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Hormonal and Systemic Regulation of Sclerostin

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Abstract

The Wnt/ β -catenin signaling pathway plays an essential role in osteoblast biology. Sclerostin is a soluble antagonist of Wnt/ β -catenin signaling secreted primarily by osteocytes. Current evidence indicates that sclerostin likely functions as a local/paracrine regulator of bone metabolism rather than as an endocrine hormone. Nonetheless, circulating sclerostin levels in humans often reflect changes in the bone microenvironment, although there may be exceptions to this observation. Using existing assays, circulating sclerostin levels have been shown to be altered in response to both hormonal stimuli and across a variety of normal physiological and pathophysiological conditions. In both rodents and humans, parathyroid hormone provided either intermittently or continuously suppresses sclerostin levels. Likewise, most evidence from both human and animal studies supports a suppressive effect of estrogen on sclerostin levels. Efforts to examine non-hormonal/systemic regulation of sclerostin have in general shown less consistent findings or have provided associations rather than direct interventional information, with the exception of mechanosensory studies which have consistently demonstrated increased sclerostin levels with skeletal unloading, and conversely decreases in sclerostin with enhanced skeletal loading. Herein, we will review the existent literature on both hormonal and non-hormonal/systemic factors which have been studied for their impact on sclerostin regulation.

Keywords

bone; osteocyte; sclerostin; hormone; parathyroid; estrogen; diabetes; loading; unloading

Introduction

The canonical Wnt signaling pathway is central to osteoblast biology and plays a direct role in osteoblast differentiation, proliferation, and activity. Accordingly, stringent regulation of Wnt signaling is critical for promotion and maintenance of skeletal health and avoidance of skeletal pathology. Sclerostin is a 213-amino acid glycoprotein secreted primarily by osteocytes which functions as a potent inhibitor of Wnt signaling. As first demonstrated in

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humans and subsequently confirmed in murine models, inactivating mutations in *SOST*, the gene which encodes the sclerostin protein, are associated with significant increases in rates of bone formation and bone mass [1, 2]. Even more intriguing is the observation that individuals heterozygous for inactivating sclerostin mutations have sclerostin levels which are approximately half those of control subjects, but have bone formation rates and bone mass which are substantially increased when compared to persons without *SOST* gene mutations [3]. These observations strongly suggest that regulation of sclerostin levels may be a clinically valid approach to increase bone mass and limit fracture risk.

While much has been learned about sclerostin over the past decade, it is increasingly evident that much remains to be understood before we can harness the true potential of this molecule for the optimization of human skeletal health. Significant current limitations include our current understanding of natural biologic variables [including but not limited to the effects of age, sex, total body bone mineral content (BMC), circadian and seasonal variability; whether sclerostin fragments retain biologic activity; and the mechanism(s) by which sclerostin is cleared from the circulation] in addition to significant limitations associated with the performance characteristics of the current commercially available assays for sclerostin measurement (summarized in Table 1) [4–8].

Another key point that has emerged from recent studies is that sclerostin likely functions as a local/paracrine regulator of bone metabolism rather than as an endocrine hormone. Thus, mice with deletion of LRP4, which facilitates the local effects of sclerostin in bone, have high bone mass despite having elevated circulating sclerostin levels [9]. In addition, mice generated using the *Prx1-Cre* to delete the *Sost* gene specifically within the appendicular skeleton have increased bone mass only in the appendicular, but not the axial, skeleton despite a significant reduction in circulating sclerostin levels [10]. That said, circulating sclerostin levels in humans often reflect changes in the bone microenvironment, although there may be exceptions to this observation. In the following discussion, we focus on changes in circulating sclerostin levels in humans across various conditions. Wherever possible, we point to data supporting (or refuting) the validity of circulating sclerostin measurements using an assessment of either bone sclerostin mRNA levels or corroborative data from animal models. In addition, this review is limited to only one of many Wnt antagonists (for a comprehensive review of Wnt antagonists, see Cruciat et al. [11]); other Wnt antagonists, e.g., members of the secreted frizzled-related protein (sFRP) or Dickkopf (Dkk) families, also have important skeletal actions and may be viable therapeutic targets, but a discussion of those molecules is beyond the scope of the present review.

Hormonal regulation of sclerostin

Given the intrinsic role of sclerostin in the regulation of Wnt signaling and bone metabolism, multiple studies have assessed whether changes in sclerostin levels occur in response to alterations in circulating hormone levels in clinical conditions in which there is altered skeletal metabolism. In the first portion of our manuscript, we will discuss the available data for the effects of parathyroid hormone (PTH), sex steroids, thyroid hormones, and corticosteroids on sclerostin regulation. In the latter portion of the manuscript, we will

discuss systemic factors and conditions which have been described as influencing sclerostin levels.

Parathyroid hormone

As the only currently approved skeletal anabolic agent, intermittent subcutaneous treatment with PTH (either PTH 1–34 or PTH 1–84) stimulates bone formation. However, the mechanisms by which intermittent exposure to PTH induces skeletal anabolism, whereas continuous PTH exposure results in skeletal catabolism, have remained incompletely understood. As first described in rodent models, continuous PTH infusion decreases both *SOST* mRNA expression as well as sclerostin protein levels in osteocytes [12], while intermittent PTH treatment also suppresses both *SOST* mRNA and sclerostin protein levels in epiphyseal trabeculae, secondary metaphyseal trabeculae, and diaphyseal bone [13]. Notably, PTH treatment failed to suppress *SOST* mRNA or sclerostin levels in mice devoid of the PTH/PTH-related peptide (PTHrP) type 1 receptor in osteocytes [14]. These findings highlight the importance of PTH/PTHrP receptor signaling for the effects of PTH on osteocytic sclerostin production and bone anabolism, although recently a sclerostin-independent skeletal anabolic effect of intermittent PTH treatment has also been described and shown to be the result of PTH effects on Wnt10b production by T cells [15].

To assess the impact of intermittent PTH in humans, our group prospectively treated 27 postmenopausal women with PTH 1–34 for 14 days, and compared changes in serum sclerostin levels in these subjects to 28 women who did not receive treatment. Consistent with the described rodent data above, intermittent PTH treatment decreased serum sclerostin levels by 12.7% ($P < 0.0001$), with no change seen in the control subjects ($P < 0.02$ for the between group difference) (Figure 1A) [16]. In further analyses from this study, bone marrow plasma obtained at the end of the 14 day treatment cycle from 19 women in each of the PTH-treated and control cohorts showed that serum sclerostin levels were highly correlated with bone marrow plasma levels ($r = 0.64$; $p < 0.0001$), with sclerostin levels in the bone marrow of PTH-treated women 24% lower than in control subjects. This close correlation between serum and bone marrow plasma levels suggests that circulating sclerostin levels may be a useful biomarker for the skeletal effect of anabolic PTH therapy. A reduction in serum sclerostin levels has also been observed in postmenopausal women treated with either intermittent PTH 1–34 or PTH 1–84 for up to 18 months [17].

Consistent with these results, Yu and al. have also demonstrated in a cohort of 53 healthy adult males that infusion of PTH 1–34 led to a reduction in circulating sclerostin levels within six hours (Figure 1B) [18]. Perhaps in contrast to these results, however, is that observation that sclerostin levels were unchanged in adult women with anorexia nervosa who received PTH 1–34 treatment for six months [19]. Reasons for this noted difference are unclear, but may reflect underlying differences in skeletal biology and/or skeletal hormonal responses in anorexia nervosa subjects [20].

To determine whether the suppressive effect of PTH on sclerostin levels occurs in pathologic as compared to pharmacologic conditions, multiple investigators have now examined humans with parathyroid gland disorders. In primary hyperparathyroidism, in which subjects have sustained inappropriately elevated circulating PTH levels due to parathyroid gland

overproduction of PTH, several studies have now documented that affected individuals have lower sclerostin levels both relative to matched control subjects, as well as to patients who have undergone parathyroidectomy and therefore biochemical resolution of their hyperparathyroidism [21–23]. Intriguingly, following parathyroidectomy, sclerostin levels were shown to normalize more rapidly than markers of bone turnover [22], consistent with sclerostin having a causal role in regulating bone cell activity.

In contrast to hyperparathyroidism, hypoparathyroidism is characterized by chronically inappropriately low PTH levels. In a cross-sectional study, serum sclerostin levels were found to be significantly higher in 20 subjects with hypoparathyroidism when compared to an equal number of either euthyroid control ($P < 0.001$) or hyperparathyroid ($P < 0.001$) subjects [24]. Although a significant correlation between circulating sclerostin levels and bone mineral density (BMD) was not found, this study did identify a positive and statistically significant relationship between circulating sclerostin levels and BMC at the lumbar spine, hip, and distal radius in subjects with hypoparathyroidism. Collectively, the above data from both rodent models and humans demonstrates a consistent inverse relationship between PTH and sclerostin levels.

Sex steroids

Given the key role of both sex steroids and Wnt signaling in regulating bone metabolism, there has been considerable interest in understanding possible cross-talk between these systems and specifically, the role of sclerostin in mediating this cross-talk. This issue has been examined in both human and mouse studies, which are summarized below. *Human studies.* As noted in earlier work [5, 6], assays for measuring sclerostin levels in human serum or plasma do differ in terms of epitopes recognized and absolute concentrations (see Table 1). This caveat notwithstanding, there is now considerable data demonstrating that estrogen reduces sclerostin production in humans. Using an in-house assay developed at Amgen, Mirza and colleagues [25] initially studied pre- and postmenopausal women and reported significantly higher serum sclerostin levels in the postmenopausal women. This relationship was, however, confounded by age, as subsequent studies have generally found an age-related increase in serum sclerostin levels in both women and in men [6, 26]. Nonetheless, in the postmenopausal women, there was a significant inverse relationship between serum sclerostin levels and the free estrogen index [(E2 + E1)/SHBG] that persisted even after age adjustment.

In a subsequent study, our group evaluated serum sclerostin levels in archived samples from direct interventional studies of sex steroid manipulation in women and in men using both an in-house and a commercial assay (Biomedica) [27]. In the first study, postmenopausal women were either untreated or treated with transdermal estradiol (E2; 100 µg/d) for 4 weeks. As previously reported by Hannon and colleagues [28], bone formation markers increased and bone resorption markers decreased early after the initiation of estrogen treatment. As shown in Figure 2A, serum sclerostin levels were reduced by E2 treatment using both assays (by ~25%). In the second study, we evaluated serum sclerostin levels using the commercial assay in men following 3 weeks of complete hypogonadism [– testosterone (T), – estrogen (E)], treatment with a physiological dose (for men) of E2 alone (–T, +E),

treatment with T alone, in the presence of an aromatase blocker that prevented conversion of T to E (+T, -E), and with T and E replacement (+T, +E). As shown in Figure 2B, complete hypogonadism (-T, -E) tended to increase serum sclerostin levels ($p = 0.051$) whereas E alone clearly reduced sclerostin levels. By contrast, T alone (in the absence of aromatization to estrogen) had the opposite effect, significantly increasing serum sclerostin levels. These data in men are generally consistent with those of Di Nisio et al. [29] who found that hypogonadal men (who are both testosterone and estrogen deficient) had higher sclerostin levels than eugonadal controls; these authors did find stronger inverse correlations between sclerostin and testosterone levels than between sclerostin and estradiol levels. Although direct interventional data are generally more robust than correlative data, further studies are needed to better define the effects of testosterone, particularly in the absence of aromatization to estrogen, on sclerostin production.

Subsequent human studies have consistently confirmed the effects of estrogen on circulating sclerostin levels. Thus, we found a similar suppression of serum sclerostin levels in postmenopausal women treated for a longer duration (4 months) with a lower dose (50 $\mu\text{g/d}$) of transdermal E2 [30]. In addition, Chung et al. [31] observed a 41% reduction in serum sclerostin levels (Biomedica assay) in a retrospective observational study of 16 postmenopausal women treated with raloxifene as compared to 32 untreated controls. Importantly, the reduction in serum sclerostin levels was not due to a suppression of bone turnover alone, as bisphosphonate-treated subjects ($n = 32$) had sclerostin levels similar to the controls.

Since there is some question as to whether serum sclerostin levels reflect changes in the bone microenvironment [32], we recently examined both serum sclerostin levels and bone sclerostin mRNA levels in needle bone biopsies obtained from 19 untreated postmenopausal women and 20 postmenopausal women treated for 3 weeks with transdermal E2 (100 $\mu\text{g/d}$) [33]. As shown in Figure 3A, serum sclerostin levels were lower in the E-treated vs. control women using both the Biomedica and Meso Scale Discovery (MSD) assays (by 29% and 18%, respectively). Importantly, we found that bone sclerostin mRNA levels were also 41% and 48% lower when assessed by RNAseq and QPCR, respectively, in the E-treated vs control women (Figure 3B).

Given the consistent suppression of sclerostin production by estrogen in humans, a logical question is whether this contributes to estrogen effects on bone turnover. This issue is difficult to address directly in humans, but some exploratory analyses are possible. First, it is important to note that sclerostin and its ability to modulate Wnt signaling may regulate not only bone formation, but also bone resorption. Thus, Tu et al. [34] recently demonstrated that sclerostin stimulates RANKL and inhibits OPG production by osteocytes. In addition, work from our group has shown that Wnt signaling directly inhibits osteoclast development [35]. Thus, it is plausible that sclerostin may, in fact, mediate the effects of estrogen not only on bone formation but also on bone resorption.

In order to explore this possibility, Figure 4 shows the time course of changes in bone formation (amino-terminal propeptide of type 1 collagen; PINP) and bone resorption (carboxyl-terminal telopeptide of type 1 collagen; CTX) following treatment with a pure

osteoclast inhibitor (zoledronic acid, Figure 4A) [36] vs a sclerostin inhibitor (romosozumab, Figure 4B) [37] or estrogen (Figure 4C) [28]. As is evident, zoledronic acid results in an acute suppression of both bone formation and bone resorption, consistent with it being a pure anti-resorptive agent. By contrast, sclerostin inhibition is associated with an initial increase in bone formation (Figure 4B). Over time, bone resorption decreases, as does bone formation, presumably due to the coupling of bone resorption and bone formation [38]. Interestingly, the time course of changes in serum PINP and CTX following estrogen treatment is qualitatively much more similar to that following romosozumab treatment than it is to bisphosphonate treatment (Figure 4C). Specifically, bone formation increases transiently following the initiation of estrogen treatment whereas bone resorption declines; over time, due to the coupling of bone resorption and bone formation [38], bone formation also declines. These correlative human data on a role for sclerostin in mediating estrogen effects on bone turnover are supported by recent studies in mice demonstrating that mice with knock-in mutations of LRP5 causing sclerostin resistance also have attenuated bone loss following ovariectomy [39]. Thus, the hypothesis that inhibition of sclerostin production by estrogen is responsible, at least in part, for estrogen effects on both bone formation and resorption is certainly plausible, but clearly warrants further testing. It should be noted that in contrast to this considerable body of evidence supporting a role for estrogen regulation of sclerostin production in humans, Liakou et al. [40] found no variation in serum sclerostin levels during the normal menstrual cycle. These data suggest that estrogen effects on sclerostin production are relevant primarily when going from complete hypogonadism to an estrogen replete state, rather than within the normal physiological estrogen range that occurs during the menstrual cycle.

Mouse studies—With some exceptions, studies in mice are generally consistent with the human data demonstrating that estrogen suppresses whereas testosterone may, in fact, increase sclerostin production. In order to test the effects of estrogen deficiency on sclerostin production and also to test whether TNF- α , which is known to be upregulated following ovariectomy in mice [41], plays a role in mediating the effects of estrogen on sclerostin production, Kim et al. performed bilateral ovariectomy or sham surgery in C57 BL/6 mice followed by treatment with PBS, E2, or a TNF- α blocker (infliximab) [42]. Using immunohistochemistry, these investigators showed that the number of sclerostin-positive osteocytes increased following ovariectomy, and this increase was prevented by E2 or by the TNF- α blocker. These findings suggested that TNF- α may mediate the effects of estrogen deficiency on sclerostin production. Consistent with these findings, Wehmeyer et al. [43] recently demonstrated that mice overexpressing TNF- α had a marked increase in sclerostin expression in osteocytes. This study was designed to examine the role of sclerostin inhibition on rheumatoid arthritis progression in a mouse model and also found that while TNF- α stimulated sclerostin production, sclerostin blocked TNF- α -induced activation of its downstream signaling target, p38, suggesting a close inter-relationship and cross-regulation between sclerostin and TNF- α . Indeed, sclerostin inhibition led to increased TNF- α signaling and more rapid progression of rheumatoid arthritis in these mice.

There is also evidence for a relationship between estrogen, sirtuin 1 (Sirt1), and sclerostin. Thus, Artsi et al. [44] found that ovariectomy in mice resulted in a marked decrease in

skeletal Sirt1 expression accompanied by an increase in sclerostin. Interestingly, oral administration of SRT3025, a Sirt1 activator, reversed the deleterious skeletal effects of ovariectomy and also reduced bone sclerostin expression.

Unlike human studies, however, not all mouse studies have found a consistent reduction in bone sclerostin levels by estrogen. Thus, Jastrzebski and colleagues [32] found that sclerostin mRNA levels were significantly lower (not higher) in femurs at 3 weeks post ovariectomy in C57 BL/6 mice and had returned to levels in sham operated mice by 6 weeks. The reasons why the findings of this study differ from the others described above are unclear.

In terms of testosterone, there is some evidence from mouse models to support the human data that unlike estrogen, testosterone may have the opposite effect and increase sclerostin production. Thus, Callewaert et al.[45] found that loading induced significantly more periosteal bone formation in male androgen receptor knock out (ARKO) as compared with WT mice and had a stronger inhibitory effect on sclerostin expression in ARKO vs WT mice. In a subsequent study, Sinnesael et al. [46] found that testosterone treatment of orchiectomized mice increased the number of sclerostin-positive osteocytes. In contrast to these findings, Di Nisio et al. [29] found that dihydrotestosterone (DHT) decreased sclerostin expression in cultured human osteocytes, suggesting that the *in vitro* (direct) effects of androgens may differ from their *in vivo* (perhaps indirect) effects on sclerostin production. Nonetheless, to the extent that estrogen and testosterone have opposite effects on sclerostin production, this may, at least in part, explain the consistent observation that in men, estrogen is the dominant regulator of bone turnover and bone density [47].

Thyroid hormone

Biochemical hyperthyroidism, either endogenous or iatrogenic, is associated with bone loss and increased fracture risk [48]. However, the mechanisms underlying these skeletal effects remain incompletely understood. As demonstrated in a cohort of patients with endogenous hyperthyroidism due to either Grave's disease or toxic multinodular goiter, pharmacologic antithyroid treatment to reduce circulating thyroid hormone levels to the normal range resulted in a rapid and significant decrease in serum sclerostin levels ($P<0.01$) [49]. This sclerostin decrease was associated with significant declines in biochemical markers of bone formation (osteocalcin; OCN) and resorption (CTX), and a simultaneous increase in PTH levels (P for each < 0.001) [50]. In a murine model of hyperthyroidism, sclerostin levels (both circulating blood levels and when excised bone was assessed for *SOST* mRNA expression) were increased relative to those of euthyroid mice, a finding which was particularly striking when considered in relation to the lower bone mass of the hyperthyroid mice ($P<0.001$) [51]. However, a recent study which examined thyroid stimulating hormone levels in two large German population-based cohorts did not identify any significant association between levels of thyroid stimulating hormone (TSH) and sclerostin [52]. Reasons for the noted differences between the studies are unclear.

Corticosteroids

Corticosteroid levels above normal physiologic levels, either due to endogenous hypercortisolism or secondary to treatment with exogenous corticosteroids, result in suppression of bone formation and increased fracture risk. In patients with endogenous hypercortisolism, serum sclerostin levels were significantly decreased ($P<0.001$) when compared to age- and gender-matched controls, while surgical correction of hypercortisolism (either via transphenoidal adrenocorticotrophic hormone secreting adenoma resection or adrenalectomy) led to a rapid rise in sclerostin levels ($P<0.01$) which was associated with increases in markers of bone formation (PINP) and CTX (P for each <0.01) [53]. In partial contrast, a study which evaluated changes in sclerostin levels following exogenous glucocorticoid initiation found no significant change in serum sclerostin levels after two months of therapy, but a slight increase in sclerostin levels relative to baseline when assessed at 12 months ($P=0.045$) [54]. In addition, in a heterogeneous population of patients with systemic autoimmune diseases, Fernandez-Roldan et al. [55] found no effect of glucocorticoid treatment on serum sclerostin levels. Reasons for these seemingly discrepant results are unclear, although one potential explanation is that sclerostin measurements in the various studies were done using different assays. Perhaps the most convincing evidence for an effect of glucocorticoids on stimulating sclerostin production are recent data from the Bellido laboratory showing that in mice, glucocorticoids increased the expression of sclerostin and the number of sclerostin-positive osteocytes, as well as altered the molecular signature of the Wnt/ β -catenin pathway by decreasing the expression of genes associated with both anti-catabolism and anabolism/survival [56].

Vitamin D

Efforts to determine whether vitamin D regulates sclerostin directly have provided mixed results. Thus two years of calcium and vitamin D supplementation (700 IU/day) in a cohort of 279 men and women increased serum sclerostin levels in men (+13.1%; $P<0.01$ versus placebo), but did not significantly change sclerostin levels in women [57]. Consistent with the findings in women, Sandal et al. [58] found no differences in circulating sclerostin levels between vitamin D deficient versus vitamin D sufficient pregnant women. The results in men are consistent with those reported to occur *in vitro*, whereby treatment of osteogenic sarcoma SaOS2 cells with 1,25-dihydroxyvitamin D induced increases in both *SOST* mRNA and sclerostin protein levels [59]. In contrast to these results, however, are those in which 44 subjects with biochemically determined vitamin D deficiency (defined as a 25-hydroxyvitamin D level <20 ng/mL) were treated with monthly intramuscular injection of 300,000 IU of vitamin D (cholecalciferol) and had a significant decline (-19.4% ; $P<0.01$) in sclerostin levels [60]. Given the well-recognized inverse relationship between vitamin D and PTH, and the effects of PTH on sclerostin levels as described earlier in this review, it appears prudent at this time to interpret vitamin D dependent effects on sclerostin with caution.

Systemic Regulation of Sclerostin

With the exception of studies examining mechanosensory and exercise effects on sclerostin, there is comparatively less direct interventional information on systemic factors which

regulate sclerostin levels relative to the data on hormonal regulation of sclerostin levels, as described above. Rather, most studies have examined associations between systemic conditions and sclerostin levels. Findings from studies which have examined the systemic regulation of sclerostin are reviewed below.

Diabetes Mellitus

Diabetes mellitus (DM) is associated with decreased bone turnover, reduced bone quality, and increased fracture risk [61, 62]. Given the role of sclerostin as a Wnt-signaling pathway antagonist and thus as an important mediator of bone formation, multiple studies have examined the impact of DM on sclerostin levels.

In a cross-sectional study of which included 128 subjects with type 1 DM (DM1) (both men and premenopausal women; mean age 43.4 years; mean DM1 duration 22.4 years) and 77 healthy control subjects matched for age, body mass index (BMI) and gender, serum sclerostin levels were found to be higher in both men ($P<0.05$) and women ($P=0.01$) with DM1 [63]. While a stronger positive correlation of sclerostin with age was seen in subjects with DM1 versus controls, sclerostin levels did not correlate with markers of bone formation (OCN) or resorption (CTX). In contrast to these findings, however, a study in pediatric (children and adolescents) subjects found no difference ($P=0.84$) in plasma sclerostin levels between subjects with DM-1 and healthy matched controls [64].

Like those with DM1, subjects with DM2 also suffer from reduced bone formation rates and increased fracture risk. In a cross-sectional study of 74 subjects with DM2 and 50 control subjects, Garcia-Martin et al. found that sclerostin levels were significantly higher ($P<0.001$) in DM2 subjects relative to controls, and that sclerostin levels were also significantly higher ($P<0.001$) in male versus female subjects with DM2 [65]. Similar evidence for increased sclerostin levels as compared to healthy control subjects has also been documented in adult DM2 cohorts from Italy [66], Saudi Arabia [67], and China [68]. Intriguingly, Heilmeier et al. recently demonstrated that DM2 subjects at high fracture risk due to a prior fragility fracture had significantly higher serum sclerostin levels when compared to DM2 subjects without a history of fracture (+31.4%; $P=0.01$), non-diabetic controls with fracture (+25.2%; $P=0.03$), and healthy control subjects (+22.4%; $P=0.03$) [69].

Finally, recent work also demonstrates that subjects with either impaired fasting glucose or impaired glucose tolerance, precursor conditions for the development of DM2, also have higher sclerostin levels; further, in these pre-diabetic subjects, sclerostin levels are also positively associated with insulin resistance [70]. Consistent with these findings, Confavreux et al. [71] found that men with metabolic syndrome had higher sclerostin levels than controls, although this appeared to be due to their higher bone mass, as adjustment for whole body BMC eliminated these differences. Whether the increased circulating insulin levels common to pre-diabetes and DM2 directly impact sclerostin levels remains unclear, but raise the possibility of an additional level of hormonal control for regulation of sclerostin levels. As an alternative explanation, however, is recent evidence which found that both high glucose levels and advanced glycation end products (AGEs) could directly increase osteocytic sclerostin production *in vitro* [72]. In contrast to these findings, however, Pereira

et al. [73] did not find effects of chronic hyperglycemia on bone sclerostin levels in a rat model of diabetes.

Immobilization/spinal cord injury/weight loss/weightlessness

As the primary skeletal cells responsive for mechanosensation, osteocytes play an integral role in the skeletal response to both loading and unloading as well documented in both *in vitro* [74] and *in vivo* rodent studies in which increased osteocyte-associated sclerostin levels were seen in response to skeletal unloading [75], and resistance to mechanical unloading-induced bone loss occurred in mice which were homozygous deficient for sclerostin [76].

In studies of healthy adult males subjected to prolonged bed rest, sclerostin levels increased markedly from baseline within 14 days (+8%; $P<0.02$) [77] and remained elevated at both 28 (+29%; $P=0.003$) and 60 (+42%; $P<0.001$) days relative to baseline [78]. Consistent with this observation, a cross-sectional study of 155 men variously affected by spinal cord injury (SCI) for at least one year found that circulating sclerostin levels were highest at one year and declined significantly over the course of the first five years following injury [79]. By comparison, subjects with a history of SCI of at least five years duration had lower sclerostin levels which were highly correlated with total body BMC, raising the possibility that the lower circulating sclerostin levels observed in late-stage SCI-associated osteoporosis may reflect a decreased number of osteocytes from diminished bone mass [80]. In partial contrast to the above findings, however, a Spanish study examining subjects with recent (<6 months) SCI found that serum sclerostin levels were non-significantly increased in SCI relative to control subjects and did not change appreciatively over the course of the ensuing 12 months, remaining non-significantly different from both baseline and control subject values [81].

Relative to either prolonged immobilization or SCI, a more common etiology for skeletal unloading is rapid weight loss, particularly following bariatric surgery. Although baseline sclerostin levels were not different in female subjects undergoing bariatric surgery when matched to control subjects for race and age [82], bariatric surgery and its associated weight loss led to a rapid and sustained increase in serum sclerostin levels which peaked at six months (+135%; $P<0.001$) and remained elevated above baseline 24 months after surgery [83]. Intriguingly, however, there is now good evidence that increases in circulating sclerostin levels associated with weight loss can be attenuated by implementation of an exercise program. Thus, in comparison to a cohort of older obese adults who had a -9.6% decrease in body weight over 12 months due to diet alone and an associated 10.5% ($P<0.05$) increase from baseline in serum sclerostin levels, a matched cohort prescribed an exercise training regimen in addition to diet experienced a nearly identical -9.4% decrease in body weight, but had no significant change in serum sclerostin levels (+0.4%; $P=NS$) (Figure 5) [84]. Further, while the diet alone group had significant increases in bone turnover markers (PINP +9% and CTX +31%) at 12 months, the group which included exercise training in addition to diet showed a decrease in bone turnover (PINP -15% and CTX -13%) over this time frame ($P<0.05$ for between group differences) [85].

Finally, astronauts exposed to 4–6 months of weightlessness during missions to the International Space Station showed a 10–15% increase in circulating sclerostin levels despite regular use of an Advanced Resistance Exercise Device [86]. Based on these findings, both

routine exercise and continuous exposure to gravity are likely important factors for regulating sclerostin levels.

Skeletal loading/exercise

In contrast to skeletal unloading, increased skeletal loading induces adaptive increases in both bone mass and strength via bone deposition on loaded surfaces [87]. Consistent with an integral role for sclerostin in this process, a mouse model of axial ulnar loading demonstrated significant reductions in both *SOST* mRNA and sclerostin protein levels which were most profound at the sites of greatest load-induced strain stimulus [75].

Despite clear evidence for sclerostin suppression in response to skeletal loading in rodents, however, data from human exercise studies has been less consistent, with some studies demonstrating suppression of sclerostin levels [88] and others showing no changes or even increases in measured sclerostin values [89–91]. Reasons for these differences are unclear, but may reflect inherent limitations in the reported studies (timing of blood collections relative to exercise; duration of exercise; sclerostin levels measured in peripheral blood rather than directly at the site of increased skeletal loading; inclusion of children and adolescents – in whom sclerostin levels have been demonstrated to change during normal growth) or available assays [6].

Collectively, the available data from both animals and humans strongly supports an essential role for sclerostin in the mechanosensory response to skeletal unloading and loading (exercise), with precise regulation of osteocyte-produced sclerostin permitting integration of local and regional osteogenic signals in response to mechanical input to modulate Wnt/ β -catenin signaling.

Normal growth and aging

In a cross-sectional study our group recently performed of 56 males and 62 females aged 6–21 years, serum sclerostin levels were found to be significantly higher in males than females ($P=0.008$) [92]. In this pediatric population, sclerostin levels were non-linear in both males and females, correlating positively with bone age prior to the pubertal onset in both sexes, and negatively thereafter. For females, this split-point occurred at a bone age of 10 years, while in males it occurred at a bone age of approximately 14 years.

Several groups have examined sclerostin levels in adults. In a large cross-sectional study of 362 women and 318 men aged 21–97 years, sclerostin levels were higher in male as compared to female subjects (33.3 versus 23.7 pmol/L; $P<0.001$) [26]. Of note, however, not all studies have been able to demonstrate higher sclerostin levels in men as compared to women, with results in one study shown to be dependent upon the commercial assay used [5]. In both premenopausal women and postmenopausal women not maintained on E therapy as well as in men, sclerostin levels were positively correlated with age ($P<0.001$) and increased 2.4-fold and 4.6-fold in women and men, respectively, over the lifespan [26]. Interestingly, when matched for total body BMC, women and men aged > 60 years had higher sclerostin levels relative to subjects aged 21–39 years, demonstrating that despite presumptively equal numbers of osteocytes, sclerostin levels were higher with aging.

Increases in sclerostin with aging in women was likewise seen in cross-sectional studies of women from both Saudi Arabia [93] and Japan [94]. Of note, a positive correlation of serum sclerostin levels with BMD/total body BMC has been seen in a number of studies [5, 26, 95, 96]. However, the significance of this positive association of sclerostin levels with bone mass remains unclear. It is possible, for example, that a higher total body bone mass reflects an increased total number of osteocytes, leading to higher circulating sclerostin levels. Alternatively, this may represent a homeostatic mechanism, whereby higher bone mass is associated with increased sclerostin production by individual osteocytes to thereby limit further increases in bone mass that might be detrimental to the organism.

To establish whether increases in serum sclerostin levels with age are reflective of sclerostin levels at the bone tissue level, we undertook a study in which we performed bone biopsies in 20 young and old women (mean ages 30.0 and 72.9 years, respectively) and compared circulating sclerostin levels to bone mRNA sclerostin levels [97]. While serum sclerostin levels were increased by 46% in the old versus young women, we found no difference in bone sclerostin mRNA levels ($P=0.845$) between the groups, although for technical reasons, we were unable to measure sclerostin protein levels in the bone tissue *per se*. These results suggest that, in contrast to the concordant decreases in circulating and bone sclerostin mRNA levels following treatment with estrogen [33], increases in circulating sclerostin levels observed with aging, both by us and others, may not be due to increased osteocytic production of sclerostin. Whether the noted increased sclerostin levels reflect reduced sclerostin clearance from the circulation, increased non-skeletal production, an artifact related to measurement, or some other etiology, remains unclear.

Malignancies

Given the propensity of many cancers to metastasize to bone and/or induce bone loss and increase fracture risk, several studies have examined sclerostin levels in an array of malignancies. To date, the majority of work has focused on monoclonal gammopathies, a spectrum of plasma cell disorders demarcated by monoclonal gammopathy of undetermined significance (MGUS) on one end and multiple myeloma on the other end. Although sclerostin levels in subjects with MGUS are not increased relative to control subjects [98], overexpression of sclerostin by plasma cells is a frequent finding in multiple myeloma [99, 100]. Further, increased circulating sclerostin levels are associated with both increased osteolytic disease (a clinical hallmark of multiple myeloma), and decreased overall survival [101, 102]. More recent findings suggest that bone marrow stromal cells and osteoblasts present within the bone marrow may also secrete sclerostin in multiple myeloma [103]. Sclerostin levels are also significantly elevated in men with prostate cancer, and were shown to be further increased by treatment with androgen-deprivation therapy [104, 105]. Whether higher sclerostin levels in men with metastatic prostate cancer reflect a compensatory physiologic response to the osteoblastic lesions which most commonly occur in prostate cancer is unknown, but merits further study. Finally, data on the role of sclerostin in breast cancer remains limited, although pre-clinical studies suggest that at least some breast cancer cells may secrete sclerostin under the regulation of the Runt-related transcription factor, Runx2 [106].

Renal disease

In chronic kidney disease (CKD), emerging evidence suggests that increased sclerostin expression and associated suppression of osteocytic Wnt/ β -catenin signaling can be an early event in CKD-mineral and bone disorder (CKD-MBD), occurring even prior to the well-recognized rise in PTH that occurs with declining renal function [107, 108]. With progressive renal dysfunction, however, the increase in PTH levels leads to some repression of sclerostin levels, although relative to normal subjects, sclerostin levels in CKD subjects typically remain elevated [109, 110]. Whether currently available commercial assays accurately measure sclerostin levels in patients with renal dysfunction remains an open question [7, 111]. In addition, whether elevated sclerostin levels represent sclerostin release from osteocytes in bone or from calcified vascular sources is unclear. Despite these caveats, however, there is convincing evidence that improvement in renal function following transplant is associated with a rapid reduction in serum sclerostin levels, which decline even more rapidly than serum PTH levels [112], although a gradual increase in sclerostin levels has been shown to occur with progressive time since transplant [113]. Whether altered sclerostin levels in CKD result directly from the progressive decline in renal function is unclear, although multiple factors known to increase with progressive renal dysfunction, including inflammatory cytokines, protein-bound uremic toxins, and fibroblast growth factor 23 (FGF23) [114–116] may play a role in sclerostin regulation.

Conclusions

As described in this review, studies in both humans and animals over the past decade have clearly demonstrated a pivotal role for sclerostin as a negative regulator of bone mass. Although circulating and, as demonstrated in some instances summarized here, bone sclerostin mRNA or protein levels in humans and in mice change in response to a diverse array of factors including hormonal, systemic, and mechanosensory stimuli, additional studies are needed to demonstrate a clear role for the observed changes in sclerostin production in mediating the skeletal effects of the various stimuli. Stringent regulation of sclerostin levels, particular locally within the bone marrow microenvironment where sclerostin functions as an autocrine and/or paracrine factor, is likely of critical importance for the optimization of skeletal health.

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Highlights

- Circulating sclerostin levels are altered in response to a number of stimuli.
- Sclerostin acts locally, but circulating levels may reflect changes in bone.
- Estrogen suppresses circulating and bone sclerostin mRNA levels in humans.
- Parathyroid hormone also suppresses sclerostin levels.
- We also review other physiological and pathological stimuli affecting sclerostin.

Figure 1.

(A) Percent change from baseline in circulating serum sclerostin levels in the control ($4.7 \pm 2.6\%$) and PTH-treated ($12.7 \pm 1.9\%$) women. *, $P < 0.02$ for comparison with the change in control women. Adapted from Drake et al. [16], with permission. (B) Changes in sclerostin during infusion of PTH 1–34 at a dose of 0.55 U/kg per hour. Serum sclerostin levels decreased within 6 hours and remained suppressed over 18 hours. *, $P < 0.01$ for comparison with change from baseline. Adapted from Yu et al. [18], with permission.

Figure 2.

(A) Percent change from baseline in serum sclerostin levels in control or estrogen-treated postmenopausal women using 2 different sclerostin assays. P-values for differences in changes in the control vs estrogen-treated women are as indicated. *** $P < 0.001$ for significance of change from baseline. (B) Percent change from baseline in serum sclerostin levels in men following manipulation of testosterone (T) or estrogen (E) levels (please see text for details). The P-values for the E and T effects are based on a two factor ANOVA model. Briefly, this compares changes in the +E vs -E groups for the E effect and changes in the +T vs -T groups for the T effect. * $P < 0.05$, ** $P < 0.01$, and † $P = 0.051$ for significance of change from baseline. Reproduced from Mödder et al. [27], with permission

Figure 3.

(A) Effects of estrogen on serum sclerostin levels using either the Biomedica (solid bars) or Meso Scale Discovery (MSD) (hatched bars) assays. Note the difference in scales for the two sclerostin assays. (B) Effects of estrogen on bone sclerostin mRNA levels by RNAseq or QPCR. * $P < 0.05$; ** $P < 0.01$. Data are from Farr et al. [33].

Figure 4.

(A) Effects of zoledronic acid (adapted from Devogelaer et al.[36]), (B) romosozumab (adapted from McClung et al. [37]) and (C) transdermal estrogen (adapted from Hannon et al. [28]) on bone formation (serum PINP) and bone resorption (serum CTX).

Figure 5. Changes relative to baseline in serum sclerostin levels in older obese adults treated with diet plus exercise versus diet alone. Values are mean $\pm$ SEM. * $P < 0.05$ for the comparison of the values to baseline, and to the diet plus exercise group. Adapted from Armamento-Villareal et al. [84].

Table 1

Characteristics of commercially available assays for circulating sclerostin.

	BioMedica	TECOmedical	MSD	R&D Systems
Assay type	ELISA	ELISA	ECL	ELISA
Primary Ab	Polyclonal	Polyclonal	Polyclonal	Monoclonal
Secondary Ab	Monoclonal	Monoclonal	Polyclonal	Polyclonal
Intra-assay CV (%)	7	<4.2	4	2
Inter-assay CV (%)	10	<4.8	4	< 10
Detection Limit (pg/mL)	73	9	1.1	3.8
Detection Range (pg/mL)	0–5455	50–3000	1–100000	31–2000
Fragments detected	Yes	Yes	No	Unknown

CV: coefficient of variation; ELISA: enzyme-linked immunosorbent assay; ECL: electrochemiluminescence assay; MSD: Meso Scale Discovery.