The role of anti-osteoporosis drugs in fall risk

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ABSTRACT

Osteoporosis is a common skeletal disease characterized by reduced bone mass and micro-architectural deterioration, which leads to an increased risk of fractures. A significant concern associated with osteoporosis is the risk of falls, which can result in fractures and other related complications. This review examines the role of anti-osteoporosis drugs in the prevention of falls, focusing on pharmacological interventions that have shown promise in reducing the incidence of falls in osteoporotic patients. Falls in older people often lead to fractures, decreased mobility and reduced quality of life.

Given that individuals with osteoporosis are more susceptible to fractures, it is essential to explore therapeutic strategies aimed at mitigating fall risk in this population. Anti-osteoporosis drugs have been developed primarily to improve bone mineral density and strength. The most extensively explored in this sense is probably vitamin D. Several meta-analyses have indicated that vitamin D could reduce the risk of falling compared with placebo. For this nutrient, important in vitro and experimental research data are available showing, overall, a positive effect on muscle. However, there is emerging evidence that large bolus doses and/or high levels of vitamin D may increase the risk of falls. Denosumab, a monoclonal antibody against RANKL (receptor activator of nuclear factor-κB ligand), is widely used to treat osteoporosis, and its influence on falls, although supported by a recent systematic review, is currently under investigation. Understanding the relationship between anti-osteoporosis medications and fall prevention is critical in comprehensive management of osteoporosis. Although these drugs are primarily used to improve bone health, their influence on falls is an intriguing topic.

KEYWORDS

Falls, denosumab, vitamin D, romosozumab.

Introduction and epidemiology of falls in older people

Falls among older adults are a significant public health concern worldwide. As populations age, the incidence and impact of falls continue to rise, posing challenges for healthcare systems, caregivers and individuals themselves [1].

Falls, in fact, are among the leading causes of injury-related morbidity and mortality in older adults. According to the World Health Organisation, an estimated 646,000 individuals die from falls globally each year, making falls the second leading cause of unintentional injury death, after road traffic accidents [2]. Moreover, for every fatal fall, there are numerous non-fatal falls resulting in injuries, hospitalisations and reduced quality of life [2]. The prevalence of falls increases with age, with the highest rates observed in individuals aged 65 and older. Studies have shown that approximately one in three community-dwelling older adults experience a fall each year [3].

Various intrinsic and extrinsic factors contribute to the risk of falls in older people. Intrinsic factors include age-related physiological changes, chronic health conditions, cognitive impairment, and medication use [4]. Musculoskeletal weaknesses, balance and gait disorders, visual impairment, and neurological disorders also increase the risk of falls [4]. Extrinsic factors include environmental hazards such as slippery floors, poor lighting, uneven surfaces and inadequate footwear. Additionally, socioeconomic factors, including poverty, social isolation and limited access to healthcare, can exacerbate the risk of falls among older adults. At the same time, some medications, such as benzodiazepines, may significantly increase the risk of falls [5].

However, an increasing body of research is reporting that some commonly used anti-osteoporosis drugs may decrease the risk of falling, and could potentially be the only medications to have this effect. Therefore, in this narrative review, we discuss the role, in fall risk, of some medications commonly used to treat osteoporosis.

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Vitamin D: effect on falls

The most extensive literature dealing with anti-osteoporosis medications and fall risk concerns vitamin D.

Low vitamin D status is associated with skeletal muscle fibre atrophy, muscle pain, weakness, and increased risk of sarcopenia and associated falls, both in active and non-active individuals [6,7].

Muscle biopsies in adults with marked vitamin D deficiency have shown predominantly type II muscle fibre atrophy [7]. It is to be noted that type II muscle fibres are fast-twitch fibres and the first to be recruited to prevent a fall. Thus, the fact that vitamin D deficiency primarily affects type II fibres may help to explain the fall tendency observed in vitamin D-deficient elderly individuals [8].

The identification of a vitamin D receptor (VDR) in skeletal muscle cells has provided evidence of the important role of vitamin D in skeletal muscle function and metabolism [9,10].

Several mechanisms have been suggested to mediate the effects of vitamin D on muscle strength, function and metabolism. They include myogenesis, cell proliferation and differentiation, regulation of protein synthesis and mitochondrial metabolism [11].

Molecular mechanisms underlying the action of vitamin D on muscle tissue have both genomic and non-genomic effects. Genomic effects are initiated by binding of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] to its nuclear receptor (VDR), which results in gene transcription of mRNA and subsequent protein synthesis. Non-genomic effects of vitamin D are mediated through plasma membrane-bound proteins, whose nature remains somewhat controversial [11].

Both genomic and non-genomic effects are involved in intracellular calcium handling. Contractile force generation is a process mediated by calcium ions, resulting in activation of the interaction between myosin and actin filaments. Therefore, regulation of cytosolic calcium concentration is critical to proper maintenance of muscle function [11].

The sarcoplasmic reticulum (SR) initiates muscle contraction by releasing calcium through the ryanodine receptor (RyR) channels into the cytosol, and facilitates muscle relaxation by means of active reuptake of calcium by the sarcoendoplasmic reticulum calcium ATPase (SERCA) pump, a membrane transporter located on the SR membrane. The SERCA pump's primary function is reuptake of cytosolic Ca^{2+} into the SR lumen following muscle contraction, using energy derived from ATP hydrolysis. This allows the cytosolic Ca^{2+} concentration to be maintained at low levels, i.e., of between 50 and 100 nM. Therefore, SERCA induces muscle relaxation and, at the same time, restores the SR calcium store that is necessary for muscle contraction. During excitation-contraction coupling events associated with muscle force generation, Ca^{2+} ions are released through the RyR channels in the SR membrane, increasing the cytosolic Ca^{2+} to 1-2 μM for a few milliseconds. This high concentration of Ca^{2+} ions facilitates the interaction of calcium with troponin to trigger the sequence of events leading to force production [12].

A recent study in VDR knockout mice suggested that low serum vitamin D levels lead to inadequate VDR signalling (genomic pathway) in mature myofibres, reducing the activity of the SERCA pump and, consequently, altering the dynamics of muscle contraction by decreasing Ca^{2+} reuptake into the SR, thereby prolonging the relaxation phase of muscle contraction. The authors concluded that vitamin D-VDR signalling has minimal influence on the regulation of muscle mass in mature myofibres, but has a significant influence on muscle strength. They also suggested that muscle weakness induced by vitamin D deficiency is possibly caused by excitation-contraction uncoupling [13].

Another recent study in mice lacking VDR activity in skeletal muscle suggested that vitamin D plays a role in maintaining adequate muscle performance by controlling ATP metabolism. The results indicated that pyrophosphate production through ATP degradation is involved in the vitamin D-VDR signalling in skeletal muscle and influences muscle function. The authors proposed a working model of 1,25$(OH)_2D_3$-VDR signalling in skeletal muscle cells based on the regulation of ATP metabolism at the cell membrane niche. According to this model, 1,25$(OH)_2D_3$-VDR signalling in muscle increases protein expressions of connexin 43, a releaser of ATP into the extracellular space, and of the ATP-metabolizing enzyme ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1). The subsequent extracellular ATP degradation by ENPP1 increases pyrophosphate, which inhibits calcium accumulation in muscle cells [14].

In addition to genomic actions (whose physiological effects can take a few hours to appear, since RNA and proteins need to be synthetised), 1,25(OH)2D3 elicits rapid (in the seconds to minutes range) non-genomic cellular effects, which are claimed not to involve the nuclear VDR and do not require the activation of genes. One of these non-transcriptional responses is increased influx of calcium into the cell.

Potential explanations for the rapid non-genomic vitamin D-triggered pathway, suggested by various authors, are that vitamin D signalling is mediated either by a VDR associated with plasma membrane, including caveolae (small invaginations of the plasma membrane), or by a different membrane-bound receptor.

The best described vitamin D-binding membrane-associated protein is the enzyme PDIA3 (protein disulphide isomerase family A 3), also called 1,25D3-MARRS (membrane-associated rapid response to steroid). Activation of the rapid response to vitamin D requires an interaction of PDIA3 with caveolin 1, the main caveolar protein. PDIA3 mediates several 1,25(OH)2D3-dependent membrane signalling cascades and stimulates opening of Ca^{2+} channels. However, the mechanisms and physiological relevance of non-genomic vitamin D-triggered pathways are still unclear [15,16].

Several randomized clinical trials (RCTs) and meta-analyses of RCTs regarding the effect of vitamin D supplementation on prevention of falls have been performed in the past 20 years.

Earlier meta-analyses reported conflicting results (either beneficial effects or no benefit) probably because they combined studies dealing with:

- population groups that differed in initial vitamin D status, age, setting (community dwelling vs nursing home), and degree of mobility;
- different vitamin D doses and dosing schedules (including daily and bolus dosing);
- different achieved levels of 25(OH)D after supplementation;
- combined supplementation of vitamin D + calcium or supplementation of vitamin D alone (vs placebo);
- different intervention periods, ranging from a few months to several years.

A meta-analysis, by Bischoff-Ferrari *et al*. (2009), of 10 RCTs

involving a total of 3050 participants (8 RCTs with 2426 participants receiving either vitamin D2 or vitamin D3 and 2 RCTs with 624 participants treated with active forms of vitamin D) reported that supplemental vitamin D (700-1000 IU/day) reduced the risk of falling among older individuals by 19%, and to a similar degree as active forms of vitamin D. Achieved serum 25(OH)D concentrations of 60 nmol/L or more resulted in a 23% fall reduction [17].

After this seminal paper, Wu *et al*. (2017) conducted a meta-analysis of 26 RCTs with 16540 older individuals. They reported a reduction in fall risk with vitamin D plus calcium, but not with vitamin D alone [18].

On the contrary, a meta-analysis of 37 RCTs with 34144 participants by Bolland *et al*. (2018) showed no effect of vitamin D supplementation on falls. However, it focused on vitamin D monotherapy and excluded studies which compared vitamin D plus calcium and placebo. Additionally, the authors did not compare specific dose subgroups with the controls [19].

The 2018 USPSTF recommendation, which opposed vitamin D supplementation to prevent falls in adults aged 65 years or older, included only 7 RCTs with 7531 participants and concentrated only on vitamin D3 or active forms of vitamin D and on the community-dwelling setting [20].

More recent meta-analyses concluded that the combination of vitamin D and calcium has beneficial effects on fall prevention. A meta-analysis of 47 RCTs with 58424 participants (mainly elderly females and principally community-dwelling individuals) by Thanapluetiwong *et al*. (2020) showed that vitamin D significantly reduces fall incidence only when it is co-administered with calcium [21].

A meta-analysis of 31 RCTs involving 57857 participants by Ling *et al*. (2021) concluded that vitamin D supplementation reduces fall risk in the vitamin D-deficient elderly population. The analysis showed that combined supplementation of vitamin D (daily doses of 700-1000 IU) and calcium (daily doses of 1000-1200 mg) was significantly associated with a 12% reduction in the risk of falling [22]. An important finding was that although vitamin D supplementation alone had no effect on fall risk in elderly adults with basal serum 25(OH)D levels higher than 50 nmol/L, it reduced this risk by 23% when the baseline serum 25(OH)D concentration was lower than 50 nmol/L. The meta-analysis included the results from the Vitamin D and Omega 3 Trial (VITAL), the largest placebo-controlled RCT of supplemental vitamin D in the United States, which found that vitamin D (2000 IU/day) did not prevent falls in generally healthy, community-dwelling older adults with a mean serum 25(OH)D level at baseline (data available only for 16757 participants, corresponding to approximately 65% of the total) of 77 nmol/L [23]. A meta-analysis of 38 RCTs involving 61350 participants by Wei *et al*. (2022) showed that 700 IU to 2000 IU of supplemental vitamin D per day reduced fall risk by 13% among ambulatory and institutionalised elderly individuals. The effect of vitamin D in preventing falls depended on additional calcium supplementation: vitamin D with no calcium supplementation did not reduce the risk of falls, while the pooled risk reduction for falling was 17% in the presence of 500-1000 mg/day of supplemental calcium. Furthermore, the effectiveness of vitamin D in preventing falls depended on the 25(OH)D serum level in the intervention group, since the pooled risk reduction for falling was found to be 23% in trials with 25(OH)D concentrations ≥60 nmol/L [24].

Kong *et al*. (2022) conducted a meta-analysis of 32 RCTs with 104363 participants (21 of the RCTs, accounting for 36793 participants, had falls as outcome). Participants were mainly elderly females, and had a median follow up of 24 months. The authors showed that vitamin D supplementation with a daily dose of 800 to 1000 IU was associated with a 19% lower risk of falls in the general population (community-dwelling subjects), while intermittent administration was not. Fall risk was significantly reduced both with vitamin D supplementation alone and with the co-administration of calcium. Patients with vitamin D deficiency at their baseline showed a 22% fall risk reduction after vitamin D supplementation [25].

Taken together, these findings suggest that vitamin D could decrease the risk of falls in older people, even though the role of calcium supplementation is not entirely clear.

The very recent network meta-analysis of 35 RCTs involving 58937 community- and institution-dwelling elderly individuals by Tan *et al*. (2024) showed that vitamin D supplementation with 800-1000 IU/day significantly lowered the incidence of falls (by 15%) regardless of setting. According to the subgroup analysis, daily administration of 800-1000 IU vitamin D reduced the risk of falls by 22%, whereas intermittent administration (weekly, monthly or yearly intake) of vitamin D had no preventive effect on falls. Furthermore, vitamin D was only beneficial for fall prevention in populations with vitamin D deficiency [mean baseline 25(OH)D concentration ≤50 nmol/L] [26] (Table I).

There is a substantial body of evidence that vitamin D supplementation with loading doses resulting in high 25(OH)D serum levels adversely affects fall risk in older adults who are at increased risk of falling [24].

Bolus doses of vitamin D given annually, at a dose of 500,000 IU [27], or monthly, at a dose of 100,000 IU [28] or 60,000 IU [29], resulted in a significant increase in the number of falls.

High daily doses of vitamin D (4000 and 4800 IU/d) to increase serum 25(OH)D concentrations to above 112 nmol/L might also induce an increased risk of falls in elderly women [30].

A recent clinical trial in healthy community-dwelling men and women aged ≥ 65 years, who were treated with 700 IU of vitamin D plus 500 mg of calcium or placebo daily for three years, showed intra-trial mean 25(OH)D (whether attained by supplementation or diet and sun exposure) to be significantly associated with fall risk in a U-shaped pattern. The risk of falling was higher in those with 25(OH)D levels < 22 ng/mL and it was progressively higher at intra-trial mean 25(OH)D values > 40.5 ng/mL [31].

The basis for increased fall risk with large bolus doses of vitamin D and/or high 25(OH)D levels may be related to the observation that 25(OH) D levels above 100 nmol/L (40 ng/mL) are associated with increased circulating levels of fibroblast growth factor 23, which impairs the 1-alpha hydroxylation of 25(OH)D to 1,25$(OH)_2$D (calcitriol), and also promotes 24-hydroxylation of 25(OH)D to the inactive form of 24,25$(OH)_2$D. Therefore, a very high vitamin D status may cause insufficiency of the active metabolite calcitriol [32,33].

Table I Characteristics of meta-analyses and RCTs evaluating the effects of vitamin D treatment on fall risk.

REFERENCE AND TYPE OF STUDY	STUDY GROUP (N = number of par-ticipants)	INTERVENTION	DURATION OF TREATMENT	BASELINE MEAN 25(OH)D SE-RUM LEVEL	OBSERVED EFFECTS ON FALLS
Bischoff-Ferrari *et al.* (2009) [17] Meta-analysis	8 RCTs, N = 2,426 (women 81%) Approximate mean age 80 years Community-dwelling and living in nursing homes	Daily **vitamin D2/ D3** 700-1000 IU **± calcium**	2 - 36 months	Not assessed	Daily vitamin dose of 700-1000 IU re-duced fall risk by 19%. Achieved serum 25(OH)D levels ≥ 60 nmol/L resulted in a 23% fall reduc-tion.
Wu *et al.* (2017) [18] Meta-analysis	26 RCTs, N = 16,540 Mean age ± SD ranging from 67± 2 to 92 ± 6 years	**Vitamin D** • 200 - 1000 IU/day (800 IU/day in 11/26 RCTs) • in 6 RCTs total dosage ranged from 300,000 IU/36 months to 600,000 IU/6 months **± calcium**	1 - 60 months	Not assessed	Reduction in fall risk with vitamin D plus calcium, but not with vitamin D alone
Bolland *et al.* (2018) [19] Meta-analysis	37 RCTs, N = 34,144 Unselected populations of community-dwelling women and men aged ≥ 65 years	**Vitamin D alone in the majority of RCTs** Daily dose mostly < 1000 IU/day (excluded trials which compared vitamin D + cal-cium and placebo)	≤1 year for most studies	Only 4 trials were done in popula-tions with baseline mean serum 25(OH)D level <25 nmol/L	Vitamin D supplementation did not pre-vent falls. No differences between the effects of higher and lower doses of vitamin D and in subgroup analyses of RCTs using doses > 800 IU/day
Grossman *et al.* (2018) [20] Meta-analysis	7 RCTs, N = 7,531 Mean age 71 – 77 years Community-dwelling	**Vitamin D ± calcium** • 700 IU or 800 IU daily; 150,000 IU/3 months or 500,000 IU annually; • 2 RCTs administered 1 µg of 1-hydroxycho-lecalciferol daily or 0.25 µg of calcitriol twice daily Excluded trials in vitamin D-depleted individuals	9 months up to 5 years	Ranging from 65.9 to 79.4 nmol/L	Vitamin D supplementation did not pre-vent falls. Calcitriol showed a reduction in falls and in people experiencing a fall. Annual high-dose cholecalciferol (500,000 IU) showed an increase in falls, people experiencing a fall, and injurious falls.
Thanapluetiwong *et al.* (2020) [21] Meta-analysis	47 RCTs, N = 58,424 Mainly elderly females (age < 80 years), and principally community-dwelling	**Vitamin D ± calcium** • 37 trials with vit D3 • 7 trials with vit D2 • 1 trial with vit D2 and D3 • 2 trials with vit D analogues	Less or more than 12 months	Not assessed	Vitamin D significantly reduced fall incidence only when co-supplemented with calcium.
Ling *et al.* (2021) [22] Meta-analysis	31 RCTs, N = 57,857 Mean age • 61 - 89 years in 21 RCTs with vit D alone • 67.4 - 85.2 years in 10 RCTs with Vit D + calcium	**Vitamin D alone** 21 RCTs (N = 51,984) daily or intermittent doses of 400-60,000 IU **Vitamin D + calcium** 10 RCTs (N = 5883) Vit D 700-1000 IU daily + calcium 1000-1200 mg daily	<1 year 1-3 years >3 years	<50 nmol/ and ≥50 nmol/L	Vitamin D supplementation alone reduced fall risk by 23% in the vitamin D-deficient population [baseline serum 25(OH)D level < 50 nmol/L] Vitamin D + calcium reduced fall risk by 12%.
LeBoff *et al.* (2020) [23] RCT	N = 25,871 Men ≥ 50 years Women ≥ 55 years (mean age 67.1 years) Community-dwelling	**Vitamin D** 2000 IU/day	5.3 years	77 nmol/L available for 16,757 partici-pants (approxi-mately 65% of all participants)	Vitamin D supplementation did not decrease fall risk in generally healthy adults not selected for vitamin D insufficiency
Wei *et al.* (2022) [24] Meta-analysis	38 RCTs, N = 61,350 Adults > 50 years Community-dwelling and institutionalized	**Vitamin D ± calcium** Vit D ≥ 700 IU/day or < 700 IU/day	2 months up to 63 months	Ranging from 25 to 86.77 nmol/L (available only in 8 studies)	Daily vitamin dose of 700-2000 IU re-duced fall risk by 13% among ambulatory and institutionalized elderly individuals. The effectiveness of vitamin D in pre-venting falls depended on: • supplemental calcium of 500-1000 mg/day; • achieved serum level in the intervention group (≥ 60 nmol/L)

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Kong *et al.* (2022) [25] Meta-analysis	32 RCTs, N = 104,363 21 RCTs N = 36,793 with falls as outcomes Median age 72 years (range 53-85) Most studies included women (75% of participants; range 15-100%) Community-dwelling and institutionalized	**Vitamin D ± calcium** • 8 studies: <800 IU/d • 15 studies: 800-1000 IU/d • 9 studies: >1000 IU/d • Daily dose in 26 RCTs • Intermittent dose in 6 RCTs	Median follow-up duration 24 months (range 9-120)	Available in 23 studies, but data not shown in the paper	Daily vitamin dose of 800-1000 IU reduced fall risk by 19% in community-dwelling subjects (study numbers insufficient to determine the result for institutionalized participants). No reduction of fall risk in studies with vitamin D dose <800 or>1000 IU/day and with intermittent doses The risk of fall was significantly reduced both with vitamin D supplementation alone and with the co-administration of calcium. Patients with vitamin D deficiency at their baseline showed a 22% risk reduction of falls after vitamin D supplementation.
Tan *et al.* (2024) [26] Network meta-analysis (NMA)	35 RCTs, N = 58,936 Community-dwelling and institutionalized elderly individuals	**Vitamin D ± calcium** • 6 studies: <800 IU/d • 19 studies: 800-1000 IU/d • 18 studies: >1000 IU/d • 11 studies (31.4%): vitamin D + calcium	3 months up to 5 years	• 18 studies: ≤50 nmol/L • 11 studies: >50 nmol/L* *NMA only per-formed in 9 stud-ies	Vitamin D supplementation with 800-1000 IU/day was associated with a lower fall risk in older adults with vitamin D defi-ciency. [baseline serum 25(OH)D level ≤ 50 nmol/L] No reduction of fall risk in studies with vitamin D dose <800 or>1000 IU/day and with intermittent doses

Denosumab and bisphosphonates

After vitamin D, denosumab (Dmab) is probably the drug most extensively explored for its potential to prevent falls in older people. In studies where data on falls were lacking, physical performance data were available.

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study, investigating the antifracture efficacy of Dmab in 7868 postmenopausal women with osteoporosis, showed a significantly lower incidence of falls in the Dmab arm. In this pivotal placebo-controlled trial, 4.5% of the women receiving Dmab during the 3-year study reported falls as adverse events, compared with 5.7% of women in the placebo group (log-rank p = 0.02). This finding excluded falls associated with fractures [34].

To date, few human studies have examined the relationship between Dmab, muscle function and fall risk.

One study compared Dmab (n=51) with zoledronic acid (n=28), combined with vitamin D supplementation, to examine changes in the muscle strength, balance and physical performance of 79 community-dwelling older adults. After a 6-month observation period Dmab conferred a clinically significant increase in multidirectional agility by improving gait speed, and Timed Up and Go test and Four-Square Step Test performances. No differences in falls were found versus zoledronate [35].

An observational prospective study confirmed the beneficial effects of both Dmab (n=15) and alendronate (n=25) on skeletal muscle mass and function in elderly patients with hip fracture, finding no significant differences between treatment groups 1 year after hip surgery [36].

In a longitudinal prospective study, 135 patients with postmenopausal/senile osteoporosis treated with Dmab for 5 years were compared with a control group of 272 patients stratified into two subgroups – 136 receiving alendronate (5-year therapy) and 136 receiving zoledronate (3-year therapy). Dmab significantly reduced fall risk while the bisphosphonates did not. Compared with the bisphosphonates, Dmab showed the highest significant positive effect on both physical performance and muscle strength. Importantly, one year after discontinuation of Dmab a significant worsening of both fall risk and sarcopenia measures was observed [37].

A retrospective propensity score-matched (sex, age, BMI, follow up time) cohort study examined the effects of denosumab versus bisphosphonates (alendronate 70 mg weekly or i.v. ibandronate 3 mg every 3 months) and vitamin D alone on muscle performance in patients with low bone mineral density. The study included 150 osteopenic or osteoporotic patients receiving Dmab (n=60), bisphosphonates (n=30), or basic therapy (n=60). Vitamin D supplementation was provided in all patients prior to the initiation of anti-resorptive treatment, to normalize 25(OH)D levels (≥30 nmol/L). The Dmab group showed a significantly higher increase in lower limb muscle performance, as measured by force on the chair rising test, compared with the patients treated with bisphosphonates [38].

An ad hoc exploratory analysis pooled data from five placebo-controlled trials of Dmab to assess possible reduction in fall incidence. The subjects included postmenopausal women with osteoporosis (FREEDOM study), postmenopausal women with low bone mass, men with osteoporosis, women with nonmetastatic breast cancer receiving adjuvant aromatase inhibitors and men with nonmetastatic prostate cancer receiving androgen deprivation therapy. The analysis included 10036 individuals (mean age approximately 72 years; men 16.9%); 5030 received Dmab 60 mg subcutaneously once every 6 months for 12 to 36 months, and 5006 received placebo. Calcium and vitamin D supplementation was applied equally in the Dmab and placebo groups. The results suggested that Dmab can reduce the number of fallers by approximately 20% [39].

The benefits of RANK inhibition on muscle function and fall risk might potentially be explained by the fact that muscle RANK is a key regulator of Ca^{2+} storage, SERCA activity and function of fast-twitch skeletal muscles, as observed

by Dufresne *et al*. [40,41]. Using mutant mice with a specific RANK skeletal muscle deletion ($RANK^{mko}$), they demonstrated that RANK inactivation reduces SERCA activity but protects against sciatic denervation-induced muscle dysfunction and favours a fast-twitch muscle phenotype. In addition, they showed that RANK deletion in denervated extensor digitorum longus muscle — this is a phasic muscle, composed almost exclusively of fast-twitch fibres — increased total intracellular calcium (over 97% of which is stored in the SR) and specific force, and the levels of STIM-1 (stromal interaction molecule-1), which functions as sensor for Ca^{2+} store in the SR lumen. To explain the apparent discrepancy between the increase in total intracellular calcium and the decrease in SERCA activity, the authors suggested that the STIM-1/Orai-1 calcium channel complex [42-44] compensates for the decrease in SERCA activity, refilling SR Ca^{2+} stores and improving muscle function in the absence of muscle RANK.

Furthermore, it has been demonstrated that RANKL/RANK signalling plays a key role in muscle metabolism and the development of sarcopenia [45]. One study showed that RANK worsens while its inhibitors Dmab and osteoprotegerin improve muscle strength and insulin sensitivity in osteoporotic mice (which either overexpress RANKL and develop severe osteoporosis or lack the myogenic factor *Pparb* and concomitantly develop a combination of osteo/sarcopenia associated with impairment of glucose homeostasis) and humans [45]. The authors concluded that Dmab could represent a novel therapeutic approach for sarcopenia [45].

To our knowledge, no studies on fall outcome are available for selective oestrogen receptor modulators (SERMs), teriparatide and abaloparatide.

Romosozumab

Romosozumab, a monoclonal antibody against sclerostin that increases bone formation and inhibits bone resorption, is a new medication for the treatment of osteoporosis, particularly in women affected by severe osteoporosis [46].

A meta-analysis of four RCTs involving 12128 postmenopausal women with osteoporosis showed that 12 months of treatment with romosozumab decreased overall fall risk by a non-significant 16%, but a subgroup analysis including double-blind studies indicated a statistically significant 20% reduction in this risk [47].

The question of how romosozumab might influence fall risk remains open. Interestingly, a recent study found a negative correlation between serum sclerostin levels and skeletal muscle mass, suggesting a possible role for this osteokine as a marker of low muscle mass [48].

Conclusions

Falls are multifactorial events, and it is never easy to reduce the risk of falling, even with multidimensional and multidisciplinary interventions. While medications are often cited as potential risk factors for falling, some literature is now showing that anti-osteoporosis drugs could have a protective effect on this outcome. Vitamin D is the most explored of these medications, and has been found to have an effect on muscle and therefore on falls. As for the other drugs commonly available for the treatment of osteoporosis, their role in reducing the risk of fractures is promising. However, we feel that there is a need for further studies in which fall risk is used as a primary outcome and tests of strength and physical performance as secondary outcomes.

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