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Sclerostin - A New Biomarker Studied In Patients With CKD And On HD Treatment

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Summary :
Sclerostin is a relatively new bone biomarker - a small protein that is synthesized in osteocytes. Sclerostin exerts its effects by binding to membrane receptors found on the plasmalemma of osteoblasts. Sclerostin has antianabolic effects on bone formation. Thus, it inhibits bone formation by regulating osteoblast function. Sclerostin production is inhibited by parathyroid hormone and by certain cytokines, including prostaglandin E2. Its production is stimulated by calcitonin.
The main objective of our study was to compare serum sclerostin values in predialysis patients and patients undergoing hemodialysis treatment.
In clinic of nephrology and dialysis in UMHAT "St.Marina" Varna - Bulgaria a comparative analysis of serum sclerostin values in predialysis patients (control group) and patients undergoing dialysis treatment was performed.
A total of 89 patients were studied - 59 on HD and 30 - control group.
The results showed that patients undergoing extracorporeal treatment had up to 3 times higher serum sclerostin values compared to the control group - pre-dialysis patients, and in terms of sex characteristics, men had higher serum sclerostin values than women.
The study demonstrates that in patients with CKD, renal elimination of sclerostin increases with decreasing renal function. In patients undergoing dialysis, sclerostin was an independent predictor of bone loss. Serum sclerostin levels correlated significantly with age and were higher in men than in women.
Key words : *sclerostin , bone mineral disorders, chronic kidney disease, predialysis patients, hemodialysis treatment.*

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I. Introduction

Patients with CKD on haemodialysis treatment are at risk of complications such as anaemia, electrolyte disturbances (e.g. hyperkalaemia, hyperphosphataemia) and CKD-BMD, including secondary hyperparathyroidism, changes in vitamin D activation and renal osteodystrophy. Control of elevated serum phosphorus, calcium levels, restoration of vitamin D levels, and suppression of PTH production remain targets for effective treatment of CKD-BMD.

Sclerostin is a relatively new bone biomarker, a small protein that is synthesized in osteocytes. It exerts its effects by binding to membrane receptors located on the plasmalemma of osteoblasts. Sclerostin has antianabolic effects on bone formation.(1);(3); It thus inhibits bone formation by regulating osteoblast function. Its production is inhibited by parathyroid hormone and by some cytokines, including prostaglandin E2, and is stimulated by calcitonin.Increased serum levels result from increased production of sclerostin in uremic patients, which has been demonstrated using immunohistochemical staining in bone biopsies of patients with CKD. The mechanisms underlying increased bone biomarker production in chronic kidney disease are unknown. PTH - receptor signaling is a known inhibitor of sclerostin expression. However, serum sclerostin levels are approximately twice as high in dialysis patients with bone disease compared with healthy individuals. Sclerostin concentrations are increased in disorders such as: hypoparathyroidism, Paget's disease, multiple myeloma, and in cancer-induced bone disease, and are decreased in primary hyperparathyroidism, as well as by mechanical stimulation of the bone.(2);(4) There are no data on sclerostin metabolism. Because sclerostin expression is reduced by mechanical loading of the skeleton, low physical activity, which is common in patients with renal disease and may cause sclerostin-serum levels to rise.(5);(6)

Blocking sclerostin in humans by antibody administration is considered to be a promising mechanism enhancing physiological processes of mineralization in bone through osteoanabolic properties that stabilize bone mineral density in postmenopausal osteoporosis. Intracellular signaling processes are also involved in cardiovascular development and in cardiovascular disease processes such as smooth muscle cell proliferation

and atherosclerosis (7);(8);

II. Objective

The main objective of our study was to compare serum sclerostin levels in predialysis patients and patients undergoing hemodialysis treatment and to evaluate the effect of treatment with etelcalcetide (Parsabiv) on serum sclerostin levels in hemodialysis patients.

III. Material

In the Clinic of Nephrology and Dialysis of the University Hospital "St. Marina"Varna – Bulagaria fot the firtst time comparative analysis of serum sclerostin values in predialysis patients (control group) and patients undergoing dialysis treatment was performed.

A total of 89 patients were studied - 59 on HD and 30 - control group.

The assay used to measure sclerostin levels was performed by ELISA (Enzyme-linked immunosorbent assay) on fully automated equipment and using the manufacturer's protocols (Biomedica Medizinprodukte GmbH & Co, Wien, Austria). According to the instruction manual for the Human Sclerostin HS EIA kit provided by Biomedica (Vienna, Austria), the reference limits for sclerostin are 0-240 pmol/L or 0 - 5.40 pg/mL.

IV. Results

When comparing the sclerostin values of the control group and the HD treatment group, a statistically significant difference was found ($p<0.001$).

Table 1. Descriptive statistics of serum sclerostin in control group and HD treatment group

		pc	Average	median	Standard deviation	Std. Error
Sclerostin value pmol/l	HD	59	207	201	52.9	6.89
	Control group	30	61.5	63.5	17.5	3.20

Table 2. Comparison of serum sclerostin values in control group and HD treatment group

Independent Samples T-Test																	
	95% Confidence Interval																
			Statistic		df		p		Mean difference		SE difference		Lower		Upper		
Sclerostin value pmol/l		Student's t		14.6	[a]	87.0		< 0.001		145		9.95		125		165	

The results showed that patients undergoing extracorporeal treatment had up to 3 times higher serum sclerostin values compared to the control group - predialysis patients (Fig. 1).

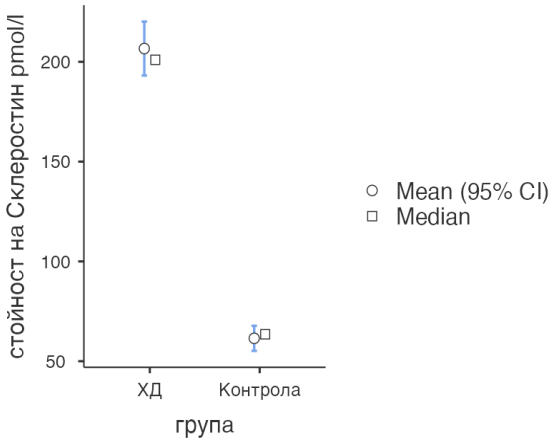

Fig. 1. Comparison of serum sclerostin values in control group and HD treatment group

Table 3. Descriptive statistics of serum sclerostin by sex in control group and HD treatment group

		pc	Average	median	Standard deviation	Std. Error
Sclerostin value pmol/ll	ж	40	132	156	54.7	8.65
	м	49	179	215	94.0	13.4

From the comparative analysis of serum sclerostin values by sex, statistical significance (p<0.001) was found (Table 4).

Table 4. Comparison of serum sclerostin values by sex

					95% Confidence Interval	
		Statistic	p	Mean difference	Lower	Upper
Sclerostin value pmol/l	Mann-Whitney U	594	0.001	-56.0	-82.0	-

From the analysis of the results, it was found that in terms of sex characteristics, men had higher values of serum sclerostin than women (Fig. 2).

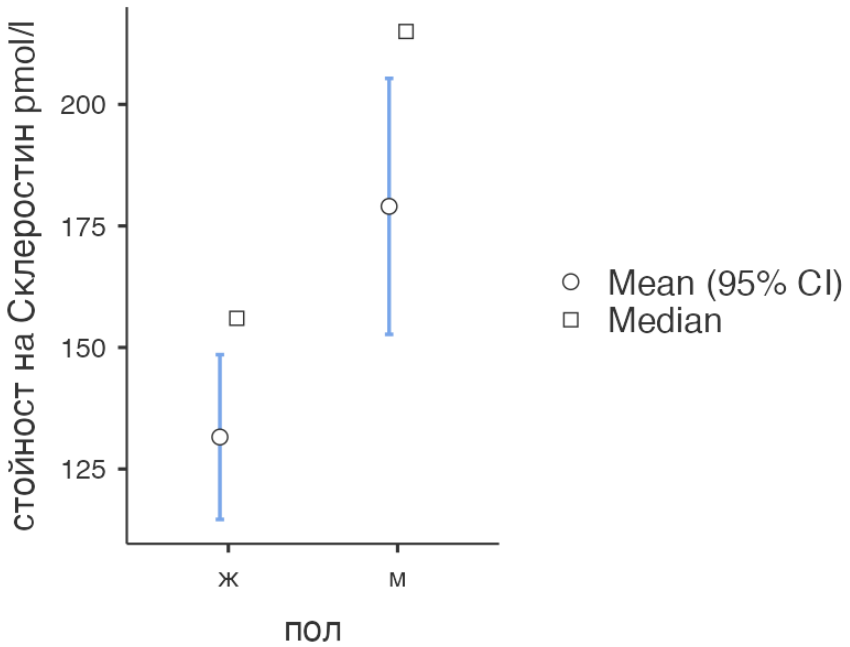

Fig. 2. comparison of serum sclerostin values by sex

The effect of etelcalcetide (Parsabiv) treatment on serum sclerostin levels in hemodialysis patients was evaluated.

A descriptive characterization of sclerostin levels in hemodialysis patients with and without Parsabiv treatment is presented in Table 5.

Table 5: Descriptive statistics of serum sclerostin in patients with and without Parsabiv treatment						
		pc	Average	median	Standard deviation	Std. Error

Table 5: Descriptive statistics of serum sclerostin in patients with and without Parsabiv treatment

		pc	Average	median	Standard deviation	Std. Error
Sclerostin value pmol/l	HD without treatment with Parsabiv	32	131	124	19.3	3.41
	HD with Parsabiv treatment	27	251	256	39.7	7.64

The comparative analysis again revealed a statistically significant difference (p<0.001) (Table 6) (Figure *3).*

Table 6. comparison of serum sclerostin values in HD patients on Parsabiv treatment and HD patients without Parsabiv treatment

						95% Confidence Interval	
		Statistic	df	p	Mean difference	SE difference	Lower	Upper
Sclerostin value pmol/l	Student's t	-15.1 [a]	57.0	<0.001	-120	7.93	-136	-104

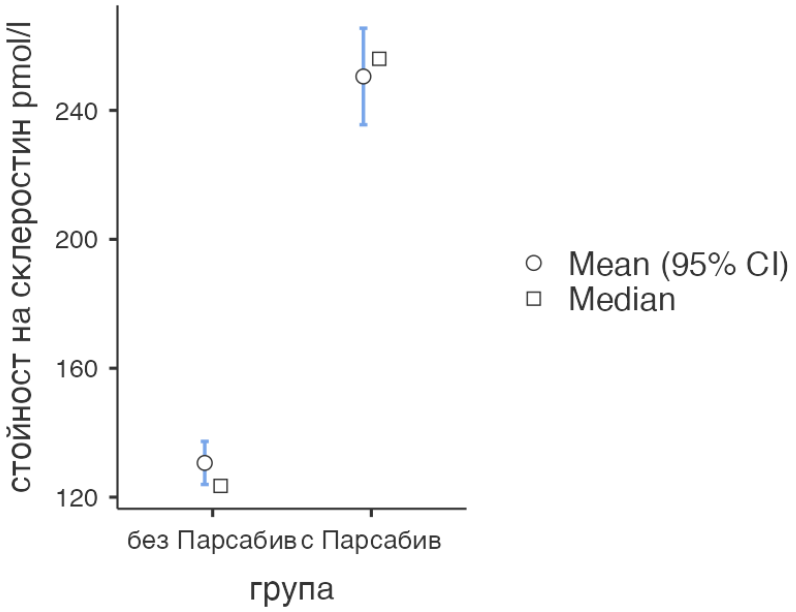

Fig.3. comparison of serum sclerostin values in HD patients on Parsabiv treatment and HD patients without Parsabiv treatment

From the results, etelcalcetide (Parsabiv) controlled secondary hyperparathyroidism and increased sclerostin levels in hemodialysis patients (Fig.3).

V. Conclusion

With impaired renal function, there is a progressive alteration of mineral homeostasis, with disruption of normal serum and tissue concentrations of phosphorus and calcium, as well as changes in circulating hormone levels. CKD-BMD syndrome is an extremely important complication of kidney disease. It describes the complex bone and mineral abnormalities that occur in chronic kidney disease and is an important contributor to CKD-related cardiovascular disease and high mortality rates.

High serum levels of sclerostin in patients with CKD are likely to be dependent on the accumulation of sclerostin in serum due to a decline in glomerular filtration rate (GFR) and/or increased production of sclerostin by osteocytes.

Our study demonstrates that in patients with CKD, renal elimination of sclerostin increases with decreasing renal function. In patients undergoing dialysis, sclerostin was an independent predictor of bone loss. Serum sclerostin levels correlated significantly with age and were higher in men than in women.

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