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Review Article

Bone Homeostasis and Therapeutic Implications of Sclerostin in Type 2 Diabetics

Cory Stein[1], Gabrielle M Gear[1], Marshall Gillette[1], Meaghan Tranovich[1], Sudipta Baroi[1], Beata Lecka-Czernik[2] and Nabil Ebraheim[3]*

[1]*Department of Orthopaedic Surgery, University of Toledo, Toledo, Ohio, United States*

[2]*Professor, Department of Orthopaedic Surgery, University of Toledo, Toledo, Ohio, United States*

[3]*Department Chair, Department of Orthopaedic Surgery, University of Toledo, Toledo, Ohio, United States*

***Corresponding Author:** Nabil Ebraheim, Department Chair, Department of Orthopaedic Surgery, University of Toledo, Toledo, Ohio, United States.

Received: October 05, 2020; **Published:** November 27, 2020

Abstract

Diabetes mellitus is a known risk factor for a number of orthopedic conditions and complications, including fractures. Despite increased bone mineral density, fracture risk is increased in type 2 diabetes patients. Fractures may result from the poor bone quality associated with this condition. The morbidity and mortality related to diabetic fractures places a significant socioeconomic burden on healthcare, thus investigations are needed to improve management options. Sclerostin plays a role in various bone diseases such as osteoporosis and osteoporotic fracture and may be a potential therapeutic target. Anti-sclerostin therapy has been recently approved by FDA for treatment of postmenopausal osteoporosis. There is a premise that this therapy could be extended to treatment of diabetic bone disease as well. This article reviews sclerostin's role in bone homeostasis, potential therapeutic targets, potential use of anti-sclerostin therapy to improve fracture healing and highlights a need to design clinical trials for testing antisclerostin therapy to prevent fractures and improve fracture healing in diabetes.

Keywords: *Sclerostin; Type 2 Diabetes Mellitus; WNT Signaling; Mechanical Loading; Hormonal Signaling; Bone Quality; Osteoblast*

Abbreviations

Fzd: Frizzled; LRP5: Lipoprotein Receptor-Related Protein 5; LRP6: Lipoprotein Receptor-Related Protein 6; GSK3β: β-catenin by Glycogen Synthase Kinase 3β; TCF: T-Cell Factor; OPG: Osteoprotegerin; BMPs: Bone Morphogenic Proteins; NO: Nitric Oxide; PGE2: Prostaglandin E2; RANKL: Receptor Activator of Nuclear Factor Kappa B; PTH: Parathyroid Hormone; PTHrP: PTH/PTH-Related Peptide; Receptor (PPR); rhSCL: Recombinant Human Sclerostin; MEPE: Matrix Extracellular Phosphoglycoprotein; ASARM: MEPE-Derived Acidic Serine- and aspartate-rich motif peptides; BMD: Bone mineral Density; AGEs: Advanced Glycation End Products; P1NP: Pro-Peptide Of Type 1 Collagen; CTX: CrossLaps; rhBMP-2: Recombinant Human Bone Morphogenetic Protein; Scl-Ab: Sclerostin Monoclonal Antibody; DKK-1: Dickkopf-1; IFM: Interfragmentary Movement; FGF: Fibroblast Growth Factor; VEGF: Vascular Endothelial Growth Factor; EPO: Erythropoietin; CV: Cardiovascular

Introduction

Bone remodeling is critical in the maintenance of bone mass, mineral homeostasis, and the mechanical integrity of the human skeleton. Osteocytes play a pivotal role in the regulation of bone remodeling. Osteocytes are mature descendants of osteoblasts that have become embedded within the bone matrix tissue. Osteocytes make up about 90% of the total bone cells and have the greatest life span, living up to 25 years [1,2]. Other important cells in bone remodeling include osteoblasts, which play an anabolic role to create bone, and osteoclasts,

which play a role in mineral homeostasis and the resorption of bone. Together these cells are important in maintaining the fine balance of blood calcium levels, bone density, and bone remodeling. This coordinated activity is critical in remodeling secondary to mechanical loading and fracture healing.

Sclerostin, a product of the SOST gene, is a glycoprotein secreted primarily by osteocytes that plays a vital role in the complex network of regulatory proteins and paracrine molecules that communicate and carry out bone remodeling [3]. Sclerostin inhibits the Wnt signaling pathway in osteoblasts leading to decreased bone formation and increased bone resorption, has pro-resorptive effects on bone through mechanical loading, and functions to regulate hormonal signals to direct bone remodeling and mineralization [3-6]. This article reviews the role of sclerostin in bone homeostasis and discusses potential therapeutic targets to increase bone quality and density in type 2 diabetics.

Sclerostin and the WNT pathway

Wnt-mediated signals are a critical regulator of bone remodeling and cartilage homeostasis. Activation of the Wnt receptor complex results in osteoblast differentiation and new bone formation [4,6]. The Wnt pathway can be further subdivided into the canonical and noncanonical pathways. For the canonical pathways, the critical intracellular signaling molecule is β-catenin, which halts osteoclastogenesis, and increase osteoblastogenesis and bone formation [7]. Normally, Wnt ligand binds the frizzled (Fzd) receptors and one of the coreceptors, lipoprotein receptor-related protein 5 (LRP5) or LRP6, which prevents phosphorylation of β-catenin by glycogen synthase kinase 3β (GSK3β) in the cytoplasm. β-catenin is then stabilized and translocated into the nucleus to regulate the expression of target genes with the T-cell factor (TCF) complex, eventually stimulating stem cells toward osteoblasts differentiation (Figure 1A) [8]. The noncanonical pathways work independently of β-catenin and there are multiple different non-canonical pathways that deal with differentiation, cell polarity, and migration. In one pathway, Wnt ligands activate noncanonical pathways through enhancement of LRP5/6 expression, promoting osteoblast differentiation. These pathways are not as well understood and the effect of sclerostin on them is not well known [8,9].

Osteocytes modulate the Wnt receptor complex by producing sclerostin, which antagonizes the canonical Wnt-β-catenin signaling through negative feedback. Sclerostin binds to LRP5 and LRP6, preventing the activation of the Wnt receptor complex. This allows phosphorylation of β-catenin by GSK3β, inhibiting translocation to the nucleus for eventual osteogenesis and causing β-catenin to go toward degradation (Figure 1B) [7,10]. Osteocyte Wnt-β-catenin signaling also indirectly suppresses differentiation of osteoclasts and bone resorption through stimulation of Osteoprotegerin (OPG)release from cells of osteoblastic lineage [11-13].

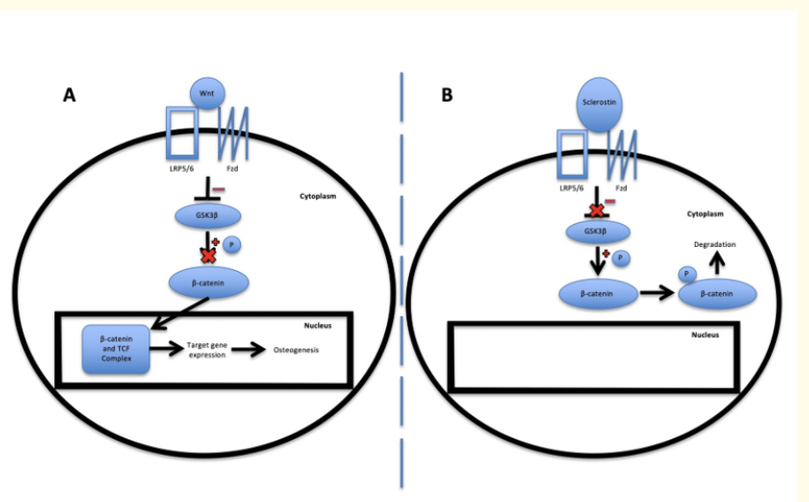

Figure 1: *A- Wnt glycoproteins bind to the LRP 5/6 coreceptor in osteoblasts which upon binding to the Fzd coreceptor result in formation of Wnt receptor complex and activation of Wnt signaling pathway. This prevents phosphorylation of GSK3β in the cytoplasm. β-catenin is then stabilized and translocated into the nucleus to regulate the expression of target genes with the TCF complex, eventually stimulating stem cells toward osteoblasts for osteogenesis. B- Sclerostin antagonizes the canonical Wnt-β-catenin signaling through negative feedback. Sclerostin binds to LRP-5/6, preventing the activation of the Wnt receptor complex. This allows phosphorylation of β-catenin by GSK3β, inhibiting translocation to the nucleus for eventual osteogenesis and causing β-catenin to go toward 347 degradation [7,8,10,14,67].*

Additionally, crosstalk of the Wnt pathway with other signaling pathways exists to regulate osteogenic differentiation. Bone morphogenic proteins (BMPs) are major osteogenic factors that contribute to osteogenic differentiation and may act to down-regulate Wnt signaling via sclerostin [8], indicating the role of BMPs in balancing osteogenesis. In experimental mouse models, knockdown of BMP receptor type 1 in osteoblasts results in increased Wnt signaling and decreased sclerostin expression leading to greater bone mass [14,15]. The antagonist relationship of sclerostin with the canonical Wnt receptor pathway has contributed to a greater understanding of the pathogenesis of specific bone disorders such as osteoporosis. The mechanisms of the Wnt signaling pathway and how to exploit it has only begun and the clinical benefits could vastly improve bone fracture prevention and healing [7].

Sclerostin and mechanical loading

Sclerostin functions as a major mediator for integrating mechanical, local, and hormonal signals sensed by osteocytes to direct bone remodeling [3]. As mechanical loading strains are increased, osteocytes down-regulate sclerostin expression, which ultimately results in increased bone formation. Inversely, as loading strains are decreased, there is increased sclerostin production causing bone loss [16]. In order for this process to occur, mechanical load must be converted to a hormonal response. When mechanical loading acts on osteocytes, it increases intracellular calcium channel action, which leads to the release of nitric oxide (NO), ATP, and prostaglandin E2 (PGE2). These factors activate the Wnt signaling pathway, which inhibits bone resorption and promotes bone formation (Figure 2). When bone loading is decreased, these factors are not released, and bone resorption can occur [17].

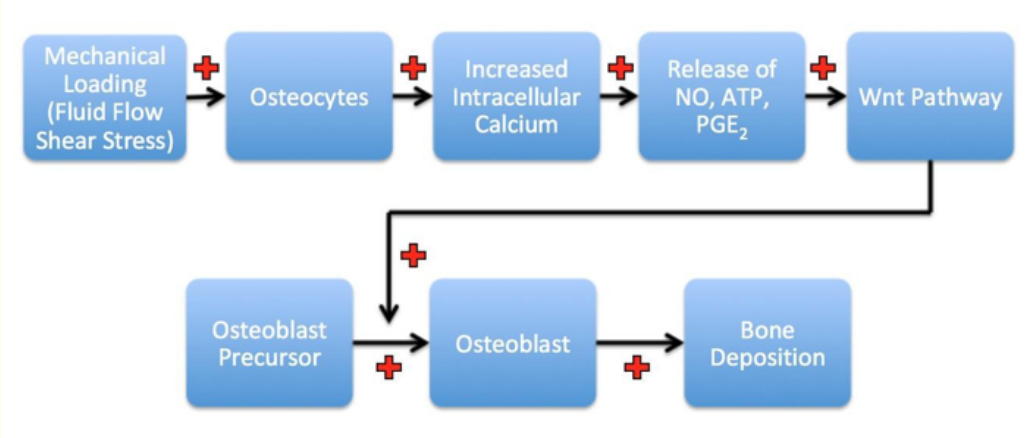

Figure 2: *Mechanical loading, in the form of fluid flow shear stress, acts on osteocytes to increase intracellular calcium. This causes a release of NO, ATP, and PGE2 that activates the WNT signaling pathway. Osteoblast precursors are then stimulated to form osteoblasts, which cause bone deposition [17].*

Sclerostin and hormonal signaling

Sclerostin plays a role in hormonal control by influencing the expression of receptor activator of nuclear factor kappa B (RANKL) and OPG by osteocytes. Sclerostin leads to the up regulation of RANKL and the downregulation of OPG, resulting in an increased RANKL:OPG ratio. An increased ratio leads to elevated osteoclast mediated resorption (Figure 3) [5]. Determining methods potentially targeting sclerostin could lead to the down regulation of RANKL expression in osteocytes, limiting resorption and preventing fractures.

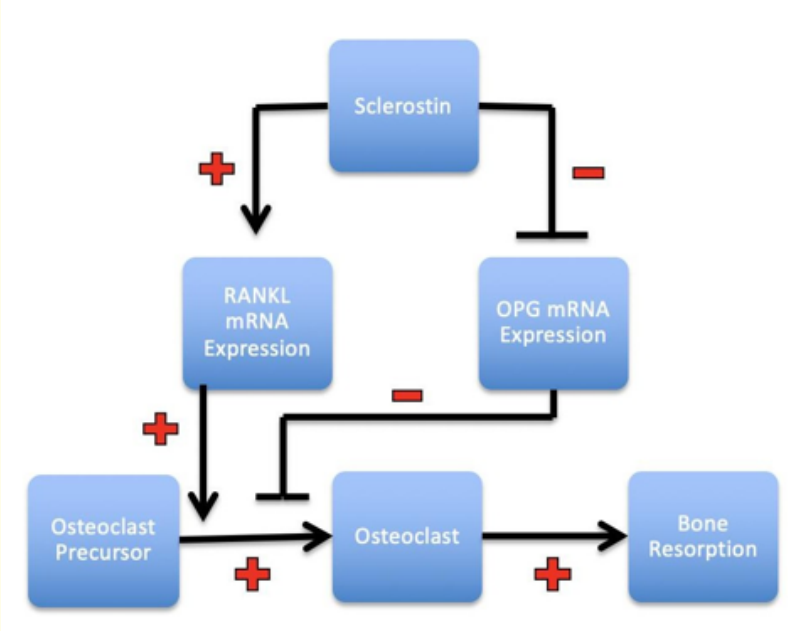

Figure 3: *Sclerostin causes an increase in RANKL mRNA expression and a decrease in OPG mRNA expression, resulting in an increased RANKL/OPG ratio. RANKL then stimulates osteoclast precursors to form osteoclasts that cause bone resorption [5,17].*

Another hormone that sclerostin interacts with is parathyroid hormone (PTH), but these have an antagonist relationship. Normally, Sclerostin binds to LRP5, LPR6 and LRP4 inhibiting the WNT pathway and antagonizes several BMPs, which are critical for osteoblastogenesis and the regulation of osteoblast activity. However, it was found that upregulation of PTH causes SOST levels to be suppressed, which then increased the number of osteoblasts and bone formation. PTH inhibits sclerostin via the cAMP-signaling pathway downstream of the PTH/PTH-related peptide (PTHrP) receptor (PPR) and binding to the ECR5 enhancer in SOST gene regulatory sequence (Figure 4) [18].

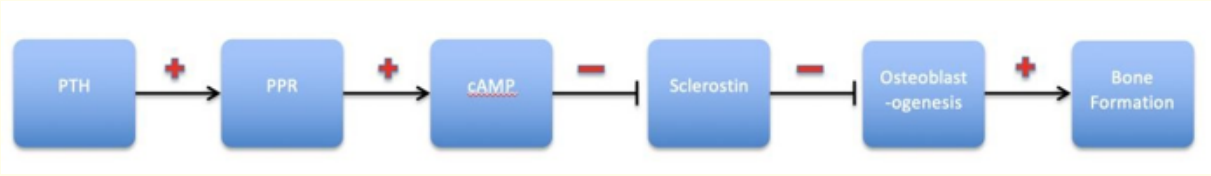

Figure 4: *PTH acts on the PTH/PTH-related peptide (PTHrP) receptor (PPR), which increases the levels of cAMP and blocks the negative effects of sclerostin. With the down regulation of sclerostin, osteoblastogenesis can occur and lead to increased bone formation [19].*

Sclerostin also plays a role in bone mineralization. Human osteoblasts exposed to recombinant human sclerostin (rhSCL), inhibited *in vitro* mineralization [19]. This occurs by the decreased expression of mature markers DMP1 and PHEX and increased expression of

matrix extracellular phosphoglycoprotein (MEPE) and MEPE-derived acidic serine- and aspartate-rich motif (ASARM) peptides [3]. The end result is decreased bone mineralization, suggesting that sclerostin is indirect negative regulator of bone mineralization through the reduction of DMP1 and PHEX expression (Figure 5) [3,19].

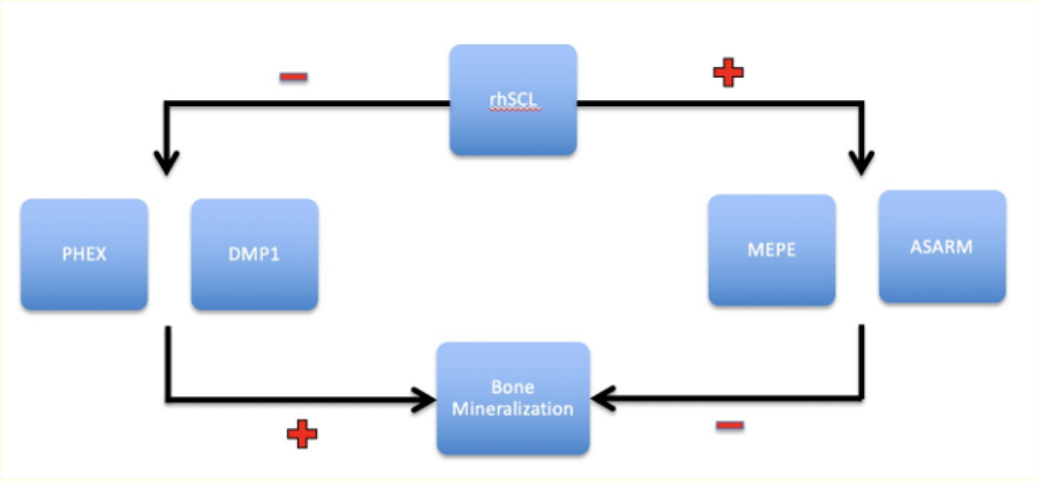

Figure 5: *rhSCL inhibits PHEX and DMP1, two factors that increase bone mineralization. rhSCL activates MEPE and ASARM, two factors that decrease bone mineralization. As a result, rhSCL causes overall bone mineralization to decrease [3,19].*

Sclerostin and bone quality in diabetics

Diabetes has been shown to negatively affect bone quality, which results in increased fracture rates [20]. Patients with type 1 diabetes have been shown to have a decreased bone mineral density (BMD), while patients with type 2 diabetes have an increased BMD as compared to age-matched nondiabetic individuals. However, both groups have increased risk of fracture [21]. Type 2 diabetics have between a 2 - 4 fold increase in fractures while type 1 diabetics exhibit a 7–14 fold increase in fractures [22]. Accumulation of advanced glycation end products (AGEs) and low bone turnover are speculated to be major contributors to the altered bone quality seen in diabetic patients [23-25]. Evidence has pointed toward compromised bone quality, rather than atypical BMD, as the underlying basis for fragility fractures in type 2 diabetic patients. This could be due to increased cortical porosity, alterations in bone remodeling, and decreased bone material properties [26]. Cortical porosity was shown to be further increased in type 2 diabetics when complicated by peripheral vascular disease [27]. The combination of increased intracortical porosity and trabecular bone thickening results in compromised bending load in patients with type 2 diabetes mellitus [28].

A recent meta-analysis showed the molecular markers of bone resorption and formation were significantly decreased in both type 1 and 2 diabetic patients. Levels of sclerostin were significantly increased in both types of diabetes. Specifically, the levels in type 2 diabetics were over four times greater than type 1 diabetics versus controls [29]. Another study compared an expression of SOST gene coding for sclerostin and level AGEs in femoral heads of T2D and nondiabetic postmenopausal women and found significantly higher expression of SOST and 1.5-fold higher levels of AGEs in T2D bone [30].

In vitro studies have demonstrated that hyperglycemia increases the level of sclerostin and may adversely alter bone turnover [31]. Type 2 diabetic patients have been shown to have higher circulating sclerostin levels compared to controls independent of both gender and age. Likewise, there is a positive correlation between the level of serum sclerostin and the length of time the patient has been diabetic

[32]. Another study reported that sclerostin levels were increased in type 2 diabetic patients with femoral fracture. Expression of bone formation/remodeling associated biomarkers, such as osteocalcin, amino pro-peptide of type 1 collagen (P1NP) and CrossLaps (CTX), was decreased via inhibition of the Wnt signaling pathway. This further reinforces the idea that sclerostin could be a target for decreasing fractures in type 2 diabetic patients since the Wnt signaling pathway would then be able to stimulate osteoblastogenesis [33]. Other studies have further demonstrated an association between elevated sclerostin levels and vertebral fractures [34; 35]. Low bone turnover slowing bone loss may explain this correlation between increasing circulating sclerostin and BMD. This ultimately may result in a lack of structural integrity of bone, leading to a higher incidence of fractures in diabetic patients [32].

Increased sclerostin levels in circulation of type 2 diabetic patients may have other than bone origin. Sclerostin can also be produced by the kidney, aorta and testes which brings an important question whether contribution of these organs to circulating levels of sclerostin is altered in type 2 diabetic patients [36].

Targeting sclerostin therapeutically for fracture prevention

One role for anti-sclerostin therapy is fracture prevention. Current prophylactic treatment for bone fractures are based on BMD and fracture risk assessment tools [37]. However, current guidelines utilizing BMD as a primary measure of risk may not be accurate in type 2 diabetics, as they have a higher baseline fracture risk despite having a normal to high BMD. Considering the potential role sclerostin plays in affecting the balance of bone formation and resorption in other bone diseases, inhibition with anti-sclerostin antibodies may reduce fracture risk in diabetic patients. Studies have lent support to this hypothesis. A sclerostin knockout mice demonstrated a marked increase in BMD, bone volume, bone formation, and bone strength [4]. Anti-sclerostin antibody tested in animal models of diabetes has revealed several potential therapeutic implementations. In one model of rats with type I diabetes mellitus, anabolic doses of sclerostin antibody enhanced bone formation and the effects extended well beyond the end of the dosing regimen, up to three weeks after termination of treatment [38]. Although diabetic rats did not exhibit increased sclerostin compared to controls (nondiabetic rats), anti-sclerostin therapy increased femoral neck region maximal load by 89% in the diabetic rats versus 38% in controls [39].

Romosozumab, monoclonal antibody neutralizing sclerostin in circulation had been approved by FDA in April 2019 for treatment of postmenopausal women with high risk of fractures. This approval has been preceded by a number of studies showing efficacy of romosozumab therapy, either alone or in combination with other osteoporotic drugs, to prevent fractures.

In a cohort of 7180 postmenopausal women with T-score -2.5 to -3.5 at the total hip or femoral neck, subcutaneous injection of romosozumab for 12 months lowered risk of vertebral fractures by 70%, as compared to placebo [40]. However, nonvertebral fracture risk was not significantly reduced in the overall population, unless Latin American population was excluded, which resulted in 42% reduction [41].

Recently published meta-analysis of 46 randomized controlled clinical trials comparing efficacy for fracture prevention of four non-bisphosphonate anti-osteoporotic drugs: romosozumab, denosumab, raloxifene, and teriparatide, showed that all four therapies significantly reduce vertebral fractures increase femoral neck BMD and reduce hip fracture [42]. Another meta-analysis of 33 trials involving 79,144 postmenopausal women reported romosozumab superior efficacy in prevention of vertebral fractures [43].

Therapeutic efficacy of romosozumab to prevent fractures has also been tested in combination with bisphosphonate alendronate. In ARCH clinical trial, 4093 postmenopausal women with osteoporosis and a fragility fracture were randomly assigned in a 1:1 ratio for subcutaneous romosozumab injections or weekly oral alendronate therapy for 12 months, followed by alendronate for another 12 months in both groups. Over a period of 24 months, both groups had decreased incidence of new vertebral fractures with romosozumab-to-alendronate group having superior efficacy with 48% lower risk of fractures (6.2% [127 of 2046 patients]) as compared to the alendronate-to-alendronate group (11.9% [243 of 2047 patients]) ($P < 0.001$) [44].

None of the studies testing romosozumab efficacy for fracture prevention have addressed population of patients with diabetes.

Preclinical studies targeting sclerostin for fracture healing

A number of animal studies suggested that anti-sclerostin therapy can be beneficial for fracture healing. In a rat model with osteopenia induced by ovariectomy, anti-sclerostin antibodies enhanced healing of a closed femoral fracture through the improvement of bone mass, bone strength and bone formation at the fracture region [45]. Another rat model showed that in a critical-sized femoral defect, a combination of recombinant human bone morphogenetic protein (rhBMP)-2 and sclerostin monoclonal antibody (Scl-Ab) resulted in stronger and more rigid healing compared to rhBMP-2 alone. This strengthens the idea that combining an osteoinductive agent and an antibody that promotes bone formation may enhance bone repair [46].

A separate study of Scl-Ab effects on open fracture repair using a rat femoral osteotomy model showed that blocking sclerostin can enhance fracture repair. Scl-Ab improved open fracture healing by increasing bone volume and mineralization, angiogenesis, and mechanical properties. An increase in fracture callus size was observed, suggestive of improved fracture healing [47]. Another study focused on closed femur fractures found that healing rates were enhanced in SOST knockout mice. Scl-Ab increased bone mass at the fracture site and the strength of fracture union [48]. Additionally, superior bone formation, bone mass, and bone strength were found with the use of a bispecific antibody targeting sclerostin and Dickkopf-1 (DKK-1) in both rodents and non-human primates when compared with monotherapies [49].

Study by Alzahrani., *et al*. compared fracture healing in mouse deficient of sclerostin with intact mice treated with Scl-Ab. The study inserted a tibial intramedullary pin into each mouse, performing a midshaft tibial osteotomy, and determined how the repair process changed from that of wild type mice with saline injection. While both groups demonstrated greater callus bone volume and biomechanical properties than saline injections, the SOST deletion had greater mechanical benefits after the third to fifth weeks of healing. This suggests such an injection could be beneficial for fracture healing in healthy men and postmenopausal women [50,51]. This same study was employed to determine the degree to which Scl-Ab inhibition and complete sclerostin depletion affected healing at the fracture site through evaluation of morphometric trabecular bone measures and fracture site structural strength. In both groups, bone volume at the fracture site and newly formed bone stiffness were increased compared with the saline group [50]. These studies indicate that in mice Scl-Ab penetrate fracture site and target sclerostin with the stimulatory effect on healing process.

Two recent studies clarify the exact mechanism by which Scl-Ab target healing process. In a rat osteotomy model with periosteal stripping analogous to open fracture repair found that Scl-Ab treatment led to increased callus size and strength but did not decrease time to union or improve union rate in challenged healing. Additionally, Scl-Ab anabolic effects on callus bone volume were consistent regardless of whether treatment was commenced in an early or delayed fashion [52]. This suggests that Scl-Ab can be useful for fracture repair but may be more effective as one component of polytherapy rather than a monotherapy.

Lastly, a study examined rigid or semirigid external fixation in a mouse femoral osteotomy model to evaluate Scl-Ab's influence on tissue formation in the presence of different magnitudes of interfragmentary movement (IFM). Scl-Ab increased bone volume fraction but it did not overcome the delayed healing associated with greater IFM in the semirigid fixation and delayed advanced healing in rigid fixation. This suggests that although Scl-Ab significantly accelerates the ossification stage of healing, it can cause excessive bone formation at later stages, disrupting bone remodeling and reconstitution. As such, authors advocate discontinuation of SOST inhibition at later stages of healing to allow bone remodeling and reconstitution of the bone marrow [53].

Anti-sclerostin drug trials for fracture healing

The beneficial effect of anti-sclerostin therapy on bone formation led to a clinical program to explore whether systemic administration of Scl-Ab in patients with tibial shaft fractures or hip fractures could shorten time to healing. The first study of this type was prematurely

closed due to insignificant results in time to radiological healing when compared to placebo and high regulatory demands for fracture healing studies [54]. However, recently published results of two clinical trials addressing romosozumab effect on fracture healing did not demonstrate its beneficial effect. In a double-blinded, randomized, phase-2 trial, the effect of different doses of romosozumab on the radiographic and clinical outcomes of surgical fixation of tibial diaphyseal fractures was measured. The trial consisted of 402 patients, out of which 299 received romosozumab postoperatively and the healing was assessed radiographically after 24 weeks of healing [55]. The study concluded that there was no significant difference in the time to clinical healing, no relationship between romosozumab dose and frequency of injection and unplanned revision surgery, and no treatment benefit in terms of physical function.

A second study evaluated the effect of different doses of romosozumab on the clinical outcomes of open reduction and internal fixation of intertrochanteric or femoral neck hip fractures [56]. This study included 332 older patients, out of which 243 received romosozumab up to 20 weeks postoperatively. The radiographic evidence of healing did not differ between the romosozumab and placebo groups. Both studies however did not address a possible transient beneficial effect of romosozumab on callus formation, the effect seen in animal studies. They also did not address fracture healing in diabetic patients.

Current fracture prevention treatment in type 2 diabetes

Antiresorptive drugs have been tested in the treatment of patients with diabetes and osteoporosis to improve fracture healing. Antiresorptive drugs reduce bone turnover by inhibiting osteoclast activity.

Bisphosphonates are commonly used in osteoporosis; the presence of concomitant diabetes does not have any detrimental effects on the fracture preventive potential these drugs provide [57]. The shortcomings of bisphosphonates include adverse effects on the upper GI tract, musculoskeletal pain, hypocalcemia and suppression of bone turnover [58]. Long-term use of bisphosphonates has also been implicated in atypical fractures of the proximal femur [59]. Teriparatide, is a PTH analog used as osteoanabolic therapy in osteoporotic patients that have increased bone mass and high risk for fracture. When used in patients with osteoporosis and type 2 diabetes for up to 24 months followed by observation up to 24 months, it reduced nonvertebral fractures, increased BMD, and reduced back pain to a similar degree as patients without diabetes [60]. The recognized adverse effects of teriparatide include nausea, arthralgia, hypertension, headache, and hypercalcemia [61]. Several other drugs and growth factors, including statins, PTH, BMPs, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and erythropoietin (EPO), have been targeted to assess their effect on fracture healing. However, the evidence of the effectiveness of these targets is still under assessment and further studies are required before they may be deemed useful for treatment [62].

In respect to romosozumab, studies addressing fracture prevention in diabetic population are needed. However, there are safety concerns caused by the growing number of reported serious cardiovascular (CV) effects among the users of this drug with high risk of CV events, which may include diabetic individuals with CV complications [44,63-65]. Sclerostin, which is also expressed in aorta, can prevent vascular calcification by inhibiting WNT signaling and its neutralization by romosozumab may increase aorta calcification [66]. These precautions warrant clinical studies specifically addressing the effects of anti-sclerostin therapy on fracture prevention, as well as fracture healing, in type 2 diabetic population.

Conclusion

Poor bone quality and increased risk of fracture in diabetic patients are of significant clinical concern in terms of morbidity, mortality, and overall socioeconomic burden they pose. The regulation of bone remodeling and homeostasis offer many potential therapeutic targets. Sclerostin seems to be a promising target in modulating the Wnt signaling pathway. The recently approved by FDA anti-sclerostin therapy with romosozumab improves bone quality in postmenopausal osteoporosis patients. The effects of this drug in type 2 diabetic patients, who have significantly higher levels of sclerostin than non-diabetic patients, needs to be addressed by specifically designed clinical studies.

Extending this strategy, novel treatment options could target genes responsible for upregulating sclerostin. Although guidelines exist for the prophylactic treatment of patients with low BMD, improved guidelines should be established for diabetic patients in the prevention of fractures and major orthopedic complications. The study of sclerostin modulation and its effects on type 2 diabetic patients will require a multidisciplinary approach from basic science research to clinical implementation in order to help reduce the morbidity, mortality, and the tremendous burden that diabetic fractures place on the healthcare system.

Conflicts of Interest

The authors have no conflict of interest or disclosures.

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