

Commentary on the effects of receptor activator of nuclear factor- κ B ligand inhibition on bone mass and muscle strength

The co-existence of osteoporosis and sarcopenia, known as osteosarcopenia, is a major public health problem and a social economic burden in many countries, including Asian countries. It is the most common metabolic bone and muscle disorder in older adults, especially for older women. Osteoporosis is a pathological process characterized by a decrease in bone mass and deterioration in skeletal microarchitecture, accompanied by a progressive and generalized loss of muscle mass with muscle strength or a loss of physical performance with increasing rates of disability, poor mobility, frailty, and even mortality and morbidity. Bone and muscle have been increasingly recognized as interacting tissues as a result of the mechanical effects of muscle loading on bone function¹. Some endocrine disorders are also related to osteoporosis and sarcopenia; for example, diabetes mellitus; thyroid dysfunction; vitamin D deficiency; insulin-like growth factor-1, growth hormone, sex hormones and cytokine imbalance; obesity; and malnutrition. Bone and muscle dysfunction, also characterized by the predominant atrophy of type II fibers together with smaller and fewer mitochondria, are associated with several genetic polymorphisms of the genes, such as α -actinin-3, proliferator-activated receptor gamma coactivator 1- α , glycine-n-acyltransferase, methyltransferase-like 21C, myostatin and myocyte enhancer factor 2C (Figure 1). Therefore, the denervation of single muscle fibers reduces type II fibers, which are

gradually replaced by type I fibers and adipose tissue².

To prevent osteoporosis and sarcopenia requires the adequate intake of calcium, protein and vitamin D. Regular physical activity can maintain muscle mass, and reduce the progression of sarcopenia, osteoporosis and fractures. Several kinds of medicine have been developed to study the effects on muscle for the treatment of sarcopenia, and the increase in appendicular lean body mass and several performance-based measures, including testosterone, selective androgen receptor molecules, angiotensin-converting enzyme inhibitors, activin IIR antagonists, beta antagonists, fast skeletal muscle troponin activators and myostatin antibodies³. However, only a few therapies among them are clinically used for the treatment of sarcopenia. In osteoporosis, many clinical trials recruiting Asian people have proven the efficacy and safety of medicines in reducing fracture risk; for example, ibandronate, alendronate, raloxifene, teriparatide, denosumab and zoledronate.

Recent studies have proved that receptor activator of nuclear factor- κ B (RANK)/receptor activator of nuclear factor- κ B ligand (RANKL) signaling plays an important role in bone and other tissues. The mechanism is to regulate the formation of osteoclasts and precursors that activate and survive in normal bone remodeling. Osteoprotegerin (OPG) binding to RANKL can inhibit its binding to the receptors to avoid excessive bone resorption. Thus, the RANKL/OPG ratio is a significant determinant of bone mass and skeletal integrity. Denosumab is a human monoclonal antibody binding to the RANKL cytokine with high specificity and affinity to block its action. As a result, the recruitment, maturation and

action of osteoclasts are blocked, so bone resorption slows down.

In animal studies, specifically in the soleus of wild-type mice, RANK/RANKL expression in bone and muscle to the activation of the nuclear factor- κ B pathway mainly by inhibiting myogenic differentiation, inducing bone loss, and impairing muscle structure, strength and glucose uptake, can be proved by the lower muscle volume in the limb. However, higher fat infiltration between muscle groups in huRANKLTg⁺ mice with lower maximal speed and limb force is a feature of sarcopenia, and it also decreases trabecular and cortical bone volume⁴. In contrast, OPG-Fc can reduce inflammation, restore the integrity and improve the function of dystrophic muscles in osteosarcopenic mice, suggesting that OPG can help in bone metabolism⁵ and improve muscle strength, as RANKL inhibitors can restore muscle function and glucose utilization to decrease bone remodeling, increase trabecular/cortical bone volume, in mice, and increase gastrocnemius/soleus mass, maximal force of the limb and maximal speed compared with huRANKLTg⁺ vehicle. Furthermore, in human clinical studies, the falling rate was flattened; appendicular lean mass and handgrip were increased in patients receiving RANKL inhibitor. A recent publication investigating the effects of RANKL inhibitors found that they could improve muscle strength and insulin sensitivity in osteoporotic mice and humans⁶. Accordingly, the RANK/RANKL/OPG system plays an important role not only in bone, but also in muscle metabolism.

Furthermore, recent studies have shown evidence of a potentially new mechanism relating RANKL expression to fracture risk, by decreasing bone mass, as well as muscle strength. A large

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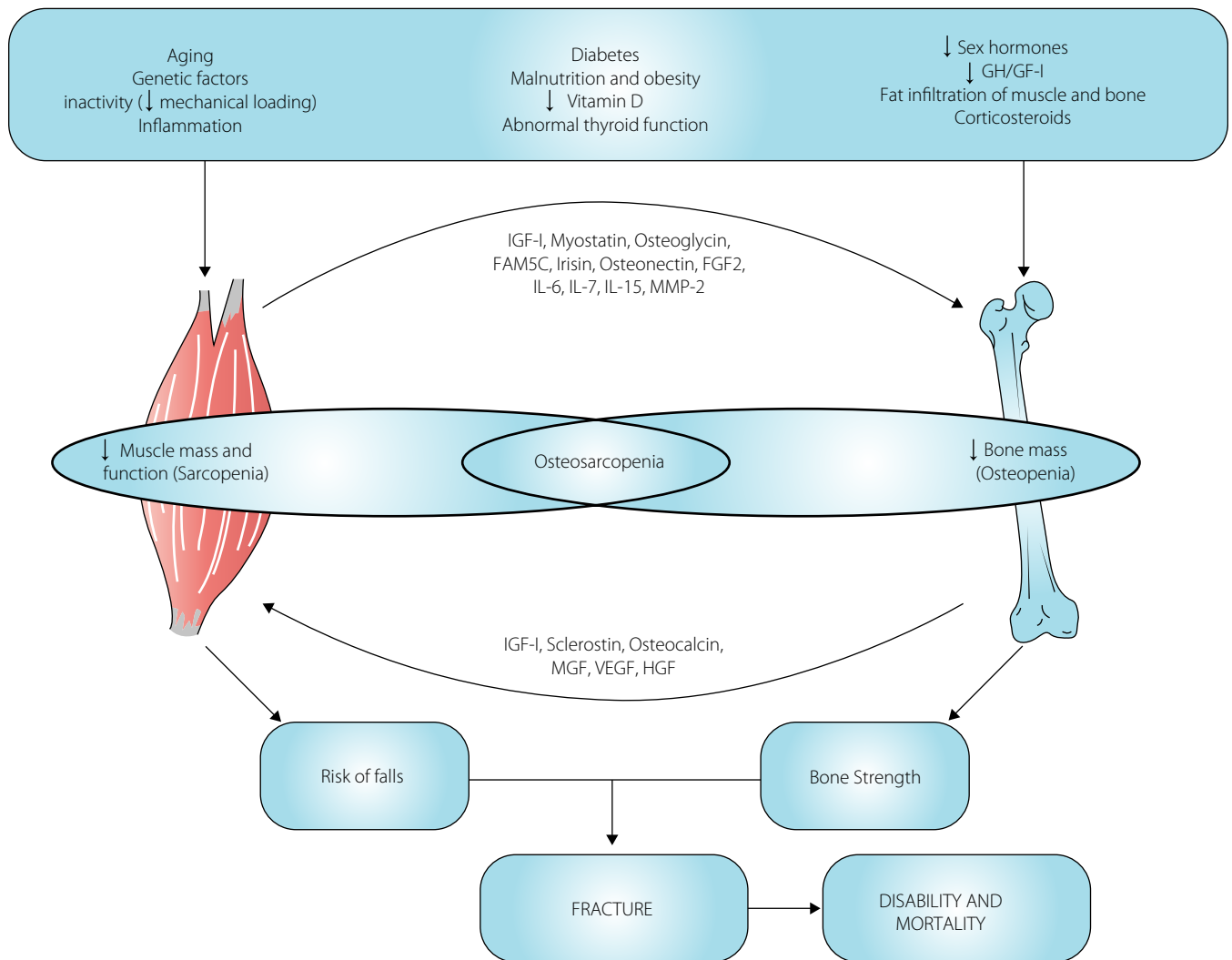


Figure 1 | The pathophysiology of osteoporosis and sarcopenia. FAM5C, family with sequence similarity 5, member C; FGF2, fibroblast growth factor 2; GH/IGF-I, growth hormone/insulin-like growth factor-I; HGF, hepatocyte growth factor; IL, interleukin; MMP2, matrix metalloproteinase-2; MGF, mechanogrowth factor; VEGF, vascular endothelial growth factor. Adapted/translated from Hirschfeld *et al.*¹, *Osteoporosis International*, 2017, by permission of Springer Nature. This image/content is not covered by the terms of the Creative Commons license of this publication. For permission to reuse, please contact the rights holder.


clinical study is anticipated to clarify the RANKL inhibitors as a novel therapeutic mechanism for sarcopenia to reduce the risk of falls or physical dependency in older people.

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DISCLOSURE

The authors declare no conflict of interest.

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REFERENCES

1. Hirschfeld HP, Kinsella R, Duque G. Osteosarcopenia: where bone, muscle, and fat collide. *Osteoporos Int* 2017; 28: 2781–2790.
2. Tarantino U, Piccirilli E, Fantini M, *et al.* Sarcopenia and fragility fractures: molecular and clinical evidence of the bone-muscle interaction. *J Bone Joint Surg Am* 2015; 97: 429–437.
3. Morley JE. Pharmacologic options for the treatment of sarcopenia. *Calcif Tissue Int* 2016; 98: 319–333.

4. Dufresne SS, Boulanger-Piette A, Bosse S, *et al.* Physiological role of receptor activator nuclear factor- κ B (RANK) in denervation-induced muscle atrophy and dysfunction. *Receptors Clin Investig* 2016; 3: e13231–e13236.
5. Dufresne SS, Dumont NA, Bouchard P, *et al.* Osteoprotegerin protects against muscular dystrophy. *Am J Pathol* 2015; 185: 920–926.
6. Bonnet N, Bourgoin L, Biver E, *et al.* RANKL inhibition improves muscle strength and insulin sensitivity and restores bone mass. *J Clin Invest* 2019; 129: 3214–3223.

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