Serum Dickkopf-1 And Calcium Deposition in Aortic Valve Are Significantly Related To The Presence Of Concomitant Coronary Atherosclerosis In Patients With Symptomatic Calcified Aortic Stenosis

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BACKGROUND I.

- Calcified aortic valve disease is a progressive mineralization of aortic valve.
- Every 50th of individuals ≥ 65 years old has calcified aortic stenosis (CAS), with 80% progressing to symptoms requiring a surgery.
- The most significant predictor of clinical progression of calcified aortic valve disease is the load of calcium in aortic valve.

BACKGROUND II.

- The process of calcium deposition in aortic valve is a multi-factorial event where several pathways interact and influence disease progression.

- OPG (Osteoprotegerin) / RANKL (Receptor Activator Of Nuclear Factor Kappa B Ligand) / RANK cytokine axis and Dickkopf-1 (Dkk-1) signaling might be along the causal pathway in regulation of valvular calcification in CAS.

PURPOSE

- The study was designed to assess serum RANKL, OPG, Dkk-1 and deposition of calcium in aortic valve in relation to the presence of concomitant coronary atherosclerosis in patients with symptomatic CAS.

METHODS

- Study group consisted of 218 consecutive patients who were undergoing cardiac catheterization being considered for AVR for symptomatic CAS.

- The history of CKD was an exclusion criterion because causing disorder of mineral metabolism, and extra-skeletal calcifications.

Baseline characteristics of patients with symptomatic CAS and **without** or **with** concomitant coronary atherosclerosis.

	Group A N=112	**Group B** N=106	**P-value**
Age years, mean (SD)	69.7 (11.5)	75.7 (8.7)	<0.001
Men N (%)	60 (53.6)	63 (59.4)	0.657
Obesity N (%)	43 (38.7)	34 (32.4)	0.633
Hyperlipidemia N (%)	37 (33.0)	38 (35.9)	0.892
Hypertension N (%)	70 (62.5)	83 (78.3)	0.024
Diabetes mellitus N (%)	33 (29.5)	43 (40.6)	0.172
Smoking (anytime) N (%)	26 (23.4)	41 (39.4)	0.081
IACE therapy N (%)	42 (37.5)	43 (41.0)	0.895
ARB therapy N (%)	12 (10.71)	20 (19.05)	0.170
Statin therapy N (%)	33 (23.7)	51 (48.6)	0.011

METHODS

Values of circulating OPG, sRANKL, Dkk-1 and deposition of calcium in aortic valve were compared between:

- **Group A** - patients **without** concomitant coronary atherosclerosis (angiographically normal coronary arteries)
- **Group B** - patients **with** concomitant **coronary atherosclerosis** (angiographically confirmed coronary artery stenosis ≥ 50%).

METHODS

- Agatston score and calcium mass of aortic valve were assessed by using 256-slice Brilliance iCT (Philips Medical Systems).

RESULTS

Comparison of studied compounds between patients with CAS and ± concomitant coronary atherosclerosis

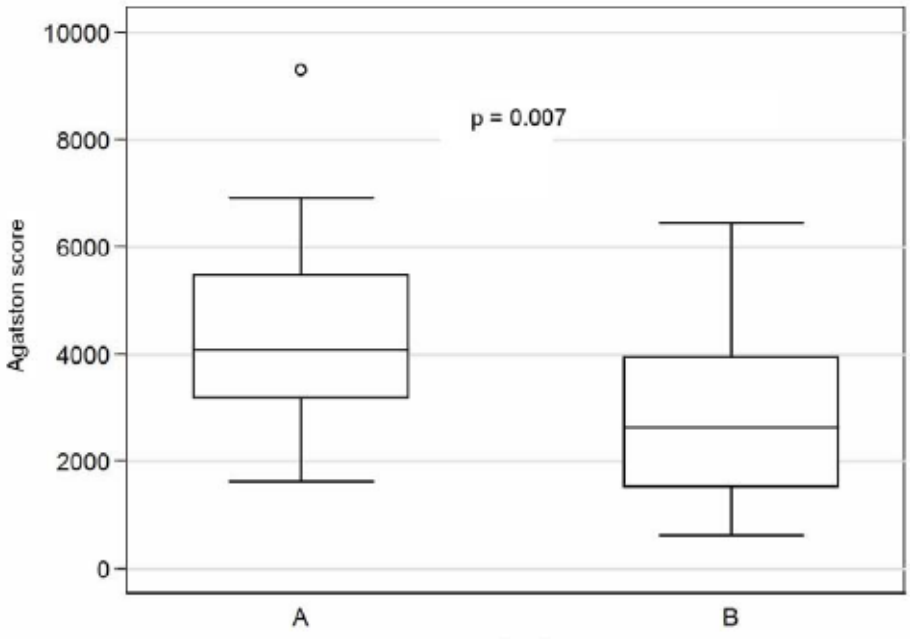
Variable	A (N=112)	B (N=106)	P-value	P_1-value	P_2-value
OPG (pmol/l); gmean (95% C.I.)	6.06 (5.58; 6.58)	7.27 (6.74; 7.84	0.007	§0.227	§§0.321
sRANKL (pmol/l); gmean (95% C.I.)	121.43 (103.37; 142.64)	92.24 (73.35; 115.99)	0.563	¶0.998	¶¶0.999
Dkk-1 (ng/ml); gmean (95% C.I.)	1.44 (1.25; 1.66)	1.01 (0.87; 1.17)	0.004	#0.010	##0.016

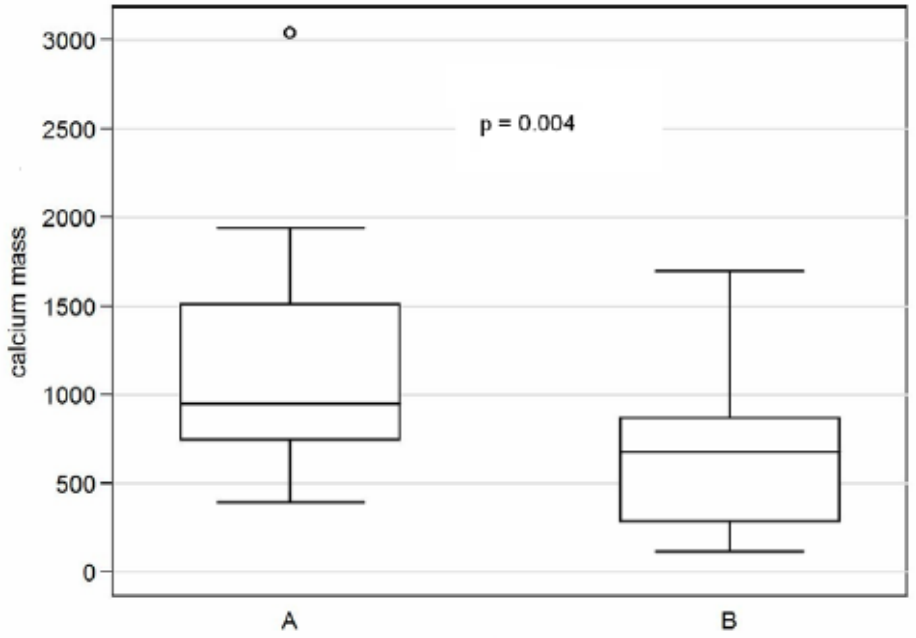
P-value for comparison A and B

P_1-value for comparison A and B after adjustment for age;

P_2-value for comparison A and B after adjustment for age and diabetes mellitus;

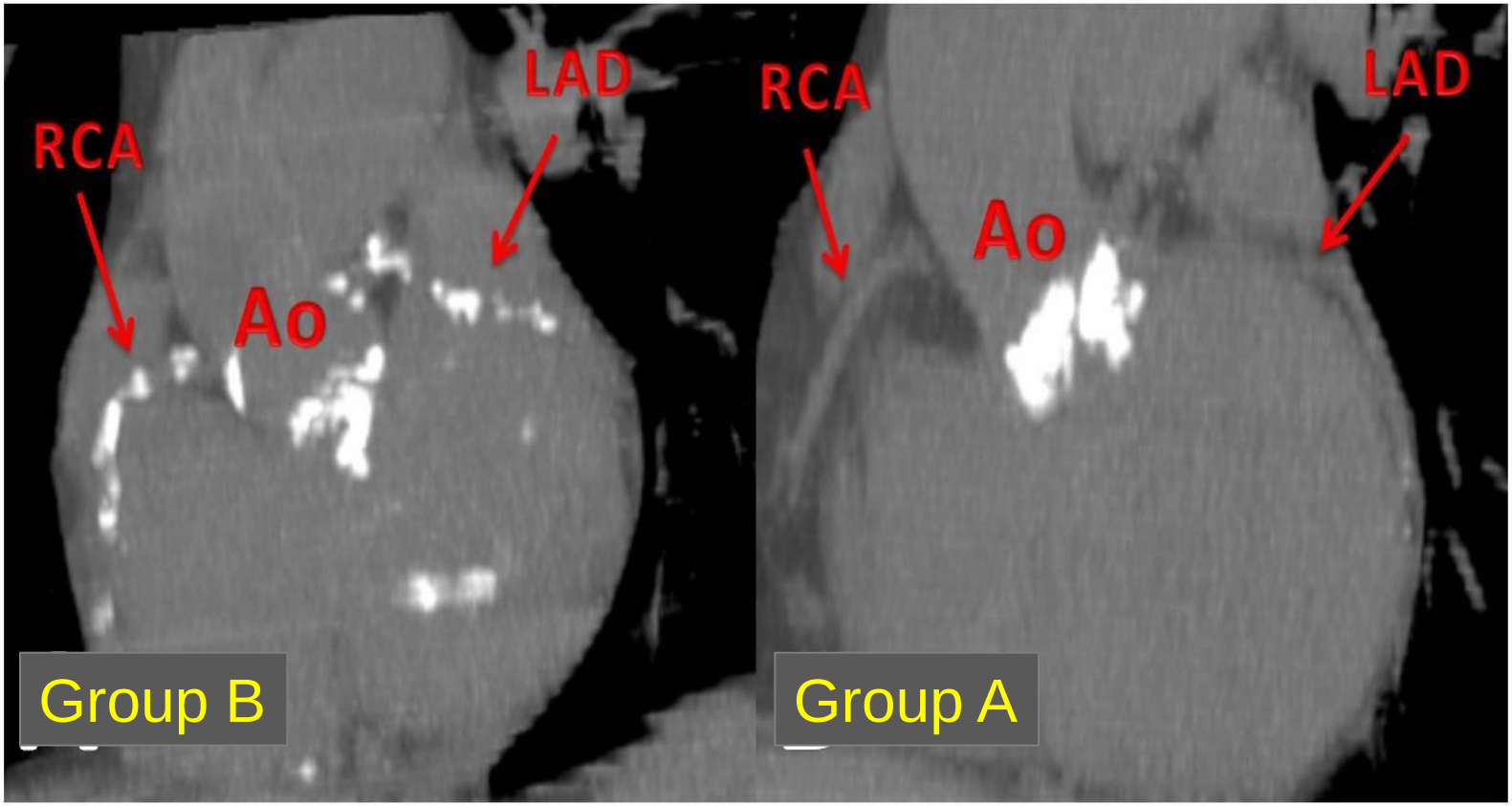
Calcium deposition in aortic valve in patients with CAS in relation to the presence of concomitant coronary atherosclerosis





Demonstration of typical noncontrast CT study of

- Group A - patient with severe CAS and without concomitant coronary disease, in contrast with
- Group B – patient with severe CAS and extensive diffuse coronary calcifications.

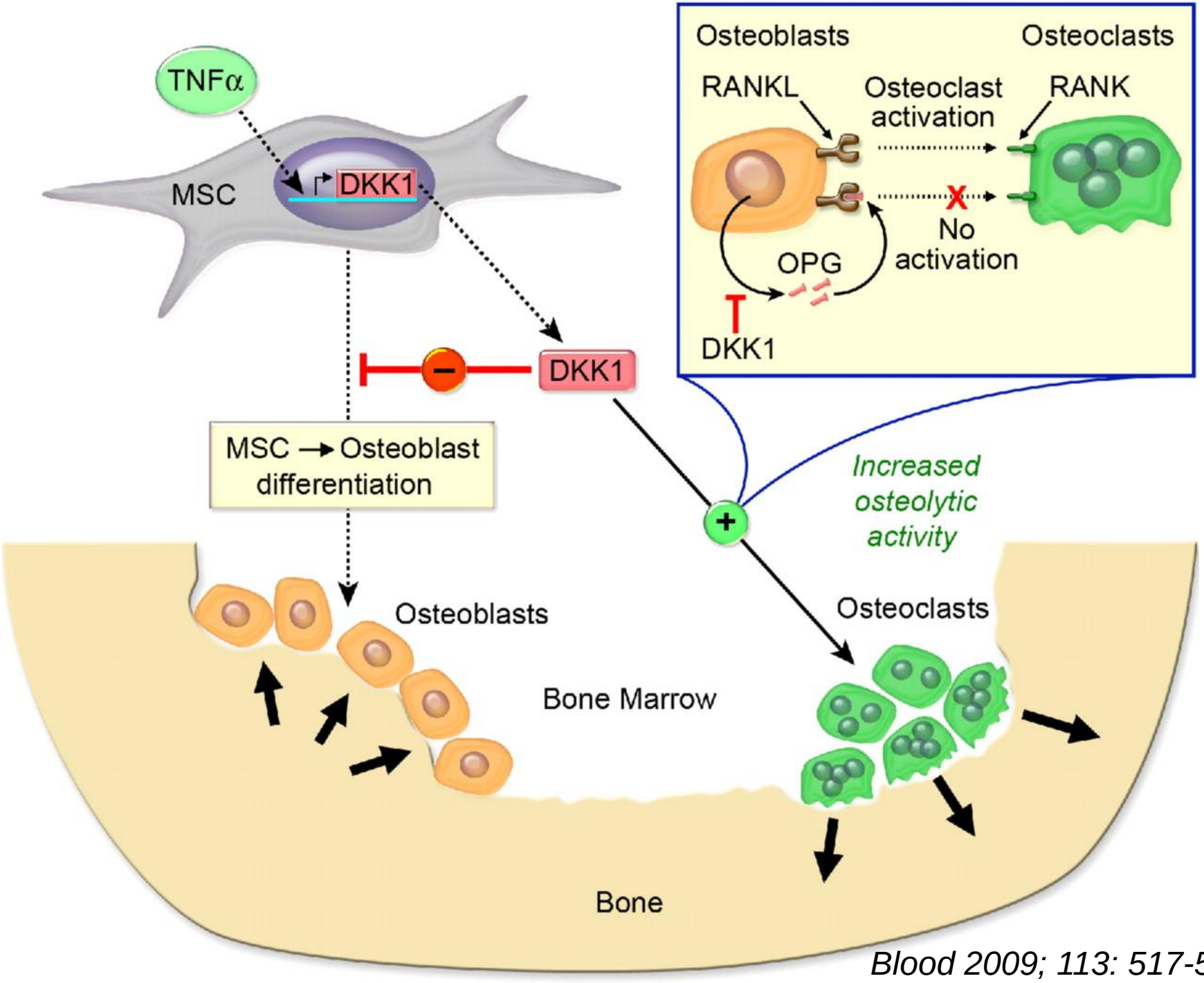


CONCLUSION

- Circulating Dkk-1 and calcium deposition in aortic valve **differ significantly in relation to the presence of coronary atherosclerosis** in patients with symptomatic CAS.
- A positive association was found between serum Dkk-1 and calcium load in aortic valve in patients with symptomatic CAS and angiographically normal coronary arteries.

CLINICAL IMPLICATIONS

- Clinical observational studies showed that aortic valve calcification is inversely correlated with low bone tissue mineral density.



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FUTURE

- It was shown that agents that block bone resorption in animal models also block vascular calcification.
- Monoclonal neutralizing anti-Dkk-1 antibody reduces osteolytic bone resorption and increases bone formation in multiple myolema.
- Our results suggest that it might be interesting for further research examining the potential impact of Dkk-1 antagonists on progression of calcified aortic valve disease.

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METHODS

- Agatston score and calcium mass of aortic valve were assessed by using 256-slice Brilliance iCT (Philips Medical Systems).
- Scans were performed with prospective ECG gating at 75% of RR interval. Standardized protocol for calcium scoring was used.
- For quantification, the data were transferred to commercially available workstation Brillance Workspace Portal v.2.6.0.27 (Philips Medical Systems, Best, The Netherlands).