

# Hyperleptinemia – Non-Haemodynamic Risk Factor for the Left Ventricular Hypertrophy Development in Hypertensive Overweight Females

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## Abstract

*Obesity is directly and strongly associated with hypertension and left ventricular hypertrophy (LVH). Development of LVH is multifactorial, caused both by haemodynamic and non-haemodynamic factors. Hypertension is the main haemodynamic factor. Humoral mechanisms, as a non-haemodynamic factor for LVH development, have not been completely explained. The aim of this study is to determine whether hyperleptinemia can be one of humoral – non-haemodynamic factor inducing LVH together with haemodynamic factors in overweight females. The study was done on thirty six adult, overweight female patients, body mass index in range 25–30 kg/m<sup>2</sup>. Patients are nondiabetic with regular renal function. Twenty one female patients were hypertensive with left ventricular hypertrophy. Control group included fifteen hypertensive female patients without left ventricular hypertrophy. In all patients was determined glucose profile and creatinine clearance, cholesterol, triglycerides, LDL, HDL. Weight, high, circumference of the waist and hips was taken. Cardiovascular determination was done applying two-dimensional ultrasound. Serum leptin level was measured using radioimmunoassay method (RIA). Results showed that serum leptin level was significantly higher in hypertensive, overweight females with LVH. This suggests that non-haemodynamic factors, such as hyperleptinemia, participate in left ventricular hypertrophy development together with haemodynamic factors in adult hypertensive, overweight females.*

**Key words:** leptin, obesity, hypertension, left ventricular hypertrophy

## Introduction

Obesity is strongly related to arterial hypertension. Both are part of metabolic syndrome X<sup>1</sup>. Uncorrected obesity often leads to atherosclerosis, increased blood pressure, cardiac hypertrophy and other vascular complications<sup>2</sup>. Left ventricular hypertrophy (LVH) is a strong predictor of cardiovascular events. Patients with LVH are at increased risk for sudden cardiac death, coronary heart disease and congestive heart failure<sup>3</sup>. Development of LVH is multifactorial, caused by haemodynamic and non-haemodynamic factors<sup>4</sup>, including preload, afterload and neurohumoral mechanisms. Hypertension is the main haemodynamic risk factor for the development of LVH. Non-haemodynamic factors, such as local and systemic neurohumoral changes, contribute to development of LVH<sup>5</sup> and they have not been completely explained.

Hyperleptinemia could be one of the neurohumoral mechanisms inducing left ventricular hypertrophy together with haemodynamic factors.

Leptin is a product of ob-gene, produced mostly in adipocytes and less in the skeletal muscles, heart, vessels and brain, so that it also has local autocrine/paracrine effects in addition to its systemic action, mediated by circulating leptin<sup>6</sup>. Physiologically leptin has circadian variations in its secretion which is lost in condition of fatness<sup>7</sup>. Serum leptin concentration is proportional to body mass and it is significantly increased in obesity<sup>8</sup>. Obesity is characterised by hyperleptinemia and possible selective metabolic leptin resistance, while sympathoexcitatory action of leptin is preserved<sup>9</sup>. Through stimulation of

cardiac sympathetic system leptin increases heart rate and blood pressure, and thus imposes greater workload on the heart causing pathophysiological changes of the heart<sup>2</sup>. Leptin also possesses cardio-renal actions which contribute to obesity-related hypertension<sup>10</sup> and lead to left ventricular hypertrophy.

The potential actions of leptin in pathophysiology of cardiovascular complications are still analysed. Most information about cardiovascular actions of leptin has been obtained in in-vitro and animal studies, so that further research in humans is widely awaited<sup>10</sup>. Leptin receptors have been isolated in rat cardiomyocytes but direct effects of leptin on cardiac structure and function still remains to be determined<sup>11</sup>. It has not been explained yet whether leptin affects left ventricular wall thickness in overweight adult humans.

## Materials and Methods

### Patients

The research was carried out on 36 adult female patients with personal history of essential hypertension for at least five years and according to their medical documentation (Table 1). Arterial hypertension is defined as blood pressure above 140/90 mm Hg. Presence of secondary hypertension is excluded in all patients. They were divided into two groups according to existence of LVH: 21 patients with left ventricular hypertrophy and 15 patients without LVH. In all patients body mass index

(BMI) was in range 25–30 kg/m<sup>2</sup>. Exclusion criteria for the study were glucose intolerance, diabetes mellitus, increased creatinine level in the morning serum taken on an empty stomach, valvular heart disease, left ventricular ejection fraction below 50% and stroke. All women were postmenopausal and possible effect of estrogen is excluded.

All patients were hospitalized on Department for Cardiovascular medicine because of first myocardial infarction and arterial hypertension. According to recent studies, serum leptin level is increased after myocardial infarction, but it returns to normal values six days following the incident<sup>12</sup>. This means that when the samples were taken to determine leptin level there was no influence of coronary incident on serum leptin level. There were neither early nor late acute complications after myocardial infarction, such as arrhythmias, pericarditis, heart failure, cardiogenic shock.

They were treated with nitrates, beta blockers and ACE inhibitors. According to recent studies, ACE inhibitors reduce proinflammatory and thrombogenic cytokines, such as leptin<sup>13</sup>.

In hospital environment they all had normal blood pressure level. Systolic blood pressure was less than 140 mm Hg and diastolic blood pressure was less than 90 mm Hg, taken three times a day during hospitalization. They were discharged from hospital fourteen days after acute event in stable condition.

Patient's history, clinical examination, electrocardiography, X-ray of the thorax, biochemical blood analysis,

TABLE 1  
DEMOGRAPHIC, ANTHROPOMETRIC, BIOCHEMICAL AND ECHOCARDIOGRAPHIC DATA

	Hypertensive females with LVH	Hypertensive females without LVH
N(%)	21 (52)	15 (50)
Age (years)	69 ± 7	60 ± 8
Weight (kg)	72.28 ± 8.95	68.73 ± 5.68
BMI (kg/m <sup>2</sup> )	27.61 ± 2.05	26.50 ± 1.80
Wc (cm)	95.619 ± 6.368	89.267 ± 8.811
Hc (cm)	101.952 ± 6.652	97.933 ± 6.766
Bg (mmol/L)	5.543 ± 0.751	5.753 ± 0.485
Serum creatinine (μmol/L)	72.857 ± 12.854	74.867 ± 10.616
Cc (mL/min)	89.178 ± 24.093	92.245 ± 22.627
Cholesterol (mmol/L)	5.920 ± 1.426	5.387 ± 1.503
Tryglicerides (mmol/L)	1.751 ± 0.773	1.823 ± 0.814
LDL (mmol/L)	3.498 ± 1.117	3.071 ± 1.403
HDL /mmol/L)	1.271 ± 0.593	1.209 ± 0.339
Leptin level (ng/mL)	26.992 ± 15.899	16.707 ± 6.911
IVS (mm)	14.667 ± 2.033	10.267 ± 0.799
PWT (mm)	12.810 ± 0.680	9.067 ± 0.799
EF (%)	59.762 ± 7.993	60.8 ± 6.516

Mean ± SD, unless otherwise stated

LVH – left ventricle hypertrophy, BMI – body mass index, Wc – waist circumference, Hc – hips circumference, Bg – blood glucose, Cc – creatinine clearance, IVS – intraventricular septum, PWT – posterior wall thickness, EF – ejection fraction

leptin level and two-dimensional echocardiography were taken for each patient. All patients gave their written informed consent. The study was approved by ethical committees of our institutions.

#### *Anthropometric determinations*

The most common methods for diagnosing overweight and obesity are based on BMI ( $\text{kg}/\text{m}^2$ )<sup>14</sup>. Weight and height were measured by standard techniques. Body mass index was calculated as body weight divided by height squared. Waist and hips circumference was taken by tape measure. Waist circumference was measured at the umbilical level, in the middle between the lowest rib and the iliac crest. Hip circumference was measured at the trochanter level<sup>15</sup>.

#### *Biochemical blood analysis*

Blood glucose level, serum creatinine level and lipidogram were measured in all patients. Blood samples for biochemical analysis were taken in the morning, on an empty stomach. All patients had regular blood glucose values, measured five times during hospitalization and according to glucose profiles. Also, they all had regular creatinine serum level. Cholesterol, triglyceride, LDL, HDL were measured before hypolipemic therapy. Creatinine clearance was calculated using Cockcroft-Gault equation.

#### *Cardiovascular determinations*

In all patients a 12-lead ECG was performed two times a day to monitor coronary heart disease stabilization. Also, X-ray of the thorax was taken to evaluate the left ventricular enlargement.

Echocardiographic determinations were obtained by two-dimensional ultrasound Siemens Acuson CV 70 with cardiologic probe P4-2. During the examinations patients were lying in the left lateral position. Intraventricular septum (IVS) and posterior wall thickness (PWT) of the left ventricle as well as ejection fraction were determined by M-mode technique<sup>16</sup>. Echocardiographic measurements were taken according to Textbook of Clinical Echocardiography by Otto (3<sup>rd</sup> edition, Elsevier Saunders 2004), where the referent value defining LVH in both sexes was 12 mm or more. The data were classified into two groups, regarding IVS and PWT. Both patients with LVH and patients without LVH were examined. Ejection fraction was measured according to Teichholz, and all the patients had normal value, which is 50% or higher.

#### *Leptin determination*

Blood samples for leptin were taken from all subjects between 7 and 7:30 a.m. on the twelfth day after myocardial infarction, on an empty stomach. Serum leptin level was measured using radioimmunoassay method<sup>12</sup>, RIA-CT KIPMR44, Biosource Europe S.A, Nivelles, Belgium. It is a radioimmunoassay with Coated Tubes for quantitative detection of human leptin in serum and plasma (coefficient of variation  $7.3 \pm 1.1\%$ ).

#### *Statistical methods*

Data are presented as mean  $\pm$  SD. All statistical tests were two-sided and carried out to a significance level (P) of 0.05. Shapiro-Wilks test of normality was used to test leptin distribution in hypertensive patients with left ventricular hypertrophy. According to results of Shapiro-Wilks test we used nonparametric Mann-Whitney test. Spearman method was used to assess univariate relations. The value  $P < 0.05$  was considered statistically significant. Data were prepared for analysis in Microsoft Excel 2003. Statistical analysis was made by SPSS 15.0 for Windows Evaluation Version and Statistica 7.1.

#### **Results**

Clinical characteristics for both groups are given in Table 1. All the patients were adults without significant differences in their build. They all had normal blood glucose and serum creatinine in the morning. There were no significant statistical differences in values of cholesterol, triglycerides, LDL and HDL between the groups.

All patients were hypertensive adult females and they were divided into two groups regarding the presence of LVH. LVH is characterised by intraventricular wall thickness, as the most significant indicator of LVH, and by posterior wall thickness. Ejection fraction (EF) was preserved in all patients, above 50%.

76.2% of female patients with LVH had increased serum leptin level in relation to referent leptin values for non obese adult females with BMI 18–25  $\text{kg}/\text{m}^2$  (6.15–10.5 ng/mL, according to Biosource Europe S.A., Nivelles, Belgium).

Leptin levels were statistically significantly higher in hypertensive females with left ventricular hypertrophy than in female group without LVH ( $p = 0.025$ ) (Figure 1).

Serum leptin level did not have positive correlation with intraventricular wall thickness in females with LVH ( $p = 0.850$ ) and with posterior wall thickness of the LV ( $p = 0.332$ ).

Anthropometric measurements were taken in all patients. Correlation analysis was made between leptin level and waist and hips circumference in female patients with LVH. Leptin level correlated positively with waist circumference in hypertensive females with LVH ( $R^2 = 0.281$ ,  $p = 0.025$ ). There was no positive correlation between leptin level and hips circumference in female patients with LVH ( $p = 0.063$ ).

Also, Spearman method was used to analyze correlation between lipidogram and leptin level in both groups of patients, with and without LVH. There was positive correlation between cholesterol level and leptin level in female patients with LVH ( $R^2 = 0.203$ ,  $p = 0.049$ ). Triglycerides, LDL and HDL did not show positive correlation with leptin level in any group of patients.

#### **Discussion and Conclusion**

This study presents influence of one of the neuro-humoral mechanisms on myocardial growth together with haemodynamic factors in adult overweight females.

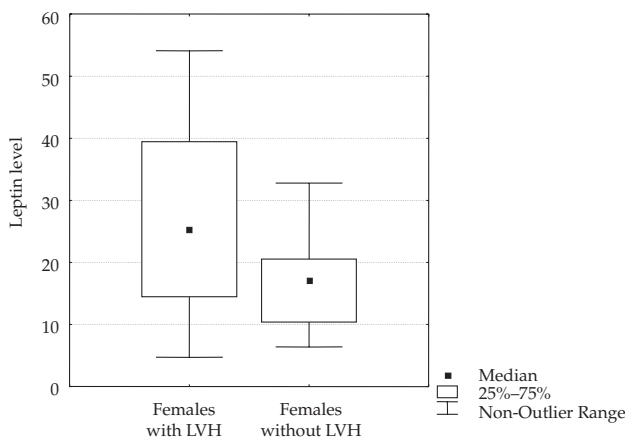


Fig. 1. Differences between leptin level in hypertensive females with LVH and hypertensive females without LVH.

The results showed that plasma leptin concentration (1) was higher in hypertensive female patients with LVH than in female patients without LVH, (2) positively correlated with waist circumference in females with LVH, (3) positively correlated with cholesterol level in female patients with LVH and (4) did not have positive correlation with intraventricular and posterior wall thickness in females with LVH.

This study provides data on relation between serum leptin concentrations and left ventricular hypertrophy in hypertensive moderately obese adult females.

Up-to-date scientific information on leptin physiology showed that leptin levels increase exponentially with fat mass increase, and most obese humans have increased leptin level<sup>17</sup>. It was believed that leptin is produced only by adipose tissue, but recent studies have shown that leptin expression has been identified in many other tissues, even in the heart<sup>6</sup>. Rat cardiomyocytes express all components of leptin system and show sex differences. Synthesis of leptin and leptin receptors was significantly higher in the heart of female rats<sup>18</sup>. Moreover, research in humans showed that sex influences plasma leptin level. Women have significantly higher leptin concentrations than men regardless of their fat mass<sup>19</sup>. Tachycardia and increased systolic and diastolic blood pressure are associated with high serum leptin level in adult obese females<sup>20</sup>. In obese humans, hyperleptinemia increases the risk for cardiovascular complications. Simultaneously, there is possible selective leptin metabolic resistance and preserved cardiovascular sympatho-excitatory actions of leptin, resulting in higher arterial pressure<sup>21</sup> and heart rate increase<sup>2</sup>. It is also confirmed that only centrally administered leptin and chronic leptin infusion increase blood pressure<sup>22</sup>. Consequently, it cannot be ruled out that high blood pressure caused by hyperleptinemia contributes to leptin induced myocardial changes, such as hypertrophy<sup>23</sup>.

Hypertension has strong influence on the left ventricle mass and some neurohumoral systems are considered

to have direct influence on left ventricular wall thickness<sup>24</sup>. Some studies discussed leptin as a possible neuro-humoral factor in development of leptin-related LVH<sup>22</sup>, but there is still question whether it has direct or indirect effect. In experimental conditions, some studies showed that leptin does not induce cardiomyocytes hypertrophy<sup>25</sup>, but the latest studies showed that leptin exerts direct hypertrophic effect on cultured cardiomyocytes in condition after coronary artery ligation<sup>26</sup>. Considering all that, there is need for further research on correlation between leptin and cardiovascular disease in humans<sup>27</sup>.

This study showed that hyperleptinemia together with haemodynamic factors contributes to development of LVH in adult overweight females. It confirmed that leptin did not correlate independently and directly with intraventricular wall thickness and posterior wall thickness of the left ventricle.

Production of leptin receptors and leptin in the humans cardiomyocytes<sup>6</sup> suggest that overweight women with LVH, besides adipocytes leptin production, had higher leptin system synthesis in the myocardium. According to results from this study main consequences on myocard result from central leptin action and less from local autocrine/paracrine action. In such conditions, pathophysiology of leptin-related LVH can be explained by haemodynamic and non-haemodynamic factors. Central effect of leptin is increase of blood pressure and heart frequency. In that way volume and pressure overload, as haemodynamic factors, become main factors in

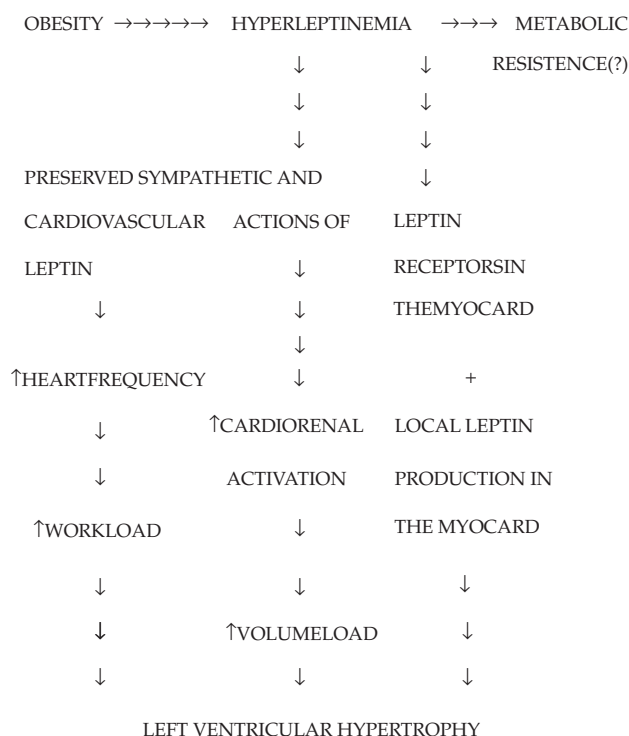


Fig. 2. Hypothetic algorithm of haemodynamic and non-haemodynamic pathway in development of LVH in hypertensive adult overweight females with LVH.

development of leptin-related LVH. Simultaneous to central action, there is local leptin action, which affects cardiomyocytes, and it should not be neglected. This effect is mediated by specific leptin receptors and involves complex and multifaceted cell-signaling pathway<sup>28</sup>. It

can be concluded that leptin in the myocard presents neurohumoral, non haemodynamic pathway in development of LVH in hypertensive overweight adult females (Figure 2).

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## HIPERLEPTINEMIJA – NEHEMODINAMSKI RIZIČNI FAKTOR ZA RAZVOJ HIPERTROFIJE LIJEVE KLIJETKE KOD HIPERTONIČNIH PRETILIH ŽENA

### SAŽETAK

Pretilost je direktno i snažno povezana s hipertenzijom i hipertrofijom lijeve klijetke (HLV). Razvoj HLV je multifaktorijalna, uzrokovana hemodinamskim i nehemodinamskim faktorima. Hipertenzija je glavni hemodinamski faktor. Humoralni mehanizmi – nehemodinamski faktori za razvoj HLV, nisu još u potpunosti razjašnjeni. Cilj studije je odrediti može li hiperleptinemija biti jedan od humoralnih – nehemodinamskih faktora koja inducira razvoj HLV zajedno s hemodinamskim faktorima kod žena s prekomjernom tjelesnom težinom. Studija je provedena na 36 odraslih žena, s prekomjernom tjelesnom težinom, BMI 25–30 kg/m<sup>2</sup>. Pacijentice su uredne bubrežne funkcije, bez šećerne bolesti. Ispitivanu skupinu čini 21 pacijentica s arterijskom hipertenzijom i razvijenom HLV, a kontrolnu skupinu čini 15 pacijentica s arterijskom hipertenzijom a bez razvijene HLV. Svim ispitanicama određen je profil glukoze, klirens kreatinina, kolesterol, trigliceridi, LDL, HDL. Mjerena je težina, visina, opseg struka i bokova. Kardiovaskularne mjere dobivene su dvodimenzionalnim ultrazvukom. Razina leptina u serumu određena je radioimmunoassay metodom (RIA). Rezultati su pokazali da je razina serumskog leptina značajno veća kod hipertoničnih žena s prekomjernom tjelesnom težinom koje imaju razvijenu HLV. Možemo zaključiti da nehemodinamski faktori, kao hiperleptinemija, sudjeluju u razvoju hipertrofije lijeve klijetke zajedno s hemodinamskim faktorima kod odraslih, hipertoničnih žena s prekomjernom tjelesnom težinom.