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# SERUM LEPTIN CONCENTRATION AND LEFT VENTRICULAR HYPERTROPHY AND FUNCTION IN MAINTENANCE HEMODIALYSIS PATIENTS

SUMMARY

**The aim of the study was to investigate the potential relationship between left ventricular hypertrophy (LVH) and fraction with serum leptin in end-stage renal failure patients undergoing regular hemodialysis treatment. A cross-sectional study included 41 patients (15 women, 26 men) with an end-stage renal disease (ESRD), undergoing maintenance hemodialysis (HD) treatment with acetate basis dialysate and polysulfone membranes. Serum leptin and predialysis creatinine and post- and predialysis BUN, calcium (Ca), phosphorus(P), serum albumin (Alb) and serum ferritin were in the patients categorized into no LVH, mild, moderate and severe LVH, according to the performed echocardiographies. The mean patients' age was 46 (±17.6) years. The average hemodialysis duration was 29.5 (±34) months (median: 18 months). The mean serum leptin was 9.5±13.8 ng/ml (median: 4.7 ng/ml). In this study, no significant association between stages of LVH with serum leptin was recorded. Also, a significant positive correlation between LV ejection fraction and logarithm of serum leptin (r=0.32, p=0.048) (adjusted to age, duration and doses of dialysis, BMI, DM, serum ferritin, calcium, phosphorus, and serum Alb) was observed. Leptin might not be an aggravator for the appearance of LV hypertrophy. This feature of leptin in maintenance hemodialysis patients, which is in contrast to general population, especially in obese patients with normal renal function, could be explained through its reverse epidemiological role in hemodialysis patients. Our results emphasize the importance of leptin in hemodialysis and clinical impact of these findings on further investigation.**

*Key words:* **leptin, hemodialysis, left ventricular hypertrophy, end stage renal failure**

## INTRODUCTION

Cardiovascular disease is the principal cause of morbidity and mortality in dialysis patients (1, 2). The principal alterations responsible are left ventricular hypertrophy and arterial disease (2). Left ventricular hypertrophy (LVH) is the consequence of combined effects of chronic hemodynamic overload and non-hemodynamic biochemical and neurohumoral factors characteristic of uremia. LVH is an independent risk factor (2-4). In recent years, much progress has been made in understanding the pathogenesis of cardiovascular disease in the uremic population (4). Dialysis patients are subject to atherosclerosis and consequent ischemic heart disease, but myocardial dysfunction and overt heart failure also are highly prevalent. In hemodialysis patients, eighty-four percent of patients have left ventricular hypertrophy, left ventricular (LV) dilatation, or low fractional shortening at the

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initation of ESRD therapy. Furthermore, LVH has been found in 38% of patients with chronic renal failure (CRF) prior to the requirement for dialysis (1,2). It is clear that the presence of LVH or LV dilatation (or both) is a poor prognostic factor (2-4). Many conventional cardiovascular risk factors in the general population are not so predictive in the end-stage renal disease (ESRD). In the general population, plasma leptin concentrations have been found associated with LV myocardial growth (5) and plasma leptin levels have been shown to be an independent risk factor for cardiovascular disease (6). Several recent studies have demonstrated that leptin is principally cleared by the kidney. Thus, serum leptin concentrations are increased in patients with chronic renal failure and those undergoing maintenance dialysis (7). In contrast to preliminary studies, its role in chronic kidney disease (CKD) and hemodialysis (HD) patients is not completely understood. For example, though serum leptin is generally elevated in CKD and HD patients, some recent studies have not shown to be a cause of uremia-related anorexia (8,9) and more recent studies on maintenance dialysis patients have suggest a paradoxically inverse association between higher serum leptin and improved markers of nutritional status (9-11), a finding that is consistent with the theory of reverse epidemiology (9-13). Indeed, leptin, similar to serum albumin, has been reported to be a negative acute phase reactant in the end-stage renal failure patients (7). Studies concerning the influence of serum leptin concentration in maintenance hemodialysis patients (MHPs) is scarce, too. In a recent study, no significant relation between leptin and LV mass (18) have been found. This study was designed to investigate the potential relationship between left ventricular hypertrophy and fraction with serum leptin in the end-stage renal failure patients undergoing regular hemodialysis treatment.

## PATIENTS AND METHODS

### Protocol

The protocol conformed to the ethical guidelines of our university, and a consent was obtained from each patient. All studies were performed on non-dialysis days, between 8 a.m. and 10 a.m.

### Patients

This cross-sectional study was carried out on the patients with an end-stage renal disease (ESRD), undergoing maintenance hemodialysis (HD) treatment with acetate basis dialysate and polysulfone membranes. There were forty-one study patients with no clinical evidence of heart failure (defined as dyspnoea in addition to two of the following conditions: increased jugular pressure, bibasilar crackles, pulmonary venous hypertension, or interstitial edema in chest x-rays, requiring hospitalization or extra ultrafiltration). Also, active or chronic infection were the exclusion criteria. These patients were assembled between January and May, 2005 and represented approximately 90% of the entire hemodialysis population of our dialysis unit.

According to the severity of secondary hyperparathyroidism, those patients were given oral active vitamin D3 (Calcitriol; Rocaltrol) (Roche Hexagon; Roche Laboratories Inc, New Jersey, USA), calcium carbonate capsule, and Rena-Gel (sevelamer; Genzyme Europe B.V.; United Kingdom/Ireland) tablets of various doses.

According to the severity of anemia, patients were prescribed intravenous iron therapy with Iron Sucrose [Venofer (international) Inc. St. Gallen / Switzerland] of various doses after each dialysis session.

Also, all patients received treatments of 6 mg folic acid daily, 500 mg Acetyl-L-Carnitine (Jarrow Formulas, Inc™ Los Angeles, CA) daily, oral vitamin B-complex tablets daily, and 2,000 U intravenous Eprex (recombinant human erythropoietin [rHuEPO] (Janssen-Cilag; CILAG- AG International 6300 Zug/Switzerland) after each dialysis session.

All the patients received antihypertensive drugs mainly with ✔ - and ß-blockers (amlodipine, atenolol) and a few of the patients underwent the treatment with angiotensin-converting enzyme inhibitors (enelapril), $AT_1$ receptor antagonists (losartan).

### Laboratory Measurements

Blood samples were obtained after an overnight fast. Each blood sample was centrifuged within 15 min. Serum leptin (normal range of values for men is 3.84 ng/mL [±1.79] and for women is 7.36 ng/mL [±3.73]) was measured by enzyme-linked immunosorbent assay (ELISA) using DRG kits (DRG Diagnostics, Berlin, Germany). Complete blood count containing hemoglobin (Hgb), hematocrit (Hct) was measured using Sysmex-KX-21N cell counter (SYSMEX CORPORATION; Mundelein, Illinois, Sysmex America, Inc.). Also, levels of serum predialysis creatinine and post- and predialysis BUN, calcium (Ca), phosphorus (P), serum albumin (Alb) and serum ferritin (by RIA method) were measured using standard kits. The body-mass index (BMI) was calculated using a standard formula (post-dialyzed weight in kilo-

grams/height in meters to present mass per $m^2$). For the efficacy of hemodialysis, the urea-reduction rate (URR) was calculated from pre- and post-blood urea nitrogen (BUN) data (14). Duration and dosage of hemodialysis treatment were calculated from the patients' records.

**Echocardiography**

All echocardiographic measurements were performed according to recommendations of the American Society of Echocardiography (15) On the basis of septal thickness, the patients stratified into no LVH (septal thickness from 6 to11 mm), mild (septal thickness from 11 to15 mm), moderate (septal thickness from 15 to18 mm) and severe LVH (septal thickness >18 mm) (4,16). LVH measurements were done at the end diastolic phase and by a single cardiologist. Percents of LV ejection fraction between 55 and 75% were considered normal (4,16).

**Statistical analysis**

The data are expressed as mean ± SD, median values and as frequency distributions. For correlations related to the LV ejection fraction partial correlation test and for correlations related to left ventricular hypertrophy, Kruskal-Wallis test were used. Duration and doses of hemodialysis treatment were calculated from patients' records and each hemodialysis session was in duration of four hours. To normalize the serum leptin data, evaluate its correlation with LV ejection fraction, the logarithm of serum leptin data was used. All statistical analysis was performed using the SPSS package (version 11.5.00) (SPSS Inc, Chicago, IL). Statistical significance was determined at a *P* value <0.05.

RESULTS

There was a total of 41 patients (15 women, 26 men). The main clinical and biochemical characteristics of the study population are summarized in Table 1. The mean patient' age was 46 (±17.6) years. The mean hemodialysis duration was 29.5 (±34) months (median: 18 months). The mean serum leptin was 9.5±13.8 ng/ml (median: 4.7 ng/ml). Table 2 summarizes the frequency distribution of LVH stages. Mean±SD of LV ejection fraction of patients was 49±11% (median=55%). In this study, no significant association between stages of LVH and serum leptin was observed (*p*N.S.). A significant positive correlation (r=0.32, p=0.048) between LV ejection fraction and logarithm of serum leptin (adjusted to age, duration and doses of dialysis, BMI, DM, serum ferritin, calcium, phosphorus, and serum Alb) was recorded, *Figure 1*.

*Table 1: Mean ±SD, M\minimum and maximum of age, duration and doses of hemodialysis and patients' laboratory results*

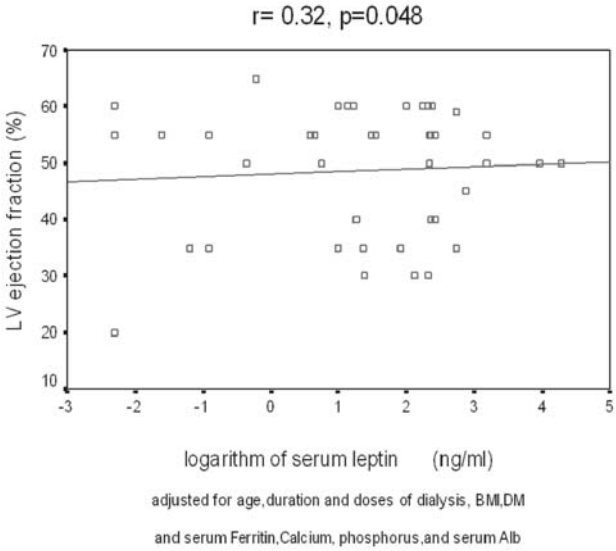
| patients= 41 | Minimum | Maximum | Mean±SD | Median |
|---|---|---|---|---|
| Age ( years) | 16 | 80 | 46±17.6 | 44 |
| DH* (months) | 2 | 156 | 29.5±34 | 18 |
| Dialysis dose (sessions) | 18 | 1584 | 268±374 | 153 |
| URR ( %) | 39 | 76 | 59±8.8 | 58 |
| Ca ( mg/d)l | 5 | 10 | 7.7±0.99 | 8 |
| Alb (g/dL) | 2.4 | 5 | 3.8±0.50 | 4 |
| Hgb (g/dl) | 5 | 13 | 9±2 | 9 |
| HCT (%) | 14 | 42 | 28±6 | 29 |
| Leptin (ng/ml) | 0.10 | 73 | 9.5±13.8 | 4.7 |
| P ( mg/dl) | 3 | 10 | 6±1.9 | 6.4 |
| BMI $kg/m^2$ | 16 | 34 | 21.5±4 | 20 |
| Ferritin (ng/dl) | 35 | 1250 | 497±286 | 420 |
| LV ejection fraction (%) | 20 | 65 | 49±11 | 55 |

**Duration of hemodialysis treatment*

*Table 2: Distribution frequency of left ventricular hypertrophy (LVH) in hemodialysis patients*

| Stages | | Frequency | Percent |
|---|---|---|---|
| LVH | Mild | 13 | 31.7 |
| | Modrate | 18 | 43.9 |
| | Sever | 10 | 24.4 |
| | Total | 41 | 100.0 |

*Figure 1: Significant positive correlation between LV ejection fraction and logarithm of serum*




DISCUSSION

Leptin has been shown to have sympathetic and vascular effects, and may increase cardiovascular risk through increased blood pressure, left ventricular hypertrophy, or atherosclerotic mechanisms (5, 6). Leptin is characterized by cardio-renal effects, potentially contributing to obesity-related hypertension including generalized sympathoactivation

(5, 6). One possibility is that leptin resistance is confined to the metabolic effects of leptin, with preservation of its sympathoexcitatory actions. Other mechanisms may contribute to the pressor effects of leptin. For instance, angiotensin II induces leptin generation. Leptin also potentiates the pressor effect of insulin. Therefore, interactions between angiotensin II and insulin with leptin could have deleterious cardiovascular effects in obesity. Additionally, leptin appears to stimulate vascular inflammation, oxidative stress and hypertrophy. These actions may contribute to the pathogenesis of hypertension, atherosclerosis and left ventricular hypertrophy (17). In the present study, a significant positive correlation between LV ejection fraction and leptin was also recorded. No significant association between stages of LVH and serum Leptin was found. In accordance with our finding, regarding the association between left ventricular hypertrophy and leptin, Zoccali et al. conducted a study on 198 patients with the end-stage renal failure. They showed that leptin was unrelated to LV mass and to systolic function (18). Previously, we have shown a protective role of leptin in hemodialysis patients (13). Based on the recent studies, regarding the reverse epidemiology role of Leptin in MHPs (6-8, 13) and the study of Zoccali et al (18), leptin might not be an aggravator for LV hypertrophy. This behavior of leptin in maintenance hemodialysis patients, which is in contrast to general population, especially in obese patients with normal renal function, could be explained through its reverse epidemiological role in hemodialysis patients.

## CONCLUSION

Our results emphasize the importance of leptin in hemodialysis and clinical impact of these findings on further investigations.

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# KONCENTRACIJA SERUMSKOG LEPTINA I HIPERTROFIJA LEVE KOMORE I FUNKCIJA KOD PACIJENATA NA DIJALIZI

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## SAŽETAK

**Cilj studije bio je da se ispita potencijalni odnos između hipertrofije leve komore i frakcije sa serumskim leptinom kod pacijenata u završnoj fazi bubrežne insuficijencije, koji su podvrgnuti redovnom tretmanu hemodijalize. U unakrsnu studiju bio je uključen 41 pacijent (15 žena i 26 muškaraca) u završnoj fazi bolesti bubrežne insuficijencije. Pacijenti su bili na dijalizi acetatnim dijalizatom i polisulfonilnim membranama. Vrednosti serumskog leptina i predijaliznog creatinina, pre i postdijaliznog BUN-a, kalcijuma (Ca), fosfora (P), serumskog albumina (Alb) i serumskog feritina su kod pacijenata gradirane u one bez hipertrofije leve komore, i u one sa blagom, umerenom i ozbiljnom hipertrofijom leve komore, u skladu sa urađenim ehokardiografima. Srednje starosno doba pacijenata je 46 godina (±17,6). Srednja vrednost trajanja dijalize je 29, 5 (±34) meseci (medijana 18 meseci). Srednja vrednost serumskog leptina je 9,5±13,8 ng/ml (medijana 4,7 ng/ml). U studiji nije zabeležena značajna povezanost između faza hipertrofije leve komore i serumskog leptina. Takođe, uočena je pozitivna korelacija između ejekcione frakcije leve komore i logaritma seruskog leptina (r= 0,32, p=0,048) (prilagođena starosnom dobu, trajanju i dozi dijalize, BMI, DM, serumskom feritinu, kalcijumu, fosforu i serumskom albuminu). Leptin ne mora da bude uzrok pogoršanja hipertrofije leve komore. Uloga leptina u tretmanu pacijenata na dijalizi, što je u suprotnosti sa većim delom populacije, naročito gojaznim pacijentima sa normalnom bubrežnom funkcijom, može se objasniti kroz njegovu inverznu epidemiološku ulogu kod pacijenata na hemodijalizi. Naši rezultati naglašavaju značaj leptina kod hemodijalize i klinički uticaj ovih nalaza na dalja istraživanja.**

***Ključne reči:*** **leptin, hemodijaliza, hipertrofija leve komore, završna faza bubrežne insuficijencije**