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Sclerostin: clinical insights in muscle–bone crosstalk

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Abstract

Sclerostin, a protein encoded by the sclerostin (*SOST*) gene, is mostly expressed in osteocytes. First described in the pathogenesis of three disorders, sclerosteosis, van Buchem's disease, and craniodiaphyseal dysplasia, sclerostin has been identified as an important regulator of bone homeostasis, controlling bone formation by osteoblasts through inhibition of the canonical Wnt signaling pathway. Recent studies have highlighted a hypothetical role of sclerostin in myogenesis, thus modulating the interaction between bone and muscle. This narrative review provides an overview of the clinical implications of sclerostin modulation on skeletal muscle mass and function, and bone metabolism. Improving knowledge about muscle–bone crosstalk may represent a turning point in the development of therapeutic strategies for musculoskeletal disorders, particularly osteosarcopenia.

Keywords

Sclerostin, osteocytes, Wnt-pathway, myoblasts, osteoporosis, muscle mass, muscle strength, falls, romosozumab, osteosarcopenia

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Introduction

Bone tissue and skeletal muscle tissue are intimately connected to each other from a biomechanical point of view.[1] While bones play a supportive role, muscles enable motor activity through the interaction of contractile proteins within the sarcomeres; furthermore, both tissues regulate energy metabolism through the production and distribution of various substrates.[2] These tissues are well known to act as endocrine organs, through the production of muscle-derived molecules, defined as myokines,[3] such as myostatin, some interleukins, irisin, and fibroblast growth factor (FGF)-2, and through substances produced by bone, such as FGF-23, prostaglandin

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(PG)E2, transforming growth factor-β, osteocalcin and sclerostin.[4] Genetic and epigenetic factors, including ageing and nutrition, contribute to the modulation of the crosstalk between bone and skeletal muscle.[5–7] An in-depth knowledge of the function of molecules involved in this complex interconnected tissue system is necessary to identify therapeutic strategies useful in the management of musculoskeletal disorders, including osteosarcopenia. In this context, sclerostin has received growing attention, and a monoclonal antibody against this glycoprotein is now available for the management of bone fragility in clinical practice. This narrative review provides an overview of the clinical implications of sclerostin modulation on the skeletal muscle mass and function, and bone metabolism.

The role of sclerostin in bone turnover and muscle regeneration

The skeleton undergoes a continuous remodeling involving various systemic and local factors, responsible for the activation of intracellular signaling pathways. Osteoclasts are multinuclear cells of hematopoietic origin that are responsible for bone resorption, while osteoblasts and osteocytes are cells of mesenchymal origin that allow, respectively, bone formation and the modulation of metabolic bone processes.[8] Osteoblasts and osteocytes produce two factors responsible for osteoclast maturation, namely, macrophage colony-stimulating factor (M-CSF, also known as colony stimulating factor 1 [Csf1]), and receptor activator of nuclear factor-kB ligand (RANK-L, also known as tumor necrosis factor ligand superfamily member 11 [Tnfsf11]), which binds to osteoclast precursors through the RANK receptor; in addition, osteoblasts and osteocytes produce osteoprotegerin (OPG), which inhibits the RANK-L–RANK interaction and consequently osteoclastogenesis and bone resorption.[9,10]

Bone formation follows an intracellular signaling cascade, regulated by Wnt proteins that bind to a co-receptor complex, composed of frizzled (Fz) and low-density lipoprotein receptor-related protein (LRP) 5/6. The signal is transmitted through intracellular recruitment of a family of proteins, called disheveled (Dvl) and, depending on the specificity of the Wnt and Fz that bind to LRP5/6, three independent signaling pathways can be activated: canonical, non-canonical or calcium-dependent. The canonical Wnt pathway (i.e., Wnt/β-catenin pathway) regulates bone formation downstream of LRP5/6 and relies mainly on the stabilization of cytosolic β-catenin. When the canonical Wnt signaling pathway is inactive, Wnt proteins are not bound to Fz and LRP5/6, and β-catenin is sequestered, phosphorylated, and degraded in the cytosol. Conversely, in the absence of Wnt inhibitors, including sclerostin, the Wnt proteins activate the Fz–LRP5/6 complex, which prevents β-catenin phosphorylation.[11] Thus, β-catenin is translocated into the osteoblast nucleus, resulting in transcription and up-regulation of genes responsible for osteoblast differentiation, proliferation, and survival.[12] There are different systems of regulation of the canonical pathway. Among the extracellular systems, a first group includes the Fz-related secretion proteins (SFRPs) that bind and neutralize Wnt proteins, acting as soluble decoy Fz receptors and preventing the binding of Wnt to Fz, while the second group includes the dickkopf proteins (DKK) and sclerostin (SOST), produced by mature osteoblasts and osteocytes, which bind to and inactivate signaling from LRP5/6 receptors.[13,14] Inhibition of the canonical Wnt pathway also results in reduced OPG production and increased *RANK-L* expression, leading to increased osteoclast differentiation.[15,16]

In mice lacking the *SOST* gene, increased OPG, but not RANK-L, was observed, demonstrating that expression of the *SOST* gene is necessary to increase the levels of RANK-L through activation of the canonical Wnt pathway.[17] Furthermore, in mice expressing the dominant active form of β-catenin in osteocytes, the use of anti-sclerostin antibodies increases OPG and decreases RANK-L levels, confirming that the increase in RANK-L levels depends on sclerostin, and suggesting that regulation of the canonical Wnt pathway is aimed at the production of bone tissue, triggered only by osteocytes and not by osteoblasts, since RANK-L levels are modulated only in osteocytes.[17] These cells, incorporated in the mineralized bone matrix, act as mechanosensors by regulating bone formation based on stimuli from mechanical stresses. Osteocytes, stimulated by the mechanical loading, produce nitric oxide (NO), PGE2 and adenosine triphosphate (ATP) responsible for the proliferation and differentiation of osteoblasts, and reduce the expression of *SOST*, with the consequent reduced inhibition of the canonical Wnt pathway.[18,19] Furthermore, PGE2 induces the differentiation of mesenchymal precursors into myoblasts, and is released from osteocytes following shear stress in order to improve muscle function.[20] Similarly, the production of Wnt1 and Wnt3a proteins, induced by shear stress, modulates the differentiation of muscle satellite cells by regulating the expression of regulatory factors of muscle tissue.[21]

In particular, Wnt3a and Wnt4 proteins seem to be involved in the crosstalk between muscle and bone: Wnt3a activates the canonical pathway, while Wnt4 activates both the canonical and non-canonical pathways, favoring the differentiation and proliferation of C2C12 myoblasts, and thus counteracting the expression of the Notch-mediated pathway responsible for satellite cell quiescence.[22] Although the mechanism has not yet been well clarified, sclerostin also acts as an inhibitor of the pathway mediated by Wnt proteins in muscle tissue, thus counteracting the mechanisms of muscle regeneration.[23–25] Sclerostin has been shown to be produced by muscle cells, and an increase in bone mass has been found in combination with a tendency to increase lean mass, without substantial changes in body weight, in mice conditionally lacking the *SOST* gene.[26,27] Sclerostin produced by C2C12 myoblasts has been demonstrated to have paracrine inhibitory effects on the differentiation of 2T3 osteoprogenitor cells, enhancing the action of sclerostin produced by osteocytes.[27]

The role of vitamin D on sclerostin

Several systemic and local factors regulate *SOST* expression by osteocytes. For example, sclerostin levels are increased in long-term immobilized patients and inversely correlate with bone formation markers.[28]

Sclerostin is produced almost exclusively by osteocytes, which also express receptors for 1,25-dihydroxyvitamin D3. Osteocytes are responsible for the production of bone tissue through the Wnt signaling pathway. The efficiency of this pathway is modulated by co-stimulation signals from pathways activated by 1,25-dihydroxyvitamin D3, or by Wnt inhibitors, such as sclerostin.[29] Treatment with vitamin D has been reported to reduce serum sclerostin in young adult women with vitamin D deficiency. In particular, Cidem et al.[30] enrolled 26 young women (aged 32.5 ± 7.2 years) who received oral calcium (1 200 mg per day for 2 months) and vitamin D3 (300 000 IU per week for 1 month). The treatment protocol provided for the administration of vitamin D3 on the first day of treatment (day 0), while the subsequent doses were administered on days 7, 14 and

21 from the start of treatment. Baseline serum levels of 25(OH)D3 and sclerostin were 5.7 ± 2.4 ng/mL and 39.1 ± 14.4 pg/mL, respectively. Following supplementation, serum 25(OH)D3 was significantly increased by 308% (62.4 ± 18.7 ng/mL, $P < 0.0001$) while serum sclerostin was significantly reduced by 17.5% (29.3 ± 8.8 pg/mL, $P < 0.0001$). Conversely, a randomized controlled trial versus placebo (with 314 subjects aged > 65 years), based on vitamin D and calcium supplementation, showed an increase in serum sclerostin levels in men in the intervention group, while no change was reported in women.[31] In particular, the serum sclerostin concentrations in men were increased by 13.1% in the group subjected to treatment, and decreased by 10.9% in the placebo group ($P < 0.005$). It remains unclear why responses to vitamin D and calcium supplementation varied according to gender, but a correlation with different baseline levels of physical activity may be hypothesized: in men, the higher reported levels of physical activity may have resulted in a greater sensitization to the increase in serum sclerostin in response to supplementation.[31]

New therapeutic strategies for bone and muscle loss: romosozumab

Romosozumab is a humanized monoclonal antibody that was approved for the treatment of osteoporosis by the Food and Drug Administration (FDA) in April 2019, by the European Medicines Agency (EMA) in February 2020 and by National Regulatory Agencies in Japan, South Korea, Australia, and Canada.[32,33] Romosozumab performs a dual action by binding sclerostin and neutralizing its effects in human bone tissue. It stimulates an increase in bone tissue production and a decrease in bone resorption, resulting in a rapid and substantial increase in bone mineral density (BMD) and a significant reduction in the risk of vertebral, non-vertebral and femoral fragility fractures. Specifically, romosozumab promotes the differentiation and activity of osteoblasts by promoting the conversion of bone-lining cells into osteoblasts, the differentiation of progenitor cells to osteoblast phenotype and the synthesis of bone matrix by mature osteoblasts. At the same time, it reduces osteoclast activity and, consequently, bone resorption, by regulating the osteoclast activators RANKL and CSF-1 and the osteoclast inhibitors OPG and CCN family member 4 (CCN4, also known as Wisp-1), the latter also having a role as a negative regulator of osteoblast differentiation.[34]

Efficacy of romosozumab on bone mineral density

Clinical trials leading to regulatory agency approval of romosozumab demonstrated significant improvements in spine and hip BMD.[34] Notably, phase 2 and 3 studies and two meta-analyses reported BMD increases in the lumbar spine of 12.1–13.3%, femoral neck of 2.2–5.9%, and total hip by 2.5–6.9% following romosozumab administration for 12 months in patients with osteoporosis, particularly in postmenopausal women.[34]

Specifically, the phase 3 STRUCTURE study had a primary endpoint of mean percent change (at 6 months and 12 months from the start of the trial) in BMD from baseline, as assessed by dual-energy X-ray absorptiometry, in postmenopausal women who had taken bisphosphonates prior to participating in the trial.[35] The romosozumab group (comprising 206 patients) and teriparatide group (comprising 209 patients), were included in the primary efficacy analysis. Over 12 months, the mean percent change from baseline in total hip BMD was 2.6% in the romosozumab group and –0.6% in the teriparatide

group.[35] In addition, post-hoc analysis revealed a possible correlation between increases in the N-terminal propeptide of type I procollagen, a marker of bone formation, and densitometric response to teriparatide or romosozumab was excluded. Indeed, although both groups showed an increase in this biomarker, only those treated with romosozumab had an increase in hip BMD.[36] The phase 3 BRIDGE study showed that treatment with romosozumab for 12 months leads to an increase in vertebral and hip BMD compared with placebo also in men with osteoporosis (Table 1).[37]

Efficacy of romosozumab on the risk of fragility fractures

The FRAME study investigated the cumulative incidence of new vertebral fractures at 12 and 24 months as the primary endpoint, in 7180 postmenopausal women with a T-score between –2.5 and –3.5 standard deviations (SDs) at the total hip or femoral neck.[38] Patients received randomized subcutaneous injections of romosozumab (at a dose of 210 mg) or placebo, monthly, for 12 months; subsequently, patients in each group received denosumab for 12 months, at a dose of 60 mg, administered subcutaneously every 6 months. At 12 months, new vertebral fractures had occurred in 16 of 3321 patients (0.5%) in the romosozumab group, compared with 59 of 3322 (1.8%) in the placebo group, representing a 73% lower risk in patients treated with romosozumab. At 24 months, vertebral fracture rates were significantly lower in the romosozumab group than in the placebo group after each group switched to denosumab (0.6% of patients in the romosozumab group versus 2.5% in the placebo group, i.e., a 75% lower risk with romosozumab).

In addition, the ARCH study, conducted in 2046 postmenopausal women, showed a reduced risk of new vertebral and hip fractures in the group of patients treated with romosozumab in the first 12 months, and subsequently with alendronate, compared with the group treated with alendronate for the whole trial duration. In particular, the sequential therapy group showed a 48%, 27% and 19% lower risk of vertebral, clinical, and non-vertebral fractures, respectively, versus women treated with alendronate alone (Table 1).[39]

The FRAME study was the pivotal trial that led to the approval of romosozumab by the regulatory agencies, while the ARCH study demonstrated the superiority of romosozumab versus another anti-osteoporotic drugs in term fragility fracture risk reduction, despite safety concerns that emerged from this trial.

Effects of sclerostin on muscle mass and function

Osteoporosis and sarcopenia share risk factors and often coexist (osteosarcopenia), increasing the incidence of frailty, falls, fragility fractures, hospitalization, and mortality. Several studies have been conducted to identify common diagnostic biomarkers and therapeutic targets in patients with both diseases.[40–42] Proteins of muscle origin (myokines), such as interleukins 6, 7 and 15, and myostatin, are responsible for greater osteoclastogenesis, while connexin 43 and osteocalcin (of bone origin), modulate catabolism at the muscle level.[43]

A role of sclerostin in muscle-bone crosstalk has been hypothesized, but the effects of this protein and those related to its pharmacological modulation on muscle tissue are still unclear.[44] For example, mice lacking the *SOST* gene show increased bone density but decreased muscle mass, suggesting that sclerostin inhibition may lead to decreased muscle mass and, theoretically, increased bone fragility and the risk of falls.[45] Conversely, a significant, albeit weak, and negative correlation between thigh muscle mass and serum sclerostin

Table 1. Effects of romosozumab on bone fragility, measured by bone mineral density (BMD) and incidence of fragility fractures.

Title and authors	Study design	Population	Intervention	Main findings
Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomized, open-label, phase 3 trial (Langdahl et al., 2017)[35]	Randomized, open-label, phase 3 trial	Women (aged 55–90) with osteoporosis who received an oral bisphosphonate for at least 3 years	Subcutaneous romosozumab (210 mg once monthly) versus subcutaneous teriparatide (20 μg once daily)	Over 12 months, significantly increased total hip BMD in the romosozumab group (+2.6%) versus teriparatide group (–0.6%)
A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis (Lewiecki et al., 2018)[37]	Randomized, placebo-controlled, phase 3 trial	Men aged 55–90 years with osteoporosis	Subcutaneous romosozumab (210 mg once monthly)	At 1 year, significantly increased lumbar spine and hip BMD (+12.1% and +2.5%) in patients receiving romosozumab versus placebo group
Romosozumab treatment in postmenopausal women with osteoporosis (Cosman et al., 2016)[38]	Randomized, double-blind, placebo-controlled, parallel-group trial	Women with postmenopausal osteoporosis	Subcutaneous romosozumab (210 mg) or placebo, monthly for 12 months; subsequently, patients in each group received subcutaneous denosumab (60 mg every 6 months) for 12 months	Significant reduction of new vertebral fragility fractures in the romosozumab group at both 1 year (–73%) and 2 years (–75%)
Romosozumab or alendronate for fracture prevention in women with osteoporosis (Saag et al., 2017)[39]	Phase 3, multicenter, international, randomized, double-blind trial	Women (aged 55–90 years) with osteoporosis	Monthly subcutaneous romosozumab (210 mg) or weekly oral alendronate (70 mg) for 12 months, followed by open label alendronate in both groups	Significant reduction of vertebral, clinical, and non-vertebral fragility fractures (–48%, –27%, and –19%, respectively) at 2 years in patients receiving sequential therapy (romosozumab–alendronate)

levels was reported in frail obese patients ($r = -0.23$, $P < 0.05$).[46]

Furthermore, although physical inactivity and immobilization are known to produce an increase in sclerostin secretion, Pickering et al.[47] demonstrated that serum levels of this protein increase sharply and significantly in response to physical activity. Specifically, in a cohort of healthy young women, 23 participants (mean age ± SD, 22.9 ± 1.5 years) who performed an exercise test had an increase in serum sclerostin from baseline of 44% (410 ± 27 versus 290 ± 19 pg/mL), while nine women (26.1 ± 3.1 years) who remained at rest showed stable serum sclerostin levels (303 ± 20 versus 294 ± 20 pg/mL). In this study, serum sclerostin levels were determined before and 5 minutes after the test, to examine the acute response of this protein to exercise.[47]

Conversely, in a cross-sectional study, Amrein et al.[48] demonstrated decreased serum sclerostin levels in a cohort (mean age, 44.1 years) of 127 men and 34 premenopausal women, in relation to vigorous physical activity, compared with levels obtained in an inactive group (43.2 pmol/l versus 51.7 pmol/l; $P = 0.04$) that did not have a significant gender difference.

A study of 129 elderly Korean patients (mean age, 69 years) found significantly lower serum sclerostin levels in those with sarcopenia, even after accounting for the confounding effects of other factors, such as age, sex, and body mass index (BMI).[48] In particular, taking into account various structural and functional parameters, such as muscle mass, grip strength, walking speed, time to complete five chair stands, short physical performance battery, and the sarcopenia phenotype score, it was highlighted that increases in mass and strength were dose-dependent in relation to increased serum sclerostin, while the association between serum sclerostin levels and physical performance was not significant. Therefore, according to the authors' conclusions, the risk of sarcopenia appears to decrease with increasing serum sclerostin levels, suggesting an anabolic action of sclerostin on muscle, compared with the known catabolic role on bone, contrary to previous studies supporting an inverse correlation between serum sclerostin levels and muscle mass.[24] Another study, conducted in 240 healthy, non-diabetic Koreans, showed the negative effects of higher serum sclerostin levels on muscle mass, independent of factors such as age, sex, BMI, fasting blood glucose and total fat mass.[49] However, there was no causal link between sclerostin concentrations and decreased muscle mass, since it was a cross-sectional study; moreover, the sample analyzed comprised only a small number of Korean men and women, certainly not representative of the entire Korean population, and only muscle mass was investigated, without any data about muscle strength or physical performance. Furthermore, in a cohort of 92 patients undergoing hemodialysis (mean age, 63 years), serum sclerostin levels showed an inverse correlation with muscle mass index ($P < 0.001$) and a positive association with diabetes ($P = 0.003$). Mean serum sclerostin levels were significantly higher in the group with diabetes versus those without diabetes (97.2 ± 46.6 versus 79.7 ± 31.2; $P < 0.044$), particularly among men (109.5 ± 50.9 versus 77.4 ± 31.2; $P < 0.044$).[49]

Taking into account the interaction between sex steroids and muscle and bone tissues,[50] Zhou et al.[51] analyzed the correlation between sclerostin and grip strength in orchiectomized rats, demonstrating a significant increase in serum sclerostin in this animal model compared with controls (279 ± 44 pg/mL versus 240 ± 20 pg/mL, respectively, at time 0; and 586 ± 57 pg/mL versus 406 ± 20 pg/mL, respectively, 8 weeks after orchidectomy, $P < 0.05$), as well as a significant reduction in grip strength of orchiectomized rats compared with the control group (1443.8 ± 75.9 g versus

1401.3 ± 90.8 g at time 0, and 1298.4 ± 32.5 g versus 1534.7 ± 29.8 g after 8 weeks, $P < 0.05$). These data suggest that higher serum sclerostin levels are associated with decreased muscle strength.

The role of sclerostin and its modulation in osteosarcopenia

Osteosarcopenia is a syndrome characterized by reduced BMD (i.e., osteopenia or osteoporosis), muscle mass, muscle strength and/or physical performance.[52] It is estimated that the prevalence of this condition will tend to increase drastically to such an extent that, by 2050, approximately 2 billion individuals aged >60 years may be diagnosed with osteosarcopenia.[53] The mechanism underlying the concomitant loss of bone density and muscle mass may be explained, in addition to the same mesenchymal derivation of bone and muscle tissues,[54] by the interaction of nutritional, endocrine, or neuronal regulators between muscle and bone. Indeed, not only the ground reaction forces and the direct biomechanical interactions on the tendons, but also the local growth factors, myokines and osteokines, are key regulators of muscle-bone crosstalk.[55] Sclerostin appears to play a key role in this mechanism, regulating bone production in response to mechanical loading.[56] Some evidence has shown that an abnormal Wnt signaling pathway may be a cause of sarcopenia. Considering the interconnections that exist between Wnt signaling and other pathways involved in skeletal muscle regeneration, the role of the Wnt-mediated pathway in regulating skeletal muscle in the elderly remains ambiguous, probably due to the pleiotropic effect of Wnt.[57] Moriwaki et al.[58] conducted a study on the correlation between serum concentrations of bone- and muscle-derived factors and parameters of body composition and physical function in 254 subjects (aged at least 40 years). Serum sclerostin was increased and related to factors such as age (in men $r = 0.318$, $P = 0.002$; in women $r = 0.180$, $P = 0.024$), BMI, heel speed of ultrasound, skeletal muscle mass index, and grip strength. However, this study did not reveal any relationship between serum sclerostin and physical function, probably because it included active, non-immobile patients; immobilization is known to cause an increase in serum sclerostin, which translates into a loss of bone tissue.[28] Therefore, it is probable that in the case of subjects who already presented an adequate mechanical load on bones and muscles before being enrolled, the study did not show a significant correlation between serum sclerostin levels and physical function.

Furthermore, osteocalcin, produced by osteoblasts, might be another potential connection between increased muscle mass and bone density. A study by Mera et al.[59] demonstrated that osteocalcin is required to avoid age-related muscle mass loss in mice and that exogenous osteocalcin increases muscle mass in aged mice. Since inhibition of sclerostin by romosozumab results in increased osteoblast differentiation from progenitor cells and consequently increased osteoblast activity,[60] it may be hypothesized that an increased number of osteoblasts is responsible for the increased levels of osteocalcin and consequently of muscle mass. Therefore, romosozumab, resulting in an increase in muscle mass, would have a positive effect on frailty and the risk of falls,[61] thus representing an effective treatment against osteosarcopenia.

The role of sclerostin and its modulation on the risk of falls

Low BMD, bone fragility, and falls are major risk factors for osteoporotic fractures.[62–64] The risk of fracture is 1.5 to 6.7 times greater in patients who have experienced falls in the previous 12 months;[63,64]

Table 2. Effects of sclerostin and its modulation on muscle mass and muscle function.

Title and authors	Study design	Population	Intervention	Skeletal muscle-related outcome measures	Main findings
Effects of pharmacologic sclerostin inhibition or testosterone administration on soleus muscle atrophy in rodents after spinal cord injury (Phillips et al., 2018)[43]	Animal study	5-month-old male rats	Scl-AbIII anti-sclerostin monoclonal antibody in rats with moderate-to-severe contusion-induced spinal cord injury	Cross-sectional area of the soleus muscle	Anti-sclerostin antibody does not prevent muscle atrophy after spinal cord injury (lack of LRP5/6 co-receptors on soleus fibers)
The roles of sclerostin and irisin on bone and muscle of orchiectomized rats (Zhou et al., 2022)[51]	Animal study	3-month-old male rats	Orchiectomy	Grip strength	The significant increase in serum sclerostin corresponds to a significant reduction in muscle strength in orchiectomized rats versus controls.
Decreased serum level of sclerostin in older adults with sarcopenia (Ahn et al., 2022)[47]	Cross-sectional study	129 patients (mean age, 69 years), of which 20 affected by sarcopenia	N/A	ASM and SMI (ASM/ height^2), handgrip strength, SPPB	The risk of sarcopenia appears to decrease with increasing serum sclerostin levels
Association of serum sclerostin levels with low skeletal muscle mass: The Korean Sarcopenic Obesity Study (KSOS) (Kim et al., 2019)[24]	Cross-sectional study	240 healthy Korean adults	N/A	Total and regional lean mass Total fat mass percentage of total body fat. ASM	Negative effects of sclerostin on muscle mass, regardless of age, sex, BMI, fasting blood glucose and amount of total fat mass.
Changes in thigh muscle volume predict bone mineral density response to lifestyle therapy in frail, obese older adults (Armamento-Villareal, 2014)[45]	Randomized controlled trial	107 obese patients (mean age, 70 years)	Exercise and/or diet for 12 months	Thigh muscle volume Muscle strength of the knee flexor and extensor muscles	Weak significant inverse correlation between thigh muscle mass and serum sclerostin
Serum sclerostin, body composition, and sarcopenia in hemodialysis patients with diabetes (Medeiros et al., 2020)[49]	Cross-sectional study	92 hemodialysis patients (mean age, 63 years), of which 41 with diabetes and 60 with sarcopenia	N/A	Muscle strength, SMI, physical performance	High serum sclerostin is found in patients with diabetes on hemodialysis with low muscle mass versus patients with normal SMI
One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study (Lewiecki et al., 2019)[72]	Phase 3, randomized, double-blind, placebo-controlled study	7180 women with postmenopausal osteoporosis (mean age, 70.9 years)	12 months of romosozumab followed by 24 months of denosumab	Risk of falls	Statistically significant reduction in the risk of falls after 12 months of treatment with romosozumab versus control group

(continued)

Table 2. Continued.

Title and authors	Study design	Population	Intervention	Skeletal muscle-related outcome measures	Main findings
Risk of falls in postmenopausal women treated with romosozumab: Preliminary indices from a meta-analysis of randomized, controlled trials (Mockel et al., 2020)[62]	Meta-analysis	12 128 women with postmenopausal osteoporosis	Romosozumab for 12 months and with a sequential approach (romosozumab →antiresorptive)	Risk of falls	Romosozumab tends to reduce the risk of falls by 12–20% in postmenopausal women with osteoporosis

ASM, appendicular skeletal muscle mass; BMI, body mass index; LRP, low-density lipoprotein receptor-related protein; SMI, skeletal muscle mass index; SPPB, Short Physical Performance Battery.

therefore, since 90% of hip fractures in elderly patients are caused by falls,[65] it is mandatory to assess the risk of falling and to provide a patient-tailored multifactorial intervention for preventing falls in older people.[66] In the context of preventing the risk of fall, it is necessary to take into account both non-pharmacological interventions, mainly based on therapeutic exercise, and the potential ancillary effects of anti-osteoporotic pharmacological therapy, as demonstrated by various studies. For example, denosumab has been shown to reduce the risk of falling by 22% compared with placebo, as reported in a pooled analysis of more than 10 000 patients.[67] Similar findings have been reported in patients treated with romosozumab, in a meta-analysis of phase 2 and phase 3 randomized trials that included postmenopausal women with low BMD, or osteoporosis, receiving romosozumab 210 mg, once monthly for 12 months.[62] The analysis included studies reporting fall risk data at 12 months,[68–72] and at 33–36 months, of treatment.[70–72] In this context, only the FRAME study,[72] based on a sequential approach (12 months of romosozumab followed by 24 months of denosumab), met all the inclusion criteria of the meta-analysis, including data on the risk of falling, while none of the other studies involving the administration of romosozumab reported such data at 12 months of treatment. Specifically, subgroup analysis of the double-blind studies found a statistically significant 20% reduction in the risk of falls with romosozumab compared with the control group (risk ratio [RR] 0.80; 95% confidence interval [CI] 0.71, 0.92; $P \leq 0.01$; $n = 11\,211$) at 1 year, while two studies were included in the fall risk assessment of romosozumab at 12 months followed by antiresorptive treatment, for a treatment period of 33–36 months, demonstrating a statistically significant reduction in the risk of falls by 12% (RR 0.88; 95% CI 0.80, 0.96; $P \leq 0.01$; $n = 11\,211$). Thus, data

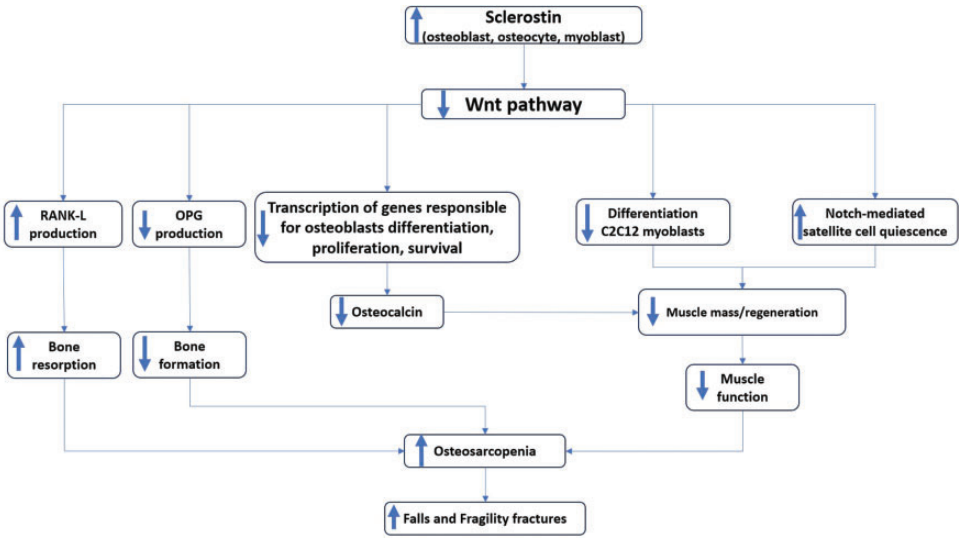

Figure 1. Overview of the effects of sclerostin on bone and muscle. Sclerostin blocks the Wnt pathway, the latter having bone protective effects by reducing receptor activator of nuclear factor-kB ligand (RANK-L) production, increasing osteoprotegerin (OPG) production and transcription of genes for osteoblasts survival and activity; moreover, the Wnt pathway also positively acts on skeletal muscle, by increasing myoblast differentiation and reducing satellite cell quiescence, thus improving muscle mass and function. Thus, modulation of the Wnt pathway through the block of sclerostin might counteract osteosarcopenia and its clinical consequences.

reported in the literature suggest that romosozumab and denosumab may be appropriate therapeutic options for frail patients with a high risk of falling.

How romosozumab affects the risk of falls in postmenopausal women with low BMD has not been investigated in the various studies. The effect of antiosteoporotic drugs on the risk of falling may be related to the role they play in bone-muscle crosstalk. Since patients with bone fragility typically also have muscle weakness,[73] the risk of falling may be reduced by the increase in muscle mass caused by romosozumab. However, this hypothesis is not supported by the evidence available to date. Regarding the well-known correlation between thigh muscle volume and BMD, if we consider that some studies have shown that obese and frail patients, who perform physical activity, show a significant increase in thigh muscle mass and bone density, and while non-exercising patients show decreased BMD and muscle volume, changes in muscle mass may be predictive of site-specific BMD changes.[46] Since romosozumab has been shown to be effective in increasing lumbar spine and total hip BMD by 13.7% and 6.2%, respectively, compared with baseline,[40] it may be hypothesized that romosozumab is also able to determine an increase in muscle mass, comparable to that of BMD.[62] However, considering the divergent data existing in the literature, the effects of this drug on muscle mass, strength, physical performance, and risk of falling, are still to be defined (Table 2, Figure 1).

Conclusions

Skeletal muscle and bone are intimately connected, not only due to their anatomical and biomechanical relationships, but also thanks to an endocrine and paracrine

regulation system. Sclerostin, which is mainly produced by osteocytes, although recently revealed to be also produced by muscle cells undergoing differentiation, inhibits bone production and plays a role in the regeneration of skeletal muscle tissue. This glycoprotein plays an increasingly emerging role in pathologies of the musculoskeletal system, representing a promising therapeutic target for the treatment of diseases related to the intracellular signaling cascade mediated by Wnt proteins, including osteosarcopenia.

Author contributions

Each author contributed individually and significantly to the manuscript. AM and GI participated in the design of the study, and contributed to data collection and manuscript writing. Both authors have read and agreed to the published version of the manuscript.

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