JGG 2016;64:75-80

Review

Ageing, muscle and bone

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The ageing process is characterized by a decline in muscle mass and strength, when this process outreaches pathological levels it is defined sarcopenia. This condition is associated with greater likelihood of recurrent falls and greater risk of mortality and less consistently associated with risk of hip fracture and functional limitation. On the other hand, ageing heavily affects bone inducing changes in bone structure – progressive decrease in trabecular thickness and increase in cortical porosity –, loss of bone mass and increase in bone turnover.
There is an important interplay between muscle and skeletal systems: muscle contractions during anti-gravitational and physical activities apply mechanical stress to bones, influencing bone density, strength and microarchitecture, thus a decrease in muscle function is related to lower bone strength and predisposes to osteoporosis. Osteoporosis and sarcopenia show multiple common pathogenetic pathways, both systemic and local: reduction in anabolic hormones, chronic inflammatory condition, inactivity. In particular, several skeletal muscle-derived cytokines are able to directly influence bone. Vitamin D adequate levels are crucial for both bone and muscle function. Musculoskeletal impairment causes an important burden of disability and disease in older patients, a better understanding of pathogenesis and muscle-bone crosstalk could lead to improve prevention strategies and therapeutic options.

Key words: Sarcopenia, Osteoporosis, Elderly

INTRODUCTION

The ageing process is characterized by a decline in muscle mass and strength, when this process outreaches pathological levels it is defined sarcopenia. There is an important interplay between muscle and skeletal systems: muscle contractions during anti-gravitational and physical activities apply mechanical stress to bones, influencing bone density, strength and microarchitecture, thus a decrease in muscle function is related to lower bone strength and predisposes to osteoporosis. Osteoporosis and sarcopenia show multiple common pathogenetic pathways, both systemic and local: reduction in anabolic hormones, chronic inflammatory condition, inactivity. Vitamin D adequate levels are crucial for both bone and muscle function. Musculoskeletal impairment causes an important burden of disability and disease in older patients, a better understanding of pathogenesis and muscle-bone crosstalk could lead to improve prevention strategies and therapeutic options.

SARCOPENIA AND OSTEOPOROSIS

Sarcopenia has been defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as 'a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death'. Diagnosis is based on low muscle mass and low muscle function

Received: May 16, 2016 - Accepted: June 8, 2016

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(either low strength and/or low physical performance) [1]. Similarly, the International Working Group on Sarcopenia provided a consensus definition of sarcopenia as 'age-associated loss of skeletal muscle mass and function' and proposed to base diagnosis on a low whole-body or appendicular fat-free mass in combination with poor physical functioning [2].

Peak skeletal muscle mass and bone density are achieved in young adulthood. After 45 years of age, skeletal muscle mass progressively declines in men and women, particularly in the lower body [3].

In a recent review, the prevalence of sarcopenia was 1-29% (up to 30% in women) for older adults living in the community, 14-33% (up to 68% in men) for those living in long-term care institutions and 10% for those in acute hospital care; the prevalence of sarcopenia increased with age [4].

In the European Male Ageing Study, which examined a population of 518 men aged 40-79 years with a mean follow-up of 4.3 years, appendicular lean mass started to decrease from 50 years of age, but mean annual loss was significantly greater in subjects older than 60 years. Men significantly lost gait speed and grip strength after 70 years [5].

In a recent population study, sarcopenia was associated with greater likelihood of recurrent falls and greater risk of mortality and less consistently associated with risk of hip fracture and functional limitation, although further studies are needed to determine its power in discrimination and reclassification of risk of important adverse outcomes [6].

Ageing is associated with an increase in fat mass: many tissues, including bone marrow and muscle, are gradually replaced by fat; this process takes place in men mainly after the age of 70, while in women it starts earlier with menopause and loss of estrogen [7]. With age, muscle worsens its contractile performances due to the reduction of neuronal signalling and cell recruitment, and slower fiber regeneration.

On the other hand, ageing heavily affects bone inducing changes in bone structure – progressive decrease in trabecular thickness and increase in cortical porosity –, loss of bone mass and increase in bone turnover.

This phenomena lead to physiological changes in muscle and bone composition and function, promoting the onset of sarcopenia and osteoporosis.

The two conditions often coexist and possibly represent a continuum, sharing multiple genetic, environmental and health-related intrinsic and extrinsic factors [8 9].

If morphological changes are known, factors triggering them are more obscure and a precise definition of pathways is yet to come.

MECHANICAL LOADING AND BONE

Multiple studies have demonstrated positive associations between skeletal muscle mass and bone mineral density as assessed by dual-energy X-ray absorptiometry (DXA) at various skeletal sites [10], and the increased prevalence of osteoporosis in women could be partly related to their lower skeletal muscle mass [3]. However, the advent of higher-resolution imaging technologies that perform measures of cortical and trabecular geometry and microstructure allows for much more detailed analyses of bone compartments and microstructure separately.

Recent evidences show that skeletal muscle mass adjusted for body size is significantly associated with cortical and trabecular bone geometry and microstructure at multiple skeletal sites in adult women and men [11].

In a population study, muscle size is strongly associated with bone size and bone strength in both men and women, while the positive associations between bone mineral density and muscle size in weight-bearing and non-weight-bearing limbs were attenuated after adjustment [12].

The relationship between skeletal muscle mass and cortical bone is partly mediated by the mechanical influence, particularly at load-bearing sites such as the femoral neck, lumbar spine and tibia. Loading provokes changes in bone structure: resident bone cells show adaptive response to mechanical energy and translate it into a cascade of structural and biochemical changes. Mechano-transduction depends primarily on osteocytes. Osteocytes and their processes are surrounded by fluid, loads move extracellular fluid and viscosity creates shear stress on the osteocyte cell membrane. Fluid forces are proportional to loading rate, in fact bone is more sensitive to dynamic rather than static loading.

Mechanical load on the octeocytes dendrites induces the opening of connexin 43 hemichannels on the cell body [13].

Wnt/Lrp5 and beta-catenin pathway is probably involved: mechanical strain reduces sclerostin levels, up-regulating Wnt signaling and leading to bone formation [14].

However, the age-adjusted relationships between relative appendicular skeletal muscle and cortical thickness in women and men, cortical volumetric bone mineral density (in women), and proximal femur strength in women and men remained significant after adjustment for physical activity [11].

Appendicular skeletal muscle mass is the strongest factor associated with bone mineral density at the femoral neck in a study performed on adult men aged 20 to 72 years, independent of skeletal loads evaluated through measures of physical activity and muscle strength [15].

In fact, the relationship between relative appendicular

skeletal muscle and cortical thickness at the radius, a non-load-bearing skeletal site, is also significant [11].
In a Korean population bone mineral density and appendicular skeletal muscle were measured by dual energy X-ray absorptiometry: muscle mass is positively correlated with bone density in both men and women, and skeletal muscle mass can predict bone density [16].
Another interesting hypothesis suggests that load-induced bone formation and functional adaptation could be neuronally regulated. The periosteoum nerves have a net-like structure, optimal for detection of mechanical distortion of periosteum and bone, possible actor of a sophisticated regulatory mechanism [17]. Nerves from the dorsal roots have branches entering the bone cortex in association with microvasculature [18]. There is a direct connection between individual bone cells and the brain, and bone cells express receptors for a wide range of neurotransmitters. In vitro neuropeptides influence bone formation and the formation and activation of osteoclasts for bone resorption [19].
On these premises a study on murine model analyzed adaptive response to mechanical load in the limb and in the contralateral bone; it showed that right ulna loading induces adaptive responses in other bones in both thoracic limbs; experimental neuronal blocking during loading abolished bone formation in the loaded ulna and in the other thoracic limb bones [20].

MYOKINES

Myokines are skeletal muscle-derived cytokines able to directly influence bone.
Interleukin-6 has a controversial role in bone: it is released from contracting muscle and promotes glucose uptake, contributing to the favorable effects of exercise on energy metabolism, but promotes osteoclastogenesis in vitro [21]. Data suggest that exercise under glucose deprivation may stimulate bone resorption via elevated Interleukin-6 levels [22]. Interleukin-6 also increases osteoblast differentiation in mice [23] and is required for muscle hypertrophy and recovery from muscle atrophy [24], while chronic direct interleukin-6 administration induces muscle atrophy [25].
Similarly interleukin-7 shows a double-edged role in osteoclastogenesis and bone formation: it shows a direct antiosteoclastogenic effect, while it induces osteoclastogenesis through a mechanism involving the stimulation of T-cell activation and expansion and production of RANKL and TNFα.
Interleukin-7 is a direct inhibitor of in vitro osteoclastogenesis in murine bone marrow cultures; moreover mice overexpressing human interleukin-7 in the osteoblast lineage showed increased trabecular bone volume in vivo and decreased osteoclast formation in vitro, in murine model interleukin-7 effects are verified only in females [26].
On the other hand interleukin-7 enhances T cells secretion of RANKL and pro-osteoclastogenic cytokines. Interleukin-7 production is increased in ovariectomized mice where it stimulated osteoclastogenesis [27]; antibody directed neutralization of interleukin-7 prevents ovariectomy-induced bone loss in mice. In murine model, in vivo interleukin-7 has multiple complex influence on T-cell maturation, development, and function, in ovariectomy, interleukin-7 stimulates both thymic-dependent differentiation of bone-marrow-derived progenitors and thymic-independent, peripheral expansion of mature T cells: thymectomy decreases almost by half the bone loss and stimulation of T lymphopoiesis induced by estrogen deficiency.
Indeed interleukin-7 is a potent inducer of RANKL production by human peripheral blood derived T cells [28]. In humans, interleukin-7 has shown its osteoclastogenic role in psoriatic arthritis [29] and in solid tumors bearing patients [30]; in patients with reumatoid arthritis it could contribute to the perpetuation of Th1 and TNF-α mediated pro-inflammatory immune responses [31 32]. In periodontal infections, high levels of serum interleukin-7 associated with peripheral blood B cells have been shown responsible for T-cell-dependent osteoclastogenesis [33].
Interleukin-15 overexpression in muscle reduced body fat and increased bone mass in mice, although only when systemic Interleukin-15 levels were increased as well: muscle-derived IL-15 is one of the few myokines with confirmed regulation of bone as well as fat mass, although this constitutes an endocrine rather than a paracrine mechanism [34].
Moreover muscle cells express RANKL and its decoy receptor osteoprotegerin, key regulators of bone resorption; loading acutely decreases the RANKL/osteoprotegerin mRNA ratio in myotubes [21].
Recent research explored the role of Irisin [35]. Irisin was originally known as a myokine secreted from skeletal muscle into bloodstream in response to exercise both in mice and in healthy humans. Irisin can induce transdifferentiation of white adipose tissue into brown, but it has been recently demonstrated that Irisin also has a key role in the control of bone mass, at lower concentration. In murine model low dose of recombinant Irisin increases cortical bone mineral density and positively modifies bone geometry. Irisin exerts its effect prevalently on osteoblasts by enhancing their differentiation and activity. In culture and animal model, bone tissue is more sensitive than the adipose tissue to the Irisin action [36].
Myokines, produced by muscle in response to exercise, could perform an additional regulation of mechanotransduction in bone.

HORMONES REGULATION

The musculoskeletal system undergoes precise regulation by multiple endocrine factors. In particular, skeletal muscle and bone are highly responsive to sex hormones. The age-associated fall in testosterone production is likely associated with sarcopenia, while the decrease in estradiol causes bone loss and osteoporotic fractures in men and women [37].

The insulin-like growth factor (IGF) system is also involved in muscle and bone health [38]. IGF-I and – II mediate anabolic effects on skeletal muscle and bone cells [39].

In a prospective study, in men over the age of 70, IGF-1 level was positively associated with change in gait speed, after adjustment for age, BMI, smoking, and a number of comorbidities. This association remained significant after further adjustment for sex hormone binding globulin. Recently also IGF binding protein-2 (IGFBP-2), an inhibitor of the trophic effects of IGF, has been associated with low bone mineral density and high bone resorption markers [40 41]: low circulating concentrations of IGFBP-2 are associated with low relative appendicular muscle mass in both sexes.

In a recent population study serum IGFBP-2 levels were the most robust negative predictors of relative appendicular skeletal muscle mass in both sexes [11].

Vitamin D is another key connection between bone health and muscle function.

Vitamin D is widely recognized for its role in calcium and phosphate homeostasis to maintain bone health and blood calcium levels through his action on target organs, such as intestine, kidney, and parathyroid glands, but emerging evidence has shown that vitamin D improves muscle performance and reduces falls in vitamin D-deficient older adults [17], low levels of vitamin D are also associated with muscle weakness and atrophy of type II muscle fibers [42].

The receptor for 1,25-dihydroxyvitamin D (vitamin D receptor – VDR), is expressed in skeletal muscle and is an important mediator of 1,25(OH)2D effects on muscle contractility [43].

It has been shown that certain VDR genotypic variations are associated with differences in muscle performance phenotypes: the VDR FokI (F/f) polymorphism is significantly associated with lean mass in older Caucasian men, constituting a recessive risk allele for the presence

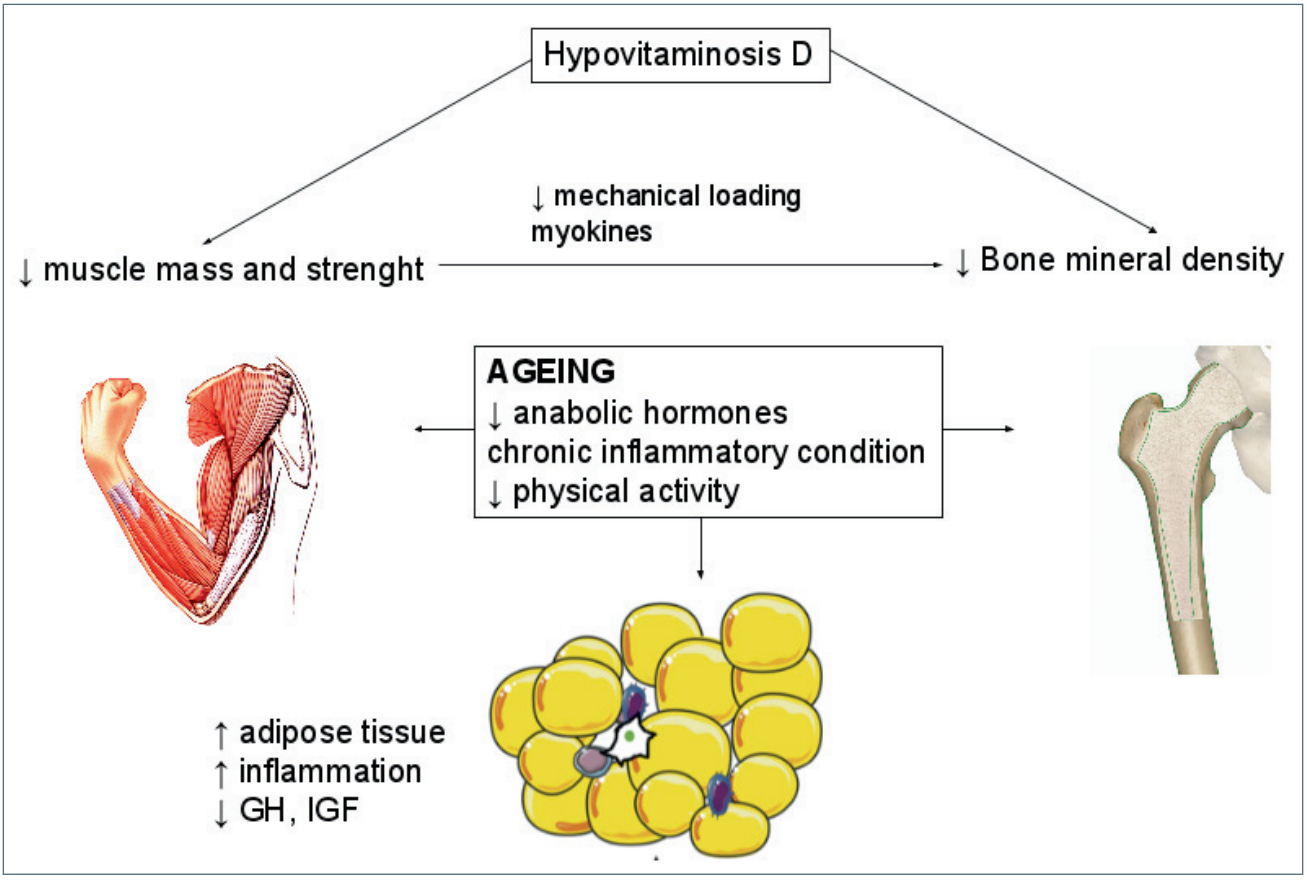

Figure 1. Muscle and bone complex interplay GH growth hormone; IGF insulin-like growth factor.

of sarcopenia [44]. In cell cultures, addition of 1,25-dihydroxyvitamin D to myoblasts increased expression and nuclear translocation of the VDR, decreased cell proliferation and promoted myogenic differentiation [45].

In murine model vitamin D depletion induces skeletal muscle atrophy: old rats show a reduction in Notch pathway activity and blunted proliferation potential assessed through marker proteins expression [46].

In the In CHIANTI population study lower vitamin D status proved associated with poor physical performance. A representative sample of 976 men and women aged 65 years or older was examined: serum 25OHD levels < 25.0 nmol/L were significantly associated with lower physical performance scores, whereas serum 25OHD levels < 50.0 nmol/L were significantly associated with low handgrip strength [47].

Moreover elderly men and women with low serum 25OHD in the Longitudinal Study of Aging Amsterdam were significantly more likely to lose handgrip strength and appendicular skeletal muscle mass over 3 years of follow-up [48].

Vitamin D supplementation intervention studies have shown that vitamin D supplementation can significantly improve muscle function and physical performance among older adults at high risk for vitamin D deficiency, institutionalized elderly women [49] and patients attending a falls clinic [50]. Others have also shown that supplemental vitamin D may improve balance and reduce the incidence of falls [51].

In conclusion, muscle and bone show a deep and complex interplay, as shown in Figure 1, a better knowledge of influencing factors and molecular pathways could lead to new pharmacological strategies to treat emerging severe conditions such as cachexia and other muscle wasting disorders.

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