10.5152/turkjnephrol.2021.4518

Original Article

Turkish Journal of Nephrology

Comparison of Plasma Levels of Preβ1-HDL with EAT Thickness in Patients with Chronic Kidney Disease

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ABSTRACT

Objective: The levels of plasma preβ-HDL increase as the stages of chronic kidney disease (CKD) progress. Epicardial adipose tissue (EAT) increases the risk of cardiovascular incidents in patients with moderate to severe CKD. The aim of our study was to compare the levels of plasma preβ1-HDL with the EAT thickness on transthoracic echocardiography in patients with CKD (stage 3-5).

Methods: Forty-four patients with CKD and 44 healthy volunteers (control group) were included in the study. Plasma preβ1-HDL was measured with ELISA (enzyme-linked immunosorbent assay) method in both groups. EAT thickness (both systole and diastole) was evaluated by the same cardiologist on the transthoracic echocardiographic method only in the patient group. $P < .05$ was accepted as statistically significant.

Results: The mean plasma preβ1-HDL level was higher in the patient group compared to the control group but did not reach statistical significance. It was determined that the level of mean preβ1-HDL was increased in CKD patients as the stages progress but the result was not statistically significant. When the level of mean plasma preβ1-HDL and EAT thickness of CKD patients were compared, a statistically significant and negative correlation was determined ($P = .013$, $r = -0.398$; $P = .006$, $r = -0.441$, respectively, for systole and diastole).

Conclusion: We determined a statistically significant and negative relationship between the levels of plasma preβ1-HDL and EAT thickness in CKD patients.

Keywords: Preβ1-HDL, epicardial adipose tissue thickness, chronic kidney disease

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Received: July 7, 2020 **Accepted:** October 22, 2020

Cite this article as: Bakırdöğen S, Ülker Çakır D, Akşit E, Ünal Çetin E. Comparison of plasma levels of preβ1-HDL with eat thickness in patients with chronic kidney disease. *Turk J Nephrol*. 2021; 30(2): 124-129.

INTRODUCTION

In the general population, increased high-density lipoprotein cholesterol (HDL-C) levels are associated with reduced cardiovascular risk. Lower serum HDL cholesterol levels are common among patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), but it is known that low HDL-C does not increase the risk of cardiovascular disease in these patients after adjustment for conventional risk factors.[1] The association of HDL-C molecule with cardiovascular outcomes depends on both the serum concentration and the properties of the molecule. Therefore, studies aimed at examining the relationship between HDL-C and cardiovascular disease risk should consider the effect of this molecule as a whole (quantity and various properties) on atherosclerosis.[2]

Both alpha (α) and pre-beta (pre-β1 and pre-β2) subtypes of HDL molecule have been defined.[3] The pre-β1-HDL is regarded as the first receptor of cellular cholesterol and thus it is important for reverse cholesterol transport.[4] Pre-β1-HDL contains apolipoprotein A-I, phospholipid, and a small amount of free cholesterol.[3] Among all the subtypes of HDL, the preβ1 has more anti-atherogenic characteristics than the others.[5] In hemodialysis patients,

the transformation of lecithin cholesterol acyltransferase (LCAT) from preβ1-HDL to alpha-migrating HDL delays due to the decrease in enzyme activity, and because of this, the levels of plasma preβ1-HDL increase. Furthermore, it was determined that plasma levels of preβ1-HDL were significantly elevated in non-dialyzed patients with advanced stages of CKD. The level of preβ1-HDL increases as the estimated glomerular filtration rate (eGFR) decreases.[6,7]

The epicardial adipose tissue (EAT) is between the visceral leaf of the myocardium and pericardium. EAT, which has a more active fatty-acid metabolism than other ectopic adipose tissues, is the site of synthesis of both cardioprotective and pro-inflammatory cytokines.[8] As it is in the visceral adipose tissue, the risk of cardiovascular disease might increase as ectopic fat deposition increases.[9] Moreover, EAT increases the risk of cardiovascular incidents in patients with moderate to severe CKD, independently from general adiposity.[10] Serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglyceride levels were found to be independent variables in predicting EAT thickness in hemodialysis patients.[11] It is unknown whether plasma preβ1-HDL has an independent predictive effect on EAT thickness in patients with CKD. The aim of our study was to compare the levels of plasma preβ1-HDL with EAT thickness on transthoracic echocardiography in patients with CKD stage 3-5.

MATERIALS AND METHODS

Participants

Forty-four patients (18 females, 26 males) with CKD, randomly selected among the patients who followed in the nephrology clinic between April 2017 and November 2018, were included in our study. Twenty-eight of the patients had hypertension, 2 had autosomal dominant polycystic kidney disease, 1 had amyloidosis, 2 had chronic glomerulonephritis, 1 had obstructive nephropathy, and 10 had an unknown etiology. The patients aged 18-80 years with CKD (stage 3-5, eGFR < 60 mL/min/1.73 m^2) and admitted to the outpatient clinic were included in the study. The patients were not selected consecutively. Due to echocardiography and laboratory procedures, a maximum of 3 person per day could be included in the study. Because there is a link between cardiovascular disease and plasma preβ1-HDL/EAT, the patients with malignancy or known cardiovascular disease, such as stable angına pectoris history of by-pass, or angiography with or without stent replacement or cerebrovascular disease, pregnancy, nephrotic syndrome, diabetes mellitus and the usage of antihyperlipidemic or immunosuppressive drugs were accepted as the exclusion criteria. As a control group, 44 healthy volunteers who are relatives of the patients (19 females, 25 males) were also included in the study.

Main Points

The mean plasma preβ1-HDL level was higher in the patients with CKD compared to the healthy volunteers, but did not reach statistical significance. The level of mean plasma preβ1-HDL increased in CKD patients as the stage progressed, but the difference was not statistically significant. There is a statistically significant and negative relationship between plasma preβ1-HDL levels and EAT thickness in CKD patients.

Informed Consent

Informed consent was obtained from each participant after receiving approval for the study from Canakkale Onsekiz Mart University Clinical Research Ethics Committee (Approval date: 28.12.2016, project no: 2016/23).

Study Design

Ten milliliters of blood samples were withdrawn from all the participants in the early hours of the morning, followed by fasting for 12 h, and the samples were studied in the clinical biochemistry laboratory. The levels of serum biochemical parameters and plasma preβ1-HDL were analyzed in the same laboratory. The EAT thickness (systole and diastole) was measured on transthoracic echocardiography of each patient by the same cardiologist (EA), simultaneously with the biochemical analysis, and the results were recorded. eGFR measurement of each patient was conducted in accordance with the CKD epidemiology collaboration equation.[12]

Laboratory Analysis

Blood samples were transferred to vacuum gel tubes for serum creatinine, total cholesterol, triglyceride, LDL-C, HDL-C, and albumin. Additionally, blood samples were transferred to ethylene diamine tetraacetic acid (EDTA) tubes for hemogram test. After the samples in the gel tubes were kept at room temperature for 30 min, they were centrifuged for 10 min at 4000 rpm. The levels of serum creatinine, total cholesterol, triglycerides, LDL-C, and HDL-C were studied with the enzymatic method, the level of albumin was studied with the colorimetric method using Roche kits (Roche Diagnostics GmbH) in Cobas c501 analyzer and a hemogram test was conducted with Beckman Coulter LH-780 (Beckman Coulter Ireland Inc Mervue, Galway, Ireland) blood cell count device on the same day.

For preβ1-HDL measurement in plasma, whole blood samples taken in EDTA tubes were carried on ice and plasma was separated by centrifugation at 3000 rpm for 15 min at 2-4°C. A 0.1 mL of plasma was taken on ice and mixed with vortex by adding 2 mL of stabilization buffer. The prepared sample was kept at −80°C until the experiment. Refreeze and re-dissolve were not performed. The levels of preβ1-HDL in plasma were measured by using commercial enzyme-linked immunosorbent assay (ELISA) (Product No:289194, Sekisui Diagnostics GmbH, Lexington, MA, USA) kits. The results were determined in ELX 808 IU model ELISA reader. Intra-day and inter-day coefficient of variation values (CV%) for preβ1-HDL were <10% and <12%, respectively.

Transthoracic Echocardiography

It was conducted on 38 of the CKD patients. Two-dimensional transthoracic echocardiography was conducted by the same cardiologist by using a 2.5 MHz transducer (Vivid 7, GE, Medical Systems) while all the patients were in a lying position on the left side. All the measurements were conducted throughout at least 3 consecutive cardiac cycles, during normal respiration and at the end of expiration. EAT was measured during ventricular systole with the vicinity of the free wall of the right ventricle by taking the aortic annulus as the reference point in the parasternal long-axis image. Two different EAT thickness measurements (mm) were conducted for systole and diastole.[13] The measurement of EAT thickness on transthoracic echocardiography was demonstrated in Figure 1.

Statistical Analysis

The data of the research was electronically transferred to Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM SPSS Corp.; Armonk, NY, USA) and analysis was conducted in this program. In the evaluation of continuous variables, mean, standard deviation, and the median, minimum, and maximum values were used. Independent samples *t* test was used to compare patient and control groups. A Chi-square test was used to compare gender item between patient and control groups. For the comparison of CKD stages, the Kruskal–Wallis test, and to find the source of statistical significance, Mann–Whitney *U* test with Bonferroni correction was used. The relationship between the level of plasma preβ1-HDL and EAT thickness of CKD patients were evaluated with Pearson correlation analysis. $P < .05$ was accepted as statistically significant.

RESULTS

Patient and control groups were similar in terms of gender ($P = .829$); however, the control group comprised of younger individuals (average age 51.9 ± 17.6 years) than those in the patient group and the difference was statistically significant ($P = .005$). The mean plasma preβ1-HDL level was higher in the patient group compared to the control group, but did not reach statistical significance ($P = .051$). Demographic and clinical characteristics of CKD patients were given in Table 1.

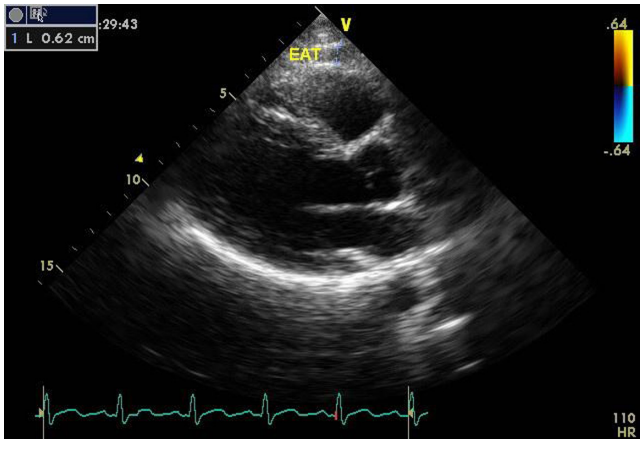

Figure 1. The measurement of EAT thickness on transthoracic echocardiography.

Table 1. Demographic and Clinical Characteristics of CKD Patients

Demographic and Clinical Characteristics	Mean ± Standard Deviation
Age (years)	61.6 ± 13.2
EAT thickness (systole, mm)	11.84 ± 3.86
EAT thickness (diastole, mm)	7.11 ± 2.71
eGFR (mL/min/1.73 m^2)	23.93 ± 15.43
Plasma preβ1-HDL (μg/mL)	13.17 ± 6.9
Serum total cholesterol (mg/dL)	188.7 ± 55.0
Serum triglyceride (mg/dL)	153.6 ± 84.7
Serum LDL-C (mg/dL)	126.3 ± 46.4
Serum HDL-C (mg/dL)	44.5 ± 13.4
Serum creatinine (mg/dL)	3.92 ± 3.28
Serum albumin (g/dL)	4.35 ± 0.56
Hemoglobin (g/dL)	11.9 ± 1.8

CKD patients were separated into 3 subgroups according to their eGFR measurements [stage 3 (eGFR: 59-30 mL/min/1.73 m^2, $n = 17$), stage 4 (eGFR: 29-15 mL/min/1.73 m^2, $n = 12$), and stage 5 (eGFR < 15 mL/min/1.73 m^2, $n = 15$), $P = .0001$]. It was found that the level of mean plasma preβ1-HDL increased in CKD patients as stage progressed, but the difference was not statistically significant ($P = .1$).

Echocardiography could not be performed in 6 patients due to compliance problems. When subgroups were evaluated in terms of EAT thickness, statistically significant results were found ($P = .027$, $P = .01$, respectively, for systole and diastole). When stage 3-4 and stage 4-5 patients were evaluated in terms of EAT thickness, no statistically significant results were found ($P > .016$ for both systole and diastole). The mean EAT thickness of stage 5 CKD patients was found to be lower than that of stage 3 patients, and the results were found statistically significant ($P = .015$, $P = .004$, respectively, for systole and diastole). Comparison of demographic findings and plasma preβ1-HDL levels of patient subgroups and the control group were given in Table 2.

When the level of mean plasma preβ1-HDL and EAT thickness of CKD patients were compared, a statistically significant and negative relationship was determined ($P = .013$, $r = -0.398$; $P = .006$, $r = -0.441$, respectively, for systole and diastole).

Table 2. Comparison of Demographic Findings and Plasma Preβ1-HDL Levels of Patient Subgroups and the Control Group

	CKD Stage 3 ($n = 17$)	CKD Stage 4 ($n = 12$)	CKD Stage 5 ($n = 15$)	Control Group ($n = 44$)	
	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)	*P*
Male/female	12/5	7/5	7/8	25/19	.585*
Age (years)	65 (38-74)	65.5 (45-79)	62 (25-78)	55.5 (18-76)	*.04***
eGFR (mL/min/1.73 m^2)	41 (30-58)	19 (15-24)	8 (3-14)		*.0001***
EAT thickness (systole, mm)	11,5 (9-19)	14 (7-19)	9 (6-16)		*.027***
EAT thickness (diastole, mm)	8 (5-12)	8.5 (4-15)	4.5 (3-10)		*.01***
Plasma preβ1-HDL (μg/mL)	11.29 (4.37-18.15)	11.04 (7.68-19.59)	14.1 (0.1-36.73)	11.51 (2.08-19.1)	.106**

min, minimum; max, maximum, *P*;*chi-square test; **Kruskal–Wallis test.

DISCUSSION

In our study, we conducted preβ1-HDL measurement with ELISA in the plasma of stage 3-5 CKD patients and healthy volunteers. Although the mean preβ1-HDL levels were higher in the patient group, this did not reach statistical significance. In CKD, as the eGFR decreases, the level of plasma preβ1-HDL increases.[6,7] It was determined that the levels of mean plasma preβ1-HDL were increased in CKD patients as the stages progressed, but the results were not statistically significant.

There are several studies in the literature on the measurement of preβ-HDL in plasma with the two-dimensional gel electrophoresis method.[14,15] Two-dimensional gel electrophoresis is the gold standard technique.[5,16] However, because the method is expensive and requires more time and advanced technical competence, it is not convenient for common use in clinical laboratories.[5] However, plasma preβ1-HDL measurement can be conducted with the ELISA method as well.[5,15,17] ELISA is a precise and repeatable method for plasma preβ1-HDL measurement.[5] Studies that compared ELISA and two-dimensional gel electrophoresis for the measurement of plasma preβ1-HDL demonstrated that the results were coherent with each other; however, the measurements that were conducted with ELISA were found to be two-thirds lower than the other method. This difference may depend on interpreting apolipoprotein A-I inadequately in the ELISA method and excessively in the other method.[5,15] In our study, we used the ELISA method for the plasma preβ1-HDL measurement in CKD patients.

In CKD patients, preβ1-HDL increases and HDL levels decrease due to a decrease in LCAT enzyme activity.[6] The separation of apolipoprotein A-I from HDL with the effect of cholesterol ester transfer protein (CETP) increases the formation of preβ1-HDL.[18] Phospholipid transfer protein (PLTP) also contributes to the formation of preβ1-HDL.[19] It was determined that LCAT and apolipoprotein A-I concentrations were decreased in patients with hemodialysis but CETP and PLTP concentration and activity did not change.[20] In human studies, lipoprotein lipase deficiency has been shown to worsen atherosclerotic outcomes.[21] Preβ1-HDL is an inhibitor for lipoprotein lipase enzyme. This may explain the reduced serum level and impaired function of HDL-C in CKD.[22]

The volume of EAT increased in CKD patients.[11] The volume of EAT can be measured with multidetector computed tomography. Moreover, the EAT thickness can be measured with echocardiography.[11] In our study, both systole and diastole EAT thickness of CKD patients were calculated on transthoracic echocardiography by the same cardiologist. In our study, there was a difference between CKD groups in terms of EAT thickness. This difference was due to the lower EAT thickness of stage 5 CKD patients. A study with similar results in this regard is available in the literature.[10] However, EAT thickness has been reported to be increased in hemodialysis patients compared to the pre-dialysis group.[23] Most patients with stage 2-4 CKD have been reported to die before starting dialysis.[24] This may explain why patients with stage 5 CKD who survived the previous stages had lower EAT thickness.

Paraoxonase (PON-1) and LCAT are enzymes involved in HDL metabolism. The activity of these 2 enzymes decreases in CKD. As a result, both plasma preβ1-HDL levels increase and the antioxidative activity of HDL particles is impaired.[7] In hemodialysis patients, a significant negative correlation was found between PON-1 activity and EAT thickness.[11] We determined a statistically significant and negative relationship between the levels of plasma preβ1-HDL and transthoracic EAT thickness in CKD patients. This result may be due to impaired HDL metabolism in CKD.

In our study, the control group was formed from healthy and voluntary people who are relatives of the patients. Therefore, there was a significant age difference between the patient and control groups. The control group consisted of younger individuals than the patient group. There is a negative but not statistically significant relationship between plasma preβ1-HDL level and age.[25] No statistically significant difference in mean preβ1-HDL levels between patient and control groups may be

because of the lower mean age of the control group compared to the other group.

Apolipoprotein A-I, phospholipid and a small amount of free cholesterol are parts of the preβ1-HDL molecule.[3] EAT may have a potential role in the physiopathology of several metabolic and cardiovascular diseases. Higher levels of apolipoprotein A-I are released from EAT compared to subcutaneous adipose tissue. In coronary artery disease, a lower amount of apolipoprotein A-I is released from EAT.[26] Preβ1-HDL or apolipoprotein A-I released from EAT in CKD are unknown. However, coronary artery disease is common in CKD.[27] EAT thickness increases in both CKD and coronary artery disease.[11,28] EAT increases the risk of cardiovascular incidents in patients with moderate to severe CKD, independently from general adiposity.[10] Patients known to have coronary artery disease were not included in our study. However, silent myocardial ischemia is common in patients with CKD.[29] In our study, a negative correlation was found between plasma preβ1-HDL and EAT thickness in patients with CKD (stage 3-5). This may be due to insufficient apolipoprotein A-I release by EAT in this population.

There were certain factors that limited our study. The analysis of other particulates such as plasma apolipoprotein A-I and M, except for preβ1 of HDL-C particulates (amount and size) and PON-1 activity was not conducted. LCAT enzyme level and serum capacity to induce ATP-binding cassette transporter-1-mediated cholesterol efflux was not examined. The numbers of patients and healthy volunteers were kept low. Since two-dimensional gel electrophoresis was not used, the results of both methods (two-dimensional gel electrophoresis and ELISA) could not be compared.

CONCLUSIONS

Our study demonstrated that plasma preβ1-HDL levels were higher in CKD (stage 3-5) patients compared with healthy controls and that preβ1-HDL was inversely correlated with EAT thickness in this population.

Ethics Committee Approval: Ethics committee approval was received from the Clinical Research Ethics Committee of Canakkale Onsekiz Mart University (Date: December 28, 2016; Number: 2016-23).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.B., D.Ü.Ç., E.A., E.Ü.Ç.; Design - S.B., D.Ü.Ç., E.A.; Supervision - S.B., D.Ü.Ç.; Resource - S.B., D.Ü.Ç., E.A.; Materials - S.B., D.Ü.Ç., E.A., E.Ü.Ç.; Data Collection and/or Proccessing - S.B., D.Ü.Ç., E.A., E.Ü.Ç.; Analysis and/or Interpretation - S.B., D.Ü.Ç., E.A., E.Ü.Ç.; Literature Search - S.B., E.Ü.Ç.; Writing – S.B., D.Ü.Ç., E.A., E.Ü.Ç.; Critical Reviews - S.B., D.Ü.Ç., E.A., E.Ü.Ç.

Acknowledgments: We would like to thank Coskun Bakar for statistical analysis (Canakkale Onsekiz Mart University School of Medicine, Division of Public Health).

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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