Relation between high serum hepcidin-25 level and subclinical atherosclerosis and cardiovascular mortality in hemodialysis patients

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Abstract

Objective: In hemodialysis (HD) patients, cardiovascular disease (CVD) is the major cause of mortality and morbidity. In atherosclerotic diseases, iron gets accumulated in the arterial wall. Hepcidin is an important hormone in iron metabolism. Furthermore, hepcidin is associated with atherosclerotic disease. Therefore, this study aims to investigate the relation of serum hepcidin-25 (SH-25) and sub-clinic atherosclerosis measured by carotid intima-media thickness (CIMT) and mortality in HD patients.

Methods: We enrolled 82 HD patients in a cross-control study. We measured SH-25 using ELISA kit and CIMT using high-resolution real-time ultrasonography. After 4 years of first assessment, we investigated the relation between all-cause and cardiovascular mortality and SH-25 and CIMT.

Results: Two patients were excluded because of renal transplantation. The survivors were younger (53.7±15.1 vs. 65.2±15.5; p<0.05) and CIMT was lower (0.83±0.2 vs. 0.95±0.2; p<0.05); however, there was no significant difference in SH-25 levels between the groups (29.1±13 vs. 32.4±22.4; p=0.767). The patients who died of CVD were significantly older (63.7±16.1 vs. 53.7±15.1; p<0.05) and had significantly higher CIMT (0.94±0.2 vs. 83±0.2; p<0.05). The SH-25 levels were statistically significantly higher in patients who died of CVD (40.3±25 vs. 29.1±13; p<0.05). Linear regression analysis showed a positive correlation between CIMT and SH-25 in the study population and in those who died from CVD (r=0.41; p<0.05 and r=0.606; p<0.05, respectively).

Conclusion: This study suggests that hepcidin is effective in cardiovascular mortality and pathophysiology of subclinical atherosclerosis in HD patients. *(Anatol J Cardiol 2018; 19: 117-22)*

Keywords: cardiovascular mortality, carotid intima-media thickness, hemodialysis, hepcidin

Introduction

Cardiovascular (CV) mortality is 20–40 times higher in patients with chronic kidney disease (CKD) than in normal population (1). There are various mechanisms taking part in the pathogenesis of cardiovascular disease (CVD) in patients with CKD (2).

Iron accumulation in the vascular cells and macrophages causes endothelial dysfunction and atherosclerosis (3). This situation is significant in hemodialysis (HD) patients undergoing iron treatment. Carotid intima-media thickness (CIMT) was reported to be associated with ferritin levels and cumulative iron treatment dosage in HD patients (4).

In 2001, a peptide named as hepcidin was discovered (5, 6). Serum Hepcidin-25 (SH-25) is a bioactive isoform of hepcidin, which is important in iron homeostasis. Ferroportin is a cellular iron exporter that is present on enterocytes, macrophages, and hepatocytes. SH-25 causes internalization and degradation of ferroportin (6). Hepcidin expression is regulated by iron treatment, anemia, hypoxia, and inflammatory signals (7, 8). Hepcidin levels are elevated in CKD (9). There is an association between ferritin and hepcidin in HD patients (9-14).

The relationship between hepcidin and CVD in different patient groups has been previously investigated (15-17). These findings suggest the possible relation between hepcidin and atherosclerosis.

Atherosclerotic changes in the carotid arteries are associated with the extent of atherosclerosis in patients with CKD. CIMT is a reliable indicator of both systemic and coronary atherosclerosis and can be measured using ultrasonography (18). Therefore, this study aims to investigate the relation between SH-25 and subclinical atherosclerosis measured by CIMT and mortality in HD patients.

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Methods

Study design and population

This cross-control prospective study was approved by the Local Ethics Committee, and informed consents were obtained from study participants.

We included 82 patients who were on chronic HD treatment between 2011 and 2015. The inclusion criterion was HD treatment for at least 6 months. The exclusion criteria were the presence of malignancy, history of trauma, surgery in the past month, and the presence of acute infection or chronic liver disease. Data on demographic findings, history of CVD, diabetes mellitus, dialysis vintage, and treatment parameters were collected.

After 4 years of first assessment, the mortality of the patient group and its relation with SH-25 and CIMT was investigated. Two of the 82 patients were excluded because of renal transplantation. The patients who lived and died due to any cause and CVD were compared in terms of clinical parameters, echocardiographic parameters, CIMT, and SH-25 levels. Also, correlation analysis of CIMT was done in patients who died of CVD; parameters found to be statistically significant were analyzed by linear regression analysis.

Biochemical analysis

Predialysis blood samples were drawn, and routine laboratory assessments were performed using standard laboratory techniques. Serum total cholesterol and triglyceride levels were measured using commercial colorimetric assay methods (GPO-PAP and CHOD-PAP; Boehringer-Manheim, Manheim, Germany). High-density lipoprotein cholesterol (HDL-C) levels were measured using the phosphotungstic acid precipitation method. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula (LDL-C=CHO – TG/5 – HDL-C), where CHO is the serum total cholesterol level and TG is the serum triglyceride level . Serum C-reactive protein (CRP) levels were detected using rate nephelometry (IMAGE) . Serum biochemical parameters (creatinine, blood urea nitrogen, glucose, electrolytes, albumin, and complete blood count) and intact parathyroid hormone levels were measured using a computerized auto analyzer (Hitachi 717; Boehringer-Mannheim). Predialysis blood samples were centrifuged at 1500 g for 10 min and stored at –80°C for measuring SH-25 levels. The DRG hepcidin enzyme-linked immunosorbent assay (ELISA) (Marburg, Germany) kit was used for measuring hepcidin-25. The range of SH-25 level was 0.78–50 ng/mL. ELISA kit was bought by the workers and the test was performed in private laboratory.

Carotid artery intima-media thickness and echocardiography measurement

The CIMT measurements and echocardiographic evaluations for all participants were performed by the same cardiologist who was unaware of the clinical and laboratory data.

Ultrasonographic B-mode imaging of bilateral carotid arteries was performed with high-resolution real-time ultrasonography using a 12 MHz linear-assay transducer (Mindray DC 7). Carotid arteries, carotid bulb, and internal carotid arteries were examined using two different longitudinal projections. At each longitudinal projection, CIMT was conducted from the site of greater thickness. CIMT was defined as the distance between the leading edges of the lumen interface at the far wall in plaque-free arterial segments. The value was expressed as an average of the maximal CIMT.

All echocardiographic measurements were made according to the recommendations of the American Society of Echocardiography (19). The left ventricle end-systolic diameter, left ventricle end-diastolic diameter (LVEDD), left ventricular posterior

Table 1. General properties of patients

Parameters	Patients (n=82)
Gender; male, %, n	43.9 (36)
Age, years	57.9±16.1
Dialysis vintage, months	124.8±16.8
Diabetes mellitus, %, n	26.8 (22)
History of CVD, %, n	35.4 (29)
Current smoker, %, n	-
SBP, mm Hg	125±17
DBP, mm Hg	77±10
Kt/V	1.49±0.28
BMI, kg/m^2	25.6±14.4
Treatment characteristics	
Prescription of ESA, %, n	87.8 (72)
Use of iron replacement therapy, %, n	67.1 (55)
Prescription of RAS inhibitors, %, n	26.8 (22)
Prescription of calcium blocker, %, n	24.4 (20)
Prescription of beta blocker, %, n	29.3 (24)
Prescription of alpha blocker, %, n	3.7 (3)
Prescription of statin, %, n	3.7 (3)
Laboratory parameters	
Haemoglobin, g/dL	10.7±1.4
Ferritin, ng/mL	754±377
TSAT, %	29.4±16.8
LDL-C, mg/dL	91.5±35.2
HDL-C, mg/dL	36.6±11.8
Albumin, g/dL	3.62±0.5
CRP, mg/L	2.22±2.72
Hepcidin-25, ng/mL	30.17±17.06
CIMT, mm	0.874±0.196

BMI - body mass index, CIMT - carotid intima-media thickness, CRP - C-reactive protein, CVD - cardiovascular disease, DBP - diastolic blood pressure, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, TSAT - transferin saturation, SBP - systolic blood pressure

Table 2. Comparison of the survivors and the dead

Parameters	Survivors (n=49)	All-cause deaths (n=31)	*P**	Deaths from CVD (n=21)	*P***
Age, years	53.7±15.1	65.2±15.5	**<0.05**	63.7±16.1	**<0.05**
Gender; male, n (%)	18 (36.7)	18 (58.1)	0.062	13 (61.9)	0.052
BMI, kg/m^2	26.9±18.2	23.9±4.9	0.296	23.2±4.5	0.168
Diabetes, n (%)	12 (24)	10 (32.3)	0.448	7 (33.3)	0.448
Hypertension, n (%)	25 (51)	17 (54.8)	0.739	17 (61.9)	0.402
ACEI-ARB, n (%)	13 (26.5)	9 (29.0)	0.807	7 (33.3)	0.445
Beta-blocker, n (%)	15 (30.6)	9 (29.0)	**<0.05**	5 (23.8)	0.353
Statins, n (%)	-	1		1	-
ASA, n (%)	13 (26.5)	9 (29.0)	0.807	7 (33.3)	0.353
DV, months	84±68	74±58	0.882	84±63	0.681
MAP, mm Hg	93±12	93±10	0.956	95±11	0.601
Kt/V	1.5±0.3	1.45±0.3	0.405	1.44±0.31	0.305
Hemoglobin, g/dL	10.8±1.4	10.6±1.3	0.836	10.6±1.5	0.758
Ferritin, ng/mL	787±388	707±349	0.148	715±344	0.189
Glucose, mg/dL	96±30	113±48	0.168	107±32	0.214
Albumin, g/dL	3.7±0.5	3.6±0.4	0.253	3.6±0.4	0.301
CaxP, mg^2/dL^2	47.7±11.8	45.3±11.1	0.293	44.2±10.3	0.135
PTH, pg/ml	660±589	723±853	0.550	825±1002	0.613
HDL-C, mg/dL	38±12	34±11	0.132	37±11	0.551
LDL-C, mg/dL	97±37	84±30	0.226	86±31	0.365
CRP, mg/L	2.1±2.9	2.3±2.6	0.398	2.4±2.5	0.324
Hepcidin-25, ng/mL	29.1±13	32.4±22.4	0.767	40.3±25.4	**<0.05**
LVMI, g/m^2	136.2±36.6	147±40	0.258	1457±36.7	0.284
LVH, n, %	33 (67.3)	24 (77.4)	0.332	16 (76.2)	0.459
CIMT, mm	0.83±0.2	0.95±0.2	<0.05	0.94±0.2	**<0.05**

Categorical data are presented as frequencies and percentages; continuous variables are presented as mean ± standard deviations or median and interquartile ranges (IQR: 25th-75th) depending on their distributions.
*Comparison of the survivors and all deaths, **Comparison of the survivors and deaths from cardiovascular disease
ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, ASA - acetyl salicylic acid, BMI - body mass index, Ca - calcium, CIMT - carotid intima-media thickness, CRP - C-reactive protein, DV - dialysis vintage, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol; LVM - left ventricular mass, LVMI - left ventricular mass index, MAP - mean arterial pressure, P - phosphorus, PTH - parathyroid hormone

wall thickness (LVPWT), interventricular wall thickness (IVWT), and left ventricular relaxation time were recorded. The body surface area (BSA) was calculated using DuBois and DuBois formula [BSA= (weight (kg) 0.425×height (cm) 0.725)×0.007184] (20). The left ventricular mass index (LVMI) was calculated using Devereux formula [LVMI (g/m^2)=(1.04 [(IVWT+LVEDD+LVPWT) 3–LVEDD3]–14 g)/BSA] (21). LVH was evaluated using data from the Framingham Heart Study, and the presence of LVH was defined on the basis of LVMI greater than 131 g/m^2 and 100 g/m^2 for males and females, respectively (22).

Statistical analysis

Data analysis was performed by using SPSS for Windows 20 (SPSS Inc., Chicago, USA). The results of the analysis of continuous variables were expressed as mean±SD and median (interquartile range: 25th–75th percentiles), whereas the results of analysis of discrete variables were expressed as frequency distributions and percentages. The Kolmogorov–Smirnov test was used for testing normality of continuous variables. Normally distributed variables were analyzed using t-test, whereas others were analyzed using the Mann–Whitney U test. The chi-square test was used for comparing discrete variables. The linear regression analysis model was used to study the relationship between CIMT and SH-25. P<0.05 was considered statistically significant.

Results

Table 1 shows the initial baseline characteristics of the patients enrolled in the first study. At the beginning, 82 patients

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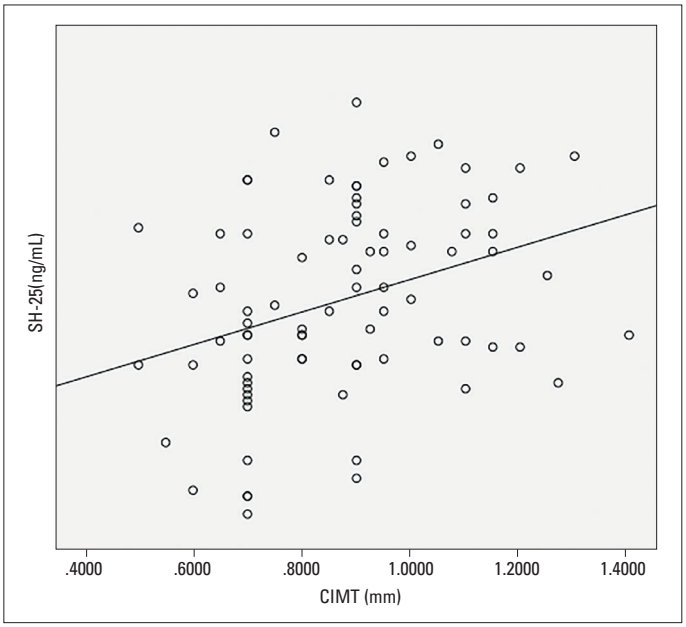

Figure 1. The correlation analysis of serum hepcidin-25 (SH-25) and carotid intima-media thickness (CIMT) in patients who died of cardiovascular disease

were involved in the study, and during follow-up, two patients were excluded because of renal transplantation. In the 4-year follow-up period, 31 of the 80 patients died. Of the 31 patients, 21 died because of CVD (14, acute coronary syndrome and seven, stroke), eight died because of infection, and two died because of gastrointestinal hemorrhage.

The patients were divided in two groups: patients who died and survivors. The survivors were significantly younger (53.7±15.1 vs. 65.2±15.5; p<0.05). CIMT was significantly lower in patients (0.83±0.2 vs. 0.95±0.2; p<0.05); however, there was no significant difference in the SH-25 levels between the groups (29.1±13 vs. 32.4±22.4; p=0.767). Table 2 shows the comparison between the two groups.

The patients who died of CVD were significantly older (63.7±16.1 vs. 53.7±1; p<0.05) and had significantly higher CIMT (0.94±0.2 vs. 0.83±0.2; p<0.05). The SH-25 levels were significantly lower in survivors than in patients who died of CVD (29.1±13 vs. 40.3±25.4; p<0.05).

A significantly positive correlation was found between CIMT and SH-25 levels in the whole study population (p<0.05, r=0.41).

Table 3. The correlation between CIMT with demographic and biochemical parameters in deaths from cardiovascular disease

Variables	CIMT	
	r	*P*
Age	0.501	**<0.05**
BMI	0.091	0.696
DV	0.196	0.396
Kt/V	0.05	0.828
MAP	0.042	0.856
Glucose	0.125	0.620
Hemoglobin	-0.22	0.926
Albumin	-0.76	0.742
CRP	0.178	0.441
Ca x P	0.338	0.134
Ferritin	0167	0.469
PTH	0.255	0.264
Hepcidine	0.606	**<0.05**

BMI - body mass index, Ca - calcium, CIMT - carotid intima-media thickness, CRP - C-reactive protein, DV - dialysis vintage, MAP - mean arterial pressure, P - phosphorus, PTH - parathyroid hormone

SH-25 was not found to be correlated with CRP (p<0.05, r=0.181). A correlation analysis of CIMT of the patients who died of CVD was done, and CIMT was found to be positively correlated with age and SH-25 (Fig. 1) [r=0.505; p<0.05 and r=0.606; p<0.05, respectively, (Table 3)]. CIMT was analyzed as a dependent variable by linear regression analysis, and the correlation of CIMT with SH-25 persisted (Table 4).

Discussion

There are two major findings of this study: (i) SH-25 was positively correlated with CIMT in the study population and (ii) SH-25 was not found to be elevated in patients who died due to all causes, but was found to be elevated in patients who died due to atherosclerotic diseases.

In many experimental animal studies, hepcidin was found to be associated with atherosclerotic disease. In mice, hepcidin

Table 4. Linear regression analysis

		Unstandardized coefficients		Standardized coefficients Beta	t	Sig.
Model		B	Standard error			
1	(Constant)	0.666	0.129	0.476	5.174	0.000
Hepcidin-25		0.003	0.001	0.282	2.372	<0.05
Age		0.003	0.002		1.405	0.177

Dependent variable: carotid intima-media thickness

was suppressed and the intracellular iron content in macrophages was reduced. As a result, the efflux capacity of cholesterol into macrophages increased and foam cell formation decreased (23). In an atherosclerotic mice model, hepcidin caused inflammatory cytokine release, intracellular lipid accumulation, oxidative stress, and apoptosis of macrophages causing plaque destabilization (24).

In two studies in patients with nonalcoholic fatty liver disease, SH-25 levels were associated with the presence of atherosclerotic plaques (16, 17). In a study of postmenopausal women, hepcidin was associated with the presence of plaques in the carotid artery when adjusted for eGFR, inflammation, and traditional CV risk factors (25). In another study, the hepcidin–ferroportin axis has been shown to be effective in macrophage inflammatory response to human atherosclerotic plaques (26). Conflicting results were obtained in two studies investigating the relation between atherosclerosis and hepcidin. In the first study in general population, no relation was observed between hepcidin and atherosclerosis (27). In another study in hypertensive patients, higher aortic stiffness was found to be correlated with lower hepcidin levels (28).

Recently, the role of hepcidin as a CV marker gained attention in the CKD population (3). Two studies, one in chronic HD patients and another in patients on peritoneal dialysis, showed an association between arterial stiffness and hepcidin level (15, 29). Likewise, in our previous study in the same cohort, CIMT was correlated with high SH-25 (30). In this study, SH-25 was increased in patients who died of CVD. Furthermore, CIMT and SH-25 were independently correlated in this patient group. Finally, in a cohort of chronic HD patients with a median follow-up of 3 years, SH-25 levels were associated with the incidence of CV events, even after stepwise adjustments of clinical and anemia-related parameters, including inflammation (31). Similarly, in our study, in 4 years, CV mortality was correlated with SH-25 levels. In another study, an independent positive correlation was observed between hepcidin and CIMT in diabetic chronic HD patients (32). In our study, there was no difference between the percentage of diabetic patients who lived and died. Therefore, we did not separately analyze the correlation in diabetic patients.

Two studies investigated the relation between hepcidin and LVMI. One study in patients with CKD who were not on dialysis showed that lower hepcidin levels were associated with higher LVMI, possibly due to the concomitant iron deficiency resulting in an anemic state (33). In a study in chronic HD patients, no association between hepcidin and LVMI was observed (34). In our study, LVMI and anemia parameters were not different between patients who died of CVD and those who lived; however, the hepcidin levels between them differed.

Systemic hepcidin, mainly produced in the liver, can have an inhibitory effect on iron release from macrophages (8, 35). Elevated hepcidin levels may be associated with atherosclerotic disease by retaining iron in macrophages in the vascular wall. This intracellular iron sequestration may induce oxidative stress, inflammatory response, and apoptosis of macrophages causing a proatherogenic environment (22, 36, 37). In our study, serum ferritin, albumin, and CRP levels were not different between the patients who lived and died. This may be because of the usage of nonsensitive inflammatory markers.

Study limitations

There are some limitations to this retrospective study. Due to the study design, CIMT was measured and changes that have occurred over time are shown. As the hepcidin levels were measured once, the possibility of change in plasma hepcidin level during the time period could not be known. In addition, this was a single-centered study; therefore, the number of patients and racial diversity is limited. Due to the study design, we cannot talk a causal relationship; therefore, interpretations should be made carefully.

Conclusion

In conclusion, the data presented in this study and recent publications suggests a wider role of hepcidin as a marker in normal biological systems. Well-designed prospective randomized trials are needed to investigate its exact role in the pathogenesis of CVD in CKD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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