REVIEW

Motor unit changes in normal aging: a brief review

IULIA TUDORAȘCU[1], VERONICA SFREDEL[1], ANCA LELIA RIZA[2], RUCSANDRA DĂNCIULESCU MIULESCU[3], SIMONA LAURA IANOȘI[4], SUZANA DĂNOIU[1]

[1)]*Department of Functional Sciences, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Human Genomics Laboratory, University of Medicine and Pharmacy of Craiova, Romania*

[3)]*Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[4)]*Department of Dermatology, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Aging is explored by multiple lines of research, in a pursuit of understanding this natural process. The motor response is usually the main dependent variable in studies regarding physical or cognitive decline in aging. It is therefore critical to understand how the motor function changes with age. The present review, aims at presenting briefly some of the most recently published works in the field, focusing on the three key components of the motor unit. The changes that the skeletal muscle undergoes aging sarcopenia, alteration of fiber type distribution and also intimate metabolic transformations. The neuromuscular junction suffers at cellular and molecular level, with possible implications of various cell components, mediators and oxidative stress. Motoneuron loss and change in their physiological properties accompany remodeling in the motor units. The applicability of knowledge in this field lies in possible interventions intended to counteract these age-related losses.

Keywords: motor unit, aging, neuromuscular junction, skeletal muscle, motoneuron.

Introduction

Recent changes in the structure of the population and estimations suggesting demographic aging, of which Romania is no exception, may justify the researchers' current interest for the aging process. Part of normal development, age-related motor decline seems to be the end result of multi-factorial causes, of which muscles and central and peripheral nervous system play their role.

This comes to justify why aging is explored by multiple lines of research, in a pursuit of understanding this natural process. The motor response is usually the main dependent variable in studies investigating physical or cognitive decline in aging. It is therefore critical to understand how the motor function changes with age. As the foundation of the motor system, the motor unit bears a lot of importance in the study of normal aging. Aging brings alterations in muscle, neuromuscular junction and motor nerve, in terms of both morphology and function.

Far from being an extensive work, or ever intending to be so, the present review, aims at presenting briefly some of the most recently published works in the field, focusing on the three key components of the motor unit.

Neuromuscular changes in elderly

Age-related alterations in neuromuscular system are recently seen [1], as caused by functional denervation, muscle wasting, and weakness, with hormonal changes, oxidative stress and mitochondrial dysfunction playing a major role [2, 3]. Given that "by the age of 70, the cross-sectional area of skeletal muscle is reduced by 25–30% and muscle strength is reduced by 30–40%" [4, 5], it is

only natural to expect changes in the skeletal muscle as underlying mechanism of age-related decline. All the more recent animal studies indicated that loss of muscle mass precedes age-related denervation of myofibers [6, 7]. Whether or not skeletal muscle is the *primum movens* of motor system aging is still arguable, but, unquestionably neural involvement is at least partly responsible [8]: motor cortex modifications [9], spinal and cortical excitability decrease [10], reduction of motor units [11], motor axon conduction velocities decrease [12].

Skeletal muscle alterations

Skeletal muscle undergoes changes that may be caused by aging, disuse and disease, sometimes being a challenge to differentiate between these factors. Regardless, findings of progressive loss of muscle mass, concurrent with loss of muscle function are documented.

Muscle morphology, neurologically determined atrophy, protein balance disturbances (due to mechanisms involving insulin growth factor 1 or other inflammatory factors, oxidative damage or intrinsic changes [13]), muscle tendon stiffness, all lead to clinical manifestations of sarcopenia: loss of muscle power and mass, and derived risk factors [14].

Much investigated, aging sarcopenia is a condition assuming progressive muscle loss with advancing age, associated with functional failure derived from this loss. Epidemiological studies give different values for the prevalence across age within populations depending on the operational definition, upon which only recently consensus definitions of 'sarcopenia' have been established [15–17]. It is not necessarily correlated with body weight, although sarcopenic obesity correlates with loss of muscle

mass [18]. Besides obesity, sarcopenia is associated with other major co-morbidities such as osteoporosis [17, 19] and type 2 diabetes [20, 21]. The etiology of sarcopenia is multifactorial and can include physical inactivity, altered endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies [16, 22]. The risk factors for sarcopenia are extensive described in literature, and include age, gender and level of physical activity [23, 24]. A particular aspect in the development of sarcopenia is the short-term disuse atrophy, since it has been suggested that different short periods of muscle disuse, due to injury or sickness (elderly are very vulnerable to both) contributes considerably to the net muscle loss observed with aging [25].

Fiber distribution alteration, with the predominance of muscle fibers type I [26], may not be a general rule. No significant changes in fiber type distribution, with increased average type IIa fiber diameter was reported, though the authors question this finding. The same longitudinal study, though discovering significant loss in muscle strength and reduction in muscle cross sectional areas in anterior muscles of the thigh, but not the posterior compartment, reported no decrease in single fiber maximal force or specific force in both types of fibers, a finding reported for the first time [27].

Progressive decrease in anabolism with increase of catabolism results in muscle force decrease and power decline, as well as reduced muscle regeneration capacity. Among the responsible causes may be neuropathic, hormonal, immunological, nutritional and physical activity factors [18, 28], with recognized gender-related differences: men show gradual decline, whereas women's muscle mass and function seems to suddenly drop after menopause [28]. The underlying mechanisms of these losses include shifts in muscle protein turnover, tissue remodeling, loss of alpha-motor-neurons, muscle cell recruitment changes and apoptosis [28, 29]. Age-related atrophy mechanisms have apparently direct application on maintenance of neuromuscular junction [30].

Another recently published review [31] focused on the metabolic pathways and mediators of muscle wasting, as exemplified in aging sarcopenia and cachexia, at the tipping point between increased catabolism and decreased anabolism. However, the factors involved in the etiology of cachexia (proinflammatory cytokines, hypermetabolism and malnutrition) are very different from those behind sarcopenia (hormonal changes, physical inactivity and neurodegenerative alterations) [32]. Among the main mechanisms at fault for muscle reduction are a sedentary lifestyle, endocrine or neuromuscular dysfunction, alterations of protein intake or metabolism, and even changes in gene expression [31, 33]. Note that is not merely a quantitative muscular loss, but qualitative mechanism may have their involvement as well, as single fiber muscle properties may change without changes in myosin content [34].

Aging muscle metabolism undergoes several other changes as well. If decline in anaerobic power seems to be affected more than aerobic power [35], there is evidence of the preference for oxidative energy production, and less for glycolysis, though the glycolytic pathway seems not to be affected by age, avoiding thus the accumulation of metabolites and reducing the energy costs [36]. Higher aerobic capacity allows greater aerobic reserve, which in turn, is associated with higher physical performance capacity in elderly [37]. Although the relationship between serum creatinine levels and muscle functional limitation is complex, correlation between the two parameters was proven in the case of the participants in the *Study of Physical Performance and Age-Related Changes* [38].

Recently discovered in nematode and identified in vertebrates and humans [39] miRNAs modulate multiple biological processes underpinning cell development, growth and death [40]. Despite it is known that the human genome contains over 1500 miRNA genes [41] and that each miRNA can regulate a large number of mRNA targets, very little is known about his specific role in gene regulation because only a few miRNA targets have been particularly experimentally analyzed [42]. MicroRNAs (miRNAs) modulate gene expression in skeletal muscle, and are associated with aging. Although several hundred miRNAs are detectable in skeletal muscle, specific miRNAs termed myomiRs, are preferentially expressed in myoblasts and myotubes [43].

Muscle decline has been looked at mostly in late years of life, but additional focus on early characteristics is justified under the light of developmental modulation of the human muscle. However, little research has been done in the direction of linking early environmental influences with molecular and cellular changes in human muscle, although size at birth seems related with muscle size in older men. The direct implication would be a lifelong approach in managing sarcopenia [44].

⊟ Neuromuscular junction

Neuromuscular junctions play a very important role both for the muscle and the motor nerves. Reviewing the cellular and molecular changes of the neuromuscular junctions, Jang and Van Remmen synthesize that "degeneration of motor neurons is followed by changes in structural and functional integrity of the neuromuscular junction (NMJ)" [1]. Animal model systems have led to a better understanding of the aging process at this level, bringing proof of functional denervation dependent on muscle activity or fiber type, changes in endplate size, terminals, sprouts, and synaptic vesicles. Exploration at subcellular level revealed that the presynaptic component may suffer in aging from decline in synaptic vesicles and mitochondrial content, with increase in endoplasmic reticulum, coated vesicles and cisternae. These last changes may be involved in calcium sequestration and neurotransmitter release. Increased turnover of neurotransmitter and defective axonal transport furthers the functional impairment of the neuromuscular junction. Another responsible factor seems to be the decrease in terminal Schwann cells, with widening of the nodes of Ranvier. At a molecular level, brain derived neurotrophic factor (BDNF), neutrophin-3 (NT-3), neutrophin-4 (NT-4), cytokines and other growth factors are modulators of neuromuscular system to a different extent in aging [1].

Oxidative stress seems to have a questionable role. From the oxidative theory of aging, it would result that

decrease of oxidative stress, by decreasing oxidant aggression or increasing antioxidant response or a combination of both, should increase life span. In the skeletal muscle, potential sources of oxidative species have been blamed on the mitochondria [1, 45–47], cytosol and membrane, the subject of comprehensive recent reviews [48, 49]. Concerns for the need to correct subsequent progressive functional loss of the muscular system have also been expressed [50, 51] the solutions currently provided varying from non-specific antioxidants, such as vitamin C, to correction of the oxidative signaling pathways.

The question, that needs answering, concerns the involvement of oxidative stress in aging or healthy aging. A synthesis of the results on animal studies on knockout or transgenic mice, with one or more of the antioxidant enzymes (superoxide dismutases, glutathione peroxidases, thioredoxins) found little support for the contribution of oxidative stress to aging, as measured by life span [52]. The reduction of the life span in the study groups was mostly attributable to a worsening of the pathologies the mice developed. A possible explanation would be that oxidative stress does not affect aging, but progression of disease, or that its role depends on the environment, meaning that it only influences life span under conditions of chronic stress. This new promising view contradicts the classic observation of involvement of oxidative stress in aging, currently rising more questions than offering answers.

The latest concerns as far as aging muscle function goes have been focused on Ca^{2+} as a key ion in many physiological processes located in the muscle and at the neuromuscular junction. Ca^{2+} sparks are pulsatile signals important to excitation-contraction coupling, as well as an index of the capacity of the muscle to maintain the homeostasis of this ion and describe the status of signaling. Aging is associated with a loss in the plasticity of the Ca^{2+} sparks due to defective calcium release, and membrane structure. This hypothesis may be the base of future treatment therapies, concentrated at this molecular level [53].

⌖ Motoneuron changes

The aging process is presumed to affect motor units by loss of motoneurons, apparent increase in slow twitch fibers, atrophy of the denervated fibers or reinnervation by neighboring fibers, generating a remodeling of the motor units by denervation – reinnervation cycles. Following this line of research, motor unit size and the threshold force for recruitment were assessed by macro-electromyography in first dorsal inter-osseous muscle, a hand muscle with approximately equal proportions of fast-twitch and slow-twitch muscle [54], and the tibialis anterior muscle, with mostly slow-twitch fibers [55]. Though the expected increase in motor unit size is suggested by the greater amplitudes the elderly registered, the size principle of motor unit recruitment is preserved. Motor unit size/recruitment threshold relationship is preserved by three possible mechanisms according to the previously mentioned authors: reinnervation of fast-twitch fibers by small, or by "mid-sized" motoneurons, or

a global decrease of all motoneurons, without excluding the morphological changes the motor unit can undergo.

Also, it seems that activation pattern does differ in old by comparison to young according to a study on the changes in Hoffmann-reflex excitability depending on age and type of contraction. Based on the results obtained from performing isometric, concentric and eccentric plantar flexions, the researchers suggested that the young would use similar activation strategies regardless of the type of plantar flexion, whereas the old would resort to synergic muscle contraction [56].

Excitability of motor neurons, either central or peripheral, is age dependent, most of the excitability indices being slightly altered with age: slightly longer strength duration time constant, smaller late depolarizing threshold electrotonus, smaller supernormality and smaller threshold changes in the current–threshold relationship for both depolarizing and hyperpolarizing currents [57, 58]. The *Baltimore Longitudinal Study of Aging* found age dependent motor unit size, firing rates [59], maximal firing rates differences in aging having been documented as well [60]. The explanation lies in altered axon metabolism, some of the mentioned indices being explained by persistent sodium channels, which increase with age [57, 61]. However, extraneural factors, such as tissue impedance and gender differences, should not be overlooked.

Spinal cord neural circuitry has control over muscle activation. Studying to what extent the aging process affects this mechanism, according to Monaco *et al.* concluded that age-related changes of the motor and nervous systems lead to old age-modified integration of information like biomechanical requirements, peripheral afference and descending inputs at spinal level. Motor primitives, muscle synergies force generators, "synchronize" muscle activation mainly depending on the biomechanical demand of the locomotion; hence, they are not significantly affected by aging" [62].

On the same note, distortion of the adjustment between primary sensorimotor cortex and motor neuronal pool is likely to contribute to a reduction in motor control in elderly [63]. All the more since "functionally relevant specialization of lateral spinal cord white matter, and an increased sensitivity to age-related decline in medial spinal cord white matter in healthy subjects" characterizes old age [64].

⌖ Motor unit firing

Healthy aging of the motoneuron was also assessed with respect to its function.

Studies on motor unit firing rates variability produced rather contradictory results, some showing significant differences between the young and old, some not reaching statistical significance. Knowing that high motor unit-firing rate may be responsible for lower force steadiness, which characterizes the elderly [65, 66], a study [66] aimed at comparing older and younger subjects by collecting information on the index and thumb during a pinching task. According to the authors, firing rate variability plays a key role in improving force steadiness, unlike motor unit synchronization, which did not seem to play a part. The same study showed, by before and after short-term light-load training comparison (meant

to improve force steadiness by reducing firing rate variability), that motor unit firing rate variability reduces with training in older subjects, though initially being similar in elderly and young, in this particular study.

Decreasing motor unit firing rates with increased variability characterize muscle fatigue, of which the elderly are expected to be, to some extent, protected due to the predominance of type I muscle fibers in the senescent muscle. Analysis of motor unit firing behavior during sub-maximal 50% maximal voluntary contraction (MVC) prolonged contraction of tibialis anterior found slight but not significant differences between young and old in time to task failure, motor unit firing rates and firing rates variability. Reporting for the first time doublet motor unit discharges (two action potentials generated close in time in order to enhance muscle force) in older adults [26], the study also confirmed the existence of motor unit firing cessation, explained as a compensatory mechanism, respecting the size principle of the motor unit recruitment. The possibility of muscle fatigue resistance being muscle dependent was discussed, as well as the contribution of neural component in adapting to force-requiring task.

Individual muscles firing rates have a slower twitch contractile speed and contractile properties, showing lower mean maximal motor unit firing rates (MUFRs). These neuromuscular findings apply for triceps surae, but the situation seems to be slightly distinct for soleus muscle, the authors concluding that individual muscle properties might not apply for whole muscle in this particular case [67]. It seems that "at least for proximal upper limb muscles, mean maximal motor unit discharge rates reductions with healthy adult aging are muscle specific and not strongly related to contractile speed" [68].

MUFRs and maximal voluntary force were also investigated in the dorsiflexor muscles of the foot in terms of age- and training-related adaptations, along with motoneuron after hyperpolarization. Although baseline examination proved superior values in the young group, after training, assessment indicated that "age-related" changes underwent a short-termed adaptation, making them comparable with values specific to the youth [69]. Nonetheless, motor neuron recovery rates and consequently contractile properties are delayed in old, in contrast with young, although both young and old suffer an important fatigue-induced reduction in MUFRs, as a study on soleus muscle shows [70].

On the other hand, it has been shown by comparing the number of functional motor units of the muscle tibialis anterior of "master runner" aged people, with healthy age-matched controls, and recreationally active young that aged people seem to benefit from life-long intense physical activity. Motor unit number estimates of masters' runners and young were both higher compared to the old [71]. The idea started from a similar animal model, the testing on humans being a first, to our knowledge. Another comparison between sportsmen and untrained, made during incremental exercise on a cycle ergometer, proved that older persons' muscle fiber conduction velocity (MFCV) does not increase with the intensity of exercise, the maximal MFCV in untrained old being significantly lower than that of young, trained or untrained. Since MFCV correlated with cardiovascular indicators in the young, the questions that arises concerns the strategies of motor units recruitment [72].

Improving theoretical knowledge is also reflected by mathematical modeling of age-related neuromuscular changes. This has given insight on recruitment, rate-coding, and force output in motor units, with direct applicability in understanding aging. The Heckman–Binder model applied on human quadriceps motor units [73] proved that elderly can reach around 50% of the force levels attained by younger individuals, with relatively similar or even slightly lower input.

⊡ Final considerations

Senescence, as a biological process assumes morpho-physiological changes, which ultimately lead to functional deterioration, motor alterations having a major impact on the quality of life. In the context of current demographical aging, the focus on normal aging is to be expected.

Current literature concurs that even the healthiest seniors' experience alterations of the cognitive and motor functions. Age-related alterations of the peripheral and cortical neural motor functions are part of the underling mechanism of motor aging, alongside skeletal system decline.

The applicability of knowledge in this field lies in possible interventions intended to counteract these age-related losses, directed at physical exercise, medication, assistive devices, and social involvement.

Physical interventions have a positive effect on functional status [74]. Its benefits in maintaining motor function are doubled by cognitive improvement, a very important desiderate, especially since a connection between memory retrieval and motor actions, as well as influence on positive or negative life experiences, has been proven [75]. Regardless, the simple reasoning behind this method is the principle "use it or lose it". Physical exercise interventions, in most of the cases submaximal [76] are beneficial at delaying aging, effects like stopping or reversing aging being highly questionable.

Medication intended to ameliorate motor deficits are targeted in multiple directions: dopaminergic and cholinergic transmission [77], anti-inflammatory drugs [78], diet [79], caloric restriction-simulating drugs [80], hormones [81–84], and vitamins [85, 86], with conflicting results.

Recently, robotic devices have been designed to accustom the needs of elderly. Also, technology-enabled cognitive training is tailored to address the cognitive decline [87, 88].

Social interaction plays an undeniable role, community dwelling adults having multiple benefits by comparison with their institutionalized counterparts [89].

All these methods have as ultimate goal to ensure not only a longer lifespan, but most important, a healthier, more fulfilling lifestyle besides the biopsychosocial challenges that old age brings. Knowledge about successful aging has expanded greatly, but general agreement on how successful aging can be achieved has not yet been clarified.

Author contribution

All authors have equal contribution.

References

[1] Jang YC, Van Remmen H, *Age-associated alterations of the neuromuscular junction*, Exp Gerontol, 2011, 46(2–3):193–198.

[2] Thompson LV, *Age-related muscle dysfunction*, Exp Gerontol, 2009, 44(1–2):106-111.

[3] Rygiel KA, Grady JP, Turnbull DM, *Respiratory chain deficiency in aged spinal motor neurons*, Neurobiol Aging, 2014, 35(10): 2230–2238.

[4] Porter MM, Vandervoort AA, Lexell J, *Aging of human muscle: structure, function and adaptability*, Scand J Med Sci Sports, 1995, 5(3):129–142.

[5] Vandervoort AA, *Aging of the human neuromuscular system*, Muscle Nerve, 2002, 25(1):17–25.

[6] Wray DW, Uberoi A, Lawrenson L, Bailey DM, Richardson RS, *Oral antioxidants and cardiovascular health in the exercise-trained and untrained elderly: a radically different outcome*, Clin Sci (Lond), 2009, 116(5):433–441.

[7] Deschenes MR, Roby MA, Eason MK, Harris MB, *Remodeling of the neuromuscular junction precedes sarcopenia related alterations in myofibers*, Exp Gerontol, 2010, 45(5):389–393.

[8] Ward NS, Swayne OB, Newton JM, *Age-dependent changes in the neural correlates of force modulation: an fMRI study*, Neurobiol Aging, 2008, 29(9):1434–1446.

[9] Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y, Lipps DB, *Motor control and aging: links to age-related brain structural, functional, and biochemical effects*, Neurosci Biobehav Rev, 2010, 34(5):721–733.

[10] Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, Ranieri F, Di Lazzaro V, *Effects of aging on motor cortex excitability*, Neurosci Res, 2006, 55(1):74–77.

[11] Campbell MJ, McComas AJ, Petito F, *Physiological changes in ageing muscles*, J Neurol Neurosurg Psychiatry, 1973, 36(2):174–182.

[12] Dalpozzo F, Gérard P, De Pasqua V, Wang F, Maertens de Noordhout A, *Single motor axon conduction velocities of human upper and lower limb motor units. A study with transcranial electrical stimulation*, Clin Neurophysiol, 2002, 113(2): 284–291.

[13] Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjær M, *Role of the nervous system in sarcopenia and muscle atrophy with aging: strength training as a countermeasure*, Scand J Med Sci Sports, 2010, 20(1):49–64.

[14] Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB, *Sarcopenia: etiology, clinical consequences, intervention, and assessment*, Osteoporos Int, 2010, 21(4):543–559.

[15] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People, *Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People*, Age Ageing, 2010, 39(4):412–423.

[16] Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M, *Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia*, J Am Med Dir Assoc, 2011, 12(4):249–256.

[17] Cooper C, Dere W, Evans W, Kanis JA, Rizzoli R, Sayer AA, Sieber CC, Kaufman JM, Abellan van Kan G, Boonen S, Adachi J, Mitlak B, Tsouderos Y, Rolland Y, Reginster JYL, *Frailty and sarcopenia: definitions and outcome parameters*, Osteoporos Int, 2012, 23(7):1839–1848.

[18] Narici MV, Maffulli N, *Sarcopenia: characteristics, mechanisms and functional significance*, Br Med Bull, 2010, 95(1):139–159.

[19] Sjöblom S, Suuronen J, Rikkonen T, Honkanen R, Kröger H, Sirola J, *Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia*, Maturitas, 2013, 75(2):175–180.

[20] Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DIW, Cooper C, *Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg?* Diabetes Care, 2005, 28(10):2541–2542.

[21] Lee SW, Dai G, Hu Z, Wang X, Du J, Mitch WE, *Regulation of muscle protein degradation: coordinated control of apoptotic and ubiquitin-proteasome systems by phosphatidylinositol 3 kinase*, J Am Soc Nephrol, 2004, 15(6):1537–1545.

[22] Evans WJ, *Skeletal muscle loss: cachexia, sarcopenia, and inactivity*, Am J Clin Nutr, 2010, 91(4):1123S–1127S.

[23] Sayer AA, Robinson SM, Patel HP, Shavlakadze T, Cooper C, Grounds MD, *New horizons in the pathogenesis, diagnosis and management of sarcopenia*, Age Ageing, 2013, 42(2): 145–150.

[24] Kim H, Suzuki T, Kim M, Kojima N, Yoshida Y, Hirano H, Saito K, Iwasa H, Shimada H, Hosoi E, Yoshida H, *Incidence and predictors of sarcopenia onset in community-dwelling elderly Japanese women: 4-year follow-up study*, J Am Med Dir Assoc, 2014, Nov 17.

[25] Wall BT, Dirks ML, van Loon LJC, *Skeletal muscle atrophy during short-term disuse: implications for age-related sarcopenia*, Ageing Res Rev, 2013, 12(4):898–906.

[26] Christie A, Kamen G, *Motor unit firing behavior during prolonged 50% MVC dorsiflexion contractions in young and older adults*, J Electromyogr Kinesiol, 2009, 19(4):543–552.

[27] Frontera WR, Reid KF, Phillips EM, Krivickas LS, Hughes VA, Roubenoff R, Fielding RA, *Muscle fiber size and function in elderly humans: a longitudinal study*, J Appl Physiol (1985), 2008, 105(2):637–642.

[28] Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, Woo J, Baumgartner R, Pillard F, Boirie Y, Chumlea WM, Vellas B, *Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives*, J Nutr Health Aging, 2008, 12(7):433–450.

[29] Baumgartner RN, Waters DL. Sarcopenia and sarcopenic-obesity. In: Pathy MSJ (ed), *Principles and practice of geriatric medicine*, John Wiley and Sons, Ltd., UK, 2006, 2:909–933.

[30] Shigemoto K, Kubo S, Mori S, Yamada S, Akiyoshi T, Miyazaki T, *Muscle weakness and neuromuscular junctions in aging and disease*, Geriatr Gerontol Int, 2010, 10(Suppl 1): S137–S147.

[31] Saini A, Faulkner S, Al-Shanti N, Stewart C, *Powerful signals for weak muscles*, Ageing Res Rev, 2009, 8(4):251–267.

[32] Argilés J, Busquets S, Orpi M, Serpe R, López-Soriano F, Muscle wasting in cancer and ageing: cachexia versus sarcopenia. In: Lynch GS (ed), *Sarcopenia – age-related muscle wasting and weakness*, Springer, Netherlands, 2011, 9–35.

[33] Thomas DR, *Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia*, Clin Nutr, 2007, 26(4):389–399.

[34] Canepari M, Pellegrino MA, D'Antona G, Bottinelli R, *Single muscle fiber properties in aging and disuse*, Scand J Med Sci Sports, 2010, 20(1):10–19.

[35] Kostka T, Drygas W, Jegier A, Zaniewicz D, *Aerobic and anaerobic power in relation to age and physical activity in 354 men aged 20–88 years*, Int J Sports Med, 2009, 30(3): 225–230.

[36] Kent-Braun JA, *Skeletal muscle fatigue in old age: whose advantage?* Exerc Sport Sci Rev, 2009, 37(1):3–9.

[37] Arnett SW, Laity JH, Agrawal SK, Cress ME, *Aerobic reserve and physical functional performance in older adults*, Age Ageing, 2008, 37(4):384–389.

[38] Odden MC, Shlipak MG, Tager IB, *Serum creatinine and functional limitation in elderly persons*, J Gerontol A Biol Sci Med Sci, 2009, 64(3):370–376.

[39] Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T, *Identification of novel genes coding for small expressed RNAs*, Science, 2001, 294(5543):853–858.

[40] Miska EA, *How microRNAs control cell division, differentiation and death*, Curr Opin Genet Dev, 2005, 15(5):563–568.

[41] Kozomara A, Griffiths-Jones S, *miRBase: integrating micro-RNA annotation and deep-sequencing data*, Nucleic Acids Res, 2011, 39(Suppl 1):D152–D157.

[42] Sood P, Krek A, Zavolan M, Macino G, Rajewsky N, *Cell-type-specific signatures of microRNAs on target mRNA expression*, Proc Natl Acad Sci U S A, 2006, 103(8):2746–2751.

[43] McGregor RA, Poppitt SD, Cameron-Smith D, *Role of micro-RNAs in the age-related changes in skeletal muscle and diet or exercise interventions to promote healthy aging in humans*, Ageing Res Rev, 2014, 17:25–33.

[44] Sayer AA, Dennison EM, Syddall HE, Jameson K, Martin HJ, Cooper C, *The developmental origins of sarcopenia: using peripheral quantitative computed tomography to assess muscle size in older people*, J Gerontol A Biol Sci Med Sci, 2008, 63(8):835–840.

[45] Jang YC, Van Remmen H, *The mitochondrial theory of aging: insight from transgenic and knockout mouse models*, Exp Gerontol, 2009, 44(4):256–260.

[46] Powers SK, Nelson WB, Hudson MB, *Exercise-induced oxidative stress in humans: cause and consequences*, Free Radic Biol Med, 2011, 51(5):942–950.

[47] Weber TA, Reichert AS, *Impaired quality control of mito-chondria: aging from a new perspective*, Exp Gerontol, 2010, 45(7–8):503–511.

[48] Powers SK, Jackson MJ, *Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production*, Physiol Rev, 2008, 88(4):1243–1276.

[49] Jackson MJ, *Free radicals generated by contracting muscle: by-products of metabolism or key regulators of muscle function?* Free Radic Biol Med, 2008, 44(2):132–141.

[50] Jackson MJ, *Strategies for reducing oxidative damage in ageing skeletal muscle*, Adv Drug Deliv Rev, 2009, 61(14): 1363–1368.

[51] Haenold R, Wassef DM, Heinemann SH, Hoshi T, *Oxidative damage, aging and anti-aging strategies*, Age (Dordr), 2005, 27(3):183–199.

[52] Salmon AB, Richardson A, Pérez VI, *Update on the oxidative stress theory of aging: does oxidative stress play a role in aging or healthy aging?* Free Radic Biol Med, 2010, 48(5): 642–655.

[53] Weisleder N, Ma J, *Altered Ca^{2+} sparks in aging skeletal and cardiac muscle*, Ageing Res Rev, 2008, 7(3):177–188.

[54] Masakado Y, Noda Y, Nagata MA, Kimura A, Chino N, Akaboshi K, *Macro-EMG and motor unit recruitment threshold: differences between the young and the aged*, Neurosci Lett, 1994, 179(1–2):1–4.

[55] Fling BW, Knight CA, Kamen G, *Relationships between motor unit size and recruitment threshold in older adults: implications for size principle*, Exp Brain Res, 2009, 197(2): 125–133.

[56] Kallio J, Avela J, Moritani T, Kanervo M, Selänne H, Komi P, Linnamo V, *Effects of ageing on motor unit activation patterns and reflex sensitivity in dynamic movements*, J Electromyogr Kinesiol, 2010, 20(4):590–598.

[57] Bae JS, Sawai S, Misawa S, Kanai K, Isose S, Shibuya K, Kuwabara S, *Effects of age on excitability properties in human motor axons*, Clin Neurophysiol, 2008, 119(10):2282–2286.

[58] Jankelowitz SK, McNulty PA, Burke D, *Changes in measures of motor axon excitability with age*, Clin Neurophysiol, 2007, 118(6):1397–1404.

[59] Ling SM, Conwit RA, Ferrucci L, Metter EJ, *Age-associated changes in motor unit physiology: observations from the Baltimore Longitudinal Study of Aging*, Arch Phys Med Rehabil, 2009, 90(7):1237–1240.

[60] Knight CA, Kamen G, *Relationships between voluntary activation and motor unit firing rate during maximal voluntary contractions in young and older adults*, Eur J Appl Physiol, 2008, 103(6):625–630.

[61] Kuwabara S, Misawa S, Tamura N, Nakata M, Kanai K, Sawai S, Ogawara K, Hattori T, *Latent addition in human motor and sensory axons: different site-dependent changes across the carpal tunnel related to persistent Na^+ currents*, Clin Neurophysiol, 2006, 117(4):810–814.

[62] Monaco V, Ghionzoli A, Micera S, *Age-related modifications of muscle synergies and spinal cord activity during locomotion*, J Neurophysiol, 2010, 104(4):2092–2102.

[63] Graziadio S, Basu A, Tomasevic L, Zappasodi F, Tecchio F, Eyre JA, *Developmental tuning and decay in senescence of oscillations linking the corticospinal system*, J Neurosci, 2010, 30(10):3663–3674.

[64] Lindberg PG, Feydy A, Maier MA, *White matter organization in cervical spinal cord relates differently to age and control of grip force in healthy subjects*, J Neurosci, 2010, 30(11): 4102–4109.

[65] Laidlaw DH, Bilodeau M, Enoka RM, *Steadiness is reduced and motor unit discharge is more variable in old adults*, Muscle Nerve, 2000, 23(4):600–612.

[66] Griffin L, Painter PE, Wadhwa A, Spirduso WW, *Motor unit firing variability and synchronization during short-term light-load training in older adults*, Exp Brain Res, 2009, 197(4): 337–345.

[67] Dalton BH, Harwood B, Davidson AW, Rice CL, *Triceps surae contractile properties and firing rates in the soleus of young and old men*, J Appl Physiol (1985), 2009, 107(6):1781–1788.

[68] Dalton BH, Jakobi JM, Allman BL, Rice CL, *Differential age-related changes in motor unit properties between elbow flexors and extensors*, Acta Physiol (Oxf), 2010, 200(1):45–55.

[69] Christie A, Kamen G, *Short-term training adaptations in maximal motor unit firing rates and afterhyperpolarization duration*, Muscle Nerve, 2010, 41(5):651–660.

[70] Dalton BH, Harwood B, Davidson AW, Rice CL, *Recovery of motoneuron output is delayed in old men following high-intensity fatigue*, J Neurophysiol, 2010, 103(2):977–985.

[71] Power GA, Dalton BH, Behm DG, Vandervoort AA, Doherty TJ, Rice CL, *Motor unit number estimates in masters runners: use it or lose it?* Med Sci Sports Exerc, 2010, 42(9):1644–1650.

[72] Lenti M, De Vito G, Sbriccoli P, Scotto di Palumbo A, Sacchetti M, *Muscle fibre conduction velocity and cardio-respiratory response during incremental cycling exercise in young and older individuals with different training status*, J Electromyogr Kinesiol, 2010, 20(4):566–571.

[73] Webber SC, Porter MM, Gardiner PF, *Modeling age-related neuromuscular changes in humans*, Appl Physiol Nutr Metab, 2009, 34(4):732–744.

[74] Peterson MJ, Giuliani C, Morey MC, Pieper CF, Evenson KR, Mercer V, Cohen HJ, Visser M, Brach JS, Kritchevsky SB, Goodpaster BH, Rubin S, Satterfield S, Newman AB, Simonsick EM; Health, Aging and Body Composition Study Research Group, *Physical activity as a preventative factor for frailty: the health, aging, and body composition study*, J Gerontol A Biol Sci Med Sci, 2009, 64(1):61–68.

[75] McDonald KC, Blackwell JC, Meurer LN, *Clinical inquiries, What lifestyle changes should we recommend for the patient with newly diagnosed hypertension?* J Fam Pract, 2006, 55(11):991–993.

[76] Gu MO, Conn VS, *Meta-analysis of the effects of exercise interventions on functional status in older adults*, Res Nurs Health, 2008, 31(6):594–603.

[77] Darbin O, *The aging striatal dopamine function*, Parkinsonism Relat Disord, 2012, 18(5):426–432.

[78] Waldstein SR, Wendell CR, Seliger SL, Ferrucci L, Metter EJ, Zonderman AB, *Nonsteroidal anti-inflammatory drugs, aspirin, and cognitive function in the Baltimore longitudinal study of aging*, J Am Geriatr Soc, 2010, 58(1):38–43.

[79] Aksenov V, Long J, Lokuge S, Foster JA, Liu J, Rollo CD, *Dietary amelioration of locomotor, neurotransmitter and mitochondrial aging*, Exp Biol Med (Maywood), 2010, 235(1): 66–76.

[80] Fontán-Lozano A, López-Lluch G, Delgado-García JM, Navas P, Carrión AM, *Molecular bases of caloric restriction regulation of neuronal synaptic plasticity*, Mol Neurobiol, 2008, 38(2):167–177.

[81] Rocca WA, Grossardt BR, Shuster LT, *Oophorectomy, meno-pause, estrogen, and cognitive aging: the timing hypothesis*, Neurodegener Dis, 2010, 7(1–3):163–166.

[82] Sorwell KG, Urbanski HF, *Dehydroepiandrosterone and age-related cognitive decline*, Age (Dordr), 2010, 32(1):61–67.

[83] Quik EH, Conemans EB, Valk GD, Kenemans JL, Koppeschaar HP, van Dam PS, *Cognitive performance in older males is associated with growth hormone secretion*, Neurobiol Aging, 2012, 33(3):582–587.

[84] Björkman MP, Sorva AJ, Tilvis RS, *Does elevated parathyroid hormone concentration predict cognitive decline in older people?* Aging Clin Exp Res, 2010, 22(2):164–169.

[85] Llewellyn DJ, Lang IA, Langa KM, Muniz-Terrera G, Phillips CL, Cherubini A, Ferrucci L, Melzer D, *Vitamin D and risk of cognitive decline in elderly persons*, Arch Intern Med, 2010, 170(13):1135–1141.

[86] Erickson KI, Suever BL, Prakash RS, Colcombe SJ, McAuley E, Kramer AF, *Greater intake of vitamins B6 and B12 spares gray matter in healthy elderly: a voxel-based morphometry study*, Brain Res, 2008, 1199:20–26.

[87] Duclos A, Flechner LM, Faiman C, Flechner SM, *Post-transplant diabetes mellitus: risk reduction strategies in the elderly*, Drugs Aging, 2006, 23(10):781–793.

[88] Steinerman JR, *Minding the aging brain: technology-enabled cognitive training for healthy elders*, Curr Neurol Neurosci Rep, 2010, 10(5):374–380.

[89] Annear MJ, Cushman G, Gidlow B, *Leisure time physical activity differences among older adults from diverse socio-economic neighborhoods*, Health Place, 2009, 15(2):482–490.

Corresponding author
Veronica Sfredel, Associate Professor, MD, PhD, Department of Functional Sciences, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania; Phone +40740–197 924, e-mail: veronicasfredel@yahoo.com