SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

RELATIONSHIP BETWEEN VITAMIN D3 SUPPLY AND BONE METABOLISM IN OSTEOPOROSIS AND PSORIATIC ARTHRITIS

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UNIVERSITY OF DEBRECEN

DOCTORAL SCHOOL OF CLINICAL MEDICINE

Debrecen, 2017

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The examination takes place at the Library of Division of Reumatology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
10th November, 2017. 11:00

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
10th November, 2017. 13:00

INTRODUCTION

1. Osteoporosis, vitamin D3 metabolism and parathormone

Osteoporosis is a progressive disorder, which leads to increased bone fragility and fracture risk through the loss of bone mass and the impairment of bone microarchitecture. According to the data published to date, approximately 600 000 women and 300 000 men suffer from osteoporosis in Hungary. The annual number of osteoporotic fractures of the hip amounts to 15 000, and that of vertebral body fractures range between 30 000 and 40 000.

The primary endpoint of osteoporosis treatment is the decrease of fracture risk both in men and women. In „high-turnover phase" of the disease antiresorptive agents should be used for treatment. Among antiresorptive agents bisphosphonates are the most widely used drugs according to their cost-effectiveness and low rate of clinical significant side effects. Randomized, controlled trials proved the efficacy of them in reduction of fracture risk. They are available in forms of both oral and intravenous administration.

The bone stock is renewed in every 10 years. The bone remodeling process in women speed up after menopause for 4 to 8 years, the bone resorption is much faster than the bone formation. In men the same process takes place due to the decreased androgen production of the testis but the slow decline in hormone production do not cause such dramatic increase of bone remodeling than in women. In elderly women the high turnover phase will turn into a slow turnover phase characterized by bone formation insufficiency and cortical bone loss. In this process the decreased muscle strength and the insufficient absorption of the vitamin D3 play an important role.

The serum $25(OH)D_3$ level provides the single best assessment of vitamin D3 status. The 25-hydroxilation of vitamin D3 is not regulated by negative feedback mechanism, therefore the absorbed and produced vitamin D3 molecules transform completely to $25(OH)D_3$. Vitamin D3 insufficiency (serum $25(OH)D_3$ < 15 ng/ml/37,5 nmol/l) leads to osteomalatia in adult and elderly patients.

The current consensus guidelines accept as normal the serum D3 vitamin level above 25 ng/ml (75 nmol/l). In the Hungarian population the calcium and vitamin D3 intake is

insufficient. The daily intake is 80 IU vitamin D3 and 665 mg calcium in average, respectively, while the recommended dietary allowances (RDA) are 800 IU vitamin D3 and 1000-1500 mg calcium.

Calcium and vitamin D sufficiency is a prerequisite to effective antiresorptive therapy, especially in the elderly population. Low vitamin D3 level triggers the compensatory release of parathormone (PTH), which increases the risk of fractures, as well as interference with neuromuscular function. Vitamin D sufficiency, as well as optimal levels of activated vitamin D3 (1,25-dihydroxy-vitamin D) can suppress PTH secretion. Above-normal PTH levels were detected in 17.4% of postmenopausal women treated for osteoporosis, and a negative correlation was found between PTH and vitamin D levels. When 25(OH)-vitamin D level decreases below 4.6 ng/mL, serum PTH level reaches the upper limit of the normal range (65 pg/mL). According to Bhattoa et al., serum 25(OH)-vitamin D3 is below normal in 56.7% of postmenopausal women in Hungary, and a significant portion of these patients expectedly have higher than normal PTH levels. Unfortunately, bone loss continues despite adequate bisphosphonate therapy and supplementation with calcium and vitamin D3 in 8 to 23% of osteoporotic patients (bisphosphonate resistance). Several publications have suggested a role for secondary hyperparathyroidism in the aetiology of bisphosphonate resistance.

2. Vitamin D3 levels and bone mineral density in patients with psoriasis and/or psoriatic arthritis

Psoriatic arthritis belongs to the immune mediated inflammatory diseases; it is classified as a seronegative spondylarthropathy (SpA). It is a type of inflammatory arthritis that will develop in patients with psoriasis or with predisposing factors for psoriasis. The inflammation may affect both axial and peripheral joints and it has several special extraarticular aspects. The pathogenesis of psoriatic arthritis is not yet fully known. Heredity plays a particularly strong role in the development of PsA**.** Both non-MHC and MHC polymorphisms associated with susceptibility predispose the TCR repertoire to auto-reactivity, which leads to synovitis and accompanying bone remodeling. Psoriatic arthritis is a Th1-type disease, therefore TNFα play the most important role among cytokines in the pathogenesis. This is supported by the fact that TNFα concentration is elevated in the synovial

membrane, in the synovial fluid, in the skin and in the serum and TNFα treatment caused significant improvement both of skin and joint symptoms. Recent studies attribute an important role to Th17-type immune response (and to the IL23/IL17 axis), to INFα produced by plasmocytoid dendritic cells and to the proinflammatory effect of antimicrobial peptides derived from keratinocytes.

The pathogenetic role of vitamin D3 deficiency in immune mediated diseases has been suggested over the past ten years. Even decades ago, the connectionbetween psoriasis and vitamin D3 supply was studied, many authors reported various, often contradictory, results on this subject.

The knowledge of vitamin D3 supply in psoriasis /PsA is important for several reasons: firstly the real or functional deficiency of vitamin D increases the tendency to bone loss and bone fractures, secondly it is a risk factor for other diseases (diabetes, cardiovascular disease, metabolic syndrome, immunmediated diseases), thirdly the detection of low serum 25OHD3 levels stimulatess the physician to correct it. Considering the immunomodulatory effect of vitamin D3 on the skin, treatment with oral vitamin D3 or activated vitamin D may play a role in psoriasis / PsA therapy.

AIMS

1. Investigation of the relationship between osteoporosis, vitamin D3 metabolism and PTH level

The aims of the present study were:

1. to assess the prevalence of secondary hyperparathyroidism (vitamin D3 deficiency) among newly diagnosed osteoporotic patients
2. to evaluate whether baseline levels of PTH influence the efficacy of anti-osteoporotic treatment (with bisphosphonates) in this population.
3. to determine the threshold, beyond which PTH level has a negative impact on the efficacy of bisphosphonate treatment.

2. Examination of bone mineral density, vitamin D3 levels and comorbidities in psoriasis / psoriatic arthritis

In our study we wanted:

1. to determine the prevalence of inadequate vitamin D3 status in patients with psoriasis/PA.
2. to estimate the prevalence of low BMD in this population
3. to identify any possible relationship between vitamin D3 status and the characteristic features of the underlying disease.
4. to examine the prevalence of differnet co-morbidities (obesity, smoking, hypertension, ischaemic heart disease, peripheral artery disease, type 2 diabetes, dyslipidemias) in psoriasis/PA.

METHODS

1. Investigation of the relationship between osteoporosis, vitamin D3 metabolism and PTH level

Type of study, Inclusion and exclusion criteria

This study was a prospective, observational, non-interventional study. Patients meeting the following criteria were eligible for inclusion: i) diagnosed idiopathic osteoporosis with a lumbar and/or femoral T-score lower than −2.5; ii) patients newly identified and enrolled to follow-up; iii) patients with laboratory findings available. The exclusion criteria were as follows: i) diagnosed secondary osteoporosis; ii) history of a malignancy; iii) renal failure (GFR <65 mL/min according to the Cockroft-Gault formula); iv) severe liver disease; v) hypo-/hyperthyroidism; vi) malabsorption syndrome; vii) hypercalcaemia; viii) hypocalcaemia; ix) history of renal calculosis; x) previous anti-osteoporotic therapy with bisphosphonates, selective estrogen-receptor modulators (SERMs), strontium ranelate, teriparatide, or calcitonin.

Study population

Two hundred and thirty-two patients met the inclusion criteria, and data from 138 (116 women and 22 men, with a mean age of 64.82 ± 10.51 years and between 43 and 81 years) were available at the time of the end of the study. Written informed consent for participation was obtained from each patient. Ninety-seven patients received alendronate, 19 risedronate, 7 zolendronate, and 15 ibandronate. At baseline, 13 patients had a prevalent vertebral, and 59 a prevalent non-vertebral fracture, while 22 had multiple fractures.

Study endpoints

The primary endpoint of the study was the change of bone mineral density (BMD) values (and T-scores) during one year with appropriate combination therapy with a bisphosphonate, vitamin D3, and calcium.

Implementation of the study

At baseline, the patient's medical history was taken, and physical examination was performed. All subjects underwent bone densitometry of the lumbar spine (L1-4 vertebrae) and of the left femoral neck with antero-posterior dual-energy x-ray absorptiometry (AP DEXA) scanning, as well as an x-ray of the dorsal-lumbar spine. Laboratory screening comprised the following: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), serum calcium and phosphate, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, serum albumin, urinary calcium/creatinine ratio, thyroid stimulating hormone (TSH), intact parathyroid hormone (iPTH), osteocalcin, carboxy-terminal collagen crosslinks (CTX).

Serum PTH was measured using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany), where the inter-assay CV was <7%. This assay employs a sandwich test principle in which a biotinylated monoclonal antibody reacts with the N-terminal fragment (1), and a monoclonal antibody labeled with a ruthinium complex reacts with the C-terminal fragment (38–84). The antibodies in this assay are reactive with epitopes in the amino acid regions 26–32 and 37–42.

We repeated the DEXA scan after a one-year (13.37 ± 1.29 months) follow-up on the average, and recorded the number of incident bone fractures and cases of renal stone formation that had occurred during this period.

The subjects received adequate bisphosphonate therapy with alendronate, risedronate, or ibandronate administered in combination with 6000 IU/week vitamin D3, as well as 1000 mg/day calcium during the follow-up period. The patients' compliance was evaluated at the scheduled quarterly visit, and a more than 80% compliance was acceptable to continue the study.

Statistical analysis

We formed two subgroups based on the change in bone mineral density (BMD) values as a result of therapy. The group of responders included all those patients in whom BMD level decreased as compared to the baseline value; the rest of the patients formed the group of non-responders. The definition of bone loss (non-responders) was made if the bone mineral density was decreased by more than 1% of the initial value, because the variation coefficient is less than 1% in the case of Lunar Prodigy DXA device, which was used in this study. The normality of the distribution of datasets was checked with Kolmogorov-Smirnov test. We compared data from two independent groups using Mann–Whitney test. A general linear model was used to identify the factors influencing the

magnitude of the change in bone density of the spine and of the femoral neck. All statistical analyses were performed with version 19.0 of the IBM SPSS Statistics software package.

2. Examination of bone mineral density, vitamin D3 levels and comorbidities in psoriasis / psoriatic arthritis

Inclusion and exclusion criteria

Eligible patients for inclusion were those with clinically/histologically confirmed psoriasis and/or PA diagnosed according to the CASPAR criteria, who gave informed consent. The exclusion criteria for participation were any other forms of inflammatory arthropathies (spondyloarthropathy, rheumatoid arthritis [RA], and autoimmune or autoinflammatory disease). Other conditions influencing BMD (such as primary hyperparathyroidism, thyroid disease, renal failure, malabsorption, malignancy, excessive alcohol abuse) were also considered as exclusion criteria. The same applied to pre-existing corticosteroid therapy, hormone replacement and previous treatment with thyroxin or vitamin D3 for over 3 months.

Study population

We conducted our cross-sectional, observational study in the population of patients followed up at the Rheumatology Department of “Kenézy Gyula” Hospital, as well as at the Department of Dermatology of the University of Debrecen, Clinical Center.

Implementation of the study

The subjects were recruited between April and September 2013. We decided the enrollment period on the basis that – according to the published work – this period is characterized by the highest 25 (OH)D3 serum levels and the lowest fluctuation. Upon inclusion and following informed consent, we acquired the medical history of the patients. Physical examination was then performed to record baseline clinical data (sex, age, body mass index [BMI]) and information on the underlying disease (age at diagnosis, duration of follow up, type and severity of psoriasis/PA). Next, we evaluated the clinical features of the underlying disease and its activity. Skin lesions controlled by topical treatment only were considered mild, whereas skin involvement requiring systemic (oral or

parenteral) therapy was regarded as moderate to severe. We assessed the severity of axial involvement using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and characterized the activity of peripheral joint disease with the three-variable Disease Activity Score in 28 Joints (DAS28). In addition to the inflammatory markers (e.g. erythrocyte sedimentation rate and C-reactive protein level), we determined (from morning, fasted blood samples) the indices of bone turnover. These included the serum levels of calcium, phosphorus, alkaline phosphatase, parathyroid hormone, vitamin 25(OH)D3, thyroid stimulating hormone, osteocalcin, and beta-crosslaps. We measured BMD of the lumbar spine (L1–4 vertebrae) and the left femoral neck by anteroposterior (AP) dual-energy X-ray absorptiometry. The scan was performed with a DPX Pro bone densitometer (GE-Lunar Radiation, Madison, WI, USA), according to the manufacturer's protocol. In patients with a history of a previous hip fracture, hip replacement surgery or severe joint destruction from inflammation, we measured BMD in the right femoral neck.

Statistical analysis

Before comparing the subsets of patients grouped according to individual symptoms and disease categories, we analyzed the distribution of continuous variables (e.g. age, BMD, laboratory parameters) with the Shapiro–Wilk test. We tested the differences between patient groups with Student's t-tests (or with Welch's d-test in the case of variables with different standard deviations) when the data were normally distributed, while we used the non-parametric Mann–Whitney U-test or Kruskal–Wallis tests for non-Gaussian variables. We applied exact test to investigate the relationships among categorical variables. The factors influencing bone density were tested using stepwise linear regression analysis. The statistical analyses were performed with the IBM SPSS Statistics version 22.0 software package (SPSS, Chicago, IL, USA).

RESULTS

1. Investigation of the relationship between osteoporosis, vitamin D3 metabolism and PTH level

On enrollment into the study, PTH levels were normal in 112 patients, while it was elevated in 26 cases. Baseline BMD measured at the L1-4 vertebrae, and at the left femoral neck by AP DEXA scanning was 0.854 ± 0.108 g/cm^2, and 0.768 ± 0.115 g/cm^2, respectively.

After a follow-up period and appropriate therapy for over one year on average, bone density increased to 0.890 ± 0.111 g/cm^2 at the lumbar spine, and to 0.773 ± 0.111 g/cm^2 at the femoral neck. Thus, the mean increase in BMD was 0.036 g/cm^2 and 0.005 g/cm^2, respectively.

We found a statistically significant ($p < 0.0001$) difference between the baseline PTH levels of patient subsets with declining or non-declining bone density (using either BMD or T-score as the basis for grouping). However, creating these subsets according to femoral bone density (based on either the BMD or the T-score), the difference between PTH values was no longer significant.

The general linear model showed a strong, significant ($p < 0.0001$) relationship between baseline PTH levels and the relative change in lumbar BMD. A similar correlation could not be demonstrated for the femoral neck, other variables (such as age, gender, etc.), and the change in BMD ($p > 0.05$).

We determined the prognostically optimal threshold of baseline PTH level, which best differentiated the subsets with declining and improving lumbar BMD from each other. According to the frequency histogram this was at approximately 60 pg/mL for the lumbar spine. Regarding the femoral neck, the frequency histogram did not show any substantial difference between the subsets with improving or declining bone density. New (incident) vertebral or non-vertebral fractures occurred in one and five subjects, respectively.

2. Examination of bone mineral density, vitamin D3 levels and comorbidities in psoriasis / psoriatic arthritis

Patients

Seventy-two patients receiving follow-up care at the Rheumatology Department of “Kenézy Gyula” Hospital or at the Dermatology Department of Debrecen University, Clinical Center were

included. The female:male ratio was 40:32, mean age of the subjects 58.5 ± 11.6 years and the mean duration of follow up 142.7 ± 147.7 months. All patients had a history of psoriasis. At the time of inclusion, however, 18 patients (25%) had only skin lesions and 31 (43%) had only joint manifestations, whereas 23 (32%) had both. According to the definition detailed below, skin involvement was considered moderate to severe in 34 patients (47%). These patients received individualized pharmacotherapy, including treatment with biological agents in five cases (ustekinumab, one; infliximab, two; and adalimumab, two). In the subset of patients with PA, joint involvement was axial in 18, oligoarticular in five, polyarticular in 29 and distal interphalangeal (DIP) in two subjects. The pharmacotherapy of PA comprised treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in patients with axial or DIP involvement, whereas those with oligo- or polyarticular disease received methotrexate as disease-modifying therapy, periodically supplemented with NSAIDs. One patient with oligoarticular PA was treated with golimumab.

Average BMI of patients was 29.08±6.88 kg/m^2, 43 patients were overweight, among them 19 patients has BMI above 30 kg/m^2. 27 patients were smoker (27%), 52 of them had hypertension (72%), 40 patients had ischaemic heart disease (55%) and 40 patients had hypercholesterolemia (55%). Number of diabetic patients was 27 (37%), while 31 patients suffer from periheral artery disease (43%).

Vitamin D3 status and its relationships

Based on the cut-off vitamin 25(OH)D3 serum level of 75 µmol/L, inadequate vitamin D3 status was ascertained in 45 patients (63%), with a serum concentration lower than 50 nmol/L in 25 (56%) of these subjects.

There was no statistically significant correlation between the 25(OH)D3 levels and the BMD according to stepwise linear regression analysis ($P > 0.1$). However, we found a significant ($P = 0.018$), negative correlation between vitamin 25(OH)D3 serum level and BMI. In overweight patients (BMI > 30), the lower quartile (Q1) was 36.34 nmol/L, the median 55.88 nmol/L and the upper quartile (Q3) 77.395 nmol/L. The corresponding values of the subjects with a normal bodyweight were 53.205, 74.43 and 97.425 nmol/L, respectively. Vitamin 25(OH)D3 levels and BMI values as continuous variables also showed a close negative correlation ($P < 0.0001$). Forty-three patients (60%) were overweight (BMI > 25) and 19 subjects (24%) in this subset had a BMI over 30 kg/m^2. Other than that, we did not detect statistically significant differences among the BMI values of the patient subsets formed according to various properties, including BMI groups according to the severity of skin disease ($P > 0.1$).

In particular, BMI values were not different between psoriatic and PA patients or among the different subsets of the latter, and the indices of disease activity were not related to BMI either. Patients with skin involvement requiring systemic therapy (moderate-to-severe psoriasis) had significantly lower serum levels of vitamin 25(OH)D3 than those for whom topical treatment proved sufficient. Their quartile points were as follows: Q1, 32.1 versus 45.33 nmol/L; median, 51.19 versus 61.17 nmol/L; and Q3, 75.03 versus 83.75 nmol/L ($P < 0.05$ in all instances). In the subset of patients with axial PA, the BASDAI score was higher in patients with inadequate vitamin 25(OH)D3 status (<75 nmol/L). However, this difference was only borderline significant ($P = 0.05$) and as such, it was considered to a trend.

In the subset of patients with polyarticular PA, however, the DAS28 score exhibited rather strong correlation with inadequate vitamin D3 status. That is, lower serum levels of vitamin 25(OH)D3 were associated with higher DAS28 scores. A similar statistical analysis of patients with oligoarticular or DIP involvement could not be performed because of the small number of cases.

BMD and its relationships

We found reduced BMD (T-scores between –1 and –2.5) in 44 of the 72 patients studied (61.1%), and the BMD values of two subjects (5.5%) were in the osteoporotic range (T-score < -2.5). Both the lumbar and the femoral neck BMD values (measured in the AP view) were correlated with disease type. In psoriatic patients with skin involvement only, BMD values were significantly lower in both of these regions than in subjects with PA only or those with simultaneous joint and skin involvement. While this correlation was more evident ($P < 0.01$) in the lumbar spine, the femoral neck BMD values of patients with PA only were significantly higher than of those with skin involvement only. The BMD values of the lumbar spine in PA patients, as well as in those with arthritis were as follows: Q1, 0.920 versus 1.036 g/cm^2; median, 0.999 versus 1.128 g/cm^2; and Q3, 1.135 versus 1.253 g/cm^2 ($P < 0.01$ in all instances). The corresponding BMD values of the femoral neck were as follows: Q1, 0.763 versus 0.862 g/cm^2; median, 0.869 versus 0.955 g/cm^2; and Q3, 0.970 versus 1.039 g/cm^2 ($P < 0.005$ in all instances).

DISCUSSION

1. Investigation of the relationship between osteoporosis, vitamin D3 metabolism and PTH level

Vitamin D3 deficiency and accompanying secondary hyperparathyroidism are extremely prevalent in the senior population of developed countries – regardless of geographical location or terrestrial latitude. The weight of this problem is illustrated – among others – by a survey conducted in Austria, the United Kingdom (UK), and Mexico. This study revealed that the proportion of patients receiving calcium and vitamin D3 supplementation was 73% in Austria, 15% in the UK, and 12% in Mexico. Furthermore, only 20% of the patients in Austria were taking vitamin D3 – where the latter was provided free to osteoporotic patients.

In 98% of patients hospitalized for non-traumatic fractures, 25(OH) vitamin D3 levels were found to be low, which was commonly associated with elevated PTH level and hence, accelerated bone loss. An inverse relationship has been shown between the risk of osteoporotic hip fractures and increased vitamin D3 intake, as well as greater adherence to supplementation.

There is an increasing number of reports suggesting that inadequate (<30 ng/mL) serum 25(OH) vitamin D3, and consecutively elevated PTH levels are among the essential factors behind bisphosphonate resistance, leading to unsatisfactory response to bisphosphonates. Previous studies have demonstrated that the increase of BMD in every skeletal region is greater in vitamin D replete patients than in those with vitamin D deficiency. Additionally, the risk of incident osteoporotic fractures is 1.77 times higher in the latter population, than in vitamin D-replete individuals.

Our findings confirm that elevated (>60 pg/mL) serum PTH levels exert an unfavorable influence on the efficacy of bisphosphonate therapy. We believe it would be important to determine PTH levels before bisphosphonate treatment is initiated. In particular, similar to a variety of other disorders, such as diabetes and hypertension, the success of anti-osteoporotic therapy is essentially dependent on a specific target PTH level (<60 pg/mL in uor case). From an economic point of view, the cost of a single PTH measurement is far less than the annual expenditure on ineffective bisphosphonate therapy.

It is controversial whether administering an initial, oral loading dose of (40000 to 300000 IU) vitamin D is justified before initiating anti-resorptive therapy in hypovitaminosis D3. The administration of a single, 300000-IU dose of vitamin D3 could successfully normalize the serum 25(OH) vitamin D3 levels of patients within three months, without major adverse effects. Regarding

the 30 ng/mL (75 nmol/L) serum 25(OH) vitamin D3 concentration as the target level, others have provided therapeutic recommendations on the single loading dose.

The fracture-reducing effect of daily supplementation with 800 to 1000 IU oral vitamin D3 is evident. In direct contrast to this, others have observed an increase (compared to placebo) in the number of falls, and fractures among their elderly female patients treated with yearly oral mega-dose (500000 IU) of vitamin D3. Although the authors could not explain this finding, the need for reducing the excessively high baseline level of PTH has not been fully addressed in previous studies.

Serum PTH levels, the vitamin D3-replete state, and supplementation with vitamin D3 are of significant importance in osteology. It is highly probable that the higher (>60 pg/mL in our study) baseline PTH levels observed before the initiation of anti-osteoporotic treatment have a clear effect on the therapy outcome. Whether long-term oral vitamin D supplementation or the administration of a single high dose vitamin D3 treatment is justified can be determined by additional large-scale studies.

This is the first study indicating the connection between the treatment efficacy and the PTH levels in newly diagnosed osteoporotic patients. Moreover, we determined a potentially “harmful” cut-off value for PTH levels. Our results suggest that the PTH levels higher than 60 pg/mL have negative prognostic value for the efficacy of anti-osteoporotic treatment.

2. Examination of bone density, vitamin D3 levels and comorbidities in psoriasis / psoriatic arthritis

Psoriasis and PA belong to the group of immune-mediated disorders characterized by abnormal antigen presentation and inflammatory reaction in the skin, joints and periarticular structures. These processes involve the release of pro-inflammatory cytokines with topical and systemic actions. Of these, receptor activator of nuclear factor-κB ligand (RANKL) and tumor necrosis factor (TNF)-a are outstandingly important. The enhanced production of these two substances has been demonstrated in peripheral T and B lymphocytes of psoriatic patients, as well as in the synovial cells of patients with PA. The stimulatory effect of TNF-a and RANKL on bone resorption is no longer in doubt. The inhibition of RANKL by denosumab has been added to the armamentarium of anti-osteoporotic therapy, and several studies have demonstrated the inhibitory effect of TNF antagonists on bone resorption in RA and in spondyloarthropathies. The data available on the relationship between psoriasis and BMD are limited and occasionally controversial. In patients with psoriasis or PA, several authors showed a significant negative correlation between BMD and the severity of skin involvement, as well as finding a positive relationship between serum osteoprotegerin level and BMD. Furthermore, data suggesting sex-specific relationships are also available. Dreiher et al. found

the incidence of osteoporosis to be significantly higher among male psoriatic patients than in non-psoriatic controls, whereas a similar difference could not be demonstrated for women. Others established that the BMD of postmenopausal women receiving ultraviolet light therapy for psoriasis is above the age-matched average. Others, again, detected a negative relationship between BMD and the duration of PA.

Our study was the first to explore vitamin 25(OH)D3 status and BMD, as well as their correlation with the clinical features of the underlying disease in Hungarian patients with psoriasis and/or PA. Only limited data have been published in the work on these three factors. In our study population, we found the proportion of patients with inadequate vitamin D3 status was either 63% or 56%, depending on where the normal limit was set (i.e. at 75 or 50 nmol/L).

Recent data on the vitamin D3 status of the Hungarian population are not available. Bhattoa et al. conducted their study in postmenopausal women aged 60 years on average. Setting the lower limit of the normal range of serum 25(OH)D3 level at 50 nmol/L, they found that 46.3% of their subjects had hypovitaminosis D3 during the spring, and 49.4% during the summer months. These proportions are lower than the 56% seen in our study during the same period of the year. This finding is particularly important in view of the fact that low serum vitamin 25(OH)D3 level is accompanied by enhanced disease activity in several disorders. The latter include immune-mediated disease (e.g. RA, chronic inflammatory bowel disease) and certain autoimmune disorders (e.g. mixed connective tissue disorder, systemic lupus erythematosus). Further, the likelihood of progression to definite disease is increased in non-differentiated collagenosis. According to the findings of a recent meta-analysis, inadequate vitamin D3 status increases the susceptibility to and the activity of ankylosing spondylitis, which belongs – together with PA – to the family of spondyloarthropathies. In a previous study, our work group has shown that the vitamin D3 analog alfacalcidol mitigates disease activity in PA. The beneficial effect of topical treatment with vitamin D3 derivatives on psoriatic skin lesions has long been known in the published work. As shown by the results of a small scale study, high-dose, oral supplementation with vitamin D3 significantly increased serum 25(OH)D3 levels, and this was accompanied by the simultaneous, substantial improvement of skin lesions. In agreement with these preliminary data, our current study found significantly lower serum 25(OH)D3 levels in patients with moderate-to-severe psoriasis than in those requiring topical treatment only. The BASDAI score, which reflects disease activity in the axial form of PA, tended to be higher in patients with inadequate than in those with adequate vitamin D3 levels. However, this difference did not reach statistical significance. On the other hand, the DAS28 score, which indicates the activity of polyarticular PA (and contains fewer subjective factors) showed a strong correlation with inadequate vitamin D3 status. These findings suggest that – similar to other immune-mediated inflammatory disorders – inadequate vitamin D3 status plays an important role in the onset of the manifestations

of psoriasis and PA.

In Hungary, the prevalence of osteoporosis in the population over 50 years of age is estimated to be 32.3% among women and 23.6% among men. At variance with these data, the proportion of patients with a low BMD and with clinical osteoporosis was similar to the age-matched averages of the Hungarian population. This finding is not surprising, because the positive influence of body mass on BMD has long been recognized in the published work. However, this relationship is not linear in the higher BMI range, and our study found that the BMI was beyond the desired limit in a substantial proportion of our patients. The inverse correlation between BMI and serum vitamin 25(OH)D3 level may provide partial explanation for the high proportion of patients with hypovitaminosis D3 in our study population. The high proportion of overweight patients can explain the lack of correlation between the 25(OH)D3 levels and the BMD as well. Pedereira et al. did not find a significant difference between the BMD values of their two patient groups with psoriasis or with PA. However, the percentage of body fat was higher in patients with PA than in those with psoriasis only. Our study did not demonstrate a statistically significant difference between psoriatic patients and those with PA. However, it is the first to describe a correlation between the BMD values of two skeletal regions and disease type. In particular, BMD values were greater in subjects with PA or with psoriasis accompanied by PA than in patients with psoriasis only.

SUMMARY

Investigation of the relationship between osteoporosis, vitamin D3 metabolism and PTH level

In our studies, we demonstrated that:

1) The elevated PTH level decreased the effectivity of treatment in newly diagnosed osteoporotic patients
2) Serum PTH levels and BMD gains during treatment correlate negatively with each other.
3) We first determined a potential harmful cut off value for PTH, above which the effectivity of bisphosphonate therapy is decreased. Our results suggested that negative effects on bone might be expected above a PTH level of 60 pg/mL.

Practical significance of results:

There are different opinions on the routine measurement of PTH level before bisphosphonate treatment is initiated. On the basis of our results, we believe it would be important to determine PTH and D3 vitamin levels before bisphosphonate treatment is initiated. In case of elevated PTH level (above 60pg/ml) an initial, oral loading dose of Vitamin D3 is justified before initiating anti-resorptive therapy.

Examination of bone mineral density, vitamin D3 levels and comorbidities in psoriasis / psoriatic arthritis

In our studies, we demonstrated that:

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1. 1. Although the prevalence of inadequate vitamin D3 status was extremely high among our patients, the proportion of subjects with low BMD values was similar to that seen in the general population.
2. We found an inverse correlation between the serum level of vitamin 25(OH)D3 and body mass index, as well as between the former and the severity of skin involvement. The activity of PA was significantly higher in patients with inadequate vitamin D3 status. BMD was significantly higher in patients with PA than in patients with skin involvement only.
3. Higher prevalence of co-morbidities were found compared to general population.

Practical significance of results:

The findings of our study draw attention to the importance of vitamin D3 status, as well as of its regular and routine monitoring in patients with psoriasis or PA, and stress the significance of screening for comorbidities. Making vitamin D3 supplementation a standard intervention in the follow-up care of this patient population should also be considered.

Registry number: DEENK/10/2017.PL
Subject: PhD Publikációs Lista

Candidate: Gyöngyvér Kincse
Neptun ID: J92PLR
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Kincse, G.**, Bhattoa, H. P., Herédi, E., Varga, J., Szegedi, A., Kéri, J., Gaál, J.: Vitamin D3 levels and bone mineral density in patients with psoriasis and/or psoriatic arthritis.
   J. Dermatol. 42 (7), 679-684, 2015.
   DOI: http://dx.doi.org/doi: 10.1111/1346-8138.12876
   IF: 1.577
2. **Kincse, G.**, Varga, J., Somogyi, P., Szodoray, P., Surányi, P., Gaál, J.: The impact of secondary hyperparathyroidism on the efficacy of antiresorptive therapy.
   BMC Musculoskelet. Disord. 13 (1), 244-249, 2012.
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List of other publications

3. Herédi, E., Végh, J., Pogácsás, L., Gáspár, K., Varga, J., **Kincse, G.**, Zeher, M., Szegedi, A., Gaál, J.: Subclinical cardiovascular disease and it's improvement after long-term TNF-[alfa] inhibitor therapy in severe psoriatic patients.
   J. Eur. Acad. Dermatol. Venereol. 30 (9), 1531-1536, 2016.
   DOI: http://dx.doi.org/10.1111/jdv.13649
   IF: 3.029 (2015)
4. **Kincse, G.**, Bhattoa, H. P., Varga, J., Szegedi, A., Kéri, J., Gaál, J.: D3-vitamin-státusz és csontdenzitás psoriasisban és arthritis psoriaticában szenvedő betegekben.
   Immunol. Szle. 6 (1-2), 10-16, 2014.
5. Horkay, E., **Kincse, G.**, Varga, J., Szabados, L., Garai, I., Gaál, J.: Anti-granulocyte scintigraphy in early rheumatoid arthritis - does it work?
   Cent. Eur. J. Med. 8 (5), 558-564, 2013.
   DOI: http://dx.doi.org/10.2478/s11536-013-0203-4
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   Immunol. Szle. 5 (1), 29-33, 2013.
7. Bodai, E., Varga, J., Surányi, P., **Kincse, G.**, Gaál, J.: Csontsűrűség és csonttörés-prevalencia osteoporosisos, légúti allergiás betegek körében.
   Immunol. Szle. 2 (1), 4-10, 2010.

Total IF of journals (all publications): 6,69
Total IF of journals (publications related to the dissertation): 3,452

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

24 January, 2017

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