Efficacy and Safety of Romosozumab as a Medication for Osteoporosis in Postmenopausal Women: A Literature Review

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A capstone project submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

Master of Physician Assistant Studies

University of Manitoba

Winnipeg

May 15, 2025

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Abstract

Introduction: Osteoporosis is a systemic skeletal condition in which bone mineral density is markedly decreased. Romosozumab, a monoclonal antibody, has been approved for osteoporosis use in Canada since 2019. Further assessment of which patient population(s) and when to use romosozumab for greatest effect is needed.

Methods: A literature search was conducted on the PubMed database, looking at any randomized controlled trial and clinical trial with the keyword “romosozumab” published between 2015 and 2025.

Results: Four studies met the criteria for inclusion. All studies demonstrated significant improvements in bone mineral density (BMD) at the lumbar spine, femoral neck, and hip. Greatest BMD gains were observed at the lumbar spine uniformly throughout the studies. Most commonly observed adverse effects in romosozumab patients include mild injection site reactions and arthralgia. Incidence of serious events related to romosozumab use was noted in one study.

Conclusion: Romosozumab was seen to significantly improve BMD and have a favorable safety profile in most patients, however limited insight into which patient population would benefit most from treatment. Currently, not enough evidence in literature to suggest romosozumab as first line treatment.

Introduction

Osteoporosis is a medical condition in which skeletal integrity is compromised by low bone density and deterioration of bone microarchitecture. Osteoporosis is defined by a decreased bone mineral density (T-score < -2.5 measured by dual-emission x-ray absorptiometry (DXA)), which compromises bone strength and ultimately increases risk of low trauma/fragility fracture(s).[1] It affects around 2.5 million Canadians, of whom approximately 80% are women.[2] The pathophysiology of this condition is multifactorial, including estrogen deficiency, excess bone remodeling during repair of microdamage, disruption of trabecular microarchitecture of bone, and reduced protection from oxidative stress with age.[1] Risk factors for osteoporosis include increasing age, female sex, hormonal factors (i.e., ovary removal at a young age), prolonged immobility, prolonged use of corticosteroids, low calcium and vitamin D intake, cigarette smoking, limited physical activity, personal and/or family history of fractures, and more.[3]

Disease Burden

The disease burden of osteoporosis is related to the higher risk and incidence of fractures, which are associated with significant morbidity and mortality.[4] In older adults, fragility fractures are associated with reduced survival for up to six years following a fracture, with a mortality rate of one in five women and one in three men following a hip fracture in the first year after the fracture.[5] In addition to mortality, patients are often unable to return to their previous ambulatory state, are left with physical disability, can no longer perform activities of daily living independently, and require more caregiver support.[6] This subsequently leads to increased care

costs, longer waits for personal care homes, and increased need for homecare, all of which further burdens the healthcare system.

Given the heavy burden of disease, understanding the pathophysiology of the condition and determining effective treatments is very important. There are multiple different classes of osteoporosis medications. These include antiresorptive therapies, which inhibit bone breakdown, such as hormone therapy, denosumab, raloxifene, and bisphosphonates. Bisphosphonates are the recommended first-line pharmacotherapy for osteoporosis per the 2023 clinical practice guidelines for osteoporosis published in the Canadian Medical Association Journal.[7] (Treatment recommendations summarized in Appendix A). On the other hand, there are anabolic medications such as sclerostin inhibitors and parathyroid hormone analogs which work by stimulating bone formation. Some osteoporosis medications, such as the bisphosphonates, have been used for over 30 years, but the anabolic medications are relatively novel.[8]

Romosozumab – Mechanism of Action

The Wnt/β-catenin pathway is a key regulator in bone tissue homeostasis and metabolism. Wnt ligand binds to lipoprotein receptor related protein 5 and 6 (LRP5/6) allowing expression of osteoblast-related genes, which promote osteogenesis and bone formation.[9] Additionally, mutations in LRP5/6 have been associated with metabolic bone disease.[9] Thus, the role of Wnt/β-catenin in bone homeostasis makes it a target for therapeutic intervention in conditions such as osteoporosis. Sclerostin is a glycoprotein secreted by osteocytes and works to inhibit the Wnt/β-catenin pathway in bone tissue, resulting in decreased osteogenesis.[9] Sclerostin also increases RANKL production and decreases OPG expression, which results in increased

osteoclast differentiation and increased bone resorption.[10] (Appendix B). Therefore, inhibition of sclerostin would lead to increased bone formation and decreased bone resorption. Romosozumab is a monoclonal antibody which works as a sclerostin inhibitor, and was approved for use in Canada in 2019.[11] As a fairly novel pharmacotherapeutic, reviewing the literature to highlight key findings is useful for a general practice medical practitioner or those who see patients with osteoporosis frequently in their practice.

This literature review aims to compare outcomes such as efficacy, fracture risk, and significant adverse effects with use of romosozumab. Evaluating the role of romosozumab in the management of osteoporosis and indications for treatment will be discussed.

Methods

PubMed database was searched between December 2024 - January 2025. Search term "romosozumab", with the following filters: "RCT" and "clinical trial", published between 2015-2025 were used. No mesh terms were used. This search produced 39 results. To select the papers to be further analysed, the following inclusion and exclusion criteria was applied:

Inclusion criteria: Post-menopausal women, BMD T-score ≤ -2.5, romosozumab dose of 210 mg subcutaneous monthly, randomized controlled trial or clinical trial, published between 2015 and 2025, published in English.

Exclusion criteria: Males, pre-menopausal women, BMD T-score > -2.5, studies published before 2015, dose-finding trials, any study that is not an RCT or clinical trial, published in a language other than English.

These criteria were applied so that the most relevant studies would be included. Incidence of osteoporosis is highest in post-menopausal women, and much less common in males. Osteoporosis is defined as a BMD T-score of ≤ -2.5, therefore that was the cut-off value used. Romosozumab dose of 210 mg was used as this is the effective dose determined by dose-finding trials and currently used in practice. Looking at results of studies with less effective dosing would not help answer the questions posed in this literature review. RCTs and clinical trials were looked at so that articles would have minimal study design bias, and factors such as safety and efficacy would be focused upon. Including studies from the last 10 years allowed for assessment of the most current findings.

Article Review

Article review was conducted by a single individual. Eligibility was based on the title, abstract, methods, and population section of each article. After review of all 39 articles, a total of four publications met all inclusion criteria, and were further analyzed in this literature review.

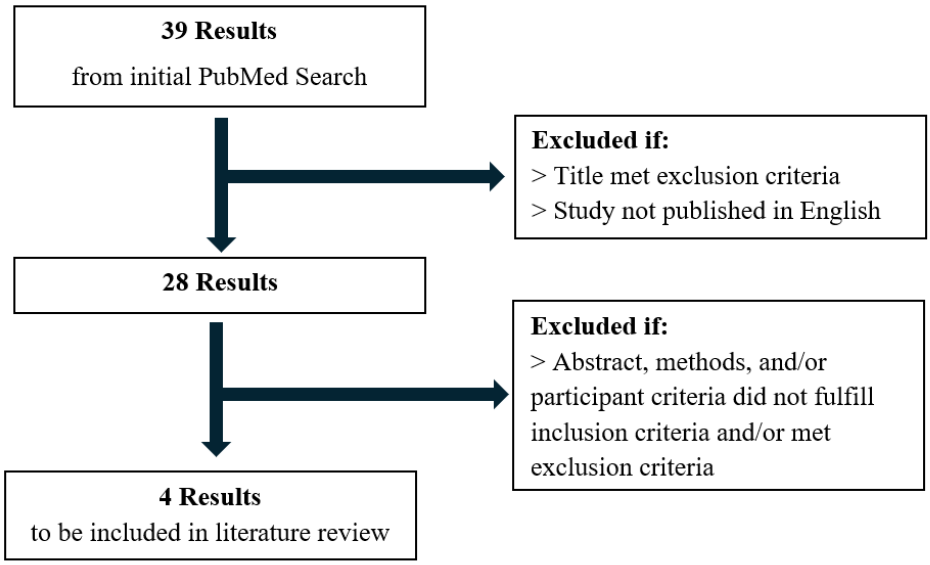


Image 1. Flowchart demonstrating methodology and article review process.

A formal ethics review board submission was not required as this was a literature review only.

Results

The first study by Cosman et al.[12] assessed the cumulative incidences of new vertebral fractures at 12 months and 24 months in a group of 7180 postmenopausal women aged 55-90 with a BMD T-score between -2.5 to -3.5 at the total hip or femoral neck.[12] The study compared the effects between romosozumab and placebo treatment for one year, followed by denosumab (antiresorptive) treatment in both groups for 12 months. Secondary endpoints such as clinical fractures, nonvertebral fractures, and BMD were also assessed.

Langdahl et al.[13] looked at the effects of romosozumab versus teriparatide (anabolic parathyroid hormone analog) in 436 postmenopausal women aged 55-90 with osteoporosis who have had at least three years of treatment with bisphosphonate prior to screening for the study, and had taken alendronate in the year immediately before screening for this study.[13] Prior studies had shown that teriparatide was not as effective at improving BMD in patients who were exposed to oral bisphosphonates versus those who were bisphosphonate treatment-naive. Thus Langdahl et al. investigated whether romosozumab would have significant efficacy outcomes when compared to teriparatide in patients who have been using bisphosphonates for multiple years. Primary study outcome was the mean percentage change from baseline in the total hip BMD after a year of treatment with either romosozumab or teriparatide. Secondary endpoints included mean percentage change from baseline at the femoral neck, lumbar spine.

The third article was a randomized pilot study performed by Mochizuki et al.[14] A one-year course of romosozumab vs denosumab in patients with rheumatoid arthritis was assessed in 51 postmenopausal women. The study outcomes included BMD at the lumbar spine, total hip, and femoral neck at 3, 6, and 12 months, disease activity score in 28 joints (DAS28-ESR), and joint damage via van der Jeijde-modified Total Sharp Score (TSS).

Baek et al. assessed efficacy and safety of romosozumab in postmenopausal Korean women with osteoporosis.[15] This was a phase three, double blinded and placebo-controlled study comparing the effect of a six-month course of romosozumab to placebo on 67 postmenopausal women aged 55-90 with osteoporosis and a BMD T-score $\leq$ -2.5 and > -4.0. In this study, the primary endpoint was the difference in the least square mean percent change from baseline in lumbar spine BMD between the two study groups at six months. Secondary efficacy endpoints were the change in BMD from baseline at total hip and femoral neck at six months.

Bone Mineral Density

All four studies assessed bone mineral density at the lumbar spine, femoral neck, and hip using DXA. All demonstrated significant BMD improvement from baseline in participants receiving romosozumab. After a 12-month period of romosozumab treatment, Cosman et al. observed a 13.3% increase at the lumbar spine, 6.9% at the total hip, and 5.9% increase at the femoral neck compared to baseline.[12] After both groups transitioned to denosumab, the romosozumab group continued to demonstrate an increase in BMD. Similarly, Langdahl et al. observed an improvement in BMD with romosozumab.[13] The percentage change of BMD from baseline to month 12 at the lumbar spine was 9.8% in the romosozumab group and 5.4% in the

teriparatide group. The total hip percentage change was 2.9% in the romosozumab group and -0.5% in the teriparatide group. The femoral neck percentage change was 3.2% in the romosozumab group compared to -0.2% in the teriparatide group.[13] Mochizuki et al. observed a similar trend. The BMD percentage change from baseline to 12 months at the lumbar spine was significant, with a 10.2% increase in the romosozumab group versus 5.0% in the denosumab group. The change in BMD was also significantly higher in the romosozumab group at the three- and six-month measurements. Both total hip and femoral neck BMD increased from baseline at month 12, however there was no significant difference between the romosozumab group and the denosumab group.[14] The study results from Baek et al. followed the same pattern, with the greatest percentage change in BMD from baseline being at the lumbar spine (9.5% at six months). The percentage change from baseline at the total hip was 2.9%, and 3.0% at the femoral neck. All changes were significant compared to the placebo group.[15] Overall, all four studies demonstrated a significant percentage change from baseline at the lumbar spine BMD when treated with romosozumab compared to placebo or other medications.

Fracture Risk

Cosman et al. was the only study to look at the cumulative incidence of new vertebral fractures at 12 and 24 months following romosozumab treatment.[12] The group receiving romosozumab had a 73% lower risk of new vertebral fractures after 12 months when compared to placebo. The incidence of new vertebral fractures after 12 months was 0.5% (16 participants) in the romosozumab group, and 1.8% (59 participants) in the placebo group.[12] Of the 16 participants with a new vertebral fracture in the romosozumab group, 14 of them experienced the fracture in the first six months, with only two participants experiencing a fracture between

months 6 to 12. Nonvertebral fractures occurred in 1.6% of romosozumab patients and 2.1% of placebo patients at 12 months, however the difference was not statistically significant. At the 24-month mark, after a year of denosumab treatment in both the romosozumab and the placebo groups, the cumulative 24-month incidence of new vertebral fractures was lower in the romosozumab group (75% lower risk compared to the placebo group). Between months 12 to 24, 5 patients from the romosozumab group and 25 from the placebo group developed a new vertebral fracture. No significant differences in risk for nonvertebral fractures or clinical fractures was noted between the romosozumab group and placebo group at 24 months.[12]

The remaining studies did not evaluate fracture incidence or risk, but did comment on fracture events in participants. Langdahl et al. observed that 3% of patients from the romosozumab group reported fractures (femoral neck, foot, rib, sternum, ulna) and 4% of teriparatide patients reported fractures (humerus, foot, forearm, pubis, radius, tibia). Additionally, hip strength gains were estimated to be significantly greater in the romosozumab group compared to the teriparatide group at 6 and 12 months. Hip strength had a 2.1% and 2.5% change from baseline at 6 and 12 months respectively in the romosozumab group, whereas teriparatide had a -1.0% and -0.7% change from baseline at 6 and 12 months respectively.[13] Mochizuki et al. also commented on fracture occurrence. There was one vertebral fracture and one wrist fracture in the denosumab group, and no fractures in the romosozumab group.[14] Baek et al. noted one femur fracture in the placebo group, with no fractures reported for the romosozumab group.[15]

Safety

There were minimal romosozumab-related side effects noted. The most common side effects between the studies included injection site reaction/hypersensitivity, and arthralgia. Only one study noted atypical femur fracture (AFF) (n=1) and osteonecrosis of the jaw (ONJ) (n=2). No positively adjudicated cardiovascular (CV) adverse events were noted in the studies assessed.

Cosman et al. observed that the incidence of adverse events was balanced in the romosozumab and placebo groups. There were seven cases of severe hypersensitivity in the romosozumab group (dermatitis, allergic dermatitis, macular rash), however a much larger group had mild injection site reactions by 12 months (187 participants (5.2%)). Two cases of ONJ occurred in the romosozumab group, one at the 12-month mark in context of ill-fitting dentures, and one after the first dose of denosumab in context of a tooth extraction. One case of AFF was noted 3.5 months after starting romosozumab, for which the authors have mentioned that the patient had prodromal pain at site of fracture prior to enrollment. Serious cardiovascular events were seen in 1.2% of romosozumab patients and 1.1% of placebo patients after 12 months. After switching to denosumab, the romosozumab group had a total of 2.3% of participants experience an adverse cardiac event over 24 months and 2.2% of placebo participants. This demonstrates that romosozumab has no increased risk of cardiac events compared to placebo.[12]

Similar to Cosman et al., Langdahl et al. reported that both romosozumab and teriparatide groups had a balanced percentage of adverse events. Serious adverse events were reported in 8% of romosozumab patients and 11% of teriparatide patients, however these were deemed to be

unrelated to treatment. As seen in other studies, a common adverse effect was injection site reactions (in 8% of patients), mostly reported to be mild, with one patient discontinuing romosozumab at day 180 of study secondary to severe injection site erythema, pruritus, and edema. Another adverse event of interest was hypocalcemia - this was observed in 1% of patients (2/3 of which were asymptomatic). Teriparatide had no cases of hypocalcemia, however did cause mild hypercalcemia in 10% of patients. No AFF or ONJ reported in either romosozumab or teriparatide groups. No adverse CV events noted. Arthralgia was seen in 10% of patients on romosozumab treatment, and 6% of patients being treated with teriparatide.[13]

Mochizuki et al. noted arthralgia (*n* =2), nausea (*n* =1), rash (*n* =1), headache (*n* =1), and hypertension (*n* =1) in the romosozumab group whereas the denosumab group experienced pain at the injection site (*n* =1) and nausea (*n* =1). No incidence of AFF, ONJ, or positively adjudicated CV events were commented on. No worsening of romosozumab on rheumatoid arthritis disease activity was observed.[14]

Baek et al. observed one hypersensitivity event (rash) with romosozumab, and one event of osteoarthritis. No events of AFF, ONJ, or positively adjudicated CV events observed at the six- or nine-month period with romosozumab treatment. Other treatment-emergent adverse effects in romosozumab group include arthralgia (*n* =1), back pain (*n* =1), extremity pain (*n* =1), lumbosacral radiculopathy (*n* =1), neurologic neglect syndrome (*n* =1), angina pectoris (*n* =1), gastritis (*n* =1), bronchitis (*n* =1), laryngitis (*n* =1), hypertension (*n* =1).[15]

Discussion

In the articles assessed, romosozumab was effective in significantly improving BMD and had a favorable safety profile throughout. Evaluating the efficacy of romosozumab compared to standard therapy (bisphosphonates) and assessing use in different populations is important for healthcare providers to consider.

Efficacy and Medication Choice

BMD and Fracture Risk

All four studies formally assessed the change in BMD after treatment with romosozumab, and while romosozumab significantly increased BMD in each study, the question arises of whether improving BMD is clinically relevant for osteoporosis – that is, does it change the disease outcome? The disease burden of osteoporosis is heavily related to the incidence of fragility fractures. Almost all types of fractures increase when a patient has low BMD, with a study by Marshall et al. demonstrating a significant increase in fracture risk with each one SD decrease in BMD.[16] Cosman et al. assessed new vertebral fracture incidence, and noticed significantly lower fracture incidence at 12 months (0.5% of romosozumab, 1.8% placebo) and 24 months (0.6% romosozumab, 2.5% placebo).[12] This was in keeping with a greater increase in BMD in the romosozumab group. However, rather than comparing to placebo, it would be of more clinical utility to compare the fracture incidence between different osteoporosis medications, namely romosozumab and bisphosphonates. Langdahl et al., Mochizuki et al., and Baek et al. also all demonstrated fewer fractures in the participants who received romosozumab, again in keeping with greater BMD gains.[13-15]

Saag et al. looked at incidence of vertebral fractures in romosozumab compared to alendronate. At both the 12-month and 24-month marks, incidence of new vertebral fractures was significantly lower in the romosozumab group compared to alendronate treatment.[17] BMD gains were also significantly greater in the romosozumab group when compared to the alendronate group.

These studies demonstrate the association between increased BMD and decreased fracture incidence seen with romosozumab use. This suggests that romosozumab may have greater improvement in reducing fracture incidence when compared to current first-line medication. However, romosozumab is a one-year treatment course, whereas bisphosphonates can be used for up to six years at a time. Studies demonstrate that the anabolic effects and BMD levels can return to baseline within 12 months of discontinuing romosozumab.[18] Bisphosphonates continue to be first-line medication given that they can have longer-term anti-resorptive effects on bone. Long-term incidence of fracture needs to be assessed between the two medications to determine if one is more effective than the other.

Throughout all studies, romosozumab-related BMD gains are seen to be greatest in the lumbar spine.[12-15] This is not different from bisphosphonates, which also demonstrate the greatest BMD gains at the lumbar spine.[19-22] This is likely because the lumbar spine is mostly composed of trabecular bone, whereas the hip is primarily cortical bone.[23] Trabecular bone is more metabolically active and has greater turnover than cortical bone.[24] Therefore, one can postulate that given the higher turnover in trabecular bone, the antiresorptive and anabolic effects of

osteoporosis medications would be higher at a site such as the lumbar spine. With increased BMD, one can expect to then see fewer fractures of the lumbar spine.

Sequence of Treatment

Understanding the appropriate sequence in which to use osteoporosis medications is of clinical utility to providers. Of the articles reviewed, Langdahl et al. was the only study with confirmed bisphosphonate use immediately before romosozumab,[13] with Cosman et al. and Baek et al. confirming that participants required an adequate washout period for medication that influenced bone metabolism, including osteoporosis medications.[12,15] Interestingly, at the 12-month mark, participants from Langdahl et al. had the least increase in BMD (9.8%)[13] compared to Cosman et al. (13.3%)[12] and Mochizuki et al. (10.2%).[14] This suggests that prior anabolic treatment may blunt the increases seen in BMD with romosozumab. It is important to note that a washout period, such as the ones in these studies, may not reflect real-life situations when patients are switching between medications. An additional consideration is that Langdahl et al.[13] required bisphosphonate use for at least three years, which is more reflective of real-life practice, where patients are put on bisphosphonates for five to six years at a time.

It has been observed that BMD is increased more in patients who are osteoporosis treatment-naïve.[25,26] At 12 months, BMD gains seen with romosozumab in the treatment-naïve group was significantly higher than patients pre-treated with bisphosphonates.[25,26] Additionally, the duration of prior antiresorptive therapy is inversely associated with BMD increases at the lumbar spine and hip.[25] Therefore, the longer the bisphosphonate treatment, the smaller the BMD gains seen with romosozumab treatment. Tominaga et al. observed that greater than one year of

bisphosphonate use attenuated the effects of romosozumab.[27] These findings support the idea that romosozumab may be used as first-line therapies to maximize BMD gains in patients who are newly diagnosed, followed by an anti-resorptive.[12,17]

A different study by Cosman et al.[28] determined that the probability of increasing BMD at the hip from a T-score of -3.0 to a target T-score above -2.5 was 61% with romosozumab-treated patients who then transitioned to alendronate, compared to a probability of 9% with alendronate alone.[28] The probability of BMD T-score increasing to > -2.5 at lumbar spine was estimated at 85% when treating with romosozumab followed by alendronate, compared to 25% probability with alendronate alone.[28] This further supports the idea of following romosozumab with bisphosphonates for greater BMD gains.

Bisphosphonates work by attaching to hydroxyapatite binding sites preferentially at areas of active bone resorption. As osteoclasts work to resorb bone, the embedded bisphosphonate is released and either causes detachment of osteoclasts or osteoclast apoptosis. This leads to decreased bone resorption.[29-31] Additionally, bisphosphonates bind to bone mineral with different affinities, with the ability to stay in the matrix for several months to years.[32] This suggests that bisphosphonates can continue to decrease bone resorption for up to years after stopping treatment. As mentioned previously, sclerostin is involved in bone resorption, which means that levels will be higher when there is greater bone breakdown. It has been noted that sclerostin levels are lower in individuals who respond to bisphosphonates, which create an antiresorptive state.[33] Given that sclerostin is the target of romosozumab, if there are lower levels of sclerostin secondary to bisphosphonate use, then it can be deduced that the efficacy of romosozumab may

be less robust. A study by Adami et al.[34] showed a positive relationship between higher baseline sclerostin levels and greater BMD gains, however there are no studies at this time demonstrating impact of romosozumab efficacy with low sclerostin levels.

Interestingly, it has been hypothesized that the bisphosphonate-related dampening of romosozumab-induced bone modeling and remodeling is more prevalent at cortical bones than trabecular bone.[35,36] The spine is mostly composed of trabecular bone, and hip is more cortical bone.[24] Therefore, using bisphosphonates prior to romosozumab may dampen BMD gains at hip more than the spine, which means there may be less of a benefit in reducing hip fractures when using romosozumab after bisphosphonates.

Clinical Utility in Different Patient Populations

Prolonged Steroid Use

Chronic steroid use is a known risk factor for osteoporosis, therefore assessing efficacy of osteoporosis medications in this population would be valuable. Mochizuki et al.[14] compared romosozumab and denosumab in RA patients to assess which is more effective. 11.5% of romosozumab group patients and 24% of denosumab group study patients were using glucocorticoids for RA management. Despite the study not demonstrating any strong evidence for romosozumab use compared to denosumab use in the setting of RA, there remains the question of whether romosozumab would be useful in patients using glucocorticoids. A study by Mok et al.[37] looked at the same medications, romosozumab vs denosumab, in chronic glucocorticoid users at high risk of fractures. Results demonstrated that romosozumab had a significantly greater increase in spine BMD compared to denosumab at 12 months. From months

12 to 24, all participants received denosumab, however the romosozumab group continued to gain spine BMD to a greater extent than denosumab up to 24 months.[37] Overall, this study demonstrated the superiority of romosozumab to antiresorptive denosumab in chronic glucocorticoid users.

Glucocorticoids influence bone health by impairing both bone formation and bone resorption.[38] Since romosozumab has a dual mechanism of action, it may be a better treatment than an antiresorptive therapy alone. Additionally, studies show that pharmacologic glucocorticoid use induces sclerostin expression,[39-41] which is a glycoprotein that blocks the Wnt pathway. Sclerostin blockade in glucocorticoid-induced osteoporosis is primarily effective in preserving bone mass through its antiresorptive effects rather than its osteoanabolic action.[42] As a sclerostin inhibitor, romosozumab may be more effective, but further research is required. Nonetheless, this data is something for clinicians to consider when managing patients who have chronic steroid exposure.

Severe Osteoporosis

The 2023 CMAJ guidelines suggest anabolic medications be used if the patient has had a recent severe vertebral fracture or ≥ 2 vertebral fractures.[7] The studies in this literature review did not focus on this population. Cosman et al.[12] excluded women with any severe vertebral fractures or if they had more than two moderate vertebral fractures. Additionally, their study population also only looked at BMD between -2.5 and -3.5.[12] Both Cosman et al. and Langdahl et al. excluded patients with recent use of medications that affect bone metabolism, which

restricts the applicability of these results to real-life patients who may have comorbidities and need medications involved in bone metabolism.[12,13]

Baek et al.[15] excluded patients with a BMD T-score of ≤ -4.0, which allows for inclusion of patients with severe osteoporosis compared to the two studies mentioned above, that had a narrower BMD range. At the six-month mark, percentage BMD gains were greater in the Baek et al.[15] population than participants in Langdahl et al.[13] and Mochizuki et al.,[14] which may suggest that romosozumab causes greater BMD gains in patients with more severe disease. A different study also noted that patients with lower BMD had a greater percentage change in their T-score following romosozumab treatment compared to patients with higher BMD.[43]

In patients who sustain a vertebral fracture, incidence of another fracture in the following year can be as high as 19.2%.[44] Multiple studies demonstrate that romosozumab is more effective at decreasing fracture incidence compared to bisphosphonates in patients with recent fractures.[17,45] Tominaga et al.[43] demonstrated that percentage change in spine BMD was significantly higher following romosozumab treatment in participants who sustained fractures within the three months prior to starting romosozumab.[43]

Overall, these findings suggest that romosozumab is better at improving BMD in high-risk patients with low BMD and recent fractures. Therefore, patients with a new diagnosis of osteoporosis and recent fracture, or severe osteoporosis should potentially receive romosozumab as first-line treatment.

Safety Profile

Cardiovascular Events

Cosman et al.[12] noted some cardiovascular events, but incidence was balanced between romosozumab and placebo groups, which decreases the likelihood of association between romosozumab and cardiac events.[12] The other three studies did not report any adverse CV events thought to be caused by romosozumab.[13-15] Cosman et al. had the largest participant enrollment (7180),[12] whereas the other studies had smaller sample sizes (436, 51, and 67 participants).[13-15] Perhaps the lack of CV events in these other studies is due to the smaller sample size, and if the sample size was larger then there may have been occurrence of adverse CV event(s). However, Saag et al.[17] reported that positively adjudicated serious CV events, such as cardiac ischemic and cerebrovascular events, occurred more frequently in the romosozumab group.

Looking further into the role that romosozumab may have on cardiovascular function, it has been discovered that sclerostin is not only expressed in osteocytes, but also in the aortic vascular smooth muscle,[46,47] although it's function in the vasculature is not clearly defined. It has been proposed that sclerostin may inhibit vascular calcification,[48,49] therefore a sclerostin inhibitor such as romosozumab would theoretically increase vascular calcification. Krishna et al.[50] performed a study which suggests that sclerostin has atheroprotective and anti-inflammatory effects in apolipoprotein E knockout mice.[50] These associations between sclerostin and vascular health could be a possible mechanism behind the cardiovascular events seen in the romosozumab groups. A study by Turk et al.[51] assessed if there was a relationship between cardiovascular adverse events and the use of romosozumab. Researchers looked at the effect of sclerostin antibody on the bone and cardiovascular system in mice and monkey models with and without

atherosclerosis. Results demonstrated that there was no effect of sclerostin inhibition on vascular calcification, cardiovascular function, plaque volumes, and no evidence of sclerostin inhibition on promoting atheroprogression or inflammation of vasculature.[51] The mechanism behind the CV-related adverse effects associated with romosozumab in a limited number of studies is not clearly understood with no discernible etiology, and needs to be further investigated. Despite multiple studies showing no significant incidence of romosozumab-related CV adverse events, until further understanding of the role of sclerostin in cardiovascular physiology is ascertained, romosozumab use is contraindicated in patients with previous MI or stroke per the CMAJ guidelines.[7]

Metabolic Bone Complications

Atypical femur fractures and osteonecrosis of the jaw are fairly rare, but are known complications of osteoporosis medications. When looking at current first-line osteoporosis treatment, evidence suggests that the longer the bisphosphonate use, the higher the risk of associated AFF and/or ONJ.[52,53] With the articles in this literature review, only Cosman et al. noticed cases of AFF and ONJ in the romosozumab cohort, with no cases reported in the placebo group.[12] The other 3 studies had no incidence of AFF or ONJ.[13-15] Antiresorptives such as bisphosphonates work by stopping bone resorption. Without bone remodelling and resorption, old bone survives past its lifespan and inadequate capillary networks lead to avascular necrosis of jaw.[54] Romosozumab also has decreased resorption, and therefore holds the risk of avascular necrosis. However, the dual effect of increasing bone formation may mitigate the risk of its antiresorptive mechanism.

Peng at al. looked at the Food and Drug Administration adverse event reporting system (FAERS) data from 2004-2021 for events of ONJ via disproportionality analysis. Between eight therapies (six bisphosphonates, denosumab, and romosozumab), romosozumab had the lowest reporting odds ratio of ONJ (6.4) when compared to all other therapies.[55] Interestingly, the onset of ONJ is fastest with romosozumab (median onset 169.5 days), which researchers hypothesize may be secondary to prior bisphosphonate therapy.[55] The clinical relevance of this is for providers to be most attentive for symptoms of ONJ at the six-month mark of romosozumab treatment. Similarly, Xiao et al. looked at reports of atypical femur fracture reported to FAERS between 2012 – 2022. Romosozumab was not associated with AFF, and most bisphosphonates had disproportionate signals for increased AFF risk.[56] With both these studies, it is important to note that romosozumab has only been in the market since 2019, whereas bisphosphonates have been used for decades (meaning greater opportunity for higher incidence of AFF/ONJ). This is a limitation to these results, and perhaps as time progresses, the incidence of AFF/ONJ may increase in romosozumab-treated patients. These findings suggest the risk of AFF and ONJ with romosozumab use is not greater than bisphosphonates, and may potentially be lower. However, direct comparison of AFF and ONJ risk between bisphosphonates and romosozumab has not been assessed.

Limitations & Further Research

This literature review, as well as many other research studies, do not focus on male patients with osteoporosis. This is likely because the disease burden is greater in women. However, in men who do suffer from hip fractures, mortality is higher.[5] This should prompt further studies assessing the efficacy and safety of osteoporosis treatment in men. All the studies

excluded participants with a history of metabolic or bone disease, and many of the studies exclude patients with vitamin D insufficiency, hyper/hypothyroidism, hyper/hypocalcemia, or history of multiple and/or severe fractures. Given that this population is at higher risk of fractures, they may require anabolic therapy in addition to antiresorptive therapy that has been previously used.

Another limitation that can be seen throughout these studies is that many of these RCTs and clinical trials were funded by the pharmaceutical companies Amgen and UCB Pharma, which are both stakeholders in romosozumab manufacturing and sales. This could have resulted in bias throughout the study design or analysis.

Further studies should focus on further assessing high-risk populations, getting a better understanding of romosozumab when used as initial treatment for osteoporosis, and evaluating the utility, efficacy and safety of multiple courses of romosozumab.

Conclusion

Romosozumab is effective at increasing BMD in patients with osteoporosis and appears to have a favourable safety profile. Romosozumab has been seen to increase BMD and decrease fracture risk and incidence, in some cases more than bisphosphonates. However, romosozumab is costly and is only approved for a one-year course of treatment.[57] Long-term effects of the medication are unknown, and currently there is inconclusive/insufficient data to suggest superiority of romosozumab over bisphosphonates. Further research is required before considering changes to osteoporosis management guidelines.

References

1. Armas LA, Recker RR. Pathophysiology of osteoporosis. Endocrinol Metab Clin North Am. 2012 Sept;41(3):475–486. doi:10.1016/j.ecl.2012.04.006
2. Government of Canada. Osteoporosis and related fractures in Canada, 2023 [Internet]. Public Health Agency of Canada; 2024 [cited 2024 Nov 1]. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/osteoporosis-related-fractures-canada-2021.html
3. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. Am J Obstet Gynecol. 2006 Feb;194(2). doi:10.1016/j.ajog.2005.08.047
4. Srivastava M, Deal C. Osteoporosis in elderly: Prevention and treatment. Clin Geriatr Med. 2002 Aug;18(3):529–55. doi:10.1016/s0749-0690(02)00022-8
5. Brown JP, Adachi JD, Schemitsch E, Tarride JE, Brown V, Bell A, Reiner M, Oliveira T, Motsepe-Ditshego P, Burke N, Slatkovska L. Mortality in older adults following a fragility fracture: Real-world retrospective matched-cohort study in Ontario. BMC Musculoskelet Disord. 2021 Jan 23;22(1). doi:10.1186/s12891-021-03960-z
6. Yeh EJ, Rajkovic-Hooley O, Silvey M, Ambler WS, Milligan G, Pinedo-Villanueva R, Harvey NC, Moayyeri A. Impact of fragility fractures on activities of daily living and productivity in community-dwelling women: A multi-national study. Osteoporos Int. 2023 Jun 19;34(10):1751–1762. doi:10.1007/s00198-023-06822-7
7. Morin, SN, Feldman S, Funnell L, Giangregorio L, Kim S, McDonald-Blumer H, Santesso N, Ridout R, Ward W, Ashe MC, Bardai Z, Bartley J, Binkley N, Burrell S, Butt D, Cadarette SM, Cheung AM, Chilibeck P, Dunn S, Falk J, Frame H, Gittings W, Hayes K, Holmes C, Ioannidis G, Jaglal SB, Josse R, Khan AA, McIntyre V, Nash L, Negm A, Papaioannou A, Ponzano M, Rodriques IB, Thabane L, Thomas CA, Tile L, Wark, JD. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. Can Med Assoc J. 2023 Oct 10;195(39):1333-1348. doi:10.1503/cmaj.221647
8. Hayes KN, Ban JK, Athanasiadis G, Burden AM, Cadarette SM. Time trends in oral bisphosphonate initiation in Ontario, Canada over 20 years reflect drug policy and healthcare delivery changes. Osteoporos Int. 2019 Jul 17;30(11):2311–2319. doi:10.1007/s00198-019-05061-z
9. Yu S, Li D, Zhang N, Ni S, Sun M, Wang L, Xiao H, Dingdong L, Liu J, Yu Y, Zhang Z, Yeung ST, Zhang S, Lu A, Zhang Z, Zhang B, Zhang G. Drug discovery of sclerostin inhibitors. Acta Pharm Sin B. 2022 Jan 21;12(5):2150–70. doi:10.1016/j.apsb.2022.01.012
10. Wijenayaka AR, Kogawa M, Lim HP, Bonewald LF, Findlay DM, Atkins GJ. Sclerostin stimulates osteocyte support of osteoclast by a RANKL-dependent pathway. PloS One. 2011 Oct 4;6(10). doi:10.1371/journal.pone.0025900

11. Markham A. Romosozumab: First global approval. Drugs. 2019 Feb 25;79(4):471–6. doi:10.1007/s40265-019-01072-6
12. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CA, Milmont CE, Chen L, Maddox J, Meisner PD, Libanti C, Grauer A. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016 Sept 18;375(16);1532-1543. doi:10.1056/nejmoa1607948
13. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK, Goemaere S, Hyldstrup L, Jodar-Gimeno E, Keaveny TM, Kendler D, Lakatos P, Maddox J, Malouf J, Massari FE, Molina JF, Ulla MR, Grauer A. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomized, open-label, phase 3 trial. Lancet. 2017 Sept 30;390:1585-1594. doi:10.1016/ S0140-6736(17)31613-6
14. Mochizuki T, Yano K, Ikari K, Hiroshima R, Okazaki K. Comparison of romosozumab versus denosumab treatment on bone mineral density after 1 year in rheumatoid arthritis patients with severe osteoporosis: a randomized clinical pilot study. Mod Rheumatol. 2022 Jun 11;33(3):490-495. doi:10.1093/mr/roac059
15. Baek K, Chung Y, Koh J, Kim IJ, Kim KM, Min Y, Park KD, Dinavahi R, Maddox J, Yang W, Kim S, Lee SJ, Cho H, Lim S. Romosozumab in postmenopausal Korean women with osteoporosis: a randomized, double-blind placebo-controlled efficacy and safety study. Endocrinol Metab. 2021 Feb 24;36(1):60-69. doi:10.3803/EnM.2020.848
16. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996 May 18;312(7041):1254-1259. doi:10.1136/bmj.312.7041.1254
17. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med. 2017 Oct 12;377(15):1417-1427. doi:10.1056/NEJMoa1708322
18. Prather C, Adams E, Zentgraf W. Romosozumab: A first-in-class sclerostin inhibitor for osteoporosis. Am J Health Syst Pharm. 2020 Sept 3;77(23):1949-1956. doi:10.1093/ajhp/zxaa285
19. Powell DE, Evans SF, Rakieh C. Bone mineral density response to long-term bisphosphonate treatment and discontinuation in a real-world clinical service. Endocr Pract. 2023 Aug;29(8):601-605. doi:10.1016/j.eprac.2023.04.011
20. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998 Dec;280(24):2077-2082. doi:10.1001/jama.280.24.2077

21. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007 May 3;356(18):1809-1822. doi:10.1056/NEJMoa067312
22. Ahadzadeh Ardebili A, Fu T, Dunnewold N, Aghajafari F, Billington EO. Bisphosphonates preserve bone mineral density and suppress bone turnover markers in early menopausal women: A systematic review and meta-analysis of randomized trials. JBMR Plus. 2023 Apr 14;7(6):e10748. doi:10.1002/jbm4.10748
23. Kim KY, Kim KM. Similarities and differences between bone quality parameters, trabecular bone score and femur geometry. PLoS One. 2022 Jan 11;17(1):e0260924. doi:10.1371/journal.pone.0260924
24. Clarke B. Normal bone anatomy and physiology. Clin J Am Soc Nephrol. 2008 Nov;3(Supplement_3):S131–139. doi:10.2215/CJN.04151206
25. Everts-Graber J, Wenger M, Oser S, Studer U, Steiner C, Ziswiler HR, Sromek K, Schmid G, Gahl B, Häuselmann H, Reichenbach S, Lehmann T. The effect of romosozumab on bone mineral density depending on prior treatment: a prospective, multicentre cohort study in Switzerland. Osteoporos Int. 2024 Jun 26;35(9):1605-1613. doi:10.1007/s00198-024-07155-9
26. Ebina K, Tsuboi H, Nagayama Y, Kashii M, Kaneshiro S, Miyama A, Nakaya H, Kunugiza Y, Hirao M, Okamura G, Etani Y, Takami K, Goshima A, Miura T, Nakata K, Okada S. Effects of prior osteoporosis treatment on 12-month treatment response of romosozumab in patients with postmenopausal osteoporosis. Joint Bone Spine. 2021 Oct;88(5). doi:10.1016/j.jbspin.2021.105219
27. Tominaga A, Wada K, Okazaki K, Nishi H, Terayama Y, Kodama Y, Kato Y. Effect of the duration of previous osteoporosis treatment on the effect of romosozumab treatment. Osteoporos Int. 2022 Jan 21;33(6):1265-1273. doi:10.1007/s00198-021-06261-2
28. Cosman F, Libanati C, Deignan C, Yu Z, Wang Z, Ferrari S, et al. Romosozumab followed by antiresorptive treatment Increases the probability of achieving bone mineral density treatment goals. JBMR Plus. 2021 Aug 31;5(11):e10546. doi:10.1002/jbm4.10546
29. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008 Sept;83(9):1032-45. doi:10.4065/83.9.1032
30. Russell RG, Mühlbauer RC, Bisaz S, Williams DA, Fleisch H. The influence of pyrophosphate, condensed phosphates, phosphonates and other phosphate compounds on the dissolution of hydroxyapatite in vitro and on bone resorption induced by parathyroid hormone in tissue culture and in thyroparathyroidectomised rats. Calcif Tissue Res. 1970;6(3):183-96. doi:10.1007/BF02196199

31. Farrell KB, Karpeisky A, Thamm DH, Zinnen S. Bisphosphonate conjugation for bone specific drug targeting. Bone Rep. 2018 Jul 3;9:47-60. doi:10.1016/j.bonr.2018.06.007
32. Chandran M. The why and how of sequential and combination therapy in osteoporosis. A review of the current evidence. Arch Endocrinol Metab. 2022 Nov 10;66(5):724-738. doi:10.20945/2359-3997000000564
33. Morales-Santana S, Díez-Pérez A, Olmos JM, Nogués X, Sosa M, Díaz-Curiel M, Pérez-Castrillón JL, Pérez-Cano R, Torrijos A, Jodar E, Rio LD, Caeiro-Rey JR, Reyes-García R, García-Fontana B, González-Macías J, Muñoz-Torres M. Circulating sclerostin and estradiol levels are associated with inadequate response to bisphosphonates in postmenopausal women with osteoporosis. Maturitas. 2015 Dec;82(4):402-10. doi:10.1016/j.maturitas.2015.08.007
34. Adami G, Pedrollo E, Rossini M, Fassio A, Braga V, Pasetto E, et al. Romosozumab added to ongoing denosumab in postmenopausal osteoporosis, a prospective observational study. JBMR Plus. 2024 Mar 10;8(4):ziae016. doi:10.1093/jbmrpl/ziae016
35. Poole KE, Treece GM, Pearson RA, Gee AH, Bolognese MA, Brown JP, Goemaere S, Grauer A, Hanley DA, Mautalen C, Recknor C, Yang YC, Rojeski M, Libanati C, Whitmarsh T. Romosozumab enhances vertebral bone structure in women with low bone density. J Bone Miner Res. 2021 Dec 16;37(2):256-264. doi:10.1002/jbmr.4465
36. Eriksen EF, Boyce RW, Shi Y, Brown JP, Betah D, Libanati C, Oates M, Chapurlat R, Chavassieux P. Reconstruction of remodeling units reveals positive effects after 2 and 12 months of romosozumab treatment. J Bone Miner Res. 2024 Jun;39(6):729-736. doi:10.1093/jbmr/zjae055
37. Mok CC, Chan KL, Tse SM, Chen SP, Tan KC, Ma WH. Romosozumab versus denosumab in long-term users of glucocorticoids: a pilot randomized controlled trial. J Intern Med. 2024 Oct 10;296(6):481-494. doi:10.1111/joim.20017
38. Buckley L, Humphrey MB. Glucocorticoid-Induced Osteoporosis. N Engl J Med. 2018 Dec 27;379(26):2547-2556. doi:10.1056/NEJMcp1800214
39. Sato AY, Cregor M, Delgado-Calle J, Condon KW, Allen MR, Peacock M, Plotkin LI, Bellido T. Protection from glucocorticoid-induced osteoporosis by anti-catabolic signaling in the absence of Sost/Sclerostin. J Bone Miner Res. 2016 Jun 5;31(10):1791-1802. doi:10.1002/jbmr.2869
40. Yao W, Cheng Z, Busse C, Pham A, Nakamura MC, Lane NE. Glucocorticoid excess in mice results in early activation of osteoclastogenesis and adipogenesis and prolonged suppression of osteogenesis: a longitudinal study of gene expression in bone tissue from glucocorticoid-treated mice. Arthritis Rheum. 2008 Jun;58(6):1674-1686. doi:10.1002/art.23454
41. Gifre L, Ruiz-Gaspà S, Monegal A, Nomdedeu B, Filella X, Guañabens N, Peris P. Effect of glucocorticoid treatment on Wnt signalling antagonists (sclerostin and Dkk-1) and their relationship with bone turnover. Bone. 2013 Nov;57(1):272-6. doi:10.1016/j.bone.2013.08.016

42. Baschant U, Henneicke H, Hofbauer LC, Rauner M. Sclerostin blockade-A dual mode of action after all? J Bone Miner Res. 2016 Sept 6;31(10):1787-1790. doi:10.1002/jbmr.2988
43. Tominaga A, Wada K, Okazaki K, Nishi H, Terayama Y, Kato Y. Early clinical effects, safety, and predictors of the effects of romosozumab treatment in osteoporosis patients: one-year study. Osteoporos Int. 2021 Mar 26;32(10):1999–2009. doi:10.1007/s00198-021-05925-3
44. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, Licata A, Benhamou L, Geusens P, Flowers K, Stracke H, Seeman E. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001 Jan 17;285(3):320-323. doi:10.1001/jama.285.3.3203
45. Inose H, Takahashi S, Teraguchi M, Kato T, Yamada K, Yasuda H, Terakawa M, Minetama M, Tomori M, Nakagawa Y, Yoshii T. Romosozumab versus bisphosphonates for preventing subsequent vertebral fractures after balloon kyphoplasty: comparison using data from two prospective multicenter studies. JBMR Plus. 2024 Oct 29;9(1). doi:10.1093/jbmrpl/ziae137
46. Balemans W, Ebeling M, Patel N, Van Hul E, Olson P, Dioszegi M, Lacza C, Wuyts W, Van Den Ende J, Willems P, Paes-Alves AF, Hill S, Bueno M, Ramos FJ, Tacconi P, Dikkers FG, Stratakis C, Lindpaintner K, Vickery B, Foernzler D, Van Hul W. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet. 2001 Mar 1;10(5):537-544. doi:10.1093/hmg/10.5.537
47. Didangelos A, Yin X, Mandal K, Baumert M, Jahangiri M, Mayr M. Proteomics characterization of extracellular space components in the human aorta. Mol Cell Proteomics. 2010 Jun 15;9(9):2048-2062. doi:10.1074/mcp.M110.001693
48. Shao J, Cheng S, Pingsterhaus JM, Charlton-Kachigian N, Loewy AP, Towler DA. Msx2 promotes cardiovascular calcification by activating paracrine Wnt signals. J Clin Invest. 2005 May;115(5):1210-1220. doi:10.1172/JCI24140
49. Zhu D, Mackenzie NC, Millan JL, Farquharson C, MacRae VE. The appearance and modulation of osteocyte marker expression during calcification of vascular smooth muscle cells. PLoS One. 2011 May 17;6(5):1-10. doi:10.1371/journal.pone.0019595
50. Krishna SM, Seto S, Jose RJ, Li J, Morton SK, Biros E, Wang Y, Nsengiyumva V, Lindeman JH, Loots GG, Rush CM, Craig JM, Golledge J. Wnt signaling pathway inhibitor sclerostin inhibits angiotensin II-induced aortic aneurysm and atherosclerosis. Arterioscler Thromb Vasc Biol. 2017 Mar;37(3):553-566. doi:10.1161/atvbaha.116.308723
51. Turk JR, Deaton AM, Yin J, Stolina M, Felx M, Boyd G, Bienvenu J, Varela A, Guillot M, Holdsworth G, Wolfreys A, Dwyer D, Kumar SV, de Koning EM, Qu Y, Engwall M, Locher K, Ward LD, Glaus C, He YD, Boyce RW. Nonclinical cardiovascular safety evaluation of romosozumab, an inhibitor of sclerostin for the treatment of osteoporosis in

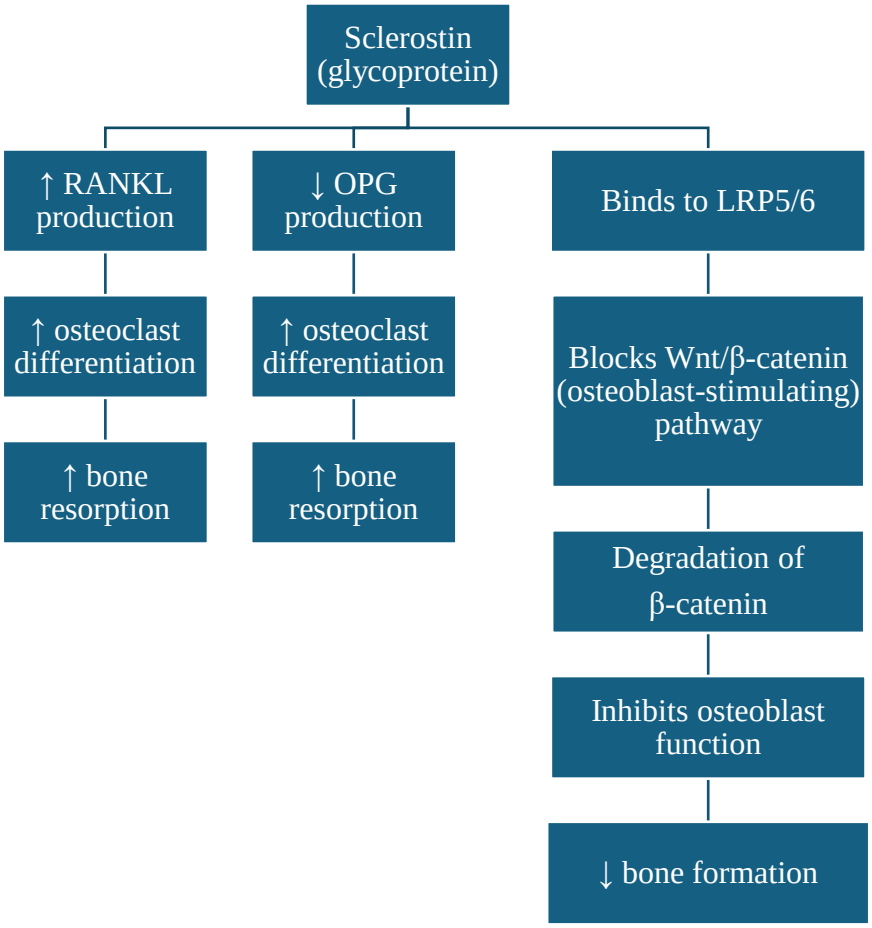
postmenopausal women at high risk of fracture. Regul Toxicol Pharmacol. 2020 Aug;115:104697. doi:10.1016/j.yrtph.2020.104697
52. Black DM, Geiger EJ, Eastell R, Vittinghoff E, Li BH, Ryan DS, Dell RM, Adams AL. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. N Engl J Med. 2020 Aug 20;383(8):743-753. doi:10.1056/NEJMoa1916525
53. Eiken PA, Prieto-Alhambra D, Eastell R, Abrahamsen B. Surgically treated osteonecrosis and osteomyelitis of the jaw and oral cavity in patients highly adherent to alendronate treatment: a nationwide user-only cohort study including over 60,000 alendronate users. Osteoporos Int. 2017 Oct;28(10):2921-2928. doi:10.1007/s00198-017-4132-y
54. Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, Grbic J, Jontell M, Landesberg R, Laslop A, Wollenhaupt M, Papapoulos S, Sezer O, Sprafka M, Reginster JY. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. Bone. 2008 May;42(5):841-847. doi:10.1016/j.bone.2008.01.003
55. Peng J, Wang H, Liu Z, Xu ZL, Wang MX, Chen QM, Wu ML, Ren XL, Liang QH, Liu FP, Ban B. Real-world study of antiresorptive-related osteonecrosis of jaw based on the US food and drug administration adverse event reporting system database. Front Pharmacol. 2022 Oct 19;13:1017391. doi:10.3389/fphar.2022.1017391
56. Xiao Y, Chen Y, Huang Y, Xiao Y. Atypical femur fracture associated with common anti-osteoporosis drugs in FDA adverse event reporting system. Sci Rep. 2023 Jul 5;13(1). doi:10.1038/s41598-023-37944-x
57. Canada's Drug Agency. Romosozumab (Evenity). Canadian Journal of Health Technologies. 2021 Nov 29;1(11):1–17. https://canjhealthtechnol.ca/index.php/cjht/article/view/SR0676/410

Appendix

Appendix A: Summary of recommendations from 2023 clinical practice guidelines for osteoporosis (CMAJ).

Population	**Pharmacotherapy of choice**
Meet criteria for pharmacotherapy	Bisphosphonate (oral preferred)
Postmenopausal women <60 years old or within 10 years of menopause, who prioritize alleviation of menopausal symptoms	Menopausal hormonal therapy as an alternative to bisphosphonate
Contraindications/intolerance to bisphosphonates	Denosumab
Recent, severe vertebral fracture (within past 2 years, >40% vertebral body height loss)	Consider anabolic therapy (teriparatide or romosozumab), followed by antiresorptive therapy
≥2 vertebral fractures	Consider anabolic therapy (teriparatide or romosozumab), followed by antiresorptive therapy
Postmenopausal women with contraindications/intolerance to all suggested therapies	Raloxifene is preferred over no therapy (if not at high risk of VTE)

Appendix B: Mechanism of action of sclerostin. If romosozumab binds to sclerostin, all downstream function is inhibited. Thus, romosozumab would decrease bone resorption and increase bone formation.



Appendix C: Percent BMD change at each time point for all four articles included in this literature review.

	Cosman et al.	Langdahl et al.	Mochizuki et al.	Baek et al.
6 months	9.7	7.2	Numeric value not provided	9.5
12 months	13.3	9.8	10.2	Not assessed
18 months	15.1	Not assessed	Not assessed	Not assessed
24 months	17.6	Not assessed	Not assessed	Not assessed