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Profilin as a Novel Biomarker for Assessing Atherosclerosis in Hemodialysis Patients

Aim	Studies have shown a significant correlation between atherosclerosis and profilin-1. However, there is no information in the literature on the concentration of profilin in hemodialysis (HD) patients. This research examined the association between profilin-1 and carotid intima-media thickness (CIMT), as a marker of early atherosclerosis in HD patients.
Material and methods	50 chronic HD patients and 38 healthy, control patients were included in this study. CIMT was measured by high-resolution ultrasonography.
Results	The HD patients were older and had higher concentrations of profilin-1, C reactive protein (CRP), uric acid, parathormone, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) than the control patients. In the HD patients, variables impacting CIMT were examined. CIMT and profilin-1 were significantly correlated (r=0.637, p<0.01), as were CIMT and age (r=0.424, p=0.002). Linear regression analysis revealed that profilin-1 is a significant and independent predictor of carotid intima-media thickness (CIMT). Higher profilin-1 levels were associated with increased CIMT values.
Conclusion	For the first time, it has been shown that HD patients had greater concentrations of profilin-1 than healthy controls. Also, an independent relationship between profilin-1 and CIMT in HD patients was demonstrated.

Keywords	Profilin-1; hemodialysis; atherosclerosis; intima media thickness
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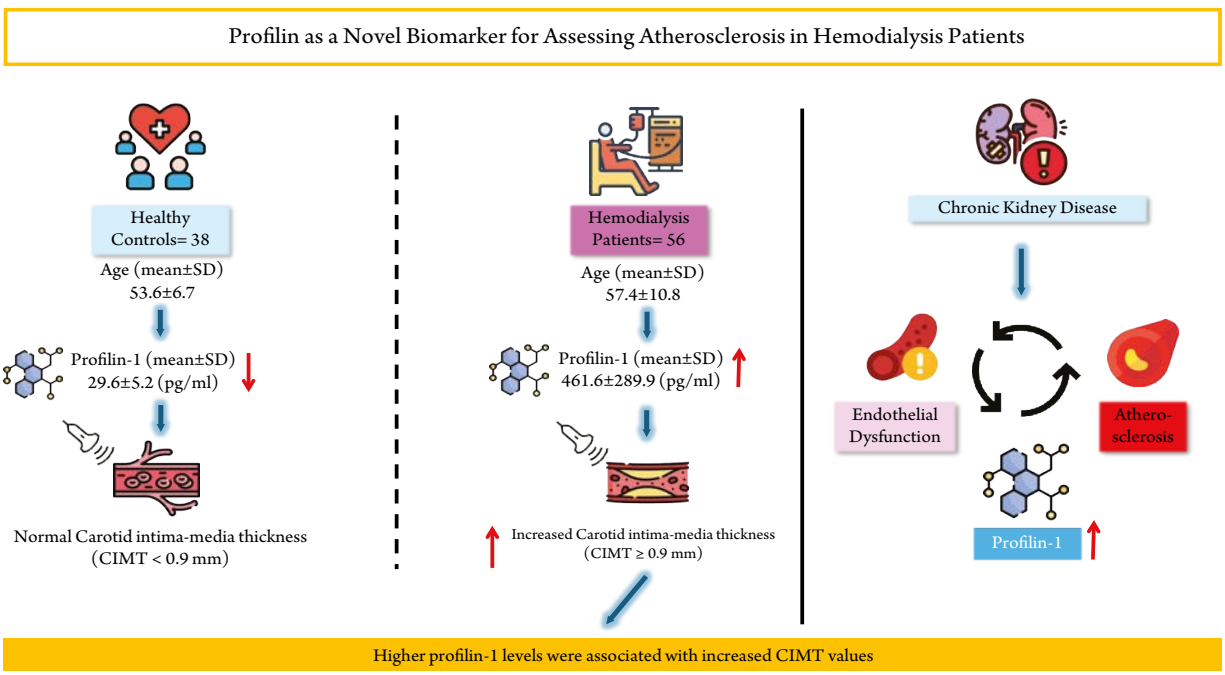
Central illustration. Profilin as a Novel Biomarker for Assessing Atherosclerosis in Hemodialysis Patients



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Introduction

Atherosclerosis is one of the primary causes of morbidity and mortality in hemodialysis (HD) patients. The incidence of atherosclerosis among these patients has significantly increased compared to that of the healthy population [1]. In HD patients, increased Framingham risk factors (e.g., hypertension, dyslipidemia, smoking, diabetes mellitus) and factors specific to chronic renal failure (e.g., anemia, secondary hyperparathyroidism) play a role in accelerating the atherosclerotic process [2]. However, traditional risk factors cannot fully explain this increased risk; thus, new biomarkers are needed [3].

Profilin-1 is a small actin-binding protein with a molecular weight of 12–15 kD. It affects cytoskeletal remodeling and vascular hypertrophy by activating hypertrophic signaling cascades [4, 5]. Recent studies have shown how profilin-1 overexpression plays a crucial role in the development of atherosclerosis [6]. In fact, thrombosis, vascular remodeling, and atherosclerosis are all affected by profilin-1, and there is a strong correlation between profilin-1 and the extent of atherosclerosis [7].

Carotid intima-media thickness (CIMT) is a valuable marker of atherosclerosis [8]. Several studies have evaluated the role of CIMT as an indicator of coronary artery disease (CAD) since CIMT has the potential to detect atherosclerosis in its subclinical phase, is easily measurable, and reflects the extent of atherosclerosis [9, 10]. CIMT is associated with concentric left ventricular hypertrophy in HD patients, and CIMT is a standalone predictor of cardiovascular events [11, 12]. However, specific study of the profilin-1 concentrations in the HD patient population is still required. Thus, we examined the relationship of profilin-1 with CIMT as an index of atherosclerosis in HD patients.

Material and methods

Patients

Fifty-six HD patients between the ages of 18 and 80 who had been receiving HD treatment for at least a year at Ahi Evran University Medical Faculty Hospital were initially included in this study. Six patients with infections and malignancy were excluded from the trial. In addition, 38 healthy, control patients were included in the study.

The study was carried out in compliance with institutional and national ethical standards. Ahi Evran University Medical Faculty Clinical Research Ethics Committee authorized the study, and all participants provided written informed permission.

Biochemical analyses

Blood for laboratory investigations were drawn in the morning after fasting overnight for at least 8 hr. Complete blood counts were measured with flow cytometry (Sysmex XT 2000I analyzer, Sysmex Corporation, Kobe, Japan). Blood glucose, creatinine, albumin, and serum lipids were measured by enzymatic colorimetric methods. Ferritin and C-reactive protein (CRP) were measured by an immunoturbidimetric method. Sodium, potassium, and chloride were measured by an ion selective electrodes. These biochemical parameters were measured with a Roche/Hitachi Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, USA).

Measurement of serum profilin-1

Profilin-1 was measured using an ELISA kit according to the manufacturer's instructions (Cusabio Biotech Co., Ltd., Wuhan, China). The tests were performed in 96-well plates, with 100 µl of standards and samples added to each well. The plates were then incubated at 37°C for 2 hr. Following incubation, 100 µl of biotin antibody was added to each well, and the plate was incubated at 37°C for 1 hr. After incubation, the plate was washed three times with 200 µl of wash buffer before adding 100 µl of horseradish peroxidase-avidin. The plate was washed with 200 µl of wash buffer five times, followed by another incubation at 37°C for 1 hr. Each well then received 90 µl of 3,3′,5,5′-tetramethylbenzidine substrate solution, and the plate underwent a 20-min, 37°C, dark incubation period. 50 µl of stop solution was then added to each well, and absorbance was determined at 450 nm using a Synergy HT plate reader (BioTek Instruments, Winooski, VT, USA). The amounts of profilin-1 in each test sample were calculated based on a standard curve. The intra-assay coefficient of variation was 8%, and the detection limit was 7.8 pg/ml, according to the manufacturer's product information.

Measurement of CIMT

CIMT was evaluated as a marker of atherosclerosis in the carotid artery. An experienced radiologist conducted the ultrasonographic examination of the patients' carotid arteries using high-resolution linear probe ultrasonography with the Toshiba Aplio MX device (Toshiba Medical Systems, Tokyo, Japan).

The CIMT was precisely measured as the space between the two echogenic lines of the intima-lumen and media-adventitia interfaces, using optimal settings for depth, focus, frequency, and gain. Three different measurements of the left common carotid artery, 1–2 cm proximal to the bulbous. were taken with the patient in the supine position and with the head turned to the left. The CIMT value was calculated as the average of these measurements. The atheroma plaque in the area was not measured. Imaging was performed along the axial and longitudinal planes, and measurements were made in the rear wall.

Statistical analysis

Descriptive statistics were presented as median (range) for non-normally distributed variables and as mean ±

standard deviation (SD) for normally distributed variables. The normality of data distribution was assessed using both the Kolmogorov–Smirnov and Shapiro–Wilk tests. Statistical significance was considered at a p-value of <0.05. Comparisons between categorical variables were performed using the Chi-square test. Spearman's rank correlation coefficient was employed to evaluate correlations between continuous variables.

To investigate the predictive effect of serum Profilin-1 levels on clinical parameters in hemodialysis patients, a simple linear regression analysis was conducted. In addition, stepwise multivariate linear regression analysis was used to identify independent predictors of carotid intima-media thickness (CIMT).

All statistical analyses were carried out using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

A comparison of the biochemical data of the groups is shown in Table 1. No statistically significant difference in age was observed between the control and patient groups (p=0.069). However, significant differences were identified in hemoglobin levels, with the control group exhibiting higher values compared to the patient group (p=0.001). Statistically significant differences were also noted in triglyceride (p=0.001), HDL (p=0.001), LDL (p=0.001), phosphorus (p=0.001), PTH (p=0.001), uric acid (p=0.001), and Profilin-1 levels (p=0.001) between the two groups. In contrast, no significant differences were found in calcium (p=0.531) or CRP levels (p=0.175).

A significant positive correlation was detected between CIMT and Profilin-1 (r=0.637, p<0.01) (Table 2). The scatter plot showing the relationship between CIMT and Profilin-1 is presented in Figure 1. A significant positive correlation was also found between age and CIMT (r=0.424, p=0.002). A weak negative correlation was observed between ferritin and CIMT; however, this relationship was not statistically significant (r= –0.226, p=0.115).

A linear regression analysis (figure 1) was conducted to evaluate the effect of profilin-1 levels on carotid intima-media thickness (CIMT). The model was found to be statistically significant ($F(1,48) = 32.763$, $p < 0.001$), indicating that profilin-1 significantly predicts CIMT.

According to the regression coefficients, profilin-1 had a statistically significant and positive effect on CIMT ($\beta=0.637$, $t = 5.724$, $p < 0.001$). These findings demonstrate that profilin-1 is a strong and independent predictor of CIMT. In other words, higher profilin-1 levels were associated with increased CIMT values.

Discussion

Kidney failure is a significant risk factor for atherosclerotic heart disease, leading to higher cardiovascular mortality and

Table 1. Comparison of the biochemical data of the groups

Variable	Hemodialysis Group	Control Group	p
Age (yr)	57.4±10.8	53.6±6.7	0.069*
Hemoglobin (g/dl)	11.4 (10.7-11.9)	13.8 (13.5-14)	0.001**
Triglyceride (mg/dl)	177.5 (132-258.2)	137 (135.7-146)	0.001**
High-density lipoprotein (mg/dl)	34.5 (29.7-40)	43 (39-47)	0.001**
Low-density lipoprotein (mg/dl)	98.8±35.7	121.6±10.6	0.001*
Calcium (mg/dl)	9±0.7	9.1±0.4	0.531*
Phosphorus (mg/dl)	4.4 (4-5.4)	3.9 (3.5-4.1)	0.001**
C-reactive protein (mg/dl)	0.8 (0.5-1.7)	2 (1.6-3)	0.175**
PTH (pg/ml)	215.8 (135.6-333.3)	44 (34.7-52)	0.001**
Uric acid (mg/dl)	6.5±0.9	4.3±0.8	0.001*
Profilin-1 (pg/ml)	461.6±289.9	29.6±5.2	0.001*

PTH, parathormone. *T-test, ** Mann-Whitney U test, the groups were subjected to parametric and non-parametric tests and are given as mean±SD or median and IQR.

Рисунок 1. Correlation between profilin-1 and CIMT in HD patients. (r=0.637, p<0.001)

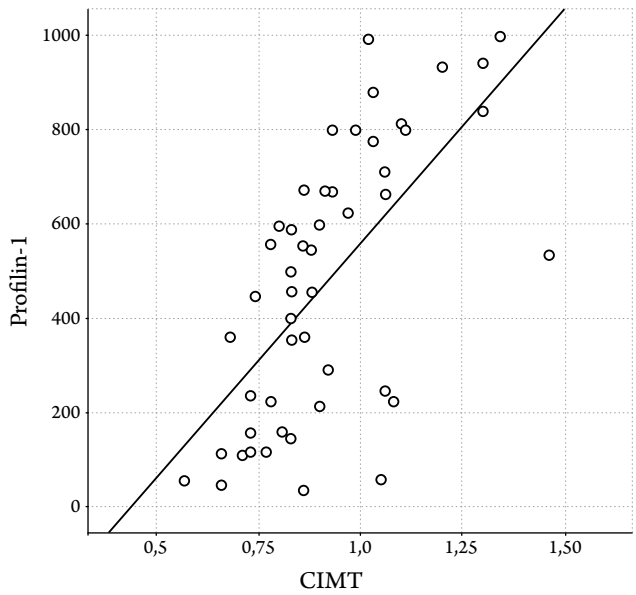

Table 2. Correlations of variables related to CIMT

Variable	r	p*
Profilin-1	0.637	<0.001
Age	0.424	0.002
Ferritin	-0.226	0.115

*: Pearson Correlation

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morbidity than in the general population. However, traditional risk variables alone are insufficient to explain this increased risk, especially in patients with chronic kidney disease who require biomarkers for atherosclerosis detection [13]. This study demonstrated for the first time that dialysis patients have elevated concentrations of profilin-1and that profilin-1 is independently associated with CIMT.

Profilin-1 is highly expressed in endothelial cells (ECs) in patients with diabetes and atherosclerotic diseases, and profilin-1 has been shown to result in adhesion and migration of endothelial cells [14]. Increased profilin-1 gene expression in ECs together with turbulent flow and homocysteine are promoting factors for atherosclerosis [15–17]. Caglayan et al. demonstrated elevated profilin-1 expression in human atherosclerotic plaques. Additionally, they identified two key associations: profilin-1 concentration levels showed a positive correlation with macrophage infiltration within plaques and were linked to a marked proinflammatory microenvironment characterized by inflammatory mediators. These findings suggest that profilin-1 may exacerbate plaque instability by driving macrophage recruitment and fostering a proinflammatory state, thereby contributing to atherogenesis [14].

In addition, Ramaiola et al. reported that profilin-1 was secreted from fully activated platelets in the thrombotic mass in the coronary arteries of patients with myocardial infarction, and, thus, profilin-1 could be a potential marker in the systemic circulation of thrombosis [18].

In hyperlipidemic mice, lowering profilin-1 expression decreased the number of atherosclerotic lesions and improved endothelial function [19]. The atheroprotective effect caused by profilin-1 reduction includes a marked reduction in macrophage infiltration into blood vessels, downregulation of CD36 expression, which regulates fatty acid import and uptake of oxidized LDL by macrophages and improve endothelial function [19]. All these preclinical and clinical correlation findings suggest a possible causal relationship between profilin-1 dysregulation and the pathogenesis and/or progression of atherosclerosis [7]. Eroğlu et al. showed a relationship between profilin-1 concentration and endothelial dysfunction in patients with CKD [20]. However, these findings had not been demonstrated in HD patients.

CIMT is easy to measure, and it is an effective predictor of the presence and extent of atherosclerosis. A CIMT value of 0.9 mm or less is considered normal [21]; most HD patients had much higher values of CIMT and of profilin-1 as shown in Figure 1.

The role of CIMT as an indicator of coronary artery disease has been evaluated in several studies [9, 10]. The Risk of Atherosclerosis in Communities Research (ARIC), which included 13,870 participants, found that CIMT was consistently greater in individuals with clinical cardiovascular disease than in those without the condition [22]. The main aim of the current study was to show the relationship between profilin-1 and CIMT in HD patients. The results showed that profilin-1 has a strong correlation with CIMT in patients with CIMT above the normal range. This finding underscores the possible role of profilin-1 in the pathogenesis of atherosclerosis in HD patients and as a marker for this condition. This new information may improve our understanding, in general, of atherosclerosis.

Study limitations

This study was conducted at a single center with a limited number of patients. In addition, profilin-1 concentrations rise independently of age as the glomerular filtration rate (GFR) decreases in patients with chronic renal failure. This complicates the identification of a specific profilin-1 concentration that would indicate the presence of atherosclerosis in the HD patient population. Future multicenter studies are required to provide more insightful information on the impact of profilin-1 on atherosclerosis in patients undergoing HD.

Conclusion

The concentration of profilin-1 in HD patients is independently correlated with CIMT and is more significantly related to CIMT than age. Thus, profilin-1 likely plays an important role in the pathogenesis of atherosclerosis in HD patients, and profilin-1 may be a useful biomarker of atherosclerosis in these patients. Further consideration of the role of profilin in the pathogenesis of atherosclerosis is warranted, particularly in HD patients.

Ethical approval

Ahi Evran University Faculty of Medicine Research Ethics Committee authorized the study (Decision number: 04/27/ 2017).

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No conflicts of interest are reported.

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