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RESEARCH ARTICLE

USEFULNESS OF SERUM PROCALCITONIN AS A PREDICTOR BIOMARKER OF ATHEROSCLEROSIS IN DIALYSIS PATIENTS.

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Abstract

Background: The most common cause of death among the patients with end-stage renal disease is coronary artery disease. It is known that inflammation plays a key role in coronary artery disease. The aim of this study was to determine the relationship between serum procalcitonin levels and atherosclerosis among dialysis patients.

Material and Method: A total of consecutive 74dialysispatients (mean age: 54.92±13.9 years and male/female: 47/27) were included in this study. All participants were divided into two groups according to presence of atherosclerosis.We have planned to compare the patients on hemodialysis (HD) and peritoneal dialysis (PD) each other considering the parameters of inflammation in particular serum procalcitonin (PCT) and C-reactive protein (CRP) with atherosclerosis. Univariate and multivariate statistical methods were used by using SPSS packet programme.

Results: The mean of ages of HD and PD patients were 59.3±11.3 and 50.7±14.9 years respectively. The levels of PCT were higher among atherosclerotic dialysis patients ($p<0.001$ and $p=0.036$, respectively). Considering the patients on hemodialysis, there were significant correlation between CRP and PCT. However this significant correlation was not observed among the patients on PD despite they had increased levels of CRP and PCT ($p<0.001$, $r=0.62$ and $p=0.362$, $r=-0.16$, respectively).

Conclusion: Combining PCT and CRP levels could be a reliable marker of chronic inflammation that is associated with atherosclerosis in dialysis patients.

Introduction:-

It's well known that the patients with chronic kidney disease (CKD) are more prone to cardiovascular morbidity and mortality than the healthy subjects. Chronic inflammation and atherosclerotic cardiovascular diseases are seen frequently in patients with CKD and are important risk factors affecting mortality and morbidity (1). Moreover, atherosclerosis is a chronic inflammatory process that develops mainly in childhood and develops as a result of endothelial dysfunction and oxidized LDL particles damaging the endothelium (2,3). It is thought that atherosclerosis and endothelial dysfunction may be associated with elevation of proinflammatory cytokines and other inflammatory factors in patients with end-stage renal disease (ESRD) due to uremia (4-6).

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In addition, increased levels of C-reactive protein (CRP) have been demonstrated to be related to malnutrition, hypoalbuminemia, erythropoietin resistance, high lipoprotein (a), low HDL concentration and high fibrinogen levels (7-9).

Today, strong link between nutritional and inflammatory markers and cardiovascular disease has been demonstrated in patients with CKD (9,10-13). With the reduction of the risk of atherosclerosis, a significant fall in both mortality and morbidity rates will be achieved in patients with ESRD.

In this study, we aimed to evaluate the role of procalcitonin (PCT) and other inflammatory markers in patients with and without atherosclerosis by grouping patients undergoing hemodialysis (HD) and peritoneal dialysis (PD) therapy.

Material and methods:-

The study group consisted of a total of 74 consecutive dialysis patients (14 women and 22 men patients on regular 3 times weekly hemodialysis and 13 women and 25 men patients on peritoneal dialysis).Patients with known malignant disease and acute or chronic inflammatory diseases were excluded.Patients undergoing HD and PD were divided into two groups according to presence of atherosclerosis.

Age, gender, educational status, marital status, duration and frequency of hemodialysis therapy, duration of peritoneal dialysis therapy and number of changes were obtained by mutual interviewing. The presence of obvious atherosclerotic disease was investigated by patient's history, physical examination and laboratory tests. For this purpose, telecardiography, echocardiography; if performed before, coronary angiography and carotid artery doppler were used. Left ventricular mass and mass index were calculated according to Devereux method as suggested by American Society of Echocardiography (14).The patients were divided into two groups, those with atherosclerosis findings grouped as 'high risk for atherosclerosis' and those without atherosclerosis findings grouped as 'low risk for atherosclerosis'.Patient's average values of serum CRP, PCT, fibrinogen and ferritin from the last six months were assessed as the markers of inflammation. BMI is obtained by dividing weight by the square of height (ie, kg/m2).This study was approved by the local ethics committee of BulentEcevit University Hospital (Ethical Application Ref: 2009-09). All individuals were fully informed about the objective of the study and agreed to participate.

Laboratory assessment:-

The levels of studied biochemical markers were analysed in blood of all people involved in the study. Serum albumin and prealbumin were measured by colorimetric method on an AU 2700 analyser (Beckman Coulter, Tokyo, Japan), according to the manufacturer's specifications and using proprietary reagents. Serum lipid levels were determined using xylidine blue with an end-point colorimetric method (Roche Diagnostics GmbH; Mannheim, Germany). While the PCT value was studied by the enzyme linked fluorescent assay (ELFA) method in Vidas (Bi-biomerieux, France), the CRP value was measured by turbidimetric latex agglutination method (Biosystems, SA, Spain).

Carotid intima media thickness measurement:-

Carotid intima media thickness (CIMT) measurements were performed using the ATL HDI 5000 ultrasound with a 5-7.5 MHz linear transducer.Thickness of the intima media was defined as the distance between the leading edge of lumen intima and the leading edge of media adventitia echo.CIMT measurements were always performed in plaque-free arterial segments. All examinations and measurements were performed by the same examiner to exclude examiner bias.

Statistical Analysis:-

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Version 13.0). Results are expressed as mean±standard deviationwhile categorical variables are presented with frequency and percentage..Parametric values are evaluated by using student t-test and non-parametric values are evaluated by using Anova. In the comparison between groups, statistically significant differences were assessed with the Wilcoxon signed ranks test or Mann Whitney U test. The linear relationship between two variables was evaluated by Pearson correlation analysis. For all statistical analyses, a P value < 0.05 indicated statistical significance.

Results:-

The mean age of HD and PD patients was 59.3±11.3 and 50.7±14.9 years respectively.There were significant increases in both PCT, CRPlevels and a decrease inalbumin levels among atherosclerotic HD patients (p<0.001).In PD patients with atherosclerosis, serum albumin levels were notably lower (p = 0.018)); on the contrary, CRP (p = 0.006), right IMT (p <0.001) and left IMT (p <0.001) were significantly higher. However, there was no significant difference for PCT (p = 0.319) values. The characteristic features of patients are given in **Table 1.**

Table 1:-Demographic features and laboratory results of the study participantswith and withoutatherosclerosis.

	HD (n=36)			PD (n=38)		
	Atherosclerotic(n =28) mean ± sd	Non-atherosclerotic (n=8) mean ± sd	p	Atherosclerotic (n=27) mean ± sd	Non-atherosclerotic (n=11) mean ± sd	p
Age (year)	60.8±9.8	54.1 ±15.1	0.140	55.6±12.0	38.6±14.9	0.001
Male/Female (%)	64.3/35.7	50/50	0.683	77.8/22.2	36.4/63.6	0.024
Duration (month)	21.1±18.8	16.8±16.4	0.563	46.9±33.2	45.2±34.4	0.889
BMI (kg/m2)	26.4±4.1	24.2±4.9	0.220	27.5±4.1	26.5±11.0	0.773
Albumin (mg/dl)	3.3±0.5	4.4±0.1	<0.001	3.1±0.4	3.7±0.7	0.018
Prealbumin(mg/dL)	30.2±8.0	33.2±16.9	0.480	39.1±12.8	45.8±19.3	0.224
TC(mg/dL)	162.8±41.4	166.3±15.1	0.716	201.0±54.1	186.6±43.4	0.440
Right CIMT (mm)	0.90±0.24	0.62±0.08	<0.001	0.80±0.22	0.56±0.92	<0.001
Left CIMT (mm)	0.95±0.29	0.63±0.07	<0.001	0.82±0.21	0.60±0.08	<0.001
CRP (mg/L)	15.9±5.2	4.3±1.6	<0.001	16.4±7.6	8.6±6.8	0.006
PCT(ng/mL)	0.20±0.12	0.09±0.04	<0.001	0.45±0.95	0.42±0.47	0.319
Fibrinogen(mg/dl)	428.5±151.8	394.1±103.4	0.553	510.9±135.9	489.7±135.6	0.665
Ferritin (ng/dl)	799.2±421.0	754.0±440.2	0.792	640.9±432.0	741.5±505.0	0.539

Abbreviations: HD: hemodialysis, PD: peritoneal dialysis, BMI: body mass index, TC:total cholesterol, CIMT: carotid intima media thickness, PCT: procalcitonin, CRP: C-reactive protein,sd: standarddeviation.

Considering the patients on hemodialysis, there was a positive correlation between the inflammatory parameters CRP and PCT, and the development of atherosclerosis (p<0.001, r=0.62). While there were increased levels of CRP and PCT, any significant correlation was not observed among the patients on PD (p=0.362, r=-0.16). Right and left CIMT were higher among the patients who had atherosclerosis and on any kind of dialysis therapy.

Table 2:- The association between CRP levels greater than 10 mg/dL and the development ofatherosclerosis

	Atherosclerosis (+) (n=55)		Atherosclerosis (-) (n=19)		p
Category	n=	%	n=	%	
CRP≥10 mg/dl	47	85	3	15	<0,001
CRP<10 mg/dl	8	15	16	85	

Abbreviations:CRP: C-reactive protein.

Prealbumin levels were significantly higher in the patients on PD compared with the patients on HD (< 0.05). This could be explained with the increased albumin synthesis stimulated with the peritoneal loss of albumin. Atherosclerotic parameters were mildly worse in the patients on HD compared to the patients on PD. The patients on dialysis who have increased levels of CRP have also increased risk of developing and atherosclerosis as shown in **Table 2.**

Discussion:-

Atherosclerotic heart disease is known to be responsible for approximately 55% of deaths in ESRD patients (10,15).When the factors affecting atherosclerosis in CKD are investigated and then two risk factors such as age and gender took out of the equation, it was determined that CRP elevation was an independent factor for atherosclerosis risk (10).

Pro-inflammatory cytokines; IL-1, IL-6, TNF and CRP can be found at high levels in patients with CKD (16). Studies showed a significant increase in serum IL-6, IL-1, and TNF-α levels in patients with renal failure, but no

difference was observed between dialysis and predialysis patients (17,18), whereas, in some studies, an increase in inflammatory markers was found in patients who started dialysis (19).

In a study conducted by Bologa et al. in HD patients, it was emphasized that increased cytokine level was correlated with low albumin levels and affected the survival rate of patients (20). Bergström et al. reported that CRP is the best indicator of serum albumin levels and predicts mortality risk better than albumin levels in patients in the first year of HD treatment (7). Stenvinkel et al. in their study, they found significantly higher CRP levels in malnutrition patients indicating an inflammatory process (10). Zimmerman et al. found that CRP and albumin were independent indicators for all causes of death in HD patients (9).Wanner et al. In a study of 280 stable HD patients; At the end of 4-year follow-up, 44% of patients died and 60% of these deaths were due to cardiovascular causes. In addition, a positive relationship between CRP levels and death was shown in these patients (21). Angela et al. reported that CRP had a strong association with cardiovascular morality as in HD patients and showed a significantly independent prognostic value in PD patients (22).

In a study to demonstrate the association of PCT (a newly identified inflammation marker) with other markers, a positive correlation was found among PCT and IL-6 and CRP, whereas a negative correlation was observed between PCT and prealbumin in HD patients (23).Similarly, Chauveau et al. in their study found increased levels of CRP and PCT associated with malnutrition (24).Güz et al.; in a study they conducted with 51 PD, 74 HD, and 34 non-uremic patients in order to demonstrate the association of PCT with CRP and other traditional inflammation markers in PD patients, they found insignificant difference in their PCT levels compared to the HD patients, although the PCT levels were higher than the non-uremic patients. In the conclusion, they stated that PCT can be used as an adjunct to markers such as CRP in the determination of inflammation and following its progression (25).

In our study, CRP and PCT were significantly higher in patients with atherosclerosis in the HD patients. While there was a significant increase in CRP levels in PD patients with atherosclerosis, the results in PD patients with malnutrition were statistically insignificant. Although, the mean values of PCT were high. This may be due to age and gender inequality. Correlatively to the literature, there was a strong positive correlation between PCT and CRP in the HD patients, while in the PD patients we could not find such a relationship. This may be due to the relative small sample size of the study. According to the results of the study, it can be said that in HD patients, PCT and CRP co-evaluation may be more sensitive in case of chronic inflammation. Further comprehensive studies will be needed to support these findings.

Conclusion:-

Atherosclerosis and inflammation are all closely related among the patients on dialysis therapy.It can be thought that inflammation is mostly associated with malnutrition and may indirectly cause atherosclerosis. Taking in consideration both of CRP and PCT levels as inflammation markers will be a reliable indicator of chronic inflammation in dialysis patients. With a better understanding of pathogenesis, we hope that unacceptably high morbidity and mortality rates in ESRD patients will be reduced.

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