Published in final edited form as:

Bone. 2017 March ; 96: 18–23. doi:10.1016/j.bone.2016.10.018.

Application of anti-Sclerostin therapy in non-osteoporosis disease models

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Abstract

Sclerostin, a known inhibitor of the low density lipoprotein related protein 5 and 6 (LRP5 and LRP6) cell surface signaling receptors, is integral in the maintenance of normal bone mass and strength. Patients with loss of function mutations in *SOST* or missense mutations in *LRP5* that prevent Sclerostin from binding and inhibiting the receptor, have significantly increased bone mass. This observation led to the development of Sclerostin neutralizing therapies to increase bone mass and strength. Anti-Sclerostin therapy has been shown to be effective at increasing bone density and strength in animal models and patients with osteoporosis. Loss of function of *Sost* or treatment with a Sclerostin neutralizing antibody improves bone properties in animal models of Osteoporosis Pseudoglioma syndrome (OPPG), likely due to action through the LRP6 receptor, which suggests patients may benefit from these therapies. Sclerostin antibody is effective at improving bone properties in mouse models of Osteogenesis Imperfecta, a genetic disorder of low bone mass and fragility due to type I collagen mutations, in as little as two weeks after initiation of therapy. However, these improvements are due to increases in bone quantity as the quality (brittleness) of bone remains unaffected. Similarly, Sclerostin antibody treatment improves bone density in animal models of other diseases. Sclerostin neutralizing therapies are likely to benefit many patients with genetic disorders of bone, as well as other forms of metabolic bone disease.

1.0 Introduction

The cell surface signaling receptor low density lipoprotein related protein 5 (LRP5) has emerged as a key regulator of bone mass.(1–3) Recessive loss of function mutations in *LRP5* cause Osteoporosis Pseudoglioma syndrome (OPPG), a disorder characterized by bone fragility and frequent pathologic fractures starting in childhood.(1) Dominant missense

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mutations in *LRP5* have the opposite effect, resulting in increased bone mass and strength by preventing inhibition of the receptor by an endogenous inhibitor, Sclerostin.(2–7) Patients with mutations in the Sclerostin gene (*SOST*) or a nearby regulatory region have a phenotype similar to patients with *LRP5* high bone mass (HBM) mutations, characterized by increased bone mass and strength.(8, 9) *LRP5* activates the canonical Wnt signaling pathway. (10–12) Signaling through *LRP5* is known to be required for the increase in bone mass seen in response to mechanotransduction.(13) Further, osteocyte production of Sclerostin is reduced by mechanical loading and increased by hind limb unloading, suggesting Sclerostin acts on the *LRP5* receptor to induce changes these changes in bone mass.(14)

1.1 *LRP5* high bone mass mutations are anabolic

Mouse models with mutations orthologous to the human *LRP5* HBM mutations recapitulate the phenotype of increased bone density and strength.(15) Mice with an *Lrp5* HBM mutation have increased bone formation compared to littermate controls indicating the mutation is anabolic, inducing bone formation. Furthermore, these mutations act locally to increase bone formation, consistent with the known production of Sclerostin by osteocytes. (15)

1.2 Sclerostin antibody therapy

Sclerostin neutralizing antibodies have been shown to be effective in improving bone density in both animal models (16–18) and humans with postmenopausal osteoporosis.(19–25) Interestingly, a short (5–week) period of Sclerostin antibody treatment in both ovariectomized mice and adolescent cynomolgus monkeys caused an increase in bone formation and reduction in bone resorption.(26) In post-menopausal women treated with Sclerostin antibody, markers of bone formation were initially increased with treatment before returning to baseline while markers of bone turnover were decreased and remained below that of the placebo group.(22, 25) These data suggest that at least in both normal bone and post-menopausal osteoporosis, Sclerostin inhibition is both anabolic and anti-resorptive, mirroring the effect on bone of increased loading. Similar improvements in bone density from Sclerostin antibody therapy have been seen in mouse and rat models of disuse related bone loss and spinal cord injury (27–31). These exciting findings raised the question of whether anabolic Sclerostin antibody therapy could be equally effective at treating genetic and metabolic disorders of bone. Currently therapies for these disorders are limited, particularly in the pediatric population, as the other anabolic medical therapy, recombinant parathyroid hormone, is not used due to the risk of osteosarcoma.(32)

2. Osteoporosis Pseudoglioma Syndrome (OPPG)

OPPG is a rare recessive disorder characterized by bone fragility and eye findings. Bone resorptive activity in these patients is normal, but bone formation is greatly reduced, resulting in bone density scores more than 5 standard deviations below the mean.(1) The finding of reduced bone formation suggested these patients would benefit from an anabolic therapy. However, as the causative mutations result in loss of function of the *LRP5* receptor, it was unclear if Sclerostin neutralizing therapy would be effective. Surprisingly, loss of the

function of both alleles of the *Sost* gene resulted in large increases in bone density and strength of an OPPG mouse model with recessive loss of function mutations in *Lrp5*, fully rescuing the phenotype.(33, 34) In addition, 3 weeks of therapy with Sclerostin neutralizing antibody increased bone mass and formation rates in the same model.(33)

This increase in bone formation was hypothesized to result from loss of Sclerostin inhibition of the closely related signaling receptor, LRP6, even in the absence of functional LRP5. This was confirmed in further experiments which demonstrated that selectively blocking Wnt1 induced LRP6 signaling reduced bone density gains in mice with both *Sost* and *Lrp5* mutations.(34) Together these results suggest that patients with OPPG could benefit from therapies that reduce Sclerostin activity, notably Sclerostin antibody. Further, selectively blocking Wnt1 induced Lrp6 signaling may benefit patients with symptoms of skeletal overgrowth from recessive *SOST* mutations as well as dominant *LRP5* HBM mutations.

3. Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI) is a genetic disorder characterized by skeletal fragility and pathologic fractures leading to bony deformities. Most patients with OI have dominant mutations in one of the type 1 collagen genes.(35) Other causes include recessive mutations in genes involved in collagen production and post-translational modification.(36) Current therapies for OI include bisphosphonates, which are anti-resorptive and prevent increased bone turnover. While bisphosphonates do not alter the underlying genetic structural disorder of collagen, these therapies have been effective in increasing bone density in both adult and pediatric patients, likely by preventing the increased bone turnover seen in patients with OI. (37–39) Data on fracture prevention is mixed, but some pediatric patients do benefit.(39, 40) In adults with mild type 1 OI, recombinant parathyroid hormone (teriparatide) has been used as an anabolic therapy. In two small studies, patients had significant increases in bone mineral density. Unfortunately, both studies were underpowered to detect fracture risk.(41, 42) No other anabolic therapies exist to treat these patients, raising the question of whether anabolic Sclerostin neutralizing therapies could improve bone properties in OI by increasing bone formation without altering the underlying collagen abnormalities.

3.1 An *Lrp5* HBM mutation or Sclerostin antibody therapy improves bone properties in mouse models of OI

Although reducing Sclerostin activity does not affect the underlying type I collagen mutations responsible for the majority of cases of OI, studies of anti-resorptive bisphosphonates have demonstrated that increasing bone mass alone, regardless of the underlying quality of that bone, can reduce fracture rates in patients with OI.(43) This suggested that increasing bone formation through Sclerostin antibody therapy could also improve bone properties in OI. Proof-of-principle experiments demonstrated that an *Lrp5* HBM mutation that prevents Sclerostin inhibition of the receptor in combination with a dominant *Col1a2* OI mutation (G610C) results in increased femoral cortical and trabecular bone as well as increased long bone strength compared to the OI mutation alone.(44) Further studies of the effect of the *Lrp5* HBM mutation on mice with OI due to haploinsufficiency of

a *Col1a1* allele (Mov13) demonstrated similar increases in cortical and trabecular bone at the femur and spine.(45)

In another mouse model of dominant OI due to a *Col1a1* mutation (Brtl), 2 weeks of Sclerostin antibody therapy in juvenile mice was enough to increase both femoral cortical and trabecular bone and long-bone strength.(46) Another study found similar results with 6 weeks of therapy in juvenile mice with a *Col1a2* mutation (G610C), although the effects of the therapy were not as large as the *Lrp5* HBM allele.(44) Further work showed that 5 weeks of Sclerostin antibody therapy in both rapidly growing and adult mice (Brtl) increased femoral cortical and trabecular bone strength, although the trabecular effects were more pronounced in the adult mice.(47, 48) Interestingly, the adult mice did not show improvements in bone density in the spine, suggesting there may be age dependent effects of Sclerostin antibody.(48)

All of the above data is from OI mutations resulting in a mild to moderate OI phenotype. Data in more severely affected animal models are mixed. In one severe model of dominant OI due to *Col1a1* mutations (Jrt), 4 weeks of Sclerostin antibody therapy increased femoral trabecular bone in rapidly growing but not adult mice and did not increase spinal trabecular bone in either the juvenile or adult mice.(49) Further, treatment did not improve long bone strength at either age.(49) However, in another severely affected mouse model of OI due to recessive mutations in the *Crtap* gene, six weeks of Sclerostin antibody therapy given to juvenile mice resulted in increased cortical and trabecular bone at both the femur and the spine as well as increased long bone strength.(50) Rapidly growing mice treated from age 1 week to age 7 weeks showed similar results in trabecular bone at the femur and spine but did not show an increase in cortical thickness, only cortical area, and there was also no improvement in strength of the long bones.(50) This data again suggests that there may be an age dependent effect on response to Sclerostin antibody in OI and further, that the specific collagen mutation may influence the response to therapy.

3.1.1 Sclerostin antibody therapy or an *Lrp5* HBM mutation do not improve bone quality in OI—While most mouse models of OI treated with Sclerostin antibody show improvements in bone mass and strength, there is little evidence of a corresponding improvement in bone quality. Mice with haploinsufficiency of a *Col1a1* allele (Mov13) and an *Lrp5* HBM allele do not show an improvement in post-yield displacement (brittleness) compared to littermates with an OI allele. Further, FTIR studies of different OI mouse models with dominant OI mutations (G610C and Mov13) and *Lrp5* HBM showed no change in the abnormal mineral to matrix ratio seen in OI bone, consistent with lack of improvement in bone quality.(45, 51) Similar results were seen in another mouse model (Brtl) when juvenile mice were treated for 2 or 5 weeks with Sclerostin antibody. There was no improvement in brittleness nor an effect on the estimated elastic modulus.(46, 48, 52) There was also no improvement in brittleness seen in the rapidly growing and juvenile recessive *Crtap* mice treated with anti-Sclerostin antibody and no improvement in increased matrix mineralization either the juvenile or adult Jrt mice treated with antibody.(50, 53) Interesting, 5 weeks of Sclerostin antibody therapy in adult mice (Brtl) did increase post-yield displacement suggesting an improvement in brittleness.(47) This again suggests an age dependent effect of Sclerostin antibody in OI.

3.2 Sclerostin antibody may both increase bone formation and decrease bone turnover in mouse models of OI

Data from mouse and human studies of post-menopausal osteoporosis suggests that Sclerostin antibody both increases bone formation and reduces bone turnover, evidence of uncoupling of osteoblasts and osteoclasts.(19, 20, 22, 25, 26) In mice with a dominant OI mutation (G610C) and an *Lrp5* HBM allele, no change was seen in serum markers of bone formation and resorption or in osteoblast and osteoclast surfaces.(44) Similar results were found after six weeks of Sclerostin antibody therapy in juvenile mice with the same mutation, except for a significant increase in osteoblast surface.(44) Interestingly, after two weeks of Sclerostin antibody therapy in a different mouse model of OI (Brtl) there was an increase in a serum marker of bone formation, but no change in a marker of bone resorption.(46) However, after five weeks of therapy in juvenile mice with the same mutation alterations in markers of bone turnover or resorption were not seen.(48) This differed from adult mice with the same mutation (Brtl) in which 5 weeks of antibody therapy resulted in an increase in a serum marker of bone formation and trend toward, although not statistically significant, decrease in a marker of bone resorption. (47) However, after six weeks of Sclerostin antibody therapy in both juvenile and adult mice with a severe dominant OI mutation (Jrt) no change was seen in serum markers of bone turnover or resorption.(49) Six weeks of Sclerostin antibody treatment in juvenile recessive *Crtap* mice did reduce osteoclast number and surface with no significant effect on osteoblasts.(50) In a younger cohort of the same mice, there was only a significant difference in osteoclast number.(50) Together, this data suggests that the greatest effect on bone formation and resorption may occur soon after the initiation of treatment, as in post-menopausal osteoporosis.(26) In addition, as with bone density and strength, there may also be age and mutation related effects on bone turnover and formation in response to Sclerostin antibody therapy.

These findings suggest that both adult and pediatric patients with OI may benefit from Sclerostin neutralizing therapies, regardless of the whether the underlying causative mutation is a dominant type I collagen mutation or recessive loss of function mutations in other genes involved in collagen processing and post-translational modification. Although the underlying bone quality would likely remain unaffected, the increased bone formation and decreased bone resorption would result in increased bone quantity able to affect an increase in bone strength that would hopefully result in fewer pathologic fractures for patients.

4. Other Disorders of Bone Density

4.1 Sclerostin inhibition improves bone loss in rheumatoid arthritis

Sclerostin inhibition has also been utilized in the treatment of non-monogenic disorders of bone density. Rheumatoid arthritis (RA), an autoimmune connective tissue disorder, can result in generalized bone loss and osteopenia.(54) Osteopenia may occur even in subclinical disease before the onset of articular symptoms.(55) Bone erosion occurs early and rapidly in the course of the disease and is associated with prolonged inflammation. Inflammatory mediators, such as synovial cytokines, that are elevated in RA induce osteoclast differentiation and activation.(55) Interestingly, DKK-1, a known inhibitor of LRP5 is

known to be induced by cytokine expression and increased in patients with RA, which could inhibit osteoblast formation and explain while periarticular bone does not undergo repair in RA as in other inflammatory arthropathies.(56) Bisphosphonates have been shown to prevent bone loss in RA, through inhibition of osteoclast activity.(54) However, the early and rapid bone loss suggests a role for anabolic therapy to treat patients who present after bone loss has already occurred. In addition, anabolic therapies such as Sclerostin antibody could help overcome the defects in periarticular bone repair while the anti-resorptive effects of Sclerostin antibody may act to prevent further bone loss.

To determine if Sclerostin inhibition could prevent or improve bone loss in RA, a mouse model of RA caused by a transgene expressing human tumor necrosis factor (TNF) was treated with 3 weeks of Sclerostin antibody. While the characteristic joint swelling and synovitis of RA were unaffected, bone loss in the spine and periarticular bone loss in the tibia was prevented and partially reversed.(57) The combination of Sclerostin antibody with anti-TNF therapy was even more pronounced.(57) Similar results were seen in a different inducible mouse model of RA. Prophylactic treatment with Sclerostin antibody prior to the induction of arthritis prevented bone loss in both the axial and appendicular skeleton, but did not prevent focal bone erosions on periarticular surfaces.(58) When the mice were treated with Sclerostin antibody after the induction of arthritis, the bone loss at axial and appendicular sites was restored, but the periarticular bony erosions were not healed.(58) These data suggest that anti-Sclerostin antibody is effective at treating bone loss, regardless of the timing of therapy during the course of RA, but unfortunately, there is little effect on focal, periarticular bone erosions. Interesting, a more recent study found that Sclerostin blocks one of the steps of TNF-alpha mediated joint inflammation in mice, suggesting Sclerostin may have a protective effect on joint destruction.(59) Further studies are needed to determine the efficacy of Sclerostin inhibition in inflammatory arthritis and the effects on disease progression.

4.2 Sclerostin antibody improves bone properties in renal failure

Patients with chronic kidney disease are at risk of developing renal osteodystrophy, characterized by alterations in bone turnover and mineralization likely related to PTH elevation from secondary hyperparathyroidism, which predisposes patients to fragility fractures.(60) There is concern about using purely anti-resorptive therapies in these patients as they may suppress PTH and lead to the development of adynamic bone disease.(60) Wnt signaling is known to be altered and Sclerostin levels increased in patients with chronic kidney disease.(61) In a mouse model of progressive chronic kidney disease (CKD), 5 weeks of Sclerostin antibody therapy in adult animals improved bone density in animals with low PTH levels, but not high PTH levels. However, there was no difference between wildtype and CKD bone density in the untreated group.(62) Calcium, phosphorus and FGF23 levels were unaffected by treatment. Unfortunately, no improvement was seen in bone biomechanics by 4-point bending analysis.(62) A second study showed improvements in the bone density and mechanical properties on vertebra in adult animals with CKD treated for five weeks with Sclerostin antibody, but only if PTH levels were normalized with other therapies.(60) Further studies are needed, particularly on the effects of Sclerostin inhibition

in juvenile animals with CKD, to determine if the effects of Sclerosin antibody are greater during a period of life when bone mass accrual is still occurring.

4.3 Sclerostin antibody improves bone properties and fracture healing in inflammatory bowel disease and diabetes

Patients with inflammatory bowel disease develop bone loss secondary to chronic inflammation, similar to the generalized osteopenia seen in patients with rheumatoid arthritis and also thought to occur due to the effects of inflammatory mediators on osteoclasts.(63, 64) In addition, many of these patients require corticosteroids for disease control, further placing them at risk of significant bone loss.(65) In mouse models of induced colitis (created by introducing colitogenic T-cell populations into SCID mice), treatment with Sclerostin antibody starting just prior to T-cell transfer prevented BMD loss by DXA.(66) When Sclerostin antibody was administered for 19 days after the development of colitis, trabecular bone volume was restored to that of healthy controls and cortical bone was significantly improved.(66) Furthermore, long bone strength was significantly increased with treatment. (66) Sclerostin antibody therapy increased a serum marker of bone formation and decreased a serum marker of bone resorption from the elevated levels seen in untreated mice with colitis.(66) This data suggests that Sclerostin antibody may be an effective treatment for the bone loss seen in patients with inflammatory bowel disease.

Diabetes is a risk factor for the development of osteoporosis and bone fragility.(67) The mechanisms responsible are not well understood, but there is evidence of impaired osteoblast function.(68) Patients with Type II diabetes can have increased bone density, but still be at risk of fragility fractures due to underlying defects in bone quality.(67) Bisphosphonates cannot always be used in this population due to frequent gastrointestinal and renal complications. Previous studies have shown that Sclerostin antibody improves osteotomy fracture healing in rodents and can improve, but not always completely repair, cortical defects.(69–76) This suggests that Sclerostin antibody may not only improve bone properties in diabetes but also assist with fracture healing.

In a study of diabetic (Type 2 due to a homozygous mutation of the leptin receptor) and non-diabetic adult rats treated with Sclerostin antibody for 12 weeks, significant increases (to levels seen in non-diabetic animals or higher) in BMD at the femur and spine were seen compared to controls treated with vehicle.(77) Cortical thickness of the midshaft femur was also increased.(77) Significant improvements were also seen in long bone strength, again to levels equal or above that seen in non-diabetic animals.(77) No differences were seen in markers of bone formation or resorption at the end of the 12 weeks of therapy, but histomorphometry demonstrated increased bone formation.(77) Finally, there was significant improvement in repair of a subcritical defect in the femur in the diabetic rats treated for 12 weeks of Sclerostin antibody.(77)

Similar results were seen in a study of fracture healing in a mouse model of Type I diabetes induced by streptozotocin injections. Femoral fractures were generated at 8 weeks of age and Sclerostin antibody administered for 3 weeks subsequently. As expected, there were significant decreases in trabecular (spine) and cortical bone in the mice with diabetes compared to control animals which was significantly improved with Sclerostin inhibition.

(78) In addition, antibody treatment improved the size and bone mineral content of the fracture callus in injured animals.(78) Increased adipogenesis was seen in the bone marrow of mice with diabetes and was dramatically upregulated during callus formation and fracture repair.(78) Interestingly, Sclerostin antibody therapy did not decrease the increased adipogenesis seen at baseline in diabetes, but did reduce the increase seen callus formation, suggesting the possibility that altering Wnt signaling affects the fate of osteoblast precursor cells.(78) Together, these studies support the use of Sclerostin antibody in diabetes related bone loss as well as to improve fracture healing in these patients.

4.4 Sclerostin antibody improves alveolar bone formation after periodontitis or osteomalacia

Periodontal disease, the destruction of the tooth supporting soft tissue and bony structures by infection and persistent inflammation, is a common and difficult to treat dental disorder. Left untreated, large osseous defects can develop that are not always treatable with bone grafts and guided bone regeneration.(79) The effects of Sclerostin antibody on bone density in post-menopausal osteoporosis, as well as the effects on long bone healing, suggest that this therapy may aid in the healing of osseous defects resulting from periodontitis.(17, 22, 25, 72) Initial studies showed that systemic Sclerostin antibody administration does act on the alveolar bone typically lost in periodontitis increasing bone volume fraction (BVF) and tissue mineral density (TMD).(79)

Using a rat model of ligature induced periodontitis, Sclerostin antibody was injected 4 weeks after the initiation of periodontitis for either 3 or 6 weeks systemically or locally into palatal gingival tissue. While natural bone healing occurred for three weeks even in vehicle control treated animals, it plateaued after that time.(79) In contrast, after six weeks of systemic Sclerostin antibody administration, there was no difference in BVF or TMD of alveolar bone compared to animals without periodontitis.(79) However, the effect was more limited when the antibody injections were done locally.(79) Serum markers of bone formation were increased after three weeks of antibody therapy, but not at six weeks, and markers of bone resorption were not altered at either time point.(79) When Sclerostin antibody was injected concurrently with the initiation of periodontitis, there was no significant change in alveolar bone.(79) In similar experiments done on rats with and without ovariectomy induced osteoporosis, the loss of alveolar bone was greater in the rats with osteoporosis and periodontitis, but restored to better than control mice with six weeks of anti-Sclerostin antibody therapy.(80) There were significant increases in serum markers of bone formation and decreases in markers of bone resorption compared to ovariectomized rats with periodontitis that received vehicle control.(80)

Related experiments utilized a periostin knock-out mouse model that develops periodontal disease without intervention. These mice develop changes in osteocyte morphology corresponding to bone loss and increases in SOST expression in the setting of periodontal disease.(81) Mice lacking both periostin and SOST expression had restoration of normal osteocyte morphology as well as significant improvements in alveolar bone volume.(81) Similar results were seen with 8 weeks of Sclerostin antibody therapy in mice lacking only periostin.(81)

A similar beneficial effect on alveolar bone was seen in mice lacking dentin matrix protein-1 (DMP-1). This is a mouse model of hypophosphatemic rickets manifested by osteomalacia in the setting of low serum phosphorus levels and elevated FGF-23 levels.(82) Interestingly, Sclerostin antibody treatment for 8 weeks in both 1 month and 3-month-old animals significantly improved (but did not completely restore) alveolar bone morphology and volume.(82) Sclerostin antibody also increased long bone volume and strength suggesting there may be a role for Sclerostin inhibition in the treatment of hypophosphatemic rickets. (82) Together these studies suggest a role for systemic Sclerostin antibody therapy in the treatment of alveolar bone loss due to periodontitis and hypophosphatemic rickets induced osteomalacia.

5.0 Conclusions

Sclerostin targeted therapies have been shown to be effective at treating genetic disorders of bone in animal models, including Osteoporosis Pseudoglioma syndrome and Osteogenesis Imperfecta. There is promising data on the prevention of bone loss in other disorders, including rheumatoid arthritis, chronic kidney disease, diabetes, inflammatory bowel disease and dental disorders affecting bone. Therapies for these disorders, especially anabolic therapies capable of inducing bone formation, remain extremely limited, particularly in the pediatric population. Human trials are needed to demonstrate the effectiveness of Sclerostin antibody based therapies in these, and other related disorders, as the benefits to patients would likely be significant.

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Highlights

- Sclerostin neutralizing therapies improve bone density in Osteoporosis Pseudoglioma syndrome
- Sclerostin antibody increases bone density but not bone quality in Osteogenesis Imperfecta
- Anti-Sclerostin therapy may be useful in treating bone loss in other disorders