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Sarcopenia: a narrative review

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ABSTRACT

The loss of strength, mobility and functionality is not an inevitable part of aging. It is a result of disuse, abnormal hormonal levels, nutritional and dietary issues amongst other factors that deteriorate with aging. One of the greatest threats for the adult's ability to remain healthy and functional while growing old is the gradual loss of lean body mass- especially muscle tissue. This article appraises scientific evidence on sarcopenia. The therapeutic interventions of sarcopenia involve a variety of approaches: resistance and aerobic exercises, nutrition, supplements and vitamin formulations as well as counselling in a new way of life.

Keywords: Sarcopenia; Elderly; Muscle strength; Physical performance; Nutrition

Introduction

Irwin Rosenberg defined sarcopenia as the age-related decrease of muscle mass [49]. His aim was to underline the importance of muscle mass in the disability process. A vicious circle is created since there is an age-related decrease of muscle mass, an age-related decrease of muscle strength and the loss of muscle mass, of muscle strength and functionality lead to aging.

Even though sarcopenia is mainly observed in persons with low physical activity, it is also common in persons who remain physically active throughout their lives. [9] Therefore, it becomes clear that even though physical activity is essential, physical inactivity is not the only factor that matters.

As we grow older, hormonal levels and the need for protein are changing, motor neurons die, and we have a tendency for sedentary life.

The first workshop for sarcopenia was held by the National Institute on Aging in 1989. Since then, the definition of sarcopenia is evolving. In fact, the definition of sarcopenia is considering the loss of muscle functionality and quality (muscle strength/ muscle mass unit or alternatively the ability of the muscle tissue to produce power) as an additional factor to the decrease of the muscle mass proteins.

At this point occurs the issue of overlapping between different diseases and syndromes such as cachexia, sarcopenia, starvation and frailty. The fact is that there is no clear separation. All these conditions lead to muscle loss. Even specialized physicians find it hard to distinguish them. The difficulty lies in the strong connection these conditions have. Nevertheless, it is of great importance to separate

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VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

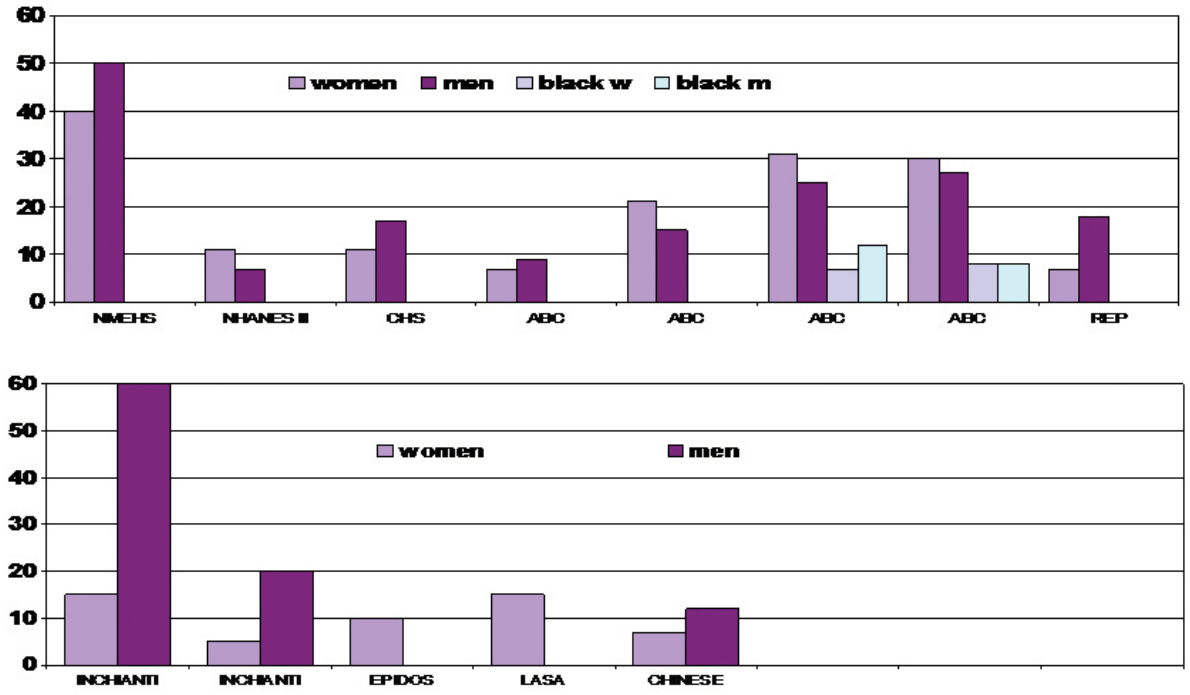

Figure 1: *Prevalence of sarcopenia in various studies in America (up) and Europe-Asia (down)*

them in everyday practice because they demand a different clinical and therapeutical approach.

Additionally, the clinician should investigate other causes, for example lateral amyotrophic sclerosis or cancer cachexia, for muscle loss, which is part of the differential diagnosis process. According to EWGSOP, sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength/physical performance with a risk of adverse outcomes such as physical disability, poor quality of life and death. [20, 21] The criteria set to diagnose sarcopenia are: 1) Low muscle mass and decreased muscle strength or physical performance (sarcopenia), 2) Low muscle mass (quantity/quality) and decreased muscle strength and physical performance (severe sarcopenia).

Anker et al introduced the ICD-10 code for sarcopenia [1]. According to the writers: "the new ICD-10-CM (M62.84) for sarcopenia represents a major step forward in recognizing sarcopenia as a disease. This should lead to an increase in availability of diagnostic tools and the enthusiasm for pharmacological companies to develop drugs for sarcopenia."

Sarcopenia is primarily age related. Secondary factors are divided into three categories. Activity related factors such as bed rest, sedentary lifestyle and deconditioning. Disease related factors such as advanced organ failure, inflammatory diseases, malignancy and endocrine disorders. Finally, nutrition related factors such as inadequate diet, malabsorption, gastrointestinal disorders and drug induced anorexia. [24]

Epidemiology

Concerning the epidemiology of sarcopenia, there has been research and data in America, Europe and Asia but certain questions arise. For example, how do these results sound since there was no accurate definition till now? Is there a different prevalence in various populations? Could we generalize the results? The prevalence of sarcopenia is between 7.5% and 77.6% when it is defined as a decrease in gait speed and grip strength, as in the EWGSOP definition. The prevalence of sarcopenia differs also according to the characteristics of the subjects and could range between 14 and 33% in residents of care

VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

TABLE 1. *Nutritional interventions in sarcopenia*

Nutritional interventions
1) Proteins and protein supplements
2) Essential amino acids, mainly branched chain
3) Nutritional supplements that combine protein and leucine
4) beta-hydroxy-beta- methyl butyrate (HMB), metabolite of leucine
5) Vitamins
6) Micronutrients

facilities, to 26% in chronic spinal cord injured subjects and is estimated much higher (78%) in hospitalized disabled subjects. [22, 25, 37]

In comparison with the annual cost of 13.6 billion dollars for osteoporotic fractures, sarcopenia consequences cost much higher: 18.5 billion dollars (data from USA). The consequences of sarcopenia are expanded to survival rate, infections, duration of hospitalization, toxicity of medical treatment and motor disability [32]. It appears that we probably need better medication in the future for the improvement of functionality in the elderly as the financial cost of such a prospect is enormous.

Pathophysiology

There are plenty of external and internal processes that contribute to the development of sarcopenia. Concerning the internal processes, the most influential factors are the decrease of anabolic hormones such as testosterone, estrogens, growth hormone etc., the increased apoptotic activity in muscle fibers, the increased pro-inflammatory cytokines (mainly TNF-a and IL-6), the oxidative stress due to accumulation of free radicals, the changes in mitochondrial function of muscle cells and the decreased number of alpha motor neurons [33]. The external factors constitute of the following facts. The inadequate intake of energy and proteins contributes to loss of muscle mass and function. Decreased intake of vitamin D has been associated with low functionality levels in the elderly. Acute and chronic comorbidities can also contribute to the development of sarcopenia in older people. Comorbidities may lead on the one hand to decreased physical activity and periods of bed rest and on the other hand to the increase of pro-inflammatory cytokines that play an important role in the activation of proteolysis (see cachexia) [33].

The muscle system is the biggest storage for proteins and during periods of stress or malnutrition, it provides continuous aminoacid supplies, so that protein synthesis continues in other key tissues. Furthermore, the skeletal muscle is the main "consumer" of energy and contributes to the BMR of the body. Therefore, muscle loss is the primary cause of age-related decrease of BMI and energy needs. Aging has effects on systemic factors influencing synthesis and degradation of skeletal muscle proteins. The protein metabolism is altered. [36]

Aging has effects also on the motor units: In sarcopenia there is a preference in the process of atrophy of the fast muscle fibers (type 2) in comparison with the slow muscle fibers (type 1). The aging process contributes to that atrophy as well. Sarcopenia disrupts this system of muscle organization. In sarcopenia atrophy <preferentially> and due to denervation of type II fibers more than type I is evident, and this integration is disrupted. [36]

Assessment

Anthropometric measures are low cost, easy to use but vulnerable to error and thus have low reliability. *Bioimpedancemetry* is an also low cost, easy to use method but vulnerable to error and thus also has low reliability. Body imaging techniques such as MRI and CT are of high cost, difficult to execute with radiation and show skeletal muscle quality. *DXA* measures skeletal muscle mass in kg and it is of low cost, reliable, and easy to use but does not give information about muscle quality. It is the gold standard method in osteoporosis but there are limited possibilities especially in frail elderly patients.

Skeletal muscle index (SMI): appendicular skeletal muscle mass (ASM)/ height^2

Values of SMI lower than 2 SD under the SMI of a young population, reference from the Rosetta study, are considered indicative of sarcopenia (women <7.26 kg/m^2 men <5.45 kg/m^2) [5]. The advantag-

VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

TABLE 2. *Trials of Selective Androgen Receptor Modulators*

Compound	Drug name	Trial	Action
MK2866 GTx-024	Ostarine Enobosarm	Phase II b Clinical Trial	Increase muscle mass
LGD - 4033	Ligandrol	Preclinical trial	Improves muscle mass
971086	GSK 971086	Clinical trial Phase I (2011)	Androgen stimulator
Karo		stopped	»

es of this index are the easy application and understanding by physicians. The disadvantages are that it needs DXA, the threshold it uses because it is calculated and based to the Rosetta study only, the difficulties in comparison between obese and thin because it does not include the fat in the calculation and the most important is that the only clinical parameter from the definition of sarcopenia in the equation is the muscle mass. Strength is not taken into consideration. However, strength produced by a muscle mass unit differs among sexes and gradually decreases with age [31].

Isometric methods of strength assessment have the disadvantage of measuring forces that do not reproduce the normal movement-static assessment. Isokinetic methods also have the limitation of movement in certain angular velocity; therefore, the condition is far from normal. The limited motion patterns which are apparently not frequently enough used in everyday activities that could possibly lead to higher results due to the repeated same measurements and eventually with the result of the bad reproducibility (isometric and isotonic measurements). In the study of muscular capabilities, the movements should be described by terms that include the elements of power, velocity and acceleration [47]. Force (N) provokes acceleration (a). Every movement is caused by a force in a certain time and because of that, it should be measured as power (force X distance=work, work/time and force X speed=power).

The currently used techniques of handgrip strength i.e. Jamar Dynamometer or knee extension strength gym equipment, are feasible in the clinical practice and easily understood. Moreover, handgrip strength could be assessed simply by measuring shaking hands with the subject. This test *is reliable but it* is loaded with subjectivity. Furthermore, it is not a reproducible and quantitative method. Concluding, the problem is the threshold, the type of test and the fact that these tests are dependent from the motive, willingness of the subject and the possibility of pain. Once again, muscle strength is once more the most important parameter according to these measurements.

Several other tests are used in the assessment *of muscle strength or physical performance (power)*: Chair stands test *, Walk test, Time up and Go Test etc. Their disadvantage is that for example the TUG test includes only the main movements of everyday life like lifting, walking, turning and seating and not stepping over an obstacle that could cause a stumble or fall [46]. We agree that all these tests are validated in various populations. However, we need multiple tests in clinical practice in order to overcome the elements that lack in certain tests.

Screening for Sarcopenia SARC – F

A simple questionnaire for screening sarcopenia without measurements is the SARC-F questionnaire in which the score ranges from zero to ten. Scoring ≥ 4 can suggest sarcopenia. It measures strength, assistance in walking, rise from a chair, climb stairs and falls. Specifically, it evaluates by asking the patient how much is the difficulty to lift 10 pounds, to walk across a room, the level of difficulty in transferring from chair to bed, the ability of climbing 10 stairs and lastly the occurrence of falls within the last year. The answers range from 0 to 2, whereas none is 0, some is 1 and a lot or unable is 2 [63].

VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

Rehabilitation and Treatment- Basic principles

The therapeutic interventions in age-related sarcopenia are exercise and training, physiotherapy interventions, appropriate nutrition, vitamins and other supplements, consulting and daily living skills training and finally pharmaceutical interventions.

Physical Activity

Exercise, especially resistance training exercises (or strength exercises), are highly effective for the prevention of sarcopenia. Resistance exercises affect the neuromuscular system, the protein synthesis and the hormones, who if not working properly lead to sarcopenia. Studies show that after a resistance training program, the activation of the motor neuron and the protein synthesis increase even in older people (they are both essential for building muscle mass) [29,50]. These changes indicate that muscle strength can be regained even in an advanced age.

To clarify the meaning of resistance exercises these are considered as a type of strength training, meaning a type of training that is going to improve the maximal strength, since it stands to reason that with gradual exercise someone could lift more weight, more times. If we take into consideration the laws of physics, it becomes more complex: If a mass of 100kg (total weight: 100 kg • 9,81 $m/s^2 \approx$ 1000 N) should be lifted in 1m, 1000NX1m=1000J of energy should be produced. If the above happens in 1sec, then mean power would be 1000J/1s=1000W and if it happens in 0,5sec then it would be 1000J/0,5s=2000W. Therefore, physics-wise, weight training targets to power and not strength.

Aerobic exercise also seems to be beneficial against sarcopenia. This type of exercise has been proven to increase protein synthesis, an essential procedure for the preservation of the muscle mass and strength in older people [53].

Electrical Stimulation (ES)

Electrical stimulation counteracts muscle decline in seniors. ES is an alternative intervention to improve muscle recovery in case the ability to perform physical exercise is limited by pathologic conditions. According to the authors, ES has been shown to improve muscle torque and functional performances of seniors and increase the size of fast muscle fibers. At molecular level, ES induced up-regulation of IGF-1 and modulation of MuRF-1, a muscle-specific atrophy-related gene. It also induced up-regulation of relevant markers of differentiating satellite cells and of extracellular matrix remodeling which might guarantee shape and mechanical forces of trained skeletal muscle as well as maintenance of satellite cell function, reducing fibrosis [34].

Nutrition

Older people have the tendency to incept less calories in general, which can lead to severe deficiency in proteins and other nutrients. The preservation of sufficient protein and calorie intake is an important aspect of the treatment of sarcopenia [10, 12, 41].

Epidemiological surveys show that chronic malnutrition (insufficient intake of proteins and energy, micronutrients' deficiency) contributes to the development of sarcopenia. The third National Health and Nutrition Examination Survey (NHANES III), a population-based cohort study, appointed that older adults with sarcopenia, malnutrition and physical inactivity had a higher risk of mortality. Similarly, in ABC Health study, among adults in the community with normal functionality, there was found that low protein intake is related to higher risk of mobility limitation. More recently, the results from the Very Important Protein (VIP) study in Italy showed an association between protein intake and muscle mass and power in all ages.

Research has shown that older adults may need more protein intake per kilogram compared to younger people, in order to maintain proper protein levels to boost muscle mass [13, 14]. Many factors contribute to higher needs in proteins in older people, including the impaired anabolic response to protein intake and the increased prevalence of inflammatory and catabolic conditions related to aging [42, 59].

According to Paddon-Jones et al, the quantity and quality of proteins a mixing of fast (such as whey protein) and slow (such as casein) absorbing milk-derived proteins has better efficiency in muscle building than soya drinks after strength training

VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

among young people. These differences are related to the content of amino acids, mainly leucine [44]. It was also found that by giving 20gr of whey protein, (signed with phenylalanine) there were higher rates of postprandial protein synthesis compared to the same quantity of casein [47]. The postprandial protein retention was higher in older people when they were given whey protein compared to casein. Apparently, slow absorbing proteins have better results in younger people, while fast absorbing proteins are better for older people [27].

There are multiple factors that contribute towards the anabolic resistance of muscle protein synthesis to food intake with aging. Physical activity performed before food intake can improve postprandial muscle protein synthesis rates irrespective of age. A reduced level of habitual physical activity forms the basis for the observed anabolic resistance in the older population. Increasing the physical activity in the elderly will increase postprandial muscle protein synthesis rates and ultimately support healthy aging. Additionally, according to the authors, the amount, protein source and time of day that dietary protein is consumed further modulate the amplitude of the stimulation of postprandial muscle protein synthesis rates, thereby improving net muscle protein accretion. [11]

Essential amino acids (EAAs) have been proven to stimulate the synthesis of muscle proteins [58], even if this result could be modified in older ages [56]. Leucine supplements and/or HMB have also been suggested as an effective approach for the improvement of stamina and muscle mass in older adults due to their impact in muscle protein synthesis. However the studies were not consistent [8, 60].

There are data supporting that creatine supplements could be helpful in muscle growth in older adults who follow a resistance training program [10, 18]. Preservation of proper levels of vitamin D in blood could also be helpful for the maintenance of muscle strength and physical condition [41].

In a 2017 meta-analysis of 8 randomized clinical studies that examine the effect of protein or amino acid supplements in muscle mass and strength in healthy older adults, Tieland et al found no evidence of positive effect of proteins or aminoacid supplements in muscle mass, strength of press leg, leg extension or hand grip [55]. Their conclusion showed that these interventions may demand simultaneous nutritional intervention or physical exercise. However, other studies came to different conclusions. For example, the PROVIDE study in older adults with sarcopenia showed that an intervention of 13 weeks with a specific nutritional supplement per os that consists of protein enriched with leucine and vitamin D, with no physical exercise, did not improve the principal outcomes (hand grip strength and SPPB) - though it led to a significant improvement in chair-stand time and in muscle mass of the spine that was evaluated by DXA [4]. Moreover, another study with an intervention of 6 months with a nutritional supplement that consisted of whey protein and vitamins D and E showed a significant improvement in measurements of muscle mass, muscle strength and anabolic indicators such as IGF-1 and IL-2 in older people with sarcopenia [6]. VIVE-2, another study of 6 months, examined the combined intervention of physical activity with or without everyday nutritional supplement of whey protein and vitamin D in older people with reduced mobility. This study did not show any major difference in walking speed or SPPB (Short Physical Performance Battery) by combining a nutritional intervention with physical exercise [26].

A well-rounded report of the International Sarcopenia Initiative (EWGSOP and IWGS) concluded that some nutritional interventions such as the essential amino acids, including 2,5gr of leucine, HMB and the increase of protein intake to 1,2gr/kg/day, could improve the muscle parameters. In 2013, an international study group (PROT-AGE) which was established by the European Geriatric Medicine Society (EUGMS) and other scientific organizations, published recommendations for dietary protein intake in healthy older people [3]. The study group concluded that older people not only need more protein than young adults, but also these specific nutritional interventions - the addition of proteins, aminoacids and other nutrients, the intake timetable and the incorporation of an exercise program- must be adopted in order to ensure the optimal digestion and absorption of proteins.

VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

Carotenoids may protect from inflammation and thus sarcopenia. Mediterranean diet is suggested to decrease the incidence of disability [54].

Drugs

Medications with neurotrophic properties, meaning *aiming to the nervous system,* are tried based on the concept of sarcopenia as a neuromuscular syndrome, i.e. trypsin inhibitors are based on the importance of a healthy neuromuscular junction (neurotrypsin damages the junction) and EN 101 (Moransen), a medication against Ache for patients with myasthenia gravis (MG) are under research.

Other drugs with anabolic action in muscles (preservation/increase in muscle fibers, promotion of muscle rehabilitation, formation of muscle fibers after damage) like testosterone, growth hormone (GH), IGF 1, Stamulumab (MYO-029), anti-myostatin Mab acts against Myostatin, Selective Androgen Receptor Modulators and older medications that are used for other diseases are currently being tested. Various formulations such as testosterone, selective androgen receptor blockers (SARMs) and ghrelin agonists can increase muscle mass, causing less or more serious side effects. The action of anti-myostatin MAb appears to increase the lean muscle mass and force. In a double-blind study in postmenopausal women, administration of a recombinant ACE-031 protein (Ramatercept) which acts as a potent myostatin inhibitor has shown statistically significant markers of muscle mass increase while improving bone and fatty tissue. The angiotensin converting enzyme inhibitor called perindopril showed an increase in the distance the patient could walk and a reduction in the incidence of fractures without significant side effects [15, 64].

Conflict of interest:

The authors declared no conflicts of interest.

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VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

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VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

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VOLUME 70 | ISSUE 3 | JULY - SEPTEMBER 2019

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