Independent correlation between ischemia modified albumin and parathormone in hemodialysis patients

Kenan Güçlü,[1] Kağan Tur,[2] Serdar Şahin,[3] Aydın Güçlü[4]

[1]Biochemistry Department, Kayseri State Hospital, Kayseri, Turkey; [2]Internal Medicine Department, Faculty of Medicine, Ahi Evran University, Kırşehir, Turkey; [3]General Surgery Department, Faculty of Medicine, Ahi Evran University, Kırşehir, Turkey; [4]Nephrology Department, Faculty of Medicine, Ahi Evran University, Kırşehir, Turkey

ABSTRACT

Hemodialysis patients are the group which oxidative stress is found more exacerbated. Ischemia modified albumin (IMA) is a new and sensitive marker for ischemia and oxidative stress. At current study we evaluated relation between IMA and biochemical parameters in hemodialysis patients. Thirty-four patients on maintenance hemodialysis were included. Pre-hemodialysis and post-hemodialysis blood samples were taken. Serum IMA and biochemistry parameters were measured. There was a positive correlation between alkaline phosphatase (ALP) and IMA (r=0.268, P<0.05), CRP and IMA (r=0.452, P=0.007), parathormone and IMA (r=0.436, P=0.010), There was a negative correlation between albumin and IMA (r= –0.338, P=0.05). Multiple regression analysis was run to predict IMA levels from parathormone, CRP and creatinine the model statistically significantly predicted relation P<0.05, R=0.506, out of four two variables added statistically significant to the prediction, PTH (P=0.006), CRP (P=0.029). In multiregression analysis, IMA was found to be associated with PTH and CRP independent of creatinine value. We showed for the first time that PTH is associated with IMA in hemodialysis patients, independent of the level of renal function.

Correspondence: Kağan Tur, Internal Medicine Department, Faculty of Medicine, Ahi Evran University, Kırşehir, Turkey.
E-mail: kaantur542@gmail.com

Key words: Ischemia modified albumin; hemodialysis; oxidative stress; chronic kidney disease; bone mineral disease; parathormone.

Contributions: KG, concept, resources, materials, data collection and processing; KT, resources, data collection and processing, analysis and interpretation, literature search, writing manuscript; SS, re-sources, materials, data collection; AG, design, supervision, resources, data collection and processing, critical review.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 5 December 2022.
Accepted for publication: 13 December 2022.

Italian Journal of Medicine 2022; 16:1560
doi:10.4081/itjm.2022.1560

Introduction

Oxidative stress (OS) has an important role at development of chronic kidney disease (CKD) and progression to end stage renal disease (ESRD). Overwhelming of antioxidant defense system by oxidative molecules such as reactive oxygen species, oxidized lipids, proteins and carbohydrates, accumulation of advanced glycation/lipoxidation end products (AGEs/ALEs) leads to renal ischemia, glomerular damage and progressive kidney injury.[1]

Although oxidative stress is present at early stages of CKD, hemodialysis (HD) patients are the group which oxidative stress is found more exacerbated. Increased OS at HD patients is associated with dietary restrictions, excessive inflammation process, hemodialysis procedure, uremic status and concomitant conditions including vascular calcification, diabetes mellitus, hyperlipidemia, hypertension. Oxidative stress and inflammation are closely linked, and both augment each other. Activation of transcription factors by OS causes expression of genes regulating proinflammatory cytokines and chemokines. Leukocyte activation is promoted by OS and OS is responsible of production of proinflammatory molecules such as oxidized lipids, AGEs. Moreover, oxidative stress is amplified with production of ROS and free radicals by cells involved at inflammatory process such as leukocytes.[2]

Chronic kidney disease-bone mineral disease (CKD-MBD) and its part secondary hyperparathyroidism (SHPT) are crucial complications

associated with fractures, cardiovascular disease, vascular calcifications and high turnover bone disease for HD patients. Parathormone (PHT) at high levels has functions as a uremic toxin which can potentially harm various systems including kidney and heart. PHT is suggested to have a role at pathogenesis of oxidative stress and inflammation.[3]

General population studies showed association between PTH and inflammatory markers such as c reactive protein (CRP).[4] Rat studies found that dietary induced hyperparathyroidism causes increased production of inflammatory cytokines.[5] Intravenous calcitriol therapy at HD patients showed decrease at the ratio of oxidized to unoxidized albumin which suggests improvement in oxidative stress.[6]

Ischemia modified albumin (IMA) is a new and sensitive marker for ischemia. Recent studies show that IMA production is related with increased oxidative stress in ischemia reperfusion models and myocardium is not the only organ affected by this status, kidney is affected as well.[7] It is suggested that end stage renal disease (ESRD) and HD patients have increased IMA levels.[8]

The amino terminal end (N-terminal) of the albumin molecule is the primary binding site for transitional metals, such as cobalt. Exposure to ischemic tissue alters the N-terminus of the albumin, decreasing its binding capacity for metals and resulting in the formation of IMA. ROS generation and superoxide radical injury can cause conversion of albumin to IMA.[9]

Increased oxidative stress and inflammation are the characteristic features of hemodialysis patients. Studies show that IMA levels increase at oxidative stress and inflammation.[10] PTH is also related with OS and inflammation. At this study we investigated association between IMA, PTH, CRP, creatinine at hemodialysis patients. To our knowledge this is the first study investigating IMA and PTH at HD patients.

Materials and Methods

Thirty-four patients with ESRD on maintenance HD were included in the study. All patients underwent three, 4-hour HD session per week. Exclusion criterias were active infection, cancer, hepatic disease and inflammatory disorders including connective disease. Study was performed according to the requirements of the Ethical Committee and written informed consent to participate at this study have taken from all participants. Ethics committee approval was obtained from Ahi Evran University Faculty of Medicine, Kirsehir, Turkey (decision number 2021-06/58-23/03/2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

All patients in the study underwent a detailed medical history and clinical examination. Demographic and clinical characteristics, including age, gender and duration of HD were recorded.

A fasting blood sample pre-HD and post-HD blood sample at the end of the dialysis session were taken from all of the patients. Serum IMA level was measured with calorimetric assay kit and results were expressed in absorbance units (ABSU). Complete blood count and routine biochemistry parameters were measured with appropriate assay kits.

Statistical analysis

Statistical analyses were performed with the SPSS package program for Windows version 25.0 statistical software (SPSS Inc., Chicago, IL, USA). Gaussian-distributed continuous variables were presented as mean ± standard deviations with their min-max median. Distributions of the numerical variables were analyzed for normality using Kolmogorov-Smirnov test. To analyze the differences, one-tailed t-test for Gaussian variables and Mann-Whitney test for non-Gaussian variables used. Correlations between continuous variables calculated using Pearson test, and Spearmen's rank correlation test was used when appropriate. P value of 0.05 or less was considered statistically significant.

Results

Mean age of patients were 61±11.2 years, mean HD duration war 6.5±5.7 years. Clinical, demographic and biochemical parameters of patients are shown in Table 1. Pre HD IMA level was 40.8±5.1 ABSU and post HD serum IMA level was 41.3±3.3 ABSU. There was not a statistically significant difference between IMA measurements taken before and after HD (r= –0.193, P=0.274). 38% of the patients was female and 62% of the patients was male. There was a negative correlation between albumin and IMA (r= –0.338, P=0.05). There was a positive correlation between alkaline phosphatase (ALP) and post HD IMA (r=0.268, P<0.05), CRP and post HD IMA (r=0.452, P=0.007), PTH and pre-HD IMA (r=0.436, P=0.010). Multiple regression analysis was run to predict IMA levels from PTH, CRP and creatinine the model statistically significantly predicted relation P<0.05, R=0.506, out of four two variables added statistically significant to the prediction, PTH (P=0.006), CRP (P=0.029). Model summary, ANOVA result of the model and coefficients of the model are shown in Tables 2, 3 and 4, respectively. Logistic regression tests were performed to calculate generate ROC curves and to prove independent relationships of IMA values between CRP and PTH values. Test results

showed the independent relationships between IMA and CRP (AUROC=0.750), PTH (AUROC=0.871, in Figure 1) (Null-hypothesis area is 0.5).

Discussion

Present study shows that there is a positive correlation between IMA and PTH (P=0.01, r=0.436), IMA and CRP (P=0.007, r=0.452) and ALP and IMA (P<0.05, r=0.268). Multiple regression analysis was run to predict IMA levels from PTH, CRP and creatinine the model statistically significantly predicted relation P<0.05, r=0.506, out of four two variables added statistically significant to the prediction, PTH (P=0.006), CRP (P=0.029). In this study, we showed for the first time that parathormone is associated with IMA independently of creatinine level.

Current research on non-traditional risk factors has revealed that oxidative stress is an important cardiovascular risk factor in uremic patients.[11] Hemodialysis patients are characterized with imbalance between pro-oxidative products and anti-oxidative defense mechanisms which resulting increase at oxidative stress and deficient anti-oxidative defense. Antioxidant defense mechanisms such as superoxide dismutase, catalase, glutathione peroxidase is found impaired at the setting of CKD and HD. Increased ROS

Table 1. Clinical, demographic and biochemical parameters of patients.

	Mean (±SD)		Mean (±SD)
Mean age (years±SD)	61±11.2	Fe	47.5±18.6
Male % (n)	%38	TIBC	220.8±71.1
HD duration (years±SD)	6.5±5.7	B12	368.7±234.1
Urea	161.7±62.4	Folate	7.3±4.6
Creatinine	9.2±2.52	ASO	105.8±105
CRP	2.87±10.63	ALT	10.3±6
Albumin	4.07±0.35	AST	12.6±5.8
Total protein	7.08±0.52	Glucose	115.1±62.4
Parathormone	362.4±317.7	Wbc	7.8±2.6
ALP	151.2±83.58	Hgb	11.1±1.2
GGT	48.47±102.17	MCH	29±1.8
Cl	98.5±3.2	MCHC	32.15±0.8
Na	137.05±2.78	RDW	14.5±1.1
K	5.78±0.70	PLT	203.7±54.2
Ca	8.79±0.74	NEU	5.2±2.3
P	4.7±1.3	LYM	1.6±0.5
Total cholesterol	155.7±37	MONO	0.6±0.19
LDL	85.4±26.9	BASO	0.044±0.024
HDL	34.8±9.9	MPV	10.5±0.9
Triglyceride	183.1±107.5	PCT	0.21±0.05
Ferritin	453.2±224.8	PDW	12.1±2.2

MCHC, mean corpuscular hemoglobin concentration.

Table 2. Model summary.

Model	R	R square	Adjusted R square	Std. error of the estimate	Model summary* R square change	Change statistics F change	df1	df2	Sig. F change	Durbin-Watson
1	0.506°	0.256	0.182	4.66148	0.256	3.442	3	30	0.029	0.601

*Dependent variable: ischemia modified albumin; °predictors: (constant), C-reactive protein, creatinine, parathormone.

production and activation of enzymatic systems including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, lipoxygenase, uncoupled nitric oxide synthase (NOS) are the causes of exacerbated oxidative stress. Activation of transcription factors by OS causes expression of genes regulating proinflammatory cytokines and chemokines. There is a tight link between OS and inflammation which is associated with disease progression, poor outcomes, increase at risk of complications such as cardiovascular disease.[2,12,13]

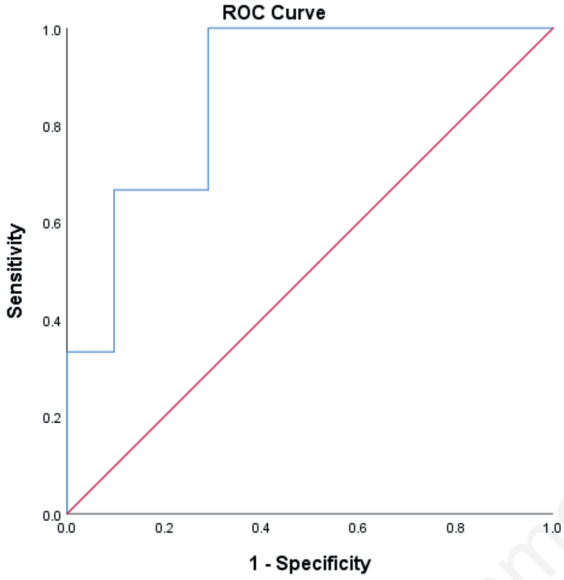

Figure 1. ROC analysis for ischemia modified albumin and parathormone (PTH). Area under the curve test result variable(s): PTH (AUROC=0.871).

Oxidative stress and inflammation process are influenced by PTH. Dietary induced hyperparathyroidism causes inflammatory cytokine production increase at rats.[5] Cheng *et al*. reported association between PTH and inflammatory markers including CRP at general population.[4] Hyperparathyroidism has also been shown to play an important role in increasing oxidative stress in hemodialysis patients.[14] Recently, IMA has been demonstrated as a novel oxidative stress biomarker in uremic patients.[8,15,16]

Human serum albumin is a plasma protein which is affected by oxidative stress in HD patients. N terminus of the albumin which its first three amino acids consisting of aspartate-alanine-histidine is the binding site for transitional metals including cobalt, nickel and copper. Free radicals, ischemia, hypoxia, inflammation, increased oxidative stress can cause degradation of this site decreasing its ability to bind metals thus resulting formation of IMA.[15,17] Although IMA is first suggested as rapid and sensitive test for diagnosis of acute myocardial ischemia, recent studies show that its potential role as biomarker is not only limited to cardiac ischemia.[17,18] In the setting of excessive oxidative stress and inflammation IMA is found increased at plethora of clinical conditions especially including ESRD.[8,19-23] HD and peritoneal dialysis patients have been shown to have higher serum IMA levels compared to renal transplantation patients and healthy subjects.[16]

IMA is found increased at HD patients compared to control groups at previous studies.[8,24] Cichota *et al*. reported that CKD patients with anemia has higher IMA levels compared to healthy controls (P<0.05).[15] Sharma *et al*. reported that IMA level can predict mortality in patients at transplantation candidate ESRD patients.[16]

Table 3. ANOVA result of model.

ANOVA*						
Model		**Sum of squares**	**df**	**Mean square**	**F**	**Sig.**
1	Regression	224.382	3	74.794	3.442	0.029°
	Residual	651.883	30	21.729	-	-
	Total	876.265	33	-	-	-

*Dependent variable: ischemia modified albumin; °predictors: (constant), C-reactive protein, creatinine, parathormone.

Table 4. Coefficients of the model.

Coefficients*						
Model		**Unstandardized coefficients**		**Standardized coefficients**	**t**	**Sig.**
		B	**Std. error**	**Beta**		
1	(Constant)	40.108	3.084	-	13.006	0.000
	Creatinine	–0.210	0.351	–0.103	–0.597	0.555
	Parathormone	0.009	0.003	0.550	2.931	0.006
	CRP	–0.193	0.084	–0.398	–2.289	0.029

*Dependent variable: ischemia modified albumin.

We have shown for the first time that IMA level is associated with PTH levels independently of creatinine levels in ESRD patients. This may imply an important role in the pathophysiology of hyperparathyroidism-induced increased oxidative stress in HD patients. At our study ALP and IMA are found positively correlated ($P<0.05$, $r=0.268$), ALP may rise in hemodialysis patients due to hyperparathyroidism. In our study, the relationship between ALP elevation and IMA may be result of hyperparathyroidism effect.

In multiregression analysis, IMA was found to be associated with PTH and CRP independent of creatinine value. Previous studies investigating relation between highly sensitive CRP (hs-CRP) and IMA at ESRD patients reported positive correlation between IMA and hs-CRP.[25] At our study, there was a very strong correlation between CRP and IMA ($P=0.007$, $r=0.452$) and our study is the first study in the literature showing independent correlation between CRP and IMA at HD patients.

Conclusions

Our study is the first study in the literature showing a correlation between IMA, PTH and CRP independent of creatinine levels at HD patients. CKD and HD are characterized with excessive oxidative stress and inflammation. IMA may play an important role in the pathophysiology of increased oxidative stress due to hyperparathyroidism in hemodialysis patients. Further studies are needed in this regard. Limitations of our study are its small sample size and lack of control group.

References

1. Liakopoulos V, Roumeliotis S, Gorny X, et al. Oxidative stress in hemodialysis patients: a review of the literature. Oxid Med Cell Longev 2017; Article ID 3081856.
2. Duni A, Liakopoulos V, Rapsomanikis K, Dounous E. Chronic kidney disease and disproportionally increased cardiovascular damage: does oxidative stress explain the burden? Oxid Med Cell Longev 2017; Article ID 9036450.
3. Toraman A, Aras F, Hekimsoy Z, Kursat S. Is there a relationship between parathyroid hormone and neutrophil lymphocyte ratio or platelet lymphocyte ratio? Acta Endocrinol (Buchar) 2019;5:96-101.
4. 4. Cheng SP, Liu CL, Liu TP, et al. Association between parathyroid hormone levels and inflammatory markers among US adults. Mediat Inflamm 2014; Article ID 709024.
5. Lütfioğlu M, Sakallioğlu U, Sakallioğlu EE, et al. Dietary-induced hyperparathyroidism affects serum and gingival proinflammatory cytokine levels in rats. J Periodontol 2010;81:150-7.
6. Tanaka M, Tokunaga K, Komaba H, et al. Vitamin D receptor activator reduces oxidative stress in hemodialysis patients with secondary hyperparathyroidism. Ther Apher Dial 2011;15 161-8.
7. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes–review and clinical implications. Clin Chem Lab Med (CCLM) 2011;49:177-84.
8. Turedi S, Cinar O, Yavuz I, et al. Differences in ischemia-modified albumin levels between end stage renal disease patients and the normal population. J Nephrol 2010;23:335-40.
9. Albarello K, Santos GA, Bochi GV, et al. Ischemia modified albumin and carbonyl protein as potential biomarkers of protein oxidation in hemodialysis. Clin Biochem 2012;45:450-4.
10. Duarte MM, Rocha JB, Moresco RN, et al. Association between ischemia-modified albumin, lipids and inflammation biomarkers in patients with hypercholesterolemia. Clin Biochem 2009;42:666-71.
11. Himmelfarb J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. Semin Dial 2009;22:636-43.
12. Duni A, Liakopoulos V, Roumeliotis S, et al. Oxidative stress in the pathogenesis and evolution of chronic kidney disease: untangling Ariadne's thread. Int J Mol Sci 2019;20:3711.
13. Liakopoulos V, Roumeliotis S, Zarogiannis S, et al. Oxidative stress in hemodialysis. Semin Dialysis 2018;970.
14. Noyan T, Avci G, Şekeroğlu M, Erkoç R. The investigation of relationship between secondary hyperparathyroidism and oxidative stress in patients with chronic kidney disease. Turkish Nephrol Dialysis Transplant J 2009;18:69-75.
15. Cichota LC, Moresco RN, Duarte MM, Silva JE. Evaluation of ischemia-modified albumin in anemia associated to chronic kidney disease. J Clin Lab Analysis 2008;22:1-5.
16. Sharma R, Gaze D, Pellerin D, et al. Ischemia-modified albumin predicts mortality in ESRD. Am J Kidney Dis 2006;47:493-502.
17. Bar-Or d, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia - a preliminary report. J Emerg Med 2000;19:311-5.
18. Nepal M, Jaisawal S, Gragain M, et al. Ischemic modified albumin (IMA) as a novel marker for ischemic heart disease and surrogate marker for other high oxidative-ischemic conditions. J Cardiovasc Dis Res 2017;8.
19. Menon B, Ramalingam K, Krishna V. Study of ischemia modified albumin as a biomarker in acute ischaemic stroke. Ann Neurosci 2018;25:187-90.
20. Omma A, Sandikci SC, Colak S, et al. Serum calprotectin and ischemia modified albumin levels as markers of disease activity in Behçet's disease. Postepy Dermatol Alergol 2018;35:609-13.
21. Hakkoymaz H, Nazik S, Seyithanoğlu M, et al. The value of ischemia-modified albumin and oxidative stress markers in the diagnosis of acute appendicitis in adults. Am J Emerg Med 2019;37:2097-3001.
22. Reddy SV, Suchitra MM, Pradeep V, et al. Ischemia-modified albumin levels in overt and subclinical hypothyroidism. J Endocrinol Invest 2015;38:885-90.

23. Sunnetcioglu A, Asker S, Alp HH, Gunbatar H. Increased asymmetric dimethylarginine and ischemia-modified albumin levels in obstructive sleep apnea. Respir Care 2016;61:1038-43.
24. Mehmetoglu I, Yerlikaya H, Kurban SS, et al. Oxidative stress markers in hemodialysis and peritoneal dialysis patients, including coenzyme Q10 and ischemia-modified albumin. Int J Artif Organs 2012;35:226-32.
25. Turkmen K, Tonbul HZ, Toker A, et al. The relationship between oxidative stress, inflammation, and atherosclerosis in renal transplant and end-stage renal disease patients. Renal Failure 2012;34:1229-37.