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Effect of hemodiafiltration on sclerostin level and bone specific alkaline phosphatase in comparison with high flux dialysis

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RESEARCH

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ABSTRACT

Background

Sclerostin (sScl), an osteocyte-derived glycoprotein acts as a soluble inhibitor of the Wnt signaling pathway and bone formation. Its serum levels increase with the progression of CKD. The present study investigated the effect of hemodiafiltration (HDF) on sScl and bone specific alkaline phosphatase (BS-AP) in comparison with high flux hemodialysis (HF-HD).

Methods

A prospective study was conducted upon 32 ESRD patients; 16 on regular HF-HD and 16 shifted to 3 months of HDF.

Result

There was a significant reduction of predialysis sScl and BS-AP with a significant increase in sScl reduction ratio in the HDF group after 3months. SScl had a significant positive correlation with total but not BS-AP.

Conclusion

sScl and BS-AP significantly decrease but are poorly correlated with each other in HDF. So either sScl reduction does not translate into better bone turnover or the BS-AP is not a suitable biomarker to assess bone turnover in HDF.

Key Words

Bone specific alkaline phosphatase, End stage renal disease, high flux hemodialysis, Haemodiafiltration, Serum sclerostin.

Introduction

Chronic kidney disease (CKD) is affecting 41% of the Western population. CKD also confers an increased fracture risk. The gold standard to assess bone turnover is doubtless bone histology. However, bone biopsies are invasive and cannot be repeated. Moreover, bone histomorphometry is performed in a limited number of (hyper) specialized centers and may not be available for all clinicians. For these reasons, bone biomarkers are used for both the diagnosis and monitoring of bone turnover. Sclerostin is a 22-kDa glycoprotein produced by the SOST gene. Physiological post-natal expression of sclerostin is restricted to osteocytes, cementocytes and chondrocytes[1]. By antagonizing the canonical Wnt pathway in osteoblasts, sclerostin reduces bone formation. In patients with CKD, sclerostin levels were negatively correlated with the glomerular filtration rate (GFR), independent of serum parathyroid hormone (PTH) concentrations. Sclerostin levels increase along the progression of CKD. In haemodialysis (HD) patients, sclerostin levels correlate negatively with histomorphometric parameters of bone turnover, osteoblast number and function[2].

Bone specific alkaline phosphatase (BS-AP) is a homodimeric glycoprotein; as an ectoenzyme, it is anchored to themembr ane of osteoblasts through glycosylphosphatidylinositol (GPI). Consequently, its activity is a general indicator of the bone formation rate in skeletal tissue. However, because the activities of osteoblasts and osteoclasts are intertwined during normal bone remodeling, BS-AP measurements provide an indication of overall bone turnover. BS-AP plays a major role in bone mineralization. Its serum concentration seems independent from glomerular filtration rate. There is a slightly higher correlation between bone formation rate (BFR) and BS-AP than total ALP.

Our study aimed to determine the effect of three months thrice weekly hemodiafiltration on sScl level and BS-AP in comparison with high flux dialysis in stable HD patients. As the molecular weight of sScl permits its removal by

convective transport, it is then possible to determine whether longitudinal data on sScl in high flux HD patients differ from those in individuals being treated by post-dilution online haemodiafiltration (HDF)[3].

Materials and methods

Patients and study design

A prospective study was concluded upon 32 randomly selected ESRD patients on regular HF-HD. Patients ≥18 years of age were eligible for inclusion if they had been treated with HF-HD three times per week for at least 6 months with intact PTH levels ranging from 100-600 pg/ml [4]. High flux group patients were treated with high flux dialyzers for at least three months while HDF group patients started de novo HDF and followed up for three months. The exclusion criteria for HDF or high-flux HD groups was patients with acute renal failure, history of fractures, Low physical activity (bed ridden) or PTH >600 or <100.

Data collection

At baseline, data on demographics, medical history, biochemical values and treatment characteristics were collected. Serum samples for laboratory parameters of chronic kidney disease-mineral bone disease (CKD-MBD) as corrected serum calcium, phosphorus, total alkaline phosphatase, intact parathormone (iPTH), BS-AP and sScl were drawn before dialysis. Routine samples were analyzed using standard techniques, and were measured in a single run, at the start of the study (first session at month 0) and after 3 months in the HDF group. Predialysis Δ change of different laboratory markers after 3 months in the HDF group was analyzed (predialysis value before and after 3 months in the HDF group)[5].

As regard sScl and BS-AP, blood samples were collected immediately before and just after hemodialysis from the arterial line of the hemodialysis. SScl and BS-AP reduction ratios were calculated as follows

[(sScl pre-HD- sScl post-HD)/ sScl pre-HD]x100

[(BS-AP pre-HD- BS-AP post-HD)/ BS-AP pre-HD]x100

Where pre-HD & post-HD values were taken before and after the first session of HDF in the HDF group and before and after a regular session on HF-HD. This was not repeated in the HF-HD group at 3 months as this group did not undergo any change in their HD protocol. As mentioned above, The HF-HD group were already on high flux dialysis over at least the last 3 months before the study[6].

Samples were stored at −80°C. SScl and BS-AP were measured using an enzyme-linked immunosorbent assay. Detection range was 16-1000 pg/ml for sScl and 1.6 -50 ng/L for BS-AP.

Stastical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

I- Descriptive Statistics: median and interquartile range (IQR) were used for non-parametric data.

II- Analytical Statistics: Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Wilcoxon Signed rank test was used to compare two related samples, matched samples, or repeated measurements on a single sample to assess whether their populations mean ranks differ. Chi square test was used to examine the relationship between two qualitative variables but when the expected count is less than 5 in more than 20% of the cells; Fisher's Exact Test or Monte Carlo correction was used. Student t-test was used for normally distributed quantitative variables, to compare between two studied groups. Paired t-test was used for normally distributed quantitative variables, to compare between two periods P-value: Level of significance: P>0.05: Non significant (NS), P<0.05: significant (S), P<0.01: highly significant (HS).

Results

In the present study, there was no statistically significant difference between the 2 groups as regard the sex, age, dry weight and BMI (P-values: 0.127, 0.13, 0.2, and 0.39) respectively. There was no statistically significant difference between the 2 groups as regards the etiology of ESRD (MCp: 0.195), the duration on HD (P-value: 0.073). All patients had arteriovenous fistulas as vascular access except one patient with a permanent catheter in group B. As regard dialysis parameters there was no statistically significant difference between both groups as regards blood flow rate, interdialytic weight gain, ultrafiltration rate. Patients in group A were maintained at a median dialysate flow rate of 800 ml/min and a mean of 756.3 ± 51.23 ml/min, whereas in group B, it had a median of 500 ml/min and a mean of 500.0 ± 0.0 ml/min. (P-value: <0.001)[7]. There was no statistical difference between both groups as regard the dose of Ca supplementation (mean=1550.0 mg ± 630.9 and 1381.8 mg ± 914.1 in group A and B respectively) (P=0.321). Alfa calcidol supplement had a mean of 0.78 mcg ± 0.31 in group A Vs. 0.38 mcg ± 0.27 in group B (p=0.015).

Table 1 shows that there was no statistically significant difference between the 2 groups as regard the demographic data. Table 2 shows no statistically significant difference

between HDF group and HF-HD group as regard predialysis serum corrected ca, po4, PTH levels, serum total Alkaline phosphatase, BS-AP and sclerostin levels at baseline (p1) but with significant decrease in BS-AP and sclerostin levels (P2=0.003 and 0.001) respectively between group A after 3 months of HDF compared to HF-HD group[8]. Also there was a significant difference within group A before and after receiving 3 months of HDF as regards BS-AP and sclerostin levels (P=0.013 and 0.008) respectively as well as all other measured parameters of CKD-MBD.

Table 3 shows there was a statistically significant rise of sScl reduction ratio in group A after 3 months of HDF vs. the HF-HD group (P-value: 0.015).

Table 4 shows that sclerostin delta change had a significant positive correlation with total but not bone specific alkaline phosphatase delta change, and a significant negative correlation with HGB delta change. There was no statistically significant difference between sclerostin delta change and Ca × PO4, PTH, BS-AP.

There was no statistical difference in the control group after three months.

Discussion

The demographic study of the present work revealed that there was no significant difference between the two groups regarding the age (p value 0.130), dry weight (p value 0.208), sex (p value 0.127) and BMI (p value 0.391) (Table 1). Also, there was no statistically significant difference between the two groups regarding duration of HD, etiology of renal failure, HCV state, blood pressure, blood pump speed, vascular access and ultrafiltration rate.

As regard serum calcium, phosphorus, iPTH, total alkaline phosphatase, results of the present study revealed no significant difference between group A before or after 3 months on HDF and group B, although there was significant reduction in all these CKD-MBD measured parameters within the same group A before and after 3 months of HDF (table 2). Our results agree with different studies as those of Richard et al. (8) study where patients were randomized to either hemodiafiltration or high-flux hemodialysis and followed for 12 months. There were no statistically significant changes in the serum concentrations of calcium and phosphorus over the duration of the study between the groups. Also, Dekker et al. (9 study that included 64 stable dialysis patients on a trice weekly 4-hour schedule, with a dialysis vintage of minimum 3 months, 30 patients on hemodialysis and 34 patients on HDF. This study compared the two groups as regard serum calcification propensity. There was no difference in the HD and HDF group as regard serum calcium (2.24 mmol/L pre dialysis and 2.46 mmol/L post dialysis in high flux group *versus* 2.31 mmol/L pre dialysis and 2.47 mmol/L post dialysis in HDF group).

On the other hand, our results showed a significant decrease of both BS-AP and sclerostin levels (P2= 0.003 and 0.001) respectively in group A after 3 months of HDF compared to HF-HD group (figure 1 and 2). Małyszko et al. (10) study was performed on 62 patients with end-stage renal failure treated by means of chronic hemodialysis (n=45) and hemodiafiltration (n=17) for a mean time of 12±2 months. HD group showed higher level in BS-AP than patients on HDF (45.0 ± 31.5 ng/ml in HD group, 31.6±21.2 ng/ml in HDF group with P-value <0.05). Also, there was a statistically significant difference between HDF group post-3months and HF-HD group as regard sclerostin reduction ratio (P2-value:0.015) (Table 3, Figure 3).Study showed a significant sScl change of −4.5 pmol/L/year (P=0.02) in patients treated with HDF, while sScl remained stable in patients treated with HD (P=0.09). This may be related to the use of low flux dialyzers in their study. Table 4 shows that sclerostin delta change had a significant positive correlation with total but not bone specific alkaline phosphatase delta change. So either the sScl reduction with HDF does not translate into better bone turnover or the BS-AP is not a suitable biomarker to assess bone turnover with HDF[9].

An important strength of the present study is the use of serial measurements for sScl; the predialysis level delta change before and after 3 months and the sScl reduction ratio within a single dialysis session. Secondly, randomized patients to either HD or HDF, which made it possible to analyze the causal effect of dialysis modality on sScl. Thirdly, the assessment of all sScl measurements in a single run, at a central laboratory, eliminated inter-assay variability. One limitation of our study is the small number of patients and the short duration of the study. Furthermore, no other biomarkers of bone metabolism (such as osteocalcin and FGF23) or bone histomorphometry were available [10].

Conclusion

SScl and BS-AP both significantly decrease with HDF. Yet, they are not significantly correlated. So either the sScl reduction with HDF does not translate into better bone turnover or the BS-AP is not a suitable biomarker to assess bone turnover with HDF. Further larger, bone histomorphometric studies are needed to correlate the variations in sScl and BS-AP with bone turnover during HDF.

References

1. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney

disease. Kidney Int. 2014;86(4):810-8. Doi: https://doi.org/10.1038/ki.2013.547
2. Jadoul M, Albert JM, Akiba T, et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2006;70(7):1358-66. Doi: https://doi.org/10.1038/sj.ki.5001754
3. Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nature medicine. 2013;19(2):179-92. Doi: https://doi.org/10.1038/nm.3074
4. Pelletier S, Dubourg L, Carlier MC, et al. The relation between renal function and serum sclerostin in adult patients with CKD. Clin J Am Soc Nephrol. 2013;8(5):819-23. Doi: https://doi.org/10.2215/CJN.07670712
5. Cejka D, Herberth J, Branscum AJ, et al. Sclerostin and Dickkopf-1 in renal osteodystrophy. Clin J Am Soc Nephrol. 2011;6(4):877-82. Doi: https://doi.org/10.2215/CJN.06550810
6. Phan TC, Xu J, Zheng MH. Interaction between osteoblast and osteoclast: impact in bone disease. Histol Histopathol. 2004.
7. Delanaye P, Dubois BE, Jouret F, et al. Parathormone and bone-specific alkaline phosphatase for the follow-up of bone turnover in hemodialysis patients: is it so simple?. Clinica Chimic Acta. 2013;417:35-8. Doi: https://doi.org/10.1016/j.cca.2012.12.009Ward
8. RA, Schmidt B, Hullin J, et al. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. J Am Soc Nephrol. 2000;11(12):2344-50. Doi: https://doi.org/10.1681/ASN.V11122344
9. Dekker M, Pasch A, van der Sande F, et al. High-flux hemodialysis and high-volume hemodiafiltration improve serum calcification propensity. PLoS One. 2016;11(4):e0151508. Doi: https://doi.org/10.1371/journal.pone.0151508
10. Małyszko J, Małyszko JS, Kozminski P et al. Markers of bone metabolism in hemodialyses and hemodiafiltration. Renal failure. 2007;29(5):595-601. Doi: https://doi.org/10.1080/08860220701392181
11. Lips L, de Roij van Zuijdewijn CL, Ter Wee PM, et al. Serum sclerostin: relation with mortality and impact of hemodiafiltration. Nephrol Dial Transplant. 2017;32(7):1217-23. Doi: https://doi.org/10.1093/ndt/gfw246

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards;

Disclosures: Nothing to disclose. No funds or any financial support have been taken.

Ethical approval

All procedures performed in the study were in accordance with the ethical standards of the Ain Shams University Hospitals ethics committee and with the Helsinki declaration for ethical standards. The Ain Shams Institutional Review Board has verified the study but provided no IRB number.

Informed consent

"Informed consent was obtained from all individual participants included in the study."

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Figures and Tables

Table 1: Baseline demographic characteristics difference between the HDF Vs. HF-HD groups.

	HDF Group (n = 16)		HF-HD Group(n = 16)		P
	No.	%	No.	%	
Sex					
Male	9	56.3	13	81.3	0.127
Female	7	43.8	3	18.8	
Age (years)					
Min. – Max.	17.0 -70.0		36.0 – 67.0		0.13
Mean ± SD.	47.38 ± 18.68		55.31 ± 7.40		
Median	54		56		
Dry weight (kg)					
Min. – Max.	35.0 – 135.0		62.0 – 110.0		0.208
Mean ± SD.	72.50 ± 22.46		80.94 ± 13.56		
Median	69		77		
Min. – Max.					
Mean ± SD.	17.0 – 40.0		18.0 – 33.0		0.391
Median	22.69 ± 5.62		24.19 ± 3.99		
Median	20.5		24		

Table 2: Difference between the HDF and the HF-HD groups as regard predialysis biomarkers of CKD-MBD.

Pre-dialysis	HDF Group (n= 16)		HF-HD Group (n= 16)
	Month 0	After 3 Month	
Corrected Serum Calcium (mg/dl)			
Min. – Max.	7.80 – 10.70	7.30 – 9.60	6.90 – 9.60
Mean ± SD.	8.90 ± 0.87	8.43 ± 0.64	8.57 ± 0.75
Median	8.75	8.35	8.80
difference	p_1=0.261, p_2=0.575, p_3=0.012*		
Serum Phosphorus (PO4)(mg/dl)			
Min. – Max.	1.90 – 7.40	2.80 – 5.70	2.40 – 6.0
Mean ± SD.	4.74 ± 1.52	3.96 ± 0.86	4.37 ± 1.13
Median	4.90	3.80	4.50
difference	p1=0.443, p2=0.256, p3=0.034*		
Intact PTH (pg/ml)			
Min. – Max.	109.0 – 590.0	134.0 – 594.0	191.0 – 600.0
Mean ± SD.	406.8 ± 81.0	349.2 ± 56.4	357.3 ± 38.6
Median	447.0	388.0	335.0
difference	p1=0.462, p2=0.806, p3=0.002*		
Serum total Alkaline phosphatase (U/L)			
Min. – Max.	65.0 – 551.0	68.0 – 300.0	84.0 – 394.0
Mean ± SD.	166.1 ± 119.1	127.6 ± 61.92	173.8 ± 84.96
Median	120.0	105.0	155.0

difference	p_1=0.509, p_2=0.052, p_3=0.003*		
BS-AP (ng/l)			
Min. – Max.	7.50 – 22.50	6.0 – 18.0	12.0 – 34.0
Mean ± SD.	13.91 ± 4.46	12.19 ± 3.09	17.66 ± 6.05
Median	13.50	12.50	16.0
difference	p_1=0.082, p_2=0.003*, p_3=0.013*		
Sclerostin (sScl) (pg/ml)			
Min. – Max.	540.0 – 1487.0	500.0 – 1200.0	825.0 – 1420.0
Mean ± SD.	1018.5 ± 299.5	876.9 ± 205.7	1163.9 ± 236.2
Median	1111.0	900.0	1250.0
difference	p_1=0.136, p_2=0.001*, p_3=0.008*		

p1: p values for Mann Whitney test for comparison between HDF group (at month 0) and HF-HD group.

p2: p values for Mann Whitney test for comparison between HDF group (after 3 Month) and HF-HD group.

p3: p values for Wilcoxon signed ranks test for comparison between month 0 and after 3 months in the HDF group

Table 3: Difference between the HDF and the HF-HD groups as regard serum Sclerostin and BS-AP reduction ratio pre- and post-dialysis.

Reduction ratio (%)	**HDF Group (n = 16)**		**HF-HD Group (n = 16)**
	month 0	**After 3 months**	
Sclerostin (sScl) (%)			
Min. – Max.	10.0 – 43.0	12.50 – 46.0	8.0 – 36.0
Mean ± SD.	24.72 ± 1.34	30.34 ± 1.22	18.97 ± 4.87
Median	20.50	31.90	17.90
Difference	p1=0.062, p2=0.015*, p3=0.179		
BS-AP (%)			
Min. – Max.	2.70 – 20.0	3.0 – 20.0	2.90 – 26.0
Mean ± SD.	7.85 ± 1.22	10.76 ± 1.84	14.07 ± 1.51
Median	6.80	10.0	13.75
Difference	p1=0.020*, p2=0.212, p3=0.066		

Table 4: Correlation between predialysis Δ change of sScl and different laboratory markers after 3 months in the HDF group.

IDF group	**Sclerostin Delta change**	
	R	**P-value**
Ca Δ change	0.004	0.988
Serum albumin(mg/dl) Δ change	0.117	0.667
Corrected ca(mg/dl) Δ change	0.011	0.968
PO4(mg/dl) Δ change	-0.247	0.356
Ca × PO4 Δ change	-0.199	0.460
PTH (pg/ml) Δ change	0.047	0.862
Total alkaline phosphatase Δ change	0.506*	0.046

Hemoglobin (HGB) (gm/dl) Δ change	-1.000**	0.000
BS-AP Δ change	0.024	0.930

Figure 1: Comparison between predialysis sScl in group A (after 3 months on HDF) and group B on HF-HD.

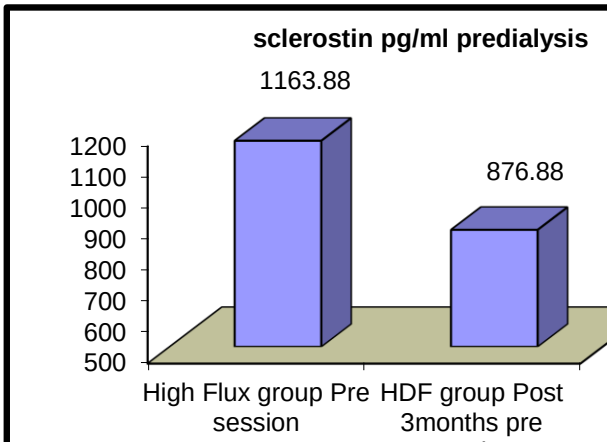


Figure 2: Comparison between predialysis BS-AP in group A (after 3 months on HDF) and group B on HF-HD.

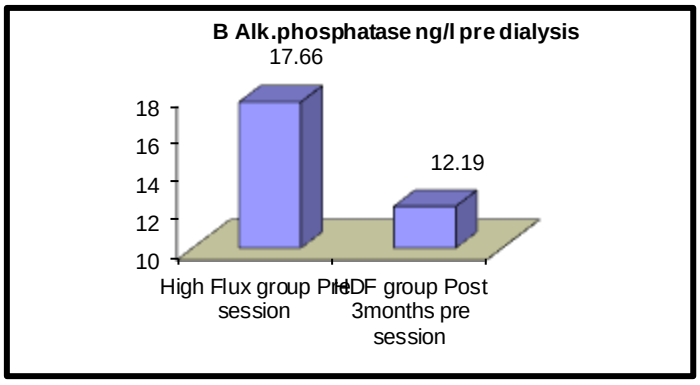
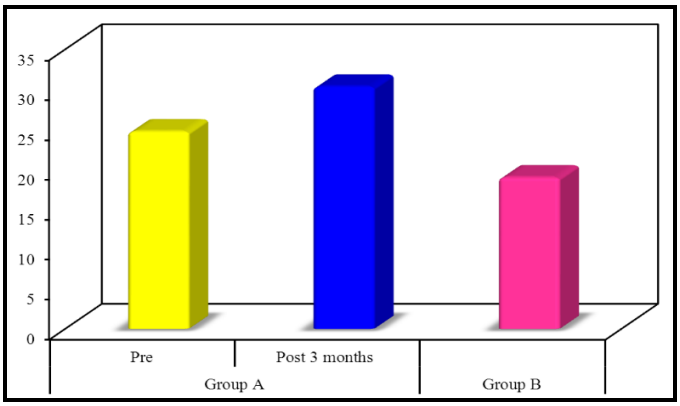


Figure 3: Comparison between the two studied groups according to sScl reduction ratio.



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