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Are deferrable the mobility impairments in older aging?

Aula Guariento, Accademia Galileiana di Scienze Lettere ed Arti in Padova (Italia), 16 Febbraio 2016

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Abstracts

***A ciascuno il suo:* a brief personal history in translational myology at turn of millennium**

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In 1940 and thanks to L.E. Heilbrunn[1] the scientific hypothesis on the possible role of calcium ion in muscle contraction was published. Nevertheless, Ca^{2+} was not recognized as an indispensable factor of contraction up to the paper of A. Weber that appeared in 1959 and in which it was shown that Ca^{2+} exerts its effect having the filament proteins as target; just a ionic concentration of 0.2 mM was capable to induce the muscle contraction.[2] The goal of the calcium ion on the filaments is a protein, troponin C, identified some years later by Ebashi and Kodama.[3] It is important to note that a few years earlier in 1954, at the same time and in the same issue of the Nature, AF Huxley and Niedergerke[4] and HE Huxley and Hanson,[5] published the hypothesis of "sliding filaments theory" on the mechanism of action of muscle contraction. Starting from the seventies of the last century, the studies on Ca2+ exploded (together with calcium related proteins or Calcium Binding Proteins or CBP) linked to the mechanisms of signal transduction with problems and surprises related to mechanisms of phosphorylation and de-phosphorylation of protein substrates. In particular, in skeletal muscle were identified: the principal proteins (Ryanodine receptor or RYR, Dhyidropiridine receptor or DHPR and Calsequestrin or CSQ) capable of coupling the electrical phenomena occurring in the sarcolemma with the release of Ca^{2+} from the terminal cisternae of the sarcoplasmic reticulum.[6] To assure a precise coordination of Ca^{2+}handling regulation during contraction of skeletal muscle, several different CBP, as well as S100, were proposed.[7] In striated muscle, S100 demonstrated highest expression in cardiac muscle, followed by slow twitch and fast twitch skeletal muscle, respectively. S100 binds specifically to a CaM binding site on RyR1 and enhances the Ca^{2+} release flux resulting from coordinated opening of multiple RyR1s.[8]

Muscle requires two cofactors to function: load and innervation. If both or one of the them are impaired, muscle becomes atrophic through a mechanism of protein degradation that develops into proteasomes and lysosomes (autophagy).[9]

However, the muscle is a surprising tissue because even when it seems to have almost disappeared, as a consequence of a long time denervation, it is able to regenerate, if exposed to daily cycles of functional electrical stimulation (FES).[10]

Ageing of muscle tissue is a complex process (Sarcopenia) that is usually associated with a decrease in mass, strength, and velocity of contraction triggered by reactive oxygen species (ROS) that have accumulated throughout one's lifetime. Exercise as a method to prevent or at least delay sarcopenia has been discussed in many scientific reports. While on the one hand, it seems clear that exercise is effective in reducing the loss of muscle mass, on the other it appears that physical activity increases both the mechanical damage and the accumulation of free radicals as results of increase in the aerobic metabolism of the involved muscles.[11]

How to take advantage of physical exercise, limiting the adverse effects, is the main goal for further successful managements of age-related power decline.

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The Epidemiology of Aging

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The marked fall in birth and mortality rates that has taken place over the last century has modified the demographic structure of the

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Italian population: there are now 13,220,000 persons over 65; they represent more than 21% of the population and make Italy the country with the highest percentage of elderly persons in Europe (it has been estimated that in 2050 persons over 65 will exceed 33% and those over 85 will make up approximately 8% of the population).[1]

The primary aim of geriatric and gerontology research is that of gaining information to reduce disability and increase the functional autonomy in elderly adults in order to guarantee individuals' greater wellbeing during their later years.

As far as physical disability is concerned, particular interest has been dedicated to sarcopenia which has been defined by the European Working Group on Sarcopenia in Older People as a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength. It has been estimated that the prevalence of sarcopenia in the general elderly population in Italy is at 10%; those affected have three times the risk of physical disability and two times the risk of mortality.[2]

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Decline of skeletal muscle power based on world records of Master athletes from 30 to 110 years

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Both strength and power developed by human skeletal muscles decline with increasing age.[1,2] The athletic world records of the Master athletes of age ranging from 35 years to 100 years are an excellent proof of such decline in every track and field competition. The world record performances of running, jumping and throwing events can be transformed into dimensionless parameters proportional to the power developed in the trials. Such parameter ranges from 1 for the Senior world record (i.e. the maximum human performance) to lower values for the Master athletes of increasing age down to 0 for a null performance.[3,4] With this procedure the declines of the power parameter with increasing age can be analysed and compared: the trend-lines start to decline very close to the age of 30 years and arrive to 0 around the age of 110 years for every athletic discipline (running, jumping and throwing).[5] The comparison of the various trend-lines shows significantly different rates of decline. Each declining trend-line reaches a "critical" threshold at different ages for the running, jumping and throwing activities. Such thresholds indicate different age limits for most of everyday tasks: walking, climbing stairs and lifting weights above a table. The decline of the Master world records, transformed into a dimensionless power parameter declining from 1 toward 0 with increasing age is the decline of the power developed by each one of us, starting from 1 in our youthful age and declining toward lower values with increasing age. There are no reason, for each one of us, to decline differently from the world record-men, provided that each of us remains in stable fitness condition without disabling pathologies.

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Fit and healthy muscle fibers at 90 years and beyond are a reality!

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The age-related loss of skeletal muscle mass, and strength contributes to disability and mortality associated with advanced aging. The aetiology of this syndrome is multifactorial including: alterations in endocrine function, chronic syndromes, and inflammation, however muscle deconditioning caused by reduced mobility appear to play a pivotal role in this phenomenon. Recently, utilizing the human-model of the oldest-old (~90 years old) and varying levels of limb disuse, our group demonstrated that the progressive fall in skeletal muscle use, plays a significant role in the exacerbation of cellular ageing and the loss of muscle mass.1 Moreover, in a different study we investigates both in vivo and in vitro muscles properties, of locomor- and non-locomotor muscles, which experience differing degrees of disuse during the lifespan.2 The outcomes of this study indicate than in the oldest-old, neither advanced aging nor disuse, per se, impact intrinsic skeletal muscle function, as assessed in vitro and in vivo, but volitional muscle function is attenuated by age and exacerbated by disuse. These observations imply that the limiting factors for the reduction in force generation capacity with advanced aging resides outside the contractile machinery of the skeletal muscle cells. Moreover, the loss of muscle mass is the consequence of a greater loss of muscle fibres, caused by denervation 3, and a reduction in size of the remaining fibres. Interestingly, the assessment of the single fibres utilized for contractile measurements did not reveal this latter effect. Therefore, this dissociation between atrophy and the more pronounced reduction in skeletal muscle voluntary force with advancing age imply that additional physiological mechanisms are responsible for this phenomenon. In this scenario it has been suggested that age- and disuse-related changes in neural control play a significant role in this decline in muscle voluntary force. Specifically with regards to aging, it has been documented that there is a significant age and neural-dependent decrease in

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dihydropyridine receptor (DHPR) functional expression that is responsible for an uncoupling of the excitation–contraction process, which results in an incomplete activation of the myofibrillar machinery.4 Moreover, increasing evidence points to a decline in neural influence on skeletal muscle at later ages, and this might also lead to changes in muscle structure which together result in excitation–contraction uncoupling. 5 Taken together, these studies support the concept that in vivo force characteristics, are largely dependent upon neural activity, including a possible involvement of DHPR, and consequently influence excitation–contraction coupling.

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How physical rehabilitation changes the course of aging in muscle and joints

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Sedentary persons, but even healthy persons experience a steady decline in their life. Understanding the biologic changes that occur with age and their social implications is essential for a physiatrist to maximize an aging patient's quality of life and functional independence. Sarcopenia, contributes to the functional consequences of aging because of changes in muscle fibers. By age 80 years, up to 50% of peak skeletal muscle mass can be lost, leading to functional decline. Age-related decreases in androgens and other growth factors may contribute to this process with selective loss of type II muscle fibers.[1] Older adults have larger postural sway, slower gait velocity, and slower reflexes. Slow walking speeds have been associated with an increased risk of fractures, hospital admissions, institutionalization, and death. Postural hypotension, impaired proprioception, vision, and other sensory losses affect balance and coordination[2,3] and increase the risk of falls. An aggressive multidisciplinary approach for the elderly may help to continue or resume a productive and functional existence. Multimodal approach includes: patient education, exercise, physical, occupational, and kinesiotherapy, the use of the orthotics, the physical modalities, and psychosocial, medical and pharmacologic treatment. *Physical Activity and exercise*: Regular physical activity reduces the risk of many conditions associated with aging, including cardiovascular disease, diabetes, and stroke and it is recommended as treatment for many of these same conditions. Physical training increases muscle mass, helping to combat age-related sarcopenia.[4] Balance training reduce falls and injuries from falls. Physical activity decreases risk of dementia and cognitive decline in older adults, it improves mood and is effective for treatment of depression. With appropriate guidance and a personally tailored exercise program based on patient's fitness goals and functional abilities, older persons can achieve improvements in performance and general well-being. Exercise programs generally consist of four major components: strength, endurance, balance and proprioception, and flexibility.[5] *Exercise is therapy*: some conditions warrant further diagnosis and treatment before beginning exercise.[6] A staged prescriptive approach is better, first targeting the urgent needs of the patient, and then including other modalities. *Supplemental Treatments:* Modalities are physical agents that are used to produce a therapeutic response in tissues. They are supplemental treatments in a multimodal management program that should always include exercise, physical, occupational, or kinesiotherapy regimens. The major modalities used in common practice are heat, cryotherapy, lasertherapy and electrotherapy. Before selecting a modality, one must understand the physiologic effects each exerts on tissues. The target tissue, the depth and intensity of heat or cooling desired, and patient characteristics are all factors to consider when writing the prescription: especially in the elderly, the use of modalities is not without limitations. It is of fundamental interest of aging Europe the healthcare and research for the elderly. By employing a multimodal approach the physiatrist may restore, preserve, and, hopefully, even enhance cognitive and motor functions of older population, improving their quality of life.[7,8]

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Home-based Bed-Gym and FES in borderline mobility impairments: Fighting permanent or progressive muscle weakness by do-it-yourself, take-home strategy

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All permanent or progressive muscle contractility impairments (including aging-related muscle power decline and ventilation insufficiency) need permanent managements. Beside eventual pharmacology therapy a home-based physical exercise approach is helpful. Awaiting development of implantable devices for muscle stimulation, i.e., of electroceuticals, as effective as pace-makers for cardiac arrhythmias or cochlear implants for hearing loss, education of hospitalized patients to take-home physical exercise managements is an effective low cost alternative. Frail elderly due to advanced age or associated diseases are often hospitalized for long periods of time. There, their already modest amount of daily physical activity is reduced, contributing to limit their independence up to force them to the bed. Inspired by the proven capability to recover skeletal muscle contractility and strength by home-based Functional Electrical Stimulation (h-bFES) and functional Magnetic Stimulation (fMaS) even in the worse cases of neuromuscular traumatic injuries,[1-3] but, mostly, by common sense, we suggest a short (15-20 minutes) daily sequence of ten simple physical exercises that may be performed in bed (Bed-Gym). In a few days in hospital Bed-Gym may increase muscle strength, fatigue resistance and independence in daily life activities. Bed-Gym helps also to mitigate the bad mood that accompanies mobility limitations, strengthening confidence in recovering partial or total independence.[4] Continued regularly, Bed-Gym may help to maintain the independence of frail older people and to reduce the risk of the possible serious consequences of accidental falls. Bed-Gym may also mitigate eventual high blood pressure, a major risk factor in elderly.[5]

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