The relationship between leptin serum concentrations and hypertension in patients on the end stage of renal disease

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Abstract

Introduction-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 hypertension in intermittent hemodialysis patients.

Methods: We studied 47 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 (HOMA-IR). Serum bicarbonate levels were measured in gas machine. We recorded the blood pressure as the mean of 10 measurements during a treatment month. Kaplan-Meier curve and Cox regression model were performed to predict the role of leptin levels on established hypertension.

Results: Leptin serum concentrations were positively associated with insulin and BMI (r= 0.331, p= 0.02 and r= 0.453, p= 0.001 respectively). Kaplan-Meier analyses showed that leptin serum concentrations less than the mean value equal to 8.12 ng/ml were significantly associated with both, established hypertension and defined by serum bicarbonate less than 22mmol/L metabolic acidosis state (log-rank=9.7, p= 0.002 and log-rank=3.6, p= 0.04 respectively). Cox-regression analysis showed that leptin was a inverse significant predictor for hypertension after adjustment for covariates.

Conclusion: We observed inverse association between high leptin serum concentrations and hypertension in intermittent hemodialysis patients. The underlying pathophysiological mechanisms for

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a such relationship may comprise a complicated leptin resistance affected by body adiposity, metabolic acidosis status and oxidative stress.

Key words: leptin; metabolic acidosis; hypertension; hemodialysis

1. Introduction

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 (TNF-α) and adiponectin, possibly caused by both, passive accumulation from reduced renal excretion and metabolic abnormalities induced by uremia.[1] Leptin, which belongs to IL-6 family of cytokines, plays an important role in the regulation of body weight through its central effects on appetite and peripheral effects on the regulation of energy expenditure.[2] Apart from metabolism, leptin has systemic effects including regulation of hematopoiesis, wound healing, lipolysis, blood pressure homeostasis, reproduction and immune function.[3,4] Also, the leptin receptor has been identified on endothelial cells, and leptin has been reported to promote both angiogenesis and inflammation.[5] Disorders associated with hyperleptinemia such as obesity and insulin resistance are major risk factors for assessed by increased arterial stiffness cardiovascular disease.[6]

Since leptin is mainly secreted by adipose tissue, serum leptin levels are directly proportional to adipocyte mass.

The current studies provide evidence that the real role of leptin on the patients in end stage of renal disease is complicated rather than clear.

In this study we observed the relationship between leptin serum concentrations and hypertension in patients on intermittent hemodialysis.

2. Material and Methods

2.1 Subjects

This is a retrospective cross-sectional study of a cohort of 47 dialysis patients, 30 males and 17 females, on mean age 58.5 ± 0.6 years old. The data collection became during a time of 60 months, from the 1st of July of 2007 until the end of June of 2012.

Those with autoimmune diseases, infections, malignancy or another catabolic condition were excluded from our study. Also, patients without regular vascular hemodialysis access and who had dialysis catheter were not included in the study.

The treatment modality which were applied was on-line predilution hemodiafiltration (on-l HDF) in total patients.The mean time on hemodialysis was 7.7 ± 6.8 years.

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 by high-flux synthetic membrane, defined by a ultrafiltration coefficient >20 ml/h[7] and a 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 concentration of 1.50-1.75 mmol/L, a sodium concentration of 138-145 mmol/L and low molecular weight heparin as anticoagulant therapy. The final concentration of bicarbonate in dialysate was 32 mmol/L. Dialysis dose defined by Kt/V/day for urea, which was calculated according to the formula of Daugirdas[8]. Patients were excluded if they had Kt/V for urea < 1.2.

We excluded the patients with multiple intradialytic 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 were in a good status, on free regular diet and they did not have interdialytic peripheral oedema, interdialytic orthostatic hypotension or other characteristics of an inaccurate dry body weight.

Patients with pre-dialysis blood pressure ≥140/90 (n= 18, a ratio of 38.3%) were considered hypertensive,

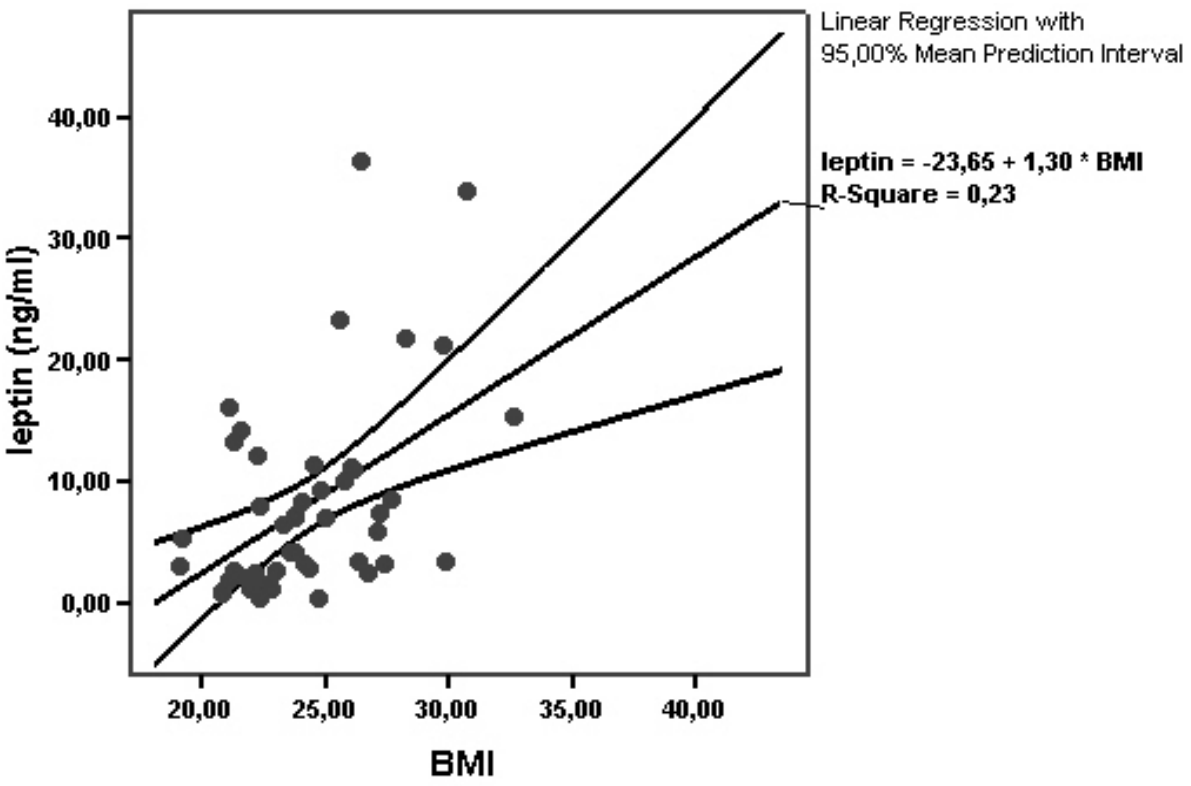

Figure 1. Correlation between leptin serum concentrations and BMI (r= 0.453, p= 0.001)

or if they were receiving anti-hypertensive drugs.

14 of the studied patients were current smokers (a ratio of 29.8%).15 patients (31.9%) were preserving a residual renal function (RRF) and they excreted up to 100 ml of interdialytic urine volume.

Calcium channel blockers, beta-blockers or inhibitors of angiotensin II receptors were included in the receiving medications by our patients.Also, 8 of the enrolled patients were receiving statin. Only calcium-free phosphate binders were prescribed. Nobody of our patients was receiving NaHCO3 per os. The total of studied patients was on erythropoetin-a or-β therapy.

The underling renal diseases were hypertensive nephrosclerosis (n= 17, 36.2%), chronic glomerulonephritis (n= 13, 27.7%), polycystic kidney disease (n= 6, 12.8%), diabetic nephropathy (n= 4, 8.5%), and other/unknown (n=7, 14.9%).

2.2 Approval and Consent

The study was approved by the ethics committee of the Hospitals "Laiko, University General Hospital of Athens" and Renal Unit of "Diagnostic and Therapeutic Center of Athens Hygeia SA".Written informed consent was obtained from all subjects.

2.3 Blood collection

In the study participated patients blood was drawn just before the start of the mean weekly dialysis session in a twelve hours fasting state from the vascular access.In the end of the treatment the blood pump speed was reduced to < 80ml/min and blood samples was obtained at 2 min post-dialysis from the arterial dialysis tubing for the calculation of the adequacy of dialysis by Kt/V for urea.

Samples were centrifuged immediately, serum was separated and processed for various assays.

2.4 Laboratory measurments

Albumin, high density lipoproteins (HDL) and low density lipoproteins (LDL) were measured by biochemical analysis. The ratio of LDL / HDL was calculated.

High sensitivity C-reactive protein (hsCRP) and

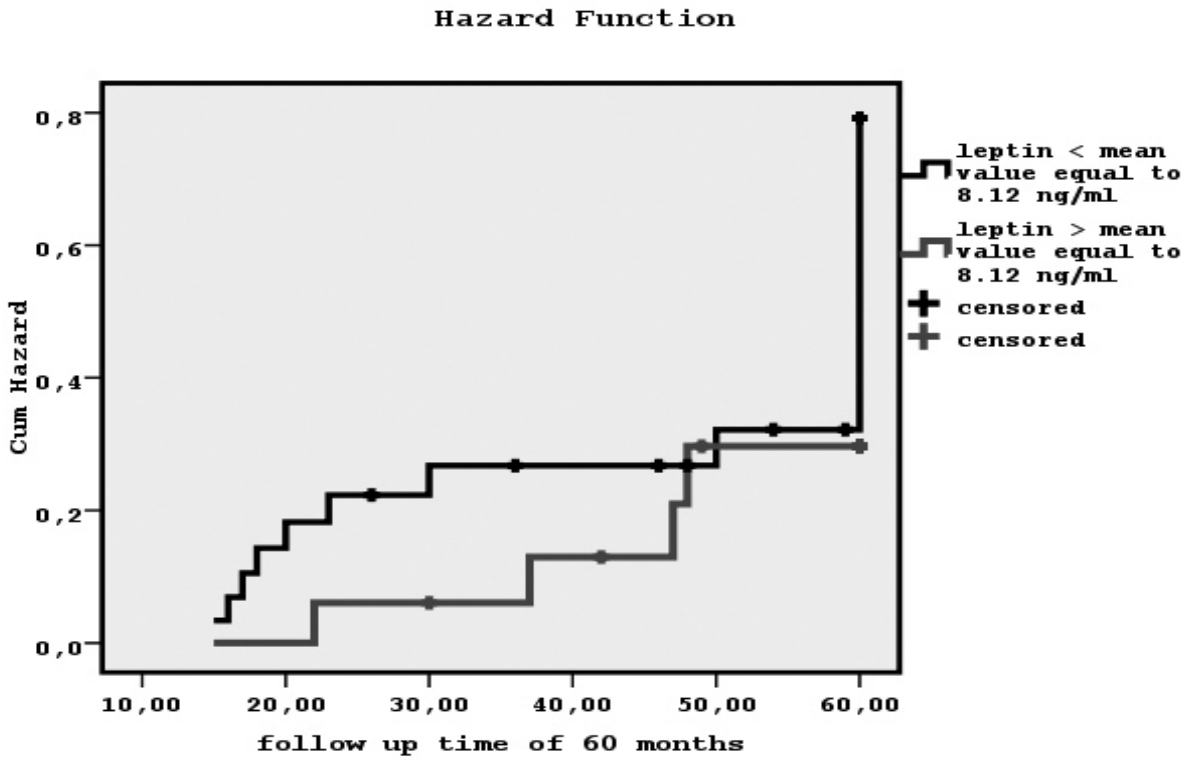

Figure 2. The influence of lower or higher than mean value of leptin equal to 8.12 ng/ml on hypertension during a follow up time of 60 months by Kaplan-Meier curve (log-rank= 9.7, *p*= 0.002).

oxidized LDL (ox-LDL) serum concentrations were measured using enzyme linked immunoabsorbed assays (ELISA, Immundiagnostik AG., Germany and Immundiagnostik AG. Stubenwald-Allee, Bensheim respectively) according to manufacturer's specifications.

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).[9] The concentrations of intact-parathormone (i-PTH) were also measured by radioimmunoassay (CIS bio international/France).

Metabolic acidosis was defined by serum bicarbonate concentrations less than 22.0 mmol/L,which were measured in gas machine (Roche, combas b 121) by an electrode-based method taking care of the blood specimens.[10]

Normalized protein catabolic rate for dry body mass (nPCR) was calculated from the urea generation rate.[11] Body mass index (BMI) was obtained from height and post-dialysis body weight.

2.5 Blood pressure measurements

Predialysis peripheral systolic and diastolic blood pressures (SBP and DBP respectively) in enrolled patients 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).

2.6 Data analysis

Data were analyzed using SPSS 15.0 statistical package for Windows (SPSS Inc, Chicago, Illinois) and expressed as mean ± standard deviation or as median value (interquartile range) for data that showed skewed distribution; Differences between mean values were assessed by using unpaired t-test for two groups and data that showed skewed distributions were compared with Mann-Whitney U- test.

Correlations between variables were defined by Pearson and Spearman coefficient and p values less

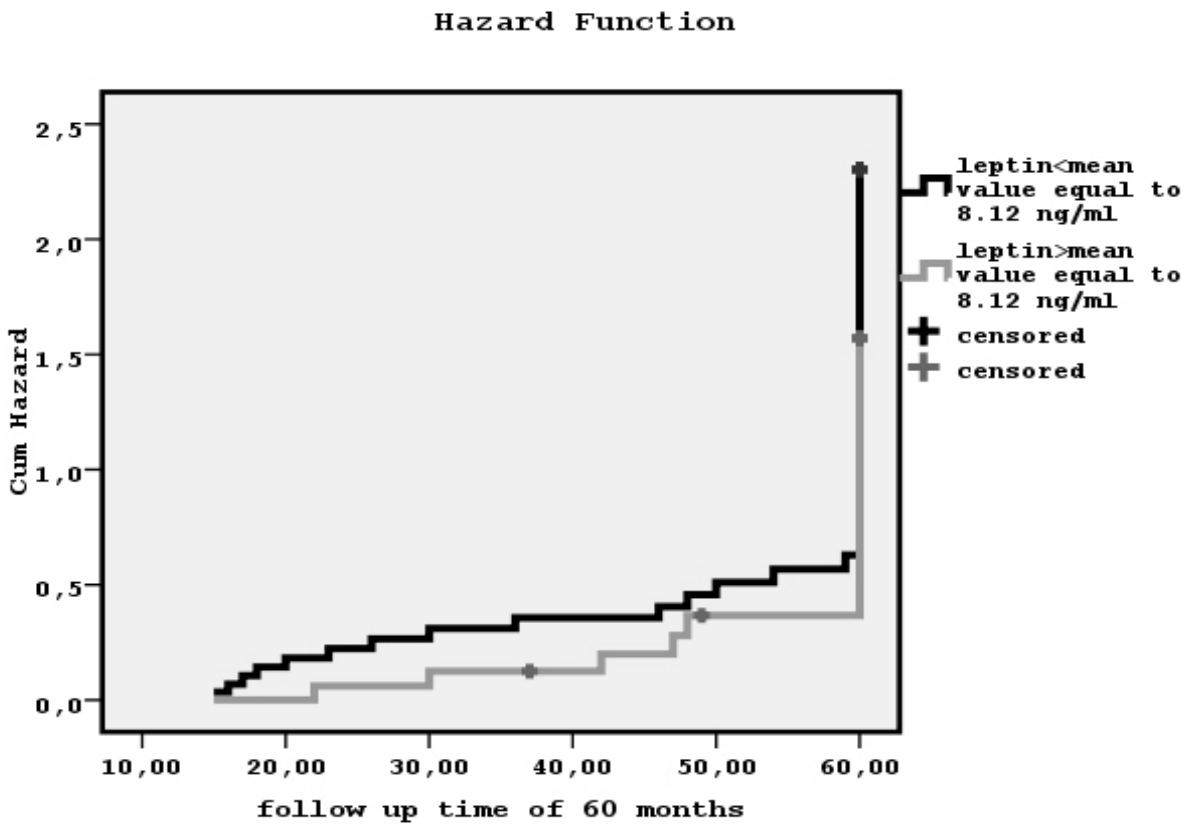

Figure 3. The influence of lower or higher than mean value of leptin equal to 8.12 ng/ml on serum bicarbonate concentrations less than 22 mmol/L during a follow up time of 60 months by Kaplan-Meier curve (log-rank= 3.6, *p*= 0.04)

than 0.05 were considered significant. Because of the duration study was different in our data, the relationships between categorical variables were defined by log-rank tests with Kaplan-Meier analysis. We performed a Cox regression analysis by enter method to investigate serum leptin concentrations as a possible independent predictor of high blood pressure adjusting for the traditional and specific risk factors for dialysis patients, such as age, defined by interdialytic urine volume RRF, defined by Kt/V for urea dialysis adequacy, diabetes mellitus and smoking.Also, we examined by built model the role of leptin on low serum bicarbonate (less than 22 mmol/L) after adjustment for confounders.A control for multicolinarity became.

3. Results

Leptin serum concentrations were positively associated with insulin and BMI (*r*= 0.331, *p*= 0.02 and *r*= 0.453, *p*= 0.001 respectively, **Figure 1**).

We divided the patients to two groups according to the mean value of leptin (8.12 ng/ml), as leptin showed normal distribution. In **Table 1**, the differences between the groups of patients with serum leptin levels more (*n*= 17) or less (*n*= 30) than the mean value equal to 8.12 ng/ml are shown.We observed that the patients with high leptin values had significantly increased insulin levels, insulin resistance, BMI and hsCRP than the patients with lower leptin levels.Also, the same group of patients presented elevated i-PTH, the LDL/HDL ratio, nPCR, serum bicarbonate concentrations, but decreased urine volume, ox-LDL and SBP, DBP and MBP in comparison to the patients with leptin values less than 8.12 ng/ml.

Kaplan-Meier analyses showed that leptin serum concentrations less than 8.12 ng/ml were significantly associated with both, established hypertension and defined by serum bicarbonate less than 22mmol/L metabolic acidosis state (log-rank=9.7,

Table 1. **Differences between groups of patients according to lower or higher than mean value leptin equal to 8.12 ng/ml in a total of 47 enrolled in the study patients**

	Patients with serum leptin less than 8.12 ng/ml (*n*= 30, 63.8%)	Patients with serum leptin more than 8.12 ng/ml (*n*= 17, 36.2%)
Sex (males / females)	20 (42.6%) – 10 (21.3%)	10 (21.3%) – 7 (14.9%)
Age (years)	59.8 ± 14.3	56 ± 17.2
Dialysis vintage (years)	8.2 ± 6.8	6.6 ± 7.01
Kt/V for urea	1.4 ± 0.20	1.4 ± 0.23
nPCR (g/Kg/day)	2.3 ± 0.54	2.5 ± 0.4
Urine volume (ml/day)	250 ± 169	221 ± 152.3
BMI (Kg/m2)	23.5 ± 2.5*	25.8 ± 3.3
Serum bicarbonate (mmol/L)	19.6 ± 2.03	20.2 ± 2.4
i-PTH (pg/ml)	166.6 ± 176	223.2 ± 269.1
Leptin (ng/ml)	3.47 ± 2.3*	16.3 ± 8.4
Albumin (gr / dl)	4.0 ± 2.2	4.0 ± 2.3
LDL/HDL	2.2 ± 0.9	2.4 ± 0.6
hsCRP (mg/L)	6.8 ± 5.4*	10.1 ± 6.05
oxLDL (ng/ml)	151.2 ± 202.7	131.1 ± 138.2
Insulin (μU/ml)	15.5 ± 8.8*	27.8 ± 21.9
HOMA-IR	3.88 ± 3.04*	7.7 ± 7.9
SBP (mmHg)	128.4 ± 21.07	127.4 ± 20.9
DBP (mmHg)	79.9 ± 9.2	78.7 ± 9.7
MBP (mmHg)	96.08 ± 11.9	94.9 ± 12.3
Diabetes mellitus (yes / no)	2 (4.3%)/28 (59.6%)	2 (4.3%)/15 (31.7%)
Hypertension (yes / no)	14 (29.8%)/16 (34%)*	4 (8.5%)/13 (27.7%)
Smoking (yes / no)	10 (21.3%)/20 (42.6%)	4 (8.5%)/13 (27.7%)
Serum bicarbonate (less / more than 22mmol/L)	27 (57.4%)/3 (6.4%)*	12 (25.5%)/5 (10.6%)
Residual renal function (yes / no)	8 (17%)/22 (46.8%)*	7 (14.9%)/10 (21.3%)

*: $p < 0.05$

p= 0.002 and log-rank=3.6, p= 0.04 respectively, hazard functions in **Figures 2 and 3**).

Cox-regression analysis by enter method showed that leptin was a inverse significant predictor for existed hypertension after adjustment for age, defined by interdialytic urine volume RRF, defined by Kt/V for urea dialysis adequacy, diabetes mellitus and smoking without significant multicolinarity (**Table 2**).

Controversially, leptin was not found as an important factor for defined by less than 22 mmol/L serum bicarbonate metabolic acidosis state adjusting for confounders (**Table 3**).

4. Discussion

Leptin suppresses appetite and increases energy expenditure, playing a homeostatic role in the regulation of food intake and in maintaining body com-

Table 2. Cox-regression analysis for the prevalence of leptin on manifestation of hypertension adjusting for confounders

	B	*p*-value	Odds ratio	Confidence interval
age	0.121	0.1	1.1	0.9 – 1.3
Urine volume	0.000	0.8	1.0	0.9 – 1.007
Kt/V for urea	3.35	0.4	28.5	0.06 – 133.7
Diabetes mellitus	1.38	0.3	4.009	0.1 – 97.1
smoking	1.56	0.3	4.7	0.2 – 105.1
leptin	- 0.28	**0.04**	0.7	0.5 – 0.99

Table 3. Cox-regression analysis for the role of leptin on serum bicarbonate concentrations less than 22 mmol/L in relation to confounders

	p-value	Odds ratio	Confidence interval
age	0.6	1.01	0.9 – 1.08
Sex	0.08	0.09	0.006 – 1.3
Diabetes mellitus	0.7	2.2	0.02 – 208.4
Dialysis vintage	0.3	1.1	0.8 – 1.4
Urine volume	**0.04**	1.007	1.001 – 1.13
nPCR	0.4	2.2	0.2 – 17.09
Serum albumin	**0.01**	0.001	0 – 0.7
leptin	0.1	0.8	0.7 – 1.05

position in general population.[12] In patients with end-stage renal disease malnutrition and hypoalbuminemia are common and powerful predictors of morbidity and mortality in this population.[13]

On the other hand, it has been already recognized that a substantial number of patients with end-stage renal disease have serologic evidence of an activated inflammatory state.[14] Leptin modifies the systemic inflammatory response and the inflammatory microenvironement in renal disease may be associated with elevated expression of leptin gene.[15] Indeed, in this study and in our previous studies, we observed that the patients with higher leptin serum concentrations had more activated inflammation defined by increased hsCRP levels, in comparison to the patients with lower leptin values.[16,17] 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.[18]

One potential relationship between malnutrition and inflammation in renal disease patients may be the appetite suppression and the link between inflammation and anorexia could derive 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, due to the controversial relationship between leptin and inflammation.[18]

Additionally, previous studies reported that leptin levels were elevated in ESRD patients with normal and mild malnutrition, although they were lower in severe and moderate category of malnutrition score. [20,21] The decreased serum levels of leptin in severe category of malnutrition group might be associated with acquired leptin receptor resistance.[20]

In agreement, the leptin resistance could be the explanation for the significantly higher BMI in patients with higher leptin serum concentrations comparatively to those with lower leptin in our data. We also observed significantly positive association between leptin and BMI.

On the other hand, leptin decreases hypothalamic NPY (Neuropeptide Y) levels, which is one of the most potent orexigenic peptides and enhances sympathetic activity with hyperinsulinemia, resulting in appetite suppression and modulation of insulin sensitivity.[1] High leptin triggers insulin resistance and vice versa.[22] Indeed, in present study, we noted significantly positive association between leptin and insulin levels and the patients with higher leptin serum concentrations had significantly elevated insulin and insulin resistance than the patients with lower leptin.

In agreement to our findings, enhanced chronic systemic inflammation, hyperleptinemia and reduced insulin sensitivity are often associated in patients with chronic renal disease, contributing to cardiovascular morbidity and mortality in these patients.[23] However, there are reports which revealed that low serum levels of leptin rather than high leptin levels are independent predictors of mortality.[21,24]

Strong evidence indicates an important role of leptin on hypertension.[25] The role of leptin on cardiovascular system to maintain normal blood pressure seem to be balanced in lean individuals with normoglycemia and leptin sensitivity. Its actions refer to blood pressure lowering mechanisms (via vasodilation, by promoting nitric oxide release from the endothelium), but also to mechanisms that increase blood pressure.[26]

However, in obese hyperleptinemic subjects or other leptinresistant conditions as in renal disease, the homeostatic control of blood pressure is impaired. It has been reported that leptin causes endothelial dysfunction and enhances the activity of angiotensin II on blood pressure, activating the sympathetic nervous system and contributing to increased sympathetic tone to renal vasculature, vascular stiffness and hypertension in obesity.[27] Another previous study showed that hyperleptinemia was inversely associated with vasodilatation of resistance arteries in elderly population of 1016 subjects.[28]

In this study, we observed that the patients with higher leptin levels had lower measured blood pressure than the patients with lower leptin. Also, the most of our patients with established hypertension presented low serum leptin concentrations and leptin was shown as an inverse independent risk factor for manifestated hypertension adjusting to confounders.

Hence the blood pressure in intermittent hemodialysis patients is fluid overload depended, we could support that a liquid imbalance did not influence the measured blood pressure in our data due to our exclusion criteria that we determined during this study.

Complicated leptin resistance may be included in the implicating factors for the reverse association between high leptin levels and hypertension in our data, or we could attribute our findings to reverse causality. Furthermore, recent study has reported that the relationship between leptin and incident hypertension was totally mediated by body adiposity meaning a positive strong association between leptin and hypertension closely connected to high body adiposity or obesity.[29] We did not include obese subjects in our data, despite the patients with higher leptin had higher BMI than the patients with lower leptin, but still in normal range.

Recently, it has been recorded that the adipose tissue is composed of at least two kinds of adipose tissue, the white and the brown adipose tissue with different morphology and function.[30] The white adipose tissue is not only an energy reservoir but also a secretory organ of certain molecules including leptin, TNF-α and AII involved in vascular function and hypertension. The brown adipose tissue secretes also leptin, nerve growth factor with different role as compared to white adipose tissue and nitric oxide. However, there is not yet evidence for the regulatory role of these two kinds of adipose tissue in renal disease patients, their relationship with the manifestation of hypertension and acquired leptin resistance in these patients.

Another factor, which may intervene in the relationship between leptin and hypertension in renal disease patients, could be the uncorrected metabolic acidosis state which is linked to activated inflam-

mation, vascular calcification and arterial stiffness.[31] Indeed, in this study the patients with higher leptin levels and lower blood pressure had also better metabolic acidosis status and lower lipid oxidation (oxLDL), even if they had higher i-PTH levels, another implicating factor to vascular calcification by bone disease disorders in these patients. Controversially, previously, it has been reported an inverse link between leptin, bone mass and PTH in dialysis patients suggesting that leptin may be implicated in low bone turnover in these patients, likely by the function of central nervous system.[32]

Concerning the role of leptin on uncorrected metabolic acidosis (serum bicarbonate less than 22mmol/L), we did not observed leptin as an significant predictor adjusting for confounders, despite in unadjusted association the most patients with low leptin had uncorrected metabolic acidosis.

By the findings of this study, we could suggest that the accepted strong positive association between leptin and hypertension, due mainly to the aquired leptin resistance in renal disease patients, may be more complicated and still unclear in these patients. Activated inflammation, insulin resistance and bone disease activation by high leptin serum levels can participate in vascular dysfunction and hypertension.

However, multiple metabolic and neurotropic variables including metabolic acidosis status and oxidative stress may have a different regulatory role in this relationship, which must be investigated by bigger studies.

5. Conclusions

In this study we observed inverse association between high leptin serum concentrations and hypertension in intermittent hemodialysis patients. The underlying pathophysiological mechanisms for a such relationship may comprise a complicated leptin resistance affected by body adiposity, metabolic acidosis status and oxidative stress.

6. Limitation

The limitation of our study is mainly the small number of included subjects.

Conflict of Interest

All authors declare no conflict of interest.

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Περίληψη

Η σχέση μεταξύ λεπτίνης ορού και υπέρτασης σε ασθενείς στο τελικό σταδιο νεφρικής νόσου

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Εισαγωγή: Η λεπτίνη ρυθμίζει την φλεγμονώδη αντίδραση και την δράση της ινσουλίνης αλλά οι μηχανισμοί με τους οποίους επηρεάζει την αγγειακή νόσο δεν έχουν διελευκανθεί. Μελετήσαμε τη σχέση μεταξύ των επιπέδων λεπτίνης ορού και υπέρτασης σε ασθενείς σε αιμοκάθαρση.

Μέθοδος: Μελετήσαμε 47 ασθενείς σε on-line αιμοδιαδιήθηση. Η επάρκεια κάθαρσης καθορίσθηκε με το Kt/V για την ουρία. Η λεπτίνη και η ινσουλίνη μετρήθηκαν με ραδιοανοσολογική μέθοδο. Η αντίστα-

ση στην ινσουλίνη υπολογίσθηκε με το ομοιοστατικό μοντέλο προσδιορισμού αντίστασης της ινσουλίνης (HOMA-IR). Τα επίπεδα των διττανθρακικών του ορού μετρήθηκαν σε μηχάνημα αερίων αιματος. Καταγράψαμε την αρτηριακή πίεση ως τον μέσο όρο 10 μετρήσεων κατά την διάρκεια ενός μήνα θεραπείας αιμοκάθαρσης. Καμπύλη Kaplan-Meier και μοντέλο παλινδρόμισης εφαρμόσθηκε για την πρόβλεψη του ρόλου των επιπέδων της λεπτίνης στην εγκατεστημένη υπέρταση.

Αποτελέσματα: Τα επίπεδα της λεπτίνης συσχετίσθηκαν θετικά με την ινσουλίνη και BMI (r= 0,331, p= 0,02 και r= 0,453, p= 0,001 αντίστοιχα). Kaplan-Meier αναλύσεις έδειξαν ότι τα επίπεδα της λεπτίνης μικρότερα από την μέση τιμή ίση με 8,12 ng/ml συσχετίσθηκαν σημαντικά αφ'ενός με την εγκατεστημένη υπέρταση και αφ'ετέρου με την μεταβολική οξέωση καθορισμένη με επίπεδα διττανθρακικών μικρότερα από 22 mmol/L (log-rank= 9,7, p= 0,002 και log-rank=3,6, p= 0,04 αντίστοιχα). Η ανάλυση παλινδρόμησης έδειξε ότι η λεπτίνη ηταν αντίθετος σημαντικός παράγοντας για υπέρταση μετα προσαρμογή σε συμπαράγοντες.

Συμπέρασμα: Παρατηρήσαμε αντίθετη σχέση μεταξύ υψηλών επιπέδων λεπτίνης ορού και υπέρτασης σε ασθενείς σε αιμοκάθαρση. Οι υποκείμενοι παθοφυσιολογικοί μηχανισμοί για αυτή τη σχέση μάλλον περιλαμβάνουν επιπεπλεγμένη αντίσταση στη λεπτίνη επηρεασμένη από την σωματική λιπομάτωση και την κατάσταση μεταβολικής οξέωσης και οξειδωτικού stress.

Λεξεις ευρετηρίου: λεπτίνη, μεταβολική οξέωση, υπέρταση, αιμοκάθαρση

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