ORIGINAL ARTICLE

The association between serum hepcidin-25 level and subclinical atherosclerosis in peritoneal dialysis patients

Periton diyalizi uygulanan hastalarda serum hepsidin-25 düzeyi ile subklinik ateroskleroz arasındaki ilişki

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ABSTRACT

Objective: Recently, the role of hepcidin as a cardiovascular marker in the chronic kidney disease (CKD) population has gained interest. The aim of this study was to investigate the relationship between serum hepcidin-25, inflammation, iron parameters, and carotid intima-media thickness (CIMT) in peritoneal dialysis (PD) patients.

Methods: A total of 58 patients (30 male, 51.3%; mean age: 46.8±13.6 years; mean dialysis duration: 69.2±39.1 months) were included in this cross-sectional study. Clinical and routine laboratory data were recorded and the CIMT and hepcidin values were determined. The study population was divided into 2 groups according to the median hepcidin value of 60 ng/mL. Correlation analysis and logistic regression analysis were performed to determine the relationship between the hepcidin level and other parameters.

Results: Age (p=0.003), systolic blood pressure (p=0.039), body mass index (p=0.031), glucose (p=0.028) level, C-reactive protein (CRP) level (p<0.001), and CIMT (p=0.011) were found to be statistically significantly higher in the high hepcidin group. In correlation analysis, hepcidin was positively correlated with age (p<0.001), dialysis duration (p=0.041), glucose (p=0.015), ferritin (p=0.005), CRP (p<0.001), and CIMT (p=0.035). In multivariate linear regression analysis, age (p<0.001) and CRP (p=0.005) were found to be related to CIMT.

Conclusion: Hepcidin-25 was strongly associated with both age and CRP in patients undergoing PD treatment. The results suggest that hepcidin may be involved in the pathophysiology of atherosclerosis. Prospective studies should be carried out in this patient population to determine whether hepcidin has an effect on atherosclerosis.

ÖZET

Amaç: Kronik böbrek yetersizliği olan hastalarda kardiyovasküler belirteç olarak hepsidinin rolü üzerine ilgi son zamanlarda artmıştır. Bu çalışmanın amacı periton diyalizi (PD) uygulanan hastalarda serum hepsidin-25 (SH-25) düzeyi ile enflamasyon, serum demiri ile ilgili parametreler ve ateroskleroz göstergesi olan karotis intima medya kalınlığı (KİMK)'nın ilişkisini araştırmaktır.

Yöntemler: Bu kesitsel çalışmaya 58 hasta (30 erkek %51.3, ortalama yaş 46.8±13.6 yıl, ortalama diyaliz süresi 69.2±39.1 ay) alındı. Klinik ve rutin laboratuvar verileri kayıt edildi ve KİMK ve SH-25 değerleri tespit edildi. Hepsidin ortanca değerlerine (60 ng/mL) göre çalışma grubu ikiye ayrıldı. Ayrıca, SH-25 düzeyi ile diğer parametrelerin ilişkisinin belirlenmesinde korelasyon analizi ve lojistik regresyon analizleri uygulandı.

Bulgular: Yüksek SH-25 grubunda yaş (p=0.003), sistolik kan basıncı (p=0.039), vücut kitle indeksi (p=0.031), glikoz (p=0.028), C-reaktif protein (CRP) (p<0.001) ve KİMK (p=0.011) istatistiksel olarak daha yüksek tespit edildi. Korelasyon analizinde SH-25, yaş (p<0.001), diyaliz süresi (p=0.041), glikoz (p<0.015), ferritin (p=0.005), CRP (p<0,001) ve KİMK (p<0.035) ile pozitif ilişkili bulundu. Çok değişkenli doğrusal regresyon analizinde yaş (p<0.001) ve CRP (p=0.005) KİMK ile ilişkili bulunmuştur.

Sonuç: Periton diyalizi tedavisi uygulanan hastalarda SH-25 hem yaş hem de CRP ile güçlü bir şekilde ilişkilidir. Çalışmanın sonuçları PD uygulanan hastalarda enflamasyon ve ateroskleroz patofizyolojisinde hepsidinin de etkili olabileceğini düşündürmektedir. Bu hasta popülasyonunda hepsidinin ateroskleroz üzerine etkisinin olup olmadığı geriye dönük çalışmalarla gösterilmelidir.

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Cardiovascular disease (CVD) is the most common cause of death in end-stage renal disease, and chronic kidney disease (CKD) is associated with the acceleration of CVD. Several mechanisms, such as inflammation, oxidative stress, endothelial dysfunction, and vascular calcification, are involved in the pathogenesis of CVD in CKD.[1,2]

Hepcidin is a peptide with antimicrobial activity. It is produced in the liver and excreted in the urine. Hepcidin-25 is a biologically active form that has an important role in iron metabolism. Hepcidin induces the internalization and breakdown of ferroportin, which carries cellular iron into the erythrocytes, macrophages, and hepatocytes.[3,4] Hepcidin secretion is regulated by iron accumulation, hypoxia, erythropoietic demand, and inflammatory signals.[5] The level of hepcidin was found to be higher in CKD patients, and more prominent in hemodialysis (HD) patients.[6,7] Recently, the relationship between hepcidin and CVD was investigated in different patient groups and the findings suggested that hepcidin might have a role in the development of atherosclerosis.[8–10]

Assessment of atherosclerotic changes in the carotid arteries with Doppler ultrasonography is a useful screening test that can indicate the higher risk for systemic atherosclerotic vascular disease both in the general population and CKD. Currently, carotid intima-media thickness (CIMT) measured with Doppler ultrasonography is used as a simple, available, and reliable method in the evaluation of atherosclerosis.[11]

Absolute and functional iron deficiency anemia is prevalent in HD patients. This condition is more prominent in peritoneal dialysis (PD) patients, who generally use oral iron therapy. This may suggest the presence of a higher hepcidin level. There are scarce data in the literature about hepcidin in the PD population. Additionally, no study has assessed the relationship between the serum hepcidin level and CIMT in PD patients. Therefore, the aim of this study was to investigate the relationship between CIMT, inflammation parameters, iron parameters, and the hepcidin-25 level in PD patients.

METHODS

Study population

In this cross-sectional study, a total of 58 patients undergoing PD in 1 center were included. All of the data, including demographic, clinical, and laboratory characteristics, were collected and recorded from the hospital visit files of the patients. Patients with known inflammatory or infectious disease, collagen vascular disease, malignancy, anemia or bleeding, chronic liver disease, or a history of an acute cardiovascular event or surgery in the previous 6 months were excluded from the study.

Abbreviations:

BMI	*Body mass index*
CIMT	*Carotid intima-media thickness*
CKD	*Chronic kidney disease*
CRP	*C-reactive protein*
CVD	*Cardiovascular disease*
HD	*Hemodialysis*
HDL-C	*High-density lipoprotein cholesterol*
LDL-C	*Low-density lipoprotein cholesterol*
PD	*Peritoneal dialysis*
SBP	*Systolic blood pressure*
T-chol	*Serum total cholesterol*
TG	*Triglyceride*

Informed consent was obtained from all of the participants before study enrollment and the study protocol was approved by the institutional local ethics committee.

The patients' height and weight were measured after dialysis fluid was completely drained and body mass index (BMI) was calculated according to the standard formula. Blood pressure was measured after at least 15 minutes of rest during an outpatient clinic control visit, and an average of 3 measurements taken at 3-minute intervals was determined. Pulse pressure and mean arterial pressure were calculated according to the standard formula. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or antihypertensive drug use.

Carotid intima-media thickness measurement

Ultrasonographic B-mode imaging of the bilateral carotid arteries was performed with a high-resolution real-time ultrasound system with a 12-MHz linear assay transducer (DC-7; Mindray Bio-Medical Electronics, Shenzhen, China). Evaluations were performed by a single, experienced physician who was unaware of patient clinical status, with the patients lying in the prone position with the head extended and turned in the opposite direction. The carotid arteries, carotid bulb, and internal carotid arteries were examined using 2 different longitudinal projections. In each longitudinal projection, CIMT was calculated from the site of greater thickness. CIMT was defined as the distance between the leading edge of the lumen interface at the far wall in plaque-free arterial segments. The value was expressed as an average of the maximal CIMT.

Measurement of hepcidin-25 and routine blood parameters

Blood samples were taken from a peripheral vein after overnight fasting and were allowed to stand for about 1 hour at room temperature, and then centrifuged at 2000 rpm for 10 minutes. All samples were stored at -800C until the measurement of hepcidin-25 was performed. A DRG Hepcidin 25 (bioactive) HS enzyme-linked immunosorbent assay kit (DRG Diagnostics GmbH, Marburg, Germany) was used to assess hepcidin-25. The analytical sensitivity of the test is 0.135 ng/mL.

Serum total cholesterol (T-chol) and triglyceride (TG) levels were measured using a commercial colorimetric assay (glycerol phosphate oxidase-p-aminophenazone and cholesterol oxidase phenol 4-aminoantipyrine peroxidase methods; Boehringer Mannheim GmbH, Mannheim, Germany), high-density lipoprotein cholesterol (HDL-C) level was measured using the phosphotungstic acid precipitation method. Low-density lipoprotein cholesterol (LDL-C) was calculated with the Friedewald formula (LDL-C=T-Chol-TG/5-HDL-C). C-reactive protein (CRP) was assessed using an automated turbidimetric method. Routine serum biochemical parameters were studied with a standard computerized autoanalyzer (Hitachi 717; Boehringer Mannheim GmbH, Mannheim, Germany). In our unit, biochemical parameters are evaluated every 2 months in routine follow-up; the mean serum chemistry values for the previous 6 months were used in the statistical analysis.

Serum and urine dialysate urea and creatinine values were analyzed using a computerized autoanalyzer (Hitachi 717; Boehringer-Mannheim). RenalSoft (Baxter International, Inc., Deerfield, IL, USA) English-language software was used to calculate Kt/V and creatinine clearance, and the urea distribution volume was calculated with the same software according to the Watson formula.[12] Residual renal function was expressed as the mean value of the sum of residual urea and creatinine clearances. A peritoneal equilibration test was performed according to the method described by Twardowski et al.[13]

Statistical analysis

Data analysis was performed by using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to test the normality of continuous variables. The results of the analysis of continuous variables were expressed as mean±SD or median (25^{th}-75^{th} interquartile range) while categorical variables were expressed as the number of cases and percentages. The study population was categorized into groups of low (≤60 ng/mL) or high (>60 ng/mL) hepcidin-25 level according to the median serum hepcidin-25 value of 60 ng/mL. Categorical variables were compared using a chi-square or Fisher's exact test, and continuous variables were analyzed with the Student's t-test or the Mann-Whitney U test. Pearson's correlation coefficient was used for continuous variables with normal distribution and Spearman's correlation coefficient was used for continuous variables that were not normally distributed. In addition, the independent effect of each variable on CIMT was assessed using multivariate linear regression analysis. A level of $p<0.05$ was accepted as significant.

Table 1. Baseline characteristics of the study population

Variables	n=58
Gender/male, n (%)	30 (51.3)
Age, years	46.8±13.6
Dialysis duration, months	69.3±39.2
Causes of ESRD, n (%)	
Hypertension	13 (22.4)
Chronic glomerulonephritis	10 (17.2)
Other	7 (11.9)
Diabetes	6 (10.3)
Unknown	22 (37.9)
Concomitant disease, n (%)	
Hypertension	34 (58.6)
Hyperlipidemia	18 (31)
Diabetes mellitus	7 (12.1)
History of cardiovascular disease	6 (10.3)
Current smoker, n (%)	12 (20.7)
Systolic blood pressure (mm Hg)	128 (120–150)
Diastolic blood pressure (mm Hg)	80 (70–90)
MBP (mm Hg)	95 (89.5–110)
Body mass index (kg/m^2)	25.4±3.9
SAPD/APD (%)	83/17
Renal residual function, n (%)	20 (34.4)

ESRD: End stage renal disease; MBP: Mean blood pressure; APD: Assisted peritoneal dialysis; CAPD: Continuous ambulatory peritoneal dialysis.

Table 2. Medications of the study population

Variables	n=58	
	n	%
Phosphorus binders		
Calcium acetate	42	72.4
Sevelamer	8	13.8
No binder	5	8.6
Aluminum-containing	3	5.2
Active vitamin D	38	65.5
Oral iron	41	70.7
Erythropoietin	33	56.9
Anti-hypertensive		
Calcium channel blockers	23	39.7
Beta-blocker	14	24.1
Alpha blocker	8	13.8
Renin angiotensin system blocker	6	27.6
Anti-hyperlipidemics		
No	42	72.4
Statin	10	17.2
Gemfibrozil	6	10.3

Table 3. Laboratory findings of the study patients

Variables	n=58
Blood urea nitrogen (mg/dL)	116±28
Creatinine (mg/dL)	9.5±2
Glucose (mg/dL)	100 (91–109)
Albumin (g/dL)	3.8±0.4
C-reactive protein (mg/dL)	0.75 (0.35–1.93)
Hemoglobin (g/dL)	11.1 (10–12.3)
Ferritin (ng/mL)	196 (81.75–376)
Ferritin >500 ng/mL, n (%)	13 (22)
Transferrin saturation, %	19.4 (12.7–27)
Calcium, (mg/dL)	9.2 (8.2–9.7)
Phosphorus, (mg/dL)	5±1.3
CaXP product (mg^2/dL^2)	46±13
Parathormone (pg/mL)	436 (195–700)
Total cholesterol (mg/dL)	187±45
Triglyceride (mg/dL)	150 (109–220)
Low density lipoprotein (mg/dL)	112±36
High density lipoprotein (mg/dL)	36 (30–48)
Uric acid (mg/dL)	5.3 (4.6–6)
Kt/V	2.1±0.46
Hepcidin-25 (ng/mL)	62.2±19.3
Carotid intima-media thickness (mm)	0.75 (0.65–0.85)
Carotid plaque, n (%)	9 (15.5)

RESULTS

Fifty-eight patients participated in the study (30 male; mean age: 46.8±13.6 years). The median CIMT was 0.075 mm (0.065-0.085 mm) and the mean hepcidin value was 62.2±19.3 ng/mL. Demographic and somatometric characteristics, co-morbid diseases, medical treatments, and the baseline laboratory values of patients are provided in Tables 1–3.

The median hepcidin-25 value was 60 ng/mL and the study population was divided into 2 groups according to this median value. The demographic, somatometric, laboratory, and CIMT data of the 2 groups were compared (Table 4). In the high hepcidin group, age [41 years (33.5–47 years) vs 52 years (43–62 years); p=0.003], SBP (123±22 mm Hg vs 134±15 mm Hg; p=0.039), BMI (24.3±3.8 kg/m^2 vs 26.5±3.7 kg/m^2; p=0.031), glucose (97±15 mg/dL vs 110±27 mg/dL; p=0.028), CRP [0.5 mg/dL (0.26–0.81 mg/dL) vs 1.64 mg/dL (0.6-3.0 mg/dL); p<0.001] and CIMT (0.73±0.14 mm vs 0.83±0.16 mm; p=0.011) were significantly higher when compared with the low hepcidin group. In the high hepcidin group, ferritin values tended to be higher but the difference was not statistically significant [160 ng/mL (60–386 ng/mL) vs 250 ng/mL (107–402 ng/mL); p=0.069]. Hemoglobin and transferrin saturation values were similar in both groups (p=0.810 and p=0.540 respectively).

In correlation analysis, age (r=0.431; p<0.001), dialysis duration (r=0.269; p=0.041), glucose (r=0.319; p=0.015), ferritin (r=0.366; p=0.005), CRP (r=0.585; p<0.001), and CIMT (r=0.277; p=0.035) (Fig. 1) were correlated with hepcidin-25 (Table 5). In multivariate linear regression analysis, age (p<0.001) and CRP (p=0.005) were associated with CIMT (Table 6).

DISCUSSION

The main finding of this study is the strong association between serum hepcidin-25 level, age, and CRP. Again, it has been shown that body iron overload may also affect the serum hepcidin level via inflammation. These associations between age and CRP as determinants of CIMT and hepcidin-25 may suggest

Table 4. Demographic, clinical, and laboratory data of the patients according to low and high hepcidin-25 level

Variables	Hepcidin ≤60 (ng/mL) (n=29)	Hepcidin >60 (ng/mL) (n=29)	*p*
Age, years	41 (33.5–47)	52 (43–62)	0.003
Gender, male (%)	13 (44.86)	17 (58.6)	0.293
Diabetes mellitus, n (%)	2 (6.9)	5 (17.2)	0.227
Smoking, n (%)	7 (24.1)	5 (17.2)	0.517
Hyperlipidemia, n (%)	9 (45)	9 (45)	1
Dialysis duration, months	77±39	61±37	0.119
Systolic blood pressure (mm Hg)	123±22	134±15	0.039
Diastolic blood pressure (mm Hg)	80±14	82±10	0.578
Mean arterial pressure (mm Hg)	94±16	102±20	0.091
Body mass index (kg/m^2)	24.3±3.8	26.5±3.7	0.031
Kt/V	2.04±0.38	2.19±0.53	0.301
Renal residual function, n (%)	9 (52.6)	9 (52.6)	1
Blood urea nitrogen (mg/dL)	119±27	113±30	0.420
Creatinine (mg/dL)	9.8±2	9.3±2	0.331
Glucose (mg/dL)	97±15	110±27	0.028
Albumin (mg/dL)	3.80±0.4	3.76±0.4	0.745
C-reactive protein (mg/dL)	0.5 (0.26–0.81)	1.64 (0.6–3.0)	<0.001
Hemoglobin (g/dL)	11.5±2.2	11.4±1.9	0.810
Transferrin saturation, %	23±15	21±14	0.540
Ferritin (ng/mL)	160 (60–386)	250 (107–402)	0.069
Calcium (mg/dL)	9.2±0.6	9.2±0.7	0.770
Phosphorus (mg/dL)	5.1±1.3	4.9±1.3	0.594
Calcium-phosphorus product (mg^2/dL^2)	47±13	45±13	0.661
Parathormone (pg/mL)	478 (236–700)	310 (155–687)	0.356
Total cholesterol (mg/dL)	178±51	195±37	0.142
Triglyceride (mg/dL)	117 (89–220)	169 (121–222)	0.506
Low-density lipoprotein cholesterol (mg/dL)	103± 37	121±33	0.051
High-density lipoprotein cholesterol (mg/dL)	41±13	38±12	0.442
Uric acid (mg/dL)	5.2±0.8	5.4±1.0	0.575
Carotid intima-media thickness (mm)	0.73±0.14	0.83±0.16	0.011
Carotid plaque, n (%)	3 (10.7)	6 (21.4)	0.277

a role of increased hepcidin induced by inflammation in the complex pathophysiological process of systemic atherosclerosis.

The hepcidin level is high in non-dialysis CKD patients as well as in dialysis patients, and this may be caused by inflammation and elevated iron stores or reduced clearance.[6,14,15] The hepcidin levels in the present study population were similar to those reported in the literature.[16,17] Approximately 30% of the patients had renal residual volume, and there was a positive correlation between dialysis duration and hepcidin. This supports an inverse relationship between renal clearance and hepcidin level.

It is well known that anemia, iron deficiency, and inflammation are prevalent in CKD patients. A strong association between ferritin and hepcidin has been demonstrated in studies conducted with CKD.[6,7,18–22] However, hepcidin was correlated with CRP in some studies, while this correlation did not exist in others.[6,7,23,24] There may be a threshold value for hepcidin to induce inflammation.[17,18,21,22] In a large study, a relationship between hepcidin and CRP was observed

Table 5. Correlation analysis of variables with serum hepcidin-25

Variables	Hepcidin-25	
	r	*p*
Age	0.431	<0.001
Dialysis duration	-0.110	0.410
Systolic blood pressure	0.230	0.082
Diastolic blood pressure	0.035	0.797
Body mass index	0.209	0.115
Blood urea nitrogen	0.037	0.783
Creatinine	-0.148	0.267
Albumin	-0.057	0.672
Hemoglobin	-0.173	0.194
Transferrin saturation	-0.109	0.417
Ferritin	0.366	0.005
Total cholesterol	0.132	0.332
Triglyceride	0.153	0.252
Low-density lipoprotein cholesterol	0.220	0.096
High-density lipoprotein cholesterol	-0.167	0.209
Uric acid	0.085	0.526
C-reactive protein	0.585	<0.001
Glucose	0.319	0.015
Carotid intima-media thickness	0.277	0.035

Table 6. Multivariate linear regression analysis of factors associated with carotid intima-media thickness

Parameters	β	SD	t	*p*
Age	0.478	0.000	3.935	<0.001
Mean arterial pressure	0.140	0.000	1.354	0.182
Glucose	-0.035	0.000	-0.317	0.752
C-reactive protein	0.348	0.001	2.922	0.005
Hepcidin-25	0.028	0.000	0.225	0.823

only in patients with a relatively low ferritin value (<530 ng/mL).[19] In our study, there was a strong association between CRP and the serum hepcidin-25 level, similar to what has been described in the literature. In addition, the number of patients with a ferritin level >500 ng/mL in the study population was remarkably lower. However, ferritin and hepcidin levels had statistically significant positive correlations, and the ferritin level was higher in high hepcidin group, but not statistically significant. It should also be kept in mind that ferritin is a natural acute phase reactant and may be affected by medical treatments.

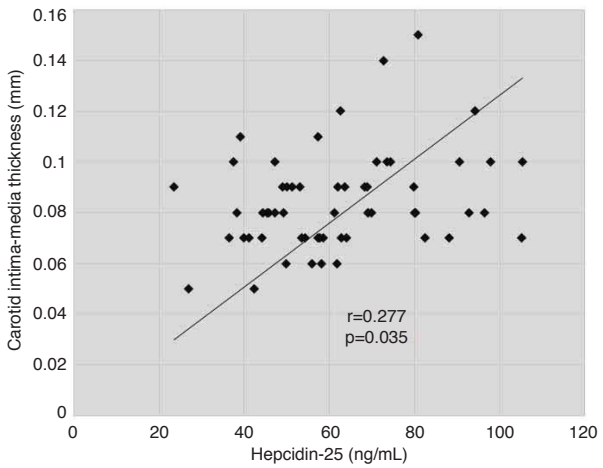

Figure 1. Correlation between carotid intima-media thickness and serum hepcidin-25 level.

Recent evidence has shown a new conceptual role for hepcidin as a biomarker for CVD. The possible role of hepcidin in the development of atherosclerosis and CVD is supported by several studies. Experimental animal studies have provided evidence for the involvement of hepcidin in atherosclerotic processes.[25,26] In clinical and epidemiological studies, hepcidin and markers of vascular stiffness, atherosclerosis, and CVD were found to be associated.[9,10,27,28] The relationship between hepcidin and arterial stiffness has been demonstrated in both HD and PD patients.[8,16] In addition, a positive correlation between hepcidin and CIMT in HD patients has been reported.[18,29] A recent prospective study of HD patients demonstrated a correlation between hepcidin level and the incidence of CV events.[30] The results of the current study indicated that CIMT was higher in the high hepcidin group. However, although the positive correlation between hepcidin and CIMT was also observed in the correlation analysis, the effect of hepcidin on CIMT was not detected in linear regression analysis.

The local or systemic increase of hepcidin causing iron retention in vascular macrophages may be involved in the pathogenesis of atherosclerosis. This intracellular iron sequestration may result in a proatherogenic environment, possibly mediated by oxidative stress, inflammatory responses, and macrophage apoptosis, resulting in clinical events.[26,31,32] Recently, a study of PD patients has shown an association between oxidative stress, hepcidin, and arterial stiffness.

[16] The data of our study support a strong association between hepcidin and inflammation. Intracellular iron load causing oxidative stress and apoptosis may, in turn, cause increased inflammation.

A recent study has shown that both the hepcidin level and CIMT are higher in diabetic HD patients than in non-diabetic HD patients.[18] In addition, it has been reported that hepcidin may negatively affect insulin resistance.[33] In our study, the relationship between glucose and hepcidin may suggest that hepcidin contributes to the development of accelerated atherosclerosis through insulin resistance and glucose metabolism.

There are some limitations in this cross-sectional study. Due to the design of the study, CIMT was measured and changes that occurred over time were shown. However, hepcidin levels were measured only once and the possibility of change in the serum hepcidin level during the period of the study cannot be known. Other limitations of this single-center study are the lack of a control group and the relatively small number of patients. While the serum hepcidin level may be considered to be affected by age, inflammation, and body iron level, careful interpretation should be made about a causal relationship with a high hepcidin level. The cross-sectional design of this study allows only for reference to an association, rather than a cause-effect relationship between them.

In conclusion, our study results revealed an association between the serum hepcidin-25 level and inflammation in PD patients. The association between hepcidin and CIMT supports the hypothesis that hepcidin may contribute to the development of atherosclerosis. Well-designed prospective studies are needed to determine the role of hepcidin in atherosclerosis pathophysiology, especially in the CRF population.

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