

Clinical and Technical Review

Sclerostin

a specific biochemical marker
of osteocyte function

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Sclerostin – a specific biochemical marker of osteocyte function

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I. Introduction

a. Discovery and Function of Sclerostin

Metabolic bone diseases, including osteoporosis, hyper and hypoparathyroidism are characterized by altered bone mass and bone structure leading to an increased susceptibility to fracture. These alterations mainly result from abnormalities in bone remodeling i.e. a tightly controlled balanced process between bone formation and bone resorption. Abnormalities of bone turnover can be assessed in vivo non invasively by measuring the activity or the secreted products of the osteoblasts and osteoclasts respectively. Different assays for bone formation and bone resorption markers are available that have been shown to be useful not only for a better understanding of the pathophysiological processes involved in bone diseases, but also to improve patient management [1].

Osteoblasts and osteoclasts are not the only bone cells. Osteocytes which are terminally differentiated cells embedded within a mineralized matrix also play an important role in bone remodeling (figure 1). Indeed, these cells comprise a network of canaliculi which are believed to participate in the regulation of the targeted remodeling process by sensing micro fractures. This mechanism is crucial for replacing altered bone tissue by a new collagen matrix with optimal biochemical competence. Osteocytes are also important in the termination of the remodeling cycle by secreting factors such as sclerostin which inhibits osteoblast activity and promote their apoptosis.

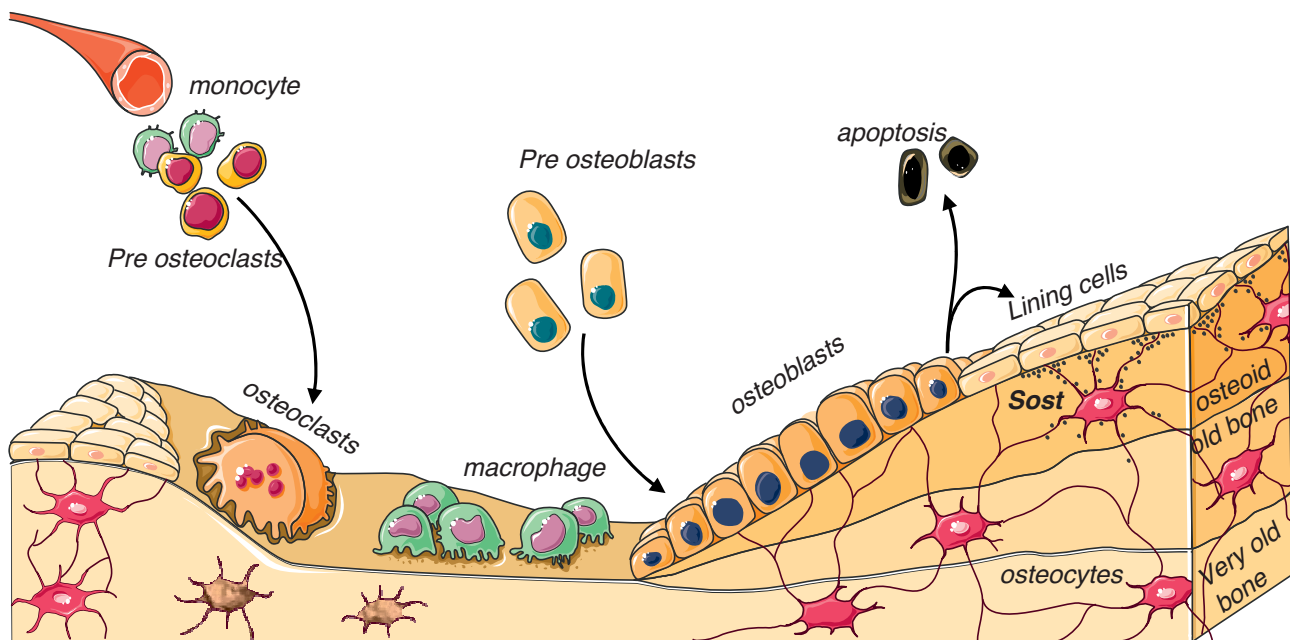


Figure 1:

The different phases of bone remodeling and the role of sclerostin (SOST).

In normal bone remodeling, sclerostin produced and secreted by newly embedded osteocytes may be transported to the bone surface, where it inhibits osteoblastic bone formation and prevents overfilling of the bone remodeling unit

Rare genetic disorders, namely sclerosing dysplasias, sclerosteosis and van Buchem disease has led to the identification of important osteocyte signaling pathways that regulate bone formation. These bone disorders are characterized by progressive generalized osteosclerosis [2 – 5]. The manifestations are most pronounced in the mandible and skull, with characteristic enlargement of the jaw and facial bones leading to facial distortion, increased intracranial pressure, and entrapment of cranial nerves. Histological studies showed that there is evidence of increased bone formation and increased osteoid that mineralize normally, while no consistent pattern of osteoclast number or activity has been reported [6 – 8]. The genetic defect that leads to sclerosteosis was identified in a gene called SOST, which is located on chromosome 17q12-21 and encodes for the protein sclerostin.

Although SOST mRNA is expressed in many tissues during embryogenesis, sclerostin protein has been reported only postnatally in osteocytes, mineralized hypertrophic chondrocytes, and cementocytes. As expected, sclerostin is not expressed by osteocytes in bone biopsies of patients with sclerosteosis and van Buchem disease, supporting the function of the genomic region deleted in these patients in the regulation of sclerostin expression in bone [9]. Addition of exogenous sclerostin to osteogenic cultures inhibited proliferation and differentiation of mouse and human osteoblastic cells and their apoptosis [10, 11]. In vivo, analysis of SOST knockout mice showed significant increases in bone mineral density (BMD), cortical and trabecular bone volume, bone formation rate, and bone strength [12]. All together these in vitro and in vivo animal data support a negative effect of sclerostin on bone formation. Data on the effect of sclerostin on osteoclastic bone resorption in humans are scarce and inconsistent, with unaffected, low, or increased bone resorption.

Sclerostin is a member of the DAN (differential screening–selected gene aberrant in neuroblastoma) family of glycoproteins. This family consists of a group of secreted proteins that share the ability to antagonize bone morphogenetic protein (BMP) activity, although sclerostin is not a classical BMP antagonist [13]. Sclerostin has been shown to bind LRP5, an essential membrane-bound cofactor of the canonical Wnt signaling, and its closely related coreceptor LRP6 and, thereby, could inhibit this pathway, which is pivotal in regulation of the osteoblastic function (figure 2) [14, 15]. The exact mechanism by which sclerostin secreted by osteocytes inhibits Wnt-mediated bone formation remains however still unclear.

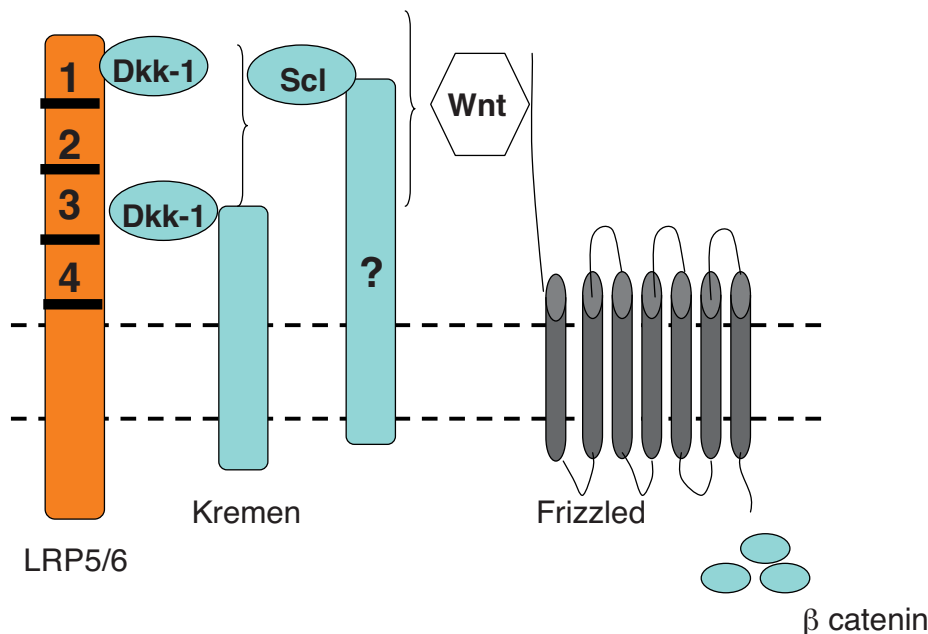


Figure 2:

Schematic model of the canonical Wnt signaling pathway.

The formation of complexes of Wnts with Frizzled receptors and LRP5/6 coreceptors leads to the accumulation of b-catenin in the cytoplasm and translocation into the nucleus. The antagonist Dkk1 inhibits canonical Wnt signaling by the formation of complexes with LRP5/6 and Kremen, resulting in the removal of LRP5/6 from the membrane. Dkk1 binds to the first and third β -propellers of LRP5/6. The antagonist sclerostin inhibits canonical Wnt signaling by binding to probably the first β -propeller of LRP5/6. Whether sclerostin requires a cofactor like Kremen for Dkk1 to exert its antagonistic effect remains to be established (reproduced from van Bezooijen RL, Papapoulos SE, Hamdy NAT, Lowik CWGM (2008) SOST/sclerostin; an osteocyte-derived inhibitor of bone formation that antagonizes canonical Wnt signaling. In: Raisz, LG, Martin TJ, Bilezikian JP (eds) Principles of bone biology. Academic Press, New York, pp 139–152)

b. Regulation of sclerostin expression

Several local and systemic factors have been suggested as possible regulators of sclerostin expression by osteocytes. Intermittent administrations of parathyroid hormone (PTH) are associated with strong anabolic effects. Part of these effects may be mediated via sclerostin as PTH has been shown to inhibit its expression both in vitro and in vivo. In vitro, PTH decreased SOST transcription by osteoblasts and osteocytes within 4 hours [16, 17]. In vivo, PTH administration resulted in a decrease in SOST mRNA and sclerostin protein in mice and rats [17, 18]. The importance of SOST regulation by PTH is further supported by the observations that the anabolic effects of PTH are blunted in SOST-deficient mice as well as in mice overexpressing SOST [19]. 1, 25-dihydroxyvitamin D₃, the biologically active metabolite of vitamin D, alone or in combination with retinoic acid also increases SOST expression in human osteoblastic cells in vitro [20]. The specific effect of glucocorticoids on SOST expression depends on the experimental models. In vitro, dexamethasone suppressed SOST expression in osteoblasts [20], while in vivo treatment of mice with prednisolone increased SOST expression in tibiae. These findings suggest that the inhibition of Wnt signaling by the upregulation of sclerostin may participate to the suppression in bone formation mediated by glucocorticoid.

Among local factors, BMP2, -4, and -6 have been shown to stimulate SOST expression in osteoblastic cells in vitro [20]. More recently it has been reported that the matricellular protein periostin is required for SOST inhibition and plays an important role in the changes of bone mass and structure in response to loading [21].

c. Effect of inhibition of sclerostin on bone metabolism in vivo

As sclerostin is a secreted protein, one attractive approach to stimulate bone formation is to develop antibodies inhibiting the biological activity of sclerostin, a strategy which has been successful with denosumab, a humanized antibody against RANK-L [22]. Such sclerostin antibodies have already been shown to increase BMD, bone volume, and bone strength in ovariectomized rats [23, 24] and primates [25] and to reverse bone loss in a model of colitis [26]. Anti-sclerostin antibodies have also been shown to be efficient in preventing bone loss in a mice model of disuse-bone loss [27] and fracture healing in an adult rat closed femoral fracture model [28]. In male monkeys, anti-sclerostin antibody increases the duration of bone formation at remodelling sites and increases modelling-based bone formation, while reducing bone resorption [29]. A recent placebo-controlled study in 48 healthy postmenopausal women demonstrated that a single injection of a monoclonal antibody against sclerostin markedly increased bone-formation markers and BMD [30]. Serum N-propeptide of type I collagen (PINP), a sensitive index of bone formation, reached a peak between 14 and 25 days after antibody administration and returned to baseline values after 2 to 3 months. Conversely the bone-resorption marker serum C-terminal crosslinking telopeptide of type I collagen (CTX) decreased to a minimum 14 days after the antibody injection and returned to baseline values after about 2 months.

In summary, sclerostin is a specific osteocyte secreted factor which is an important negative regulator factor of osteoblast function and bone formation both in vitro and in vivo. The measurement of sclerostin may thus be very useful to investigate the activity of osteocyte in vivo and the modulation of their functions by mechanical loading and treatments in osteoporosis and other bone diseases.

II. Circulating sclerostin and bone metabolism

Recently different assays, mostly in-house ELISA tests, have been developed to detect changes of sclerostin in blood. Below are summarized the major clinical findings obtained with these assays.

a. Serum sclerostin in healthy subjects and patients with osteoporosis: Age-related changes and association with bone turnover, BMD and hormones

Serum sclerostin was measured in children including 6-21 yr-old girls (n = 62) and boys (n=56). Children were classified into 5 groups by bone age (BA): Group I (pre-puberty, BA 6- 8 yrs), Group II (early puberty, BA 9-11 yrs), Group III (mid-puberty, BA 12-14 yrs), Group IV (late puberty, BA 15-17 yrs) and Group V (post-puberty, BA 18-21 yrs) [31]. Serum sclerostin levels were slightly higher in the girls prior to puberty, tended to decrease in both sexes during puberty, but remained significantly higher in the boys compared to the girls in Groups III-V. There was little correlation of serum sclerostin with trabecular wrist bone BMD and structural features assessed by peripheral quantitative computed tomography (QCT) in either gender. Conversely, serum sclerostin was inversely associated with cortical thickness and volumetric BMD in girls ($r = -0.34$, $p = 0.007$ for both) and positively correlated with the cortical porosity index in both girls ($r = 0.30$, $p = 0.02$) and boys ($r = 0.41$, $p = 0.002$). These data suggest that in children, sclerostin may play an important role in determining cortical BMD and structure.

Mirza et al [32] measured serum sclerostin in 20 premenopausal women and 20 untreated postmenopausal subjects. They found that serum sclerostin was significantly higher in postmenopausal women than in premenopausal controls (1.16 ± 0.38 vs 0.48 ± 0.15 ng/ml, $p < 0.0001$). Another group of investigators measured serum sclerostin levels in a population-based sample of 123 premenopausal, 152 postmenopausal women not on estrogen treatment and 318 men, age 21 to 97 yrs [33]. In women and in men, serum sclerostin levels increased over-life by an average of 2.4- and 4.6 fold ($p < 0.0001$), respectively. These data suggest that increased sclerostin production by osteocytes may be involved in the age-related impairment of bone formation. Serum sclerostin was found to be positively associated with total BMD in elderly women and men, but not in premenopausal women and younger men [33]. In postmenopausal women, serum sclerostin correlated negatively with total and free estradiol and with intact PTH [32]. Both free estradiol and PTH were independently associated with serum SOST in a multiple variable model. To support these cross-sectional associations the effect of estradiol and intermittent PTH on serum sclerostin was investigated in interventional studies of postmenopausal women.

Four weeks treatment with transdermal 17 beta estradiol resulted in a 27 % decrease of serum sclerostin ($p < 0.001$ vs controls) [34]. Circulating sclerostin levels also decreased significantly in 27 postmenopausal osteoporotic women receiving PTH 1-34 for 14 days (-12.7 %, $p = 0.017$ vs controls) [35]. Interestingly in this latter study, bone marrow plasma and peripheral serum sclerostin levels were significantly correlated ($r = 0.64$, $p < 0.0001$), suggesting that circulating levels may be a good index of local bone production. Conversely, a recent study found no effect of the bisphosphonates alendronate, residronate and ibandronate on serum sclerostin levels, contrasting with the marked reduction in conventional markers of bone turnover [36]. Treatment with nasal calcitonin also does not have any significant effect on serum sclerostin levels (unpublished results).

In summary these clinical data suggest that:

- 1) Serum sclerostin increases with age both in women and men, possibly contributing to the age-related decrease of bone formation,**
- 2) Both estradiol and PTH, two key bone metabolism-regulating hormones, may be important negative regulators of sclerostin secretion in postmenopausal women and**
- 3) Serum sclerostin is poorly associated with bone turnover markers and does not change with bone resorption targeted therapies including bisphosphonate and calcitonin, indicating that its measurements provide additional informations on bone metabolism which are not captured by current biochemical markers.**

b. Serum sclerostin in non-osteoporosis metabolic bone diseases

Immobilization induced bone-loss

Disuse osteopenia is found commonly in immobilized subjects and is characterized by rapid loss which results from an excess of bone resorption which is not associated with a compensatory increase of bone formation. Serum sclerostin was measured in 40 institutionalized postmenopausal women who had a single episode of stroke onset of 6 months or longer and were unable to walk without physical assistance, but had no significant cognitive deficits [37]. Immobilized subjects had serum sclerostin levels which were on average 2.9 fold higher ($p < 0.0001$) than in 40 age-matched postmenopausal controls. Interestingly, in this clinical situation serum sclerostin was strongly negatively correlated with serum bone alkaline phosphatase ($r = -0.91$, $p < 0.0001$), a marker of bone formation, but moderately positively associated with serum CTX ($r = 0.391$, $p = 0.012$).

Arthritis diseases

Ankylosing spondylitis (AS) is an inflammatory disease that predominantly affects axial joints and intervertebral spaces. Local inflammation leads to bony proliferations along the periosteal and enthesal sites. This disease is thus a model of abnormal local increased bone formation. Using immunohistochemistry, it was shown that compared to healthy subjects and patients with rheumatoid arthritis, the expression of sclerostin in the osteocytes of the lumbar of subjects with AS was markedly decreased [38]. Interestingly this local defect in sclerostin expression within the osteocytes was associated with a marked reduction in circulating sclerostin levels. Importantly, low sclerostin levels predicted ankylosis of the spine in AS patients [38]. Decreased expression of sclerostin was also reported in the osteocytes of the subchondral bone of patients hip OA [39] - another condition associated with subchondral bone sclerosis- although no data on serum levels in these subjects was reported.

These data indicate that in pathological human disorders characterized by localized increased bone formation, SOST expression by the osteocytes is decreased. These local alterations can be detected by circulating sclerostin in subjects with AS. Sclerostin mediates some of its effects on bone formation through the Wnt/LRP signaling pathways. Wnt signaling is a key regulator of bone metabolism in RA, OA and AS [40, 41] and sclerostin is highly specific for osteocytes. Thus, its measurement may be more useful than members of the Wnt/LRP family such as Dickkopf-1 which are expressed by several tissues. Serum sclerostin may also be useful in other conditions characterized by focal alterations of bone formation, including myeloma.

Primary hyperparathyroidism

The levels of serum sclerostin, measured by a multi-array electrochemiluminescence assay, were measured in 25 patients with untreated primary hyperparathyroidism (PHPT), 49 patients with cured PHPT after successful parathyroidectomy (PTx) and 77 healthy subjects [42]. Serum sclerostin levels were significantly lower in patients with PHPT than in PHPT subjects after PTx and healthy controls. There was no difference in serum sclerostin between PHPT patients after PTx characterized by normal PTH levels and healthy controls, indicating that treatment was successful in normalizing serum sclerostin. In patients with untreated and treated PHPT, serum sclerostin negatively correlated with serum PTH ($r = -0.44$, $p < 0.0001$), but not with conventional bone turnover markers. These clinical data are consistent with the inhibitory effects of PTH on SOST mRNA in vitro and on the effect of intermittent administration of PTH 1-34 on circulating sclerostin in postmenopausal women [16, 17, 35].

Renal osteodystrophy

Patients with renal osteodystrophy, are characterized by alterations of bone remodelling which, when assessed by histomorphometry, can range from high bone remodelling, as observed for example in case of secondary hyperparathyroidism to very low bone turnover, as seen in patients with adynamic bone diseases. The various forms of bone remodelling abnormalities can vary according to the disease stage and are difficult to assess with current bone markers. Because PTH, one of the regulator of Sclerostin expression, is the key factor mediating the bone remodelling abnormalities in renal osteodystrophy, the measurement of serum sclerostin may be useful in this disease. A recent cross-sectional study showed that in patients with kidney disease on haemodialysis, serum sclerostin was negatively correlated with intact PTH and was a strong predictor of high bone remodelling states and osteoblastic number as assessed by histomorphometry [43]. Thus, the measurements of serum sclerostin, together with intact PTH and bone markers may be useful in the diagnosis of high bone remodelling in renal osteodystrophy.

III. The new TECO ELISA for serum sclerostin.

a. Assay principle

The TECO® Sclerostin EIA Kit is a 96 wells two sites immuno-capture ELISA. The two antibodies used in the ELISA have been raised against human recombinant sclerostin and are highly specific for this molecule. Serum samples or standards (human recombinant sclerostin) are incubated with a biotinylated polyclonal antibody as well as with a Horseradish Peroxidase (HRP)-labelled secondary monoclonal antibody that specifically recognizes human sclerostin in streptavidin coated wells. After the overnight incubation at 2 – 8 °C, the unbound material is washed away. After this washing step, TMB substrate is added to the well which reacts with the HRP and colour is formed. After a 15 minutes incubation, the reaction is stopped with HCl and the plate is read using a plate reader at 450 nm. The amount of colour generated is directly proportional to the amount of sclerostin in the sample.

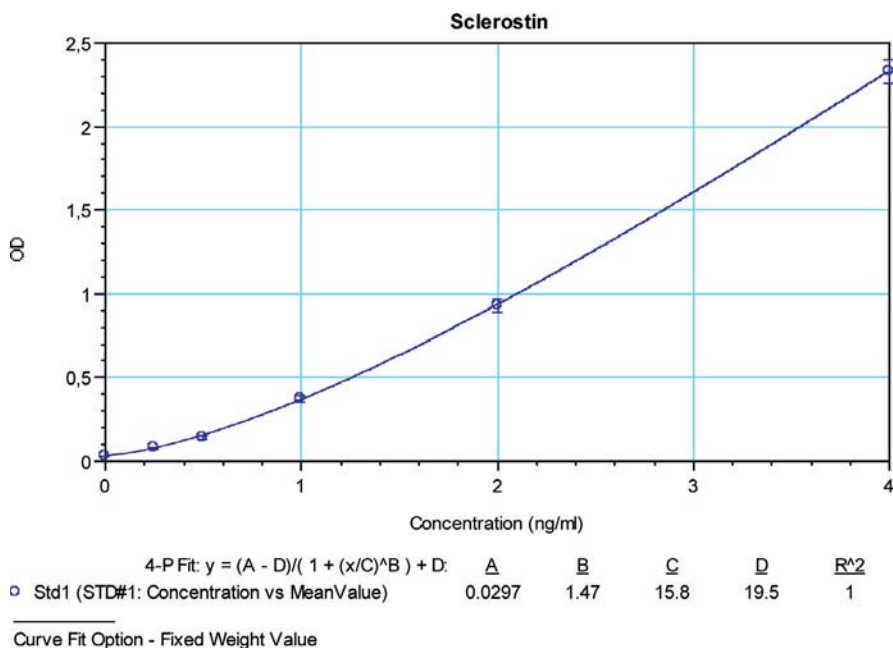
b. Standardization

Recombinant Sclerostin is used as standard material which has been quantified by Amino acid analysis.

c. Technical performances of the TECO ELISA for serum sclerostin.

I. Standard curve

A typical standard curve of the TECO ELISA for serum sclerostin is shown below



II. Lower limit of detection (LLOD)

The mean LLOD, defined as the concentration of sclerostin corresponding to the OD value of standard 0 + 3 standard deviations, is **0.13 ng/ml**.

III. Precision

Intra-Assay variation: (n=12)

Sample	Mean (ng/ml)	SD (ng/ml)	CV (%)
Sample 1	1.83	0.07	4.1
Sample 2	1.07	0.04	3.8
Sample 3	0.77	0.06	8.0
Sample 4	0.48	0.03	6.0

Intra-assay variations are for all samples below 10 %

Inter-Assay variation (n=12 different runs):

Sample	Mean (ng/ml)	SD (ng/ml)	CV (%)
Sample 1	1.79	0.06	3.3
Sample 2	1.00	0.04	4.3
Sample 3	0.63	0.04	6.5
Sample 4	0.46	0.04	9.0

Inter-assay variations are for all samples below 10 %

IV. Linearity

Linearity was assessed by serially diluting serum samples with sample diluent and comparing observed values with expected values. Five different samples with neat values of 1.98, 2.21, 2.48 and 2.61 ng/ml were diluted 2, 4 and 8-fold. Observed recoveries ranged from **103 to 109 %**.

V. Recovery of spiked standards

Recovery of spiked standards was tested by adding different concentrations of human recombinant sclerostin (0.5, 1 and 2 ng/ml) in 8 different serum and plasma human samples presenting with various levels of endogenous sclerostin. Spiked recovery ranged from 88 % to 111 %, indicating that the ELISA recognizes with similar affinity endogenous sclerostin and the human recombinant sclerostin used as standard.

VI. Sample Stability

At 4 °C

Sample	Days					Mean (ng/ml)	SD (ng/ml)	CV (%)
	0	1	2	5	9			
Sample 1	1.64	1.50	1.56	1.56	1.52	1.55	0.06	3.6
Sample 2	0.93	1.02	0.93	0.87	0.89	0.93	0.06	6.5
Sample 3	0.62	0.57	0.59	0.64	0.62	0.61	0.03	4.3
Sample 4	0.50	0.46	0.46	0.47	0.48	0.47	0.02	3.6
Sample 5	0.35	0.33	0.34	0.34	0.34	0.34	0.01	2.5
Sample 6	0.36	0.37	0.38	0.38	0.38	0.37	0.01	2.5

Serum sclerostin is stable up to 5 days at 4 °C

At room temperature

Sample	Days					Mean (ng/ml)	SD (ng/ml)	CV (%)
	0	1	2	5	9			
Sample 1	1.64	1.58	1.64	1.61	1.58	1.61	0.03	1.9
Sample 2	0.93	0.99	1.07	1.02	0.92	0.99	0.06	6.2
Sample 3	0.62	0.65	0.64	0.65	0.66	0.64	0.02	2.4
Sample 4	0.50	0.53	0.50	0.50	0.49	0.50	0.01	2.8
Sample 5	0.35	0.36	0.31	0.30	0.32	0.33	0.03	8.4
Sample 6	0.36	0.29	0.30	0.29	0.27	0.30	0.03	11.4

Serum sclerostin is stable up to 5 days at room temperature.

Freeze and thaw cycles

Sample	Sclerostin (ng/ml) at day 0	Sclerostin (ng/ml) after 3 freeze/thaw cycles	Recovery (%)
Sample 1	1.64	1.54	94
Sample 2	0.93	0.87	93
Sample 3	0.62	0.58	94
Sample 4	0.50	0.49	99
Sample 5	0.35	0.34	95
Sample 6	0.36	0.42	116

Serum sclerostin is stable for up to 3 freeze/thaw cycles

d. Clinical studies with the new TECO sclerostin ELISA

I. Age, menopausal and gender variation of serum sclerostin

Serum sclerostin was measured in 60 premenopausal women (mean age: 44 yrs from 39 to 48 yrs), 60 postmenopausal (mean age: 55.5 yrs from 40 to 88 yrs) belonging to the OFELY study cohort [44] and 18 healthy men (mean age 46 yrs, from 16 to 79 yrs). All premenopausal women had regular menses and serum follicle stimulating hormone levels below 16.7 units. Menopause was defined by an absence of menses for at least 12 months. The mean, SD and minimum and maximum values are shown in the table below.

Group	N	Mean ng/ml	SD ng/ml	Min-max ng/ml
Premenopausal women	60	0.56	0.13	0.35 – 1.75
Postmenopausal women	60	0.69	0.20	0.36 – 0.81
Men	18	0.66	0.18	0.27 – 1.20

In premenopausal and postmenopausal women considered together there was a strong positive association between serum sclerostin and age ($r=0.37$, $p<0.0001$). When pre and postmenopausal women are considered separately, serum sclerostin also increased with age in premenopausal ($r=0.37$, $p<0.001$), but not in postmenopausal women (figures 3, 4, 5). The mean values of serum sclerostin is significantly higher in post than in premenopausal women ($p<0.001$). These data obtained with the new TECO ELISA are in agreement with the studies described above, and suggest that sclerostin may play a role in the age-related decrease of bone formation.

Sclerostin in pre and postmenopausal women

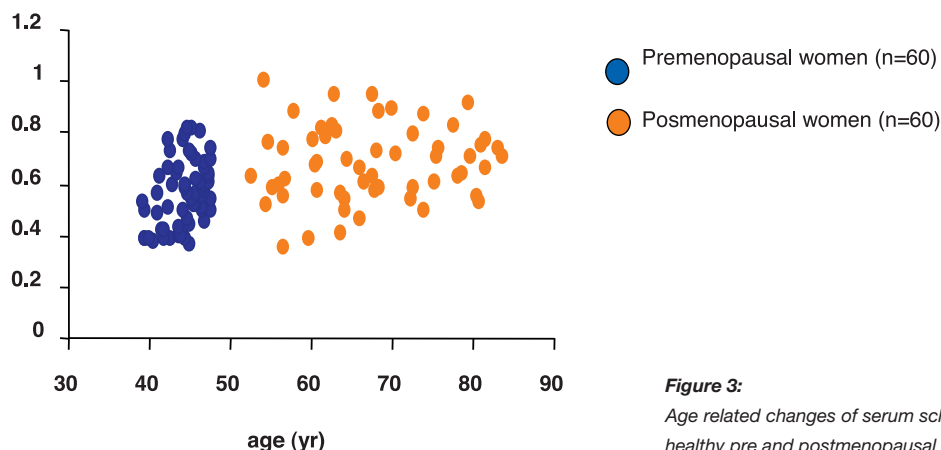


Figure 3:
Age related changes of serum sclerostin by TECO Medical ELISA in healthy pre and postmenopausal women

Age and gender dependence

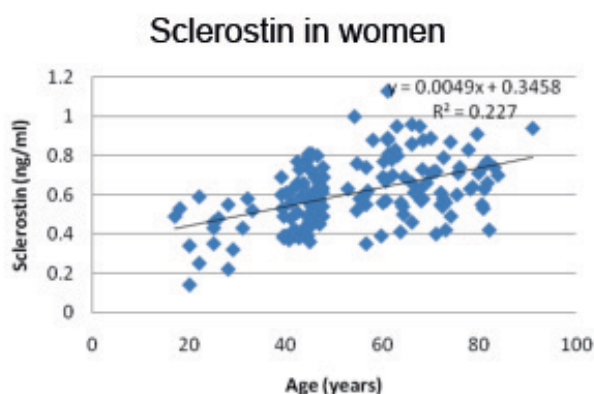


Figure 4

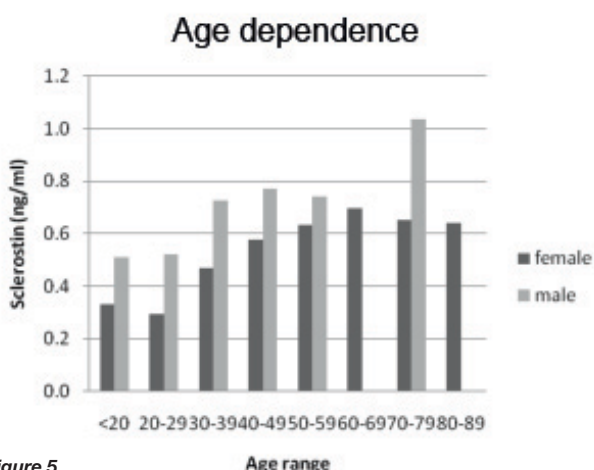


Figure 5

II. Association of serum sclerostin with markers of bone turnover and BMD in healthy subjects.

In the 120 pre and postmenopausal women of the OFELY cohort, serum sclerostin was not correlated with the formation markers, serum PINP and the resorption marker, serum CTX. When pre and postmenopausal women were analysed separately, similar results were observed. An absence of relationship between sclerostin measured by the TECO ELISA and the resorption markers, CTX and TRAP5b, or the formation marker, osteocalcin, was also found in another population including 18 healthy premenopausal women, 20 healthy postmenopausal women and 20 men and in 64 premenopausal women with idiopathic osteoporosis [45].

These data are in agreement with those reported in studies performed with other assays, and indicate that in healthy subjects serum sclerostin provides information on bone metabolism, i.e. osteocyte activity, which is not reflected by conventional bone markers.

In the pre and postmenopausal women of the OFELY study, serum sclerostin did not correlate with total hip and lumbar spine BMD, assessed by DXA. Interestingly, however a recent study reported that serum sclerostin measured by the TECO ELISA was negatively associated with the trabecular bone fraction volume measured by QCT and serum insulin-like growth factor- a potent anabolic growth factor- in 40 healthy premenopausal women [45]. In the OFELY study, serum sclerostin was not associated with fracture risk (IOF abstract). Whether serum sclerostin could predict fracture risk in men remains to be investigated.

III. Serum sclerostin in patients with hypo and hyperthyroidism.

Because PTH is a negative regulator of SOST expression, it may be speculated that in conditions characterized by chronic abnormal parathyroid gland functions such as hypoparathyroidism (HypoPT) and primary hyperparathyroidism (PHPT), serum sclerostin is altered. To test this hypothesis, serum sclerostin was measured in 12 patients with hypo PT (mean age 49 yrs), 13 patients with PHPT (mean age: 64 yrs) and 52 healthy controls (mean age 46 yrs) [46]. As shown on figure 6 serum sclerostin was markedly higher in patients with HypoPT than in healthy age-matched controls ($p < 0.0001$) and subjects with PHPT. These findings are consistent with the inhibitory effect of PTH on SOST expression. In this study, there was however no difference in serum sclerostin between PHPT and healthy controls, contrasting with the decreased levels observed after short-term treatment with exogenous PTH 1-34 of postmenopausal women [35]. This unexpected finding may be related to the difference in age between controls and patients -PHPT subjects being 18 years older than controls- or the fact that in chronic state of PTH excess, sclerostin may not be altered.

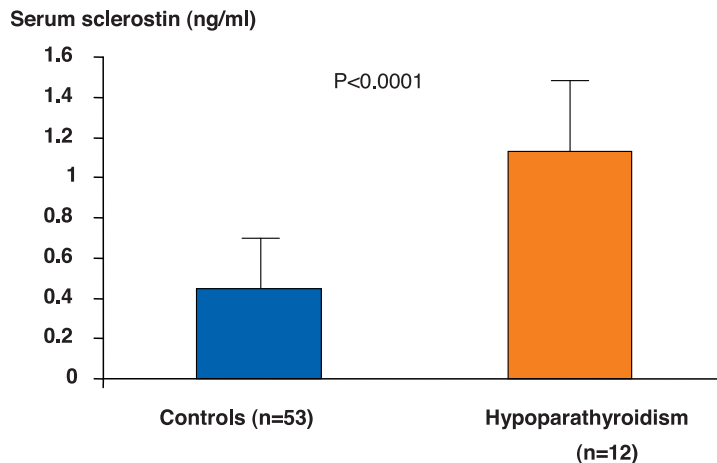


Figure 6:

Serum sclerostin by TECO Medical ELISA in healthy controls and in patients with hypoparathyroidism.

From Costa et al, 2010 [46]

Bars show the mean +1SD

Conclusion

The discovery of the pivotal role of the osteocyte-derived factor sclerostin in osteoblastic function and bone formation is one of the major breakthroughs in bone metabolism of the last few years. Already drugs blocking the inhibitory effect of sclerostin are being developed with very promising preclinical and early clinical data.

The novel TECO ELISA for serum sclerostin allows accurate and precise measurements of this important regulatory factor. Clinical data indicate that this assay is able to detect age-related increases of serum sclerostin in women and men and its modulation by endogenous PTH secretion. This novel assay should thus be useful for a better understanding of biological functions of osteocytes and their regulations by therapies.

The measurement of serum sclerostin may be particularly useful in several clinical applications. These include the investigation of the biological mechanisms responsible for bone alterations in patients with arthritis (RA, AS and OA) and renal osteodystrophy, in combination with conventional bone markers and PTH levels. Another clinical situation where serum sclerostin could add novel and useful information is the monitoring of patients treated with PTH 1-34 or Denosumab. Finally ongoing preclinical and clinical studies will investigate the clinical utility of serum sclerostin in patients with myeloma, haemodialysis and cardio vascular diseases.

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