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Original Research

GESDAV

The relationship between leptin and arterial stiffness in patients on dialysis

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ABSTRACT

Aim: Leptin modifies the systemic inflammatory response and insulin action, but the mechanisms by which it affects vascular disease is unclear. We studied the relationship between leptin serum concentrations and arterial stiffness in dialysis patients. **Materials and Methods:** We studied 76 patients on on-line hemodiafiltration. Dialysis adequacy was defined by Kt/V for urea. Leptin and insulin were measured by radioimmunoassays. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance. High sensitivity C-reactive protein (hsCRP) and oxidized low-density lipoprotein (ox-LDL) serum concentrations were measured by ELISA. The ratio of LDL/high density lipoproteins was calculated, and serum bicarbonate levels were measured in gas machine. Arterial stiffness was assessed as carotid-femoral pulse wave velocity (c-f PWV) and carotid augmentation index (Aix). **Results:** We observed significantly positive correlation between leptin and body mass index, insulin and hsCRP ($r = 0.397$, $P = 0.001$, $r = 0.284$, $P = 0.02$ and $r = 0.244$, $P = 0.04$ respectively), but the correlation between leptin and Aix was significantly reverse ($r = -0.251$, $P = 0.04$). The higher leptin values were correlated with mildly elevated serum bicarbonate levels, which were inversely associated with hsCRP, c-f PWV and Aix ($r = -0.384$, $P = 0.005$, $r = -0.719$, $P = 0.001$ and $r = -0.527$, $P = 0.001$, respectively). **Conclusion:** We observed an inverse association between leptin and arterial stiffness may confounded by metabolic acidosis and obesity in dialysis patients.

KEY WORDS: Arterial stiffness, dialysis, leptin, metabolic acidosis

INTRODUCTION

Leptin is the most common of the adipokines secreted by adipocytes, which modifies the systemic inflammatory response and insulin action increasing insulin resistance [1]. Disorders associated with hyperleptinemia such as obesity and insulin resistance are major risk factors for cardiovascular disease [2]. Arterial stiffness, associated with abnormalities in the structure or function of the vascular wall, has shown to be an important parameter for the assessment of cardiovascular risk among the markers of arterial disease [3].

Previously, the leptin receptor has been identified on endothelial cells, and leptin has been reported to promote both angiogenesis and inflammation [4]. Furthermore, it has been shown using experimental methods, that leptin induces reactive oxygen species (ROS) generation by increasing fatty acid oxidation via a protein kinase A activation, which may play an important role in the progression of atherosclerosis in insulin resistant obese diabetic patients [5]. In addition, leptin induced expression of monocyte chemoattractant protein-1, a CC chemokine, which plays an important role in the early phase of atherosclerosis by initiating monocyte/macrophage recruitment to the vessel wall [6], and its expression is actually known to be up-regulated in human atherosclerotic plaques [7].

Enhanced chronic systemic inflammation and reduced insulin sensitivity are often associated in patients with chronic renal disease, contributing to cardiovascular morbidity and mortality in these patients [8]. However, the pathophysiological mechanisms by which leptin induces inflammation and affects vascular disease is still unclear in this population of patients.

In this study, we studied the relationship between leptin serum concentrations and arterial stiffness in patients on hemodiafiltration.

MATERIALS AND METHODS

Subjects

We studied 76 hemodialyzed patients (HD median duration = 5.0, interquartile range 3-10 years), 47 men and 29 women on mean age 62.2 ± 15 years. We dropped out all enrolled patients in the same dialysis modality, and we applied on-line- predilution hemodiafiltration, in contrast to our previous published study [9]. The present study is a secondary analysis continuously to previous research.

We excluded the patients with multiple intra-dialytic hypotensive episodes, chronic persistent hypotension,

fibrillation, need to change blood pressure (BP) medications and the patients with interdialytic weight gain of >5% of total body weight. The enrolled patients did not have interdialytic peripheral edema, high BP, interdialytic orthostatic hypotension or other characteristics of an inaccurate dry body weight.

Also, those with significant infection or malignancy were excluded from our study.

Despite some of the enrolled patients suffered from coronary disease and controlled peripheral vascular disease, the patients of our dialysis department with myocardiac infarction, significant heart failure or strong manifestation of peripheral vascular disease were excluded from the study, similarly to our previous study.

The hemodialysis treatment was performed 3-times weekly with a dialysis time of 3.5-4 h per session, a filter of 1.5-2 m^2 surface area and the blood flow of 350-400 ml/min. A bicarbonate-based ultrapure buffer dialysis solution was used with a dialysate flow rate of 500-600 ml/min, a calcium (Ca) concentration of 1.50-1.75 mmol/L, a sodium concentration of 138-145 mmol/L and low molecular weight heparin as anticoagulant therapy. We used high-flux synthetic membrane, defined by a ultrafiltration coefficient >20 ml/h [10]. Dialysis dose was defined by Kt/V for urea, which was calculated according to the formula of Daugirdas [11]. Patients were excluded if they had Kt/V for urea <1.2.

In our data, the renal failure was caused by hypertensive nephrosclerosis at a ratio 33% and chronic glomerulonephritis at a ratio 30%.

Blood Collection

Blood samples were drawn just before the start of the mean weekly dialysis session in 12 h fasting state from the vascular access. At the end of the treatment, the blood pump speed was reduced to <80 ml/min and blood samples were obtained at 2 min post-dialysis from the arterial dialysis tubing for the calculation of the adequacy of dialysis by Kt/V for urea. The blood samples were centrifuged and kept at a temperature of −80°C.

Laboratory Measurements

Albumin, Ca corrected for the albumin levels, phosphate (P), alkaline phosphatase, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) were measured by biochemical analysis and hemoglobin values were also measured. The ratio of LDL/HDL and Ca × P products were calculated.

The concentrations of leptin and insulin were measured by radioimmunoassays (Active Human Leptin IRMA DSL-23100i, Webster, USA) and (BioSource Europe S.A., Belgium), respectively. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) [12].

High sensitivity C-reactive protein (hsCRP) and oxidized LDL (ox-LDL) serum concentrations were also measured by ELISA (Immundiagnostik AG., Germany, Immundiagnostik AG. Stubenwald-Allee, Bensheim respectively).

Metabolic acidosis was defined by serum bicarbonate levels, which were measured in gas machine (Roche, Combas b 121) taking care of the blood specimens [13].

Normalized protein catabolic rate for dry body mass was calculated from the urea generation rate [14]. Body mass index (BMI) was obtained from height and post-dialysis body weight.

Hemodynamic Measurements

Pre-dialysis peripheral systolic BP (SBP) and diastolic BP (DBP) were calculated as the mean of 10 measurements during a treatment month using an automatic sphygmomanometer OMRON M4-I (Co. Ltd. Kyoto, Japan). Mean peripheral pre-dialysis BP (MBP) was calculated as: MBP = DBP + 1/3 (SBP−DBP).

Before the mid-week dialysis session, the patients were allowed to rest for at least 10 min prior to their haemodynamic measurements. Arterial stiffness was measured as carotid-femoral pulse wave velocity (c-f PWV) and carotid augmentation index (Aix) using the SphygmoCor system® (AtCor Medical Pty. Ltd., Sydney, Australia) according to manufacturer's specifications. In each subject two sequences of measurements were performed, and their mean was used for statistical analysis. Pulse pressure was derived.

Approval and Consent

The study was approved by the ethics committee of the Hospital "Laiko, University General Hospital of Athens." Written informed consent was taken from all subjects.

Data Analysis

Data were analyzed using the SPSS 15.0 statistical package for Windows (SPSS Inc., Chicago, Illinois, USA) and expressed as mean ± standard deviation or as the median value ± interquartile range for data that showed skewed distributions; differences between mean values were assessed by using paired-*t* test and Mann–Whitney U-test. Correlations between variables were defined by Pearson and Spearman coefficient and $P < 0.05$ were considered to be significant. We performed a linear-regression analysis to investigate if leptin can act as a potential independent predictor of c-f PWV and Aix values after adjustment for the age, dialysis adequacy, dialysis vintage, and acidosis status in studied patients.

RESULTS

We divided the patients to two groups according to the leptin mean value (8.5 ng/ml), as leptin showed normal distribution (n>8.5 ng/ml or n<8.5 ng/ml [n = 38]). Characteristics and

differences between two groups of patients are listed in Tables 1 and 2. We observed that the patients with higher leptin values had significantly increased BMI, but significantly reduced Aix values ($P < 0.05$) than the patients with lower leptin values [Figure 1]. Also, the higher leptin was associated with elevated insulin, HOMA-IR, Ca × P products, hsCRP and serum bicarbonate levels, than lower leptin serum concentrations. However, the patients with higher leptin presented lower c-f PWV and ox-LDL, than the patients with lower leptin [Table 2].

Correlations

In total patients, we observed a positive correlation between leptin and BMI, insulin and hsCRP ($r = 0.397$, $P = 0.001$, $r = 0.284$, $P = 0.02$ and $r = 0.244$, $P = 0.04$ respectively), but the correlation between leptin and Aix was significantly reverse ($r = -0.251$, $P = 0.04$). Serum bicarbonate levels were inversely associated with hsCRP, c-f PWV [Figure 2] and Aix ($r = -0.384$, $P = 0.005$, $r = -0.719$, $P = 0.001$ and $r = -0.527$, $P = 0.001$, respectively).

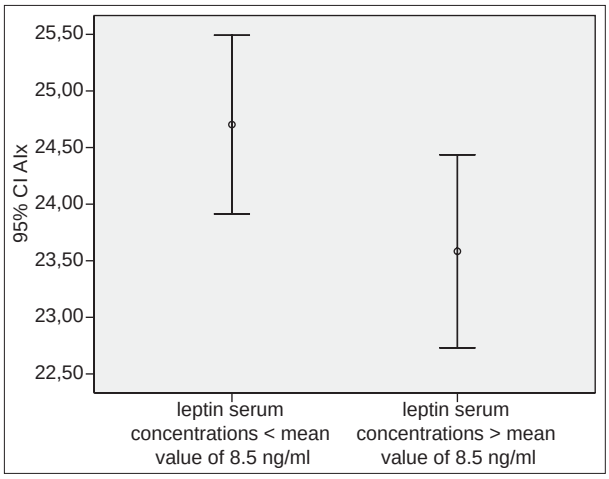

Figure 1: Carotid augmentation index values in dialysis patients with less or more than the mean leptin value = 8.5 ng/ml ($P < 0.05$)

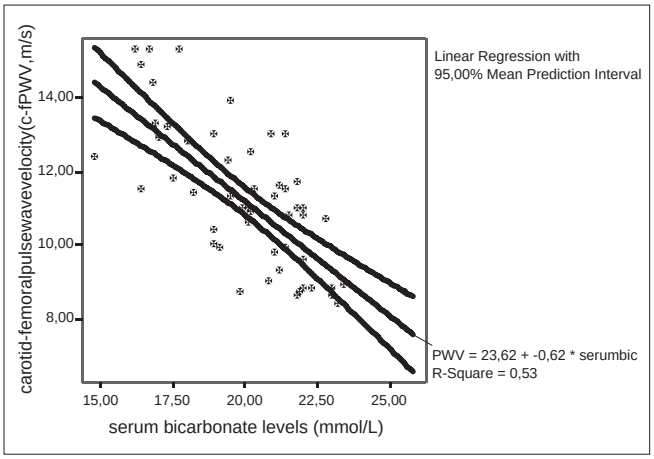

Figure 2: Correlation between serum bicarbonate levels and carotid-femoral pulse wave velocity in dialysis patients ($r = -0.719$, $P = 0.001$)

The built linear regression analysis showed that the old age, the acidosis state and leptin serum concentrations can act as potential independent predictors of Aix values in our patients, after adjustment for dialysis adequacy and dialysis vintage [Table 3].

For the prediction of c-f PWV values, leptin was not found as a significant factor.

DISCUSSION

The end-stage of renal disease (ESRD) is characterized by increments of plasma concentrations of hormones produced by adipose tissue known as adipocytokines (including leptin, resistin, tumor necrosis factor-alpha and adiponectin), possibly caused by both passive accumulation from reduced renal excretion and metabolic abnormalities induced by uremia [1].

Previously, it has been shown that leptin promotes both angiogenesis and inflammation and that the inflammatory microenvironment in renal disease may be associated with elevated expression of leptin gene [15]. Indeed, it has been already recognized that a substantial number of patients with ESRD have serologic evidence of activated inflammatory state [16]. In the present study, we observed significant

Table 1: Characteristics of the studied population, *n*=76 (47 males/29 females)

Characteristic	Minimum	Maximum	Mean/ median	SD/interquartile range
Age (years)	24	87	62.23	15.01
Dialysis duration (years)	0.5	27	-/5.0	-/3-10
BMI (Kg/m^2)	18.9	32.9	24.4	3.03
Kt/V for urea	1.2	2.01	-/1.29	-/1.25-1.49
nPCR (g/Kg/day)	1.12	4.31	2.43	0.57
SBP (mmHg)	85	182	132.2	21.2
DBP (mmHg)	55	97	81.5	9.7
MBP (mmHg)	65	125.3	96.4	12.6
c-f PWV (m/s)	8.3	15.2	11.3	1.83
Carotid (Aix)	20	29	24.19	2.18
PP (mmHg)	20	118	58.2	19.2
Leptin (ng/ml)	0.28	36.6	8.5	8.2
Insulin (μU/ml)	3.16	83.12	-/15.2	-/10.9-26.7
HOME-IR (mmol/L)	1.0	27.94	-/3.42	-/2.0-6.4
hsCRP (mg/L)	0.12	20.2	7.97	5.8
Ratio LDL/HDL	0.49	4.9	2.3	0.8
ox-LDL (ng/ml)	31.04	867.09	-/69.2	-/50.7-111.9
Ca (mg/dl)	6.7	11.4	9.4	0.7
P (mg/dl)	1.8	11.2	5.4	1.9
ALP (U/L)	53	463	171.9	79.3
Ca×P deposits	16.9	104	51.4	17.9
Serum bicarbonate (mmol/L)	14.8	25.5	20.09/-	2.28
Albumin (g/dl)	1.4	4.6	-/4.0	-/3.8-4.2
Hemoglobin	7.9	15.1	11.8	1.3

nPCR: Normalized protein catabolic rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure, c-f PWV: Carotid-femoral pulse wave velocity, Aix: Augment index, PP: Pulse pressure, HOME-IR: Homeostasis model assessment of insulin resistance, hsCRP: High sensitivity C-reactive protein, LDL: Low-density lipoprotein, HDL: High density lipoproteins, ox-LDL: Oxidized low-density lipoprotein, ALP: Alkaline phosphatase, Ca: Calcium, P: Phosphate, SD: Standard deviation

Table 2: Differences between groups of studied patients (n=76) according to leptin mean value (less or more than 8.5 ng/ml)

	Patients with leptin serum concentrations (n=38)		P value
	<8.5 ng/ml	>8.5 ng/ml	
Age (years)	60.5±14.6	63.2±15.6	0.4
BMI (Kg/m^2)	23.7±2.6	25.3±3.1*	0.03
Kt/V urea	1.4±0.2	1.3±0.2	0.7
nPCR (g/Kg/day)	2.4±0.5	2.4±0.4	0.9
MBP (mmHg)	98.1±11.9	97.9±12.6	0.9
c-f PWV (m/s)	11.4±1.9	10.9±1.7	0.3
Aix	24.7±2.3*	23.5±2.01	0.04
PP (mmHg)	57.7±19.8	57.9±20.8	0.9
Leptin (ng/ml)	3.6±2.5	15.8±8.5*	0.001
Insulin (μU/ml)	17.7±10.7	23.5±18.7	0.1
HOME-IR (mmol/L)	4.7±3.7	6.1±6.7	0.3
hsCRP (mg/L)	7.3±5.4	9.3±6.1	0.1
Ratio LDL/HDL	2.2±0.9	2.3±0.6	0.8
Ox-LDL (ng/ml)	156.6±200.9	93.2±76.9	0.08
Ca (mg/dl)	9.4±0.7	9.4±0.8	0.9
P (mg/dl)	5.3±1.8	5.5±2.1	0.6
ALP (U/L)	184.3±92.8	153.4±52.2	0.1
Ca×P deposits	50.3±16.7	53.1±21.1	0.5
Serum bicarbonate (mmol/L)	19.7±2.02	20.2±2.4	0.4
Albumin (g/dl)	4.0±0.2	3.9±0.6	0.6
Hemoglobin	11.8±1.17	11.8±1.2	0.9

*P<0.05, BMI: Body mass index, ox-LDL: Oxidized low-density lipoprotein, nPCR: Normalized protein catabolic rate, MBP: Mean blood pressure, c-f PWV: Carotid-femoral pulse wave velocity, Aix: Augment index, PP: Pulse pressure, HOME-IR: Homeostasis model assessment of insulin resistance, hsCRP: High sensitivity C-reactive protein, LDL: Low-density lipoprotein, HDL: High density lipoproteins, ox-LDL: Oxidized low-density lipoprotein, ALP: Alkaline phosphatase, Ca: Calcium, P: Phosphate

Table 3: Potential independent predictors of carotid Aix values in studied patients

	Beta	t	Significant	Lower	Upper
Age	0.258	1.975	0.05	−0.001	0.085
Kt/V for urea	−0.120	−0.932	0.3	−4.451	1.639
Dialysis vintage	−0.045	−0.339	0.7	−0.115	0.082
Serum bicarbonate	−0.443	−3.540	0.001	−0.802	−0.219
Leptin	−0.237	−1.917	0.04	−0.149	0.004

Aix: Augment index

correlation between leptin and hsCRP in total patients, also supported by the findings of our previous study [9] and the patients with higher leptin serum concentrations had higher hsCRP values than the patients with lower leptin values. However, there is a discrepancy for the relationship of leptin levels with chronic inflammation, and it has been supported that leptin may be a negative acute phase protein in chronic hemodialysis patients [17].

On the other hand, leptin suppresses appetite and increases energy expenditure, playing a homeostatic role in the regulation of food intake and in maintaining body composition in general population [18]. In patients with ESRD malnutrition and hypoalbuminemia are common and powerful predictors of morbidity and mortality in this population. One potential relationship between malnutrition and inflammation in renal disease patients is appetite suppression and the link between inflammation and anorexia may be through the leptin [19]. However, it has been already supported that inflammation is unlikely to reduce appetite causing malnutrition in dialysis patients through a leptin-mediated mechanism because leptin is a negative rather than a positive acute phase protein in this population of patients [17]. In this study, in agreement with other previous study, we noted significantly positive association of leptin with BMI and the patients with higher leptin serum concentrations had significantly higher BMI than the patients with lower leptin values [20].

Furthermore, leptin modulates insulin sensitivity and high-leptin triggers insulin resistance and vice versa [1,20]. In fact, in this study we observed significantly positive association of leptin with insulin and insulin serum concentrations and insulin resistance values defined by HOMA-IR were also elevated in patients with higher leptin serum concentrations.

In opposite, we observed significantly inverse association of leptin with Aix and the patients with higher leptin serum concentrations had significantly lower Aix values than the patients with lower leptin serum concentrations. Furthermore, higher leptin was associated with lower c-f PWV values, than lower leptin serum concentrations.

In addition, our multivariable model confirmed independent association between leptin and arterial stiffness determined by Aix values with an inverse way, adjusted for age, dialysis adequacy, dialysis vintage and acidosis state.

Recent study showed that the hyperleptinemia was associated inversely with vasodilatation of resistance arteries in the elderly population of 1016 subjects [21]. Additionally, other previous studies had observed a positive association between PWV and leptin/adiponectin ratio adjusted for gender and age and suggested that leptin regulates the osteoblastic differentiation and calcification of vascular cells and that the artery wall may be an important peripheral tissue target of leptin action [22-24]. Also, recently, it has been reported that leptin causes endothelial dysfunction and enhances the activity of angiotensin II on BP, activating the sympathetic nervous system and contributing to vascular stiffness and hypertension in obesity [25].

Moreover, in this study we observed that the patients with higher leptin serum concentrations had a better acidosis state assessed by mildly higher serum bicarbonate levels in combination to lower ox-LDL values, than the patients with lower leptin. Previously, it had been shown that leptin induced generation of ROS in aortic endothelial cells promoting oxidative stress and lipid acid oxidation, resulting in the progression of atherosclerosis in insulin-resistant obese diabetic patients [5].

Metabolic acidosis is a common condition particularly in end stage renal disease patients resulting in inflammatory stimulation, lipids oxidation and oxidative stress [26,27]. Maintenance dialysis therapies are often not able to completely correct the base deficit. In the present study, serum bicarbonate levels were inversely associated with hsCRP, c-f PWV and Aix, as we also showed in our previous study [9]. Supportingly,

our multivariable model showed an independent association between acidosis state and arterial stiffness determined by Aix values, in combination to the role of leptin and old age on the prediction of arterial stiffness. It has already been reported the role of metabolic acidosis on vascular calcification related to arterial stiffness as the mineral metabolism disturbances act through the existing metabolic acidosis in dialysis patients [28]. Even though the influence of acidosis on vascular calcification is complicated, acidosis promotes inflammation of the arterial wall, releasing cytokines that may induce vascular calcification and arterial stiffness, in agreement with the findings of our previous and present studies [9,28,29].

Based on findings of this study, we could suggest that the elevated leptin serum concentrations were associated with reduced arterial stiffness, due may to better acidosis status, which was correlated with the elevated leptin values in dialysis patients. Such finding may be a reverse causality or a compensatory mechanism versus to the hurtful actions of the increased leptin serum concentrations in these patients. Another confounding factor for the association between leptin and arterial stiffness may be the obesity. Alternatively, the findings of this study could also show that leptin may be a mediator for the relationship of metabolic acidosis and obesity with the impaired vascular function in this population of patients. However, more studies need to support a such hypothesis.

CONCLUSION

We observed an inverse association between leptin and arterial stiffness may confounded by metabolic acidosis and obesity in patients on hemodiafiltration.

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