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Sclerostin High Sensitive

The role of Sclerostin in bone disorders, Chronic Kidney Disease and calcification processes

- Sclerostin is a key negative regulator of bone formation
- Inhibition of Sclerostin stimulates bone formation
- Predictive of improved survival in hemodialysis and renal transplant patients
- Elevated serum Sclerostin levels indicate calcification

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SCLEROSTIN

Sclerostin is a glycoprotein encoded by the SOST gene and secreted by osteocytes. It is involved in bone formation, Chronic Kidney Diseases and calcification of e.g. Vascular and Aortic Valves.

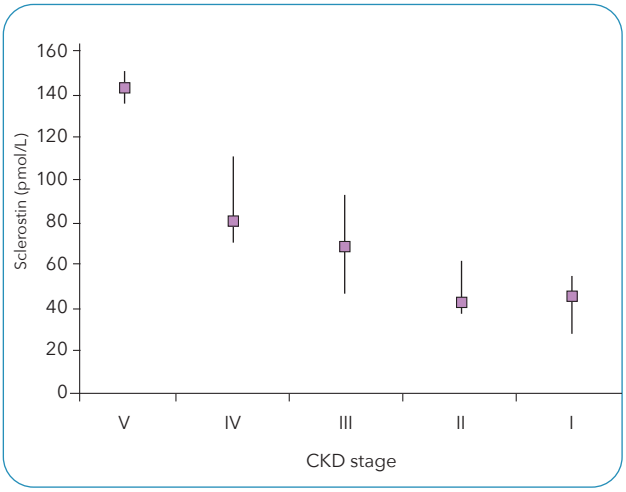
SCLEROSTIN IS A KEY NEGATIVE REGULATOR OF BONE FORMATION

> Sclerostin is specifically secreted by osteocytes, inhibiting osteoblast function and bone formation.
> Sclerostin levels in serum reflect the levels in bone marrow.
> PTH, estrogen, and mechanical loading inhibit Sclerostin expression and thereby stimulate bone formation [2].

SCLEROSTIN IS INCREASED IN RENAL DISEASE

> In Chronic Kidney Disease (CKD), Sclerostin is up to 4-fold increase compared to patients without CKD.
> Sclerostin increases with CKD stage and declining kidney function [3].

In table 1 additional results and conclusions from studies measuring Sclerostin in serum of patients with Chronic Kidney Diseases are summarized.

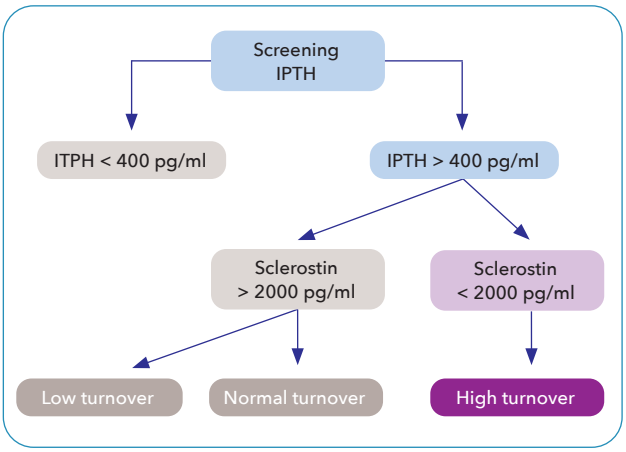


Adapted from Pelletier et.al., 2013 [3]

SCLEROSTIN IN PATIENTS ON HEMODIALYSIS

> Sclerostin is negatively correlated with intact PTH and a strong predictor of high bone remodeling states and osteoblastic number. The algorithsm depicted from the publication by Cejka [4] is proposing a diagnostic strategy to diagnose osteodystrophy in dialysis patients.
> Elevated Sclerostin levels are associated with longer life span [5].

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

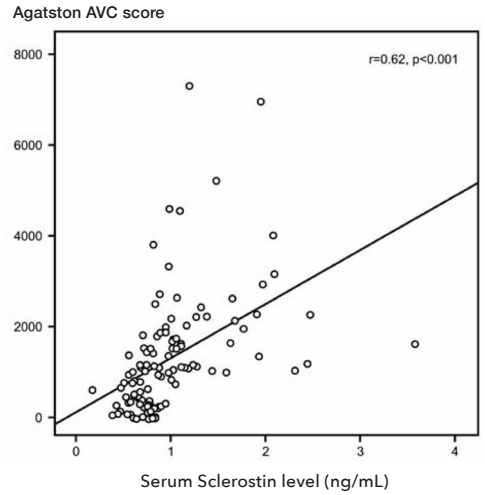


Adapted from Cejka et.al., 2014 [4]

SCLEROSTIN IS AN IMPORTANT PLAYER IN VASCULAR AND AORTIC VALVE CALCIFICATION

> Recent studies indicate that Sclerostin is an important player in Aortic Valve (AV) & Vascular Calcification (VC).
> Immunohistochemistry (IHC) and PCR data demonstrated an association between the presence of AVC and local Sclerostin production/deposition in aortic valves, indicating a role of Sclerostin in AVC.
> Patients with echocardiographically proven AVC (n = 115) showed increased Sclerostin serum levels compared to healthy controls; The severity of AVC correlated with increased Sclerostin levels [6].
> VC/AVC seems an actively regulated process that shares morphological similarity with bone formation, with Sclerostin playing a key role.

Additional publications listed in table 2 confirm the value of measuring Scleostin as indicator of calcification.



Serum Sclerostin levels as a function of AVC severity [6].

High circulating Sclerostin levels are associated with improved survival in hemodialysis and renal transplant recipients

> VC/AVC is common in CKD and drives the enormously elevated cardiovascular mortality in patients with CKD, End Stage Renal Disease and renal transplant recipients.
> High circulating Sclerostin levels are associated with improved survival in hemodialysis and renal transplant recipients [7]

ALL RECENT DATA SUPPORT THE THESIS THAT:

> Sclerostin is up-regulated in the vascular wall during Vascular and Aortic Calcification as part of a local counter-regulatory mechanism directed to suppress calcification.
> Higher Sclerostin levels are predictive of longer survival.

Table 1: Studies analyzing the clinical value of measuring Sclerostin in patients with Chronic Kidney Disease

1st Author	Title	Journal	Year	Page	Study details	Conclusion by the authors	Legend
Brandenburg, VM.	From skeletal to cardiovascular disease in 12 steps-the evolution of Sclerostin as a major player in CKD-MBD	Pediatr Nephrol. 2015 Mar 4. [Epub ahead of print] PMID 25735207	2015	-	Review	In conclusion, Sclerostin has made its way down the road from the bone niche to the cardiovascular field. Due to its strong links to CKD, Sclerostin qualifies as a novel mediator of CKDMBD. Based on our current knowledge, Sclerostin may be considered as one of the driving forces of the calcification paradox in the bone-vascular axis. The available data about Sclerostin and CKD-MBD as summarized in the present review originate solely from studies in adults.	CKD-MD (Chronic Kidney Disease – Mineral and Bone Disorder)
Moysés, RM.	Sclerostin, Osteocytes, and Chronic Kidney Disease - Mineral Bone Disorder	Semin Dial. 2015 Aug 19. [Epub ahead of print] PMID 2628812	2015	-	Review	In patients with Chronic Kidney Disease (CKD), serum levels are elevated several fold relative to healthy individuals. Emerging data suggest that these changes are associated with increased fracture rates.	CKD (Chronic Kidney Disease)
Desjardins, L.	Uremic toxicity and Sclerostin in Chronic Kidney Disease patients	Néphrologie & thérapeutique	2014	20 - 24	140 CKD stages 2-5D	Our results indicate that Sclerostin levels are elevated in CKD patients and are associated with inflammation, vascular lesions, uremia and (potentially) mortality.	CKD (Chronic Kidney Disease)

Table 2: Studies analyzing the clinical value of measuring Sclerostin as indicator of calcification

1st Author	Title	Journal	Year	Page	Study details	Conclusion by the authors	Legend
Kuipers, AL.	Association of circulating Sclerostin with Vascular Calcification in Afro-Caribbean men	Atherosclerosis	2015	218–223	191 men / serum & CT of CAC and AAC / Multivariable logistic regression models	This is the first study to show that, among Afro-Caribbean men, greater serum Sclerostin concentrations were associated with prevalence and extent of CAC.	CAC (Coronary Ateria Calcification)
Paccou, J.	The relationships between serum Sclerostin, bone mineral density, and vascular calcification in Rheumatoid Arthritis	The Journal of clinical endo-crinology and metabolism	2013	219–229	67 chronic HD pts / MS-CT	Serum Sclerostin levels were significantly and independently associated with AAC in RA patients.	RA (rheumatoid arthritis) ; AAC (abdominal aortic calcification)
Brandenburg, VM.	Relationship between Sclerostin and Cardio-Vascular Calcification in hemodialysis patients: a cross-sectional study	BMC nephrology	2013	317–325	115 patients; echocardiographi-cally proven AVC	We found a strong association of Sclerostin with calcifying aortic heart valve disease in haemodialysis patients. Sclerostin is locally produced in aortic valve tissue adjacent to areas of calcification.	HD (hemodialysis); MS-CT (multi-slice computed tomogpraphy)
Koos, R.	Sclerostin as a potential novel biomarker for Aortic Valve Calcification: an in-vivo and ex-vivo study	The Journal of heart valve disease	2013	3024–3030	100 HD patients / survival analysis	Patients with AVC showed increased Sclerostin serum levels ompared to a healthy reference population, and it was revealed that the severity of AVC may be linked to increased Sclerostin serum levels. Moreover, the PCR and staining data demonstrated an increased Sclerostin expression in parallel to prototypic markers of osteogenic transdifferentiation, indicating a role of Sclerostin in the valvular calcification process.	AVC (Aortic Valve Calcification)

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Sample type	Plasma (heparin plasma preferred sampel type), Serum, Cell culture					
Sample preparation	Samples should be collected without hemolysis.					
Reference values	Subjects	Mean (ng/ml)	SD (ng/ml)	Mean (pmol/l)	SD (pmol/l)	N
	Pre-menopausal female	0.48	0.14	21.12	6.16	20
	Post-menopausal female	0.58	0.17	25.52	7.48	19
	Men	0.64	0.15	38.16	6.6	10

References:

[1] Recker, Robert R.; Benson, Charles T.; Matsumoto, Toshio; Bolognese, Michael A.; Robins, Deborah A.; Alam, Jahangir et al. (2015): A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density. In: Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 30 (2), S. 216–224

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[5] Viaene, Liesbeth; Behets, Geert J.; Claes, Kathleen; Meijers, Bjorn; Blocki, Franck; Brandenburg, Vincent et al. (2013): Sclerostin: another bone-related protein related to all-cause mortality in haemodialysis? In: Nephrol Dial Transplant. 28 (12), S. 3024–3030.

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