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DOCTORAL SCHOOL OF INTERDISCIPLINARY MEDICINE

Ph.D. Thesis

EFFECTS OF PHYSICAL ACTIVITY ON THE AGING PROCESS

- with non-invasive follow-up and invasive cross-sectional researches -

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I.: **Szablics P, Orbán K, Szabó S, Dvorák M, Ungvári M, Béres S, Molnár AH, Pintér Z, Kupai K, Pósa A, Varga C.** *Effects of aerobic workout on the changes in the characteristics of dynamics of the center of gravity in different age categories.* Physiol Int. 2019 Jun 1;106(2):140-150. doi: 10.1556/2060.106.2019.13.

II.: **Koltai E, Bori Z, Osvath P, Ihasz F, Peter S, Toth G, Degens H, Rittweger J, Boldogh I, Radak Z.** *Master athletes have higher miR-7, SIRT3 and SOD2 expression in skeletal muscle than age-matched sedentary controls.* Redox Biol. 2018 Oct;19:46-51. doi: 10.1016/j.redox.2018.07.022. Epub 2018 Aug 7.

List of abbreviations:

a – *acceleration*

acyl-CoA – *acetyl coenzyme A*

ADP - *adenosine diphosphate*

AF – *abdomen fold*

Akt – *protein kinase b*

AMP - *adenosine monophosphate*

ANOVA – *analysis of variance*

APAS 3D system – *ariel performance analysis system 3 dimension*

ATP - *adenosine triphosphate*

BF% - *body fat percentage*

BIA – *bioelectric impedance*

BMI – *body mass index*

BSA – *bovine serum albumin*

BW – *body weight*

CaMKII – *Ca^{2+}/calmodulin-dependentproteinkinase II*

cDNA – *complementary DNA*

CG – *centre of gravity*

CMJ – *counter movement jump*

COX - c*ytochrome C oxidase*

COX4 – *cytochrome C oxidase subunit 4*

CP – *creatine phosphate*

CuZnSOD – *SOD1*

Cyanine-3-pCp – *cytidine-5'-phosphate-3'-(6-aminohexyl) phosphate*

DNA – *deoxyribonucleic acid*

dNTP – *deoxynucleotid*

ECSOD – *SOD3*

EGFR – *epidermal growth factor receptor*

FAD^+ - *flavin adenine dinucleotide+*

FM – *fat mass*

FM/BW – *fat mass-body weight ratio*

FOXO – *forkhead box protein O*

FOXO1 – *forkhead box protein O1*

fps – *frame per seconds*

G1 – *second childhood*

G2 – *adolescence*

G3 – *mature age I*

G4 – *mature age II*

G5 – *ageing*

GAPDH – *glyceraldehyde 3-phosphate dehydrogenase*

HDL – *high-density lipoprotein*

HF – *hip fold*

HIV – *human immunodeficiency virus*

HR – *heart rate*

Hrest – *rest heart rate*

HRmax – *maximal heart rate*

HRP – *horseradish peroxidase*

IGF1 - *insulin like growth factor 1 hormone*

ISO – *unit of photosensitivity*

l – *lenght*

m – *mass*

MAPK/ERK – *mitogen aktivated protein kinase/extracellular signal-regulated kinases*

MCU – *mitochondrial Ca uniporter*

MGF – *mechano growth factor*

miR-423 – *microRNA-423*

miR-7 – *microRNA-7*

miRNA - *microRNA*

MnSOD – *SOD2*

mRNA - *messenger RNA*

mtDNA – *mitochondrial DNA*

mTOR – *mechanistics target of rapamycin*

NAD^+ - *nicotinamide adenine dinucleotide+*

nNOS – *nervous nitrogen oxide synthase*

PCR – *polymerase chain reaction*

PGC1a, PPARGC1a, PPARαsignal – *peroxisome proliferator-activated receptor gamma coactivator 1-alpha*

P_i – *inorganic phosphate*

PI3K – *phosphoinositide 3-kinases*

PPAR – *peroxisome proliferator-activated receptor*

PVDF – *polyvinylidene difluoride*

qPCR – *quantitative polymerase chain reaction*

qRT-PCR – *real-time quantitative polymerase chain reaction*

Rho- GTPase – *Rho-guanosine-5'-triphosphatase*

RNA – *ribonucleic acid*

RNase – *ribonuclease*

ROS – *reactive oxygen*

rRNA – *ribosomal RNA*

RSI – *reactive strength index*

RT-PCR – *real-time polymerase chain reaction*

SD – *standard deviation*

SDS – PAGE – *sodium dodecyl sulfonate - page*

SEM – *standard error of mean*

SF – *scapula fold*

SI - *international system of units*

SIRT1 – *sirtuin1*

SIRT3 – *sirtuin3*

Sirtuin – silent mating type information regulation 2 homolog

SJ – *squat jump*

SMM – *skeletal muscle mass*

SMM/BW – *skeletal muscle mass-body weight ratio*

SMM/FM – *muscle-fat ratio*

SOD – *superoxide dismutase*

SREBP – *sterol regulatory element-binding proteins*

t – *time*

TBST – *tris-buffered saline-Tween-20*

TF– *thigh fold*

TRF – *triceps fold*

type I – *muscle fibres with slow oxidative metabolism*

type IIa – *muscle fibres with fast oxidative glycolytic metabolism*

type IIb – *muscle fibres with fast glycolytic metabolism*

v – *velocity*

VEGF – *vascular endothelial growth factor*

VO_2 – *vital capacity*

VO_2max – *maximal vital capacity*

WC – *waist circumference*

WHO - *world health organization*

WHR – *waist – hip ratio*

Δ% - *percentages of delta*

ΔD – *difference of delta*

Δs – *change of traveled distance in short time*

Δt – *elapsed time*

Δv – *change of velocity in short time*

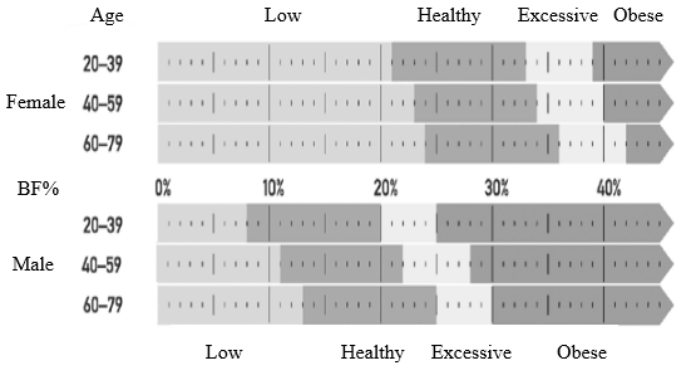
$\Delta\Delta C_1$ – *cycle threshold*

Contents:

1 Introduction

1.1 Body composition and intensity of training

Expected human lifetime and the prevalence of obesity increased during the last century (Mau and Yung, 2018). The presence of overweight and obesity has doubled since 1980 indicated by the data of World Health Organization (WHO). All over the word nearly 500 million people were obese and 1.4 billion people were overweight in 2008 (Schwingshackl et al., 2013). The body mass index (BMI) and body fat percentage (BF%) are appropriate methods to determine the severity of overweight *(Figure 1)* (Flegal et al., 2009; Gallagher et al., 2000).



	Thin	Normal	Overweight	Moderate obese (1st level of obesity)	Serious obese (2nd level of obesity)	Dangerous obese (3rd level of obesity)
BMI	<18.5	18.5-24.9	25-29.9	30-34.9	35-39.9	≥40

Figure 1: Physique categories of BF% and BMI
(BF%: body fat percentage, BMI: body mass index)
(Halmy, 2018)

Researchers and clinicians often use the BMI which is derived from body weight (BW) to stature. This method cannot be applied to athletes. BMI can be calculated by using the next simple formula (McArdle et al., 2006):

$$BMI = body\ mass\ (kg) \div stature^2\ (m^2).$$

Application of BF% is more accurate to describe body composition. Calculation of this parameter is more difficult than of BMI, nevertheless it can be applied for people with different physical appearances. Two formulae can be mentioned:

From BMI (McArdle et al., 2006):

$$BF\% = 63.7 - 864 \times (1 \div BMI) - 12.1 \times sex + 0.12 \times age + 129 \times Asian \times (1 \div BMI) - 0.091 \times Asian \times age - 0.030 \times African\ American \times age$$

(sex:1 for male, 0 for female; Asian = 1 and 0 for others, African American = 1 and 0 for others, European = 0 for Asian and 0 for African American; age in years)

From anthropometric data (Mészáros, 1990):

Male: $BF\% = 3.7234 + 0.1999 \times TF + 0.2876 \times AF - 0.0209 \times HF - 0.0054 \times SF \pm 3.93$

Female: $BF\% = 9{,}0075 + 0{,}1769 \times AF + 0{,}2327 \times HF + 0{,}2249 \times SF + 0{,}0542 \times TRF \pm 4{,}49$

(TF = thigh fold, AF = abdomen fold, HF = hip fold, SF = scapula fold, TRF = triceps fold, every fold in mm)

Overweight can be detected based on other anthropometric parameters like waist circumference (WC) and waist - hip ratio (WHR). The accepted rates of WC are 94-102 cm for males and 80-88 cm for females. The extent of male WHR should not exceed 0.9,while the female WHR must be under 0.8 (Rodler, 2008). Determination of WC and WHR is simple, they should be measured in centimetres (McArdle et al., 2006).

$$WHR = waist\ (abdomen)\ circumference\ (cm) \div hip\ circumference\ (cm)$$

Nowadays these calculations are rarely used, usage of bioelectric impedance (BIA) is more preferred. The method of BIA can measure the resistance of the body against weak alternating current based on the different conductivities of tissues. Body composition can be measured with this system - fat mass (FM), body water, skeletal muscle mass (SMM) – referring either to the whole body or to its parts. Method of BIA and method of calculation might show differences in the results of body composition (Tóth, 2014). Independently of the measurement method, the greater the degree of obesity is, the higher the risk factor for diseases is (McArdle et al., 2006).

1.2 Muscle tissue

Based on the book by Radák (2019), muscle is a significantly adaptable tissue. Status of the muscle system determines movements and the quality of life. Although muscle tissue is specialised for movement, it has many other important functions like metabolism of sugar and fat or operation of the immune system. There are three different types of it. Smooth muscle

tissue is not under voluntary control, it can produce weak and long lasting contractions and fatigues slowly. Cardiac muscle has smooth and striated parts mixed, it has powerful contractions, cannot be influenced by volition and does not fatigue. Striated muscle performs movements, it has the strongest contraction, but it is very exhaustible (Radák, 2019). Anatomically separable muscles are covered by epimysium. Muscle fibres covered by endomysium make up muscle bundles. Muscle fibres can also be referred to as special muscle cells, with many nuclei situated under the sarcolemma (cell membrane of the muscle cell). The protein fibres responsible for movement are the so called myofibrils, which consist of repeating units, sarcomeres. Sarcomere is the functional unit of a striated muscle fibre, in which there are thin and thick filaments. Sarcomeres are separated by plate Z. The thin filaments (actin, tropomyosin, troponin complex) connect at plate Z, in an area called line I. Zone H is located in the middle of the sarcomere, where the thin filaments do not reach into, if the sarcomere is relaxed. Line A is the joint zone of the thin and thick (myosin) filaments (Pavlik, 2019). Myosin filaments surrounded by six thin filaments make up the middle part of the sarcomere. In case of contraction the areas of line I and zone H decrease, while in stretching these areas increase. During contraction thin filaments slide between thick ones, giving the name ‘sliding filament theory' (*Figure 2*) (Radák, 2019).

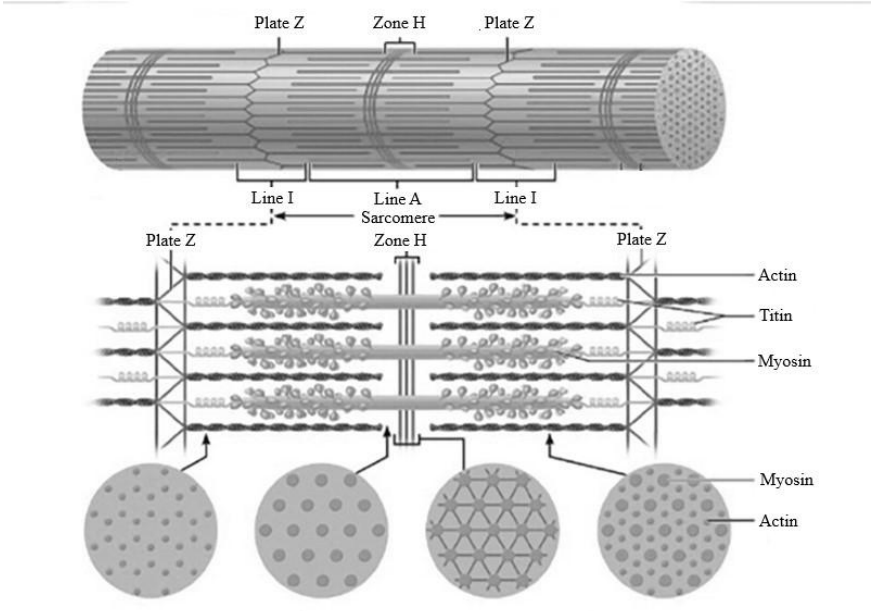


Figure 2: Structure of sarcomere
(http://www.naturalstrength.hu/architecture.html)

During a stimulus Ca ions are released from the sarcoplasmic reticulum and by connecting to troponin C actomyosin complex can be formed (muscle contraction). Both binding of myosin to actin and its detachment from it need energy (Pavlik, 2019). Human

body can produce adenosine triphosphate (ATP) either from creatine phosphate (CP) or from carbohydrates, fats, and proteins during different catabolic processes. Energy recovery is possible by the anaerobic alactic way, when CP and adenosine diphosphate (ADP) react to produce ATP and creatine or two molecules of ADP yield ATP and adenosine monophosphate (AMP). The anaerobic lactic way of energy recovery can be observed in the cytoplasm if carbohydrates and proteins are broken down without O_2. In oxygen deficient conditions from glucose via glycolysis and from deaminated amino acids pyruvic acid can be formed, which is then transformed to lactic acid. Lactic acid is transported in bloodstream to liver where its decomposition to recyclable compounds occurs. The aerobic energy recovery is associated with mitochondria, where no lactic acid is formed. Acetyl coenzyme A (acyl-CoA) is produced from pyruvic acid resulting from carbohydrates and proteins, besides from glycerol and fatty acids of fats after beta oxidation. Next step of energy recovery is citric acid cycle, while the last one is terminal oxidation. In these processes CO_2, H_2O and ATP are produced. Hydrogen atoms provided by different compounds are transported by nicotinamide adenine dinucleotide + (NAD^+) and flavin adenine dinucleotide + (FAD^+). In case of an anaerobic process, hydrogen atoms are transported to lactic acid, while in aerobic conditions to terminal oxidation (*Figure 3*) (Szőts, 2018).

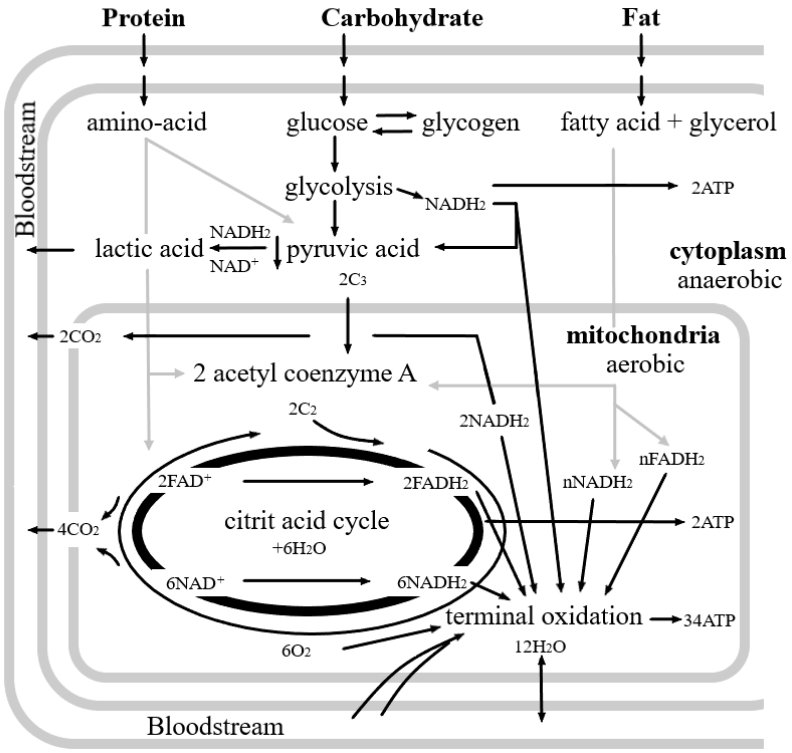


Figure 3: The energy recovery processes
(Szőts, 2018)

Many protein molecules are bound to the sarcolemma, which are receptor, transport, structure proteins and enzymes. One of the most important functions of the cell membrane is the transport process, which can be passive or active. Titin is the largest protein in the muscle, lack of which causes atrophy. Nebulin is another huge protein, which helps elasticity of the muscle. Calmodulin has small molecular mass and regulates the processes of Ca regime. Dystrophin has structural importance (similar to actin alpha and beta) the absence of which causes atrophy. Nervous nitrogen oxide synthase (nNOS) is connected to dystrophin, so it is an important regulator by producing nitrogen monoxide for processes of the muscle system like regereration of muscle injuries and muscle hypertrophy (Radák, 2019).

1.2.1 microRNA

The functions of deoxyribonucleic acids (DNA), ribonucleic acids (RNA), messenger RNA (mRNA) are well known in genetics, but the role of microRNAs (miRNAs) is less evident. miRNAs are short non-coding RNAs, which render the translation of mRNA impossible by posttranscriptional processes. They have a role in muscle regeneration, in metabolic processes, in immune functions and in development of inflammatory diseases (Boehler et al., 2017). Micro RNA-7 (miR-7) is a typical miRNA, which influences wound healing, fibroblast differentiation (Midgley et al., 2016), chronic inflammation, and respiratory diseases (Akbas et al., 2012).

1.2.2 Forkhead family

Forkhead box protein O (FOXO) is a transcription protein belonging to the Forkhead family of transcription factors (in humans FOXO1, 3, 4, 6), which can help transfer the information from DNA to mRNA (Tzivion et al., 2011). FOXO1 protein has a role in gluconeogenesis and glycogenolysis by signalling to insulin and also in adipogenesis of preadipocytes (Nakae et al., 2003; Puigserver et al., 2003).

1.2.3 Sirtuins

The human body has 7 silent mating type information regulation 2 homolog (sirtuin) proteins, which are NAD^+ dependent deacetylase transcriptional factors. These enzymes regulate the antioxidant activity of the cell, the mitochondrial energy homeostasis (Vargas-Ortiz et al., 2019), and remove the connected acetyl group from the histone protein, so the

DNA is not able to unwind, this way making transcription impossible (Radák, 2019). Sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3) activate the antioxidant function of mitochondria, the ATP production with the regulation of oxidative capacity of mitochondria and the biogenesis (Vargas-Ortiz et al., 2019).

1.2.4 PGC1a

Mitochondrial DNA (mtDNA) bears the genetic code of a protein complex found in the electron transport system of terminal oxidation. Other mitochondrial proteins are encoded in the DNA of the nucleus and get into the mitochondria via transport processes. Complexes found in the membrane of the mitochondrion are responsible for the reduction of O_2 to water and for the formation of ATP, which is the energy storing molecule used by all types of cells (Radák, 2019). The protein coded by the gene of PPARGC1a is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1a) (Mulder, 2017), which is the main regulator of the mitochondrial biogenesis. PGC1a is a transcriptional coactivator, which regulates genes influencing energy metabolism and plays part in development of metabolic diseases. This protein is activated by endurance trainings, it affects the formation of slow-twitch muscle fibres (Liu and Lin, 2011). It is also integrator of the external cell marks against reactive oxygen made in oxidative stress by activating antioxidant enzymes like superoxide dismutase (SOD) 2 (Li and Susztak, 2018). The functions of PGC1a are influenced by SIRT1 (Rodgers et al., 2005).

1.2.5 Superoxide dismutase

The most important function of SOD enzyme is to make hydrogen peroxide from reactive oxygen (ROS), the superoxide anion (which is created by metabolic processes) (Mandl, 2002). ROSs are responsible for many diseases (Borgstahl and Oberley-Deegan, 2018), because they have high activity and their unpaired electrons can connect with other free unpaired electrons thus can damage the biochemical functions of the cell membrane, the elements of the electron transport chain and DNA (Flynn and Melov, 2013; Mandl, 2002). SODs have 3 forms in humans: Cu/ZnSOD (SOD1) in cell plasma, MnSOD (SOD2) in mitochondria and ECSOD (SOD3) in extracellular space (Borgstahl and Oberley-Deegan, 2018). Motor nerve problems (Flynn and Melov, 2013) and cancer can be formed without SOD2 (Borgstahl and Oberley-Deegan, 2018). During enzymatic antioxidation water and oxygen are formed from hydrogen peroxide by peroxidase and catalase enzymes (Mandl, 2002).

1.2.6 Cytochrome proteins

Cytochrome proteins are connected to the membrane of the mitochondrion and take part in metabolic regulation (Kocha et al., 2015). Cytochrome C oxidase (COX) catalyses reduction of oxygen to water on the inner membrane of mitochondria, by helping the electron transport from reduced cytochrome C to molecular oxygen in the membrane and by taking the protons to the outside of the inner membrane to form a proton gradient, which helps the synthesis of ATP. The largest COX enzyme is cytochrome C oxidase subunit 4 (COX4), which also helps the transfer of electrons from hydrogen to molecular oxygen (Kocha et al., 2015; Timon-Gomez et al., 2018).

1.2.7 Mitochondrial Ca uniporters

Mitochondrial Ca uniporters (MCU) are transmembrane proteins, which pull in Ca ions needed for physiological processes from the cell plasma into the mitochondrion (Szanda, 2011). In striated and cardiac muscle tissue a large number of mitochondria is found, which are situated near myofibrils, the major consumers of ATP. In the matrix of the mitochondrion enzymes are located, necessary for the citric acid cycle. Mitochondria are essential for energy releasing processes and production of ATP. Quantity of mitochondria in the SMM can be significantly increased by systematic workouts (Radák, 2019).

1.2.8 Insulin-like growth factor 1

Insulin-like growth factor 1 hormone (IGF1) is molecularly similar to insulin, which affects development in young age, but acts anabolically in older age by stimulating proliferation of satellite cells. It also helps growth and regeneration of muscles (Forcina et al., 2019).

1.2.9 Mechano growth factor

Mechano growth factor (MGF) is a variation of IGF1, which influences development and muscle regeneration (Matheny et al., 2010).

1.2.10 Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a signal protein stimulating blood vessel formation, that can be increased by physical activity (Gianni-Barrera et al., 2018; Silva et al., 2012) .

1.3 Types and contractions of muscles

Red coloured slow-twitch muscle fibres are used continuously, while white coloured fast-twitch muscle fibres are used only occasionally. Type of the muscle fibre is determined by usage and innervation. Muscle fibres of the human organism contain slow-twitch and fast-twitch fibres, too. Alpha motor neurons and the innervated muscle fibres are called motor units. A single motor neuron can activate different quantities of muscle fibres. Motor neurons leave the spinal cord to innervate muscles. Motor units can differ significantly in size and in stimulus threshold. Large motor units have higher stimulus threshold and innervate fast-twitch muscle fibres, while small motor units have lower stimulus threshold and innervate slow-twitch muscle fibres. Motor units can vary in their physiological, biochemical, histochemical, and genetic characteristics (Radák, 2019). From a physiological point of view fast fatigable, fast fatigue resistant, fast intermediate, and slow fibres can be identified. Based on their biochemical characteristics muscle fibres with fast glycolytic metabolism (type IIb), with fast oxidative glycolytic metabolism (type IIa), and with slow oxidative metabolism (type I) can be differentiated (Pavlik, 2019). One of the basic laws of evolution is being economical, which means economical fibre function in muscles. Red colour is provided by the high iron content, which is mainly the result of the great number of mitochondria and the presence of myoglobin. The most economical fibres are the slow ones with excellent oxygen uptake, oxydative enzyme activity, and high number of mitochondria. Due to low stimulus threshold red fibres start working immediately at the beginning of contraction. Fast fibres are uneconomical and produce a lot of lactic acid. White fibres with high stimulus threshold can only be activated by high intensity stimuli (*Table 1)* (Radák, 2019).

Characteristics	Fast-twitch fibres	Slow-twitch fibres
Time to maximum effort	50-80 msec	100-200 msec
Quantity of myoglobin and mitochondria	low	high
Typical method of ATP production	anaerobic	aerobic
Quantity of glycogen	high	low
Vascular network	sparse	rich
Fatigue	tired quickly	tired slowly
Size of nerve cell	large	small
Threshold of stimulus	high	low
Magnitude of effort	large	small

Table 1: Differences between the fast-twitch and slow-twitch fibres *(Radák, 2019)*

Methods of sport workouts are mostly mentioned only when people talk about regular trainings, although methods of recreational workouts are also needed for preservation of health, regeneration and physical-psychical refreshment. Sport workout is the work of professional athlete, which has financial obligation and needs renunciation. During sport workouts the highest possible physical performance is required without risking damage to health. Recreational workout is part of the active relaxation with regular movements for health (Fritz, 2009). More differences between the sport and recreational workouts are shown in Table 2.

Features	Sport workout	Recreational workout
Age group	age of 6 - 35 years	age of 6 - 80/90 years
Weekly training numbers	3 - 22 times	3 - 4 times
Training intensity	light - very heavy	light - heavy
Workout duration	20 min - 4 h	30 min - 40 min
Percentage of HRmax	65 - 100%	65 - 85%
Characteristic of activity	regular, continuous	regular, continuous

Table 2: Differences between sport and recreational workouts
(HRmax: maximal heart rate) (Fritz, 2009)

Muscle contraction has three types. In concentric contraction the strength of muscle work is enough to overcome external resistance, so the muscle shortens. This contraction requires the largest amount of energy, but the maximum strength is the smallest. During isometric contraction the length of muscle does not change, because the strength of muscle and the external resistance are equal. According to mechanics without displacement there is no work, but due to effort the energy requirement is significant. In case of excentrical contraction external resistance is higher than muscle strength, so the muscle extends. Quite interesting, that the energy requirement of this type of contraction is the smallest, while the maximal strength is the greatest (Pavlik, 2019; Radák, 2019).

The designation of training load is based on two physiological parameters, heart rate (HR) and vital capacity (VO_2), which increase during physical activity. The intensity of the workout is determined by the percentage of maximal heart rate (HRmax) or the percentage of maximal vital capacity (VO_2max). (*Table 3*) HRmax can be calculated with the next simple formula (Wilmore and Costill, 2004):

$$HRmax = 220 - age$$

(HRmax: maximal heart rate, age in years)

For people between the age of 21-51 VO_2max can be estimated with this formula (Radák, 2019):

$$VO_2max = HRmax / HRrest \times 15.3$$

(VO_2max: maximal vital capacity, *HRmax: maximal heart rate, HRrest: rest heart rate)*

VO_2max can be estimated for everyone with the Cooper Running Test (12 minutes constant running) (Radák, 2019):

$$VO_2max = (ran\ meters - 504.9) / 44.73$$

The exact determination of the HRmax and VO_2max can be measured under laboratory conditions.

Relative intensity			
HRmax	**VO_2max or HRmax reserve**	**Rating of perceived exertion**	**Classification of intensity**
< 35%	< 30%	< 9	very light
35 - 59%	30 - 49%	10 - 11	light
60 - 79%	50 - 74%	12 - 13	moderate
80 - 89%	75 - 84%	14 - 16	heavy
≥ 90%	≥ 85%	≥ 16	very heavy

Table 3: Connection between intensity, HRmax and VO_2max
(HRmax: maximal heart rate, VO_2max: maximal vital capacity) (Wilmore and Costill, 2004)

During training periods different energy gaining processes are observed, which depend on the intensity and duration of exercise. ATP is the main energy source for muscle work. ATP decomposes to ADP, to AMP and to inorganic phosphate (P_i) during energy utilization. Energy consumption can happen with oxygen (aerobic) or without oxygen (anaerobic); the method depends on the intensity and extent of workout (*Figure 4*) (Radák, 2019).

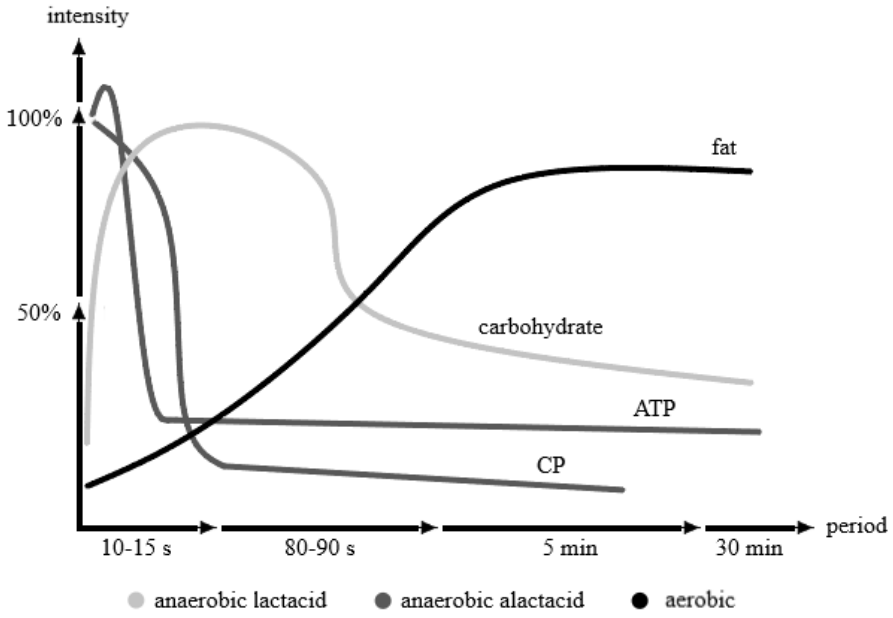


Figure 4: The processes of energy gaining
(ATP: adenosine triphosphate, CP: creatine phosphate) (Radák, 2019)

1.4 Measurements of movements

Strength is the ability of muscle to work against resistance. The strength exerted by the muscle at the point of muscle attachment is much greater than that required to overcome resistance. Properly the anatomy of joints and muscles, the decrease of joint angle changes the length of leverage. This alteration changes the extent of strength, which is needed to displacement. Extensor muscles of knee can have the highest effort at kneeangle of 90-130° (Pavlik, 2019). The muscle-tendon system consists of several elements: contractile component (muscle fibres), serially connected elastic component (tendon) and parallelly connected elastic component (connective tissue elements). Work of the contractile component results displacement, however mechanical energy can be stored in the elastic components (for example: prestressed positions), which can be regained during contraction (Radák, 2019). Agility is a capacity to perform movements in the shortest possible time, which depends on muscle strength and movement coordination. The improvement of nerve regulation, which includes technical ability, innate innervation, fine motor coordination, is essential for advanced coordination (Pavlik, 2019). The motor units join a movement in a specific order. This is a very important neuro-mechanical quality of the muscle, the name of which is intramuscular coordination (synchronisation of motor units). If more motor units join the

movement at the same time, then the motion will be stronger and faster. Intermuscular coordination is a synchronised operation of muscles. This coordination is determinative in the move, which needs different muscle groups. The technical quality of movement depends on the specific joining order of muscles (for example: when agonistic muscles start working, antagonistic muscles get relaxed). The output of movements is regulated by intramuscular and intermuscular coordinations (Váczi, 2015).

For the measurement of rapid strength and reactive strength of the lower limb jump tests are often used. Several types of vertical jumps from the floor, like squat jump (SJ) and counter movement jump (CMJ) are determined. SJ starts from 90° kneeangle and measures the concentric strength of knee extensor muscles (concentric contraction cames after isometric contraction). CMJ starts from stand and measures the force-ability of elongation-contraction cycle of knee extensor muscles (concentric contraction cames after excentric contraction). Differences between the characteristics of SJ and CMJ can give information about the reactive strength of the lower limb (Petridis, 2015):

$$RSI = CMJ - SJ$$

(RSI: reactive strength index; CMJ: height of counter movement jump in cm; SJ: height of squat jump in cm).

Human movements are based on the quality of nerve-muscle functions, but researchers applied methods of physics to characterise them. Barton wrote in his book in 1983 that physical laws and physiological events are examined by biomechanics. Two fields of mechanics, namely dynamics and kinematics, help analyse movements. Analysts need basic quantities of the SI system (International system of Units), like length (symbol: l, unit: m), mass (symbol: m, unit: kg) and time (symbol: t, unit: s) to determine the characteristics of movements. For monitoring movements a reference system is used, which can compare position and place. Space has three dimensions and its two dimensional form is the rectangular coordinate system. Investigation of movements of objects in space can be realized with a point or points, which are typical for the shape of the object (like: point-like object, object part, bigger object) (Barton, 1993). A characteristic point of an object or a body is the centre of gravity (CG), which could be analysed from different aspects: displacement, velocity ($v=\Delta s/\Delta t$) and acceleration ($a=\Delta v/\Delta t$). The segments of body have their own CGs (segments are delimited by the rotation axes of articulations), which are located between the two epiphysises by percentages. The CG of the body can be determined in space or in a

coordinate system, based on the location of CGs of the segments. Human movements might be appropriately characterised by the moves of the body CG (Szablics, 2015). For instance when the CG is sinking during the swinging move of CMJ, the activity of muscle is low. Compared to this, before the take-off motion of CMJ, the activity level of muscles becomes high and starts lifting the CG (Bobbert and van Soest, 2001; Finni et al., 2000).

There are lots of available instruments and methods for biomechanical measurements, which can help the accurate analysis of vertical jump (Petridis, 2015):

- Sargent Jump Test: Firstly the height of hit, while standing on the floor, shall be measured on a scale, which is fixed to the wall, then the height of the hit in a vertical jump. The difference of the values gives the rise of CG.
- Abalakov jump test: One end of a measuring tape is fixed to the Abalakov meter (which is on the floor), while the other end of it is fixed to a belt. When the participant is performing a vertical jump, the measuring tape is being pulled out of the Abalakov meter, so after landing the pulled out measuring tape shows the rise of CG.
- Contact mat: the device calculates the rise of CG from the time of fly (from take-off to landing), with the Bosco-formula:

$$rise\ of\ CG = time\ of\ fly^2 \times 1.226$$

- Force platform: the device calculates the rise of CG from the quantity of force (what the participant exerts on the floor) and the time of fly.

Video analysis is another possible method to observe the characteristics of vertical jump. It can measure the rise of CG, the flying time, the joints angle, the position, velocity and acceleration of CG and body parts during moves. For the video analysis one only needs a good quality camera, which could make a video recording by precisely set conditions. The video camera should be able to record a movement with high frame rate, short shutter speed, small angle of view and brightness magnification. For the precise analysis of high speed movements high frame rate is needed, the unit of which is the frame per seconds (fps). By applying short exposition time the frames of even fast movements will not be blurred. The video camera should be placed at a suitable distance from the movements, so as to avoid the distortion of the lens sides. To achieve this, an appopriate lens is necessary, which can take sharp shots at a small angle of view with zoom. Light is very important for the recording,

which can be natural coming from the sun or artificial from a non-vibrating light source. Brightness could be enhanced by the setting of the blende or by the camera function of ISO (unit of photosensitivity). The camera should be positioned on a tripod at the height of the CG of the recorded person. Coordinate frames (which make a quadrat or a cube and their plane is perpendicular to the plane of the lens) and a fix point are needed for the recording, as they can provide the benchmark. Marker points used on the segments of the moving person (such as: on joints, bone epiphyses, muscle adhesion and origin), can make the analysis later easier. One camera shall be used for 2 dimensional analysis, while two or more cameras are necessary for 3 dimensional analysis. In case of using more cameras, it is important to record the angle of the axes of the lenses, and a fix point and a set moment should be applied (which are in the viewing angles of the cameras), because these help to synchronise the records (Szablics, 2015).

1.5 Aging and muscles

Many of the aging theories deal with the functions of cells and muscles. The apoptosis theory states that during the continuous renewal process of cells proteins and mitochondria with deficient structures are created, which due to the programmed cell death (apoptosis) are not able to inherit the false information. In aging these prevention mechanisms are not completely fulfilled, so the risk factor of cancer is increased (Radák, 2019). Foundations of the aging process are summarized in the free radical theory. Free radicals have one or more unpaired electrons, which search for their opposite spin pair with high reactivity. The human body needs these molecules for maintaining immunity and energy recovery, but accumulation of free radicals can damage the structure of the cell membrane, proteins, enzymes and DNA. At a young age producing and neutralising processes are equal. At an older age cells produce more free radicals, because free radicals producing enzymes have higher activity, the enzymatic system of antioxidant protection decreases and the level of restorative enzymes of oxidative injuries is lower (Radák, 2019; Toldy, 2009). One of the aging theories related to the genetic code is the sirtuin theory. SIRT proteins protect the DNA against injuries that can cause apoptosis, but activation of genes becomes more difficult. Adaptability decreases with age, but activation of SIRT proteins can increase life span. SIRT1 has effects on FOXO proteins, PGC1a and other factors of transcription, which influence the expression and activation of many antioxidant level regulators and oxidative injury repair enzymes (Radák, 2019). The mitochondrial theory focuses on mtDNA. The main target of ROS is the mtDNA. Injuries of the mitochondrial genome always affect important genes, however, damage of the

nuclear genome is the most serious. Many of the mistakes made by injuries and damage are repaired by correcting mechanisms, but the activity of these processes decrease with age, thus the destruction of genome becomes faster (Toldy, 2009). The theory of constant metabolic potential has proved that high metabolism results in shorter life span. Calorie restriction decreases the level of IGF1, which causes higher activity of antioxidant enzymes thus the maximum lifetime could be longer. Constant high metabolism, causing shorter life span, must not be confused with periodical high metabolism (during sport) affecting health in a positive way (Radák, 2019).

40% of the human body mass is skeletal muscle, which includes 60% of the total protein content. It is necessary for movements and body posture and also important for metabolic functions like storage of energy in form of glycogen. Effect of aging reduces significantly muscle mass and function, which is in connection with well-being and mortality (McLeod et al., 2016). Systematic exercise modifies the properties of muscles, for instance cross section (Narici et al., 2004), number of fibres (Aagaard et al., 2010; Power et al., 2016), strength (Englund et al., 2017), endurance capacity (Radak et al., 2002), mitochondrial function (Hood et al., 2016) and insulin sensitivity (Sogaard et al., 2018).

Regular physical workout could be a natural method to reduce sarcopenia. The difference between sarcopenia (muscle mass and muscle strength dwindle) and dynapenia (muscle strength lessens) must be distinguished (Clark and Manini, 2008; JafariNasabian et al., 2017). Skeletal muscle function of elderly people is deteriorating, which causes a loss in muscle mass; a reduction in the ability of muscle fibres to process triglycerides; an increase of lipids on cell membranes and infiltration of fat into the muscles tissue (Lang et al., 2010). On average 30 years old women and men lose 25% of their muscle strength by the age of 70 and it is doubled by the age of 80 (Szentesi et al., 2019). The progressive decline in the number of muscle fibres starts at the age of 50, and at the age of 80 half of the fibres are lost (Faulkner et al., 2007). Effects of aging change the miRNA profile of skeletal muscle (McCormick and Goljanek-Whysall, 2017; Raz et al., 2018), and decreases the dynamics of mitochondrial function (Drake and Yan, 2017; Kim et al., 2017; Koltai et al., 2012). Physical activity is associated with lots of biochemical and functional changes in the epigenetic of skeletal muscle, such as in the miRNA profile (Koltai et al., 2010; Moreira et al., 2017; Ntanasis-Stathopoulos et al., 2013; Silva et al., 2017). Just to name one, the effects of short and long term exercises change the number of miRNAs (Nielsen et al., 2010; Russell et al., 2013). Quantity of miRNA influences regeneration of skeletal muscles, mitochondrial biogenesis and

gene expression. Endurance physical activity increases the miRNA level of muscle that target transcription in inflammation, metabolism, and muscle atrophy. These mechanisms are discernible both in healthy people and in patients with polymyositis or dermatomyositis (Boehler et al., 2017). A study from 2010 revealed that hypertrophic stimulation changes miRNA levels. It was observed that functional mechanical overloading by synergistic muscle ablation increased modification in miRNA level, which controls hypertrophy and atrophy (Koltai et al., 2010). This is why systematic exercise could reverse detrimental effects of aging in the mitochondrial function and the miRNA profile. Previous studies have proved connection between less physical activity and aging (Ingram, 2000); connection between muscle wasting and decreased oxidative capacity (Degens and Alway, 2006).

2 Aims

One of the targets of my research was to explore the beneficial effects of medium level intensive training on the body composition and on the dynamics of movements. I was concerned about the differences between the improvements of the younger and the elder groups after systematic physical activity. I also wanted to know whether there was any connection between the changes of body composition and the characteristics of daily movements after five months of training.

My further aim was to gain insight into the biochemical nature of muscles of elderly people with different lifestyles and to find out what could influence their aging, health and quality of life. I also wanted to detect the differences between the mitochondrial functions and miRNA levels of master athletes over sixty-five and of their inactive contemporaries.

3 Materials and methods:

3.1 Non-invasive follow-up research

3.1.1 Participants

Ninety-two physically inactive participants (56 females and 36 males) were chosen for this study; they were randomly selected untrained volunteers. The participants were 31.66 ± 19.27 years old. They were divided into five groups based on their ages (Filatova et al., 2014): G1: second childhood (n = 14; females: 8-11 and males: 8-12 years old; mean age 11.5 ± 0.14 years, average BMI 25.12 ± 0.88), G2: adolescence (n = 20; females: 12-15 and males: 13-16 years old; mean age 13.1 ± 0.25 years, average BMI 27.73 ± 2.05), G3: mature age I (n = 22; females: 21-35 and males: 22-35 years old; mean age 26.55 ± 1.09 years, average BMI 26.69 ± 1.32), G4: mature age II (n = 23; females: 36-55 and males: 36-60 years old; mean age 47.52 ± 1.48 years, average BMI 26.91 ± 0.92), and G5: ageing (n = 13; females: 56-74 and males: 61-74 years old; mean age 63.46 ± 1.23 years, average BMI 28.43 ± 1.38). The human examinations were carried out under the licence of the Regional Research Ethics and Science Committee of the University of Szeged (WHO 2658).

3.1.2 Exercise programme

The training programme was based on earlier studies (Araya et al., 2012; Davidson et al., 2009; Haskell et al., 2007; Lee et al., 2005; Ross and Rissanen, 1994) and included aerobics, spinning, table tennis and swimming. Recreational training periods of 60 min were used, repeated three times a week for five months at 80.36% ± 0.51% of the HRmax. During exercise the heart rate was constantly controlled with polar heart rate monitors (Polar Team System, Finland) (Ko and Choi, 2013). Examinations on the body composition and the dynamics of movements were performed at the beginning and at the end of the training sessions, always under the same circumstances.

3.1.3 Measurement of body composition

Body composition was assessed using data obtained by bioelectrical impedance analysis (BIA; Biospace InBody230® Body Composition Analyzer, Seoul, Korea). Changes in BW, FM, SMM, BMI, BF%, and WHR were observed in the study (Ko and Choi, 2013). The fat mass – body weight ratio (FM/BW) and skeletal muscle mass – body weight ratio (SMM/BW) were calculated from these body composition data. Losses in BW with constant SMM indicate an increase in the ratio of SMM/BW (Lee et al., 2005).

3.1.4 Measurement of dynamics of movements

In this investigation simple movements (like crouch and CMJ), were used to simulate daily movements (like sitting down or standing up from a chair, and climbing stairs). The measurement is not influenced by anthropometric parameters (height, limb length) in crouch and CMJ and that was important in designing the methods of research. These movements are appropriate to measure the differences between the characteristics of dynamics of the CG before and after the recreational training programme.

The APAS 3D system was used for movement analysis (Ariel Dynamics Inc., Ariel Performance Analysis System, version 12.3.0.2®, USA). The measurements were taken in two dimensions with a 2 × 2 m reference frame and four reference points. Ten marker points were used on joints such as ankles, knees, hips, shoulders, elbows and 1 marker point was used on the forehead. CG was calculated by the software based on the reference and marker points. The participants performed two different simple movements, crouch and CMJ, to test which can describe better the changes in the characteristics of the CG's dynamics after the training programme. These movements were recorded at a speed of 30 fps with a camera (Casio EX-F1®, Tokyo, Japan). The participants were instructed to perform the moves as quickly as they could and in the widest possible movement range. The changes in position, maximal velocity and maximal acceleration were analysed regarding the CG of the moves.

3.1.5 Statistical analysis

Data are expressed as mean ± SEM (standard error of mean). The percentages of delta (Δ%) within the first and the last examinations are highlighted for the statistical analysis. Initially, one-sample t-test was used to determine the significance of the changes separately in the groups. Later, analysis of variance (ANOVA) was used with the difference of delta (ΔD) of the groups to detect significant differences between the changes in the parameters of the groups. The possible connection in the body composition and the dynamics of movements were investigated with correlation. The significance level was $p \leq 0.05$ for all comparisons.

3.2 Invasive cross-sectional research

3.2.1 Participants

The perfect participants to study the effect of aging (per se on muscle, not confounded by disuse) are athletes over 35 years (Rittweger et al., 2004). We recruited 26 master athletes (10 females and 16 males) at the European Veterans Athletics Championships in 2010 (Nyíregyháza, Hungary). Control participants (n=18, 13 females, 5 males) were also recruited.

The participants provided written informed consent before inclusion. For this study we have selected 10 master athletes 65 ± 5 years and 13 sedentary subjects 64.67 ± 2.08 years old. The master athletes reported that they all had been training for more than sixty years, while control subjects were sedentary. The investigation was approved by the local ethics committee (File number: 10826-0/2010-1018EKU, research permission number: 15/ 07/2010-24/07/2010) and performed in compliance with the Declaration of Helsinki.

3.2.2 Muscle biopsy

Muscle biopsies were obtained from the vastus lateralis using a conchotome or needle biopsy technique as described earlier (Radak et al., 1999). Samples were frozen in liquid nitrogen and stored at −80 °C until biochemical analysis.

3.2.3 RNA isolation

Total RNA, including miRNA, was isolated from muscle biopsy samples by miRNeasy Mini Kit (Qiagen #217004) according to the instructions of the manufacturer.

3.2.4 miRNA microarray analysis

miRNA expression analysis was performed on 4 samples from master athletes (68.75 ± 8.54 years old) and on 4 samples of sedentary subjects (70.25 ± 11.3 years old) gained by skeletal muscle biopsy samples with Agilent Human miRNA Microarray Release 14.0 8×15K resolution array (Agilent Technologies, USA), that distinguishes 887 human miRNAs. The microarray was performed according to the instructions by the manufacturer (Agilent miRNA microarray protocol 2.4). Hundred ng of total RNA were dephosphorylated and marked with cytidine-5'-phosphate-3'-(6-aminohexyl) phosphate (Cyanine-3-pCp) dye using the miRNA Complete Labeling and Hyb Kit (Agilent Technologies, USA). Purification of the marked RNA was performed by Micro Bio-Spin P-6 column (Bio-Rad Laboratories; Hercules, CA, USA) and then hybridised onto the Human miRNA Microarray Release 14.0 microarray slides. After hybridization, slides were washed at room temperature and scanned using an Agilent DNA microarray scanner. Raw data were extracted with the Agilent Feature Extraction Software 11.0.

3.2.5 Detection of mature miRNAs in skeletal muscle

The TaqMan miRNA reverse transcriptase kit and TaqMan miRNA assays (Applied Biosystems, Foster City, CA) were used to quantify mature miRNA expression levels. Each target miRNA was quantified according to the manufacturer's protocol with minor

modifications. Briefly, reverse transcriptase reactions were performed with miRNAspecific reverse transcriptase primers and 5 ng of purified total RNA for 30 min at 16 °C, 30 min at 42 °C, and finally 5 min at 85 °C to heatinactivate the reverse transcriptase. All volumes suggested in the manufacturer's protocol were halved, as previously reported (Gallagher et al., 2010). Real time polymerase chain reaction (RT-PCR) for each miRNA (10 µl total volumes) were performed in triplicate, and each 10-µl reaction mixture included 2.4 µl of 10×-diluted reverse transcriptase product. Reactions were run on a PRISM 7900HT Fast Real-Time PCR System (Applied Biosystems) at 95 °C for 10 min, followed by 40 cycles at 95 °C for 15 s and 60 °C for 1 min. Twofold dilution series were performed for all target miRNAs to verify the linearity of the assay. To account for possible differences in the amount of starting RNA, all samples were normalised to microRNA-423 (miR-423). All reactions were run singleplex and quantified using the cycle threshold ($\Delta\Delta C_t$) method (Livak and Schmittgen, 2001).

3.2.6 mRNA expression levels

3.2.6.1 Complementary DNA synthesis

Complementary DNA (cDNA) was synthesised using a Tetro cDNA Synthesis kit (Bioline #BIO-65026 Luckenwalde, Germany) in accordance with the manufacturer's instructions. Briefly, the reaction conditions were as follows: 1 µg of RNA, 1 µl of random primers, 1 µl of 10mM deoxynucleotid (dNTP), 1 µl of ribonuclease (RNase) inhibitor, and 0.25 µl of 200 U/µl reverse transcriptase in a final volume of 20 µl. The solution was incubated for 10 min at 25 °C for primer annealing, followed by 42 °C for 60 min for primer elongation, and followed by 80 °C for 5 min termination. cDNA samples were stored at −20°C.

3.2.6.2 Real time quantitative RT-PCR (qRT-PCR) reaction.

Based on the principle of the SybrGreen detection method, EvaGreen® dye (Biotium, Hayward, CA, USA) was used to detect polymerase chain reaction (PCR) products. The PCR was performed using a primer pair specific for mRNA of VEGF, SIRT1, FOXO1, MCU, IGF-1, PGC1a and MGF isoforms (for sequences of mRNA genes used in the study see Table 4). PCR amplifications consisted of equal amounts of template DNA, 10 µl of ImmoMix™ complete ready-to-use heat-activated 2× reaction mix (Bioline GmbH, Luckenwalde, Germany), 1 µl of 20x EvaGreen (Biotium, Hayward, CA, USA), 2.5 µl of 10 nmol/L forward and reverse primer (IBAGmbH, Göttingen, Germany) and water to a final volume of 20 µl. Amplifications were performed in a Rotor-Gene 6000 thermal cycler (Corbett Life

Science/Qiagen, London, UK) at 95 °C for 10 min, followed by 40 cycles of 95 °C for 10 s, 60 °C for 20 s and 72 °C for 30 s in triplicates. The validity of the signal was evaluated by melting analysis and agarose gel electrophoresis. Human 28 S ribosomal RNA (rRNA) gene served as an endogenous control gene (*Table 4*).

Reference genes.

H-28S-F	AGCCGATCCATCATCCGCAATG
H-28S-R	CAGCCAAGCTCAGCGCAAC
H-FOXO1-F	AAGAGCGTGCCCTACTTCAA
H-FOXO1-R	CATCCCCTTCTCCAAGATCA
H-IGF1/MGF-F	CGAAGTCTCAGAGAAGGAAAGG
H-IGF1/MGF-R	ACAGGTAACTCGTGCAGAGC
H-IGF1-F	GCTCTTCAGTTCGTGTGTGGA
H-IGF1-R	GCCTCCTTAGATCACAGCTCC
H-MCU-F	CACTGTTGTGCCCTCTGATG
H-MCU-R	ACTCTGTCAATTCCCCGATCC
H-PPARGC1A (PGC-1a)-F	GTGAAGACCAGCCTCTTTGC
H-PPARGC1A (PGC-1a)-R	TCACGTCTCCATCTGTCAGC
H-SIRT1-F	TGCGGGAATCCAAAGGATAATTCAGTGTC
H-SIRT1-R	CTTCATCTTTGTCATACTTCATGGCTCTATG
H-VEGFA-F	AGGAGGAGGGCAGAATCATCA
H-VEGFA-R	CTCGATTGGATGGCAGTAGCT

Table 4: Reference genes

3.2.7 Western blots

Tissue homogenates of the muscle biopsy samples were generated with an Ultra Turrax® (IKA®-Werke) homogeniser using 10 vol of lysis buffer (137mM NaCl, 20mM Tris-HCl, pH 8.0, 2% NP-40, 10% glycerol and protease inhibitors). Five to ten micrograms of protein were electrophoresed on 10-12% v/v polyacrylamide sodium dodecyl sulfonate – page (SDS-PAGE) gels. Proteins were electrotransferred onto polyvinylidene difluoride (PVDF) membranes. The membranes were subsequently blocked in 0.5% bovine serum albumin (BSA), and after blocking incubated with primary antibodies (SIRT3 1:2500 Abcam #ab40006, SOD2 1:2500 Sigma-Aldrich #SAB1406465, COX4 (D-20) 1:2500 Santa Cruz #sc-69359, Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) 1:50000 Sigma-Aldrich #G8795) overnight at 4 °C. After incubation with primary antibodies, membranes were washed in tris-buffered saline-Tween-20 (TBST) and incubated with horseradish peroxidase (HRP) - conjugated secondary antibodies (1:50000, Jackson ImmunoResearch Europe Ltd).

After incubation with secondary antibodies, membranes were repeatedly washed. Membranes were incubated with chemiluminescent substrate (Thermo Scientific, SuperSignal West Pico Chemiluminescent Substrate #34080) and protein bands were visualised on X-ray films. The bands were quantified by ImageJ software, and normalised to GAPDH, which served as an internal control.

3.2.8 Statistical analysis

Data gathered from the miRNA array validation and gene expression experiments were analysed with an unpaired Mann-Whitney U-test, and unpaired, two-tailed Student's t-test or χ_2 test were used for quantitative PCR (qPCR) and Western blot variables, as appropriate. Data are presented as mean ± standard deviation (SD). Significance level was set at $p < 0.05$.

4 Results:

4.1 Non-invasive follow-up research

4.1.1 Changes in body composition

The differences and changes in body composition were examined after participating for 5 months in the study (*Figure 5*).

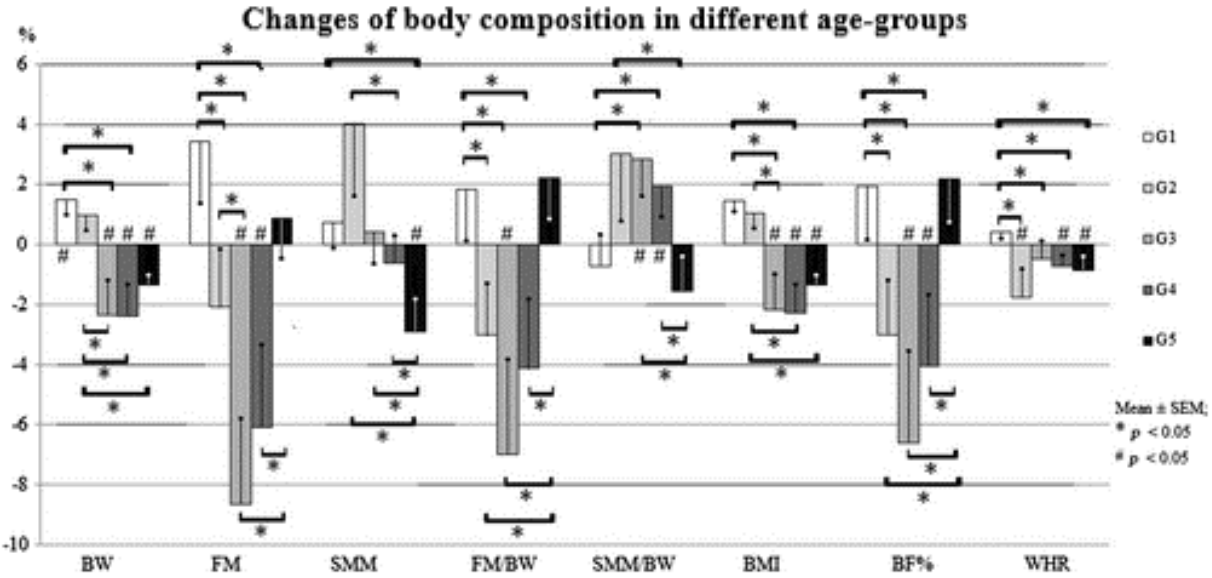


Figure 5: Changes of body composition in different age-groups

*(Values are means ± SEM. G1: second childhood; G2: adolescence; G3: mature age I; G4: mature age II; G5: ageing; BW: body weight; FM: fat mass; SMM: skeletal muscle mass; FM/BW: fat mass–body weight ratio; SMM/BW: muscle mass–body weight ratio; BMI: body mass index; BF%: body fat percentage; WHR: waist–hip ratio. *Significant differences between changes of groups; #Significant changes in groups; $p \leq 0.05$)*

After the training programme, the BW significantly changed in G1 (1.48%± 0.45%), G3 (−2.36%± 1.24%), G4 (−2.37%± 1.03%), and G5 (−1.36%± 0.36%). The FM significantly reduced in G3 (−8.64%± 3.5%) and G4 (−6.08%± 2.88%). Moreover, the SMM has also shown significant decline during the examination in G5 (−2.9% ± 1.02%).The FM/BW showed reduction in G3 (−7.02%± 3.12%), and the SMM/BW upgraded in G3 (2.86%± 1.27%) and G4 (1.96%± 1.03%). The BMI normalised in G3 (−2.16%± 1.23%), G4 (−2.28%± 1.04%), and G5 (−1.33%± 0.37%). The results show that the BF% decreased in G3 (−6.6%± 2.98%) and G4 (−4.05%± 2.32%). The WHR improved in G2 (−1.77%± 0.91%), G4 (−0.71%± 0.35%), and G5 (−0.87%± 0.46%).

The ANOVA revealed differences in the improvements of body composition parameters between the groups (*Figure 5*). The data show significant differences in BW between G1 and G3 (−3.84%), G1 and G4 (−3.86%), G2 and G3 (−3.34%), G2 and G4 (−3.36%), and G2 and G5 (−2.34%). The changes of FM were significantly different between G1 and G2 (−5.51%), G1 and G3 (−12.07%), G1 and G4 (−9.51%), G2 and G3 (−6.57%), G3 and G5 (9.5%), and G4 and G5 (6.94%). There were significant differences in the changes of SMM between G1 and G5 (−3.63%), G2 and G4 (−4.63%), G2 and G5 (−6.93%), G3 and G5 (−3.35%), and G4 and G5 (−2.3%). We detected differences in the changes of FM/BW between G1 and G2 (−4.89%), G1 and G3 (−8.88%), G1 and G4 (−5.97%), G2 and G5 (5.25%), G3 and G5 (9.25%), and G4 and G5 (6.34%). We observed significant differences in changes of SMM/BW between G1 and G3 (3.57%), G1 and G4 (2.67%), G2 and G5 (−4.56%), G3 and G5 (−4.41%), and G4 and G5 (−3.5%). The statistical analysis revealed further remarkable differences in BMI between G1 and G3 (−3.63%), G1 and G4 (−3.75%), G2 and G3 (−3.21%), G2 and G4 (−3.33%), and G2 and G5 (−2.38%). We found significant differences in changes of BF% between G1 and G2 (−4.98%), G1 and G3 (−8.55%), G1 and G4 (−6.01%), G2 and G5 (5.21%), G3 and G5 (8.78%), and G4 and G5 (6.23%). There were significant differences in changes of WHR between G1 and G2 (−2.21%), G1 and G3 (−0.93%), G1 and G4 (−1.14%), and G1 and G5 (−1.31%).

4.1.2 Changes in the dynamics of movements

Figure 6 represents the changes in the dynamics of movements, which demonstrate that the 5-month recreational training programme improved the lifting of the position of the CG in G3 (12.18%± 5.61%), G5 (15.98%± 6.98%), and the sinking of the position of the CG in the G2 (16.8% ± 9.16%), the G3 (40.08% ± 11.43%), G4 (61.29% ± 23.47%), and the G5 (34.73%± 8.74%) during CMJ. The measurement showed significant changes in the velocity of the CG in G2 (−9.97% ± 5.29%), G4 (16.49% ± 6.88%), and G5 (14.69%± 5.37%); however, changes could also be seen in the acceleration of the CG in G3 (313.71% ± 166.38%) and G5 (17.27%± 5.22%) during CMJ.

Changes in the characteristics of CMJ showed significant differences considering the lifting of position between G2 and G3 (15.51%), G2 and G4 (17.45%), and G2 and G5 (19.31%); the sinking of position between G2 and G4 (44.49%) (*Figure 6A*); the velocity of CG between G1 and G4 (20.13%), G1 and G5 (18.32%), G2 and G3 (19.86%), G2 and G4 (26.28%), G2 and G5 (24.47%) (*Figure 6B*); and the acceleration of CG between G2 and G3 (327.3%) G3 and G5 (−330.98%) (*Figure 6C*).

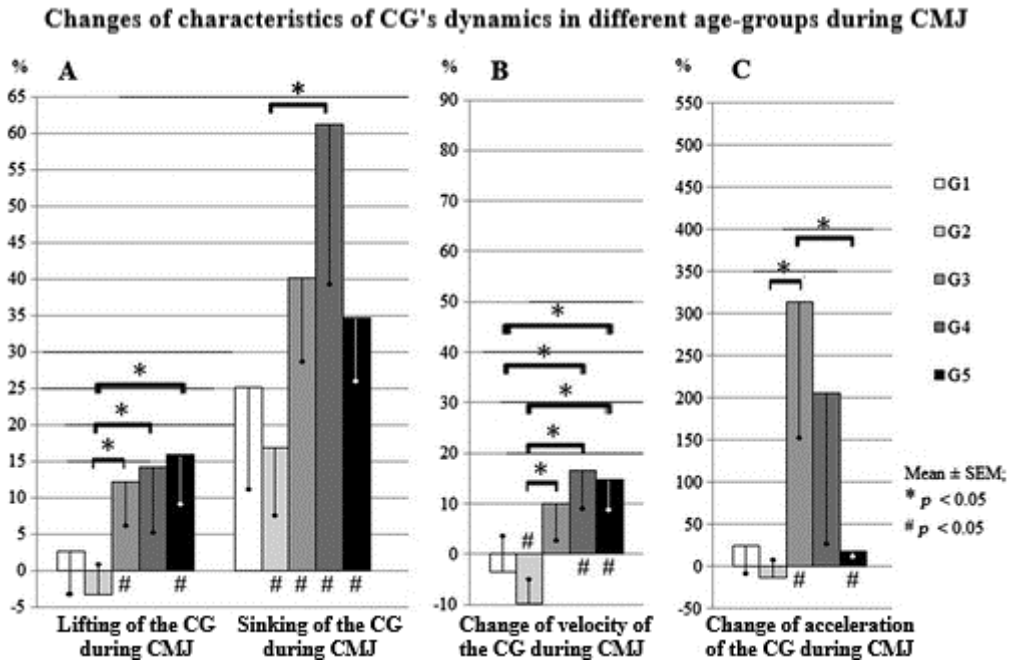


Figure 6: Changes in characteristics of CG's dynamics in different age-groups during CMJ

*(„A" Differences between the groups in lifting and sinking of CG; „B" Differences between the groups in the velocity of CG; „C" Differences between the groups in the acceleration of CG. Values are means ± SEM; CG: center of gravity; G1: second childhood; G2: adolescence; G3: mature age I; G4: mature age II; G5: ageing. *Significant differences between changes of groups; #Significant changes in groups; $p \leq 0.05$)*

Changes in the characteristics of crouch also showed significant differences. The velocity of the CG in G4 (88.68% ± 25.12%) and G5 (48.92%± 10.08%) and the acceleration of the CG in G4 (273.18% ± 123.22%) and G5 (514.93% ± 276.23%) increased during crouching (*Figure 7*).

Furthermore, crouch data showed significant changes between G1 and G4 (30.28%) with regard to the sinking of the CG (*Figure 7A*). The changes in crouch specify significant differences in the velocity between G1 and G4 (85.41%), G1 and G5 (45.66%), G2 and G4 (75.79%), and G3 and G4 (76.19%) (*Figure 7B*). Changes were also observed in the acceleration of CG between G1 and G4 (283.58%), G1 and G5 (525.34%), and G3 and G4 (234.74%) (*Figure 7C*).

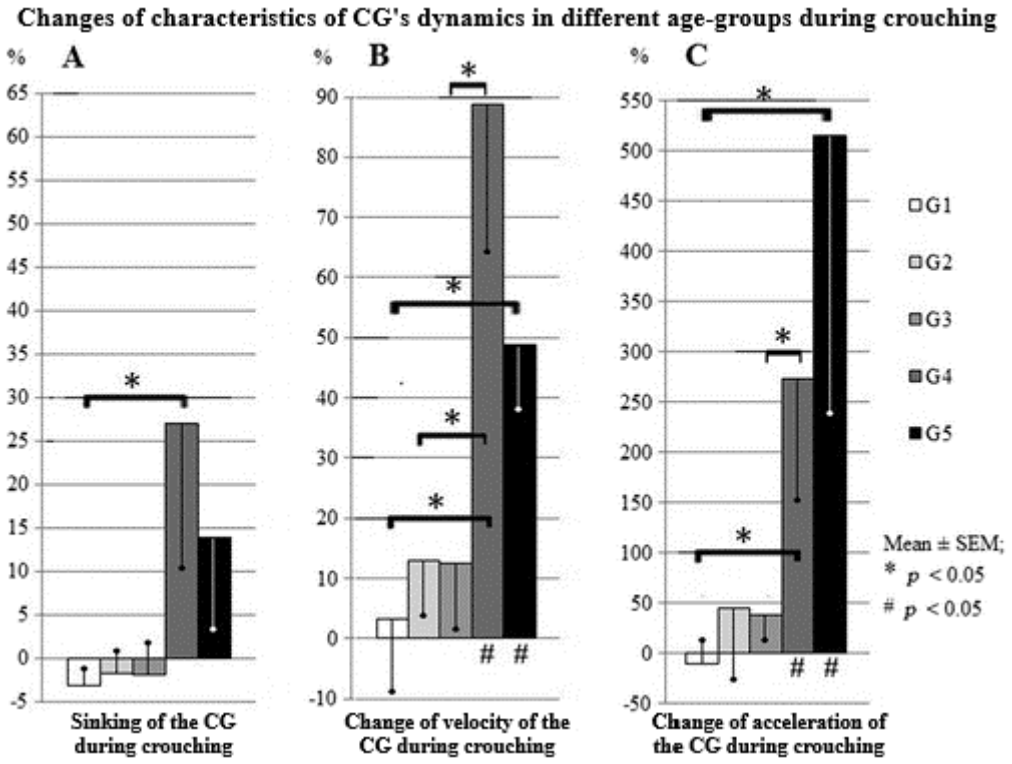


Figure 7: Changes in characteristics of CG's dynamics in different age-groups during crouching

*(„A" Differences between the groups in sinking of CG; „B" Differences between the groups in the velocity of CG; „C" Differences between the groups in the acceleration of CG. Values are means ± SEM; CG: center of gravity; G1: second childhood; G2: adolescence; G3: mature age I; G4: mature age II; G5: ageing. *Significant differences between changes of groups. #Significant changes in groups; $p \leq 0.05$)*

4.1.3 Correlation between the changes in body composition and the dynamics of movements

During the CMJ exercise, the lifting of the CG demonstrated notable correlations with FM (r = −0.52), SMM (r = 0.45), FM/BW (r = −0.5), SMM/BW (r = 0.5), and BF% (r = −0.49) in G2 and BW (r = −0.48), FM (r = −0.43), SMM/BW (r = 0.46), and BMI (r = −0.46) in G3. Similar correlation was observed between the sinking of position during CMJ and BW (r = 0.7), FM (r = 0.51), BMI (r = 0.69) in G1; BW (r = 0.57) in G2; SMM/BW (r = 0.43) in G4; and the BW (r = −0.67), FM (r = −0.63), FM/BW (r = −0.56), BMI (r = −0.65), BF% (r = −0.55), and WHR (r = −0.7) in G5. The velocity of CG during CMJ did not show any correlation with the changes in body composition parameters. However, correlation was shown between the acceleration of CG and the decrease in BW (r = −0.46) or BMI (r = −0.52) in G2. The statistical analysis proved significant correlation between the sinking of CG during crouching and FM (r = 0.49), SMM (r = −0.47), FM/BW (r = 0.47), SMM/BW (r = −0.5), BF% (r = 0.46), and WHR (r = 0.65) in G2; BW (r = −0.76), FM (r = −0.74), FM/BW (r = −0.69), SMM/BW (r = 0.78), BMI (r = −0.76), BF% (r = −0.69), and WHR (r = −0.55) in G4;

and the SMM (r = 0.55) and WHR (r = 0.73) in G5. The velocity of CG during crouching also showed correlation with the BW (r = −0.44), FM (r = 0.54), SMM (r = −0.75), SMM/BW (r = −0.68), BMI (r = −0.72), BF% (r = 0.65) in G2 and the BW (r = −0.55), BMI (r = −0.56), and WHR (r = −0.89) in G5. The acceleration of CG data also presented remarkable correlation with BW (r = −0.5) and BMI (r = −0.57) in G2 and WHR (r = −0.74) in G5.

4.2 Invasive cross-sectional research

First we performed miRNA array from the biopsy muscle samples of master athletes and of control subjects. The microarray analysis revealed that 21 of the 887 miRNA sequences were lower in master athletes than in control muscles (*Figure 8*). Four miRNAs were selected based on the greatest difference in the miRNA array (indicated in the box in *Figure 8*) for further qPCR analysis. This revealed that only miR-7 was expressed more ($p < 0.05$) in the muscles from controls than in those from master athletes (*Figure 9).*

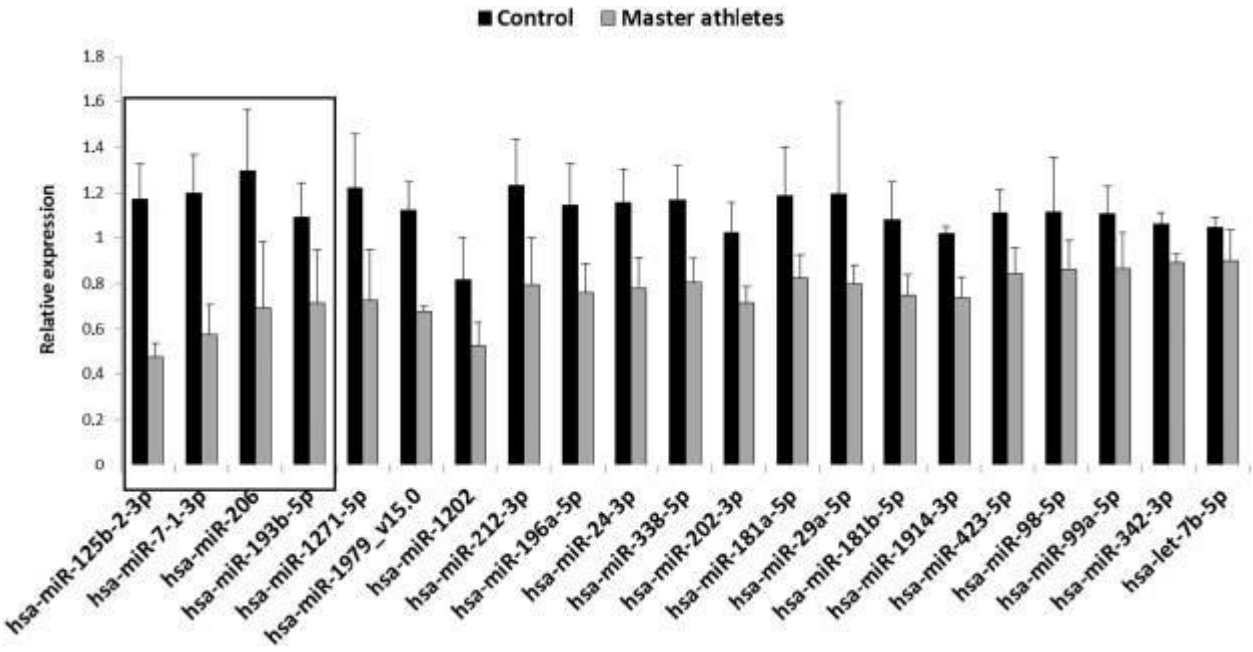


Figure 8: miRNA array profile of master athletes and sedentary subjects.

(The array screened for 887 miRNAs and 21 of them showed significant difference between sedentary and master athletes. Results are expressed mean ± SD, N = 4 in each group, $p < 0.05$)

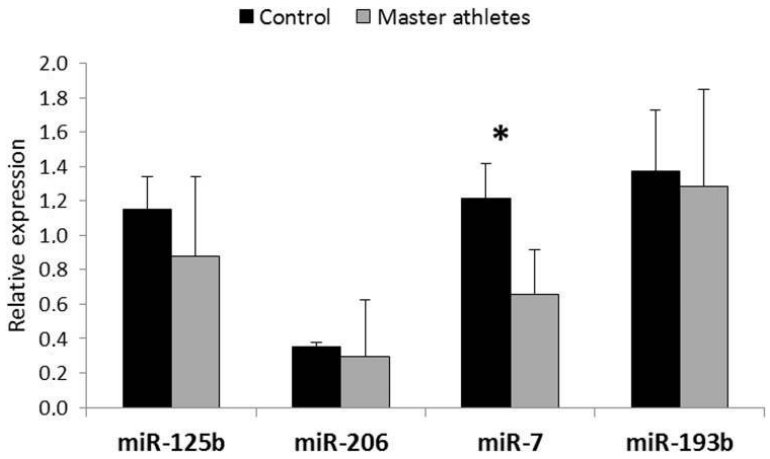


Figure 9: q-PCR results of miRNA levels.

*(Four microRNAs were selected to q-PCR measurements and only miR-7 analysis showed significant difference. Results are expressed mean ± SD, N = 4 in each group, *p < 0.05)*

Then from the remained muscle samples, key mitochondrial mRNA (*Figure 10*) and protein (*Figure 11*) contents were measured. SIRT1 ($p < 0.01$) and FOXO1 ($p < 0.05$) mRNA levels were higher in master athletes than in control groups (*Figure 10*), while the SIRT3 and SOD2 proteins ($p < 0.01$; *Figure 11*) from the muscle samples of master athletes were higher than in the control subjects.

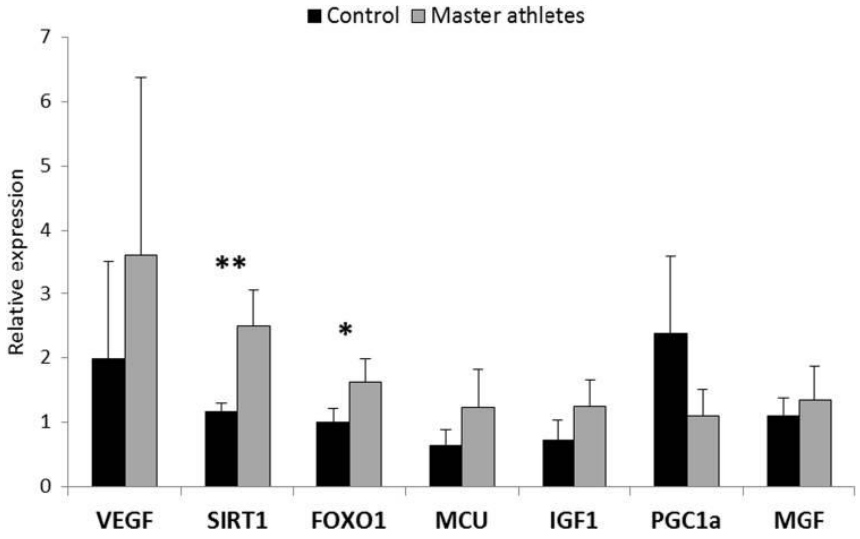


Figure 10: mRNA levels of selected regulatory proteins in master athletes and sedentary subjects.

*(The mRNA levels of seven key proteins were studied: SIRT1 and FOXO1 mRNA levels were significantly higher in skeletal muscles of master athletes than in sedentary subjects. Results are expressed mean ± SD, N = 10 in master athletes and N = 13 in control groups. ** p < 0.01, *p < 0.05)*

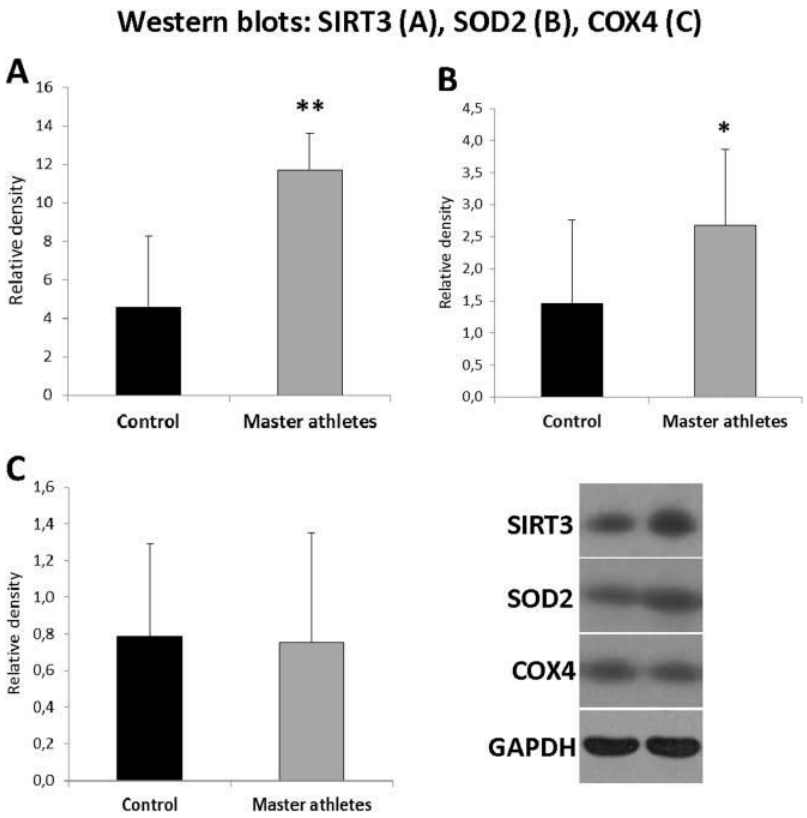


Figure 11: Protein levels of SIRT3, SOD2 and COX4.

*(Immunoblot data revealed that SIRT3 and SOD2 levels of master athletes were significantly elevated compared to controls. Results are expressed mean ± SD, N = 10 in master athletes and N = 13 in control group. ** $p < 0.01$, *$p < 0.05$)*

5 Discussion

A lot of studies deal with the effects of physical activity on body composition. The parameters of body composition did not change substantially due to regular recreational trainings in the groups of 8-12 and 12-16 years old children. The BW increased without the changes of body composition in G1, which is normal at this age. The increase of BW is caused by the lack of restriction on nutritional uptake, because other researches detected changes of BF% and BMI in this age class, with nutrition guidance and comparable training programme (Militao et al., 2013; Poeta et al., 2013). Similar results are discerniable in G2, but the body shapes of them changed (WHR decreased) despite that they also did not receive dietary recommendation. Lee et al. in 2012 achieved a similar result among children, with an aerob exercise programme and a defined diet, which reduced the WC of kids (Lee et al., 2012). After the physical activity programme the observed changes of body composition were the following in G3: the BW, FM, FM/BW, BMI, BF% decreased and the SMM/BW improved, in G4: the BW, FM, , BMI, BF%, WHR were lower and the SMM/BW was higher. These results are consistent with the investigation of Ross and co-workers who were successful in decreasing the BW and WC of adults, with a specified diet and training (Ross and Rissanen, 1994); and with research of Lee et al. who were also capable of reducing the FM and increasing the SMM, muscle-fat ratio (SMM/FM) of participants, with weight maintenance diet and workout programme (Lee et al., 2005). In case of adults, regular exercise can have positive effects on body composition and physique on its own even without a diet. BW, BMI and WHR of the elderly decreased in the investigation, but unfortunately the significant weight loss resulted in reduction of SMM. In specific researches, where workouts were not only recreational but also included strength and endurance development, weight loss was caused by fat loss (Davidson et al., 2009) and even an increase in muscle mass was observed (Trouwborst et al., 2018). Other findings of investigations showed similar results of physical activity on body shape, for example reduced WC (Davidson et al., 2009) and WHR (Araya et al., 2012). The changes of body composition in different age-groups can decrease the risk of obesity and help the prevention of metabolic syndrome (Eckel et al., 2010). Obesity is a risk factor of many chronic, non-communicable diseases such as insulin resistance, diabetes, hypertension, heart diseases, and dyslipidaemia. Chan et al (1994) showed significant correlation between BMI and diabetes in men with higher BMI than 35kg/m^2. They concentrated on finding a connection between WHR - diabetes, and between WC-diabetes. Based on their data, WC is a better indicator than WHR, but the dominant risk

factor of diabetes is BW (Chan et al., 1994). Results of Wilson et al (2002) demonstrated the correlation between heart diseases and obesity. The risks of hypertension and coronary heart disease were appreciable in the participants with BMI ≥ 25 (Wilson et al., 2002). Dyslipidaemia is an important factor in the connection of high BMI and increased risk of heart diseases. Positive correlation is proven between the level of triglycerides and BMI. However, a more important problem is the inverse connection between the level of lipoprotein (high-density lipoprotein - HDL) cholesterol and BMI. Similar correlation can be seen between the level of cholesterol and other measurements of body composition (WHR, WC) (Bray, 2004). A non-invasive follow-up research verified that recreational workout programme can make positive changes in the body composition. This study has the same outcome as the previous ones, but results also showed differences between the age-groups. The elder participants achieved more indicative changes in the parameters of body shape than the youngers. Significant differences were observed in the changes of FM, BF% in groups aged 21-60. The younger groups reduced FM/BW and increased SMM, SMM/BW more significantly than the elderly, because their body adapts better to workouts, thus changes of tissue ratio are easier (Deschenes, 2004), but targeted training could prevent the aging-associated loss of muscle mass and muscle strength (Distefano and Goodpaster, 2018).

The operation of muscle changes during the process of aging, which could bring about different diseases, while certain aging related diseases could also change the biochemical function of muscles. The level of miR-7 increases with aging, which plays a crucial role in transformation of growth factor-beta 1 dependent fibroblast to myofibroblast differentation and this way wound healing is impaired (Midgley et al., 2014). Chronic inflammation, specifically the interferon-linked inflammation may cause higher level of miR-7 and decline of fibroblasts (Midgley et al., 2016). Facioscapulohumeral muscular dystrophy is also related to inflammation (Wang and Tawil, 2016), and to the increased expression of miR-7 in muscle (Dmitriev et al., 2013). Sarcopenia-associated inflammation could be responsible for the miR-7 expression in old muscle. Effects of physical activity may reduce the expression of inflammatory markers, thus the occurrence of systemic inflammation in muscle (Degens, 2010). The muscles of master athletes have lower miR-7 levels than of coeval sedentary people, which can underpin the anti-inflammatory effect of lifelong sport. Observations on the impact of systemic inflammation on miR-7 induction emphasise that expression of miR-7 increases in peripheral blood mononuclear cells of HIV (human immunodeficiency virus) patients (Ballegaard et al., 2017), and in airways of patients suffering from allergic rhinitis

(Shaoqing et al., 2011), and from chronic obstructive pulmonary disease (Akbas et al., 2012), in conditions related to systemic or local inflammation. Expression of epidermal growth factor receptor (EGFR) was reduced (via degradation of its mRNA) by elevated miR-7 regulation in aged cells, but it could also interact with the EGFR dependent signalling pathway like mitogen aktivated protein kinase/extracellular signal-regulated kinases (MAPK/ERK), Ca^{2+}/calmodulin-dependentproteinkinase II (CaMKII), Rho-guanosine-5'-triphosphatase (Rho- GTPase), phosphoinositide 3-kinases (PI3K), protein kinase b (Akt) and mechanistics target of rapamycin (mTOR) (Midgley et al., 2014). These signal pathways are essential to wound healing in striated muscle (Li et al., 2013). Midgley et al. demonstrated why miR-7 is so important for the function of fibroblasts: after an oestradiol treatment the level of miR-7 diminished, the expression of EGFR mRNA increased, and the functionality of aging fibroblasts were restored (Midgley et al., 2016). miR-7 also has a significant part in lipid metabolism. Cross-talks between peroxisome proliferator-activated receptor (PPAR), sterol regulatory element-binding proteins (SREBP), and liver X receptors signalling pathways are mediated by miR-7 (Singaravelu et al., 2018). SREBP is activated by miR-7, which is regulated by PPAR-α signal. Sebaceous lipogenesis and down-regulation of miR-7 are also associated (Schneider et al., 2013). High level of endurance needs high level of energy supply. Brenmoehl and co-workers proved in mouse model that to develop extreme endurance the level of PPAR-α and the intensity of lipogenesis increased significantly (Brenmoehl et al., 2013), thus probably systematic training mediated metabolic changes could increase miR-7 mediated section of fat metabolism. SIRT3 is also important for lipid metabolism and an invasive cross-sectional research showed that the skeletal muscles of master athletes had higher protein levels of SIRT3 than of inactive participants. The fatty-acid oxidation disorders during fasting and the decreased ATP levels are hallmarks of SIRT3 ablation (Hirschey et al., 2010). SIRT3 regulates fatty-acid metabolism by the deacetylation of acyl-CoA dehydrogenase and medium-chain acyl-CoA dehydrogenase (Bharathi et al., 2013), so SIRT3 ablation greatly influences lipid metabolism. ATP-synthase F-complex can be deacetylated by SIRT3 (Vassilopoulos et al., 2014), thus SIRT3 regulates ATP production directly, which explains the decreased production of ATP in SIRT3 knock-out mice. The age related decline of SIRT3 level is generally accepted (Joseph et al., 2012), explaining the decline of ATP production during aging. The level of SIRT3 can be increased significantly by lifelong regular exercise, and the effect of physical activity is also powerful against the age-related functional deterioration of mitochondria. SIRT3 promotes the antioxidant activity and the decreased ROS level of mitochondria by deacetylating 2 critical lysine residues on SOD2

(Qiu et al., 2010). Therefore, the age-associated decline of mitochondrial function and the oxidative stress can be attenuated by systematic exercise, by means of the increased level of SIRT3 and the activaton of SOD2 (Joseph et al., 2016). The limited sample size narrowed the number of proteins in the skeletal muscle that could have been tested for the effects of lifelong training. The mRNA levels of SIRT1 and FOXO1 were higher in the muscles of master athletes than in sedentary subjects. Several studies have demonstrated that the age–associated deterioration of the level and activity of SIRT1, as well as its changes of functions, can be prevented by physical activity (Koltai et al., 2012; Koltai et al., 2010; Radak et al., 2011; Radak et al., 2013). FOXO 1 takes part in mitochondrial metabolism, glycolytic and lipolytic flux, thus it is an important factor in the adaptive response for the energy challenge during training (Sanchez et al., 2014). Senescence phenotypes decrease, because FOXO1 becomes deacetylated by SIRT3, this way the expression of SOD2 is elevated (which is one of the FOXO1 target genes) (Zhang et al., 2013).

It is never too late to start an active lifestyle. The body is able to adapt to regular exercise even in old age (Radák, 2019), which is reflected not only in the improvement of body composition and in its biochemical functions, but also in the dynamic marks of movement. The follow-up research shows increased range of motion in phase of CG sinking during CMJ in all age-groups except in the youngest ones. Of course, this does not necessarily mean that they can also achieve a significant result in the lifting of CG, as the muscles of the lower limb can exert the greatest force only in a certain angular range (Pavlik, 2019), which helps displacement. The results of the CMJ examination of adolescents clearly show the age-specific movement disintegration (Farmosi, 2011). G3 jumped higher after the training programme, with improved acceleration and range of motion, but the velocity of CG did not change significantly. In 36-60 years old participants, the extent of CG sinking increased significantly, so they were able to reach higher velocity with unchanged acceleration over longer distance. It is interesting, that lifting of CG did not change significantly in CMJ. These results can be explained by the fact that maximal acceleration can be measured after CG sinking in CMJ, and if it is only present for a short time, then the maximal velocity of movement does not necessarily change. The height of jump is clearly influenced by the speed. If maximal velocity is reached well before the moment of take-off, it worsens the lifting of the CG, while if it is closer to the moment of leaving the ground, it improves the lifting (Barton, 1993). Thus, it is possible that at the same maximal velocity, the height of the jump may improve significantly or the rate of rise will not change despite a significant change in

velocity of CG. All the examined parameters of the dynamic characteristics of the jump in G5 increased significantly as a result of recreational training. Measurements in the elderly age also show similar results by applying other exercise programmes (Araya et al., 2012). The aging-assotiated loss of strength is slower than the loss of explosive power, this way the daily movements, like standing up from a chair, slow down (Skelton et al., 1994), nevertheless, this deterioration can be prevented or reduced by systematic physical activity (Radák, 2019). By examining the dynamic marks of crouching, G4 and G5 achieved significant improvements in velocity and acceleration of CG by the end of the workout, although there were differences between the improvements of movement characteristics. In most cases the elder participants produced more significant improvements in dynamic marks of CMJ (G3, G4, G5) and crouching (G4, G5) than the younger ones. This can be explained in several ways. From a physiological point of view during growth the movement coordination of adolescents disintegrates (Farmosi, 2011). From a sociological point of view, school-aged children, who are inactive in their leisure time, must have physical education lessons every day, so recreational exercise does not have such an important impact for them. (Magyar Közlöny, 2011). Cross-sectional studies detected that in older age-groups muscle explosiveness, antagonistic muscle functions (which may limit movement efficiency) (Izquierdo et al., 1999), and muscle strength (Hakkinen and Hakkinen, 1991) show worse results than in younger age-groups. Due to systematic physical activity intermuscular (Radák, 2019) and also intramuscular coordination (Maejima et al., 2007) can improve. The primary increase in strength of untrained, inactive people is due to the improvement in the synchronization of motor units, i.e. neuromuscular coordination (Radák, 2019). Based on these, the significant change in the characteristics of dynamics in the older age-group can be explained.

Movement characteristics can be influenced by body composition also, among many other things. Higher body fat decreases the velocity of movements. Stenholm et al. (2009) measured people over the age of ≥ 65 in a 6 year follow-up research and they detected significant (15%) contrast between the walking speed of normal and obese body type participants (Stenholm et al., 2009). Simple tasks, like walking or stair climbing, are difficult for obese individuals caused by the lack of muscle strength (Miller et al., 2013). Systematic physical activities affect the development of physical capacity and facilitate daily movements, too. Research of Araya et al. (2012) demonstrated the effects of physical activity on body composition and physical qualities. Based on their data, optimized body composition and systematic physical activity can increase the height of jump, but they did not focus on

correlation between the two variations (Araya et al., 2012). The positive effects of regular exercise showed several connections between the changes of dynamic marks of movements and body composition. Improvement in the lifting of CG in CMJ was positively influenced by the decrease of BW, FM and BMI, as well as by the increase of the SMM/BW in the age-group of 21-35. Improvement of CG sinking before CMJ was helped by the increase of SMM/BW in the 35-60 years old participants and by the decrease of BW, BMI, and WHR in G5. In case of crouching , the velocity of movement was increased by the decreased BW, BMI, and WHR in the elderly age-group, while acceleration was only positively affected by the decreased WHR. Correlation calculations showed several connections between changes of movement dynamics and body composition, but by non-significant differences these relationships were not clear.

To get an accurate picture of the effects of training in the elderly, a larger scale research would be needed. The study should be conducted in more age-groups, but with a larger number of participants and with more categories per age-groups (for example: athlete, recreational athlete and inactive individuals). A recreational training programme ought to be defined in addition to the usual activities supplemented by a weight-maintaining diet. The research shall concentrate on body composition, movement dynamics, biochemical, and neuromuscular parameters in the groups. Body composition determination should be supplemented by SMM/FM and WC. Movement analysis shall measure the location of maximal velocity and of maximal acceleration in the motion, the average velocity and acceleration of movement. Similar biochemical parameters should also be considered and the neuromuscular changes should be researched in the muscles of the lower limb by EMG.

The most promising results are detected in the working-age and in near-retirement age-groups, as an outcome of recreational training and regular sport. Decreased miR-7 level in muscles by lifelong physical activity could lead to repression of sarcopenia-associated inflammation and to better fat metabolism. Increased SIRT3 level could aid more effective fat metabolism, production of ATP, and antioxidant function by SOD2 in striated muscles of physically active people. Lifelong regular sport may soothe the age-related decline in the antioxidant system and in the energy metabolism of muscle tissue. The positive effects of regular exercise are caused by even low-intensity training, but in elderly people, these alone

are not enough to significantly improve body composition and reduce the risk of obesity, although they can change the dynamics of movement. Based on these, it can be stated that by ensuring systematic physical activity muscle function and regeneration improve, the state of health consolidates, activity, work ability and ease of movements can remain lasting in old age.

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