DOI: 10.4149/BLL_2018_102

Bratisl Med J 2018; 119 (9)
566 – 571

CLINICAL STUDY

Relationship of epicardial fat tissue thickness with oxidant biomarkers in chronic kidney disease

Karatas A[1], Canakci E[2], Bektas O[3], Bayrak T[4], Bayrak A[4], Altınbas A[2], Turkmen E[5]

Department of Internal Medicine, Nephrology Branch, Ordu University, School of Medicine, Ordu, Turkey. **karatas55@hotmail.com**

ABSTRACT

INTRODUCTION AND OBJECTIVE: IMA and MPO are elevated in serum in case of end-stage renal disease. Epicardial fat tissue thickness has been considered an indicator for cardiovascular diseases recently. The present study was aimed to examine the relationship of epicardial fat tissue thickness (EFTT) with IMA and MPO levels in patients with CKD.

MATERIALS AND METHODS: Predialysis CKD patients admitted to the Nephrology outpatient clinic, patients on haemodialysis and healthy volunteers were included, 111 patients were in the study. EFTT measurement was performed with the transthoracic view using an ECHO device.

RESULTS: The analysis conducted among the groups in terms of IMA, MPO levels, and EFTT revealed a statistically significant difference ($p < 0.001$). It was determined to be the lowest in the healthy volunteers, slightly increased in the pre-dialysis group whereas it was quite high in the haemodialysis group. According to the correlation test performed, we observed that IMA, MPO levels, and EFTT were found to be highly correlated to progression of CKD.

CONCLUSION: We believe that we have introduced three novel follow-up parameters, such as: IMA, MPO, EFTT to literature for the follow-up of CKD. As the levels of IMA MPO and EFTT increase, the severity of CKD increases *(Tab. 4, Fig. 1, Ref. 25)*. Text in PDF *www.elis.sk.*

KEY WORDS: chronic kidney disease, epicardial fat tissue thickness, ischemia-modified albumin, myeloperoxidase.

Abbreviations: CKD – chronic kidney disease, MDRD – modification of diet in renal disease, BMI – body mass index, DM – diabetes mellitus, IMA – ischemic modified albumin, MPO – myeloperoxidase, EFTT – epicardial fat tissue thickness, HD – haemodialysis, CAD – coronary artery disease, CIMT – carotid intima-media thickness, GFR – glomerular filtration rate

Introduction

Ischemia-modified albumin is a molecule with protein structure, which was considered a cardiac ischemia indicator in recent years and was constantly investigated (1). IMA is elevated in serum in end-stage renal disease, liver failure, cerebrovascular diseases, multiple trauma, some neoplastic diseases and infections (2).

Recent studies showed that myeloperoxidase (MPO) played an important role in inflammation and cardiovascular diseases (3). CKD is a chronic inflammatory process and cardiovascular diseases occur more commonly in patients with CKD compared to normal population. Epicardial fat tissue thickness has been considered an indicator for cardiovascular diseases recently. Epicardial fat tissue thickness (EFTT) is the thickness of the visceral fat tissue of the heart. It is derived from the brown fat tissue during embryogenesis. Although it is present intensively in the atrioventricular and interventricular grooves in the adult heart, it is also observed on the free surfaces of both atria and around the appendices. The epicardial fat tissue is a two-tailed task spectrum and plays a role in both prophylactic and inflammatory processes. Epicardial fat tissue thickness was studied in chronic renal failure cases in the studies conducted and usually was found to be high (4). However, there are studies demonstrating that oxidative markers (MPO, IMA) and epicardial fat tissue thickness were increased in patients with CKD among the recent studies, the present study was aimed to examine the association of epicardial fat tissue thickness (EFTT) with IMA and MPO levels in patients with CKD.

Materials and methods

Ethical approval was obtained from Ordu University Clinical Research Ethics Committee for the present study (Date 26.10.2017 Decision No: 129). Predialysis CKD patients were admitted to Ne-

[1]Department of Internal Medicine, Nephrology Branch, Ordu University, School of Medicine, Ordu, Turkey, [2]Department of Anesthesiology and Reanimation, Ordu University School of Medicine, Ordu, Turkey, [3]Department of Cardiology, Ordu University, School of Medicine, Ordu, Turkey, [4]Department of Medical Biochemistry, Ordu University, School of Medicine, Ordu, Turkey, and [5]Ordu State Hospital, Clinic of Nephrology, Ordu, Turkey

Address for correspondence: A. Karatas, MD, Ordu Universitesi Tip Fakultesi, Egitim ve Arastirma Hastanesi, Nefroloji Klinigi, 52200 Merkez, Ordu, Turkey.
Phone: +90. 532. 5790772

phrology outpatient clinic of Ordu University, Faculty of Medicine, patients on haemodialysis and healthy volunteers were included in the study. The cases included in the study were adult cases, who had chronic kidney disease for at least 1 year and, who were in the age range of 18–65 years. The patients with malignancy, those aged under 18 years or over 65 years and patients, who refused to participate in the study (who did not sign the informed consent document) were excluded. Demographic characteristics (age, weight, height, gender, body mass index) of each case were recorded. In order to measure the epicardial fat tissue thickness (EFTT), patients and healthy volunteers were sent to the cardiology outpatient clinic to undergo ECHO. EFTT measurements of the HD patients were performed at the HD unit. EFTT measurements were obtained using GE Vivid 7 device (General Electric Medical Systems, Milwaukee, Wisconsin) with the 2.5–3 MHz transducer, which was available in the cardiology outpatient clinic of our hospital. EFTT was assessed by transthoracic view using the two-dimensional echocardiographic method. EFTT was measured in the parasternal longitudinal axis view, during the diastolic phase of the heart, at its widest place, from the hyperechogenic area consistent with the density of EFTT remaining in between the free wall of the right ventricle, where the perpendicular line drawn by taking the aortic annulus as reference passed. Measurement value was expressed in cm.

Statistical analysis

Normality assessment of the data was made using the Kolmogorov–Smirnov test. The means of two independent groups were compared with the student t-test, whereas the means of more than two independent groups were compared with one-way analysis of variance (ANOVA). After the analysis of variance, different groups were determined by the Tukey multiple comparison test and the results were expressed in letter representation. Correlation analysis was performed in order to determine the associations among the variables and Pearson correlation coefficients were calculated. The level of significance (α) were taken into account as 5 % for the interpretation of calculations and results. All calculations were performed using SPSS v25 (IBM Inc., Chicago, IL, USA) statistical package program.

Results

The IMA levels were found to be statistically significant among the groups in the analyses conducted ($p < 0.001$). It was determined to be the lowest in the control group (healthy volunteers), slightly increased in the pre-dialysis group whereas noted to be quite high in the haemodialysis group (Tab. 1).

The MPO levels were found to be statistically significant in the analyses conducted among the groups ($p < 0.001$). It was determined to be the lowest in the control group (healthy volunteers), slightly increased in the dialysis group whereas found to be quite high in the pre-dialysis group (in contrary to IMA). We can state that MPO levels, which are one of the inflammation markers, are also increased in correlation with disease progression. MPO is an oxidant enzyme and it also shows partial antioxidant properties. In the pre-dialysis group, it can be sug-

Tab. 1. Descriptive statistics values and comparison results for IMA.

Group	n	Mean	Std. Error	Std. Deviation	Min.	Max.
Control	31	0. 369C	0.022	0. 120	0. 210	0. 669
Predialysis	43	0. 440B	0.012	0.077	0. 237	0. 595
Dialysis	37	0. 535A	0.018	0. 107	0. 366	0. 842
p-value			0.000***			

NS – non-significance, * p > 0.005, ** p < 0.05, *** p < 0.01, statistically significant (p < 0.001). The difference among the groups without a common letter is statistically significant (p < 0.05)

Tab. 2. Descriptive statistic values and comparison results for MPO.

Group	n	Mean	Std. Error	Std. Deviation	Min.	Max.
Control	31	350. 796C	23. 679	131. 839	111. 280	730.000
Predialysis	43	655. 497A	27. 328	179. 202	294. 870	1134. 870
Dialysis	37	536. 729B	39. 969	243. 120	112. 310	1208. 210
p-value			0.000***			

NS – non-significance, * p > 0.005, ** p < 0.05, *** p < 0.01, **** p < 0.001, statistically significant (p < 0.001). The difference among the groups without a common letter is statistically significant (p < 0.05)

Tab. 3. Descriptive statistics values and comparison results for EFTT.

Group	n	Mean	Std. Error	Std. Deviation	Min.	Max.
Control	31	4. 053B	0. 110	0. 611	2. 90	5. 60
Predialysis	43	6. 261A	0. 199	1. 302	3. 90	9. 00
Dialysis	37	6. 841A	0. 196	1. 194	4. 50	9. 50
p-value			0.000***			

NS – non-significance, * p > 0.005, ** p < 0.05, *** p < 0.01, statistically significant (p < 0.001) The difference among the groups without common letters is statistically significant (p < 0.05)

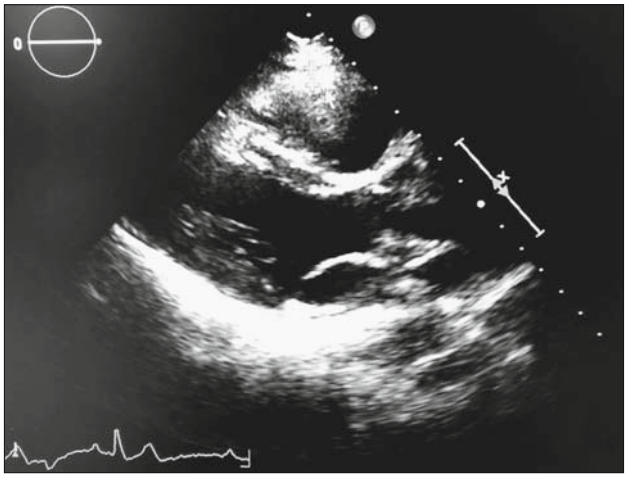

Fig. 1. Echocardiographic finding demonstrating the epicardial fat tissue thickness (0. 5 cm) of the control group.

gested that the balance inclines towards the antioxidant direction since antioxidant enzyme systems will come into play with the onset of disease progression. Therefore, the higher levels of MPO in the pre-dialysis group may be associated with this reason (Tab. 2).

The analyses conducted revealed a statistically significant difference among the groups in terms of EFTT ($p < 0.001$). It was determined to be the lowest in the control group (healthy volunteers), slightly increased in the pre-dialysis group whereas noted to be quite high in the haemodialysis group (Tab. 3). Increased epicardial fat tissue thickness (EFTT) secondary to chronic inflammation increased in correlation with the progression of CKD. The echocardiographic image showing the EFTT of the control group was presented in Figure 1.

In order to determine the associations among the variables investigated in the scope of the study, correlation analysis was performed for all the individuals included in the study as well as for each group separately.

The correlation analysis revealed a positive correlation of IMA with age, creatinine level, PTH, ferritin level (p and r values; $p = 0.032$, $r = 0.204$; $p < 0.001$, $r = 0.462$; $p = 0.008$, $r = 0.25$; $p < 0.001$, r = 0.4,92, respectively) whereas a negative correlation with MDRD, HDL and albumin levels. p and r values were given, respectively ($p < 0.00$, $r = –0.515$; $p < 0.001$ $r = –0.275$; $p < 0.001$ $r = –0.462$). These results demonstrated that IMA levels were highly correlated with the progression of CKD. The correlation analysis performed for MPO showed a positive correlation with age and triglyceride level (p and r values; $p = 0.015$ $r = 0.230$; $p < 0.001$ $r = 0.506$, respectively). MPO showed a negative correlation with the MDRD levels ($p < 0.001$ and $r = –0.341$). EFTT showed a high positive correlation with age, creatinine level, triglyceride level, PTH, ferritin, IMA, MPO levels. (p and r values; $p < 0.001$, $r = 0.493$; $p < 0.001$, $r = 0.502$; $p = 0.028$, $r = 0.208$; $p = 0.025$, $r = 0.213$; $p < 0.001$, $r = 0.396$; $p < 0.001$, $r = 0.372$, respectively). EFTT had a negative correlation with MDRD, HDL and albumin levels (p and r values; $p < 0.001$, $r = –0674$; $p < 0.001$, $r = –0347$; $p < 0.001$, $r = –0569$, respectively) (Tab. 4).

Tab. 4. Correlation coefficients and significance levels among the variables of all patients (n = 111).

		AGE	CREA	MDRD	TRIG	HDL	ALB	PTH	FER	IMA	MPX
MDRD	r	-0. 361	-0. 789								
	p	0.000***	0.000***								
TRIG	r	-0.054	0. 158	0. 155							
	p	0. 571	0.098	0. 104							
HDL	r	-0.086	-0. 406	0. 345	0. 205						
	p	0. 368	0.000***	0.000***	0.031*						
ALB	r	0. 319	0. 592	0. 660	-0.040	0. 298					
	p	0.001**	0.000***	0.000***	0. 678	0.001**					
CRP	r	0.035	0. 165	-0. 293	0. 190	0. 155	-0. 225				
	p	0. 717	0.083	0.002**	0.046*	0. 104	0.017				
PTH	r	-0.045	0. 554	-0. 476	0.046	-0. 186	-0. 255				
	p	0. 639	0.000***	0.000***	0. 635	0.051	0.007*				
FER	r	0. 149	0. 757	0. 607	0.080	-0. 393	-0. 477	0. 376			
	p	0. 119	0.000***	0.000***	0. 402	0.000***	0.000***	0.000***			
VIT D	r	0. 148	-0.064	-0.030	0.055	-0.034	0.084	-0.031	-0.098		
	p	0. 122	0. 504	0. 759	0. 567	0. 722	0. 385	0. 749	0. 309		
IMA	r	0. 204	0. 462	-0. 515	0.010	-0. 275	-0. 462	0. 250	0. 492		
	p	0.032*	0.000***	0.000***	0. 920	0.003**	0.000***	0.008**	0.000***		
MPX	r	0. 230	0. 136	-0. 341	0. 506	-0. 151	-0. 184	0.064	-0.012	-0.008	
	p	0.015*	0. 154	0.000***	0.000***	0. 115	0.054	0. 502	0. 897	0. 936	
EFTT	r	0. 493	0. 502	-0. 674	0. 208	-0. 347	-0. 569	0. 213	0. 396	0. 429	0. 372
	p	0.000***	0.000***	0.000***	0.028*	0.000***	0.000***	0.025*	0.000***	0.000***	0.000***

r – Pearson correlation coefficient; * statistically significant ($p < 0.05$); ** statistically significant ($p < 0.01$); *** statistically significant ($p < 0.001$)

Discussion

The present study revealed a high level of correlation between the oxidant enzymes of IMA and MPO levels and progression of CKD. Likewise, we noted that EFTT, which is considered to increase secondary to chronic inflammation, chronic atherosclerosis, was also highly correlated with disease-follow-up parameters of CKD. At the same time, EFTT was positively correlated with IMA and MPO levels. These results suggest us that from now on IMA, MPO and EFTT can be follow-up parameters for monitoring disease progression in CKD, in other words, that they have prognostic values.

IMA resulting from the changes occurring in the N-terminal region of the circulating albumin in ischemic conditions is a recently identified marker indicating tissue ischemia and oxidative stress (5).

The experimental study by Kocan et al reported that IMA is a non-selective marker for renal ischemia-reperfusion injury. The authors created renal ischemia in three groups of rats against the control and sham group at different time periods (20 minutes, 30 minutes and 40 minutes), analysed IMA levels in the rat serum and examined the kidneys of the rats histopathologically. As the duration of ischemia increased, they stated that IMA level increased and histopathological examination revealed that the grade of ischemia and IMA level were highly associated (6). Our study also had similarities with the study by Kocan et al. The facts that IMA level was the highest in the dialysis groups among the groups, that IMA level increased as age and creatinine levels increased and that IMA level decreased as the level of MDRD increased suggests that IMA has a prognostic value in CKD.

The correlation of oxidative biomarkers and IMA level with gender, BMI, GFR, ACR (albumin/creatinine ratio) was examined in a study conducted by Cournot et al in type 2 diabetic patients. IMA was found to have a negative correlation with BMI and GFR, while it was detected to have a positive correlation with ACR. IMA was not found to have a significant association with age and gender in the same study (7). Our study is partially in agreement with the study by Cournot M et al. We detected a positive correlation between age and IMA levels in our study. Similarly, as the grade of CKD increased, IMA levels increased significantly as well. Regarding the association noted between the prognosis of DM and IMA level by Courmot et al, we observed a correlation in a way that IMA level increased as GFR decreased. The present study is the first study in the literature examining the relationship between CKD stages and IMA level.

Ukinc et al investigated the association of IMA levels with hyperglycemia, blood pressure, lipid levels, CRP and microalbuminuria in their study conducted on 50 patients with Type 2 diabetes without macrovascular disease and acute ischemia and 30 healthy volunteers. IMA level was found to be higher compared to the healthy control group, the plasma levels of IMA were determined to have a correlation with CRP and microalbuminuria. They considered that elevated IMA levels could be the indicator of underlying subclinical vascular disease in patients with type 2 diabetes (8). Our study is consistent with the study by Ukinc et al.

MPO plays a basic role in the formation of oxidants by the immune system during the oxidative burst process. Especially, it is predicted that the MPO-H_2O_2-Cl system of activated phagocytes plays an important role in tissue damage resulting from inflammation (e.g., atherosclerosis, glomerulosclerosis and ischemia-reperfusion injury) and that identifying and measuring specific biomarkers of this oxidase system may reflect the disease status (9, 10).

Jelić-Knezović N et al noted a strong positive association between the HbA_1c level, which is an indicator of glycemia, and MPO in their study conducted on patients with Type 2 DM (11). Afshinnia F et al stated that MPO levels increased as the stage of CKD increased and that a mild decline occurred in the advanced stage CKD (stage 5) in their study (12). The results of the present study and those of the study by Afshinnia et al are exactly consistent with each other. It is known that haemodialysis application increases oxidative stress. MPO levels were taken at the dialysis access to avoid this adverse effect in the HD patient group. We think that the MPO levels in the HD group are low due to the pre-dialysis group. Likewise, also in our study, MPO levels were highest in the pre-dialysis group and it was followed by the HD group and it was found to be the lowest in the control group. Our results are consistent with the findings in literature.

Various studies and evidence published so far on epicardial fat tissue suggest that epicardial fat tissue is anatomically and clinically associated with the morphology and function of the heart. The epicardial fat tissue is a metabolically active organ producing numerous bioactive molecules that can affect cardiac functions significantly. The close anatomic relationship between the myocardium and epicardial fat tissue may suggest the presence of this small fat deposition's paracrine effect (13). The effects of the epicardial fat tissue, which is a biochemically active organ, on the heart were investigated and it was seen that a prominent inflammatory response occurred in the epicardial fat tissue of the subjects with coronary artery disease and that this inflammatory response was independent of BMI and DM. Also, neither the correlation of this local inflammatory response with plasma inflammatory response was observed nor it could be shown that this response was reduced locally with conventional anti-ischemic treatment (14). In the observational cross-sectional study by Bhuiyan GR et al, the relationship between the epicardial fat tissue thickness (EFTT) and coronary artery disease (CAD) was investigated. A total of 123 patients were included in that study and epicardial fat tissue thickness (EFTT) measurements by echocardiography were compared with the findings of the coronary angiography. Echocardiographic epicardial fat tissue thickness (EFTT) was found to be significantly higher in the patients with CAD compared to those with normal coronary arteries (6.67 ± 2.24 mm vs 4.61 ± 1.62 mm, $p < 0.001$). Also, EFTT was observed to increase with the severity of CAD (multivessel disease 7.99 ± 2.12 mm and single vessel disease 5.93 ± 1.97 mm, $p < 0.001$). The Gensini score was determined to be significantly correlated with EFTT ($r = 0.617$, $p < 0.001$).The optimal cut-off value of epicardial fat tissue thickness (EFTT) as a determinant of angiographic CAD was 6.44 mm with a sensitivity of 45.31 % and specificity

of 92.86 % [ROC area 0.756, p < 0.001, 95% CI (0.66–0.85)]. Echocardiographic epicardial fat tissue thickness (EFTT) was found to be significantly correlated with the presence and severity of coronary artery disease detected angiographically. The present study stands out among the first studies assessing the association of CKD disease progression with EFTT in the literature. Bhuiyan et al found a strong association between the disease severity of CAD and EFTT (15). In the present study, we also noted a strong association of EFTT with creatinine and MDRD levels indicating CKD progression. Our results were totally consistent with the literature findings.

Aydin et al investigated the relationship between epicardial fat tissue thickness (EFTT) and carotid intima-media thickness (CIMT) in the HD patients compared to the control group. Both EFTT and CIMT were found to be significantly higher in the HD patients compared to the control group. The authors stated that measuring EFTT by echocardiography for screening cardiovascular disease in the HD patients is a practical, non-invasive, inexpensive, rapid method. They also noted that mortality and morbidity secondary to cardiovascular disease of HD patients could be prevented with EFTT and CIMT measurements (16).

When the literature was examined, the association of EFTT with pre-diabetes, insulin resistance, hyperlipidaemia, hypertension, metabolic syndrome, the presence and severity of coronary artery disease and subclinical atherosclerosis was noted (17–22) Given that CKD patients with atherosclerotic vascular disease have a high morbidity and mortality, EFTT, a simple and non-invasive measurement method, can be predicted to have an important role in the prognosis follow-up of CKD disease (23, 24). Abdallah et al examined the relationship between serum paraoxonase levels with EFTT in the HD patients compared to the control group and paraoxonase was found to be lower in the HD patients compared to the control group since it is an antioxidant enzyme (25). IMA and MPO, our biomarkers, are in the class of oxidant enzymes. Therefore, it is quite normal that they were detected to be high in the HD patients in our study in contrast to the study by Abdallah et al. Whereas they found EFTT higher in the HD patients compared to the control group as in our study. Our results are consistent with the results of the study by Abdallah et al.

In conclusion, we believe that we have introduced three novel follow-up parameters such as: IMA, MPO, and EFTT to literature as the follow-up parameters for CKD. As the levels of IMA and MPO increase, the severity of CKD increases as well. Likewise, there is also a positive correlation between EFTT and the severity of CKD. We suggest that longer-term studies with larger populations are required for identifying the prognostic values.

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Received April 9, 2018.
Accepted May 3, 2018.