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Non-traditional Relationship between Carotid Intima-media Thickness and Mean Platelet Volume, Serum Magnesium and 25-OH-Vitamin D3 Level in Chronic Kidney Disease

Refika Karaer[1], Saime Paydaş[1*], Kairgeldy Aikimbaev[2], Damla Karacor[3], Mustafa Balal[1] and Nurten Dikmen[3]

[1]Departments of Nephrology, Medical Faculty, Cukurova University, Adana-01330, Turkey.
[2]Departments of Radiology, Cukurova University, Adana-01330, Turkey.
[3]Departments of Biochemistry Cukurova University, Adana-01330, Turkey.

Authors' contributions

This work was carried out in collaboration between all authors. Authors RK and SP participated in concept and design, data collection and data analysis, in creation of manuscript involving critical writing and revising of the content. Author KA participated in measurement of carotis intima media thickness of all patients. Authors DK, MB and ND participated in collection of blood sample. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aım: Cardiovascular diseases are the most important causes of mortality and morbidity in chronic renal disease. The purpose of this study is to determine the relationship between glomerular filtration rate, serum levels of calcium, phosphorus, magnesium parathormone, vitamin D, lipids

**Corresponding author: E-mail: spaydas@cu.edu.tr;*

and hematological parameters and carotid intima-media thickness (CIMT) in chronic renal patients and healthy indiviuals.
Methods: Twenty-seven healthy individuals [(control group (CG)] and 53 patients with chronic renal failure (CRF) (GFR 15-59 ml/min) [study group (SG)] were included in this case control study. All participants' characteristics, physical examination and laboratory tests results were recorded. Same radiologist measured bilateral CIMT by color Doppler ultrasonography.
Results: CG and SG were similar for age, gender. Besides CIMT was higher in patients with chronic renal failure, CIMT were correlated with systolic blood pressure (SBP), platelet, magnesium, alkaline phosphatase (ALP), parathormone (PTH) positively, 25-OH vitamin D3, high density lipoprotein (HDL) negatively. In CG CIMT was positively correlated with SBP, body mass index (BMI), serum levels of albumin, glucose, ALP, and mean platelet volume (MPV).
Conclusion: CIMT was higher in patients with CRF compared to healthy controls. Besides the serum levels of glucose, albumin, HDL, and BMI, CIMT were correlated with non-traditional factors such as higher serum magnesium and PTH level, 25-OH vitamin D3 deficiency in patients with chronic renal failure.

Keywords: Carotid intima media thickness; platelet; magnesium; secondary hyperparathyroidism.

1. INTRODUCTION

Cardiovascular diseases (CVD) are the most important causes of mortality and morbidity in chronic renal patients due to accelerated atherosclerosis. These patients have a risk of mortality 10-20 times higher than general population [1,2]. The patogenesis of atherosclerosis in chronic kidney disease is somewhat different from general population and is also affected by non-traditionals factors such as genetic factors, inflammation, hyperparathyroidism, malnutrition [3,4]. Atherosclerosis can be evaluated by measurement of carotid intima-media thickness (CIMT) with ultrasonography which is a simple, reliable, non-invasive method [5,6].

The purpose of this study is to determine the possible factors that affect on CIMT which is the indicator of cardiovascular diseases in chronic renal patients and healthy individuals.

2. PATIENTS AND METHODS

Fifty-three chronic renal patients (GFR 15-59 ml/min) [study group (SG)] and 27 healthy controls [control group (CG)] were included into this case-control study. Exclusion criteria were as follows: acute infection, chronic inflamatory disease, malignancy history. All participants' age, gender, body mass index (BMI), primary renal disease, blood pressure (BP) were recorded. BMI was calculated using weight/ height^2 (kg/m^2). Complete blood count, biochemical parameters such as serum levels of glucose, BUN, creatinine, calcium (Ca), phosphorus (P), magnesium (Mg), total cholestrol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), ferritin, C-reactive protein (CRP), parathyroid hormone (PTH), 25-OH-vitamin D3, alkaline phosphatase (ALP), total protein, albumin were measured. The carotid arteries were evaluated with a high resolution B-mod ultrasonography using a 12.0 MHz linear transducer. All measurements were performed by the same experienced radiologist due to not being the difference of experience. CIMT was defined as the distance between the inner echogenic line (lumen-intima interface), and the outer echogenic line, which represents the collagen-containing media-adventitia layer. The measurements were taken while the patients were in supine position with the head turned 45° to the opposite of the measurement side. Three measurements were taken at the posterior wall of both common carotid arteries 2 cm proximal to the bulbus, CIMT was defined as the distance between the leading edge of the first bright line and the second bright line. The arithmetic mean value of three measurements of posterior wall of right and left carotid arteries was calculated and recorded as CIMT. The protocol of the study was contucted in accordance of the ethical principles stated in the decleration of Helsinki. It was approved by Ethics council of the University of Çukurova and all participants gave written informed consent.

2.1 Statıstıcal Analysıs

All statistical analysis were performed with statistical analysis program (SPSS 15). All data are expressed as mean and standart deviation. For non-normally distrubuted variable Mann Whitney U test, for normally distrubuted variable Independent Sample T Test were used. Chi-square test was used to investigate dependency

between variable. For non-normally distrubuted variable the Spearman Correlation Coefficient was used to analyze the correlation between CIMT and other risk factor variables. A p value less than 0.05 was considered statistically significant.

3. RESULTS

There was no significant difference in CG and SG for age and gender. Mean age was 51.02± 13.61 in SG and 52.14±12.66 in CG. Primary renal disease of our patients were glomerulonephritis (%17), diabetes mellitus (DM) (%37.7), hypertension (%13.3), amyloidosis (%3.7) and unkown (%28.3). The comparison of laboratory parameters and demographic characteristics of SG and CG were shown in Table 1. BMI, hemoglobin, total protein, albumin and 25-OH-vitamin D3, levels were significantly lower in SG compared to CG. CIMT, BUN, creatinine, P, Mg, PTH, ALP, glucose, CRP, white blood cells (WBC), ferritin levels were also higher in SG than CG. There were no significant differences in systolic BP, diastolic BP, platelets, mean platelet volume (MPV), total cholestrol, HDL, LDL, TG, calcium between SG and CG. The parameters correlated with CIMT in two groups were shown in Table 2. In SG CIMT was positively correlated with platelets, magnesium, ALP, PTH, systolic BP and negatively correlated with HDL, 25-OH-vitamin D3. In CG CIMT was negatively correlated with MPV, albumin and positively correlated with systolic BP, BMI, ALP, glucose.

Table 1. The comparison of laboratory parameters and demographic characteristics of study and control group

	Control group (n:27)	Study group (n:53)	p
Systolic BP (mmHg)	123.15 ± 17.82	130 ±17.43	0.125
Diastolic BP (mmHg)	78.7 ± 10.43	78.96 ± 9.01	0.687
BMI (kg/m^2)	29.86 ± 5.47	26.61 ± 6.27	**0.006***
BUN	13.3± 8.29	53.66± 27.47	**0.000***
Creatinine	0.78± 0.35	4.99± 3.26	**0.000***
Ca (mg/dl)	9.36 ± 0.34	9.18 ± 0.58	0.317
P (mg/dl)	3.48 ± 0.54	4.62 ± 1.30	**0.000***
Mg (mg/dl)	2.06 ± 0.22	2.29 ± 0.44	**0.001***
ALP (U/L)	57.93 ± 19.41	75.06 ± 25.62	**0.002***
PTH (pg/ml)	71.62 ± 53.17	273.02 ± 216.04	**0.000***
25-OH-Vitamin D3 (ng/ml)	15.92 ± 7.17	11.91 ± 7.27	**0.011***
Albumin (g/dl)	4.11 ± 0.31	3.45 ± 0.50	**0.000***
CRP (mg/dl)	0.51 ± 0.41	1.77 ± 2.57	**0.000***
Glucose (mg/dl)	96.04 ± 22.25	116.75 ± 36.95	**0.007***
HDL (mg/dl)	41.24 ± 9.46	37.40 ± 10.45	0.064
LDL (mg/dl)	122.7 ± 33.81	112.91 ± 47.59	0.198
Triglyceride (mg/dl)	142.81 ± 91.39	177.44 ± 169.46	0.299
WBC (µL)	6687.41 ± 1494.03	8246.42 ± 1988.06	**0.000***
Platelets (µL)	314851.85± 386250.39	272716.98 ± 87413.78	0.250
MPV (Fl)	8.23 ± 1.86	8.21 ± 1.59	0.955
CIMT(cm)	0.06 ± 0.01	0.08 ± 0.02	**0.002***

*PTH: Parathyroid hormone, ALP: Alkaline phosphatase, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglycerides CIMT: Carotid intima-media thickness , MPV: Mean platelet volume, BMI: Body mass index , WBC: White blood cells, BP: Bloodpressure, *: p" significant*

Table 2. The parameters correlated with carotid intima-media thickness in study and control groups

Study group			Control group		
Parameters	**R**	**p**	**Parameters**	**R**	**p**
Systolic BP	0.323	0.018*	Systolic BP	0.442	0.021*
Platelets	0.278	0.044*	BMI	0.571	0.002*
Mg	0.359	0.008*	Albumin	-0.464	0.015*
ALP	0.329	0.016*	Glucose	0.462	0.015*
PTH	0.281	0.042*	ALP	0.464	0.015*
25-OH Vitamin D3	-0.282	0.042*	MPV	-0.638	0.000*
HDL	-0.330	0.016*			

*PTH: Parathyroid hormone, ALP: Alkaline phosphatase, MPV: Mean platelet volume, BP: Blood pressure, HDL: High density lipoprotein, BMI: Body mass index *:p:significant*

4. DISCUSSION

Chronic kidney disease is an important risk factor for the development of cardiovascular disease. CIMT, considered as the indicator of cardiovascular disease, was higher in chronic renal patients than control group as other studies (7,8). In both group, systolic blood pressure and serum albumin level were found to be correlated with CIMT. In SG CIMT was positively correlated with systolic blood pressure, PTH, ALP, Mg and platelet, negatively correlated with HDL and 25-OH vitamin D3. But a correlation wasn't found between CIMT and LDL, TG, glucose levels. This finding has demonstrated the inadequacy of explanation by only traditional factors such as diabetes mellitus, dyslipidemia about accelerated atherosclerosis in chronic kidney disease. In contrast to in patients with chronic kidney disease, BMI and glucose correlated with CIMT in control group.

Malnutrition and inflamation have been thought to associate with increased CIMT in SG due to the lower level of BMI, total protein and albumin, the higher level of CRP and WBC compared to CG. Although albumin level was within normal limit in CG, albumin was negatively correlated with CIMT. This finding has demonstrated that albumin effects not only chronic renal patient but also healthy individuals. The correlation between CIMT and glucose, systolic BP, BMI in CG has shown the effect of classical risk factors such as diabetes mellius, hypertension, obesity on healthy people.

Platelets play an important role in coagulation, inflammation, thrombosis and atherosclerosis by secreting mediators in blood circulation [9,10]. The positive correlation between CIMT and platelet count in SG was also found. Mean platelet volume is also reported as the important determitant of platelet activity besides the platelet count. The increased MPV values represent that platelets contain more granules, produce greater amounts of vasoactive and prothrombotic factors, in other words they are likely to be more reactive [11]. The increase on MPV value was identified in the studies carried out on patients who have stable cardiac disease and/or have suffered after myocard infarction. It has been emphasized that elevated MPV may be a prognostic and/or predictive indicator in cardiovascular diseases [11,12]. But there isn't a proof concerning elevated MPV that can be an indicator of cardiac disease in healhty individuals. Altough platelet count and MPV value were higher in CG than SG, the negative correlation between CIMT and MPV was found in CG. The same correlation wasn't found in SG.

As the studies researching the factors playing a role in the development and progression of atherosclerosis such as 25-OH vitamin D3, PTH, ALP, magnesium, which were associated with Ca-P metabolism [13,14]. We found correlations between CIMT and higher PTH and ALP levels, lower 25-OH vitamin D3 level. These findings were consisitent with secondary hyperparathyroidism. Serum P levels were higher than control but serum Ca was similar to control group it may be related with higher PTH. Also any correlations were not found between serum levels of P and Ca and CIMT. In contrast to some studies, there was a positive correlation between CIMT and higher magnesium level in our study. We explain the positive correlation between CIMT and higher magnesium levels in the study group by the fact that renal patients with higher magnesium levels have more advanced kidney disease and so have more risk of atherosclerosis. Experimental and clinical trials have shown that low magnesium level plays a role in development of CVD [15,16]. It can say that high magnesium level has been thought to contribute to CIMT due to association with secondary hyperparathyroidism. Additionally, high magnesium level may be a protection mechanisim against accelerated atherosclerosis.

Epidemiological studies have reported that vitamin D deficiency is prevalent in all societies [17,18]. In our study 25-OH vitamin D3 deficiency was found in both two groups. 25-OH Vitamin D3 was lower in SG than CG significantly. Vitamin D is a hormone stored in the adipose tissue. Lower BMI in SG than CG can contribute to this difference besides the renal synthesis of vitamin D and other factors.

The limitations of this study are; the inadequancy of numbers of participants, not analysing sub-groups according to GFR, and our research being a case control study considering the fact that CIMT may change in a long term.

5. CONCLUSİON

CIMT was higher in patients with chronic renal failure. The platelet count and parameters which were associated with secondary hyperparathyroidism like as ALP, high magnesium and low 25-OH vitamin D3 level were found important in the increase of CIMT besides HDL and systolic BP.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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