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Interaction Between Bone and Muscle in Older Persons with Mobility Limitations

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Abstract

Aging is associated with a progressive loss of bone-muscle mass and strength. When the decline in mass and strength reaches critical thresholds associated with adverse health outcomes, they are operationally considered geriatric conditions and named, respectively, osteoporosis and sarcopenia. Osteoporosis and sarcopenia share many of the same risk factors and both directly or indirectly cause higher risk of mobility limitations, falls, fractures and disability in activities of daily living. This is not surprising since bones adapt their morphology and strength to the long-term loads exerted by muscle during anti-gravitational and physical activities. Non-mechanical systemic and local factors also modulate the mechanostat effect of muscle on bone by affecting the bidirectional osteocyte-muscle crosstalk, but the specific pathways that regulate these homeostatic mechanisms are not fully understood. More research is required to reach a consensus on cut points in bone and muscle parameters that identify individuals at high risk for adverse health outcomes, including falls, fractures and disability. A better understanding of the muscle-bone physiological interaction may help to develop preventive strategies that reduce the burden of musculoskeletal diseases, the consequent disability in older persons and to limit the financial burden associated with such conditions. In this review, we summarize age-related bone-muscle changes focusing on the biomechanical and homeostatic mechanisms that explain bone-muscle interaction and we speculate about possible pathological events that occur when these mechanisms become impaired. We also report some recent definitions of osteoporosis and sarcopenia that have emerged in the literature and their implications in clinical practice. Finally, we outline the current evidence for the efficacy of available anti-osteoporotic and proposed anti-sarcopenic interventions in older persons.

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CONFLICT OF INTEREST

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Keywords

Bone-muscle; sarcopenia; osteoporosis; disability; aging

1. INTRODUCTION

The ability of humans to move in their environment mainly depends upon the interaction of bone and muscle. The skeleton provides the framework that supports the body, it gives its characteristic shape and provides the mechanical integrity for locomotion and protection. The muscles, which make up 50% of the body mass, act on bones and joints to generate the many different coordinated movements necessary for human life, as we know it.

The bone mass and architecture are adjusted to control the strains produced by mechanical load and muscular activity. Bone is made up of specific bone cells, collagen proteins and minerals (calcium and phosphate) both including in the matrix that provides maximal strength in a lightweight form. Collagen fibers are incredibly strong, but too flexible and elastic to support the body. The minerals give to the bone its hardness and rigidity. The structural units of the bone are called Haversian systems. Each system consists of concentrically arranged layers of hard, inorganic material surrounding a microscopic Haversian canal. Blood vessels and nerves pass through this canal. Materials are exchanged between the living cells and the blood vessels in the Haversian canal by the way of canaliculi. The living bone cells (osteocytes) lie along the interfaces between contiguous concentric layers of the matrix and live as long as 50 years, in contrast to osteoclasts and osteoblasts, which are relatively short-lived and transiently present on a small fraction of the bone surface [1,2]. Osteocytes are the orchestrators of the remodeling process. They sense the sites of old bone and direct the homing of osteoclasts (and perhaps osteoblasts) to the site that is in need of remodeling. In addition, they produce factors that influence osteoblast and osteoclast generation as well as mineral homeostasis, they mediate the homeostatic adaptation of bone to mechanical loading and control or modify the mineralization of the matrix produced by osteoblasts [3–5].

Skeletal muscle is made up of many multinucleate cells, called fibers, which run the entire length of the muscle. Each muscle fiber contains a large number of parallel tube-like structures, called myofibrils, which in turn contain units called sarcomeres. This is where the contraction occurs with the thin filaments (actin) sliding between the thick filaments (myosin dimers), along with numerous other regulatory proteins. The force generated by the muscle fiber is proportional to the number of myofibrils it contains. Muscles are innervated by motor neurons. The motor unit is the combination of a single motor neuron and the muscle fibers innervated by its branches. Acetylcholine released from the axon end of the motor neuron branch binds to receptors on the fiber cell surface and causes the release of calcium from the sarcoplasmic reticulum. Thus, in the presence of calcium, the myosin component attaches the actin within the sarcomere generating power. After a sequence of chemical transformations via actin-induced breakdown of adenosine triphosphate (ATP), free energy is released to generate both force production and movement of actin within the sarcomere, thereby causing the whole muscle to generate force and movement [6]. Motor

units are differentiated into three main classes based on the specific type of myosin dimers expressed in the fibers. Slow motor units contain type I myosin that is rich in mitochondria and myoglobin, has high capacity for sustained delivery of ATP from oxidative metabolism and, is able to transduce energy at a relatively slow rate for long periods of time. Fast fatigable motor units express type IIx myosin that transduces energy from the glycolysis of glycogen at a faster rate than type I myosin, thus providing considerable energy over a relatively short time period and generating more force at higher velocity than slow motor units. Fast fatigue-resistant motor units contain type Ha myosin, that transduces energy at a rate which is intermediate between slow and fast fatigable motor units. These motor units are intermediate in cross-sectional area (CSA) between type I and type IIx and are also intermediate in term of the number of fibers and the velocity of contraction [6].

The interaction between muscles and bones generates movements. The mechanical properties of both skeletal and muscle systems, i.e. musculoskeletal system, and the complexity of their physical interfacing and molecular signaling clearly influence the forces transmitted to the surroundings, the speed of motion of the bones that the muscles attach to, and the stresses involved within the bones.

Aging is accompanied by changes in the musculoskeletal system including a decrease in lean mass and bone, and an increase in fat mass [7]. In the Delmonico *et al*. longitudinal study, men aged 85+ years have significantly lower body weight and lean mass than those aged 65–69 years and experience cross-sectional and longitudinal losses of muscle mass and strength that are twice what is observed in women [8]. Women, on the other hand, experience over 50% larger lifetime loss of bone mass and strength, driven by loss of estrogens [9]. Even if weight is maintained constant over life, with aging the body becomes relatively fatter due to the gradual replacement of many tissues, including bone marrow and muscle, by fat. Furthermore, the musculoskeletal system undergoes inevitable physiological changes of its structure, in terms of mass, geometry and composition, that changes gradually impair functionality and at certain impoverishment threshold they promote the onset of pathological conditions, named osteoporosis and sarcopenia [10–12]. Both conditions co-exist in older people and share genetic, environmental and health-related intrinsic and extrinsic factors [13–15]. For instance, many pathological conditions, i.e. diabetes, use of steroids, being bedridden, may accelerate the progression of musculoskeletal age-related changes and the onset of their disabling consequences. Indeed, age-related sarcopenia and osteoporosis when not recognized and treated, increase the risk for falls and fractures, thereby making older individual more susceptible to mobility limitations and, ultimately, to severe disability [16, 17].

Within this framework, we aim to review the current literature in order to I) summarize the age-related bone and muscle changes; II) examine the interactions between muscle and bone from mechanical to biological levels; III) analyze the pathways through which age-related musculoskeletal changes, osteoporosis and sarcopenia negatively impact mobility; IV) outline the current evidence for the efficacy of the pharmacological and non-pharmacological countermeasures for age-related musculoskeletal changes and their disability burden.

2. MUSCULOSKELETAL AGE-RELATED MODIFICATIONS

The progressive loss of musculoskeletal mass and strength, commonly named osteopenia for bone and sarcopenia for muscle, is considered an universal phenomenon with structural and functional features secondary to a complex and multifactorial etiology. Bone undergoes loss of density, changes in the geometry, i.e. their cortical and medullary area, and modifications in the architectural characteristics, i.e. trabecular thickness and cortical porosity, as well as in the number and activity of osteoprogenitor cells within the bone marrow (BM) environment. Muscle shows myogenic and neurogenic adaptations in the composition and the contractile properties of the fibers, loss of motor neurons, less muscle cell recruitment at the neuromuscular junction, unbalance in muscle protein turnover, increased cell signaling pathways leading to apoptosis, and decreased muscle regeneration. Several morphological aspects of age-related bone-muscle changes are known, but the triggers and the many factors accelerating them are still to be defined. Recognizing the age-related changes and the underlying causes and mechanisms is expected to facilitate the development of agents to blunt these processes and to design intervention trials that target one or more of such underlying mechanisms.

2a. Bone

Bone density—Both sexes lose areal bone mineral density (aBMD) at relatively slow rates starting at around age 40, approximately 0.5% per year. Women experience an accelerated loss of aBMD in their 50s, approximately 3% to 5% per year, at the onset and during menopause. Postmenopausal women lose trabecular BMD rapidly in their vertebrae, pelvis, and ultradistal wrist, while less rapid is the cortical bone loss in long bones and vertebrae. About 8–10 years after menopause, a slower age-related bone loss becomes prominent and continues for the rest of life [18]. Men, who do not experience sudden loss of gonadal sex steroid secretion, have slower age-related bone loss through their adult life past about age 40 [19, 20]. However, the age-related reduction in bone mass is disproportionally related to skeletal weakening, thus suggesting that architectural changes are important determinants of bone quality and strength.

Bone geometry—Both sexes have a specific age-related rate of periosteal apposition and endocortical reabsorption. A steeper periosteal apposition in men than in women increases the total bone area at both central and peripheral sites, while a larger endocortical reabsorption, much higher in women than men, widens the medullary cavity [21, 22]. In humans and mice alike, the rate of endosteal bone loss is comparable between males and females, whereas periosteal apposition is substantially more pronounced in males, leading to different patterns of cortical expansion [23]. Periosteal apposition in men occurs mostly at younger ages, whereas in women it is evident across the entire lifespan. Endocortical reabsorption in women occurs over the aging process and may considerably exceed the effect of periosteal apposition as compared to men. In spite of specific sex- and age-related geometric changes, the cross-sectional moment of inertia—a derived parameter that summarizes how parallel changes in bone material and in bone geometry translate into changes in bone mechanical properties—declines over the lifespan in both sexes, but in women more steeply as compared to men [24].

Cortical and trabecular bone—Both cortical and trabecular bone undergo age- and sex-related physiological changes, albeit to a lesser extent in the cortical area. The most evident modifications in cortical bone are the decreased cortical BMD and cortical thickness, the increased cortical porosity and the widening of the medullary cavity [25, 26]. Cortical age-related changes are not generalized even at the same cortical envelope, but the magnitude of cortical porosity increases with proximity to the endosteal surface, particularly in women, thus contributing to their enhanced severity of osteoporosis [27]. Cortical porosity results from a negatively balanced osteonal remodeling, which leads to a progressive increase in the size of osteonal canals that merge each other and become superosteons. The number of osteonal canals decreases from the sixth decade and onward [28], resulting in a significant deficit of cortical mineralized matrix and minor resistance to fracturing. Advanced porosity combined with concomitant endosteal and periosteal bone loss results in marked focal thinning and apparent weakening of the cortex.

The most pronounced age-related modifications in bone architecture are the reduction in trabecular thikness, number and connectivity density. The thinning processes equally shift down the thickness of all trabeculae, leading to the clearance of the smallest interconnecting struts and removal of a higher percentage of the thin struts compared with the thicker trabeculae. In males, with aging the rate of bone loss is inversely related to the thickness of individual trabeculae, with the thickest struts remaining unaffected [29, 23]. The thickest trabeculae are probably those in direct continuation (with no branching) with the cortex and, as observed primarily in males, it appears that they benefit from the relative cortical resistance to age-related thinning [30, 31]. It is well documented that age-related thinning and/or loss of interconnecting struts precedes the deterioration of the main struts, which in part explains the discrepancy between the age-related decreases in bone density and bone strength [32]. The thinning and clearance of interconnecting struts make the trabecular bone more susceptible to buckling under normal compression loads and vulnerable to unusual or off-axis loads.

Bone cells, matrix and microcracks—With aging the bone turnover becomes attenuated and unbalanced, such that the amount of deposited bone is less than that removed. The half-life of the bone matrix is extended, as is its exposure to fatigue damage and microfracture, resulting in inferior material properties [33]. The major bone cell population consists of osteoclasts, terminally differentiated myeloid cells that are uniquely adapted to remove mineralized bone matrix, osteoblasts, developed from pluripotent mesenchymal stem cells in bone marrow, and osteocytes, which are osteoblasts terminally differentiated and surrounded by un-mineralized osteoid matrix. The signals that lead to differentiation of osteoblast precursors decrease, while those promoting their apoptosis increase with age. Both mechanisms may contribute to the loss in osteoblast numbers and may account for a significant reduction in bone formation.

Rather than having a fixed lifespan, osteocytes die by a stochastic process occurring at a fractional rate of about 2.5% per year. In deep bone (more than 45 μm from the surface) that is rarely or never remodeled, osteocyte density declines exponentially with age, approaching an asymptotic value which at the age of 75 years is about 40% of the value at age 20 [34]. Osteocyte death is a major contributor to the decline of bone mass and strength with age,

and the likely mechanisms are the autophagy failure and nuclear pore “leakiness” associated with oxidative stress damage [35]. Therefore, osteocyte death is evidently dependent on the biological age of the bone, not on the chronological age of the subject. Another aspect observed in elderly individuals is the decline in osteocytic lacunae, the increased amount of hypermineralized calcium phosphate inclusions and deprivation in osteocytic canaliculi. The age-related deprivation in osteocytic canaliculi is more pronounced in the endosteal than in the periosteal part of the cortical envelope. The progressive accumulation of hypermineralized inclusions is sometimes referred to as micropetrosis. Based on the size and distribution of the inclusions it has been suggested that they are hypermineralized occluded lacunae. It is yet unclear how the lacunar occlusion affects bone function [36].

The rate of bone remodeling and the amount of bone deposited with each cycle of remodelling decrease with aging, possibly due to a reduction in the number of cell precursors of osteoblasts, stem cells from which these precursors are derived and osteoblasts’s lifespan. The net result is a decrease in the amount of bone with age, starting fairly early in life [37, 38].

The process of mineralization is also affected by reduced age-related bone remodeling. Mineralization is the percent of the solid phase of bone that is mineral; a related measure is tissue mineral density (TMD) which is mineral content per volume of solid tissue [39], and is not the same as BMD, which is defined as mineral content per total area (aBMD) or volume (vBMD), and is thus influenced by porosity in bone. Data suggest an age-dependent increase in average mineralization of cancellous and cortical tissue in women and men (18–96 years), partly due to accumulation of elderly tissue fragments [40, 41].

Microcrack, a rather new micro structural feature that dramatically increases with age, consists of microscopic damage that accumulates in bone tissue due to mechanical stress associated with physiologic loading [42]. The microdamages result in part from the embrittlement of bone collagen due to advanced glycation end products (AGEs) and the detrimental changes in the collagen protein network [43–45]. The cracks propagate easier through old bone tissue; therefore, bone becomes more brittle as it ages and less capable of absorbing energy before it fractures [46]. Microdamages are thought to have a marked impact on bone strength and are associated with bone fragility fractures [23].

Bone marrow—Age-related bone changes may depend on the structure and function of BM that contains mesenchimal stem cells (MSCs) [47]. MSCs give rise to several different phenotypes, including osteogenic and myogenic cells, hematopoiesis-supportive cells and adipocytes. Although the cell population size in the BM remains relatively constant, with aging there is a shift in balance from a stroma that actively supports osteogenesis and exuberant hematopoiesis to one that is primarily adipogenic and supports an altered form of hematopoiesis. The BM of young individuals is virtually devoid of adipocytes. In osteoporotic and older subjects, an adipose replacement in BM and an increased adipogenic differentiation of MSCs at the expense of osteoblast differentiation have been demonstrated [48, 49]. The cause for this age-related shift in phenotypic expression might be due to coexisting changes in systemic and local factors to which the bone precursors are exposed. Among factors intrinsic to stromal cells and BM environment are somatic mutations, altered

gene expression and cellular differentiation, reduced mitochondrial activity and/or mitochondrial dysfunction with increased reactive oxygen species (ROS) generation, altered response to growth factors, accumulation of AGEs and increased expression of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)- α.

Hormones—Among systemic factors that influence bone remodeling, a major role is played by age-related declines in sex steroids, i.e. estrogens and testosterone, growth hormones, vitamin D and PTH. Several lines of evidence show that low estrogen levels contribute to bone loss and fracture risk later in life [50, 51]. In postmenopausal women, a threshold level of serum bioavailable (non-sex hormone binding globulin [SHBG]-bound) estradiol below 11 pg/mL leads to trabecular bone loss, whereas a threshold level below 3 pg/mL to cortical bone loss [52]. Estrogens contribute to bone health by modulating several pathways: decreasing the differentiation of osteoclast precursors by blocking RANKL/M-CSF-induced activator protein-1-dependent transcription [53, 54]; suppressing RANKL production by osteoblastic cells, T- and B-lymphocytes; inhibiting the activity of mature osteoclasts by direct receptor-mediated mechanisms [55]; modulating the production of IL-1, IL-6, TNF-α, macrophage colony-stimulating factor (M-CSF), and prostaglandins [56]; enhancing osteoblast differentiation [57]; inducing osteoclasts apoptosis mediated by transforming growth factor (TGF)-β [58]; and increasing osteoprotegerin (OPG) and TGF-β production by osteoblastic cells [59]. Therefore, estrogen deficiency favors bone resorption by increasing osteoclast recruitment and activity, probably by decreasing their apoptosis. Longstanding estrogen deficiency leads to chronic negative calcium balance due to reduced intestinal calcium absorption [60] and renal tubular calcium resorption [61]. Unless negative calcium balance is compensated with adequate calcium supplementation in presence of sufficient levels of vitamin D, secondary hyperparathyroidism develops, leading to an increased bone resorption. Indeed, the increase of PTH as a compensatory response to low calcium levels, stimulates osteoclast activity, which maintains normal serum calcium levels at the expense of bone mineralization. Other multiple factors may increase the PTH secretion with age, including vitamin D deficiency which is common in postmenopausal women [62] and in older men [63]. Although PTH secretion increases in aging men similar to what is seen in aging women [19, 52], it has been more difficult to demonstrate a direct role for PTH in causation of age-related bone loss in men [64].

For many years it was assumed that decreased serum testosterone, a dominant gonadal steroid in men, is responsible for male age-related bone loss. It likely contributes to a reduced fracture risk in men because of its influence on increasing bone size during growth and development [10] and favoring bone periosteal apposition, at least in rodents [65]. Recent data clearly suggest that the age-related decline of free testosterone levels might play a role in bone loss of older men mainly because it is the substrate for aromatase, which converts testosterone to estrogen. Therefore, decreasing levels of bioavailable estrogen may play a significant role in mediating age-related bone loss in men, similar to women [66]. Cross-sectional observational studies show that age-related bone loss at various skeletal sites in men correlates better with serum estradiol than testosterone, and serum total or bioavailable estradiol positively correlates with BMD [67–69].

Ultimately, with aging bone remodeling and formation might be blunted by the low production of growth factors, i.e. GH and IGF-I, necessary for osteoblast differentiation and function. The age-related decrease in amplitude and frequency of GH production by the pituitary gland leads to decreased liver production of IGF-I. Both IGF-I and IGF-2 levels decrease with age, but IGF-2 less rapidly. Decreased systemic and local skeletal production of IGF-I and -2 as well as increased levels of growth factor binding proteins might down-regulate bone modeling and up-regulate remodeling in older persons which is not adequate to maintain BMD [70, 71].

2b. Skeletal Muscle

Muscle mass, strength and tissue composition—Lean muscle mass and strength decline starting approximately at 40 years of age to become 25% of body weight at 75–80 years old. Skeletal muscle CSA and muscle circumference decrease by 40% from the age of 30 to 60 years and by 25–40% per decade after 60 years, with a steeper trend in men compared to women [110–112]. The loss of muscle strength is as great as 20–40% by the 7th decade and greater after 80 years [113]. The velocity at maximal power decreases by roughly 18% between ages 20–29 and 50–59, and by a further 20% between 60–69 and 80–89 [113]. Overall, the loss of muscle mass, strength and power appears greater in men as compared to women, steeper in older as compared to younger persons and superior in the lower limbs than in the upper limbs [72, 73].

The age-related decline of muscle mass is associated with an accelerated loss of the type IIx (fast) as compared to type I (slow) fibers, and a decrease of the myosin content per half-sarcomere. At the microstructural level, the average CSA of type I fibers slightly declines and the percentage of the total muscle CSA occupied by type I oxidative fibers tends to increase with age, whereas type IIx fast glycolytic fibers become thinner and atrophic. However, the muscle atrophy does not explain entirely the age-related decline in muscle strength. A deficit in contractile force (force normalized to muscle CSA) in aging skeletal muscle has been described and the loss in specific force is a widespread phenomenon involving fast-and slow-twitch fiber. Impairment in the mechanism of excitation-induced elevation of intracellular calcium and energy conversion from ATP into mechanical response might lead to decrease in muscle tension, clinically manifested as muscle weakness [74,75].

Furthermore, as the muscle mass decrease with aging, the area previously occupied by muscle fibers is replaced by fat and connective tissue. Even the residual muscle tissue components might be infiltrated by lipids, which can be contained within the adipocytes as well as deposited within the muscle fibers. The intra-myocellular lipids might result from net buildup of lipid due to reduced oxidative capacity of muscle fibers with aging [77, 76, 77].

Ultimately, as with precursor cells in BM, muscle satellite cells might express both adipocytic and myocytic phenotypes. The expression of the adipocytic phenotype increases with aging [78]. From a biological perspective, this process is still relatively poorly understood in terms of its extent and spatial distribution. However, from a functional point of view, it has been demonstrated that the fat content of skeletal muscle is inversely

associated with bone strength at both trabecular and cortical level of the tibia and the femur, increasing the risk for fragility fractures [79, 80].

Motor unit structure and properties—According to some authors, neurogenic mechanisms might drive the age-related changes in muscle tissue and performance. These include the reduction in the number and size of the spinal cord motor neurons, alterations in axonal flow and in the neuromuscular junction. As the motor units are lost via neurodegeneration of the multiple levels of nervous system involved in their control, remaining motor units tend to recruit denervated fibers and to cluster similar fiber types changing the fiber type into that of the motor unit. As the type II fibers are recruited into slow motor units, there is a net conversion of type II fibers into type I fibers, with an increase in hybrid type I and II fibers. The reinnervation of fast fibers by axonal sprouting from slow fibers causes the final motor units to lose the mosaic-like appearance typically of young muscle tissue [81, 82]. Although the functional significance of motor unit remodeling still needs to be determined, the single fiber intrinsic force and the aggregate power-generating capacity of the remaining or clustering fibers decline with aging. Several factors might explain these findings: the increased noncontractile area within the motor units, the actin-myosin cross-bridge instability between the fibers, and the alterations of the excitation-contraction coupling process [83, 84]. Other findings suggest alterations of the myelin sheaths, reduced number of spinal cord motor neurons, increased size of terminal areas and few synaptic vesicles in the neuromuscular junction, high amount of neurotransmitters released in nerve impulses. However, the loss of motor neurons and the changes in conduction velocity in peripheral nerves might be irrelevant with aging and they often occur after the eighth decade when the loss in muscle mass and strength are already established [85].

Muscle regeneration—From a different prospective, the poor muscle regeneration by satellite cells in response to injury is considered the cause of impaired reinnervation of the myofibers [86]. The satellite cells are resident progenitors, located beneath the basal lamina of myofibers, responsible for postnatal growth, repair, and maintenance of skeletal muscle. They are generally considered as unipotent stem cells with the ability to differentiate into myogenic cell linage. In normal condition and undamaged muscle, satellite cells are maintained in a quiescent status, while muscle injury activates them. In humans, the number of satellite cells declines with aging, the response of satellite cells to activating stimuli is delayed and the secondary proliferative expansion reduced [87–89]. These age-related changes might be enhanced by modifications of the niche environment, i.e. thickening of the interstitium, reduced blood supply and remodeling of neuromuscular junction, and by the expression of local diffusible molecular regulators, called myogenic regulatory factors (MRF) [90].

Pre-clinical studies have found that the expression of MRFs, such as myogenic determination factor (myoD), myogenic regulatory factor 5 and myogenin, is decreased in older compared to younger skeletal muscle. A reduced or delayed expression of MRFs in humans might impair the proliferation and differentiation of myoblasts more than their number [91, 92]. Myostatin, a member of the transforming growth factor-beta superfamily,

is a negative regulator of the differentiation and the proliferation of myogenesis by reducing myoD and myogenin. The effect of age on myostatin expression is still under investigation. A cross-sectional study does not report changes between young and older men in myostatin expression in the vastus lateralis muscle, while a similar study in older women find a 56% increase in myostatin expression at the same site [93–95]. Ultimately, the age-related impairment of muscle cellular regeneration has been attributed to modifications of Notch and Wnt signaling pathways. Notch receptor activation usually controls myoblast proliferation, but in aged muscle there is a decreased Notch expression. The increased Wnt signaling with aging might promote the conversion of the satellite cells from a myogenic to a fibroblastic lineage, thus inhibiting myogenicity and contributing to muscle fibrosis and impaired muscle repair [96–98].

Protein unbalance—A long-term unbalance between the rate of protein synthesis and the rate of their breakdown might sustain age-related loss of muscle tissue. The muscle protein unbalance is due to nutritional, hormonal, local, systemic and environmental factors. The anorexia of aging and its underlying mechanisms contribute to muscle impoverishment by reducing total and essential amino acid intake. In addition, the decreased expression of anabolic hormones with aging does not support adequate protein synthesis, while the increased expression of endocrine and inflammatory factors usually sustain protein degradation. The ubiquitin-proteasome pathway is the most important mechanism for protein degradation in skeletal muscle cells. This system involves a series of enzymatic steps in which the proteins are targeted by an enzyme system that binds them to a polypeptide ubiquitin. The ubiquitinized proteins are then transferred to the proteasome complex and degraded into short peptides which are finally recycled as free intracellular amino acids. This pathway is promoted by inflammatory cytokines, such as TNF-α and IL-6, by hormones such as Cortisol and angiotensin, as well as by ROS [99].

Hormones—Several studies have shown that age-related decrease in anabolic hormones, i.e. GH, IGF-I, insulin and sex-steroids, and the increase in catabolic hormone, i.e. Cortisol, and angiotensin might affect skeletal muscle by causing fiber atrophy. At molecular level, anabolic hormones stimulate muscle protein synthesis through the activation of the phosphatidyl inosito13 kinase/serine-threonine kinase AKT system and the mammalian target of rapamycin and SGKI. Anabolic hormones might also inhibit muscle atrophy by phosphorylating the forkhead protein FOXO and inactivating FOXO, which reduces the expression of the E3 ligase, atrogin I, and subsequently prevents protein degradation by shrinking the expression of the ubiquitin-proteasome system [100,101].

GH and IGF-I are well-known promoters of protein synthesis in skeletal muscle fibers. GH-induced muscle growth might be mediated in endocrine manner by circulating IGF-I, but also in autocrine-paracrine manner by direct expression of IGF-I and GH receptors on target muscle. Their effects on muscle are mediated by a set of transmembrane receptors that bind insulin and IGF-I. They regulate proliferation, differentiation and fusion of skeletal muscle precursor cells by activating a complex array of cell signaling pathways which are anabolic, anticatabolic and antiapoptotic. The age-related loss of IGF-I has been linked to low protein synthesis, low muscle cell activity and motor neuron function, alteration of the pathways

controlling the calcium-induced contractility of muscle fibers, impaired proliferation of muscle progenitor cells and weakened integration with the existing fibers during the muscle repair process [102–104].

The epidemiological findings concerning the effects of estrogens and testosterone on age-related muscle changes are still controversial. Estrogens might have a direct effect on muscle mass since it has been shown that skeletal muscle has estrogen α-receptors (ER-α) on the cell membrane. The detrimental effects of low estrogen levels on muscle mass might be mediated by an increase of proinflammatory cytokines, such as TNF-α and IL-6. Age-related decline in testosterone levels might also impair muscle protein synthesis, but its effects on muscle might be modulated by several other factors, including genetic background, nutrition and exercise [105–108].

Although insulin resistance has been associated with detrimental muscle tissue features, i.e. mass loss, fiber atrophy, intramyocellular fat mass deposition and mitochondrial dysfunctions, the role of insulin in the onset and progression of sarcopenia is still controversial [109].

Regarding catabolic hormones, Cortisol is known to stimulate degradation and to inhibit synthesis of muscle proteins [110]. Long-term exposure to high Cortisol levels has negative effect on muscle strength and mass mainly through detrimental effects on type II muscle fibers, as demonstrated by glucocorticoid-mediated atrophy [111]. In clinical setting, high levels of Cortisol have been found in sarcopenic older persons as compared to those not sarcopenic [112]; low muscle density, atrophy and weakness in patients with Cushing's syndrome as compared to those without such a condition; and in older individuals with poorer physical performance [113,114].

Other hormonal factors might modulate age-related sarcopenia. Low levels of vitamin D are associated with low muscle mass, low muscle strength and increased risk for falls. The nuclear effects of 1,250H vitamin D have been described in muscle cells and low levels of vitamin D impair muscle anabolism. The PTH might also modulate the muscle tissue functioning through an increase in intracellular calcium or an induced pro-inflammatory pathway [115].

Inflammation—Several lines of evidence point to inflammation as a chronic age-related condition associated with loss of muscle mass and strength, and weakness in the elderly. Low grade inflammation increases the expression of pro-inflammatory cytokines and higher levels of IL-6, TNF-α, IL-1β and /or IL1β have been associated with sarcopenia. Comparison of skeletal muscle biopsies from younger and older subjects showed increased expression of genes up-regulated by inflammatory factors. Age-related subclinical inflammation might promote muscle atrophy by accelerating muscle cell protein degradation and weakening muscle protein synthesis. Both increased IL-6 and TNF-α levels are linked with higher concentration of Cortisol, cause DNA fragmentation and apoptosis by stimulating NFkB to produce caspase 8. Pro-inflammatory cytokines may also stimulate MRF-1, which activates the ubiquitin-proteasome system. In older men and women, higher levels of IL-6 and C-reactive protein (CRP) are associated with a two- to threefold greater

risk for losing more than 40% of grip strength over 3 years [116–120]. In animal studies, the administration of IL-6 or TNF-α increases skeletal muscle breakdown, decreases the rate of protein synthesis, and reduces plasma concentrations of IGF-I. However, blood IL-6 should be differentiated from the muscle-derived form of IL-6 produced during exercise. The former is considered proinflammatory playing an intimate role with IL-1β and TNF-α in the induction of sickness behavior, the latter might have anti-inflammatory effects by inhibiting TNFα and the apoptotic pathway. In addition, evidence suggests that disease-related inflammation (congestive heart failure, renal failure, rheumatoid arthritis or cachexia secondary acquired immunodeficiency or cancer) might contribute to the debilitating muscle atrophy [121–123].

Oxidative stress—Age-related deterioration of muscle function may involve damage of muscle proteins by ROS and nitrogen oxidative species (NOS) generated during oxidative metabolism. Muscle contraction implies rapid changes in oxygen flux and energy supply, thus increasing the electron leakage from the mitochondrial electron transport chain and the exposure of muscle protein to oxidative stress. Fast-twitch glycolytic fibers might be more susceptible to oxidative stress than slow-twitch aerobic fibers. These fibers produce more ROS via mitochondrial oxidative phosphorylation but have higher antioxidant capacities that prevent or attenuate oxidative damage [124], Post-translational chemical modification of proteins induced by ROS and NOS might affect their structural and functional integrity up to impair the muscle contraction [125, 126]. Furthermore, the high concentration of heme-containing protein, i.e. myoglobin, and the accumulation of ROS over time might damage cell components, including mitochondria and DNA sequences, both conditions conferring greater sensitivity to oxidative damage. Alteration of mitochondrial DNA (mtDNA) increases with age in skeletal muscle, and the frequency of abnormal mitochondrial regions is higher in muscles strongly affected by sarcopenia. The mtDNA modifications induced by ROS might prompt muscle cell apoptosis, mitochondrial structural changes and electron transport chain uncoupling until to impair cell respiration and metabolic functions [127–129].

Apoptosis—That is a programmed cell death contributing to the loss of myonuclei and theoretically of the complete muscle fibers. Intrinsic and extrinsic stimuli might be responsible for the induction of apoptosis which is ultimately mediated by signals as ligands for the death receptors and calcium regulators. Intrinsic pathways to apoptosis are those initiated by ROS and activated by disturbances in intracellular calcium homeostasis, which involves caspase-12. Since accelerated apoptosis of myocytes has been associated with mtDNA mutations in the muscle tissue, it has been postulated that apoptosis can be the link between mitochondria dysfunction and loss of muscle mass. Extrinsic stimuli or ligand-induced apoptosis are mediated by the TNF-α receptor which causes the activation of initiator caspase-8 and then the executor caspase-3, -6 and -7. The role of extrinsic factors might be more relevant within aging and associated with an increased level of several caspases [130].

3. EVIDENCE FOR BONE-MUSCLE INTERACTION

The relationship between muscle and bone has been regarded as self-evident for many years, but confirmed through direct measurement of muscle and bone mass in recent decades. Appendicular skeletal muscle mass and muscle CSA positively correlate with BMD at several body sites [131–137]. Handgrip strength reveals the strongest positive correlation with the forearm and upper limb BMD [138–141], but a weak association with femoral [142, 143] and lumbar BMD [144]. Based on these findings a site-specific muscle-bone relationship has been postulated. Muscle area is positively associated with cortical bone area in children, young and adult persons, with a higher endosteal apposition in women while a greater periosteal expansion in men [145]. Muscle volume and estimated torque of lower leg have been suggested to explain differences in structural bone strength [146]. Except one study that shows a positive association between walking parameters and higher bone stiffness index, no further observational data support correlation between measures of physical performance and leg or lumbar spine BMD [147,148].

Exercise interventions in postmenopausal women produce a small but significant increase in the trabecular and cortical vBMD, especially among those in longer duration exercise programs (12 months) and within 10 years from menopause [149]. In men, exercise interventions positively impact hip BMD with changes almost superimposed to that caused by unsupervised 30 minute walking [150]. On the contrary, microgravity by decreasing the muscle stimuli on bone may induce substantial and significant loss of trabecular and cortical bone in the hip and somewhat smaller losses in the spine [151]. Six month bed rest, used to simulate the effects of microgravity and disuse, is associated with a reduction in bone density of tibia and trabecular density of radius, a loss in the trabecular number and increase in trabecular separation at both sites, independent of nutritional and physical exercise countermeasures [152]. Conversely, a positive association has been demonstrated between BMD of various skeletal sites and marker of physical performance, i.e. walking speed and distance, step length, one-leg-stance time [153].

Few studies investigate the coexistence of advanced bone and muscle loss. Middle-aged and elderly community-dwelling men with sarcopenia are more likely to have osteoporosis than those with normal skeletal muscle mass (Odds Ratio = 3.0; 95% CI=1.6–5.8) [154]. Hip fractured men have higher probability to be sarcopenic than women, but in both sexes sarcopenia is significantly associated with osteoporosis [155,156].

The close coupling between muscle and bone systems has been largely discussed in the context of the “bone-muscle unit” proposed within the mechanostat theory [157]. Bone adapts its morphology and strength to the long-term loads exerted by muscle contraction, as a result of physical activity and gravitational forces. Bone responds to the varying strains imposed by increases or decreases of mechanical loading conferred by muscles, with sharp losses or modeling effects triggered when strains fall below or exceed set-points. The set-points are gender-specific and might depend on the interaction with systemic factors [158].

Osteocytes are the mechanosensors of modifications of fluid flow within bone canaliculi occurring during deformation of bone microarchitecture secondary to loading forces.

Osteocytes initiate the bone remodeling cycle thought the recruitment of osteoclasts to the bone surface [159]. Although the exact mechanisms by which osteocytes act as a mechanosensor is yet to be revealed, the sensing of mechanical strain leads to changes of ion channel activities, stimulation of mitogen-activated protein kinase (MAPK) and transcription of gene patterns depending on the target cells. Individual mechano-responsiveness have been shown to depend on genetics and gender, while controversial remains the role of age [160].

Emerging research points to a bidirectional signaling between muscle and bone, broadening the relationship beyond that of a purely mechanical perspective. Systemic and local non-mechanical factors may also modulate the skeletal mechano-responsiveness *per se* with direct effects ("help or hinder") on the mechanosensitivity threshold. Anabolic hormones influence loading related bone formation in a permissive manner by lowering the modeling set point, thus promoting bone gain, and raising the remodeling set points, reducing bone loss. Estrogen, GH and IGF-I that decline as a function of age, are critical factors for the maintaining of the mechano-sensing and -responsiveness threshold in the bone-muscle unit [161].

According to *in vitro* and early-stage loading-induced *in vivo* responses, estrogens hold a permissive role on the osteogenic effects of mechanical loading. At the cellular level, bones respond to mechanical loading by a series of molecular events that depend on the presence of functional ER-α and -β Prompted by the findings that the number of ER-α declines with aging and after menopause, postmenopausal osteoporosis *perse* would be attributable to the de-sensibilizzation of bones to loading stimuli and the amplified action of pro-resorption cytokines induced by estrogen-withdrawal [162, 163].

Along with *in vivo* animal models, GH and its downstream effector IGF-I, seems to potentiate the effect of muscle loading due to exercise, as demonstrated on periosteal bone formation at several sites (vertebrae, femoral diaphysis, neck and distal metaphysis) [164]. In older men, those with higher IGF-I circulating levels have increased femoral neck density [165]. The reduced expression of IGF-I in muscle, which remains lower in the older as compared to the younger men, might let down the mechanosensitivity of osteocytes. In addition, animal and co-colture models confirm that skeletal muscle is a local source of IGF-I and fibroblast growth factor 2 (FGF-2). Both molecules act as osteogenic-related factors by binding their receptors localized at the periosteum.

A paracrine mechanism for increasing mechanosensitivity has been also hypothesized. Since bone receives anabolic stimuli from muscle in the form of paracrine signals, then it is also possible that catabolic changes in muscle produce anti-osteogenic modifications in bone. Such a relationship has been revealed between myostatin and bone. In spite of its inhibitory effects on muscle, myostatin is considered an important myokine for bone. Myostatin deficiency or loss of myostatin function increases osteogenic differentiation of BM-derived stem cells, bone mass and bone repair [166]. Thus, conditions up-regulating myostatin secretion would cause muscle atrophy and suppress bone formation through its antiosteogenic effects.

More recently, the possibility of a relationship between bone and fat has also been acknowledged. With respect of aging, changes in body composition mainly consist of fat gain and muscle loss, which are accompanied by loss of muscle quality. Independent of BMD, muscle CSA and strength, fatty infiltration of muscle fibers increases the risk for fractures in the Health-ABC participants [167, 168]. Direct and indirect feedback loops link adipose tissue to bone, at least in part mediated by the effects of leptin. This is a cytokine-like hormone secreted by adipocytes via central and peripheral means. Centrally, leptin prevents bone mass accrual through the combined action of the sympathetic nervous system (SNS) and cocaine- and amphetamine-regulated transcript (CART) activation. In the brainstem leptin inhibits the synthesis and release of serotonin from the raphe nuclei. Brain-derived serotonin binds to HTR2C receptors of ventro-medial neurons of the hypothalamus, decreases signaling of the SNS, and thus increases bone mass accrual [169]. On one hand, leptin reduces serotonin synthesis and increases SNS signaling on the osteoblasts via β2 adrenergic receptors. The SNS activity might support bone resorption and loss through the inhibition of osteoblast proliferation and the promotion of RANKL expression. On the other hand, leptin binds to receptors on the neurons of the arcuate nuclei and increases the expression of CART gene, that decreases RANKL expression by osteoblasts and inhibits bone resorption. Whether CART affects gene expression in osteoblasts via a direct or indirect mechanism remains currently unknown [170].

Peripherally, leptin interacts with BM stromal cells increasing the expression of osteogenic genes, directing the MSC to the osteogenic instead of the adipogenic pathway and inhibiting the expression of the receptor activator of nuclear factor-κB-ligand, the major downstream cytokine controlling osteoclastogenesis. Leptin might also enhance osteoblastic differentiation and activity by inhibiting their apoptosis, stimulating *de novo* collagen synthesis and mineralization [171–174].

Intriguing studies have linked leptin to osteoprotegerin (OPG) expression and bone derived osteocalcin (OC). Leptin might stimulate stromal cells to increase expression of OPG and ESP gene in osteoblasts. ESP gene encodes for the intracellular protein tyrosine phosphatase (OST-PTP), favoring the maturation of undercarboxylated OC. Undercarboxylated OC acts as a hormonal factor modulating the pancreatic β-cell proliferation, the secretion of insulin by β-cells and the insulin sensitivity in muscle, liver, and adipose tissue via the expression of an insulin sensitizing adipokine (the adiponectin gene), and the production of testosterone by the Leydig cells [175]. On the contrary, the insulin signaling causes a decrease in osteoprotegerin (OPG) expression and OPG/RANKL ratio, enhancing bone resorption, stimulating OC decarboxylation and inhibiting osteoblast differentiation [173,176].

However, interventional studies suggest that leptin may play a more important role in patients with leptin deficiency. Despite the fact that patients with congenital leptin deficiency have age- and gender- appropriate bone mineral content and bone mineral density, leptin treatment increases their skeletal maturation [177]. In women with hypothalamic amenorrhea, a significant increase in bone-formation markers after leptin administration has been described [178]. However, whether the increase in bone-formation markers is a direct effect of leptin or mediated by restoration of estradiol and IGF-I levels remains unknown. More research is needed to fully elucidate the role of leptin in central

regulation of bone metabolism, since it is unclear if the data derived from rodent studies will apply to humans.

A common multigenetic control on the muscle-bone system may also contribute to the development and preservation of lean mass, BMD and muscle-bone strength. It is becoming apparent that there are several genes involved in the genetic control of maturation, development, and decline of musculoskeletal systems [179–181]. The heritability of lean mass, measured with DXA, has been estimated to vary between 56% and 84% [182] as well as those of bone strength, measured with section modulus of femoral neck, has been reported to be 40 to 55% [183]. However, whether and how these genetic traits interact in order to maintain or promote muscle and bone mass and quality over the lifespan is unknown.

4. OSTEOPOROSIS AND SARCOPENIA: FROM DEFINITION TO THE IMPACT ON MOBTLITY LIMITATION

4a. Osteoporosis, Fragility Fractures and Disability

Definition—Osteoporosis is a skeletal disorder in which the reduction in bone strength predisposes to an increased risk for fractures. It is often referred to as a silent disease, as many individuals do not realize they are affected by it until a fracture occurs [184]. According to the World Health Organization (WHO) criteria, the diagnosis of osteoporosis is officially made based exclusively on BMD that lies 2.5 standard deviations (SD) or more below the average value for young healthy women (a T-score of <-2.5 SD). Although the BMD is considered a good predictor of absolute risk for fracture (absolute risk for hip fracture and for any fracture increase 2.6-fold and 1.6-fold, respectively, per SD decrease in BMD), with aging there is a progressive loss of the power of BMD on predicting hip fracture risk [185,186].

Despite the T-score is still considered the key characteristic diagnostically and it provides an intervention threshold, it has been clear for long time that the risk for fracture increases with age at any given T-score. At the same threshold of 2.5 SD, the risk for fracture rises dramatically from 50 to 80 years of age and most fragility fractures occur in individuals with T-scores greater than >2.5 SD. To date, the combination of clinical factors, such as age, previous fractures, chronic diseases and drug treatment, with bone density estimation seems to better identify subject with high risk of fractures [187,188].

Epidemiology—Osteoporosis affects more than 75 million people in the United States, Europe and Japan and it causes more than 8.9 million fractures annually worldwide. All osteoporotic fractures are more likely to occur in women, mainly due to their lower BMD, different bone geometry, higher life expectancy and an increased risk for falling compared with men. Men lose about half as much bone with aging as women, and suffer one-third the number of fragility fractures as women [189,190].

Disability associated with osteoporosis—Fragility fractures, usually occurring after a low energy trauma at the distal radius, proximal femur, vertebral body or proximal humerus, mainly depend on a compromised bone strength even in the absence of low BMD. Indeed,

bone fragility is a function of the “quantity” of bone, estimated by measuring BMD, and the “quality” of bone, a complex and multidimensional set of bone properties including microarchitecture, turnover, mineralization, and damage accumulation [191–193].

Forearm fractures tend to occur at earlier ages than hip and vertebral ones with a peak incidence in women between 40 and 65 years of age. A prior wrist fracture increases the risk of a future wrist fracture about threefold and doubles the risk of any osteoporotic fracture [194]. In developed countries, one-fifth of Colle’s fracture results in hospitalization and only 50% of patients report a good functional outcome after 6 months [195].

Vertebral fractures cause pain and limitation of the spinal movement, affecting considerably the overall quality of life. Spinal mobility is impaired even in the absence of significant pain (one-third of the vertebral fractures are asymptomatic), and often such undiagnosed vertebral fractures are associated with disability. Dorso-lumbar fractures have the worst impact on spinal mobility. Pain and disability become worse with each new fracture, as does mortality. The probability to suffer a new vertebral fracture increases fivefold during the first year post-fracture compared with the non-fractured patients. One-fifth of patients with vertebral fracture requires hospitalization, and some will require subsequent long-term care [196]. Co-morbidity commonly associated with vertebral fractures, particularly kyphosis, obstructive and restrictive lung disease, bed rest, may contribute to the loss of quality of life and increased mortality at older age [197].

Hip fracture often causes catastrophic disability. Although in developed countries, most hip fractured patients undergo surgical repair of the fracture or replacement of the joint, 20–25% of them die within 1-year. About half of the patients lose their prior level of physical function and many lose their independence and require long-term care [198]. Only half of the survivors will walk again and often not at the same level as prior to the fracture. Assuming no pain prior to a hip fracture, 47% of patients reported bone pain one or more years post-fracture with approximately 23% reported mild pain, 24% moderate pain and 2% severe pain [199]. About 30% of women and 22% of men with a prior history of fracture experience a new fracture during the next 5 years [200]. An official report from the Northern Sydney Area [201] showed that after a 12-month follow-up of community-dwelling patients suffering a hip fracture, 76% were unable to walk as well as before their fracture, and 22% required a new nursing home admission. These findings are similar to those found in a recent meta-analysis on the long-term disability after hip fractures [199], where 20% of subjects with a fracture were no longer able to shop independently as a result of the fracture and 42% of them had not returned to their pre-fracture mobility levels after 1 year. After an osteoporotic fracture rehabilitation is lengthy and many individuals never regain their pre-fracture level of mobility, which may have a significant impact on lifestyle, well-being and quality of life [202].

Therefore, osteoporosis and fragility fractures have a great health and social impact causing for an individual several clinical and health-related consequences, including short-term pain and mobility limitation, increased risk of fracture, chronic disability, the need for long-term care and premature death [203–205]. In the Americas and Europe osteoporotic fractures account for 2.8 million disability-adjusted life years (DALYs) annually and approximately

1% of the DALYs attributable to non-communicable diseases, somewhat more than accounted for by hypertension and rheumatoid arthritis [206]. Older persons with high risk of fractures deserve more attention as an opportunity for prevention of future disability and for reducing health and social impact [207, 208]. Unfortunately, they are not recognized consistently by health care professionals and currently, prevention strategies remain suboptimal [209, 210].

4b. Sarcopenia, Falls and Disability

Definition—Sarcopenia is the term originally coined to describe progressive age-related loss in muscle mass. According to updated definition sarcopenia is a "syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk for adverse outcome, physical disability, poor quality of life and death" [211–213]. Criteria for the clinical diagnosis of sarcopenia, such as the presence of low muscle mass accompanied by low muscle strength and/or low physical performance, have been defined [214]. Specifically, Evans suggests that the diagnosis of sarcopenia should be considered in all older patients who are bedridden, cannot independently rise from a chair, or who have a measured gait speed <1.0 m/s. Patients who meet these criteria should further undergo body composition assessment using dual-energy X-ray absorptiometry with sarcopenia being defined as an appendicular lean/fat mass 2 SD less than that of young adult [216]. The definition of sarcopenia should include the accompanying deterioration of muscle function or muscle weakness. However, some authors suggest that the muscle weakness is inevitable, but not proportional consequence of muscle loss, and therefore, this term should not be used interchangeably with sarcopenia [77]. Practically, this is supported by the evidence that muscle strength does not correlate directly with muscle mass, and the relationship between strength and mass may not be linear [7, 215]. Some authors have argued that with regards to terminology, dynapenia would be a better acronym to describe age-related decline in muscle strength and function [216]. This, however, has not yet been uniformly incorporated into clinical use.

Epidemiology—Within the existing literature, sarcopenia is a highly prevalent condition in older people, with 45% of the older U.S. population having a moderate degree of sarcopenia and 10% have severe sarcopenia. The prevalence of sarcopenia increases considerably with age ranging from 5% to 13% in 60 to 70 years, to 11% to 50% for the population aged 80 years and older [217, 218]. Sarcopenia seems to be more prevalent in men (68%) as compared to women (21%) as demonstrated among Italian NH residents [219]. Estimates from the WHO suggest that there are 600 million people aged 60 years or older in the year 2000 and that the number will increase to 1.2 billion by the year 2025. Conservative estimates based on the prevalence of sarcopenia and the WHO population counts suggest that sarcopenia affects more than 50 million people today and that it will affect more than 200 million people over the next 40 years [220].

Disability associated with sarcopenia—In older persons, sarcopenia is related to falls and physical disability leading to reduced quality of life [217], to increased risk for nursing home placement [221], home healthcare [214], hospitalization and overall healthcare expenditures [222, 223]. Several cross-sectional and longitudinal studies have shown that

sarcopenia explains, at least in part, the high rate of functional impairment, that is a limitation in mobility performance, and physical disability, defined as difficulty or inability in performing activities of daily living, in older persons [224]. Using the definition based on height-adjusted appendicular muscle mass of 2 or more SD below the mean of young adults, sarcopenia has been associated with having difficulty walking in older men and increased risk for fracture in older women [225, 226]. The likelihood of having physical disability was estimated approximately 4 times greater (OR 3.66 IC95% 1.42–10.02 in men and OR 4.08 IC95% 1.52–11.31 in women) in sarcopenic older men and women than in older persons with a normal muscle mass participating in the New Mexico Elder Health Survey [227]. In the Health Aging and Body Composition study, older adults in the lowest skeletal muscle mass quintile (adjusted for height and fat mass) are 80% to 90% more likely to have mobility impairment than older adults in the highest quintile [228]. In the US National Health and Nutrition Examination Survey, the likelihood of functional impairment and physical disability is approximately twofold greater in older men and threefold greater in older women with severe sarcopenia than in older adults with a normal muscle mass. In the same population the relationship between muscle index and physical disability does not appear linear and the odds ratios for physical disability increase in a graded fashion when moving from the low risk to the high risk categories. Based on these findings, approximately 10% of the older American population is considerably more likely to have physical disability and 35% of them is somewhat more likely to have physical disability due to sarcopenia [229]. However, because of the lack of temporality, these early cross-sectional studies cannot infer causation about the relationship between sarcopenia and physical function. Longitudinal findings from prospective cohort studies have examined the influence of sarcopenia, as determined by muscle mass, on the development of functional limitations or disability. Among the participants in the Health, Aging and Body Composition Study, it has been showed that muscle size in the mild-thigh is a weak to modest predictor of a loss in physical function over a 2-to 3-year follow-up [230], while the risk of developing mobility limitations over 2.5 years was found 90% higher in men and 68% higher in women within the lowest muscle size than those in the highest muscle size quintile [12]. In addition, severe sarcopenia is a modest risk factor for the development of physical disability in older women, but not in older men over 8 years of follow-up [227]. Because the influence of sarcopenia on the development of disability appears to be weaker than what was suggested from cross-sectional observations, it implies that the nature of the relationship between sarcopenia and disability is bidirectional. That is, sarcopenia leads to disability, and disability in turn leads to sarcopenia. This pattern of relationship is biologically plausible. Physical disability would lead to a reduced physical activity level, a reduced physical activity level would result in decreased anabolic stimuli to skeletal muscle, and the decreased anabolic stimuli to skeletal muscle would cause significant muscle loss over time.

An additional pathway linking sarcopenia to physical disability may include falls and fear of falling. The evidence that sarcopenia is a risk factor for falls relies on small and heterogeneous studies in which data concerning falls are collected retrospectively. Both lower and upper extremity muscle weakness is a risk factor for falls, with odd ratios consistently higher for institutionalized than community-dwelling older adults [231]. Among men (mean age 74 years) those with sarcopenia have higher risk for falling (OR 2.58 CI95%

1.42–4.73) [230] as well as men aged 50–85 years without sarcopenia are less likely to report a fall in the previous year [232]. Given the increasing aging of the population, the high prevalence of sarcopenia and disability due to sarcopenia impose a significant, although modifiable, economic burden on healthcare services in the majority of industrialized nations [233]. In 2000 it was estimated that the healthcare costs in the United States associated with sarcopenia were $18.5 US billion, which were about 1.5% of total healthcare expenditure [234]. The great health and socio-economic burden of sarcopenia and its consequences clearly makes the condition a priority among the interventions of the health care systems.

5. INTERVENTION STRATEGIES TO COUNTERACT DISABILITY ASSOCIATED WITH SARCOOSTEOPOROSIS

The prevention of mobility limitation and disability associated with the progression of sarcopenia and osteoporosis is mainly based on non-pharmacological interventions, that include nutrition and physical activity, and calcium plus vitamin D supplementation. To date, pharmacological agents are available to counteract the progression of osteoporosis and the onset of fragility fractures, but still needed to be developed and tested for the prevention of sarcopenia and its consequences in humans.

5a. Non-pharmacological interventions

Nutrition—The contribution of nutritional deficiencies and anorexia of aging to the pathogenesis of osteoporosis [235] and sarcopenia has long been recognized. However, the effects of adequate nutrition has not been studied extensively and much of the research in this area is relatively new and minimally based on large intervention trials. The nutrients that have been most consistently linked to sarcopenia and osteoporosis in older adults are vitamin D, proteins, and antioxidants, including carotenoids, selenium, vitamins E and C [236].

Vitamin D—A significant proportion of older population is vitamin D deficient (< 30 ng/ml) owing to low dietary intake, reduced sunlight exposure, and impaired hydroxylation in the liver and kidneys [237]. Vitamin D deficiency is associated with bone loss due to several mechanisms, including reduced calcium absorption, secondary hyperparathyroidism, reduced muscle mechanical stimuli and complex genomic and nongenomic pathways, currently less well understood [238–240]. Vitamin D supplementation may reduce bone loss by reversing secondary hyperparathyroidism and may maintain muscle strength, muscle function, and balance by enhancing at genomic level the transcription of a range of proteins, including those involved in calcium metabolism. The role of vitamin D and the extent to which it has direct effects on normal muscle strength and physical function remains controversial [241–244]. Much of the epidemiological literature is consistent with the possibility that there are direct effects of vitamin D on muscle strength. Systematic review of vitamin D supplementation concludes that it can be advised in older people with low vitamin D levels to prevent sarcopenia and falls. A meta-analysis confirmed that vitamin D dietary supplementation (700–1000 IU per day) may increase muscle strength and performance and reduce the risk of falling by 19% in community-living elderly and nursing home residents with low vitamin D level [245, 246].

Supplementation with vitamin D and calcium decreases bone loss in adult and older persons [247], increases BMD at several body sites [248] and reduces the risk for non-vertebral fractures [249]. A meta-analysis of 17 trials of calcium and calcium in combination with vitamin D (52,625 participants, 46,108 receiving the combination) indicates a 12% reduction in fractures of all types (RR 0.88, 95% CI 0.83 to 0.95) [250], while a meta-analysis from Cochrane collaboration (eight trials involving 46,658 participants), confirms that the combination of vitamin D with calcium significantly reduces hip fractures (RR 0.84, 95% CI 0.73 to 0.96), particularly among older persons living in institutional care [251]. Similarly, a meta-analysis examining 11 studies including 52,915 patients shows that oral vitamin D with - but not without - calcium supplementation reduces fracture risk in adults [252]. The efficacy of supplementation with vitamin D and calcium increases with the degree of vitamin D insufficiency, with age (effect was also greater in people aged > 70 years compared with those aged 50 to 70 years, and in those living in care institutions compared with those living in the community), with a better compliance (rates > 80%). However, the protective effects of vitamin D have not been showed constantly, and in postmenopausal women with adequate vitamin D levels, calcium supplementation may be as effective as vitamin D [253,254].

Protein—Dietary proteins are considered a key nutrient at older age providing amino acids for the synthesis of muscle protein. Absorbed essential amino acids strongly stimulate muscle protein synthesis and inhibit protein breakdown, resulting in a positive net protein balance in both the young and older persons [255–257]. Aging does not inevitably reduce the anabolic response to a high-quality protein meal, which occurs in the presence of low protein and carbohydrate intake. The unbalance between protein and carbohydrate intake may blunt the dose response relationship between protein synthesis and leucine plasma disposal, possibly due to the effects of insulin resistance [258–261].

The majority of evidence regarding the protective effects of protein to prevent osteoporosis and sarcopenia are from observational studies. Small intervention trials have been conducted in older persons to investigate the effect of protein supplementation on muscle metabolism and sarcopenia, but no intervention trial has investigated the protective effects on bone health. A greater loss of lean mass over 3 years was found among older community-dwelling men and women who had low energy-adjusted protein intake at baseline. The differences were substantial, such that the persons with protein intakes in the top fifth of the distribution lost 40% less lean mass over the follow-up period when compared with those in bottom fifth. Protein and amino acid supplementation may have the potential to slow sarcopenic muscle loss. However, whilst some trials show that amino acid supplementation may increase lean mass and improve physical function, other trials have not been successful [262–265]. To date, the daily intake of protein to prevent sarcopenia is equal to 1.2–1.5 g/kg, though the current recommended daily intake for adults is 0.8 g/kg [266]. Older adults should be encouraged to consume a diet higher in lean meat rather than vegetable-based sources or consume essential amino acid supplements particularly if they are engaging in resistance training [267]. There is a general agreement that amino acid supplements without adequate leucine content do not stimulate protein synthesis [268, 269, 264]. In addition, it is more important to ingest a sufficient amount of high-quality protein (25–30 g) with each

meal rather than one large bolus, because greater than 30 g in a single meal may not further stimulate muscle protein synthesis [270]. Ultimately, interventions combining protein or amino acid supplementation with exercise training may be potentially more advantageous on skeletal muscle and physical function. The consumption of a high protein meal has been shown to increase muscle protein synthesis in older adults by >50%, combining a high protein meal with resistance exercise increases synthesis more than 100% [271]. The long-term effects of combined exercise training and high protein intakes are not clear [267].

Similarly, the role of protein intake on the maintenance of bone health and the prevention of osteoporosis and fractures remains controversial [272]. Protein might play a role in the maintenance of BMD through different mechanisms, e.g. by increasing IGF-I, calcium absorption, muscle strength and mass, which all could benefit the skeleton [273]. In a prospective study carried out on more than 40,000 women in Iowa, higher protein intake was associated with a reduced risk of hip fracture, independent of calcium and vitamin D. The association was particularly evident with protein of animal rather than vegetal origin, and the relative risk for hip fracture seemed to decrease parallel to the intake of animal protein [274]. Contradictory results have also been observed. A slightly higher risk for forearm fractures was observed in women consuming more than 95 g per day protein as compared with those consuming less 68 g per day, whereas no association was found with hip fracture [275]. Data from the 1999 to 2002 National Health and Nutrition Examination Survey did not show any protection against fractures in postmenopausal women with adequate total calcium intake in presence of inadequate dietary protein intake, suggesting that an optimal balance between calcium and protein intake is required [275]. Positive correlations were found between BMD and protein intake in a longitudinal research within the Framingham study [276], in a cohort of older men and women receiving calcium and vitamin D supplements [277], in older women consuming less than 66 g protein per day as compared to those eating more than 87 g per day [278, 279]. Conversely, a high diet ratio between animal over vegetable proteins induced a higher rate of bone loss at the femoral neck and an increased risk for hip fractures in older women [280]. It has been hypothesized that excessive protein intake (particularly animal) would create a fixed metabolic acid load due to the high sulfur amino acid content. If the kidneys and lungs are not able to completely handle this diet-induced acid load, a source of additional buffer would be necessary. The large carbonate reservoir of the skeleton would be called upon to provide this buffer, and calcium would consequently be excreted with the carbonate. The clinical consequences would be an increased calciuria potentially favoring bone loss and hip fracture [281].

Antioxidants—Whether high antioxidant intake and status are beneficial in promoting better physical performance, muscular and bone strength is still controversial. Antioxidant intake and circulating levels as well as markers of oxidative damage have been variously correlated with sarcopenia [282], bone remodeling processes, fractures and physical function in older adults [283–285]. Among clinical trials, supplementation with antioxidant lycopene seems to reduce oxidative stress and bone resorption [286]; supplementation of ascorbic acid together with alpha-tocopherol may be useful in preventing or aiding in the treatment of age-related osteoporosis [287]; 6-month daily antioxidant supplements (600 mg vitamin E and 1,000 mg vitamin C daily) offered some protection against bone loss in the lumbar spine

BMD similar in the extent as resistance exercise, although combining both interventions does not seem to produce synergic effects [288].

Even more controversial are the studies concerning the use of antioxidant supplementation for the prevention of sarcopenia. Studies that evaluated oxidative-stress protection showed that carotenoids or carotenoids-rich foods are protective against decline in muscle strength and walking disability among older community-dwelling adults [288]. Other antioxidants, such as α-tocopherol, ascorbic acid, selenium and polyphenols have been studied in older subjects. However, foods may be a favored source of antioxidants for their content of multiple antioxidant substances, vitamins, minerals and fibers, and more studies are needed before older persons should be advised to take antioxidant supplementation for the prevention of sarcopenia and osteoporosis [289].

Physical exercise—Inactivity causes loss of muscle mass and strength at all ages. Older adults who are less physically active are more likely to develop sarcopenia, osteoporosis and to increase the risk for fractures [15, 290–294]. Exercise has been reported as one of the best non-pharmacological ways to improve muscle and bone mass throughout life, and to prevent and treat sarcopenia and osteoporosis. However, not all exercise regimens have the same positive effects. Exercise interventions such as resistance training are used in attempt to restore muscle force. Strength training in sedentary older and younger persons improves metabolic capacities, increases glycogen storage, and enhances oxidative enzyme activity. Aerobic exercise (i.e. swimming, running, walking) involving high-repetition, low-intensity muscle contractions leads to minimal strength gain in comparison to the low-repetition, high-intensity stimulus of resistance training in which strengthening and endurance activities are included. Aerobic exercise may increase muscle area, without causing hypertrophy, and may have muscle quality improving effects, even among the frail older population [295, 296]. Aerobic exercise may increase the mitochondrial volume and enzyme activity, decrease the body fat infiltration of muscle tissue, and stimulate protein synthesis and satellite cell activation [297, 298]. However, it is not clear defined the amount of training, whether aerobic or resistance type in nature, may need intensity more than typical for leisure type of physical activity in order to have significant effects [299, 300].

Data in older men and women suggest a positive association between current exercise and hip BMD, but the effects on fracture are not clear since they are not reported as an endpoint. Strength exercise seems to be a powerful stimulus to improve and maintain bone mass during the ageing process. Among regular exercisers, those who reported strenuous or moderate exercise had higher BMD at the hip than did those who reported mild or less exercise. Similar associations were seen for lifelong regular exercisers and hip BMD. Furthermore, high-intensity strength training effectively maintains femoral neck BMD as well as improves muscle mass, strength, and balance in postmenopausal women compared to nonexercising controls. Then, resistance training would be useful to maintain BMD and to reduce the risk for falls in older adults [241, 301–303].

Multi-component exercise programs of strength, aerobic, high impact and/or weight-bearing training alone or in combination with nutritional or pharmacological agents, may help to increase or at least prevent decline in bone mass with ageing, especially in postmenopausal

women [304, 305]. In a randomized study of women at least 10 years past menopause, the group receiving calcium supplementation plus exercise had less bone loss at the hip than did those assigned to calcium alone. The feasibility, sustainability, and safety of power resistance training in older adults and the influence of nutritional supplementation with power training need to be confirmed by larger longitudinal trials [269]. Of note, walking that provides a modest increase in the loads on the skeleton above the gravity has proved to be less effective in osteoporosis prevention [306]. Weight-bearing exercise, such as walking, can be recommended for older adults who should be encouraged to start slowly, but they should gradually increase the time walked each day.

From the clinical perspective, an important facet of the effects of exercise on muscle and bone tissue is that prevention of sarcopenia and osteoporosis with exercise may not have sufficient power to occur at short period of time, especially among the elderly [307, 311]. Consequently, it is widely accepted that prevention of both conditions should be carried out throughout the entire lifespan.

From a health-care prospective, some issues arise regarding the implementation of exercise training into the community or at home that often may be the only option for frail older people.

5b. Pharmacological interventions

A variety of drugs of proved clinical efficacy are available in the field of osteoporosis and fracture prevention. The most commonly used anti-fracture drugs are those slowing bone resorption, i.e. bisphosphonates (BPs), selective estrogen receptor modulators (SERMs), denosumab as anti-RANKL monoclonal antibody, and those stimulating bone formation, i.e. PTH and teriparatide, while strontium ranelate appears to act through both mechanisms. Despite several and large clinical trials have been conducted, the anti-fracture efficacy of these treatments in older population (>75 years old) mainly relies on subgroup or pooled analysis [308–311].

Conversely, several pharmacologic agents have been proposed to prevent or counteract sarcopenia, including recombinant anabolic hormones, angiotensin II converting enzyme inhibitors (ACEIs) and anti-myostatin agents, but their use is still far from clinical practice.

Anti-osteoporotic drugs—Several randomized clinical trials and metanalysis have been conducted to evaluate the antifracture effects at several bone sites of the available anti-osteoporotic drugs [312–320]. Although few data are available in older groups [321], there is acceptable evidence to recommend the BPs, strontium ranelate, or teriparatide for vertebral fracture relative risk reduction (RRR) in persons aged > 75 years [311, 322]. A significant RRR of vertebral fracture at 1 year has been demonstrated for risedronate (RRR 81%; $p<0.001$), teriparatide (RRR 65%; $p<0.05$) and strontium ranelate (RRR 59%; $p=0.002$), and at 3 years for risedronate (RRR 44%; $p=0.003$), alendronate (RRR 38%; $p<0.05$), strontium ranelate (RR 32%; $p=0.013$) and denosumab in high risk fracture women (16.6% placebo vs. 7.5% denosumab; $p< 0.001$) [322].

Concerning the non-vertebral fractures, there is evidence for protective effects of strontium ranelate after 1 and 3 years of treatment (RRR 41%; p=0.027 and RRR 31%; p=0.011) [311], for denosumab (HR 0.80; p=0.01) [321] and zoledronic acid (HR 0.73, p=0.002) after three years with efficacy almost superimposed to those of younger persons [325]. Risedronate demonstrated to reduce non-vertebral fracture only in a combined analysis of subjects participating in the HIP study (70–79 years and ≥80 years groups) [323].

The studies that specifically investigated hip fracture prevention as the primary outcome — the HIP study [326], the Clodronate Study [322, 324] and the FREEDOM Study (Denosumab: post-hoc analysis and 2-year extension) [321, 323, 325], suggest a weak efficacy after 3 years of treatment. Hip fracture reduction was demonstrated for risedronate in a subgroup analysis including women with osteoporosis (those 70 to 79 years old), where the incidence of hip fracture among those assigned to risedronate was 1.9%, as compared with 3.2% among those assigned to placebo (RRR 0.6; p=0.009). Clodronate showed hip fracture reduction in unselected community-dwelling older women at 1 and 3 years. Denosumab significantly reduced the risk of hip fractures in a subgroup analysis among those older than 75 years (2.3% placebo vs. 0.9% denosumab; p<0.01) or with a baseline femoral neck bone mineral density T-score of -2.5 SD or less (2.8% placebo vs. 1.4% denosumab; p= 0.02) [322, 323]. Strontium ranelate showed antifracture hip efficacy, as a secondary outcome, in the subgroup analysis of women aged ≥80 years [326] and those aged >74 years with more severe osteoporosis of the femoral neck participating in the TRO-POS study [327]. In the pooled analysis from the HORIZON study, the incidence of hip fracture was not affected by zoledronic acid, whereas a reduced incidence of all fracture types appeared in the subgroup of those younger than 75 years [325]. There is no evidence on hip fracture prevention for teriparatide and clodronate at 3 years in the older groups [311, 328, 313, 314]. Teriparatide demonstrated a reduction of low back pain and improvement in quality of life which lasted for at least 18 months after its discontinuation [329]. A critical point in the choice of treatment for osteoporosis in elderly patients is the time to onset of the efficacy. This evaluation is necessary since we know that after a vertebral fracture the risk of subsequent fracture increases fivefold in the first year [200] and these patients who sustain a first fragility fracture are at an increased risk of subsequent fractures in all sites [330, 331]. Strontium ranelate studies reported reduced morphometric and clinical vertebral fractures within 12 months in postmenopausal osteoporotic women [319, 330]. In those aged 80 and over on strontium ranelate, reduction in morphometric vertebral, non-vertebral fractures and any clinical fractures were also observed within 12 months [332]. The earliest efficacy strontium ranelate on hip fracture prevention was observed at 36 months in those aged 74 years and older with BMD T-score less than -3.0 SD [330]. A significant hip fracture reduction was found after 12 months of denosumab treatment in subjects aged ≥75 years with a baseline femoral neck T-score of -2.5 SD or less [322].

In the absence of direct treatment comparison for anti-osteoporotic drugs, some authors proposed an indirect treatment comparison (ITC) approach assessing the relative efficacy in reducing the rates of fractures in a sample of 59,209 post-menopausal women. Using a Bayesian analysis that looked at seven studies including four drugs, specifically zoledronate (1 study), alendronate (3 studies), ibandronate (1 study) and risedronate (2 studies), the ITC approach indicated that zoledronate had the highest efficacy in preventing vertebral and hip

fractures, while risedronate had the highest efficacy in reducing non-vertebral non-hip fractures [333, 334]. The last updated ITC analysis in osteoporosis medications, concluded that based on the combination of effect size and probability of being most efficacious, teriparatide, zoledronate and denosumab are consistently ranked highest for reducing non-vertebral and vertebral fractures [335].

Potential anti-sarcopenic agents: hormones—Although testosterone levels positively correlate with muscle mass and strength [336], protein synthesis, the number of satellite cells [337], testosterone replacement is not recommended for the prevention or treatment of sarcopenia because of side effects, i.e. fluid retention, gynecomastia, polycythemia, sleep apnea [338], increased risk of prostate cancer, and low benefits to physical performance. Newer agents, specific androgen receptor modulators (SARMs), may hold more promise for anabolic effects on skeletal muscle without the side effects, but they are in early stages of clinical investigations [339].

Reduced levels of circulating estradiol seem to correlate with impaired muscle performance and sarcopenia in older women [340]. However, the effect of hormone replacement therapy (HRT) in women is controversial. HRT might decrease the loss of muscle mass and improve physical functioning [341], but it is also implicated with breast cancer [342] and it is not recommended in older adults. Similarly, tibolone (a synthetic steroid with estrogenic, androgenic, and progestogenic properties) is not recommended until further research is conducted to determine the long-term safety in older adults [269].

The effects of recombinant GH supplementation alone or in combination with sex steroids or exercise [343–345] to counter the effects of sarcopenia in older people are weak and still under debate [346]. Some studies demonstrated an increase in muscle mass, but not in muscle strength, others have shown an increase in both muscle mass and strength after administration of GH supplementation [347, 348]. In addition, the combination of GH replacement and exercise training does not improve the effects brought by exercise alone [349]. To date, the use of rGH in older non-hypopituitary adults is not supported as it did not show efficacy, while have reported a high incidence of side effects, i.e. fluid retention, gynecomastia, orthostatic hypotension, carpel tunnel syndrome and increased risk of cancer [350].

Potential anti-sarcopenic agents: anti-myostatin and ace-inibitor—It has been hypothesized that molecules blocking my-ostatin pathway increase muscle mass and play a pivotal role in preventing sarcopenia at older age. Mutations of the myostatin gene was found to correlate with exaggerated muscle hypertrophy [351], while over expression of myostatin to induce extensive muscle loss. However, even if myostatin deficiency increases muscle mass in animal models, the structure and function of muscle tendons are impaired making them smaller, stiffer and brittle [352, 353]. One study tested the use of recombinant antibody to myostatin, i.e. MYO-29, in patients with muscular dystrophy. Initial results have shown a good safety and tolerability profile for the administration of myostatin inhibitors [354] but further studies are needed. Recently, the administration of a soluble activin type 2B receptor demonstrates to reduce the availability of myostatin by binding it and to increase muscle weight more than myostatin inhibitors [355].

With respect to ACEIs, that are drugs widely used in treating hypertension and heart failure, the results of three cohort studies report favourable changes in body composition and physical function in older adults. A randomized controlled trial of ACEIs showed higher exercise capacity and fewer falls in older participants with existing impairment of activities of daily living [356]. Conversely, a study comparing the effects of nifedipine with ACEIs in older people found no difference between treatments in muscle strength, walking distance or functional performance [357]. It is possible that frailer subjects have a tendency to more cardiovascular problems and benefit more. Then, the mechanism for ACEIs action on skeletal muscle are yet to be elucidated. However, they may involve an improved cardiac output and blood flow to muscle, a reduced proinflammatory status, an improved endothelial function and muscle glucose uptake, and a positive modulation of the IGF-I system.

CONCLUSION

For many years the relationship between muscle and bone has been regarded as self-evident among the age-related changes in body composition. Currently understanding the bone-muscle changes associatd with aging and the underlying pathophysiological processes is a priority, because of the growing of the old population and the health- and economic burden associated to the development of sarcopenia, osteoporosis and their consequences. In the clinical practice a consensus has been reached about the threshold of bone loss at that it should be considered a disease, however older persons at high risk for fractures are still not recognized consistently or systematically by health care professionals, and prevention strategies remain suboptimal despite evidence for their efficacy. In addition, osteoporosis often co-exists with sarcopenia in older persons. As regard of sarcopenia, we are still in need of specific population clinical cut scores to distinguish it as a clinical disease, instead of a condition normal for chronological ageing, and of clear definitions of its clinical outcomes. In this context, we believe that future research should focus on the simultaneous assessment of both osteoporosis and sarcopenia, for instance using the DXA which is already an essential part of the diagnosis of osteoporosis, and should concentrate on exploring and making a consensus about the clinically relevant dimensions and outcomes resulting from their interactions. Whether not recognized and treated on time, both osteoporosis and sarcopenia lead to inevitable and irreversible deterioration of the structure and function of musculoskeletal system, that impair functionality making older individuals more susceptible to falls, fractures and permanent severe disability.

Several morphological and functional aspects of bone-muscle aging are known. However, the triggers and many local or systemic factors accelerating bone-muscle loss leading to sarco-osteoporosis are still to be defined. As regard the muscle-bone interaction, for a long time it has been supported that both systems interact each other from a mechanical point of view, with bones that adapt their morphology and strength to the long-term loads exerted by muscle contraction as a result of opposing gravity and physical activities. Then, systemic and local non-mechanical factors, including hormones, cytokines and other trophic agents, have been discovered to modulate the mechanostat effect of muscle on bone strength.

Emerging evidence points to a bidirectional crosstalk between osteocytes and muscle cells mediated by biochemical and common molecular signaling. Adipokines may impact bone-

muscle interaction via central and peripheral pathways, as well as other factors, including neuroendocrine age-related modifications, lifestyle changes, nutritional habits and candidate genes.

Recognizing bone-muscle changes with aging and highlighting the underlying pathophysiological mechanisms help to develop agents or interventions to blunt these processes and to design intervention trials that target one or more of such underlying mechanisms. In this scenario, older population is the most significant target group for prevention and treatment of health- and disability-related consequences of sarcopenia and osteoporosis, although it is widely accepted that their primary prevention should be carried out with multifactorial interventions throughout the entire lifespan.

To date, we are far from the development and validation of pharmacological agents to eventually counteract or treat sarcopenia. With exception of ACEIs, as a pharmaceutical intervention that can improve muscle exercise capacity in functionally impaired older people, the most compelling evidence to combat sarcopenia is resistance training either alone or in combination with nutritional supplements. As some older people are unable or unwilling to embark on exercise training programs, alternative treatment options need to be developed. Several pharmacologic approaches are under investigation and most of them hold promise for a greater understanding of the mechanisms to fight or reverse sarcopenia.

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