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

Examining the effects of functional training on health in old age by

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EXAMINING THE EFFECTS OF FUNCTIONAL TRAINING ON HEALTH IN OLD AGE

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Head of the **Examination Committee: László Majoros, PhD**
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The Examination takes place at the library of Department of Medical Microbiology, Faculty of Medicine, University of Debrecen
on 20th of June, 2024, at 12:00

Head of the **Defense Committee**: **László Majoros, PhD**
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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
on 20th of June, 2024, at 14:00

1. INTRODUCTION

Thanks to the continuous development of medicine, the proportion of elderly people in society is constantly increasing, the average age is increasing, while fewer and fewer children are born, and this leads to an upset of the population balance. The number of people over the age of 60 is growing rapidly, which affects health, quality of life and the economy. In Hungary, the proportion of people aged 60 and over was only 9.8% in 1930, by 1990 this figure had already increased to 18.9%, and in 2011 it was 23%, and by 2050 it is expected this number will already reach 30 percent or even exceed it.

With aging, the strength and mass of the skeletal muscles continuously decrease, this process is called sarcopenia. However, sarcopenia can develop not only because of aging, but also after the development of many chronic diseases. The loss of strength with advancing age is very closely related to the actual decrease in muscle mass, as a result of which the muscle tissues are transformed into non-contractile tissue. One of the elements of sarcopenia is the loss of muscle mass, which can be accompanied by a gradual decline in muscle strength and functional abilities, as well as causing weakness and falling. Sarcopenia is a predictor of increased falls in old age. The prevalence of sarcopenia among 60-70-year-olds can be 5-13%, while this rate increases to 19-53% in people over 80 years of age. If the diagnosis is made in time, the process can be slowed down or even stopped in some cases if the person concerned receives appropriate care and treatment, since the remaining muscle mass can be developed even in old age.

In the first part of my work, I investigated the effects of functional training in terms of sarcopenia, body composition and spine mobility in the elderly. In the second part of the research, we examined the effects of physical activity on immune parameters among the same group of patients.

1.1. Age-related changes in skeletal muscle - sarcopenia

Among the major changes associated with aging is a significant decrease in skeletal muscle mass, with consequent declines in muscle strength and functional capacity. Muscle strength and muscle mass increase continuously during youth, and their maximum is usually reached around the age of 40. Their decline begins at the end of the age of 50: the muscle mass of the lower limbs decreases by 1-2% per year, while their muscle strength decreases by 1.5-5% per year. After the age of 80, approximately 40% of the maximum muscle mass and muscle strength remains. In 1989, at Rosenberg's suggestion, the term sarcopenia was coined to name

this muscle loss, which was derived from the Greek words sarx (flesh) and penia (loss). Sarcopenia has since been defined as a progressive and general decline in skeletal muscle strength, mass, and function with age. In 2010, based on the proposal of the European Working Group on Sarcopenia in Older People (EWGSOP), the diagnosis of sarcopenia can be made in the case of the joint detection of low skeletal muscle mass and reduced physical performance, where low skeletal muscle mass is the basic criterion, in addition to which it is present or reduced muscle strength or reduced physical performance (reduced functional abilities) or both. However, based on the Working Group's 2019 guidelines, the lack of muscle strength should be considered the main clinical feature of sarcopenia, as it was recognized that muscle strength is a more important indicator of adverse outcomes than muscle mass. Based on the new definition, weak muscle strength is the primary criterion, reduced muscle mass is the second, and reduced physical performance is the third. The presence of sarcopenia is likely if the first criterion is present, and the diagnosis is certain if, in addition, reduced muscle mass or muscle quality appears. The working group created a staging schedule, so it is easier to determine the severity of the condition during clinical treatment. The pre-sarcopenia state is characterized by low muscle mass, which has no effect on physical performance or muscle strength. In the case of sarcopenia, one of the three factors, such as low muscle mass, weakening of muscle strength, or low physical performance appears among the elderly. In the case of severe sarcopenia, we can speak of a severe stage when all three criteria for the definition are met.

Sarcopenia is characterized by muscle atrophy, loss of muscle fibers, reduction in the number and size of motor units, and increased fibrosis and fat accumulation. Loss of muscle mass usually occurs due to a combination of two factors: muscle atrophy and muscle cell death. In the background of this, the altered expression of the factors of protein synthesis and degradation was observed at the molecular level. In addition, the degree of muscle regeneration deteriorates due to the finite capacity and reduced function of the satellite cells, and the innervation of the muscle fibers is also disturbed, as the number of motor units also decreases. In old age, therefore, not only regeneration abilities suffer, but also catabolic reactions predominate, the functioning of mitochondria is impaired, insulin sensitivity decreases, the quality of neuromuscular impulse transmission deteriorates, and changes are also reflected at the level of gene expression. Sarcopenia is therefore a multifactorial disease, including neurological factors related to the loss of motor neurons, endocrine changes resulting from the reduced expression of hormones (such as testosterone or growth hormone (GH), and changes resulting from a sedentary lifestyle.

The presence of sarcopenia increases the risk of falls and thus fractures, making it difficult to perform everyday activities; have been shown to be associated with heart disease, respiratory disease, and cognitive impairment. In addition, we can also encounter mobility disorders. Sarcopenia contributes to the reduction of the quality of life of the elderly and the deterioration of their ability to provide for themselves.

With timely diagnosis of sarcopenia, proper care and treatment of the patient, the process can be slowed down or even stopped. Interventions to improve the condition focus primarily on exercise therapy and nutritional therapy. In addition to all this, however, pharmacotherapy can also play an important role. Based on meta-analyses of drug therapies for sarcopenia, ten pharmacological interventions that seem beneficial can be mentioned: vitamin D, pioglitazone combined estrogen-progesterone, dehydroepiandrosterone, growth hormone, growth hormone-releasing hormone, combined testosterone-growth hormone, insulin-like growth factor-1, testosterone and ACE inhibitors.

1.2. Age-related immunological changes

In old age, many changes occur that affect almost every element of the immune system and result in a gradual deterioration of immune functions. At the same time, immune homeostasis breaks down, so elderly individuals become more vulnerable to tumors and autoimmune diseases, as well as infections. Previous studies have described an absolute decline in naïve T cells with advancing age, which is associated with a relative increase in various memory T cell populations, primarily effector memory T cells. The changes affecting B-lymphocytes are somewhat similar to those observed in T-cells. Aging also affects the immunoglobulin genes, reducing their somatic hypermutation, resulting in a decrease in the affinity of the specific immunoglobulin for the given antigen. This reduces the quality and efficiency of the response to pathogens.

1.3. The effects of regular exercise on skeletal muscle and the immune system

Although no intervention is currently able to stop the biological aging process, there is increasing evidence that regular exercise can prevent many chronic and degenerative diseases, such as cardiovascular disease, high blood pressure, osteoporosis, cancer, cognitive impairments, dementia, or the development of depression or can slow down their deterioration in old age.

Regular physical activity can help maintain muscle strength and mass. Based on research, resistance training leads to an improvement in muscle function due to the regenerating neuromuscular system, increased protein synthesis, a decrease in anabolic resistance and an increase in the number of satellite cells in the muscle fibers, while aerobic exercises, on the other hand, stimulate heart function and blood circulation, improve mitochondrial functions and they contribute to reducing the symptoms of sarcopenia by regulating metabolism. Although there are only a limited number of studies available so far, studies so far suggest that combining different types of exercise into one program may improve muscle strength and physical performance the most among patients with sarcopenia.

The immunomodulating effect of physical activity largely depends on the given form of exercise, its intensity and duration. Based on literature data, higher-intensity exercise increases the anti-inflammatory response and reduces the activity of the immune system, thereby helping to treat and prevent symptoms associated with chronic inflammatory disease. However, strenuous and long-lasting training can impair immunological functions to such an extent that it can lead to significant damage to the body's immune defenses and an increased risk of developing infections. Exhaustive exercise leads to a decrease in the proportion of immunocompetent cells with effector function, as well as a decrease in the levels of several inflammatory cytokines. On the other hand, regular moderate-intensity physical exercise, in addition to reducing the risk of cardiovascular diseases and cancer, improves immunological functions and strengthens the immune response, thereby reducing the tendency to infections. The literature on the effects of physical activity and sports on the immune system is constantly expanding, however, certain immunological changes following physical activity, such as the increase or decrease in the proportion of Treg cells, are still not clear, and there is limited information available regarding the immunological effects of sports activities in old age, therefore in our research we focused on the areas.

1.4. Functional training

Maintaining and improving daily movement functions plays a prominent role in the elderly. The functional training method was developed as a result of the increasingly close connection of training science and rehabilitation, which continues to develop even today. The main feature of functional training is that it develops skills by practicing everyday movements, it is a form of training that can be used in any age group, and the equipment required is simple and cheap. The basis of the approach is prevention, tailored to individual performance. The movements

performed on weekdays are mostly complex demands, during the application of the training, the arrangement of these movements into a movement chain is carried out. The conditions and intensity of the execution can be modified gradually, so for example, by changing the starting position, the support surface, or by increasing the number of repetitions, the number of series, the speed, or even by reducing the rest time, the degree of difficulty can be increased. We can simultaneously affect endurance, muscle strength, speed, balance and coordination by changing the appropriate parameters.

2. OBJECTIVES

The aim of the research was to investigate the measurable effectiveness of functional training among women over 60 years of age. In our first study, the effect of the functional training program was assessed along the lines of physical condition and the functionality of the locomotor system, while in our second study, we assessed the functioning of the immune functions.

In old age, physical activity decreases, joint range of motion deteriorates and poor posture develops. Movement coordination ability declines, circulation deteriorates, muscle mass and strength decrease, ligaments and muscles shorten. Maintaining functional movements in old age is essential for performing safe daily activities, however, performing functional movements requires complex and multi-factorial function development, because no single physical ability is sufficient in itself to be effective. The aim of our first study was to assess how functional training changes the functionality of the locomotor system among women over 60 years of age. Due to the high prevalence of hypertension in the elderly, those affected are most often treated with ACE inhibitors, the effects of which on sarcopenia are controversial. In the course of our study, we had the opportunity to evaluate our results among patients receiving and not receiving ACE inhibitor treatment, thus we also performed a comparative analysis during the processing of our measurement results. In order to evaluate the change in physical condition, we performed body composition analyses, which, in addition to the exact body weight, gave a comprehensive picture of the ratio of skeletal muscles and body fat for the whole body, as well as for its various parts. The severity of sarcopenia was assessed with the Short Physical Performance Battery (SPPB) test, and the change in grip strength of both hands was determined with a digital hand dynamometer. In the course of our work, we assessed and evaluated the functional state of the spine, the ability to balance, posture and movement coordination, as well as the degree of forward head posture.

Studies in recent decades have shed light on the immunobiological effects of physical activity and various sports activities, which significantly depend on the type, intensity and duration of the given exercise. However, limited information is available regarding the immunological effects of sports activities in old age, so we focused on this area during our research. In the framework of our second study, we therefore studied the effects of regular functional training on the immune system and general physical condition of people over 60 years of age who previously had a sedentary lifestyle and who did not suffer from immune diseases, allergies or other serious chronic diseases. During the laboratory tests, we determined

the percentages of the following cells from peripheral blood using a flow cytometer: T, helper and cytotoxic T cells, early and late activated T cells, naive, effector, central memory and effector memory T cells, Th1, Th2, Tr1, Th17 cells and Treg cells. In addition to examining qualitative differences, we also performed an in vitro functional test of Treg cells. Through our studies, we were able to get a more accurate picture of the immunomodulating effects of physical activity and the direction and dynamics of immunological changes caused by exercise in older age.

3. MATERIALS AND METHODS

3.1. Examination process, training protocols

In order to achieve the objectives of the research questions, we formed two groups using functional training. The participants of the exercise program were selected from the female members of the Debrecen Pensioners' Club. The inclusion criteria for the study were the following: age 60 years or older, ability to walk, female gender and at least mild sarcopenia. It was also a criterion that, in addition to their daily activities, they could not do regular training in the previous 3 months. In the first study, patients who had low vitamin D levels (<75 umol/l), were taking statins, had undergone oophorectomy, had a reduced GFR (glomerular filtration rate) compared to their age, or were on a protein-free diet , because they are confounding factors with regard to sarcopenia. Exclusion criteria for the second study were: ongoing viral or bacterial infection; allergic or autoimmune disease; chronic disease treated with continuously applied drug therapy, cancer; alcohol or drug addiction, because these are disturbing factors in the assessment of immunological parameters.

The study subjects were recruited by personal inquiry. Participation in the study was voluntary and anonymous, and patients were not rewarded for their participation. The examination was preceded by oral and written patient information, which provided the patient with information about the course and duration of the examination, the handling of the data, and the method of feedback of the results. The persons participating in the study signed a declaration of consent after being informed, number of DE and TUKEB ethics permits: DE RKEB/IKEB: 4879-2017, 25040-4/2017/EÜIG). All experiments performed were in accordance with the Declaration of Helsinki.

During the examination, we developed a unique training method adapted to the elderly. During the exercise program, polimorbidity was taken into account, special attention was paid to joint protection and the safety of exercises depending on age. In the first study, the participants took part in a 55-minute exercise program twice a week for 6 months, while in the second study, the participants took part in a 60-minute functional training program twice a week for 6 months, at the UniFit Fitness and Gym Center in Debrecen. All sessions took place under the supervision of a physiotherapist in order to minimize the risk of injury.

In study I, the participants performed cyclic aerobic exercises for 15 minutes at 50% of HRmax in the first three months, and at 55% of HRmax in the second 3 months. After the warm-up and aerobic exercises, muscle strength-building exercises followed for 20 minutes. The muscles of the upper and lower limbs and trunk were trained with TRX exercises: the

participants performed TRX Squat, TRX Low Rows, TRX Push Up and TRX Standing Hip Drop exercises. The difficulty of each exercise was determined individually (the angle of inclination was set between 10° and 45°) so that the participant was able to perform 12 intense repetitions. The participants performed the exercises in pairs, thus ensuring adequate rest time between repetitions. At the end of the training session, they performed balance exercises while sitting on a fitball for 10 minutes, and then at the end of the class, stretching was performed in accordance with the principle of gradation.

In the second study, the workouts started with a 10-minute warm-up on a treadmill, elliptical trainer, or exercise bike. Participants first performed low-intensity aerobic exercise and increased the intensity to 40–50% of maximum heart rate (HRmax) to protect the joints; after that, the intensity was increased to 50-60% of HRmax for the next 20 minutes. The heart rate was monitored using the heart rate measuring system of the devices. After that, TRX muscle strengthening training was performed for 20 minutes in accordance with the above. In order to improve the balance ability, after the TRX, the participants performed exercises with the Fit ball for 10 minutes, with assistance for the first 3 weeks and then without assistance. Each 10-minute workout ended with stretching.

The first training program lasted 6 months, while the second training program lasted 6 weeks. The structure of the functional training program was similar in both the 6-month and 6-week studies, with the difference that by the end of the longer-term study, we were able to achieve a higher load in the senior age group. During the examination, the measurements were taken by the same physical therapist before the start of the exercise program and at the end of the exercise program. The training of the group of people taking ACE inhibitors and those not taking them took place at the same time, they participated in the same exercise program. For the laboratory experiments, peripheral blood samples were collected the day before the start of the program and on the 3rd day after the last training session.

3.2. Test sample

3.2.1. Study I. - Effect of functional training on the locomotor system

In our first study group, we included eighteen female volunteers over the age of 60 (mean age: 66.17±1.18 years) with mild to moderate sarcopenia, who have been taking ACE inhibitors for at least 6 months at a stable dose, with regulated blood pressure. Eighteen volunteers over 60 years old (mean age: 66.55±1.29 years) with mild and moderate sarcopenia,

who do not take ACE inhibitors, were included in our control group. One person dropped out and stopped the exercise program, so we analyzed the data of 17 patients in our study.

3.2.2. Study II. - The effect of functional training on the immune system

The second sample consisted of 29 healthy elderly female volunteers (average age: 67.03±3.74 years). The participants enrolled in the study were non-smokers and abstained from any physical exercise or sports activity, special diet and vitamin supplements for at least 3 months before the study.

3.3. Research tools

During the first examination, we used instruments suitable for measuring physical condition; while in the second study we also performed a laboratory analysis in addition to the use of some tools for measuring physical conditions. The tools used in the two stages of the study are presented in the first table.

Table I. - Measuring devices used in functional training groups

Measuring device	Study I.	Study II.
Short Physical Performance Battery	Yes	Yes
Schober-test	Yes	No
Kobra-test	Yes	No
Wall-occiput distance	Yes	No
Delmas-index	Yes	No
Inbody 270 body composition	Yes	Yes
Hand grip	Yes	Yes
Blood sampling and blood cell count analysis	No	Yes
T-cell subgroup definition	No	Yes
In vitro functional examination of CD4+CD127lo/-CD25+ Treg cells	No	Yes

3.3.1. Short Physical Performance Battery Test

The Short Physical Performance Battery (SPPB) is one of the best tools for assessing functional abilities. This is an objective examination that includes five tests on the function of the lower limbs. The SPPB is based on three timed tasks, which are tests of standing balance, walking speed and standing up from a chair. A four-point scale is used for each task, the total scores range from 0 to 12, with higher scores indicating better physical performance. The best performers on the test are those who achieve 10-12 points; 0-6 points: poor performance, 7-9 points: average performance, 10-12 points: good performance. A score of 9 or less is associated with increased mortality.

The balance assessment consists of 3 different parts. During the standing balance tests, the participants try to hold the side-by-side closed position, semi-tandem and tandem positions for 10 seconds. Participants receive 1 point if they can hold the side-by-side position for 10 seconds, but cannot hold the semi-tandem position for 10 seconds. They get 2 points if they kept the semi-tandem position for 10 seconds, but couldn't keep the full tandem position for more than 2 seconds. They get 3 points if they hold the full tandem position for 3-9 seconds and 4 points if they hold the full tandem position for 10 seconds.

Usual walking speed was measured in a flat and barrier-free corridor. Based on the literature, 4 m walking is the appropriate distance for measuring walking speed over short distances. The measurement area was demarcated with two clearly visible colored tapes placed at a distance of 4 m from each other. Each participant was asked to perform the walking speed protocol twice, with a 20-30 second break between the two tests. The participants were instructed to walk from one strip to the other at a pace that was comfortable and familiar to them. The walking time was measured with a stopwatch. We started the stopwatch when the participant started to walk, and we stopped the time measurement as soon as both feet of the participant completely left the designated area. The faster time of the two walks was taken into account when scoring: participants received 1 point if their walking speed was 6.52 seconds or higher; 2 points if completed between 4.66-6.52 seconds, 3 points if 3.62-4.65 seconds and 4 points if completed in less than 3.62 seconds.

During the test of standing up from the chair, we first made sure that the participants were able to stand up from the chair with their hands clasped in front of their chest. After the participants demonstrated that they could perform the action without using their arms, we asked them to stand up and sit down five times as fast as they could, with the entire surface of their soles remaining on the floor. Then we evaluated the test of standing up from five chairs: 1 point

if walking > in 16.7 seconds; 2 points if between 16.69 and 13.7 seconds; 3 points if between 13.69 and 11.2 seconds; 4 points if the task was completed in ≤11.19 seconds.

3.3.2. Schober-test

We examined the mobility of the lumbar spine with the Schober test. Method: the patient stands hip-width apart, his legs are parallel and in an extended position. Standing behind the patient, the examiner palpates the spina iliaca posterior superior (SIPS) and, sliding his hand in a medial direction, palpates the spinous process of the 2nd sacral vertebra. For the accuracy of the measurement, we mark this point with a leather felt. From this point, we measure 10 cm in the cranial direction and mark this as well. In addition to stabilizing the pelvis, we ask the patient to slowly bend forward from one vertebra to another, starting with the head, until the pelvis does not move. We ask you to hold this position while we measure the distance between the marked points. We subtract 10 cm from the obtained value, so we get the test result, which is at least 5 cm in the physiological case.

3.3.3. Kobra test

Cobra test: during the test for active motion testing of the lumbar and thoracic spine, the person tested lies on his stomach on a flat surface. You should place your two palms on the support, under your shoulders. From this position, you must push yourself up so that the upper arm is in a vertical position, the spina iliaca anterior superior remains on the ground. In the maximum position performed, the distance of the incisura jugularis from the support along the vertical axis must be measured. The obtained result forms a basis for comparison during later repeated measurements.

3.3.4. Measuring of wall - occiput distance

The position of the thoraco-cervical region can be assessed with this test; the higher the value, the greater the curvature of the thoracic spine and the forward position of the head and neck. During the test, the subject was positioned with his back to the wall so that the two corners touched the wall, and then we asked him to stand comfortably, as he used to in everyday life. In this position, we measured the distance between the wall and the occiput, in addition to physiological curvatures, the occiput, the maximum point of the dorsal curvature and the nape of the neck also touch the wall. 0 cm can be considered a physiological value.

3.3.5. Delmas-index

The test provides information about the curvatures of the spine and its mobility. We asked the test subjects to stand with their backs to us in their usual posture. It is important that their upper body is exposed so that we can carry out the measurement accurately. We measured the distance between the occiput and the S1 vertebra by stretching the centimeter tape, this became the actual length of the spine, and then we also measured the actual length of the spine, during which we measured the distance between the occiput and the S1 vertebra so that the centimeter tape was smoothed into the curves. The value of the Delmas index is a hundred times the ratio of the actual and actual length of the spine, which is between 94 and 96 in the case of physiological curvatures. If this value is below 94, the curvatures of the spine are increased, the spine is dynamic, on the other hand, if it is above 96, the curvatures of the spine are reduced and smoothed, and we can speak of a static spine that is less resistant to external forces.

3.3.6. Inbody 270 body composition analysis

Body composition analyzes were performed on an In Body 270 device (In Body, Seoul, South Korea). After manually recording the basic data - height, gender and age - the measurements took an average of 15 seconds. In addition to accurate body weight, the analysis provided a comprehensive picture of the ratio of skeletal muscle to body fat for the whole body and its various parts, including the upper and lower limbs and the trunk. Body mass indices (BMI) were also calculated during the measurements.

Bioelectrical impedance analysis (BIA) is suitable for estimating total or appendicular skeletal muscle mass. BIA equipment does not measure muscle mass directly, but gives an estimate based on the electrical conductivity of the whole body. BIA uses a conversion equation that is calibrated with reference to fat-free muscle mass measured by DEXA (dual-energy X-ray absorptiometry) in a given population. BIA equipment is affordable, widely available, and portable, especially single-frequency instruments. BIA prediction models mostly apply to the populations from which they were derived (using the so-called Sergi equation, which is based on older European populations). Age, ethnicity, and other related differences between these populations and patients should be considered in the clinic. In addition, BIA measurements can be affected by the patient's hydration status. BIA-based muscle mass determination may be preferable to DEXA due to affordability and portability. Before the test, we told the participants to come to the measurement on an empty stomach if possible. Before starting the analysis, we

asked the participants to remove their jewelry and electronic devices. After measuring the body height and recording the basic data in the machine (identification, gender, age, the measured body height), they were positioned at the designated points in a standing position, barefoot. After recording the data, the participants took magnetic electrodes in their hands and placed their fingers on the designated points. Their arms could not be in contact with their trunk, so we brought the upper limb into a slight abduction. The measurement took about 15 seconds, and the results were then printed. With the help of Inbody 270, the body's total amount of water, protein and mineral content, skeletal muscle mass and body fat mass can be examined for the whole body or segmentally for the upper and lower limbs (so any side differences can also be determined), as well as for the trunk . Although the tool is also suitable for diagnosing BMI, the ratio of body fat mass to body weight, i.e. body fat percentage, is a more suitable measuring tool for determining the degree of obesity. In addition, the device evaluates the body composition of the examined person on a 100-point scale (a very muscular participant can reach a score higher than 100). In Body 270 also recommends forms of exercise based on the current body weight of the person tested, and calculates the calorie consumption of the recommended exercise based on 30-minute workouts. The measurements were carried out based on the instructions on the manufacturer's website: https://uk.inbody.com/products/inbody-270/.

3.3.7. Hand grip examination

A CAMRY digital hand dynamometer (Camry Scale, South El Monte, CA, USA) was used to determine the grip strength of both hands. The participants were asked to squeeze the device with maximum force with the right hand and then with the left hand. The results are given in kg.

3.3.8. Blood sampling and blood cell count analysis

For laboratory experiments, peripheral blood samples were taken the day before the start of the program and on the 3rd day after the last training session. Blood samples were taken between 8:00 a.m. and 9:00 a.m. for all participants, in order to avoid circadian variations. Blood cell counts were analyzed from blood samples anticoagulated with ethylenediaminetetraacetic acid (EDTA) using an ADVIA 2120i hematology system (Siemens, Munich, Germany).

3.3.9. T cell subgroup analysis

T cells were identified based on the detection of the CD3 molecule on the cell surface. Within T-cells, T-helper lymphocytes were determined by CD4, while cytotoxic T (Tc) lymphocytes were identified by examining CD8 cell surface molecules. CD4+CD25bright Treg cells were determined by cell surface labeling of CD4, CD127 and CD25 antigens. T-cell activation markers, HLA-DR and CD69 antigens, were also examined on CD3+ T cells. Naive and memory T cells were determined above with antibodies against the following markers: CD45RA, anti-CD45RA and CD62L. Monoclonal antibodies were obtained from Beckmann Coulter (Beckmann Coulter Inc. Brea, CA, USA), Bio-Rad (Bio-Rad Laboratories, Hercules, CA, USA), Becton Dickinson (BD Biosciences, San Diego, CA, USA). The labeling of cell surface markers was performed from 100 ul of peripheral blood anticoagulated with heparin, 2.5-10 ul of monoclonal antibody was used for staining. After the samples were incubated for 30 minutes, the red blood cells were hemolyzed. The leukocytes were washed in PBS containing BSA (10 mg/L) and sodium azide (2 mg/L) and finally fixed with 2% paraformaldehyde. A mouse IgG1 antibody was used as an isotype control. The measurements were performed with a Coulter FC500 flow cytometer (Beckman Coulter) and the data were evaluated with the Kaluza 2.1a analysis software. Lymphocytes, monocytes and granulocytes were separated based on their size and granulation pattern based on the intensity of forward and side-scattered light. At least 30,000 cells were collected in the lymphocyte gate for each sample measurement.

The following monoclonal antibodies were used for intracellular staining of CD4+ T-helper cells: anti-IFN-gamma, anti-IL-4, anti-IL-10 and anti-IL-17. The following cells were distinguished: Th1: CD4+IFN-gamma+IL4-; Th2: CD4+ IFN-gamma-IL4+; Tr1: CD4+IL10+; Th17: CD4+IFN-gamma-IL17+. Monoclonal antibodies were obtained from Beckmann Coulter, BD Biosciences, and R&D (R&D Systems, Minneapolis, MN, USA). During intracellular staining of CD4+ Th cells, 1 ml of peripheral blood was diluted 1:2 with RPMI-1640 medium containing 80 mg/l gentamicin and 2 nM glutamine. 25 ng/ml phorbol myristate acetate and 1 μg/ml ionomycin were used to stimulate the cells, and the transport of de novo synthesized cytokines from the Golgi apparatus was inhibited with 10 ug/ml brefeldin-A. The cells were incubated for 5 hours at 37°C and 5% CO2. Unstimulated cells served as controls. After stimulation, the cells were labeled for CD4 antigen and incubated for 30 minutes at room temperature. The cells were then fixed for 15 minutes in the dark at room temperature using the 1st solution of IntraprepTM permeabilization reagent (Beckman Coulter). After another washing step, the cell membrane of the leukocytes was permeabilized with the 2nd solution of

IntraprepTM permeabilizing reagent and then the cells were labeled with anti-cytokine monoclonal antibodies for 30 minutes at room temperature. Afterwards, the samples were washed in PBS and finally the cells were fixed in 1% paraformaldehyde.

The measurements and evaluations were performed with a Beckman Coulter FC500 flow cytometer. The evaluations were performed with the Kaluza 2.1a analysis software. Lymphocytes, granulocytes and monocytes were separated based on their morphological characteristics. The evaluation was performed by collecting at least 5,000 CD4+ T cells.

The determined cell types were therefore the following: CD3+ T, CD4+ T helper (Th), CD8+ cytotoxic T (Tc) cells, early (CD3+CD69+) and late (CD3+HLA-DR+) activated T cells, naïve (CD62L +CD45RA+), CD45RA+ effector memory (EMRA; CD62L-CD45RA+), central memory (CD62L+CD45RA-), effector memory (CD62L-CD45RA-) and CD4+CD127-CD25bright Treg cells. And with intracellular labeling Th1 (CD4+ IFN-gamma+ IL-4-); Th2 (CD4+ IFN-gamma-IL-4+); Tr1 (CD4+ IL-10+); Th17 (CD4+ IFN-gamma- IL-17+) cells were determined.

3.3.10. In vitro functional analysis of CD4+CD127lo/-CD25+ Treg cells

CD4+CD127lo/-CD25+ T cells were separated from PBMC from peripheral, heparin-anticoagulated blood using the Ficoll gradient method using the Regulatory T Cell Isolation Kit (Miltenyi Biotech GmbH, Bergisch Gladbach, Germany) and LD and MS columns, while CD4+CD25 - cells were isolated using the CD4+ T Cell Isolation Kit, according to the protocol described by the manufacturer. The 8x104 cells/ml CD4+CD127lo/-CD25+ and CD4+ CD25-T cells isolated using magnetic microbeads were separated in 200 ul of RPMI 1640 and cultured in a 1:1 ratio mixed culture for 72 hours at 37°C and 5% in addition to CO2. To simulate polyclonal stimulation, anti-CD3/CD28 T-cell expander microbeads (Thermo Fisher Scientific, Waltham, Massachusetts, USA) were used at a concentration of 1 bead/cell. Cell proliferation was tested using the EZ4U tetrazolium-based method (Biomedica, Vienna, Austria). The optical density (OD) values were measured at a wavelength of 450 nm with a Labsystems 352 Multiskan MS device (Thermo Fisher Scientific). The OD values of the mixed cultures were corrected with the OD values of pure CD4+CD127lo/-CD25+ T cultures. The suppressor activity was calculated based on the ratio of the corrected OD values of CD4+CD25- T-cell cultures and mixed lymphocyte cultures (MLR).

3.4. Statistical analysis

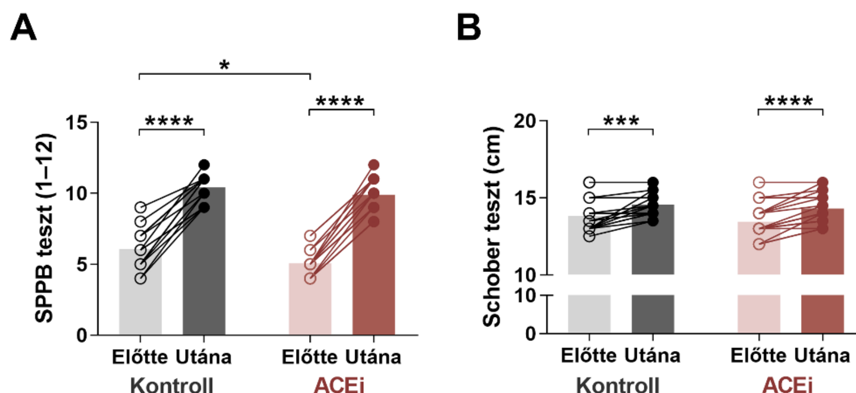
GraphPad Prism 8 software (Graphpad Software, San Diego, USA) was used for the statistical evaluation of our results. We tested the normal distribution of our data using the Kolgomorov-Smirnov test and the Shapiro-Wilk test. When evaluating the results, we used the paired t-test in the case of a normal distribution, and the Wilcoxon test in the case of a non-normal distribution. In the evaluation of the statistical tests, a value of $p<0.05$ was considered significant.

4. RESULTS

4.1. Study I: Effect of functional training on the locomotor system

Based on the SPPB measurement, at the start of the ACE group, 2 patients were placed in the moderate sarcopenia group and 16 patients were classified in the severe sarcopenia group. After the 6-month exercise program, 7 patients moved from the severe sarcopenia group to the moderate sarcopenia group and 9 patients moved from the severe sarcopenia group to the mild sarcopenia group. The 2 patients moved from the moderate sarcopenia group to the mild sarcopenia group. In the control group, 6 patients were classified in the moderate sarcopenia group and 12 patients in the severe sarcopenia group based on the SPPB test. After the six-month exercise program, 1 person dropped out of the 12 severe sarcopenia group, 4 people moved to the moderate sarcopenia group, and 7 people entered the mild sarcopenia group when the SPPB test was re-performed. The 6 patients, who were in the moderate sarcopenia group at the beginning, all moved up to the mild sarcopenia category. Based on the SPPB measurements, a significant improvement was observed in both groups as a result of the 6-month exercise program, the difference between the two groups disappeared by the end of the functional training program. In both the ACE-inhibitor and the control groups, 1-1 person was able to complete the SPPB test with a maximum of 12 points (Figure 1/A). In our study, we assessed the mobility of the spine in flexion and extension. Lumbar spine flexion was measured with the Schober test. At baseline, the average of the values measured in the group of those taking ACE inhibitors was 13.38 cm, which was not in the physiological range. After the six-month exercise program, the average of the test improved to 14.31 cm, but did not reach the physiological value (Figure 1/B).

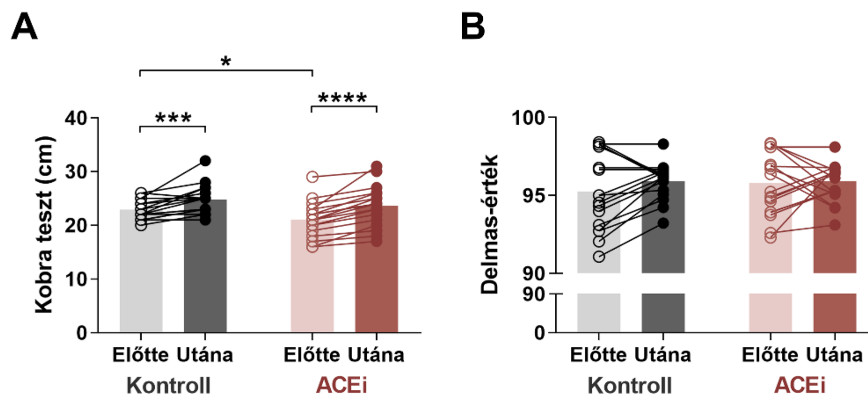
Figure 1. – Changes in the results achieved on the SPPB and Schober tests



(A) A measure of the severity of sarcopenia (SPPB value), (B) Schober test. ACEi: ACE inhibitor. The points represent individual values, the columns represent the average. * p < 0,05; ***p < 0,001; ****p < 0,0001

The Kobra test was used to measure the extension of the lumbar and dorsal spine. A significant improvement was found in both groups, the improvement was more significant in the group taking ACE inhibitors (Figure 2/A). During the examination of the Delmas index, the sagittal curvatures of the spine showed no significant changes. In the age group over 60, due to degenerative changes in the vertebrae and discs, the spine can be less mobilized in the sagittal directions (Figure 2/B).

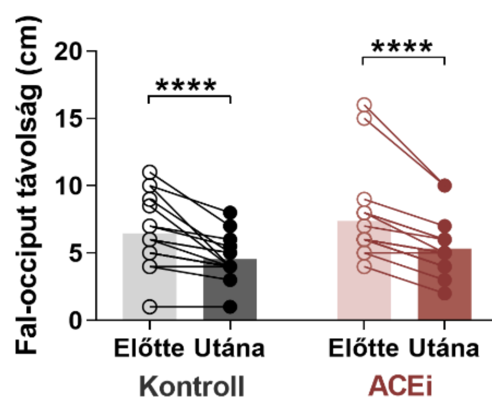
Figure 2. - **Changes in the results achieved on the Kobra and Delmas tests**



(A) Kobra-test, (B) Delmas-value. ACEi: ACE-inhibitor. The points represent individual values, the columns represent the average. *p < 0,05; ***p < 0,001; ****p < 0,0001

In the age group over 60, dorsal kyphosis typically increases due to the weakening of the lower fibers of the trapezius muscle. Shrinkage of the pectoralis muscles is also characteristic of old age posture. Among the posture measurements, the wall-occiput distance shows the change in the physiological position of the chest and shoulder girdle. The wall-occiput distance showed a significant improvement in both groups, the posture improved, there was no significant difference between the two groups.

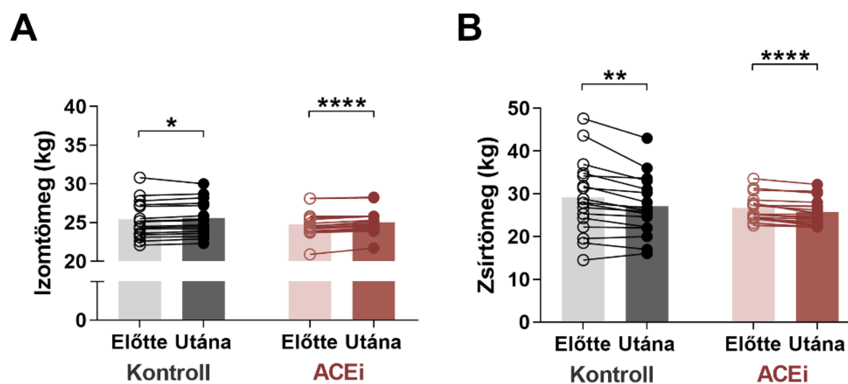
Figure 3. - Effect of functional training on wall-occiput distance in elderly women



ACEi: ACE-inhibitor. The points represent individual values, the columns represent the average. ****p < 0,0001

One important indicator of sarcopenia is muscle mass. In our study, muscle mass significantly improved in both groups as a result of the six-month functional training program. The improvement was more significant among those taking ACE inhibitors (Figure 4/A). In terms of fat mass, a significant improvement was achieved in both groups by the end of the study. There was no significant difference between the two study groups (Figure 4/B).

Figure 4. – Changes in muscle mass and fat mass



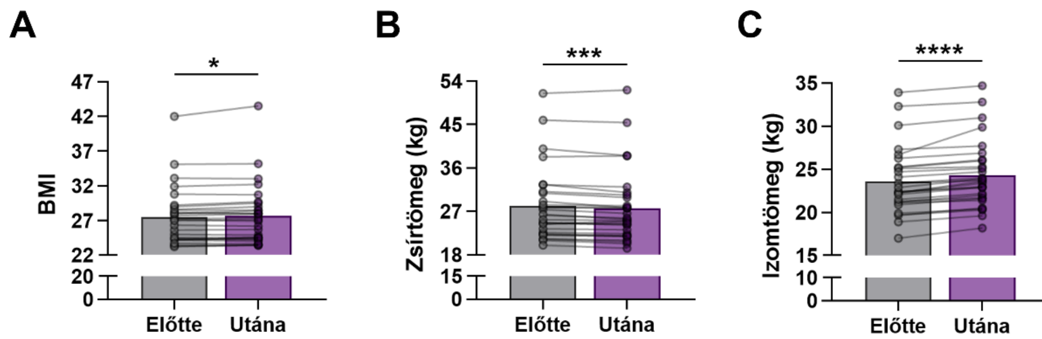
(A) Muscle mass, (B) Fat mass. ACEi: ACE-inhibitor. The points represent individual values, the columns represent the average. *p < 0,05; **p < 0,01; ****p < 0,0001

4.2. Study II.: The effect of functional training on physical performance and the immune system

4.2.1. Changes in body composition and physical performance

In order to determine the effect of regular exercise on the fitness level of the participants, measurements of body composition and physical performance were performed before the first training session and repeated after the last training session. A slight significant increase was observed between the values of BMI before and after (27.51 ± 4.132 vs. 27.66 ± 4.335; p = 0.018). The participants' body composition improved significantly, the body fat ratio decreased (28.12 ± 7.556 vs. 27.69 ± 7.597; p = 0.0001), while the skeletal muscle ratio increased (23.57 ± 3.834 vs. 24.33 ± 3.907; p = 0.0001). p <0.0001) at the end of the movement program (Figure 5/A-C).

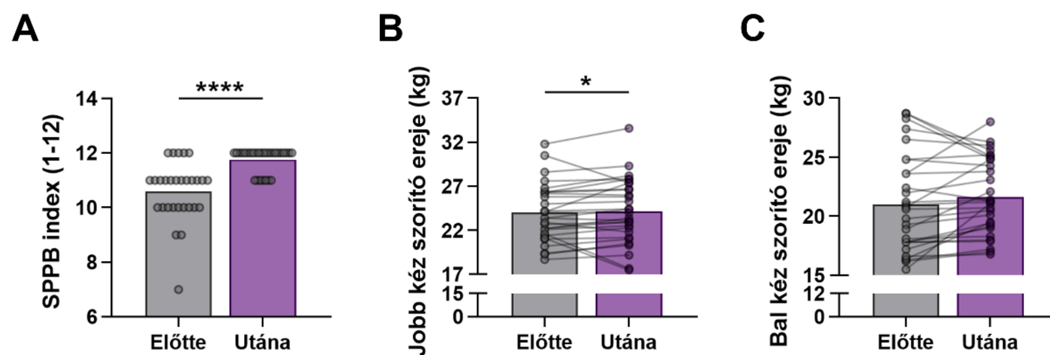
Figure 5. - Changes in body composition due to sports activity in elderly women



(A) BMI, (B) Fat mass and (C) Muscle mass. The points represent individual values, the columns represent the average *p < 0,05; ***p < 0,001; ****p < 0,0001

The participants were also able to improve their physical performance as a result of the training, as the SPPB scores increased significantly (10.59 ± 1.086 vs. 11.76 ± 0.4355; $p < 0.0001$) and hand grip strength also increased (mainly the dominant hand; 27 subjects were right-handed in the study group) (Figure 6/A-C).

Figure 6. - Results of the physical condition assessment of elderly persons before and after the exercise program

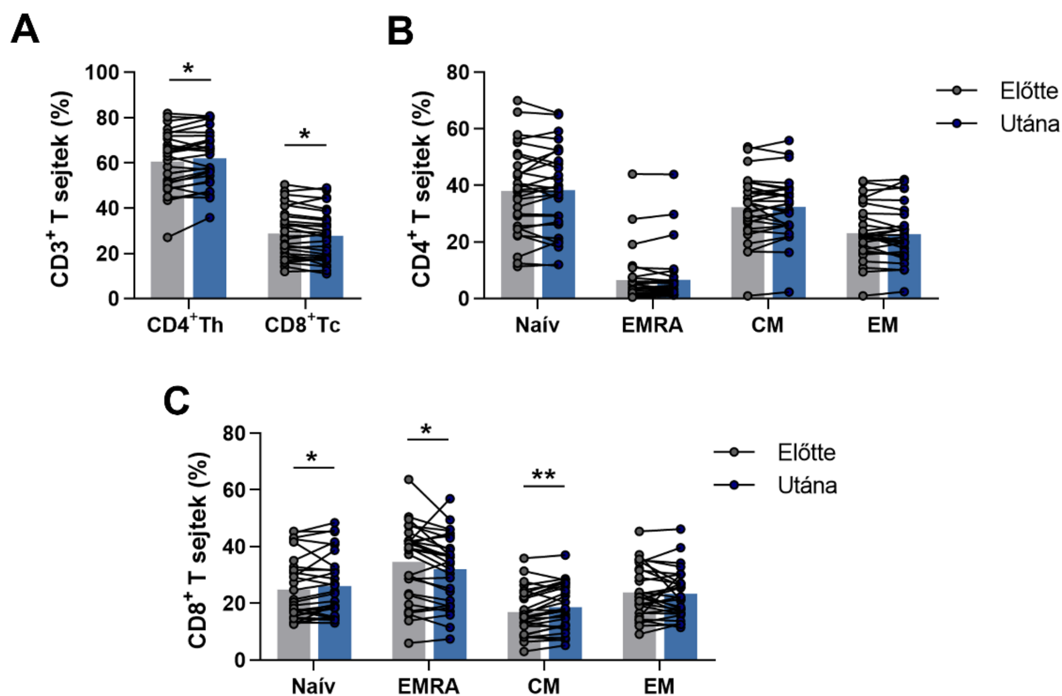


(A) Degree of severity of sarcopenia (SPPB value), (B) Right hand grip strength, (C) Left hand grip strength. The points represent individual values, the columns represent the average. * p<0,05; ****p <0,0001

4.2.2. Changes in the number and main subgroups of T-cells

The T cell numbers calculated based on the blood count results and the cell ratios determined by flow cytometry did not differ at the beginning and end of the study. However, the proportions of T cell subtypes showed a significant change in response to the exercise program. The proportion of Th cells increased significantly (60.469 ± 13.051 vs. 62.001 ± 12.105, p = 0.0177), while that of Tc cells decreased (28.764 ± 10.888 vs. 27.697 ± 10.961; p = 0.0133) (Figure 7/A).

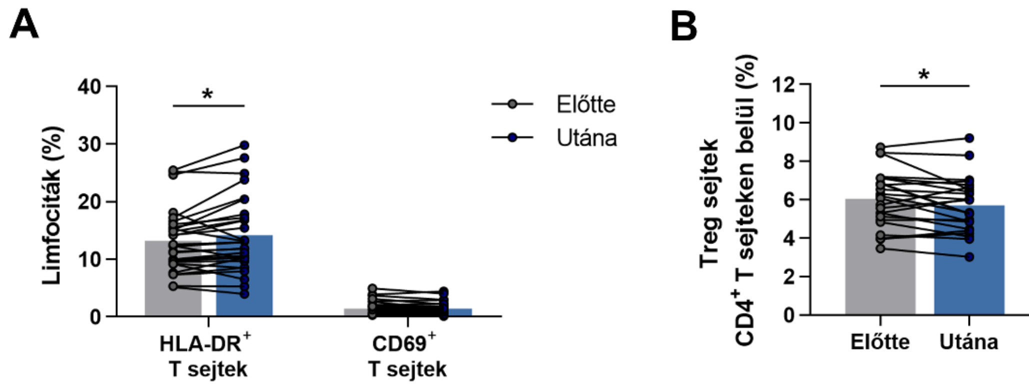
Figure 7. - Changes in the distribution of naive and memory lymphocyte subgroups after the end of the training program



(A) Proportion of T helper (Th) and cytotoxic (Tc) cells within CD3+ T cells. (B) Ratio of naïve and memory Th subgroups. (C) Proportion of naïve and memory Tc subgroups. EMRA: CD45RA+ effector memory. When evaluating the results, we used paired T-test or Wilcoxon test. The points represent individual values, the columns represent the average. *p<0.05; **p<0.01

When analyzing the proportion of activated T cells, we found that the proportion of late-activated T cells increased significantly (13.189 ± 5.396 vs. 14.144 ± 6.547; p = 0.0412) (Figure 8/A). The proportion of Treg cells with a regulatory function decreased significantly by the end of the training program (6.043 ± 1.451 vs. 5.708 ± 1.430; p = 0.0370) (Figure 8/B).

Figure 8. - Changes in activated T and Treg cell ratios

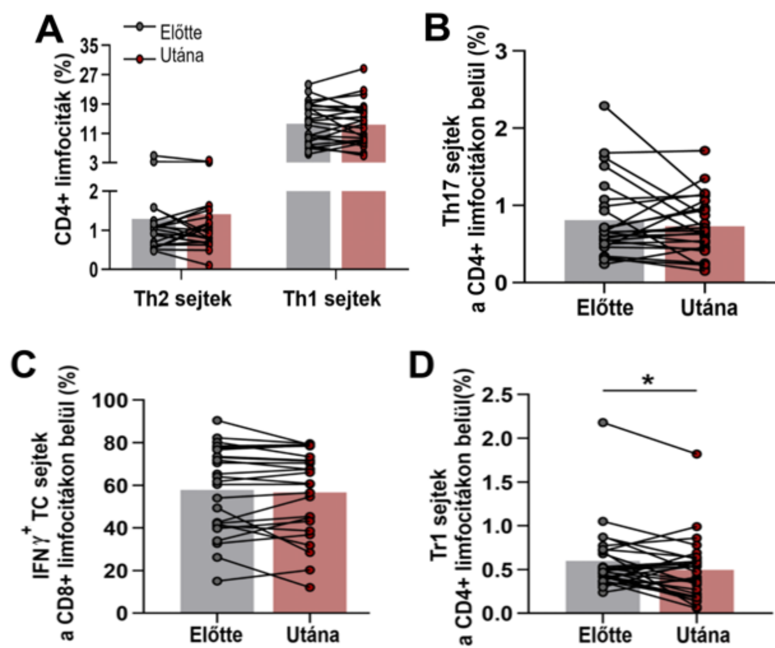


(A) The bar graph shows the frequency of activated T cells. (B) The bar graph represents the proportion of regulatory T cells. A paired T-test was used to evaluate the results. The points represent individual values, the columns represent the average. *p<0.05

4.2.3. Changes in peripheral T helper cells and cytotoxic T cells

No significant differences were found in peripheral blood Th1, Th2, Th17 and Tc cells, however, the proportion of immunosuppressive Tr1 cells was significantly reduced (0.5989 ± 0.3724 vs. 0.4952 ± 0.3588; p = 0.0391) by the end of the 6-week training program (Figure 9/A-D).

Figure 9. - Change in the ratio of T-helper cell subtypes, cytotoxic T (Tc) and type 1 regulatory T (Tr1) cells

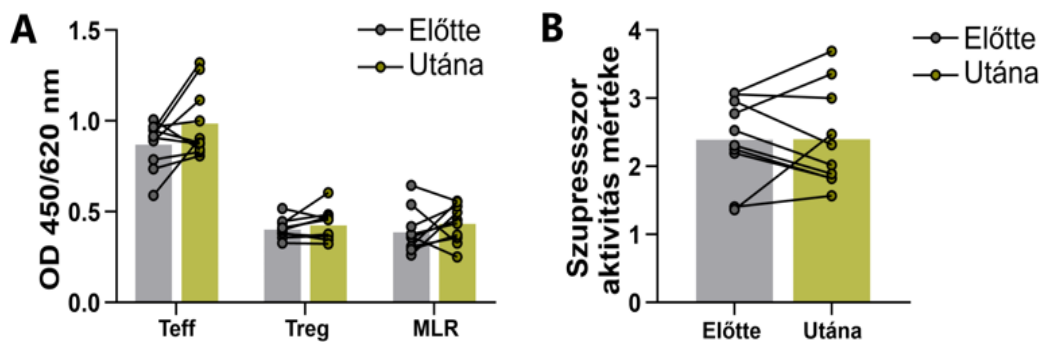


(A) Ratio of IFN-□+ Th1 and IL-4+ Th2 cells. (B) Proportions of IL-17+ Th17 cells. (C) Ratios of IFN-□ producing Tc cells. (D) Proportions of IL-10-producing Tr1 cells. A paired t-test was used for the evaluation. The points represent individual values, the columns represent the average. *p<0.05

4.2.4. Suppressive functions of $CD4^{+}CD127^{lo/-}CD25^{+}$ Treg cells

In the case of ten healthy elderly volunteers, we performed the in vitro functional tests before and at the end of the exercise program. To investigate the suppressor activity of Treg cells, magnetically isolated CD4+CD25-Th and CD4+CD127lo/-CD25+ Treg cells were cultured alone or in a mixed lymphocyte culture with effector T cells in the presence of T-cell activator anti-CD3/CD28 beads. As expected, the presence of Treg cells in the MLR co-culture caused an obvious decrease in proliferation, but there was no difference between the values before and after the exercise program. Based on all of this, the suppressor activity index of Treg cells did not show any changes as a result of training.

Figure 10. - Suppressor activity of regulatory T cells before and after an exercise program



(A) The bar graph represents the extent of cell proliferation measured in effector T-helper (CD4+CD25-), CD4+CD127lo/-CD25+ Treg and MLR cultures. In the evening of the mixed lymphocyte cell culture (MLR) and Treg cells, the corrected optical density was plotted. (B) Measurement of suppressor activity of Treg cells. A paired T-test was used to evaluate the results. The points represent individual values, the columns represent the average.

5. DISCUSSION

The main goal of the research was to investigate the measurable effectiveness of functional training among women over 60 years of age. We used two main focuses during the impact assessment. The aim of our research was, on the one hand, to assess the improvement of the condition of elderly people who had not previously been physically active as a result of functional training, in terms of changes in spine mobility, posture and physical performance. On the other hand, our goal was to observe the immune response of the elderly to physical activity in addition to the improvement in fitness.

The SPPB test was used to measure physical performance due to its complexity. Test scores are correlated with self-sufficiency, skeletal muscle function, ability to walk and balance, and risk of falls. It consists of three test parts, which examine balance, walking and standing up from a chair. Our results confirmed the assumption that functional training has a beneficial effect on physical performance. A significant improvement was observed in the aggregated scores of the SPPB test in both tested samples. We can state that the physical performance of the elderly improves significantly even after a short functional training of up to 6 weeks. In the 6-month study, the group of those taking ACE inhibitors had lower physical performance on average, which difference disappeared by the end of the 6-month training program.

When examining the mobility of the spine, we examined the flexion and extension range of motion. In the case of the flexion range of motion, i.e. the Schober test, the average of the results before the training program did not reach the physiological range of motion. Although the flexion mobility of the spine improved as a result of the 6-month training program, neither the ACE nor the control group reached the physiological range. In older age, due to the degeneration of the discs, bony and ligamentous elements of the spine, the range of motion of the lumbar spine becomes narrower, and therefore it is more difficult to achieve physiological values. There is no defined physiological value in the examination of extension, so we can only infer the improvement of the range of motion from the differences between the measurements. In our study, we could see that as a result of physical activity, the extension range of motion increased significantly, and could be improved with functional training, in both test groups.

We used two tests to examine posture during the research. The wall-occiput distance gives information about the curvatures of the back and neck, the value measured during the examination is greater, the greater the curvature of the thoracic section and the position of the head. Looking at the results of the wall-occiput distance, we can conclude that the value improved significantly in both groups as a result of the exercise program, the wall-occiput

distance decreased, thereby decreasing the degree of sloppy posture and forward head posture. There was no significant difference between the two groups. Another test used to examine posture was the Delmas index. In this case, no significant changes occurred during training. This is due to the fact that the test defines ranges, so the result is also affected if a person did not fall into the physiological range originally, it is possible that the individual condition improves, but the category remains the same. In old age, the spine is more rigid, and it is more difficult to change the sagittal curves at this age.

An important indicator of sarcopenia is the examination of hand grip strength, which was analyzed both during our short-term 6-week and long-term 6-month studies. The special equipment used in functional training, small dumbbells and TRX, increase hand grip strength. In our 6-month study, we achieved a significant improvement in the development of hand grip strength in both the right and left hands, however, the duration of the 6-week study proved to be insufficient in this regard. Our short-term results showed that we could only increase the strength of the dominant right hand, based on this we came to the conclusion that it takes more time than 6 weeks to develop the grip strength of the hand on both sides. The development of hand grip strength is important in the daily routine of the elderly, such as writing, housework, doing household chores and eating, self-care, dressing. The exercise program of the elderly should include the development of hand grip strength.

Based on the results of our research, the specially tailored exercise program for the elderly has a positive effect on the locomotor system and thus on functional abilities. Our research also confirms that physical activity is an important factor in healthy aging and maintaining good functional abilities. Functional training is an effective method for improving physical condition and performance in old age.

Body composition studies have shown that physical activity improves the fat/muscle ratio. The change in body composition in the optimal direction was already visible in 6 weeks. We achieved a significant improvement in muscle mass and a decrease in fat mass in the senior age group. In the case of sarcopenia, the primary task is to slow down muscle loss. With our study, we proved that not only can the loss of muscle mass be prevented in old age, but with active muscle strengthening exercises, it is possible to rebuild muscle mass at any age, even without a special diet.

The BMI showed a slight increase, however, the body composition analysis showed that the increase in weight resulted from the increase in muscle mass, so this can be evaluated as a positive change. Our study also proves that it is not enough to only measure body weight

in old age, because a possible increase in body weight can also result from an increase in muscle mass, and a decrease in body weight can also indicate muscle loss.

In our second study, in addition to examining improvements in physical condition, we focused on immunological changes in healthy elderly women who completed a 6-week exercise program at a moderate intensity. Due to the regular physical exercises, their body composition characteristics improved, their total body fat mass decreased, while their skeletal muscle mass increased significantly, and the latter resulted in a slight increase in the BMI value. In parallel with the change in muscle mass, muscle strength also increased, which reflects a significant improvement in the physical performance of elderly people.

Looking at our immunological test results, we observed an increase in the percentage of HLA-DR+ late activated T cells, which indicates a more activated immunological state of elderly individuals at the end of the 6-week training program. Although we also described an increase in the proportion of CD4+ Th cells during our research, the proportions of Th1/Th2/Th17 subgroups were not significantly affected by training in old age. In contrast, the proportion of CD8+ Tc cells decreased and the distribution of CD8+ Tc cell subgroups also showed significant changes at the end of the training program. These results are consistent with previous observations. A previous study reported an increase in the proportion of peripheral blood CD8+ Tc cells during both normal and high-intensity exercise; however, his percentage fell below baseline after the exercise. Importantly, in our study, the proportion of effector memory CD8+ T cells decreased, while the proportion of naïve CD8+ T cells increased as a result of training. Taking into account that aging is associated with a decrease in the number and ratio of naïve T cells and the accumulation of memory T cells with limited specificity, the applied exercise program can be effective in rearranging these cell ratios.

Regarding T-cell subsets with immunoregulatory function, the levels of immunosuppressive IL-10-producing Tr1 cells and CD4+CD127lo/-CD25bright Treg cells showed a significant decrease in elderly individuals after the 6-week functional training program. These are new observations and highlight the probably most important effect of physical exercise and sports on the immune system of older people. At the level of the adaptive immune system, the network of regulatory T cells (Tr1 and CD4+CD127lo/-CD25bright Treg) is responsible for regulating the effector functions of immune responses. The frequency of Treg cells changes with advancing age, and the number of Treg cells increases, which is believed to contribute to immunosuppression in old age. Based on a previous study, exercise can significantly increase the number of Treg cells, but it is important to highlight that this

observation is related to acute, high-intensity exercises; while the effects of moderate-intensity regular exercises have not been investigated before.

During our study, in addition to the quantitative changes, we also examined the qualitative functional changes of Treg cells. Based on the results of the in vitro functional tests examining the suppressive capacity of Treg cells, we observed neither increased nor impaired regulatory function. Therefore, the exercise-related decrease in the proportion of Treg cells does not trigger a compensatory regulatory mechanism that would increase their suppressive activity. On the other hand, a lower number of Tregs is not associated with a decline in the suppressor function of the cells, which would increase the risk of developing autoimmune disorders or allergic diseases.

Overall, our results suggest that exercise-induced changes affecting naïve and memory T cells and regulatory T cells reflect the retuning of immunological regulation and the restored reactivity of the immune system.

6. THE MOST IMPORTANT FINDINGS AND NEW AND NOVELTY RESULTS OF THE DISSERTATION

Changes in posture in old age increase the risk of falling. In our study, we were the first to examine changes in the wall-occiput distance as a result of functional training in old age. Our study showed a significant improvement, so we can conclude that posture can be improved even in the older age group.

As a result of regular functional exercise, we observed an increase in the percentage of HLA-DR+ late-activated T cells, which indicates a more activated immunological state of elderly individuals by the end of the 6-week exercise program.

During our studies, we confirmed a decrease in the proportion of effector memory CD8+ T cells and an increase in the proportion of naïve CD8+ T cells as a result of regular exercise in old age. Considering that aging is associated with a decrease in the number and proportion of naïve T cells and an accumulation of limited-specificity memory T cells, the functional training program was effective in reversing the changes in cell proportions that develop with aging.

A new observation that the levels of immunosuppressive IL-10-producing Tr1 cells and CD4+CD127lo/-CD25bright Treg cells showed a significant decrease in elderly individuals after a 6-week functional training program, which may shed light on the most important effect of regular exercise on the immune system of older persons regarding.

In addition to the quantitative changes, we were the first in the literature to examine the qualitative functional changes of Treg cells as a result of regular functional training in old age. Based on the results of the in vitro functional tests examining the suppressive capacity of Treg cells, we observed neither increased nor impaired regulatory function.

7. SUMMARY

Aging is a natural process, the impact of which occurs on biological, psychological and social levels. One of the main areas of somatic deterioration is the locomotor system, but the degenerative effect of aging also extends to immune function. Spinal mobility, muscle strength, walking speed, muscle strength of the lower limbs decrease, the condition of the bones, hand grip strength and balancing ability also deteriorate. With the progressive decline of immune function, the body becomes more and more defenseless against pathogens and tumor cells. Regular physical activity can serve as one of the most important means of slowing down all these processes.

The aim of our study was to assess how regular physical activity (regular group functional training) affects important factors of functional ability, such as spine mobility, posture and physical performance, body composition and the degree of sarcopenia. Another goal of the research was to reveal the effect of the special training program used on the immune system of the elderly. During our first study, among elderly people taking and not taking ACE inhibitors, we observed that the functional training program significantly improved spinal mobility, posture, body composition and physical performance (balance, walking speed, standing up from a chair, hand grip strength).

In our second study, we observed significant changes in naive and memory lymphocyte ratios at the end of the exercise program. The proportion of naive Tc cells increased, effector memory Tc cells decreased, and the proportion of late activated HLA-DR+ T cells increased. The proportion of anti-inflammatory interleukin (IL)-10-producing Tr1 cells and regulatory CD4+CD127lo/-CD25bright Treg cells decreased after regular training. In addition to improving physical condition and mitigating age-related sarcopenia, regular exercise can thus delay or even reverse immunological aging.

Overall, our results indicate that functional training, if properly adapted, is a suitable form of exercise for improving physical functions in old age, even in the context of a shorter program. Our results indicate that, in addition to improving physical condition and mitigating age-related sarcopenia, regular exercise can delay or even reverse immunological aging, and therefore can be particularly beneficial in maintaining proper immune functions in older age.

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