle weakness. Deterioration of respiration due to weakening of the intercostal muscles, and deformation of the ribs, which result in an increased risk of lower respiratory tract infections. Muscle weakness affecting the gluteus and proximal lower limb muscles results in a duck-like gait, difficulty standing up and climbing stairs. In severe mineralization disorders, the spine curves, is characterized by increased dorsal kyphosis and scoliosis, as well as pathological fractures, and rarely lower limb bones are deformed as well. In case of severe hypocalcemia, muscle hypotension, adynamic, and increased muscle irritability are characteristic, rarely ECG abnormalities may occur as well.

Laboratory and radiological tests help the *diagnosis*. Serum calcium levels are decreased or normal and phosphate levels are decreased. Serum alkaline phosphatase activity is high and parathyroid hormone levels are elevated. Serum osteocalcin levels are higher, serum 25-OH D3 levels are decreased, usually below 25 nmol/l, and urinary calcium level is low, phosphate levels may be decreased or normal.

Radiological symptoms characteristic of rickets include cartilage thickening of long tubular bones (knees, elbows), bone ends becoming fibrous, and trabeculae of the metaphysis becoming thinner. The presence of widened, uneven epiphyseal joints is characteristic of the bones of the radius and ulna, as well as the femur and tibia. In osteomalacia, the trabeculae on the vertebrae are blurred, biconcave deformity and compression fracture, Looser's reconstruction zones can be seen on the arch of the pubic bone, long tubular bones, ribs, and scapulae, in case of a symmetrical arrangement this is called Milkman syndrome. Pathological fractures are common in the surrounding of the Looser's zones, especially in the pubic and ischial bone.

16.3.3. Therapy

Under the age of 18, 2 000 IU vitamin D3 daily or 50 000 IU vitamin D3 once a week is recommended, checking 25-OH vitamin D3 levels every 6 weeks. After reaching the target value (75 nmol/l), it is advisable to switch to a daily maintenance dose of 1000 IU vitamin D3. In adulthood, 6000 IU daily or 50 000 IU weekly should be administered with serum 25-OH-D3 levels monitored every 8 weeks. After reaching the target value of 75 nmol/l, it is possible to switch to the daily administration of 2000–3000 IU vitamin D3. In obese patients, an average of three times the recommended dose is required. Adequate amounts of calcium should be provided through diet and medication. In the elderly, or in patients with even mildly impaired renal function and in case of impaired vitamin D activation, activated metabolite (calcitriol or alphacalcidol) should be preferred. In this case, calcium intake in the form of a drug is usually not necessary, but laboratory control is important. In vitamin D-dependent rickets type I, when 1-alpha-hydroxylase enzyme activity is lacking in the kidneys, 0.5–2 μg of calcitriol should be administered daily. In vitamin D-dependent rickets type II (VDRR-II: receptor defect), high doses (up to 50 μg/day) of calcitriol or extreme (up to 5 000 000 IU/day) vitamin D3 administration is the basis of the therapy, in the latter case with calcium supplementation of 1000–1200 mg daily. In hypophosphatemic rickets, in addition to 1–3 μg of calcitriol per day, 20–40 mg/kg (max. 3 g) of phosphate per day is the therapy. In phosphate-deficient rickets, thiazide diuretics may be considered in addition to strong phosphate supplementation.

Tumor-induced osteomalacia may heal after the removal of the tumor. Drug-induced mineralization disorders heal after discontinuing the drugs. As the incidence of the latent osteomalacia in the elderly is 10–30%, adequate dietary

intake of calcium and vitamin D is important, and in the elderly, oral intake of inactivated vitamin D is 1000–2000 IU daily. Increased attention is therefore needed in preterm infants, breastfed infants and the elderly. In addition to medication, it is important to strengthen the muscles, improve scoliosis, and contractures with exercise and other physiotherapy tools.

16.4. Primary hyperparathyroidism

16.4.1. Etiopathogenesis and epidemiology

The essence of primary hyperparathyroidism is increased production of PTH (1–84) independent of serum calcium levels. The disease is significantly more common than it is thought, with a prevalence of 1–21 cases per 1000 inhabitants, making it the third most common endocrine disorder. Increased division of parathyroid cells forms the basis of increased hormone production, histologically adenoma (80–90%), hyperplasia (5–20%) and carcinoma (1–8%) are the underlying causes. Various gene mutations (PRAD1/cyclin-D1/, menin, retinoblastoma, calcium sensor gene, etc.) can be detected in some patients. In the majority of patients, parathyroid cell division is triggered by a shift in the setting of the calcium sensor on the parathyroid cells, irradiation of the parathyroid glands, persistent calcium-D3 deficiency, hyperphosphatemia, or certain drugs (e.g. lithium, thiazide diuretics).

16.4.2. Clinical picture and diagnosis

Although the majority of patients with hyperparathyroidism (70–80%) are asymptomatic, some patients experience musculoskeletal symptoms. Muscle weakness, fatigue, intermittent synovitis caused mainly by pyrophosphate crystals, decreased bone mass are common, periosteal erosions, cysts (fingertips, tooth socket, vertebrae, skull) and acroosteolysis can be seen on X-rays. Renal involvement occurs in the form of polyuria, polydipsia, nephrolithiasis (60–70%) and nephrocalcinosis, and gastrointestinal involvement occurs in the form of ulcers, constipation and in recurrent pancreatitis. Neurocognitive symptoms may also occur, including sleep disturbances, impaired concentration, forgetfulness, neurosis and / or depression, confusion, but paranoid symptoms can also occur. Persistently high calcium levels can cause cardiovascular symptoms (valve calcifications, ECG abnormalities, accelerated atherosclerosis).

Diagnosis is based on laboratory and imaging tests. The disease is characterized by high calcium and PTH levels and low phosphate levels. However, this

is only generally true, as calcium levels are not necessarily high in vitamin D3 deficiency and phosphate levels are not necessarily low in renal failure. However, tubular phosphate resorption is abnormally low (<76%) in all cases. Ultrasound (unfortunately not sensitive enough) can be used to localize the enlarged parathyroid gland, but the sensitivity of parathyroid subtraction scintigraphy (MIBI-Tc) and MRI is significantly higher. As a principle, ultrasound used in case of intact neck (MIBI-Tc) and ultrasound in combination with MRI in case of operated neck has a good chance of detecting abnormal parathyroid gland.

16.4.3. Treatment

The first procedure to be chosen is surgical removal of the enlarged parathyroid gland(s). In symptomatic cases, surgery is justified in case of decreased BMD (T-score <–2.5), renal complication, hypercalcemia above 3 mmol/l, and appearance of radiological or neuropsychiatric symptoms. If the patient is asymptomatic, in case of co-occurrence of decreased BMD (T-score <–2.5), calcium levels above the normal upper limit of 0.25 mmol/l, creatinine clearance below 60 ml/min and low traumatic fracture, the patient should be referred for surgery. If surgery is contraindicated for any reason, for a lack of better option drug therapy needs to be given. Bisphosphonates are potentially available to inhibit bone breakdown, reduce the risk of bone fracture, hypercalcemia, but do not affect blood calcium levels. Calcimimetics (cinacalcet), which stimulate calcium sensors of parathyroid cells, do not affect bone resorption, reduction of bone mass, and fracture risk, however reduce calcium and PTH levels. Finally, it is important to know that half of the patients with hyperparathyroidism also suffer from vitamin D deficiency. The treatment of these patients with bisphosphonate may cause mineralization disturbance, so 25-(OH) D3 levels should be measured and corrected if necessary, before surgery. A low-calcium diet does not reduce serum calcium levels, but it does increase the progression of bone loss, therefore special diet does not have to be prescribed for the patient.

16.5. Paget's disease of bone

16.5.1. Epidemiology and pathogenesis

Paget's disease of bone (osteitis deformans) is characterized by a chronic disorder of bone remodeling, an abnormally increased osteoclast, and consequently increased osteoblast function. The formed bone tissue has a messy structure, is prone to deformation and fracture, and is hypervascularized. The disease was

described by Sir James Paget in 1877 in 11 patients, who named the disease as osteitis deformans. Paget's disease of bones is the second most common metabolic bone disease after osteoporosis (its prevalence is 1–3% over 55 years, and 8% over 80 years); it is more common in men than in women, and usually develops after the age of 50 years. Since the majority of cases are asymptomatic, recognition of the disease is a serious problem.

The *etiology* of the disease is still unclear. It is hypothesized that viral infection, local and genetic factors play a role in its development. The theory of viral infection is supported by viral-like inclusion bodies found in osteoclasts affected with Paget's disease, which resembled rubella, respiratory syntitial, and canine distemper virus, belonging to the paramyxovirus family. Familial accumulation of the disease has also been observed, suggesting genetic specificity, with a positive family history in 15% of patients; Paget's disease in parents has a 7–10-fold predisposition to the disease. Mutations that are common in patients almost always affect various actors in the RANK-RANKL system. The equestosoma-1 (SQTM1) and optineurin suggests NFκB signaling disorder, enhancing mutation of RANK, MCSF and OPG genes suggests pathologically elevated remodeling, and P97/vcp (ubiquitinated protein-binding ATP-ase) mutation suggests disruption of the removal of harmful intracellular proteins. DC-STAM and TM7SF4 (proteins mediating fusion of osteoclasts) suggest a disorder of osteoclast function.

The *pathomechanism* of the disease is characterized by osteoclasts and osteoblasts dysfunction. The volume of the bones increase, the trabecula becomes thicker, but their number and thus their stability decrease, and become more fragile. Osteoclasts affected by Paget's disease are abnormally large and can contain up to a hundred nuclei. Increased resorption is followed by an increase in the number of osteoblasts and increased formation. Paget's disease of bone progresses in three phases over time, but in different bones or at different locations in a bone phases may mix. In the first osteolytic phase, with the proliferation of abnormal osteoclasts, a high degree of bone resorption occurs, deep cavities are formed, which are filled with multinucleated, bizarre-shaped osteoclasts, and the location of bone marrow is filled with a hypervascular, fibrous component. In the next, mixed phase, osteoclast activity decreases and osteoblast activity increases. In the late, osteoblastic or sclerotic stage, the function of osteoblast cells dominates, extreme bone formation takes place. The three phases take place side by side, intermittently, creating a mosaic structure typical of Paget's disease.

16.5.2. Clinical picture and diagnosis

Paget's disease of bone typically occurs in old age, usually over 50 years. In 10–35% of cases, the disease is localized to one bone, which is the monostotic form. The most commonly affected bones are the vertebrae, tibia and femur. In the majority of cases, the disease occurs in polyostotic form, i.e. it affects multiple bones, most notably the pelvis, lumbar vertebrae, proximal femur, skull, tibia, and bones of the upper limbs. The size of the bones increases and bones become deformed, the skull enlarges (the patients outgrows their hat), the tibia bends like a sword sheath, abnormally large vertebrae (ivory vertebrae) are formed. Bones ache, the pain and deformity lead to limited mobility, the load-bearing capacity of bones decreases, resulting in pathological fractures.

In *diagnosis,* radiological examination is the most important, supplemented by laboratory and other examinations. Most often, the pelvis is affected. In the case of early abnormalities, a V-shaped resorption zone can be observed in the bones, thickening of the iliopectineal line (the so-called Brim sign) and acetabular protrusion on pelvic scan are indicative of the disease. Among the vertebrae, the disease occurs most frequently in the lumbar spine, an ivory vertebra or a vertebra surrounded by a sclerotic border can develop. Early changes in the skull are circumscribed osteoporosis (osteoporosis circumscripta) and late change is the typical cotton wool structure with sclerotic and lytic areas. On the long tubular bones, the cortical widens, lytic and sclerotic areas alternate. Most commonly the femur and tibia are affected. Bone scintigraphy is excellent and more sensitive for making an early diagnosis than conventional radiological examination, however, the evaluation of the images requires practice due to its low specificity. CT and MR are not normally required to make a diagnosis, but may be important in case of suspected complications (spinal stenosis, cauda syndrome, vertebral compression, tumor) or in differential diagnosis. If these imaging diagnostic procedures fail to establish a diagnosis, bone biopsy may be required.

Increased bone turnover characteristic of Paget's disease is well reflected by biochemical markers of bone metabolism. Primarily, markers of increased activity indicate disease activity. Total serum alkaline phosphatase levels are one of the oldest, inexpensive, but still well-used parameter nowadays. In the case of high alkaline phosphatase levels, bone-specific alkaline phosphatase test can be used to dispel any differential diagnostic doubts. To monitor treatment, alkaline phosphatase, osteocalcin, and urinary crosslinks should be tested together, since bone formation and resorption occur simultaneously.

A clinical picture similar to Paget's disease may be caused by Hodgkin's disease, multiple myeloma, hemangioma, malignant lymphoma, giant cell or brown tumor, osteomyelitis, and osteoblastic bone metastasis.

The most important *complications* of Paget's disease may be bone fractures, neurological and secondary degenerative abnormalities (OA), cardiac decompensation due to areas requiring increased blood supply, and tumors. Compression neuropathies can develop in anatomically preformed tunnels with consequent neurological complications, the most important of which is spinal stenosis extending to paraparesis / quadriparesis. Skull involvement can be approx. 30-60%, which can be associated with basilar invagination and hydrocephalus, as well as remodeling of the auditory ossicles typical of Paget's disease and deafness. In 1% of the cases, malignant transformation and tumorous lesions of the bones occur, most often osteosarcoma, fibrosarcoma and chondrosarcoma.

16.5.3. Treatment

In symptomatic patients the main goal of treatment of Paget's disease is to alleviate pain, reduce deformity / hearing damage, improve bone quality before orthopedic surgery, and reduce possible hypercalcemia. In asymptomatic patients, the goal of therapy is to prevent deformities, secondary abrasions, and complications; from a laboratory point of view, the goal is to normalize serum alkaline phosphatase levels. The therapy can decrease pain, bone resorption, and the rate of bone turnover, and the new bone structure will become much more lamellar. In the 1970s, for the lack of better treatment, salmon calcitonin reducing osteoclast activity, was used to treat the disease. Nowadays, the first agents of choice in treatment are *bisphosphonates,* which reduce osteoclast activity; bisphosphonates are used along with adequate calcium and vitamin D3 supplementation. Decades ago, etidronate, then tiludronate, followed by alendronate and risedronate, were options for therapy. Currently, the third-generation intravenous aminobisphosphonate and zoledronate is the most effective alternative. Zoledronate infusion administered once every 1–3 years is extremely effective in most patients. Three months after administration, serum alkaline phosphatase levels are normalized in 89% of patients and results in remission lasting several years. In case bisphosphonate therapy is ineffective, has caused intolerable side effects, or is contraindicated (most commonly due to decreased renal function), anti-RANKL antibody therapy (denosumab) may be used with similar efficacy according to the data available so far. Analgesics, NSAIDs and physiotherapy may be used for pain relief. Surgery may be considered for fractures, pseudofractures, severe bone deformities, and neurological complications.

16.6. Renal osteodystrophy (ROD)

16.6.1. Epidemiology and pathogenesis

Renal bone disease (renal osteodystrophy, ROD) is a set of bone abnormalities that occurs in patient with chronic kidney disease. ROD is essentially a special form of secondary generalized osteoporosis. ROD develops in the early stages of kidney disease in some patients, but in stage 5 its prevalence is close to 100%. Gradually deteriorating renal function is associated with metabolic and hormonal abnormalities, which result in a decrease in the quantity and quality of bone and can lead to both high-normal and low bone turnover. The main pathogenetic factors are disturbances of calcium, phosphate, and D3 metabolism with stage-varying PTH levels associated with disturbances of bone turnover. Abnormalities in bone metabolism begin in the early stages of chronic kidney disease (at GFR below 60 ml/min) and worsen without treatment as renal function deteriorate as well.

The main moments of the disease are the decrease and then cessation of vitamin D3 activation (1α-hydroxylation), in which increased production of fibroblast growth factor 23 (FGF-23), increased PTH levels, and increased release of proteins that inhibit osteoblast survival and function (sclerostin, Dickkopf-related protein-1/DKK-1/), which cannot be counterbalanced by osteoprotegerin (OPG), an inhibitor of bone resorption. In the initial stage, these factors cause an accelerated turnover characterized by increased bone resorption, which in the later stages is further increased due to hypocalcemia and phosphate retention and, in addition to bone loss, mineralization is disturbed, thereby reducing bone quality. Later, this is accompanied by a decrease in osteoblast function, which is further enhanced by phosphate-binding drugs. Tertiary hyperparathyroidism, developed due to hyperphosphatemia, leads to uncontrolled production of PTH in some patients, which further enhances the activity of bone-breaking cells. In the late stage, the slowing resorption and formation proceed side by side and the clinical picture of the so-called adynamic bone disease develops, where bone remodeling is minimized, in addition to non-mineralized osteoid, overmineralized bone tissue is becoming more and more significant. The bone abnormalities in the ROD are shown in *Table 16.5*.

Table 16.5. Bone abnormalities in ROD

• Microstructural changes
• Cortical porosity
• Cortical thinning
• Thinning and rupture of trabeculae
• Decreased bone quality
• Mineralization disorder
• Abnormal remodeling (loss of corrective mechanisms)
• Adynamic bone disease
• Low turnover
• High turnover
• Accumulation of microinjuries
• Decreased mechanical resistance
• Accumulation of glycation end products
• Reduced flexibility, increased fragility

In addition, the general risk factors for osteoporosis (mostly muscle mass loss, immobility, eating disorders, old age) further worsen bone condition. As a result, the risk of fracture is increased due to the deterioration in the quantity and quality of bone, which depending on the severity of the kidney disease, the risk of fracture increases 2–17 times compared to the age- and gender-appropriate average, and the propensity for post-fracture healing and the mortality rate after fracture also increase significantly.

16.6.2. Clinical picture and diagnosis

The diagnosis of ROD is based not only on the detection of bone loss but also on the use of methods suitable for detecting deterioration of bone quality, with DEXA, conventional X-ray and, if necessary, quantitative CT examination. Abnormal renal function, elevated PTH and phosphate, and decreased bone density with decreased or normal calcium levels alone make the diagnosis of ROD probable. The essential marker of the acceleration of bone metabolism is the alkaline phosphatase level, including increase of a specific fraction of bone. Biochemical markers of bone breakdown and construction may help in the assessment of high and low turnover forms, there are no reliable data on normal values fitted to decreased renal function, therefore, their assessment is uncertain.

The clinical picture corresponds to the clinical picture of osteoporosis with an increased risk of vertebral and nonvertebral fractures.

16.6.3. Therapy

The treatment protocol used in osteoporosis cannot be followed in the treatment of ROD, in which choosing the patients to be treated is determined by BMD (T-score), fracture risk and bone turnover rate. In principle, in addition to routine vitamin D3 supplementation, in case of elevated PTH levels, it is important to administer activated vitamin D3 derivatives, treat hyperphosphatemia, initiate calcimimetics, and later prepare for parathyroidectomy depending on PTH and calcium levels. Calcium supplementation is also important depending on calcium levels, but is not routinely recommended in patients with end-stage renal disease due to the risk of increased calcium x phosphate product and soft tissue / vascular calcification. Bisphosphonates that inhibit bone resorption can be safely administered in stages 1–2 of renal disease (GFR >60 ml/h). If the GFR is <60 ml/min, a drug is selected based on an estimate of bone turnover. Bisphosphonates are used in case of high alkaline phosphatase and PTH values 9× above the upper normal limit, and denosumab is used for GFRs below 30 ml/min. Anabolic therapy (teriparatide) is considered in case of alkaline phosphatase values below the lower limit of the normal range and PTH values 2× above the upper limit of the normal range; in intermediate case, the decision is made according to the result of the (routinely rarely used) bone biopsy.

16.7. Algodystrophy

16.7.1. Etiopathogenesis and epidemiology

In contrast to generalized bone diseases discussed above, the typical manifestation of local osteoporosis is algodystrophy. Algodystrophy induced by local factors is known in the literature by a number of other names, including Sudeck's syndrome, reflex dystrophic sympathetic syndrome (RDSS), reflex sympathetic dystrophy (RDS), algoneurodystrophy, acute post-traumatic osteoporosis (spotted) and shoulder-hand syndrome are the best known. The disease is significantly more common than it is diagnosed, with an incidence of approx. 1–5%, more common in women and young adults.

It is a microcirculatory, then dystrophic and atrophic disorder of the bones and soft tissues of one or more limbs based on changes in vegetative innervation, which can be caused by various causes. The most well-known causes are trauma to the limb, plaster fixation after fractures, inflammation, tumor or thrombosis of the limbs, but can also be caused by cardiopulmonary disease

(e.g. myocardial infarction or pulmonary embolism) and central nervous system disease (stroke, brain tumor). The cause of the disease, the original injury or damage, triggers a pain impulse that is carried by sensory nerves to the central nervous system, but at the same time abnormal vascular innervation is initiated in the efferent branch due to abnormal vegetative stimuli, which is accompanied by increased bone turnover due to increased osteoclast activation.

16.7.2. Clinical picture and diagnosis

The process can develop on any limb, but is most common on the upper limbs. If it occurs with painful limited mobility in the hand and the shoulder on the same side, it is called shoulder-hand syndrome. The disease occurs in three stages.

Stage I (acute stage): Severe and burning pain, tenderness and hypersensitivity to pain (hyperalgesia) occur at the site of initial vasodilation. Swelling and edema is characteristic of the painful region. The skin of the limb is red, hot and sweaty, and hair growth may be increased. In milder cases, it will take a few weeks, or heal with proper therapy. With inadequate therapy, the disease progresses to stage II. There is no radiological sign.

Stage II (dystrophic stage): Vasodilatation is increasingly replaced by vasoconstriction, the pain is more and more extensive, the swelling intensifies and indurates, the skin is already cool to the touch, cyanotic, at first moist and later dry to the touch. The limited mobility of the joints increases due to muscle atrophy and soft tissue contractures. This stage lasts for 3–6 months, a characteristic radiological sign being a diffuse, spotted bone atrophy.

Stage III (atrophic stage): In the classical form, the pain is constantly strong and spreads in the proximal direction of the limb. At this neglected stage, the skin, subcutaneous connective tissue and muscles also atrophy; is characterized by the skin's trophic disorders, the hair falls out, the joints become fixed in flexion contracture, this is already a largely irreversible condition. The radiological picture is characterized by diffuse osteoporosis and bone demineralization.

When making a diagnosis, taking a proper medical history and the appearance of the following 6 symptoms is important: pain, swelling, edema, decreased motor function, dystrophic and atrophic lesions, vasomotor instability and disorder, and bone atrophy as seen on the radiological picture. There are several criteria systems for the diagnosis of the disease, the most logical being the criteria system developed by Kozin et al. in 1997.

According to this, definite RDS is present with the following symptoms: pain with allodynia or hyperpathia, tenderness, vasomotor and sudomotor lesions,

dystrophic skin lesions, and swelling. RDS is likely in the presence of pain and allodynia, vasomotor or sudomotor lesions and swelling, and is possible in the presence of RDS-like vasomotor or sudomotor lesions and swelling.

In the early stages of the disease, 3-phase joint scintigraphy may be of diagnostic value, showing increased vascularization and increased bone remodeling in the late stage. This plays a role if there is no visible discrepancy on conventional X-ray. There are no specific laboratory signs. Infectious arthritis, peripheral spondylarthritis, malignancies, crystalline arthritis, RA, SLE, and injuries or other diseases of the central nervous system (e.g. syringomyelia) are considered for differential diagnosis.

16.7.3. Therapy

The goal of therapy is basically the specific treatment of the underlying disease, preferably as soon as possible, since treatment started after 6 months has had little success. It is important to alleviate pain and restore locomotor function, stop abnormal vascular reactions, and stop bone loss. Drug therapy is based on the combined use of several groups of drugs. In addition to high-dose supplementation of calcium and vitamin D3, nasal or subcutaneous calcitonin, or bisphosphonates, help prevent bone loss, nonsteroidal anti-inflammatory drugs and steroid therapy in the early phase, gabapentin, phenytoin derivatives or topical capsaicin in the late phase have good analgesic effects. The alpha-1 receptor blocker tarazosin / doxazosin, non-selective beta-blockers (pindolol, propranolol), calcium channel blockers (verapamil, nifedipine) may help to control the abnormal vascular response; in desperate cases intravenous phentolamine may be used. Invasive interventions may also be considered. There are also favorable results in the use of peripheral nerve blockers and sympathetic ganglion blockade with morphine.

Drug therapy is well complemented by physiotherapy, initially in addition to rest, passive movement, cold-warm water contrast bath therapy (vascular exercise), analgesic electrical treatments, later warm treatments, active physiotherapy and ultrasound treatment may be used.

16.8. Osteonecrosis

16.8.1. Nomenclature and etiopathogenesis

Several nomenclatures of osteonecrosis are known, e.g. aseptic, avascular, ischemic bone necrosis. Bone tissue dies primarily under sterile conditions due

to disruption of the blood supply or secondarily due to trauma or other causes (alcoholism, gout, diabetes mellitus, high-dose long-term steroids, cytostatic therapy, X-rays). Less frequently, other causes (vasculitides, bacterial and viral infections, hematological malignancies, emboli and thrombosis of various origins, sickle cell anemia, thalassemia, decompression sickness) may also be present.

Based on the frequency, *femoral head necrosis* is in the first place, followed by the development of necrosis in the humerus head and knee joint. Regarding the development of femoral head necrosis, it is important to know that the supply of subchondral bone is provided by end arteries, and the femoral head is supplied by end branches of a. circumflexa femoris medialis. Since the a. capitis femoris blood flow narrows or even ceases completely by adulthood, the disease is most common in the upper-anterior part of the head.

Primary *avascular osteonecrosis* occurs in childhood. Blood vessel disorder is suspected in the background of the disease, but the role of trauma cannot be ruled out, as a result of which the epiphysis of the developing bone dies in a sterile form. The forms of the disease occurring on different bones have been given different names based on the first descriptive person. Necrosis of the femoral head, Perthes disease occurs in preschoolers, its most important symptom being gradual limping and pain. The death of the apophysis of the tibia, characterized by pain during squatting and swelling of the tibia below the knee, occurs in grade-schoolers. Teens develops necrosis of the vertebral apophysis, characterized by Scheuermann disease, increased dorsal kyphosis and back pain, often with Schmorl's nodes in the affected spinal area. At the age of 10–16 years, mainly boys develop swelling and pressure sensitivity corresponding to tuberositas tibiae caused by aseptic necrosis of tuberositas tibiae, called Osgood-Schlatter disease. Aseptic necrosis of the os lunatum of the hand is known as Kienböck's disease. On the leg the os naviculare and aseptic necrosis of II. metatarsus (Köhler disease) or osteonecrosis of calcaneus (Thiemmann) may cause temporary limping, but there are several names of these diseases.

16.8.2. Clinical picture and diagnosis

The clinical picture is characterized by an uncertain onset, fatigue, pain and limited movement occurring with load, back pain with prolonged standing, and characteristically increased dorsal kyphosis. In the case of femoral head necrosis, initially the inward rotation, then the extension, later the abduction, and finally all the movements narrow, a limping gait develops. Involvement of the humerus is associated with shoulder tenderness and painful narrowing of move-

ment. Osteonecrosis of the femoral condyle is often accompanied by severe pain and synovitis. Long-term steroid use is prominent in the background of the disease developing symmetrically on both sides.

Osteonecrosis typically occurs in four stages. The early avascular phase is fortunately followed by revascular then healing, with smaller-bigger residual deformity. In unfavorable or neglected cases, the patient present to the doctor only in the irreversible stage, with advanced deformities and degenerative abnormalities.

If osteonecrosis is suspected, the first step in diagnosis is to obtain a bilateral radiograph of the affected area. In case of the hip, the bilateral hip scan (Lauenstein view) taken in the abducted- externally rotated position may show contour rupture, sector-like sclerosis, and in more severe cases, taste surface rupture. The Ficat classification is used to classify the radiological stages of femoral head necrosis.

In Ficat stage I, the X-ray is still negative. In Ficat stage II cystic and sclerotic lesions, larger necrotic areas are seen. The cartilage surface is still intact at this point, the process is reversible. The wedge-shaped area of increased density at the femoral head is the lateral-upper. In Ficat stage III, the joint gap widens, the cartilage surface ruptures, and the subchondral collapse (crescent sign) already causes permanent deformity and damage. In Ficat stage IV, the femoral head is flattened, the joint gap is narrowed, and severe deformities characteristic of OA occur.

If the X-ray shows a normal picture, an MRI scan capable of detecting early-stage bone marrow edema should be performed, therefore it is the most important tool for early diagnosis not only in case of hip but also other localizations.

16.8.3. Treatment

Therapy depends on localization, size, and stage of necrosis. The first step in therapy is to eliminate the suggested cause (abstinence, change of occupation, improvement of circulation, careful anticoagulation in case of embolism, optimization of medication, if possible, etc.). In the initial stage, when the process is still reversible, pain relief, relieve limb load, and strengthening muscles is important. This load relief of the lower limb can be achieved by use of crutch. Among the drugs, there are available data on the beneficial effects of bisphosphonates. In case of femoral head necrosis, early-stage (I–II) reamed medullary canal surgery helps to eliminate the pain caused by bone marrow edema, and may even cause healing of the process. In the later stages, in the vast majority

of cases, there is no real curative solution, in case of load-bearing joints and shoulder, prosthetics of the joints can contribute to the preservation of musculoskeletal functions.

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17. Soft tissue diseases

Zoltán Szabó

17.1. Introduction

Most of the regional pain syndromes are of soft tissue disease origin. Soft tissue disease / soft tissue rheumatism is defined as degenerative or inflammatory abnormalities of the subcutaneous connective tissues, tendons, tendon sheaths, entheses, bursa, ligaments and muscles. This is very common problems that need to be treated as soon as possible so that they do not turn into a chronic form. Their triggers can include overload, occupational injuries, chronic loads, and possibly a previous accident. But, sometimes infections, stress, mental strain may be the background. The symptoms, however, are most often caused by overload, the best example of which is tendovaginitis. The most characteristic location of tendovaginitis is the tendon sheaths of the forearm and the tension tendons of the fingers.

17.2. Tendinitis, tendovaginitis, bursitis and enthesitis

Acute or chronic inflammation of extraarticular / periarticular tissues (tendons, entheses, tendon sheaths and bursa) are the most common forms of soft tissue diseases. They are especially common in middle-aged and elderly. Symptoms that can be included here: certain forms of Achilles tendinitis, biceps tendinitis, epicondylitis, trochanter bursitis, humeroscapular periarthritis (PHS).

During physical examination, the patient reports pain, local tenderness, possibly swelling can be palpable. Occasionally, when the patient is moved, crepitation may be observed when the affected area is touched. Significant pain can lead to limited mobility. A special form is de Quervain tenosynovitis, or processus styloideus radii tenosynovitis, which is easily recognizable during physical examination (Finkelstein test). Another special form of tendovaginitis is the „trigger finger", in which case a symptom accompanied by popping can be observed on the palmar surface of the affected finger, and the other hand may be needed to straighten the finger. The pain in this case is usually not significant.

The cause is a lump formed on the tendon due to inflammation. (Strong flexor muscle helps the lump pass through the tendon sheath, but weaker flexor muscles are not able to do so.)

Regarding bursitis, inflammation of the bursa around the shoulder, elbow, hip and knee is the most common features. A special form of the latter is the so-called Baker's cyst, which is an inflammation of the bursa occurring medially in the form of palpable swelling. It is most commonly associated with OA and RA. 5–32% of patients with knee problems have Baker's cyst. Physical examination and ultrasound confirm the cyst. Its rupture may mimic deep vein thrombosis.

Resting is the most important therapy in case of acute forms of tendovaginitis and bursitis (e.g. plaster cast, thermosetting plastic cast, elastic bandage). In addition, 1–2 weeks of drug administration (NSAIDs, analgesics) and their topical application are usually sufficient. If this does not help, a topical steroid injection is usually effective. After reduction of acute symptoms, a few more weeks of resting may be appropriate. In chronic cases, it is important to find and eliminate the cause (e.g. overload), rule out underlying diseases (e.g. psoriasis, tuberculosis, polyarthritis) and use physiotherapic techniques (e.g. ultrasound, iontophoresis, TENS). In difficult cases, surgery may be required.

Inflammatory abnormalities of enthesis are called enthesitis. At the junction of the ligaments and bones (enthesis – enthesopathy), an inflammatory abnormality can often develop. It can be caused by overload, inflammation and injury. Tendon adhesion is painful, pressure sensitivity and swelling may be observed. In its treatment, rest, packing, physiotherapy and local injection may be considered. The incidence of enthesitis in spondyloarthropathy, psoriatic arthritis (e.g. adhesion of the Achilles tendon) is very typical. In these diseases, enthesitis is so common that the term "enthesis organ" has recently been mentioned, which also includes articular cartilage, bursa, articular adipose tissue, surrounding trabecular bone tissue, and fascia as well. Associated dactylitis and nail abnormalities should always be sought. Tennis and golf elbow are common forms of enthesitis causing pain above the lateral and medial epicondyles, respectively.

17.3. Panniculitis

Panniculitis is the inflammatory disease of subcutaneous adipose tissue. In lobular panniculitis, the inflammatory process mainly affects the lobes in adipose tissue. This form of panniculitis is often associated with vasculitis (inflammation of the blood vessels). It can be associated with several underlying diseases, e.g.

Crohn's disease, SLE (lupus profundus), dermatomyositis, gout, lipodermatosclerosis, traumatic fat necrosis, steroid administration, Wegener's granulomatosis, tuberculosis and paraneoplastic events. It can be associated with joint pain and arthritis.

Clinical presentation: painful lumps that cling to the skin appear in the adipose tissue. A skin biopsy is often required to diagnose panniculitis. Histologically, panniculitis can be lobular or septal, in addition to inflammatory signs, caseous necrosis may occur. In addition, there are additional subgroups based on the presence or absence of vasculitis.

There is no specific therapy, bed rest, NSAIDs, possible steroid treatment may be considered. Finding and treating the underlying disease is the most important.

17.4. Nerve compression syndromes

These syndromes are caused by the compression of nerves (or blood vessels) in anatomically defined bone-ligament tunnels and fissures between muscles; there are several forms of the syndrome *(Table 17.1.)*.

Numbness, pain, sensory disturbances, muscle atrophy, decreased muscle strength may be a symptom according to affected area. Neuralgic pain does not go away at rest. May be accompanied by paresis, motor weakness, and paresthesia. Provocation tests can often trigger the symptoms (e.g. Tinel's / Phalen's sign in carpal tunnel syndrome). Raynaud's syndrome can also occur as an accompanying phenomenon. Physical swelling and tenderness are most noticeable. Targeted tests can confirm the diagnosis: e.g. ENG – decreased nerve conduction velocity; X-ray: abnormalities on the thoracic outlet syndrome (TOS), etc. ultrasound, CT, MRI may provide additional help.

From a differential diagnostic point of view, diabetic neuropathy, lues, alcoholism, vascular diseases, arteriosclerosis – claudication, thrombosis may be considered. Certain conditions can contribute to the development of nerve compression syndrome, such as RA, tenosynovitis, pregnancy, hypothyroidism, amyloidosis, diabetes, space-consuming processes, anatomical abnormalities (e.g. cervical rib), gout, trauma.

The purpose of treatment is to reduce complaints, restore and maintain function. Prevention includes the avoidance of persistent, monotonous physical exertion. Medications include analgesics, NSAID administration, topical infiltration (local anesthetic and steroid). In addition to medication, rest and taking

advantage of physiotherapic techniques is important. In the event of persistent complaints despite treatment, surgical decompression may be required to prevent permanent impairment.

Table 17.1. Major nerve compression syndromes

Name of the syndrome	Affected nerve
Upper limb	
Scalenus syndrome (Thoracic outlet syndrome, TOS I.)	Brachial plexus
Costoclavicular syndrome (TOS II.)	Brachial plexus
Hyperabduction syndrome (TOS III.)	Brachial plexus
Incisura scapulae syndrome	Suprascapular nerve
Supinator tunnel syndrome	Radial nerve, profundal ramus
Pronator teres syndrome	Medial nerve, anterior interosseous nerve
Carpal tunnel syndrome	Median nerve
Cubital tunnel syndrome	Ulnar nerve
Guyon tunnel syndrome	Ulnar nerve
Lower limb	
Piriformis syndrome	Ischiadic nerve
Iliac tunnel syndrome	Femoral nerve
Ilioinguinal syndrome	Ilioinguinal nerve
Bernhardt-Roth syndrome (meralgia paresthetica)	Lateral femoral cutaneous nerve
Fibular tunnel syndrome	Peroneal nerve
Anterior tibial syndrome	Perineal nerve
Tarsal tunnel syndrome	Tibial nerve
Morton's metatarsalgia	Plantar digital nerve

17.5. Humeroscapular periarthritis (PHS)

PHS is a syndrome developed due to degenerative changes or inflammation of the soft areas around the shoulder joint. Several diseases are included in this collective term, the most common causes are considered to be degenerative abnormalities of the longhead tendon of the biceps brachii muscle and the tendon of the supraspinatus muscle.

The movements of the shoulder narrow painfully, with abduction and internal rotation sooner. Adhesive capsulitis gradually develops in the shoulder joint. Later, the muscles around the shoulder begin to atrophy. Physically, narrowing of movement, possibly crepitation, can be detected. X-rays may show calcification (e.g. in the subdeltoid bursa). Differentiation from traumatic injury and purulent inflammation is aided by ultrasound, MRI, or arthroscopy.

Preventing prolonged, strenuous strain on the joint (sports, workplace injury) would be the best prevention. If symptoms have already developed, NSAIDs, analgesics, topical treatment (NSAID gel, packing), periarticular steroids (given to the bursa or soft tissues around the inflamed tendon) or anesthetic may be considered. In addition, physiotherapy and exercise started in time after the acute stage are the most important. In difficult cases, movement of the joint under anesthesia, arthroscopy, surgical solution (surgical reconstruction of the rotator cuff, release of the subacromial space, acromion resection, etc.) may be considered.

17.6. Fibromyalgia

Fibromyalgia is a chronic, generalized pain syndrome that localizes on the musculoskeletal systems. Its prevalence is between 7 and 12%. It is probably due to a disorder of pain (hyperalgesia, allodynia), but the exact cause is unknown. Fibromyalgia shows overlaps and associations with other somatization disorders, such as chronic fatigue syndrome, irritable bowel disease, depression. It manifests itself in diffuse pain, but according to ACR (American College of Rheumatology) criteria, characteristic sensitive points are found in precisely defined places. The diagnosis requires sensitivity of at least 11 of the 18 tender points, in addition to the exclusion of other diseases causing joint pain, muscle pain and joint stiffness (partially exclusion diagnosis) *(Table 17.2.)*. Primary and secondary forms are distinguished. The latter can be associated with various underlying diseases, e.g. RA, SLE, OA, malignancies. It is usually generalized pain, but can also be a localized form, e.g. myofascial pain syndrome.

Table 17.2. Diagnostic criteria of fibromyalgia

A) History of generalized pain for at least 3 months.*
B) Pain and tenderness in 11 of the following 18 (9 points bilaterally) tender points:**
1. Origin of the trapezius pars descendent in the os occipital at linea nuchae superior
2. Lig. transversaria at CIV–VII
3. Trapezius muscle in the medioclavicular line
4. Musculus supraspinatus above the spina scapulae
5. The II. rib slightly laterally above the sternocostal joint
6. Lateral epicondyle 2 cm distal to the humerus
7. Upper-outer quadrant of the gluteal region
8. Dorsal surface of the trochanter major
9. Medial panniculus adiposus above the knee articular gap

* Generalized pain: pain occurs on both sides of the body, from the waist to the upper and lower body, as well as in the spine and anterior chest wall.
** Tenderness can be triggered by a pressure of 4 kp/cm^2 or less.

Depression and persistent diffuse pain, sleep disturbances are the leading complaint. During a physical examination, there is usually no characteristic difference beyond the sensitivity of the tender points. Laboratory tests, X-rays (to exclude possible real serological and morphological abnormalities), or EEG (abnormal alpha waves, non-REM sleep disturbances) may be considered during the diagnosis. Associated diseases: sleep disorders, irritable bowel syndrome, mitral prolapse syndrome.

It is important to inform the patient about the benign nature of the disease, and taking advantage of lifestyle changes (e.g. improving physical fitness, reducing stress). NSAIDs, analgesics are given daily, although they are usually ineffective. Tricyclic or newer antidepressants (SSRIs), gabapentin, pregabalin are also recommended, local injections (e.g. lidocaine) may also be considered. Due to the nature of the disease, the treatment is difficult. Despite all the efforts, unfortunately, less than 10% of patients go into complete remission.

17.7. Myopathies

Myopathies are muscle diseases, which may be localized or generalized (inflammatory muscle diseases or myositis [poly / dermatomyositis] are classified into other disease group). Hereditary and acquired myopathies are distinguished *(Table 17.3.)*.

Table 17.3. Division of myopathies

Toxins and medicines	steroid, alcohol, statins, cocaine, heroin, amphetamine (rhabdomyolysis)
Metabolic myopathies (primary)	glycogen storage disease (McArdle's disease / Pompe's disease), fatty acid oxidation disorders, mitochondrial diseases
Metabolic myopathies (secondary)	Endocrine (e.g. acromegaly, thyroid disease, Cushing), Uremia, hepatic insufficiency, malabsorption, electrolyte disorders (e.g. hypokalemia).
Muscular dystrophy (hereditary)	Duchenne's disease, Becker's disease, limb dystrophy, Facioscapulohumeral dystrophy, distal muscle dystrophy
Disorders of neuro-muscular transmission	Myasthenia gravis, Lambert-Eaton syndrome
Infections	trichinosis, toxoplasmosis, viruses, bacteria, fungi

Local muscle pain usually develops as a result of poor posture and exertion. In addition to pain, muscle stiffness and cramps may occur. Possibly so-called myogelotic nodules may be palpable. Diffuse myalgia includes, e.g. polymyalgia rheumatica, which is associated with symmetrical shoulder and hip pain, weakness, and accelerated ESR. In addition, congenital and drug-induced myopathies (e.g. steroid myopathy, steroid withdrawal syndrome, etc.) can also be distinguished. In addition to typical clinical symptoms, laboratory abnormalities (elevated CK [creatine phosphokinase]) and EMG may help the diagnosis. Muscle biopsy is suitable for determining the exact type. Hereditary, progressive myopathies are mainly treated by neurologists (e.g. myasthenia gravis, Lambert-Eaton syndrome, progressive muscular dystrophy, mitochondrial myopathy). If the cause cannot be treated or resolved, symptomatic treatment (analgesics, muscle relaxants, NSAIDs, steroids, physiotherapy) is often considered.

17.8. Polyneuropathies

Polyneuropathies are diseases of the peripheral nerves, usually of a symmetrical nature, resulting from an underlying disease (most often diabetes, alcoholism) *(Table 17.4.)*.

Neuropathic pain is usually constant, deep, burning, and movement has little effect on it. The patient often reports sock-like or stocking-like pain. In addition, it may be accompanied by numbness, sensory deficit, paresthesia and imbal-

ance. In case of motor involvement, reflex abnormalities and dysbasia may occur. In addition to clinical symptoms, an ENG test may support the diagnosis.

Complaints are often difficult to control, in addition to physiotherapy, the use of B-vitamin complexes, analgesics, and pregabalin therapy may be considered.

Table 17.4. Etiological division of neuropathies

Metabolic	Diabetes mellitus, amyloidosis porphyria, uremia, liver cirrhosis, gout
Infectious origin	Diphtheria, Leprosy, HIV, CMV, Treponema, Lyme
Toxic	Alcohol, medicines (INH, thalidomide), heavy metals (lead), semi-metals (arsenic), solvents
Vasculitis	Rheumatoid arthritis, PAN, Churg-Strauss syndrome (EGPA), other autoimmune diseases, cryoglobulinemia, arteriosclerosis
Hereditary	Charcot-Marie-Tooth disease / CMT
Immune origin	Guillain-Barré syndrome / GBS, chronic inflammatory demyelinating neuropathy / CIDP and variants
Paraneoplastic	Dysproteinemia, paraproteinemia
Nutritional	Malabsorption, cachexia, vitamin B1, B6 and B12 deficiency

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18. Other disorders

Boglárka Brúgós

18.1. Rare hereditary disorders of connective tissue

Hereditary disorders of connective tissue are caused by mutations in the genes encoding extracellular matrix proteins (collagen, fibrillin, fibronectin, etc.).

18.1.1. Marfan syndrome

Marfan syndrome is an autosomal dominant connective tissue disorder with a prevalence of 1:3000–1:5000. In Hungary, 2000–3000 patients are affected. Family history is common, with 49% of affected patients having a family history of the disease. A new gene mutation is likely in 25–30% of patients. The cause of classical Marfan syndrome is a mutation in a gene encoding the 350 kDa glycoprotein called fibrillin-1 (FBN1), an important component of elastic microfibrils. Mutation of the TGF-β (transforming growth factor-β) binding receptor-2 (TGF-BR-2) gene also leads to disruption of signaling pathways, development of Marfan-like syndrome, with similar clinical symptoms.

Ghent nosology was described in 1996 to distinguish true Marfan syndrome cases from Marfan-like conditions (e.g. MASS phenotype: myopia, mitral valve prolapse, borderline and non-progressive aortic aneurysm, stretch marks, skeletal abnormalities; MVPS-mitral prolapse syndrome). Ghent nosology distinguishes between major and minor criteria. In 2010, Loeys et al. proposed a modified Ghent nosology *(Table 18.1 and 18.2)* since it is difficult to recognize the disease in childhood due to symptoms that do not fully develop. Typical patients with clear evidence of ectopia lentis and aortic aneurysm but no minor skeletal symptoms do not meet the diagnostic criteria, although their follow-up would be warranted. According to the new classification, the role of the two most important symptoms is more pronounced. If the patient has a confirmed ectopia lentis and a weakness of the aortic wall / aneurysm, a diagnosis of Marfan syndrome can be made; the use of other systemic symptoms (skeletal, lung, skin involvement) is warranted if one of the two main symptoms is missing. In addition to the above-mentioned clinical symptoms, the new classification emphasizes the importance of performing genetic tests, primarily the detection of mutations in the FBN1 gene, or the detection of TGF-B-1 and -2 mutations.

Table 18.1. Modified Ghent criteria

In the absence of a positive family history
(1) Ao (Z≥2) and EL=MFS* (Marfan syndrome)
(2) Ao (Z≥2) and FBN1 mutation=MFS
(3) Ao (Z≥2) and Sist (≥7 points)=MFS*
(4) EL and FBN1 are known as Ao=MFS
EL with or without symptoms AND FBN1 mutation is not known with Ao dissection or FBN1 without mutation=ELS (ectopia lentis syndrome)
Ao (Z≤2) AND Syst (>5 symptoms of at least one skeletal) without EL=MASS
MPVS AND Ao (Z<2) AND Sist (<5) without EL=MPS
In case of a positive family history (FH)
(5) EL AND MFS in the family=MFS
(6) System. (>7 points) AND MFS in the family=MFS*
(7) Ao (Z≥2 over 20 years, ≥3 under 20 years)+pos. family history=MFS
Ao: deviation of aortic diameter at Valsalva sinus level (Z-score) or dissection of aorta
EL: ectopia lentis; ELS: ectopia lentis syndrome
FBN1: fibrillin-1 gene mutation;
MASS: myopia, mitral valve prolapse, minor aortic root dilation (Z-score>2), stretch marks, skeletal abnormalities
MFS:Marfan syndrome; MVPS, mitral valve prolapse

Table 18.2. Systemic symptoms of Marfan syndrome

Wrist and thumb sign – 3 points (wrist or thumb sign – 1)
Pectus carinatum deformity – 2 (pectus excavatum or chest deformity / asymmetry)
Foot deformity – 2 (pes planus – 1)
Pneumothorax – 2
Dural ectasia – 2
Acetabular protrusion – 2
Decreased ULSR OR arm / height AND no serious scoliosis
Scoliosis or thoracolumbar kyphosis – 1
Decreased elbow extension – 1
Facial character differences (3/5) – 1 (dolichocephalia, enophthalmus, palpebral fissures, malar hypoplasia, retrognathia
Skin stretch marks – 1
Myopia>3 diopters – 1
Mitral valve prolapse – 1
Maximum points: 20; >7 points indicate systemic involvement

ULSR (upper segment / lower segment ratio)

The most common symptom of Marfan syndrome is disproportionately long limbs resulting from increased growth of long tubular bones. Overgrowth of the ribs results in chest deformities such as pectus carinatum (chicken breast) and pectus excavatum (funnel chest). Disproportion between the lower and upper body halves is also a characteristic symptom, which leads to an arm span of 1.05 times the height. Arachnodactyly (spider fingers) caused by the elongation of the metatarsus, metacarpus, and phalanx is a striking symptom. Loose joints, arachnodactyly, lead to the characteristic *wrist symptoms* (Walker-Murdoch sign) if the patient grasps his / her wrist with his little finger and thumb, the two fingers overlap, and if the patient bends his thumb through the palm, the finger extends beyond the outer edge of the palm (Steinberg or *thumb* symptom). Severe scoliosis (>20 °) is a criterion symptom. Pes planus, the decreased extension of the elbow is a common abnormality, camptodactylia, contracture of the fingers occur in progressive disease in childhood.

The basis for making the diagnosis is ectopia lentis, i.e., dislocation of the ocular lens, which occurs in 60% of patients, although not disease-specific.

Cardiovascular symptoms affect both the heart and the vascular system. The most common heart disease is the involvement and thinning of the atrioventricular valve, which often leads to prolapse. In 25% of cases detected in childhood, mitral prolapse leads to the development of mitral insufficiency in adulthood, with progression being more common in women. The most significant and life-threatening complication in Marfan syndrome is the risk of aortic aneurysm and consequent dissection.

There is no specific rheumatic treatment, strengthening their joints in the safe range and toning the muscles is important. Control of blood pressure and treatment of hypertension are essential, primarily prophylactic beta-blocker therapy and, depending on the degree of hypertension, other antihypertensive agents should be initiated. Prophylactic beta-blocker treatment reduces the progression of the aortic aneurysm. The prophylactic surgical solution, i.e. the insertion of an aortic root graft, is justified if the aortic root diameter exceeds 55 mm.

18.1.2. Ehlers-Danlos syndrome

Prevalence of Ehlers Danlos syndrome (EDS) is 1:5000, with no ethnic differences. The disease is due to genetic abnormalities in fibrillar collagen types I, III and V and enzymes involved in post-translational modification. In 50% of classical EDS patients, the disease is due to mutations in the COL5A1 and COL5A2 genes that encode the α1 and α2 chains of type V collagen. Altogether 5% of cases

of hypermobile Ehlers Danlos syndrome are caused by mutation of TenascinX, while the vascular type is caused by mutations of the COL3A1 gene.

Villefranche nosology distinguishes 6 main types based on clinical symptoms, inheritance, and molecular abnormalities, but there are also rarer types. The most common types are classical (I/II), hypermobilic (III), vascular (IV), and kyphoscoliotic (VI) type.

Joint hypermobility is a feature of most subtypes. In patients, defective collagen is already present at birth, but symptoms often appear only at a later age. Hypermobile Ehlers Danlos syndrome is one of the most common types. Major diagnostic criteria are generalized joint hypermobility and the presence of typical skin symptoms, although much milder than in the classical subtype. The diagnosis of joint hypermobility is based on Beighton criteria, a standardized test, the 9-point scale examines spinal hyperflexion, thumb abduction, and wrist hyperflexion. In case of generalized joint hypermobility, the total score exceeds 5.

It is recommended to examine the extensibility of the skin in the distal part of the forearm or in the wrist area, the normal extensibility of the skin is 1–1.5 cm. Other more severe types of EDS should be excluded. A positive family history (occurrence of EDS or joint looseness) is required to confirm the diagnosis of hypermobile EDS; recurrent joint dislocation or subluxation, chronic joint, limb or back pain, leg deformities, frequent bruising of the skin, loose skin, prolonged wound healing, atrophic, cigarette paper-thick scars develop after injuries, functional gastrointestinal complaints (irritable bowel syndrome), orthostatic hypotension, gothic palate and dental congestion also occur.

Joint looseness, instability, increased joint mobility are common symptoms. Subluxation can also occur with minimal trauma. All joints may be affected, as well as the spine, costo-vertebral and costo-sternal joints, sternoclavicular joint, and temporomandibular joint. Joint looseness is more severe in women. Temporomandibular dysfunction is common and leads to the development of osteoarthritis. Looseness and instability of the hip joint leads to iliotibial band syndrome. Tendinitis and bursitis (e.g. trochanter major bursitis) are common.

Chronic mechanical injuries caused by loose joints lead to early osteoporosis.

Chronic pain syndrome is commonly associated with EDS, its extent is related to joint instability, and it is stronger than could be explained by physical examination or imaging. Fatigue, sleep disturbances and other mental complaints develop. The pain can be muscular, neuropathic and osteoarthritic in nature. Headache, migraine can be explained by neck muscle tension and tem-

poromandibular joint loosening. In addition to the above-mentioned, common symptoms include hemorrhage, spontaneous arterial bleeding due to vascular fragility, and intestinal and uterine rupture may occur.

Physical therapy is the primary treatment for joint complaints. Isometric, balance, resistance and functional exercises are used to strengthen the joints. The use of joint fixators, orthoses and aids can be useful.

The use of minor analgesics (acetaminophen), NSAIDs, topical NSAIDs, lidocaine-containing gels is recommended, and steroid therapy may also be warranted. In more severe cases, the use of tramadol or opioid analgesics may be warranted. In order to relieve myofascial spasm, the use of muscle relaxants and magnesium is recommended. Tricyclic antidepressants and serotonin receptor inhibitors are useful in relieving neuropathic pain. Glucosamine and chondroitin are considered for the prevention of OA. Vitamin D and calcium are recommended to prevent osteoporosis.

18.1.3. Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a hereditary disease, the main symptom is the fragility of the bones. The prevalence of the disease is 1:10,000–20,000. Symptoms of the disease include deformities due to increased bone fragility, hypermobile joints, scoliosis, muscle hypotension, and short stature. The most common extraskeletal symptoms are blue / gray sclera (thinner, more translucent choroidal veins giving the color), dentinogenesis imperfecta, hypercalciuria, hearing loss, aortic dilatation, and neurological symptoms (macrocephalia, hydrocephalus).

The cause of the disease is mutation in collagen subtype I (COL1A1, COL1A2), which accounts for 90% of cases. In addition to the gene mutations above, mutations in other genes can also cause the disease. Mutations in proteins bound to collagen I (chaperone proteins, enzymes, signaling proteins) also cause OI, these proteins are involved in the formation, hydroxylation and mineralization of collagen crosslinks.

According to the previous classification of osteogenesis imperfecta, 4 types were distinguished: Type I is mild, non-deforming; type II. perinatally lethal; type III. severe deforming; type IV. moderately deformable form. Based on the new genetic knowledge, now at least 15 types are known, the phenotype is very variable, the most severe cases are lethal in childhood, the mildest forms are characterized only by osteoporosis. In mild cases of adulthood osteoarthritis, fractures, back pain, scoliosis, tendon ruptures develop. Bone density is significantly decreased in OI. Histological examination of the bones reveals atypical,

flat, broad resorption lacunae, and severe osteoporosis. In addition to structural abnormalities, load-bearing capacity of bones has also been severely reduced.

In the treatment of the disease, pain relief, prevention of bone fractures, and the preservation of mobility is primary. Physiotherapy and rehabilitation in childhood are important in preventing fractures and ensuring undisturbed growth.

Bisphosphonates, which inhibit osteoclast function, are used in drug therapy. Intravenous bisphosphonates are the first treatment of choice in childhood, but several studies have also shown their beneficial effects in adults. Adding growth hormone improves efficiency. Teriparatide stimulates bone formation. In a recent randomized controlled trial, teriparatide increased BMD, mainly in milder forms. In childhood, denosumab has only been used in a few cases. A monoclonal antibody against sclerostin (an inhibitor of the LRP5 / Wnt system) is in clinical trials for the treatment of osteoporosis, and treatment against TGF-β also appears to be promising (TGF-β is produced by osteoblasts, increases osteoclast activity).

18.1.4. Hypophosphatasia (Rathbun's disease)

Hypophosphatasia (HPP) is a rare hereditary metabolic bone disease caused by a decrease in so-called tissue-nonspecific alkaline phosphatase (TNSALP) activity due to a mutation in the ALPL gene. TNSALP is found primarily in bone, kidney, and liver. In addition, three tissue-specific alkaline phosphatase isoenzymes are known in the body (in intestinal, placental and germ cells), their concentrations in HPP are normal. Its prevalence is 1:300 000 in Europe, its incidence is common, 1:2500 among Canadian Mennonites and Japan. Decreased enzyme activity leads to decreased mineralization of bones and teeth, resulting in the formation of soft bone, which is prone to fractures and deformities, and is characterized by early tooth loss. The symptoms of the disease vary even within the same family, mild and more severe forms of the disease can occur. The inheritance is autosomal recessive or dominant. 6 types are distinguished, one form affects only the teeth (odontohypophosphatasia), 4 types are manifested in childhood (perinatal lethal, perinatal benign, infantile, childhood) and one in adulthood. Symptomatic forms at a younger age have a poorer prognosis leading to respiratory failure and epileptiform seizures due to chest deformities.

Diagnosis of the disease is difficult due to lower alkaline phosphatase activity common in other diseases (differential diagnosis: celiac disease, pernicious anemia, hypothyroidism, magnesium, zinc deficiency, vitamin C deficiency, multiple myeloma, etc.).

Typical symptoms are bone rickets-like deformity, bone pain, short stature, non-traumatic fracture, muscle pain, muscle weakness, dental abnormalities (early loss of deciduous teeth, late teething, caries formation), respiratory failure, cramps, elevated intracranial pressure (due to craniosynostosis), and joint pain. *Radiological abnormalities:* decreased bone density, thickened trabeculae, bone outgrowths, radiolucent projection from the epiphysis to the metaphysis. Among *laboratory differences* low ALP levels, hyperphosphatemia, hypercalcemia, and hypercalciuria (nephrocalcinosis) should be highlighted. Elevated plasma PLP (pyridoxal 5′-phosphate) levels correlate with disease severity and is the most specific marker in the diagnosis of HPP. If the above-mentioned is positive, it is necessary to detect ALPL gene mutation.

Treatment of the disease depends on the clinical symptoms. Supportive treatment is important, calcium-poor diet and adequate fluid intake are required to treat hypercalcemia. In severe cases, the use of glucocorticoids and loop diuretics is recommended. Bisphosphonates can be used to treat osteopenia. Vitamin D supplementation is warranted in patients with vitamin D deficiency. In 2015, an enzyme replacement therapy, *asfotase alfa,* a recombinant fusion protein was introduced. Enzyme replacement by subcutaneous administration at a dose of 6 mg/kg/week is warranted in the most severe cases in childhood.

18.2. Rheumatological aspects of lysosomal storage diseases

18.2.1. Gaucher's disease

Gaucher's disease is one of the most common lysosomal storage diseases, belonging to the group of glycosphingolipoidoses. The disease is caused by a defect in the lysosomal acid β-glucosidase enzyme. The gene encoding lysosomal glucocerebrosidase is GBA1. In the absence of glucocerebrosidase enzyme, the enzyme substrate, glucocerebroside, accumulates in tissue macrophages infiltrating the liver, spleen, lymph nodes, lungs, and bone marrow, creating symptoms characteristic of the disease. Three subtypes of the disease are distinguished.

Type 1 Gaucher disease is a *non-neuropathic* form, 90% of the cases. Its prevalence is 1:50 000–100 000 worldwide, but its incidence among the Ashkenazi Jewish population is 1:850–1000. This form is usually confirmed in young adults, with the most favorable diseases course. It is characterized by hepatosplenomegaly, anemia, thrombocytopenia, neutropenia, bone lesions, growth retardation, increased susceptibility to infection. Type 2 Gaucher disease or *acute neuropathic* Gaucher disease form is 1% of the cases, it manifests in in-

fancy or young childhood, characterized by weight gain disorder and rapidly progressing nervous system symptoms. The incidence of *chronic neuropathic* or type 3 Gaucher disease is 7%, occurs in older children, but may also manifest in infancy. Typical symptoms are supranuclear vision palsy, mild mental retardation, choreoathetosis, and cramp attacks.

Early diagnosis of Gaucher disease is extremely important since timely initiation of enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) can prevent irreversible complications.

In Gaucher disease, the most common symptom is bone involvement, a significant event is the lack of bone remodeling. In Gaucher disease, long tubular bones (especially the distal part of the femur) are not properly remodeled, leaving the metaphysics (sections affected by flares) abnormally wide. This manifests as *Erlenmeyer flask deformity* (EFD). Based on data from the Gaucher registry (data from 1698 patients), radiological bone abnormalities can be observed in 82% of patients (94% of whom has type I Gaucher disease) prior to treatment. The mentioned symptom is independent of the severity of the organ involvement and is the most important symptom affecting quality of life. Decreased bone density (BMD) is common in patients with Gaucher disease, regardless of gender and age, osteopenia and osteoporosis can be observed. A common symptom is *intermittent or chronic bone pain*. Unspecified, dull, progressive self-limiting pain occurs in seizures lasting 1–2 days. Existing mechanical pain can be caused by abnormal bone fractures or joint damage. Bone crises and osteonecrosis (AVN-avascular necrosis) can also occur. The diagnosis of Gaucher disease is possible with the help of a simple *blood drop test* used as a differential diagnostic test, to confirm the diagnosis it is necessary to measure the activity of the enzyme β-glucosidase in leukocytes and perform a genetic test (GBA1 gene mutation test).

The introduction of ERT treatment significantly improved skeletal manifestations in patients with Gaucher disease. Most data from studies with *imiglustat* confirm the finding above, treatment prevents the development of serious complications such as fractures. ERT improves visceral symptoms as early as the first year of treatment, improvement of bone involvement requiring at least 3 years of treatment. It takes at least 8 years for decreased bone density detected by densitometry to improve. Thus, starting treatment as soon as possible has a better outcome in terms of bone symptoms, but can also slow the progression.

Another option is SRT treatment, which reduces glycosphingolipid accumulation by inhibiting glycosylceramyl precursor synthesis. *Eliglustat* treatment significantly improved L-spine BMD in a phase II. study.

18.2.2. Fabry disease

Fabry disease is a progressive X-linked hereditary lysosomal storage disease caused by decreased function or lack of α-galactosidase A enzyme. Due to the lack of the enzyme, glycosphingolipids, primarily globotriaosylceramide (GL-3), accumulate in the walls of blood vessels, myocardial cells, renal epithelial cells, and the ganglia of the dorsal root and autonomic nervous system. Its prevalence is 1:40 000. The disease affects men, women are asymptomatic carriers or their symptoms are milder. Diagnosis is often delayed for years, on average 15 years based on the latest data. The disease is characterized by an angiokeratoma below the navel, in the gluteal region, and in the upper thigh often appearing in adolescence. Characteristic symptoms include acroparesthesia, a burning, numbing chronic pain in the hands and feet, and a sudden, burning, paralyzing pain of the "Fabry Crisis," that can last from a few minutes to several days. Symptoms are provoked by stress, fever, physical exertion, and temperature changes. If the symptoms are accompanied by fever, an elevated ESR is often observed. In these cases, rheumatoid arthritis, rheumatic fever, Raynaud's syndrome, systemic lupus erythematosus, and "growth pain" should be ruled out. Anhidrosis or hypohidrosis leads to the characteristic heat intolerance of patients. Other symptoms include eye involvement (corneal haze), proteinuria, renal failure, gastrointestinal symptoms, hearing loss and tinnitus. Osteopenia is common and even severe osteoporosis are occurred at a young age.

The diagnosis can be made on the basis of a simple dried blood drop test, and confirmed by measuring α-galactosidase activity in leukocytes or by genetic testing.

Phenytoin, carbamazepine, gabapentin can be used to treat neuropathic pain. If the diagnosis is made over the age of 16 years, *agalsidase alfa* enzyme replacement therapy is recommended; in other cases only in the presence of significant symptoms (mean age 7–10 years) and in carrying women only in the case of significant organ involvement.

18.2.3. Pompe disease

Pompe disease is a rare, type 2 glycogen storage disease caused by deficiency or decreased function of the enzyme alpha-glycosidase. Its incidence is 1/40 000–1/146 000, although for late-onset disease it is more common (1/60 000) than for the classic form of the disease. The enzyme is encoded by the GAA gene. Due to the lack or decreased enzyme activity, the degradation of lysosomal glycogen is inhibited and glycogen accumulates in the lysosome; glycogen storage is abnormal in the myocardium, skeletal muscle, vascular and gastrointestinal smooth

muscle, liver, kidney and nervous system cells. Although glycogen storage is abnormal in several organs, muscle weakness is at the forefront of symptoms.

Three forms of the disease are known. The classic, infantile form of early infancy is severe, usually leading to death in the first year of life; the non-classical infantile-onset form occurs between the first and second years of life, those affected live to an average age of 3 years. The late-onset juvenile-adult form usually occurs between the ages of 14 and 32, but in anamnesis of symptoms such as clumsiness during sports, running, or scoliosis can occur as early as childhood. Characteristic symptoms occur during running, sports, stair climbing, standing up from a chair / lying position, and walking. Respiratory distress is the first symptom in some patients, others do not get air when lying down (orthopnea), headache when waking up and drowsiness occurring due to nocturnal carbon dioxide retention. One-third of patients require respiratory support.

The most common symptoms are *Trendelenburg gait* due to paresis of paraspinal and hip muscles, the hip adducts and gluteus are the weakest, due to the weakness of the tensors and abdominal muscles, lordosis and scoliosis develop; low back pain is common (and the abdomen is pushed slightly forward to maintain the balance of the torso). Due to the above-mentioned symptoms patients have fatigue and lower limb cramps are common.

The course of the disease is variable, with early-onset forms being more progressive. In late-onset forms, the average delay in diagnosis is 7–10 years. Diagnosis in early-onset forms based on the characteristic triad (cardiomegaly, muscle weakness, muscle hypotension) is not difficult. In case of characteristic symptoms, muscle weakness and respiratory distress, the disease should be considered. Among the laboratory parameters the CK enzyme, aminotransferase levels and LDH may also increase with progression. In case of suspicion, it is recommended to perform a dried blood spot test, in case of a positive test it is necessary to measure the enzyme activity from blood, fibroblast culture. Enzyme activity is also a prognostic factor for the onset of the disease, the activity is less than 1% in the infantile forms, 1–10% in the juvenile forms and 5–30% in the adult cases. Genetic testing (GAA gene mutation) is required for accurate diagnosis. Differential diagnosis: metabolic, endocrine, inflammatory, toxic myopathies, neuropathies, lower motoneuron diseases, neuromuscular junction diseases, etc.

Enzyme replacement therapy is available in the treatment, since 2003 recombinant alpha-glycosidase enzyme (Myozyme) has been used at a dose of 20 mg/kg/2 weeks. ERT treatment is currently recommended for all forms of Pompe disease at the optimal time, i.e., in infantile forms immediately, while in adult

cases in case of pronounced symptoms or progression. Physiotherapy and breathing exercises are recommended as additional treatment.

18.2.4. Ochronosis (alkaptonuria)

Homogentisic acid oxidase enzyme deficiency is a rare disease with autosomal recessive inheritance. Its incidence is 1:100 000. Homogentisic acid is deposited in polymeric form in the skin, cartilage and sclerae. It is excreted in the urine, causing dark discoloration of the urine during standing (alkaptonuria). In cartilage, it binds to collagen, causing damage. It is a progressive, degenerative musculoskeletal process.

Radiological manifestations of alkaptonuria are caused by spinal and extraspinal involvement. Spinal involvement includes intervertebral disc calcification (primarily in the inner fibers of the anulus fibrosus), ossification, intervertebral space narrowing with vacuum phenomenon, osteoporosis and vertebral compression. The lumbar spine is affected first, followed by the dorsal and cervical sections. Progressive ossification of discs can result in vertebral fusion and may occasionally resemble bamboo spine mimicking an ankylosing spondylitis; the sacroiliac joints may also be affected but not ankylotic. Calcification and ossification are also present extraspinally (pubic symphysis, rib cartilage, ear cartilage, tendons, ligaments). Synovitis occurs most frequently in the shoulders, knees, and hip joints, with radiological changes resembling osteoarthritis, although osteophytes and subchondral cysts are not typical. Rarely, rapid, progressive destructive peripheral arthropathy may be present with fragmentation of taste surfaces. The therapy corresponds to the therapy of osteoarthritis.

There is no effective therapy for the underlying disease, a tyrosine-free diet can slow progression. Another option is ascorbic acid, and nitisinone.

18.2.5. Haemochromatosis

Inherited disorder of iron metabolism (HFE gene, 6 chromosomes), is an autosomal recessive inherited disease, characterized by increased iron absorption, and deposition in parenchymal cells. Primary, idiopathic and secondary, acquired forms are known (hematological diseases, porphyria cutanea tarda, chronic hepatitis C virus, alcoholic liver disease).

Radiological features of arthropathy associated with haemochromatosis are characteristic of degenerative musculoskeletal abnormalities (50%), chondrocalcinosis (30%), diffuse osteoporosis may be present. The MCP joints, especially the 2nd and 3rd are the most commonly affected. PIP, radiocarpal joints, large joints (shoulder, elbow, wrist, hip, knee, ankle) and spine are also affected. The

disease is characterized by the presence of beak-like osteophytes on the radial side of the metacarpus heads. Wrist involvement occurs in 30–50% of patients. The progression of arthropathy is slow, in contrast to CPPD arthropathy. Both T1 and T2 weighted MRI images show a reduced intensity according to the paramagnetic property of iron. Among laboratory findings, transferrin saturation above 45% and serum ferritin levels above 300 ug/l are characteristic. Therapy includes phlebotomy, chelating agents (desferoxamine) and diet. Major causes of death include liver cirrhosis, hepatocellular carcinoma and cardiomyopathy.

18.2.6. Wilson's disease

Wilson's disease is a rare condition with autosomal recessive inheritance; a disorder of copper transport (ATP7B gene mutation) with an incidence of 1:30 000. Corneal Kayser-Fleischer ring, liver fibrosis, then cirrhosis and central nervous system symptoms are of diagnostic value.

Radiological features of Wilson's disease include osteopenia, arthropathy and chondrocalcinosis (knees). Osteopenia is most common in the joints of the hands and feet and in the spine. Osteomalacia, the development of rickets, growth retardation and pseudofractures have also been reported. Subchondral bone fragmentation, cyst formation, cortical irregularities, most commonly in the shoulder, elbow, wrist, hand and knee joints, periosteal bone formation at the adhesion of tendons and ligaments are common. Irregularity of the subchondral bone can impart a characteristic "brush" appearance.

Characteristic laboratory findings are low serum copper and ceruloplasmin levels and increased urinary copper excretion. Chelators (D-penicillamine [250–1500 mg], trientine), diet, in advanced case liver transplantation are considered.

18.3. Other rare disorders

18.3.1. Relapsing polychondritis

Relapsing polychondritis is a rare immune-mediated systemic disease characterized by recurrent, destructive inflammation of cartilage tissue, primarily affecting the ear, and laryngotracheal cartilage. In 30% of cases, it is associated with other systemic autoimmune diseases, most commonly RA. Its incidence is 3.5/1 000 000 in the US. It usually occurs in the 5th decade, with a female:male ratio of 1:3. The presence of HLA-DR4 predisposes to the disease. Anti-collagen antibodies type II., IX., XI. can be detected, other target antigens are matril-

lin-1 and COMP (cartilage oligomeric matrix protein); in addition the role of degradative enzymes in cartilage destruction is likely.

Clinical features: The onset usually means sudden general symptoms (fever, asthenia, weight loss, hepatomegaly, lymphadenomegaly), and the onset of chondritis may be delayed for months or years. Ear cartilage-chondritis is the main manifestation. During acute attacks, pain, tenderness, swelling, and warmth occurs, which spares the soft parts of the ear. Seizures may resolve spontaneously within days without therapy, but the disease returns and usually heals with residual symptoms.

Saddle-nose deformity is characteristic, especially in women, it can develop progressively without an acute history. Laryngeal chondritis is responsible for hoarseness and aphonia, pressure sensitivity above the thyroid cartilage, and inspiratory stridor. Subglottic stenosis occurs mainly in women and may require a tracheostomy. Tracheobronchial manifestations (cough, chest pain, expiratory dyspnea, common infections) also occur, but these are not specific symptoms. The disease may manifest with isolated lower respiratory tract involvement, in which case permanent stenosis as a result of secondary tracheobronchomalacia, or cartilage collapse may lead to death.

Arthralgia, non-erosive, non-deforming oligo- and polyarthritis may occur; usually seronegative. Asymmetrical, elbows, wrists, MCP and PIP joints, knees, ankles and parasternal joints are affected. Tenosynovitis and other periarticular manifestations are also common. Eye symptoms often occur either primarily or associated with Sjögren's syndrome.

Recurrent episcleritis / scleritis (necrotizing) or conjunctivitis are more common, but keratitis and uveitis also occur. Retinal vasculitis, and optic neuropathy may be present. If severe proptosis occurs, granulomatous polyangiitis and lymphoma should be ruled out. As an audiovisual manifestation, neurosensory lesions caused by vasculitis result in sudden onset of unilateral or bilateral hearing loss of varying degrees, tinnitus, and dizziness, which can be reversed by immediate administration of high-dose corticosteroids.

Skin manifestations including oral aphthosis, nodules, purpura, papules, sterile pustules, livedo reticularis, ulcers, and necrosis may be present.

Histologically, leukocytoclastic vasculitis and thrombosis can be seen. These are often associated with myelodysplasia and may cause symptoms similar to Behcet's disease.

According to the suggestions of McAdam et al. (later modified by Damiani and Levine), diagnosis can be made in the presence of 3 of the 6 clinical features (auricular chondritis, non-erosive polyarthritis, nasal chondritis, ophthalmic

symptoms, laryngotracheal cartilage chondritis, cochlear and / or vestibular involvement). Positivity of inflammatory laboratory parameters, the presence of anti-type II collagen antibody and histological examination confirm the diagnosis. Therapy is based on NSAIDs, dapsone (50–200 mg), and corticosteroids (30–60 mg/day). Other immunosuppressive agents (cyclophosphamide, azathioprine, cyclosporin-A, methotrexate, leflunomide, mycophenolate mofetil, minocycline) and plasmapheresis can be used as corticosteroid sparing agents. Some cases of TNF-α inhibitors (etanercept, infliximab, adalimumab), anakinra (a monoclonal antibody against IL-1R) have been reported for other therapies in refractory cases.

18.3.2. Sarcoidosis

It occurs in all ethnic groups, genders and ages worldwide. In most cases, the diagnosis is made between the ages of 20 and 50, there is a slight female predominance; both childhood and elderly cases occur. Its prevalence is 10–40/100000. Etiology is unknown, genetically susceptible individuals, environmental antigens lead to the development of the disease, to the T helper 1 (Th1) cell-mediated cellular immune response. It is associated with the formation of non-cheesy granulomas that heal spontaneously or develop fibrosis as a residual symptom.

Clinical manifestations range from asymptomatic disease to forms associated with acute febrile illness, severe organ failure, and systemic symptoms (fatigue, fever, weight loss). Sarcoidosis is rare in children, but may mimic juvenile idiopathic arthritis.

It can affect any organ with symptoms appropriate to that organ's involvement. More than 90% of patients have pulmonary involvement. Based on the chest X-ray, 4 stages are distinguished, depending on the presence of bilateral hilar lymphadenopathy (BHL), interstitial and alveolar infiltrates, nodules. In terms of disease course, we distinguish acute and chronic forms. Skin lesions can occur mainly in chronic forms in the form of plaques, nodules or lupus pernio. Ophthalmic complications such as chronic uveitis, cataracts, glaucoma, keratoconjunctivitis sicca, acute iritis, and conjunctivitis are also common. Arrhythmias may occur due to granulomatous cardiac involvement.

Common musculoskeletal complications give its rheumatic significance. Acute cases are characterized by symmetrical arthralgia or arthritis, primarily affecting large joints (elbow, wrist, knee, ankle), but any joint may be affected. *Sarcoid dactylitis,* wrist tenosynovitis may occur, in severe cases joint involvement may lead to deformity, ankylosis. It is often associated with erythema nodosum. The triad of acute arthritis, erythema nodosum and BHL is called *Löfgren's syndrome.*

Osteopenia and osteoporosis are often observed, in which granuloma-induced osteoclast activation plays a role, and may be iatrogenic due to corticosteroid therapy. Bone lesions occur in 3–13%, which are asymptomatic and bilateral.

Asymptomatic myopathy is common, with symptomatic myopathy occurring in less than 0.5% of cases. Rarely, the respiratory and eye muscles may also be affected. Uncommon complications include neurogranulomatosis, myelopathy, cranial neuropathy, and encephalopathy. Systemic vasculitis is rare but may be severe, with cases reported in association with Takayasu arteritis, hypersensitive vasculitis, nodular polyarteritis, microscopic polyangiitis, and eosinophilic polyangiitis.

Diagnosis is mainly based on clinical and radiological imaging and biopsy sampling. Examination of synovial fluid shows lymphocytosis and elevated total protein. Synovial biopsy may show mild synovitis, often without granulomas. Anemia, leukopenia, and thrombocytopenia may be present, hypercalcemia, hypercalciuria, elevated liver enzymes are typical in 20% of patients. Serum angiotensin converting enzyme (ACE) activity is often elevated to aid in diagnosis. A gallium 67 citrate scan can confirm lacrimary gland and salivary gland involvement.

Therapy is based on NSAIDs. In case of a more severe pulmonary process or extrapulmonary granulomatosis corticosteroids are used for 1–2 years or other immunosuppressive agents (methotrexate, cyclophosphamide, azathioprine, chlorambucil, cyclosporin-A, chloroquine, and hydroxychloroquine). Colchicine may be effective in arthritis; there are limited data on the use of TNF-α antagonists (etanercept, infliximab). Lung transplantation is considered for immunosuppressive therapy refractory cases.

The prognosis is good in the acute form, symptoms resolve spontaneously, relapse may occur, but much less frequently than in the chronic form, which often persists.

18.3.3. Sweet's syndrome

Sweet's syndrome is a neutrophil dermatosis caused by epidermal and/or dermal infiltration caused by neutrophil granulocytes in the absence of vasculitis. Sweet's syndrome is rare, characterized by female predominance (4:1).

Its pathogenesis is unknown. Hypersensitivity reaction is indicated by the following associations:

- infections, vaccinations (Streptococcus, Mycobacterium, Yersinia, Typhus, Salmonella, CMV, HIV),
- autoimmune diseases (RA, SLE, MCTD, Hashimoto's thyroiditis, Sjögren's syndrome, Behçet's disease),

- inflammatory bowel disease, malignancy (acute myeloid leukemia, lymphoproliferative diseases, solid tumors, genitourinary tract, breast and gastrointestinal tract),
- medicines (G-CSF, lithium, furosemide, hydralazine, contraceptives, minocycline, azathioprine, imatinib, bortezomib, trimethoprim-sulfamethoxazole).

Cytokine dysregulation is currently thought to play a central role (IL-1, IL-3, IL-6, IL-8, G-CSF, GM-CSF, and IFN-γ).

General symptoms, intermittent fever occur in 40–80% of patients. Clinically it is characterized by multiple or localized erythematous, purple papules, vesiculopustules, plaques, nodules, and ulcers. They are most commonly present on the face, neck, upper limbs, especially on the back of the hand. Oral lesions occur in 3–30% of patients. It may be similar to erythema nodosum in the lower extremities, especially in the rare subcutaneous form.

Ocular symptoms may include conjunctivitis, episcleritis, and iridocyclitis. Arthralgia, arthritis, and myalgia occur in ⅓ of patients. Arthritis is symmetrical, non-erosive, mainly affecting the elbows, wrists, hand joints, knees, and ankles. Organ symptoms include neutrophil alveolitis, sterile osteomyelitis, acute renal failure, splenomegaly, lymphadenomegaly, liver and pancreatic involvement, neurological and psychiatric symptoms.

Histological diagnostic abnormality is perivascular neutrophil infiltration in the absence of vasculitis. Secondary vasculitis may also be present, but it is are. Based on the diagnostic criteria, patients should meet 2 main criteria (sudden onset of typical skin lesions and histopathological criteria) and 2 minor criteria (fever, arthralgia, conjunctivitis, malignancy, leukocytosis, good response to systemic steroids but not to antibiotics).

Standard therapy is based on corticosteroids (40 mg/day) gradually tapering, NSAIDs, dapsone, colchicine, cyclosporine, doxycycline, clofazimine may be effective. Relapse occurs in 20–30% of patients.

18.3.4. Paraneoplastic syndrome

Paraneoplastic syndromes can mimic a myriad of rheumatic diseases. Based on the main anatomical localizations, articular, muscular, cutaneous, vascular, and other types of paraneoplastic symptoms can be distinguished, of which only the most significant are mentioned. Paraneoplasias in the form of other conditions usually mimic the classical picture but are therapy-resistant.

Paraneoplastic rheumatic disorders are listed in *Table 18.3.*

Table 18.3. Musculoskeletal paraneoplastic syndromes

Autoimmune connective tissue diseases • Polymyositis and dermatomyositis • Lupus-like syndrome • Scleroderma-like syndrome • Late onset Raynaud's disease
Arthritides • Secondary hypertrophic osteoarthropathy • Carcinomatous polyarthritis (RA-like disease) • Relapsing polychondritis • RS3PE syndrome • Palmar fasciitis and polyarthritis
Vasculitides • Atypical polymyalgia rheumatica • Erythema nodosum • Cryoglobulinemic vasculitis
Skin and muscle disorders • Dermatomyositis • Lambert-Eaton syndrome • Palmar fasciitis • Panniculitis • Eosinophil fasciitis
Metabolic diseases • Gout • Algodystrophy (Sudeck's atrophy) • Metastatic hypercalcemia

Carcinomatous polyarthritis occurs in 7–10% of cancer patients, usually over the age of 50, with general symptoms; but the disease is not caused by direct invasion or metastasis of the tumor. The immune response against the tumor is likely to play a role in etiopathogenesis. It can have countless appearances. It can mimic rheumatoid arthritis, but is usually seronegative, asymmetrical, nonerosive, primarily with lower limb involvement, sparing the small joints of the hand. It is most commonly associated with breast, colon, lung, and ovarian cancer, and lymphoproliferative diseases. In lymphoproliferative diseases, articular symptoms can also be caused by lymphoma infiltration of the synovium, which is rare, occurring especially in T-cell lymphomas. Atypical lymphocytes may be present in the synovial fluid. Therapy includes treatment appropriate for the given tumor, symptomatic therapy, NSAIDs, and topical corticosteroid preparations.

Benign edematous polysynovitis (RS3PE) is a rare seronegative, destructive disease, primarily affecting the MCP joints and wrists. The etiology is unclear and may be associated with T-cell lymphomas, myelodysplastic syndrome, and solid tumors (adenocarcinoma). It is characterized by systemic symptoms, fever, weight loss and a good response to corticosteroids.

18.3.5. Hypertrophic osteoarthropathy (HOA)

The prevalence of HOA is unknown. It is characterized by male dominance (9:1). The primary form is autosomal dominant inherited, occurring in the first year of life and adolescence (pachydermoperiostosis). It is characterized by periostosis, clubbed finger, facial skin thickening, scalp thickening, seborrhea, and hyperhidrosis. Familial cases also occur. Secondary forms may manifest as isolated clubbed finger, or the full spectrum of the disease may be present *(Table 18.4.)*.

HOA is characterized by excessive collagen deposition, endothelial cell activation, vascular proliferation, edema, and neoplasia, mainly distal to tubular bones. Factors involved in pathogenesis include the fragmentation of megakaryocytes in the pulmonary capillaries and the release of local growth factors (VEGF, PDGF) in the peripheral vasculature.

HOA is often asymptomatic. If HOA is accompanied by symptoms, pain occurs in the lower extremities and above the tubular bones. Large joint synovitis is common, synovial fluid is non-inflammatory in nature. Nail bed hypertrophy may be associated, but it is also characterized by hypertrophy of the skin of the face and the skin above larger tubular bones and joints.

The most common clinical manifestation is a clubbed finger with a watch-glass nail. Clubbed finger can be unilateral or bilateral and can occur in many diseases. There are no specific laboratory abnormalities. Hand and foot imaging may show acroosteolysis and periostitis with irregular or regular thickening of the cortical tubular bones. Erosion and taste narrowing are not typical.

Asymptomatic cases do not require treatment. NSAIDs are sometimes useful in cases. Case reports suggest that octreotide or pamidronate can significantly reduce pain. In secondary cases, with elimination of the cause (IBD, infectious endocarditis, cancer), the symptoms regress immediately.

Table 18.4. Etiological factors of hypertrophic osteoarthropathy

Unilateral	Hemiplegia, ductus Botalli persistens, aneurysm
Bilateral	*Lung diseases:* cystic fibrosis, pulmonary fibrosis, primary and secondary lung tumors, pulmonary and pleural infections, pleural tumors *Cardiovascular diseases:* heart disease with cyanosis, infectious endocarditis *Gastrointestinal disorders:* liver cirrhosis, hepatocellular carcinoma, malignancies of the esophagus and small intestine, inflammatory bowel disease, polyposis *Other:* malignancies, POEMS syndrome, rheumatic diseases, thymoma, AIDS, thalassemia

18.3.6. Diabetic and neurogenic arthropathies, DISH

Diabetes mellitus can have many joint manifestations, the hand is an important target for these complications. Stiff hand syndrome (cheiroarthropathy) is caused by extensive glycosylation of the skin and blood vessels, periarticular structures, and decreased collagen removal, which results in thick, inelastic tissue, flexion contracture of the small joints of the hand (MCP, PIP), which can resemble scleroderma. It is uncomfortable, but does not cause disability to work. It is exacerbated by the duration of the disease, and its development is related to the degree of hyperglycemia.

Renal, retinal, and other complications are predictive, occurring as a late manifestation in 30% of patients. Dupuytren's contracture can occur in association with stiff hand syndrome or on its own, but in contrast, it occurs early in the disease, with a prevalence of 30%. The so-called trigger finger is also a common painful complication caused by tenosynovitis of the flexor tendons. Adhesive shoulder capsulitis with or without calcifying tendinitis as well as reflex sympathetic dystrophy also occur. Sometimes recurrent painful tendinitis and bursitis develop. Carpal tunnel syndrome occurs in 25%, especially in patients with peripheral neuropathy. Nocturnal paresthesia is common, early detection is important to prevent thenar muscle atrophy.

Diffuse idiopathic skeletal hyperostosis (DISH) occurs mainly in type 2 diabetes. It is characterized by osteophyte formation juxtaarticularly, axial skeleton involvement; and AS-like spinal mobility narrowing may occur. There is little data on how well controlled diabetes slows progression.

Osteomyelitis is a common problem as peripheral sensory neuropathy results in the formation of ulcers at pressurized sites. Due to peripheral neuropathy, patients often report to the doctor only if they develop advanced osteomyelitis. Infectious complications can be avoided by conscientious foot care and proper patient education.

Charcot arthropathy affects the ankles and metatarsals. It is characterized by a sudden onset of swelling, radiologically bone fragmentation with disorganization can be seen. It is caused by a disorder and atrophy of the local microcirculation due to a disorder of central and peripheral innervation. A three-phase bone scan and MRI scan help with the diagnosis. Therapy can include resting, load relief, calcitonin, bisphosphonates, and in advanced cases, arthrodesis and total endoprosthesis (TEP).

18.3.7. Rheumatic aspects of endocrine diseases

The association between *Graves-Basedow disease and Hashimoto's t*hyroiditis *(chronic lymphocytic)* with other immune-rheumatic diseases is well known. Arthralgia and symmetrical polyarthritis are common in Hashimoto's thyroiditis. The synovial fluid is non-inflammatory but high in hyaluronic acid. Carpal tunnel syndrome is common. Myopathy is present in 25% of patients but it is not accompanied by elevated CK. Pretibial myxedema is the presence of painless purple nodules in the pretibial region, ranging in size from 1 cm nodules to confluent lesions. The cause is the accumulation of hyaluronic acid in the skin; can mimic scleroderma and morphea.

Hyperthyroidism, most commonly caused by Graves-Basedow disease, has numerous musculoskeletal implications. The most common is osteoporosis, which is often of iatrogenic origin. Onycholysis, and clubbed finger as a sub-phenomenon of thyroid acropachy (pretibial myxedema and ophthalmopathy), is a rare manifestation: periostitis around the MCP joints and thickening of the soft tissues of the fingers. Proximal myopathy is often present, rapidly improves upon reaching the euthyroid state. Adhesive shoulder capsulitis may also be present.

Cushing's syndrome is caused by cortisol overweight due to involvement of the hypothalamic-pituitary-adrenal axis (pituitary basophil tumor, ectopic ACTH-producing tumor, adrenocortical adenoma, hyperplasia). Iatrogenic Cushing's syndrome is more common. Osteonecrosis is a common late complication that manifests months, years after initiation of therapy and may occur with short-term or intermittent administration of high-dose corticosteroids. Therefore, it is important to use the lowest corticosteroid dose that can keep the underlying disease in remission. Steroid myopathy occurs in primary or secondary inflammatory myopathies. It is characterized by the fact that it is more severe in the pelvic muscles, the patient may be bedridden; may develop gradually or suddenly, myalgia may be present as well. The biopsy shows type II fiber atrophy, necroenzymes are normal. In particular, long-acting and fluorinated derivatives are dangerous in this respect. It is advisable to discontinue the corticosteroid until

improvement, if possible; it may take weeks or months for muscle strength to return. Osteopenia, osteoporosis develops rapidly, the process is dose-dependent, therefore these patients should receive calcium and vitamin D3 prophylaxis, with the administration of bisphosphonates. Arthralgia may be present, especially in the knees, at the initiation of high-dose corticosteroids. Depending on the etiology, transsphenoidal surgery, irradiation, adrenalectomy and chemotherapy are considered in the therapy.

Acromegaly is caused by a growth hormone-producing adenoma of the pituitary gland. There is evidence of an increase in muscle mass and, in some cases, bone density in the elderly treated with growth hormone. Growth hormone is produced in nocturnal pulses and stimulates the production of somatomedin C and insulin-like growth factor in hepatocytes. Somatomedin C also has various effects on tissues, osteocytes, chondrocytes, and fibroblasts.

Acromegaly a disease with an insidious onset, the diagnosis of which is often delayed by years. Carpal tunnel syndrome occurs in half of patients and is considered an early manifestation. Raynaud's phenomenon also occurs in ⅓ of patients due to soft tissue compression of the distal arteries. Early osteoarthritis affecting knees, hips and spine can develop (widening of the disc, characterized by diffuse lumbar pain, and can occur at rest and under load). In hypertrophic cartilage, fissures form and the ligaments elongate. Temporomandibular, hand and foot joints may also be affected, the enlargement of the limbs being due to cartilage thickening and soft tissue proliferation.

Early radiological examinations show a widening of the taste gap. Later, the abnormalities cannot be differentiated from idiopathic osteoarthritis. Most patients also have proximal muscle weakness, which can be an early symptom, however, CK and LDH are normal. Biopsy does not confirm inflammation, but muscle fiber diameter variability may occur.

Some patients improve after surgery for adenoma, transsphenoidal resection or irradiation, or after treatment with a somatostatin analogue (octreotide, lanreotide). More recently, a monoclonal antibody against the growth hormone receptor, pegvisomant is available in therapy.

18.3.8. Rheumatic aspects of hematological diseases

Hemophilia A is the deficiency of coagulation factor VIII, *Hemophilia* B the deficiency of coagulation factor IX. These are X-linked recessive inherited diseases. They occur only in men, heterozygous women are asymptomatic carriers. The cause of arthropathy observed in hemophiliacs is due to the destructive effect of recurrent intraarticular hemorrhage (hemarthrosis) and the consequent

synovitis, which are seen less and less nowadays due to prophylactic factor replacement.

Mainly elbows, knees and ankles are affected. The synovium thickens and turns brown due to the presence of macrophages that phagocytose hemosiderin. Late consequences are complete joint destruction, erosions, gap narrowing, and joint instability. MRI can help with the diagnosis. In addition to human recombinant factor replacement, the basis of the therapy is exercise, physiotherapy and resolving contractures. In chronic synovitis, radiosynoviorthesis is considered.

Sickle cell anemia, an inherited disease, is characterized by abnormal hemoglobin (HbS), sickle-shaped red blood cells, and manifests as symptoms of chronic hemolytic anemia. Clinically, it is characterized by anemia and tissue ischemia; due to the increased intraosseous pressure, aseptic necrosis of the femur head and vertebral bodies, and secondary OA may develop. Dactylitis, synovitis can be present as early as 6 months of age, which can be caused by infarction of the carpal bone, finger growth can also be damaged. Chronic erosive synovitis can also develop in the wrists, MCP joints. The disease predisposes to osteomyelitis caused by encapsulated pathogens *(Salmonella, S. aureus).*

Thalassemias are caused by decreased production of at least one globin polypeptide chain. ß-thalassemia is an autosomal dominant inherited disease caused by impaired production of the ß-globin chain, resulting in α-globin chain dominance that is unable to form a stable tetramer. In thalassemia minor mono- or oligoarthritis may develop. The synovial fluid in non-inflammatory. It does not require specific treatment. In severe thalassemia major osteopenia, pathological fractures can develop, and a characteristic "brush skull" develops as a result of the spread of bone marrow to the cortical.

Hyperuricemia is often present in the diseases due to increased red blood cell death, and transfusions can lead to haemochromatosis-like arthropathy. Transfusions, splenectomy and chelating agents are considered in therapy.

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19. Comorbidities in rheumatic disorders

Zoltán Szekanecz

19.1. Introduction

As a rheumatologist, I encounter every day – among the general public, but unfortunately also in the profession and among decision-makers – the misconception that arthritides, although painful, are not very serious condition that does not threaten life. Over the past decade, more attention has been paid to comorbidities and their research. For example, patients with rheumatoid arthritis (RA) have been shown to live 3–6 years shorter compared to healthy individuals. Cardiovascular (CV) diseases are responsible for 25–50% of the increased mortality. Accelerated atherosclerosis develops in systemic inflammatory diseases, including RA, which is responsible for the increased mortality. Inflammatory diseases are often associated with secondary bone loss, osteoporosis, in the development of which, in addition to traditional factors, inflammatory mediators play a key role. It is also necessary to mention that the incidence of secondary tumors in chronic autoimmune rheumatic diseases also increases. In addition, it is known that persistent, "undertreated" inflammation can increase the formation and tissue deposition of amyloid proteins, primarily causing the development of AA amyloidosis, and often causing a severe, fatal disease. Inflammatory diseases are often associated with psychiatric comorbidities such as depression and cognitive impairment. Not only are these conditions more common in inflammatory-autoimmune diseases, but they also show an accelerated course. Thus, in such patients, the CV and the risk of tumor formation increase and a much larger proportion of the bone mass is lost in one year than in the general population.

Overall, rheumatology is indeed an interdisciplinary specialty, and rheumatologists need to be in close contact with experts of other specialties. (We have already referred to this in Chapter 1 when consultations were mentioned.) In this chapter, we present primarily the comorbidities associated with arthritides and systemic autoimmune diseases.

19.2. Accelerated atherosclerosis and cardio-cerebrovascular diseases

The main cause of death of inflammatory rheumatic diseases is CV disease. In addition to traditional Framingham risk factors (obesity, smoking, dyslipidemia, insulin resistance), systemic inflammation is a major driver of atherosclerosis, moreover, it is the most important risk factor in inflammatory diseases *(Table 19.1.)*. Against the so-called "low-grade" inflammation of age-related atherosclerosis with a small-moderate increase in CRP, high-grade inflammation with high CRP levels associated with arthritis, including inflammatory white blood cells, cytokines, connective tissue-degrading enzymes, autoantibodies, cause arterial wall stiffness and manifest atherosclerosis (plaque formation) *(Figure 19.1.)*. Regarding the pathogenesis of atherosclerosis and CV disease, we do not go into further details, we refer to pathophysiology and cardiology. Increased CV morbidity and mortality were observed in arthritis (RA, AS), gout, and systemic autoimmune diseases (SLE, antiphospholipid syndrome, scleroderma).

Table 19.1. CV risk factors of inflammatory rheumatic disorders*

Classical	• age • sex • metabolic syndrome • smoking • dyslipidemia • insulin resistance and diabetes mellitus • obesity • hypertension • inactivity – positive family history
Inflammatory	• genetics • inflammatory cells and mediators – auto-antibodies and autoimmunity
Treatment-related (iatrogenic)	• NSAID • corticosteroids – cyclosporin A

**Further explanation in the text*

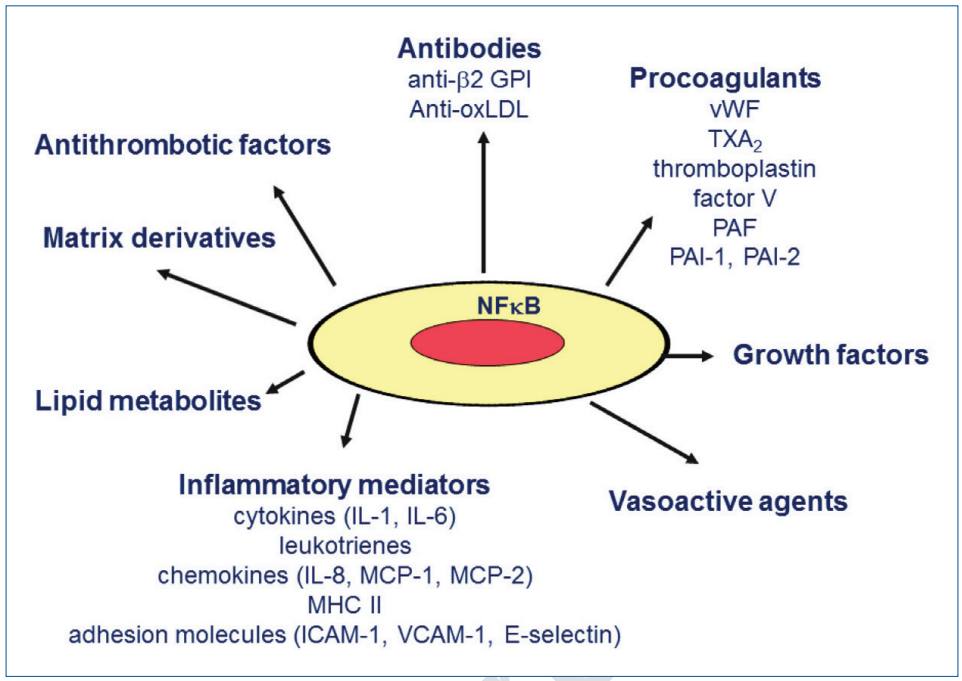

Figure 19.1. Factors of accelerated inflammatory atherosclerosis

Therefore, as the risk of CV increases to 2–3-fold in patients with rheumatic diseases, it is important to recognize this condition before the onset of manifest heart disease. Endothelial dysfunction, stiffness, and atherosclerosis can be confirmed early in the vascular subclinical state by ultrasound-based techniques. In addition, it is important to continuously monitor the blood pressure, lipid profile, blood glucose levels and body weight of all patients with inflammatory diseases. For example, RA, and gout can be considered part of the metabolic syndrome, which is characterized by the role of lipid profile and adipokines in adipose tissue, abdominal obesity, but also the so-called "rheumatoid cachexia" that causes muscle loss.

Overall, according to European League Against Rheumatism (EULAR) guidelines and several CV recommendations, inflammation has been included in the CV risk factors in several countries, including Hungary. In case of CV disease, screening for inflammatory disease should be considered, and regular blood pressure monitoring, lipid monitoring, and, if available, imaging should be part of the care of arthritis and autoimmune patients. In addition to conventional vasculoprotective therapy (aspirin, ACE inhibitors, calcium antagonists), since systemic inflammation is the primary risk factor, aggressive treatment of the under-

lying disease is essential. The latter is also supported by the fact that targeted therapies have been shown to improve CV function, reduce CV morbidity, and possibly mortality.

19.3. Osteoimmunology: inflammatory bone loss

In inflammatory diseases, such as arthritides, on the one hand, local bone resorption, on the other hand, generalized bone loss develops. In addition to female gender, age, and immobility, systemic inflammation is essential here as well. The pro-inflammatory cytokines mentioned increase the expression of RANK and RANK ligand, essential for osteoclast activation and bone resorption, causing an increased bone loss. As a result, joint erosions occur locally, which predict joint destruction, and three-quarters of arthritis patients develop generalized osteopenia or osteoporosis *(Table 19.2.)*.

Inflammatory patients should therefore be screened by densitometry, and annual bone radiographs are the most objective marker of progression of the underlying arthritides. Moreover, bone loss is an important prognostic factor: the appearance of the first erosion suggests worse outcome.

In case of bone, it is also important to prevent further bone loss by controlling the underlying inflammatory disease, but traditional pharmacological and non-pharmacological (e.g. exercise) treatments for osteoporosis should also be used. Among the drugs, bisphosphonates and denosumab are of key importance for accelerated inflammatory bone loss. In addition, denosumab has been shown to inhibit erosion formation associated with the underlying disease (e.g. RA).

Table 19.2. Risk factors of secondary osteoporosis in RA and SLE

RA	SLE
• Pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-17) • Proteases (cathepsins, MMPs) • RANK-RANKL system • Increased DKK-1 and sclerostin production • Female gender • Postmenopausal age • Relative estrogen and androgen deficiency • Low hormone D levels • Inactivity • Corticosteroid therapy (?)	• Pro-inflammatory cytokines • Photosensitivity • Inactivity (due to arthritis, myositis) • Early menopause • Nephritis-renal failure • D hypovitaminosis • Lupoid hepatitis • Corticosteroid therapy (double effect) • Use of cytotoxic agents (cyclophosphamide)

19.4. Oncoreumatology: correlations between tumorigenesis and musculoskeletal disorders

Rheumatology and oncology are connected at many points. Here we can only discuss the main correlations, those interested can find the details in the scientific literature *(Table 19.3.)*.

Table 19.3. Oncorheumatologic associations

RHEUMATIC DISEASE → TUMOR
1. Secondary malignancies in rheumatic diseases
2. Soluble tumor antigens in rheumatic diseases
3. Tumor formation with rheumatic drug therapy / Tumor recurrence with rheumatic drugs
4. Non-pharmacological treatment (physiotherapy) in cancer patient
TUMOR → RHEUMATIC DISEASE
5. Paraneoplastic syndromes
6. Autoimmune / rheumatic diseases with checkpoint inhibitor
7. Osteoporosis with hormone deprivation treatment
8. Tumors of the musculoskeletal system

Approached from the perspective of the underlying rheumatic disease, the risk of secondary tumor formation in inflammatory-autoimmune rheumatic diseases increases. In both atherosclerosis and bone loss, systemic inflammation is primarily responsible. In diseases involving B-cell activation (e.g. SLE, RA, systemic sclerosis, Sjögren's syndrome), lymphomas become more common. In addition, there is an increased likelihood of developing solid tumors in the organs most affected by inflammation. Thus, e.g. in RA and scleroderma lung cancer is the most common. In addition to inflammation, other factors (e.g. smoking and viral infections) also increase oncogenicity. It is clear that reducing the risk of inflammation reduces the risk of cancer.

Not only the underlying disease but also rheumatic drugs can be oncogenic. This has been suggested with long-term azathioprine, cyclophosphamide treatment. Previously, the same was thought about methotrexate and biologics, but the latter suggestion has been refuted, these drugs do not increase the likelihood of tumor formation, in fact, they can reduce the increased tumor risk mentioned above by suppressing inflammation.

Importantly, tumor markers used in oncology (e.g. carcinoembryonic antigen in colon cancer) may also appear on inflammatory cells and can be detectable

in the blood upon detachment. Therefore, the laboratory determination and detection of tumor markers in rheumatic diseases should be carefully evaluated.

The danger of physiotherapy procedures often used in rheumatology is also questionable. Indeed, in an active cancer patient, systemic treatments or balneotherapy may be dangerous. However, in a treated patient in remission, these procedures are definitely recommended since they improve the patient's quality of life. In any case, it is essential to consult an oncologist before using physiotherapy, especially electrotherapy.

Looking at the issue from the tumor side, tumor patients may develop a variety of musculoskeletal symptoms. These can be arthritides, muscle diseases, bone loss, or even true autoimmune diseases. Such symptoms occurring with an underlying tumor are called paraneoplastic syndrome. These need to be paid close attention to, and if an unusual rheumatic disease occurs, an underlying tumor should be looked for. The characteristic feature of paraneoplasia is that the rheumatic symptoms disappear with the removal and treatment of the tumor.

Musculoskeletal disorders can also develop with the medication of the individual tumors. On the one hand, with hormone deprivation treatment of breast or prostate cancer, bone loss and osteoporosis can occur, which should be monitored. On the other hand, with newly introduced immunotherapies (checkpoint inhibitors) in oncology, autoimmune phenomena may flare up.

Finally, tumors, mostly sarcomas (chondrosarcoma, osteosarcoma, synovial sarcoma), may occur in the musculoskeletal organs themselves, but their discussion is beyond the scope of this chapter.

19.5. Development of AA amyloidosis in rheumatic disorders

Amyloidosis refers to the extracellular deposition of fibrillar amyloid proteins. Nowadays, more than 20 types of amyloid precursors and several types of amyloidosis (AA, AL, Aβ2M, ATTR, etc.) are known. In chronic inflammatory diseases, in addition to several acute phase proteins (e.g. CRP), serum amyloid A (SAA) production is also increased. Persistent "flaming" untreated inflammation is associated with continuous SAA production, and then SAA is deposited in the kidneys, liver, spleen, and, less commonly, in the tongue and gastrointestinal tract, causing functional impairment and then insufficiency of those organs. In larger cohorts, two-thirds of AA amyloidosis cases are due to chronic inflammatory arthritis *(Figure 19.2.)*.

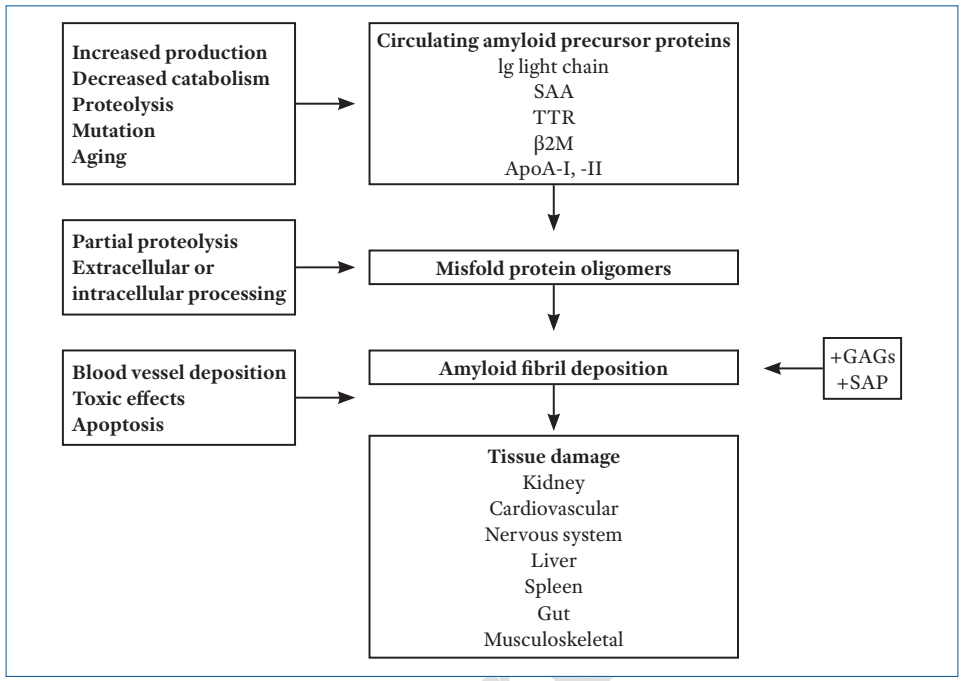

Figure 19.2. Process of systemic amyloid deposition

The disease is largely immunopathogenic, since the production and deposition of SAA is primarily stimulated by pro-inflammatory cytokines (TNF-α, IL-1, IL-6), which are produced in large amounts during systemic inflammation. Deteriorating renal function, proteinuria above 500 mg/day, weight loss followed by cachexia, general weakness may call attention to it. Histological diagnosis can be made by biopsy of the rectum wall, abdominal adipose tissue; even today, after Romhányi's Congo red staining, it is evaluated by birefringence under a polarization microscope.

In recent years, the incidence of AA amyloidosis has decreased and the prognosis has improved due to early diagnosis and more effective therapy for the underlying disease.

19.6. Psychiatric co-morbidities: depression and cognitive dysfunction

It has previously been observed that depression and cognitive dysfunction become more common in RA and other inflammatory diseases. It is not a simple association, but, like the other mentioned comorbidities, a causal relationship.

One of the main mediators of depression is CRP itself, which is induced by IL-6 in the liver. With increased inflammation and higher CRP, more severe depression was observed. There is evidence that proper treatment of the underlying inflammatory disease, has improved depression as well. It is also important that non-inflammatory fibromyalgia is specifically associated with depression. The use of antidepressants may be beneficial not only in this condition but in all diseases associated with chronic pain.

Similarly, cognitive abnormalities associated with recognition, memory, and concentration disorders have been demonstrated in these diseases. In addition to proper treatment of the underlying disease, patients can be helped with cognitive behavioral therapy.

19.7. Therapy of the underlying disease: prevention

As we have seen, the comorbidities discussed are primarily due to the underlying inflammatory disease and its activity. Thus, in addition to the traditional methods used for the treatment of atherosclerosis and osteoporosis that do not develop under such conditions, in the case of amyloidosis, CV disease, bone loss, and depression that develops for a secondary reason, the sufficiently rapid and effective treatment of the underlying disease is expected to prevent the development of complications. There is strong evidence of this in each area.

With regard to atherosclerosis and CV disease, the EULAR CV committee also made a 10-point recommendation for the prevention and treatment of CV comorbidities in patients with arthritis. This recommendation includes the need for prevention, smoking cessation, risk assessment (the risk number determined on the basis of SCORE in the average population should be multiplied by 1.5 in case of arthritis patients) and treatment. For the latter, in addition to traditional vasculoprotection, methotrexate and biologics have reduced the incidence of infarction in larger studies. This is due to the fact that biologics reduce the function of inflammatory cells and mediators that are also involved in the development of atherosclerosis, improve endothelial function, and inhibit vascular stiffness and plaque formation.

DMARDs used in rheumatology, but especially biologics are required to reduce radiological progression and the development of erosions. This already implies that the agents also have bone effects. Regarding generalized bone loss, a number of data suggest that treatment of arthritis with a biological agent slows bone loss and reduces the levels of biochemical markers of bone resorption.

As of now, there is no clear evidence that the risk of fracture is reduced as well. Agents used in the treatment of osteoporosis (bisphosphonates, anti-RANKL antibody) are also suitable for the treatment of secondary bone loss associated with inflammatory diseases.

There is less direct evidence for tumor formation. In follow-up studies, it was observed that in case of early and aggressive treatment of arthritis, a secondary tumor is less likely to develop. However, the use of highly carcinogenic agents is recommended only for the shortest time necessary.

AA amyloidosis is a rare disease making it difficult to conduct clinical trials in a large patient population. Predominantly case reports suggest that both traditional DMARDs (methotrexate, cyclophosphamide, azathioprine, leflunomide) and biologics (anti-TNF agents, IL-6 receptor blockers) effectively suppress the underlying inflammatory process, and with early, aggressive treatment, the prevalence of AA amyloidosis is reduced. In cases of developed AA amyloidosis, a reduction in renal and gastrointestinal manifestations has been observed primarily with biological therapy.

Regarding depression and cognitive dysfunction, in addition to suppressing the inflammatory activity of the underlying disease, serotonin reuptake inhibitors and tricyclic antidepressants, pregabalin and behavioral therapy may be used. Balneotherapy, e.g. carbonated bath, plays a key role in the treatment of depression associated with fibromyalgia.

Overall, therefore, comorbidities developed in chronic inflammatory rheumatic diseases are clearly driven by the underlying disease. In order to understand their development, recognizing and treating them, a fundamentally different approach should be taken than in routine management of the same conditions.

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List of abbreviations

AAS	atlantoaxial subluxation
AAV	ANCA-associated vasculitis
ABC	ATP-binding cassette (transporters)
ACA	anti-centromere antibody
ACE	angiotensin-converting enzyme
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ADA	adenosine-deaminase
AKA	anti-keratin antibody
AMP	adenosine-monophosphate
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antigen
APC	antigen-presenting cell
APF	anti-perinuclear factor
APRT	adenine-phosphoribosyl-transferase
APS	antiphospholipid syndrome
ARB	angiotensin II receptor blocker
AS	ankylosing spondylitis
ASA	aminosalicylic acid
ASAS	Assessment of SpondyloArthritis Society
ATP	adenosine-triphosphate
AZA	azathioprine
β2GPI	β2 glycoprotein I
BAFF	B-cell activating factor
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metric Index
BCG	Bacillus Calmette-Guerin
BCR	B-cell receptor
BHL	bilateral hilar lymphadenopathy

BLyS	B-lymphocyte stimulator
BMD	bone mineral density
BREG	regulatory B-cell
CAM	cancer-associated myositis
CAPS	catastrophic antiphospholipid syndrome
CCP	cyclic citrullinated peptide
CD	cluster of designation
CH50	total complement activity
CIDP	chronic inflammatory demyelinating neuropathy
CK	creatine kinase
CL	cardiolipin
CMC	carpo-metacarpal
CMV	cytomegalovirus
COMP	cartilage oligomeric protein
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CP	court period
CPPD	calcium pyrophosphate dihydrate
CREST	calcinosis, Raynaud, oesophageal dysmotility, sclerodactyly, teleangiectasia
CRP	C-reactive protein
CsA	cyclosporine A
CT	computed tomography
CTLA	cytotoxic T-lymphocyte antigen
CTX	C-terminal crosslink
CV	cardiovascular
CVID	common variable immunodeficiency
CYC	cyclophosphamide
DAG	diacylglycerol
DAMP	danger-associated molecular pattern
DAS	disease activity score
DC	dendritic cell
dcSSc	diffuse cutaneous systemic sclerosis
DECT	dual energy computed tomography
DEXA	dual energy X-ray absorptiometry
DF	diphasic
DIC	diffuse intravascular coagulation
DIP	distal interphalangeal

DISH	diffuse idiopathic skeletal hyperostosis
DLCO	carbon monoxide diffusion capacity
DM	dermatomyositis
DMARD	disease-modifying antirheumatic drug
DNS	deoxyribonucleic acid
DPYD	deoxypyridinoline
EBV	Epstein-Barr virus
EDS	Ehlers-Danlos syndrome
EEG	electroencephalography
EGPA	eosinophilic granulomatosis with polyangiitis
ELISA	enzyme-linked immunosorbent assay
EKG	electrocardiogram
EMG	electromyography
ENG	electroneurography
ERT	enzyme replacement therapy
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EuroQoL	European quality of life questionnaire
FDC	follicular dendritic cell
FDG	2-fluoro-2-deoxy-glucose
FFA	free fatty acid
FIM	Functional Independent Measure
FNO	functional capacity international classification
FRAX	fracture risk assessment tool
GAG	glucosaminoglycan
GALS	gait, arms, legs, spine
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome
GCA	giant-cell arteritis
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMP	guanosine-monophosphate
GN	glomerulonephritis
GnRH	gonadotropin-releasing hormone
GOT	glutamate-oxalacetate-transaminase
GPA	granulomatosis with polyangiitis
GPT	glutamate-pyruvate-transaminase

HAQ	health assessment questionnaire
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	high endothelial venule
HGPRT	hypoxanthine-guanine-phosphoribozyl-transferase
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	haemophagocytic lymphohistiocytosis
HPP	hipophosphatasia
HPV	human papilloma virus
HRCT	high resolution computed tomography
HSP	Henoch-Schönlein purpura
HSV	herpes simplex virus
HTLV	human T-cell leukaemia virus
IBD	inflammatory bowel disease
IBM	inclusion body myositis
IC	immune complex
ICAM	intercellular cell adhesion molecule
IFN	interferon
IIM	idiopathic inflammatory myopathy (myositis)
IL	interleukin
ILD	interstitial lung disease
IMP	inosine-monophosphate
INR	international normalized ratio
IP3	inositol-triphosphate
IVIg	intravenous immunoglobulin
ITAM	Immunoreceptor Tyrosine-based Activation Motif
JAK	Janus kinase
JDM	juvenile dermatomyositis
JIA	juvenile idiopathic arthritis
LA	lupus anticoagulant
lcSSc	limited cutaneous systemic sclerosis
LDH	lactate-dehydrogenase
LEF	leflunomide
LMWH	low molecular weight heparin
LOX	lipoxygenase
LP	long period
LPS	lipopolysaccharide (endotoxin)

LT	leukotriene
MAA	myositis-associated antibody
MCV	mean corpuscular volume
MCH	mean corpuscular haemoglobin
MCP	metacarpophalangeal
M-CSF	macrophage colony-stimulating factor
MCTD	mixed connective tissue disease
MF	monophasic
MHC	major histocompatibility complex
MHT	menopausal hormone therapy
MMF	mycophenolate mofetil
MMP	matrix metalloproteinase
MPA	medroxyprogesterone-acetate
MPA	microscopic polyangiitis
MRI	magnetic resonance imaging
MSA	myositis-specific antibody
MSU	monosodium urate
MTP	metatarsophalangeal
MTX	methotrexate
NAM	necrotising autoimmune myopathy
NET	neutrophil extracellular trap
NFκB	Nuclear Factor kappa B
NGF	nerve growth factor
NLRP3	NOD-, LRR- and pyrin-domain containing protein 3
NPSLE	neuropsychiatric systemic lupus erythematosus
NSAID	non-steroidal anti-inflammatory drug
NTX	N-terminal crossling
NYHA	New York Heart Association
OA	osteoarthritis
OI	osteogenesis imperfecta
ONJ	osteonecrosis of the jaw
OP	osteoporosis
OPG	osteoprotegerin
PAD	peptidyl-arginine-deiminase
PAH	pulmonary arterial hypertension
PAMP	pathogen-associated molecular pattern
PAN	polyarteritis nodosa
PARP	poly-ADP-ribose-polymerase
PBM	peak bone mass

PCR	polymerase chain reaction
PCT	procalcitonin
PDGF	platelet-derived growth factor
PET	positron emission tomography
PG	prostaglandin
PHS	humeroscapular periarthritis
PIP	proximal interphalangeal
PKC	protein-kinase C
PLA	phospholipase A
PLC	phospholipase C
PM	polymyositis
PMR	polymyalgia rheumatica
PP	pyrophosphate
PPI	proton pump inhibitor
PRP	platelet-rich plasma
PRPP	phosphoribosyl-pyrophosphate
PsA	psoriatic arthritis
PTH	parathyroid hormone
PTP	protein-tyrosine phosphatase
PYD	pyridinoline
QCT	quantitative computed tomography
RA	rheumatoid arthritis
RANK	Receptor Activator of Nuclear Factor kappa B
ReA	reactive arthritis
REM	rapid eye movement
RF	rheumatoid factor
RNS	ribonucleic acid
ROD	renal osteodystrophy
ROL	renal overload hyperuricemia
ROM	range of motion
ROS	reactive oxygen species
RPGN	rapid progressive glomerulonephritis
SAA	serum amyloid A
SCLE	subacute cutaneous lupus erythematosus
SD	standard deviation
SE	shared epitope
SERM	selective oestrogen receptor modulator
SF-36	short form 36 (quality of life questionnaire)
SLE	systemic lupus erythematosus

SpA	spondylarthritis, spondyloarthropathy
SRC	scleroderma renal crisis
SRP	signal recognition particle
SRT	substrate reduction treatment
SS	Sjögren-syndrome
SSc	systemic sclerosis
SSRI	serotonin-reuptake inhibitor
SSZ	sulphasalazine
STAT	signal transducer and activator of transcription
STIR	fat suppression MRI
T2T	treat-to-target
TC	cytotoxic T-cell
TCR	T-cell receptor
TENS	transdermal electronic nerve stimulator
TFESI	trans-foraminal epidural steroid injection
TFH	follicular helper T-cell
TGF	transforming growth factor
TH	helper T-cell
TIA	transient ischaemic attack
TLR	Toll-like receptor
TREG	regulatory T-cell
TNF	tumour necrosis factor
TNSALP	non-tissue-specific alkaline phosphatase
TOS	thoracic outlet syndrome
TRAP	tartarate-resistant acid phosphatase
TSH	thyroid-stimulating hormone
TUG	timed up and go
UCTD	undifferentiated connective tissue disease
NDP	undifferentiated polyarthritis
US	ultrasound
USpA	undifferentiated spondylarthritis
UV	ultraviolet
VAS	visual analogue scale
VCAM	vascular cell adhesion molecule
VEGF	vascular endothelial growth factor
WHO	World Health Organisation
WOMAC	Western Ontario and McMaster Universities Arthritis Index
XO	xanthine-oxidase

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