Sclerostin secreted by osteocytes, key negative regulator of bone formation
Osteocytes inhibit bone formation through sclerostin and stimulate bone resorption through sRANKL.
Osteocytes sense mechanical loading

this inhibits sclerostin expression which indirectly stimulates bone formation
Sclerostin regulation of bone formation

BMP: BoneMorphogeneticProtein
Sclerostin
a specific biochemical marker of osteocyte function

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Clinical Technical bulletin for most important points

**TECO* Technical Bulletin**

**TECO® Sclerostin High sensitive**

**THE ROLE OF SCLEROSTIN IN RENAL BONE DISEASE AND AORTIC VALVE CALCIFICATION**

**Sclerostin is a Key Negative Regulator of Bone Formation**

- Sclerostin is specifically secreted by osteocytes and is a key negative regulator of osteoblast function and bone formation.
- Sclerostin inhibits activation of the Wnt signaling pathway, thereby repressing differentiation and proliferation of osteoblasts.
- PTH, estrogen, and mechanical loading inhibit Sclerostin expression and thereby stimulate bone formation indirectly.
- Clinical trials with monoclonal antibodies against Sclerostin demonstrated a marked increase of bone-formation markers and BMD in women with post-menopausal osteoporosis.

**Sclerostin in Renal Disease**

- Sclerostin serum levels in Chronic Kidney Disease (CKD) patients are up to 4-fold increased compared to patients without CKD.
- Increase with CKD stage and declining kidney function (strong and inverse relationship).
- Renal elimination of Sclerostin increases with declining kidney function.
- In patients on haemodialysis:
  - Sclerostin is negatively correlated with intact PTH and a strong predictor of high bone turnover markers and osteoblast number.
  - Elevated Sclerostin levels are associated with longer life span.

Measurements of Sclerostin, together with intact PTH and bone markers may be useful in the diagnosis of high bone remodelling in renal osteodystrophy.
Clinical metabolic bone disease, detects osteocyte function

- Osteoperosis and therapy
- PTH disease
- Arthritis (Ankylosing spondilytis, OA, RA):
- Diabetes T2
- Cancer
Clinical

**metabolic bone disease**

- **Osteoporosis**: increasing age:
  - Estrogens, PTH:

- **PTH disease**:
  - ↑↑↑ PTH – Primary HyperParaThyroidism
  - (Costa et al, 2010, with TecoM assay)
  - ↓↓↓ PTH – HYPOparathyroidism -
  - (Costa et al, 2010, with TecoM assay)

- **Arthritis** (Ankylosing spondylitis, OA, RA):

- **Diabetes T2**, osteoblastic activity ↓↓↓:

- **Prostate cancer**, Multiple myeloma:
  - MM: Sclerostin a marker for altered bone turnover, therapy target
  - MM: TRAP5B is established as best marker for disease progression and monitoring the efficacy of therapy
Clinical chronic kidney disease (CKD)

- Sclerostin up to 4-fold increased compared to normals
- Sclerostin increases with CKD stage and declining kidney function
- Renal elimination of Sclerostin increases with declining kidney function.

![Graph showing increase in Sclerostin with decreasing CKD stage.](image-url)
Clinical haemodialysis patients

⇒ Sclerostin is negatively correlated with intact PTH and a strong predictor of high bone remodelling states and osteoblastic number
⇒ Elevated Sclerostin levels are associated with longer life span.
Clinical

Measurements of Sclerostin, together with intact PTH and bone markers may be useful in the diagnosis of high bone remodelling in renal osteodystrophy.
**Clinical Therapy**

**Conventional bone therapy**

- Estradiol - Sclerostin ↓↓↓↓
- Raloxifene - Sclerostin ↓↓↓↓
- PTH 1-34 administration - Sclerostin ↓↓↓↓
- Biphosphonates - Sclerostin ↔

**Hypoparathyroidism**

- PTH 1-84 administration - Sclerostin ↓↓↓↓

![Graph showing the effect of PTH 1-84 administration on Sclerostin levels.](chart.png)

- Minutes post-injection of PTH 1-84
- % change:
  - 30 minutes: -8.6
  - 60 minutes: -11.3
  - 120 minutes: -16.1

* p=0.03
Aortic Valve Calcification (AVC)

- Calcification of the aortic valve increases with age and can lead to an aortic stenosis, which blocks the flow of blood from the heart to the brain.
Vascular and Aortic Valve calcification

- Vascular & AV Calcification in > 25% of elderly over 65 yrs.
- AV Stenosis (moderate to severe valve obstruction) > 2%
- Associated with 50% increased risk of cardiovascular event
- Main cause of heart valve replacement in elderly

Clinical Factors Associated With Calcific Aortic Valve Disease
STEWART BF et al. JACC Vol. 29, No. 3 March 1, 1997:630-4 630
VC and AVC in CKD

- VC/AVC seems an actively regulated process that shares morphological similarity with bone formation, with sclerostin playing a key role.
- VC/AVC is common in CKD, driving the enormously elevated cardiovascular mortality in patients with CKD, ESRD renal transplant recipients.
- High circulating Sclerostin is associated with improved survival in haemodialysis and R transplant recipients.
Role of Sclerostin in AVC

- Sclerostin mRNA was found in AV tissue: SOST upregulated
- ICH >> local sclerostin production and deposition in calcified valves >> negative staining in control valves
Role of Sclerostin in AVC

- Patients with echocardiographically proven AVC (n = 115) showed increased Sclerostin serum levels compared to healthy controls, and the severity of AVC correlated to increased Sclerostin levels.
Important: Calcification is not caused by sclerostin – sclerostin has the opposite effect to suppress/reduce calcification; therefore sclerostin is possibly part of a local counterregulatory mechanism directed to suppress VC.
I. AVC baseline score predicts progression into severe AVC*

II. AVC progression predicts future cardiovascular events and lifetime*

III. Low sclerostin means high AVC at baseline*

IV. Higher sclerostin at baseline predicts less AVC progression and longer life span.

“je mehr Sclerostin, desto länger ist das Überleben” – Prof. Brandenburg, Aachen

*Evenepoel et al. Sclerostin serum levels and vascular calcification in prevalent renal transplant recipients: a longitudinal cohort study. Sclerostin and vascular calcification in RTRs. Submitted
Sclerostin as target for osteoporosis therapy

- Clinical trials with monoclonal antibodies against Sclerostin demonstrate a marked increase of bone-formation markers and Bone Mineral Density in women with post-menopausal osteoporosis
  - Blosozumab (Eli Lilly and Company): Phase II
  - Romosozumab (AMG 785, Amgen & UCB): Phase III
  - Similar anti-Sclerostin mAB under development by Novartis
Sclerostin as target for therapy

Increased sclerostin action is thought to be involved in osteoporosis.

Using specific sclerostin antibodies should neutralize sclerostin and its antagonist effect on bone formation resulting in an increase of bone mass.

So far this concept seems to have a positive effect in osteoporotic patients.

However
Sclerostin as target for therapy

Sclerostin is also associated with very positive effects:

a) Produced in calcified aortic valve tissue – probably in a local counterregulatory mechanism directed to suppress valve calcification

b) Elevated sclerostin levels are associated with longer life span in hemodialysed (HD) patients

**Question 1:** What is the (side-) effect of anti-sclerostin on Aortic Valve Calcification in elderly and CKD/HD patients?

- Does it negatively impact life span of HD pts. + AVC?
- Is this safe for elderly with AVC?
**Question 2:** Most osteoporosis patients tend to be elderly and have some degree of renal impairment, making it safe to assume elevated serum sclerostin levels will be found in patients receiving antisclerostin treatment.

It is unknown whether patients with CKD require higher doses of antisclerostin antibodies to counter the increase in serum sclerostin levels to achieve optimal treatment effects.

Thus, pharmacokinetic/pharmacodynamic studies with antisclerostin antibodies in patients with CKD will be needed.
Articles

- Evenepoel et al. Sclerostin serum levels and vascular calcification in prevalent renal transplant recipients: a longitudinal cohort study. Sclerostin and vascular calcification in RTRs. Submitted
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