Do plasma leptin levels predict diastolic dysfunction in patients with hypertension?

Ersan Tatli, Meryem Aktoz, Armağan Altun

Department of Cardiology, School of Medicine, Trakya University, Edirne, Turkey

Submitted: 3 May 2008
Accepted: 27 August 2008

Arch Med Sci 2009; 5, 3: 342-346
Copyright © 2009 Termedia & Banach

Corresponding author:
Ersan Tatli, MD
Department of Cardiology
School of Medicine
Trakya University, Edirne, Turkey
Phone: 902842357641/2150
Fax: 902842357652
E-mail: ersantatli@yahoo.com

Abstract

Introduction: Increased plasma leptin levels were showed in a number of cardiac problems such as hypertension, left ventricular hypertrophy, coronary artery disease and acute myocardial infarction. The possibility that leptin plays a role in the cardiovascular system was strengthened by the evidence that chronic leptin infusion had been shown to increase heart rate and blood pressure through stimulation of sympathetic nervous system activity. However, the relationship between increased plasma leptin levels and diastolic dysfunction hasn't been exactly investigated so far. Thus, we investigated relation between plasma leptin levels and diastolic dysfunction in patients with hypertension.

Material and methods: Sixty male patients with newly diagnosed essential hypertension were consecutively included in the study. Hypertensive patients were divided into two groups according to Doppler echocardiographic parameters as patients with diastolic dysfunction (group I, n = 38) and without diastolic dysfunction (group II, n = 22). Both groups were compared patients' characteristics, plasma leptin levels, glucose, insulin, insulin resistance and thyroid hormones.

Results: There were no significant differences between patients' characteristics, fasting insulin, glucose, insulin resistance, thyroid hormones. Echocardiographic evaluation showed similar values of septal and posterior wall thickness, left ventricular end-systolic and end-diastolic diameters, fractional shortening and ejection fraction in both groups. Plasma leptin levels were also found similarly in both groups (group I, 40.6 ±18.4 ng/ml vs. group I, 36.7 ±20.7 ng/ml, p = 0.650).

Conclusions: We suggested that leptin levels didn't predict diastolic dysfunction in patients with hypertension.

Key words: leptin, diastolic dysfunction, hypertension.

Introduction

Leptin, a peptide hormone produced in fat cells, was discovered in 1994 by Friedman *et al.* It decreases appetite and food intake, increases the expenditure of energy, and appears to be important for the regulation of metabolism [1, 2]. Increased leptin levels were showed in insulin-resistant conditions such as obesity and arterial hypertension [2, 3]. The possibility that leptin plays a role in the cardiovascular system was strengthened by the evidence that chronic leptin infusion had been shown to increase heart rate and blood pressure through stimulation of sympathetic nervous system activity [4, 5].

Leptin might also affect left ventricular structure and function. Left ventricular diastolic dysfunction is one of the frequent complications of

hypertension. Thus, we hypothesize that plasma leptin levels are related with left ventricular diastolic dysfunction in patients with hypertension. To determine the accuracy of this hypothesis, we investigated the relation between plasma leptin levels and left ventricular diastolic dysfunction in hypertensive patients.

Material and methods

Sixty male patients from 216 patients with newly diagnosed essential arterial hypertension were consecutively included in the study between September 2005 and October 2006. Exclusion criteria were: history of myocardial infarction, history of typical chest pain, heart failure, uncontrolled hypertension (blood pressure > 180/110 mm Hg), significant heart valve disease, cardiomyopathy, known serious arrhythmias, left bundle branch block, previous coronary artery bypass surgery, atrial fibrillation, digoksin treatment, severe chronic disease or acute illness, renal disease, diabetes mellitus, impaired glucose tolerance, usage of drugs interfering with glucose metabolism, family history of diabetes, and obesity. Patients with impaired glucose tolerance were detected by an oral glucose tolerance test [6].

Demographic, clinical and echocardiographic data were collected with a standardized sheet. Weight (to the nearest 0.5 kg) and height (to the nearest 0.5 cm) were measured while the patients were fasting overnight and wearing only underwear. Patients with body mass index (BMI) > 30 kg/m^2 were categorized as obese individuals and they were excluded from the study. Waist and hip circumferences (to the nearest 0.5 cm) were measured by using a plastic tape meter at the level of the umbilicus and of the greater trochanters, respectively, and waist-to-hip ratio (WHR) was calculated. Waist and hip circumferences were changed from cm to inch (1 inch = 2.54 cm). Blood pressure was measured with a standard sphygmomanometer in the left arm after at least 10 min of rest. Mean values were determined from measurements of three independent visits. Hypertension was diagnosed according to standard criteria.

Laboratory assays

Fasting blood samples were drawn from a large antecubital vein of each patient for determination of biochemical parameters. Fasting venous blood was tested by using standard assays for glucose, total cholesterol, triglycerides, and insulin. Insulin resistance was measured with the homeostasis model assessment for insulin resistance (HOMA-IR). HOMA-IR index was calculated [formula: fasting plasma glucose (mmol/l) × fasting serum insulin (mU/ml)/22.5] [7, 8]. Plasma free thyroxine (T4) and thyroid stimulating hormone (TSH) levels were measured using chemiluminecent enzyme immunoassay (BioDPC, Los Angeles, USA). Plasma leptin levels were determined by radioimmunoassay (Pharmacia-Upjohn Diagnostics, Tokyo, Japan) using polyclonal antibodies against highly purified recombinant human leptin (Research, Inc, St Charles, Mo, USA) [9, 10].

Echocardiographic evaluations

All echocardiographic examinations were undertaken after 20-30 min of rest with the patient breathing quietly and lying in the partial left decubitus position, using with a 2.5 MHz transducer (Vivid 3 echocardiographic equipment, Vigmed Technology, GE Healthcare, Milwaukee, WI). The echocardiographic evaluations were recorded. M mode echocardiography of the left ventricular was carried out less than two dimensional controls. The left ventricular internal dimensions, interventricular septal and posterior wall thickness were measured at end-diastole and end-systole, following the American Society of Echocardiography (ASE) recommendation [11]. Left ventricular diastolic filling pattern was recorded from the apical position with the sample volume situated between the mitral leaflet tips. The peak velocities of early (E) and late (A) diastolic filling, their ratio (E/A), and the deceleration time of the E wave (DTE) were measured, following the ASE recommendations. The isovolumic relaxation time (IVRT) was measured from the closure spike of the aortic valve to the onset of mitral inflow. Pulmonary venous flow was also measured from the apical four chamber view, and colour Doppler imaging was used to obtain a beam direction as parallel as possible to the direction of the right or left upper pulmonary vein flow. Peak velocities of systolic (S) and diastolic (D) pulmonary venous flow, S/D ratio, and peak velocity of atrial flow reversal (vel a) were measured. Diastolic dysfunction was defined when the following were present: abnormal left ventricular relaxation (E/A ratio < 1, DTE > 220 ms, and IVRT > 100 ms) or pseudonormal filling patterns (E/A ratio of 1-2, DTE of 150-200 ms, IVRT of 60-100 ms, S/D ratio < 1, and vel a ≥ 35 cm/s) [12]. Patients were divided into two groups according to Doppler echocardiographic parameters as group I (patients with diastolic dysfunction) and group II (patients without diastolic dysfunction).

Statistical analysis

Statistical analysis was performed using SPSS 11.0 software (SPSS Inc., Surrey, UK). Continuous variables are presented as mean ± SD. Statistical comparisons between groups were made using unpaired Student's *t*-test for normally distributed

variables. For non-normally distributed variables non-parametric comparisons were made using Mann-Whitney U-tests. The multivariate analysis was done using logistic regression. A probability (p) value of less than 0.05 was considered statistically significant.

Results

We found no significant differences in patients' characteristics and laboratory findings between both groups (Table I). Echocardiographic evaluation showed similar values of septal and posterior wall thickness, left ventricular end-systolic and end-diastolic diameters, fractional shortening and ejection fraction in both groups (Table II). Although leptin levels are higher in group I, there was no statistically significant difference between plasma leptin levels in both groups (group I, 40.6 ±18.4 ng/ml vs. group II, 36.7 ±20.7 ng/ml, p = 0.650) (Figure 1). Additional, we observed elevated plasma leptin levels in both groups.

Discussion

In present study, we similarly found elevated leptin levels in hypertensive patients with diastolic dysfunction and without diastolic dysfunction. Additional, we observed that leptin levels didn't predict diastolic dysfunction in patients with hypertension.

Left ventricular diastolic dysfunction is frequently seen in some conditions such as insulin resistance, hypertension and obesity [13, 14]. Recent studies showed a significant prevalence of diastolic dysfunction in selected hypertensive populations including patients who are clinically symptomatic and with normal systolic function [15, 16]. Thus, being diagnosed of diastolic dysfunction is important for hypertensive patients. Leptin is a peptide hormone produced by adipose tissue. It plays an important role in body weight control by decreasing food intake and by increasing energy expenditure [2]. Several studies showed that leptin levels increase in insulin-resistant states and hypertension [2-5]. If plasma leptin level is higher than 9.4 ng/ml in men and 27.4 ng/ml in women, it was accepted as a hyperleptinemia. The cut-off value was the 90th percentile of patients with normal weight [10]. We observed elevated plasma leptin levels in both groups. Leptin may participate in the regulation of cardiac function through sympathetic stimulation and its myogenic inhibition of cardiomyocyte contraction and has been speculated to contribute to obesity-related cardiac contractile dysfunction [17]. Positive correlation between hyperleptinemia and tachycardia has been confirmed in mildly obese or mildly hypertensive human subjects [18]. While an increase in heart rate may enhance cardiac output and provide short-term beneficial effects, sustained tachycardia may cause cardiac hypertropy and ultimately heart failure. The higher heart rate in the hyperleptinemic individuals can impose a greater myocardial workload and therefore, it can lead to pathophysiological changes and left ventricular diastolic dysfunction in the heart such as left ventricular hypertrophy and diastolic

Table I. Patients' characteristics and laboratory findings of the study groups

Parameter	Group I (n = 38)	Group II (n = 22)	P value
Age [year]	44.0 ±10.8	46.0 ±8.1	0.150
Systolic BP [mm Hg]	154 ±12	152 ±14	0.560
Diastolic BP [mm Hg]	102 ±8	100 ±10	0.260
Heart rate [beats/min]	74 ±12	80 ±8	0.520
Body mass index [kg/m^2]	26.4 ±3.4	24.6 ±4.4	0.400
Waist circumference [inch]	36.3 ±0.8	36.4 ±1.3	0.200
Hip circumference [inch]	39.4 ±0.5	36.8 ±1.1	0.480
WHR	0.94 ±0.01	0.98 ±0.01	0.630
Total cholesterol [mg/dl]	182.5 ±61.8	191.0 ±28.3	0.670
Triglyceride [mg/dl]	124.7 ±45.2	129.8 ±36.6	0.200
Free T4 [ng/dl]	1.8 ±0.68	1.56 ±0.65	0.600
TSH [µU/ml]	1.44 ±0.86	1.60 ±0.90	0.520
Fasting glucose [mg/dl]	85.0 ±12.3	83.1 ±21.4	0.950
Fasting insulin [ng/ml]	12.0 ±7.0	9.8 ±4.6	0.300
HOMA-IR	1.8 ±1.6	1.4 ±1.2	0.520

WHR – waist to hip ratio, T4 – thyroxine, TSH – thyroid stimulating hormone, HOMA-IR – homeostasis model assessment of insulin resistance

Table II. Parameters of echocardiographic evaluation

Parameter	Group I (n = 38)	Group II (n = 22)	P value
Septal wall thickness in systole [mm]	14.0 ±1.5	13.5 ±1.9	0.400
Septal wall thickness in diastole [mm]	10.8 ±1.6	10.4 ±1.6	0.509
Posterior wall thickness in systole [mm]	12.2 ±4.3	11.8 ±3.9	0.260
Posterior wall thickness in diastole [mm]	10.0 ±5.0	8.7 ±1.1	0.410
End-systolic diameter [mm]	29.3 ±6.2	31.2 ±6.6	0.480
End-diastolic diameter [mm]	46.4 ±10.0	47.9 ±6.3	0.833
Ejection fraction [%]	67.3 ±7.1	64.8 ±8.6	0.260
Fractional shortening [%]	37.3 ±5.9	35.7 ±6.8	0.300
E peak velocity [m/s]	0.52 ±0.14	0.62 ±0.10	0.003
A peak velocity [m/s]	0.60 ±0.11	0.58 ±0.08	0.060
Peak velocity E/A ratio	0.82 ±0.14	1.05 ±0.1	0.001
DTE [ms]	164.4 ±28.8	146.7 ±29.1	0.001
IVRT [ms]	84.6 ±12.0	73.1 ±9.2	0.001

IVRT – isovolumic relaxation time, DTE – deceleration time of the E wave

heart failure. Increased plasma leptin levels were showed in a number of cardiac problems such as hypertension, left ventricular hypertrophy, coronary artery disease and acute myocardial infarction [19]. However increased plasma leptin levels associated with diastolic dysfunction hasn't been exactly investigated. We demonstrated that plasma leptin level was not associated with left ventricular diastolic dysfunction in patients with hypertension. This conclusion has not been reported in the literature so far.

Galderisi *et al*. [20] showed that a relationship between plasma leptin level and left ventricular diastolic relaxation in arterial hypertension. They emphasized that increased fasting plasma leptin levels are associated with prolongation of isovolumic relaxation in arterial hypertension. Our results wasn't compatible with results of Galderisi *et al*. [20]. They included in the study three groups (40 hypertensive and 15 healthy cases) as insulin-sensitive hypertensive group (n = 15), insulin-resistant hypertensive group (n = 25) and normotensive control group (n = 15). They found that insulin-resistant hypertensive group's isovolumic relaxation time and leptin levels were significantly higher than the other groups. But, insulin-resistant hypertensive group's body mass index were also significantly higher than the others. Thus, both increased isovolumic relaxation time and increased leptin levels can depend on increased body mass index. However, in our study there wasn't any difference between two groups in terms of body mass index. One reason of incompatible between our results and theirs can caused by differences body mass index among groups in their study. Another reason can be depended on increased plasma leptin levels in our both groups. However, it should be borne in mind that our study was a small sized, well delineated pilot study. Future research in larger populations is needed to determine the relation between the plasma leptin levels and cardiac functions in obese hypertensive patients, and patients with normalweight hyper-tensive.

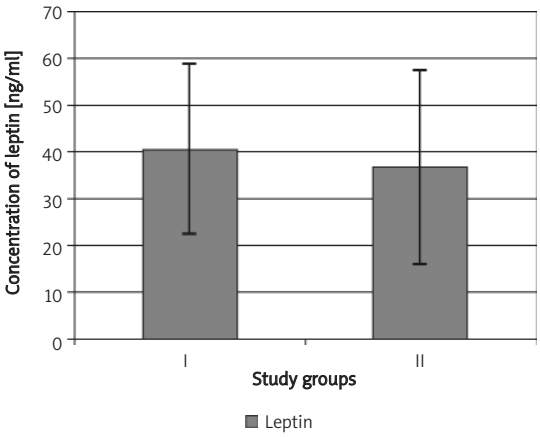

Figure 1. Plasma leptin levels of the study groups (p = 0.650)

In conclusion, the results of the present study demonstrated that leptin levels don't predict diastolic dysfunction in patients with hypertension. Further, more comprehensive studies will be needed to understand this relationship clearly.

References

1. Friedman JM. Leptin, leptin receptors and the control of body weight. Eur J Med Res 1997; 2: 7-13.
2. Halaas JL, Gajiwala KS, Maffei M, et al. Weight reducing effects of the plasma protein encoded by the obese gene. Science 1995; 269: 543-6.
3. Agata J, Masuda A, Takada M, et al. High plasma immunoreactive leptin level in essential hypertension. Am J Hypertens 1997; 10: 1171-4.
4. Casto RM, VanNess JM, Overton JM. Effects of central leptin administration on blood pressure in normotensive rats. Neurosci Lett 1998; 246: 29-32.
5. Shek EW, Brands MW, Hall JE. Chronic leptin infusion increases arterial pressure. Hypertension 1998; 31: 409-14.
6. World Health Organization: Diabetes Mellitus, World Health Organization, 1985, vol. 727; 9-17.
7. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degree glucose tolerance and insulin sensitivity. Diabetes Care 2000; 23: 57-63.
8. Mather KJ, Hunt AE, Steinberg HO, et al. Repeatability characteristics of simple indices of insulin resistance: implications for research applications. J Clin Endocrinol Metab 2001; 86: 5457-64.
9. Ma Z, Gingerich RL, Santiago JV, Klein S, Smith CH, Landt M. Radioimmunoassay of leptin in human plasma. Clin Chem 1996; 42: 942-6.
10. Mendoza-Núñez VM, Garcia-Sanchez A, Sanchez-Rodriguez MA, Galvan-Duarte R, Fonseca-Yerena E. Overweight, waist circumference, age, gender, and insulin resistance as risk factors for hyperleptinemia. Obes Res 2002; 10: 253-9.
11. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2: 358-67.
12. Garcia MJ, Thomas J, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998; 32: 865-75.
13. Jain A, Avendano G, Dharamsey S, et al. Left ventricular diastolic function in hypertension and role of plasma glucose and insulin: comparison with diabetic heart. Circulation 1996; 93: 1396-402.
14. Lind L, Anderson G, Anden B, Hanni A, Lithell HO. Left ventricular hypertrophy in hypertension is associated with the insulin resistance metabolic syndrome. J Hypertens 1995; 13: 433-8.
15. Cohn JN, Johnson G. Heart failure with normal ejection fraction: the V-Heft Study. Circulation 1990; 81 (2 Suppl): III48-53.
16. Iriarte M, Munga N, Sagastogoitia D. Congestive heart failure from left ventricular diastolic dysfunction in systemic hypertension. Am J Cardiol 1993; 71: 308-12.
17. Ren J, Relling DP. Leptin-induced suppression of cardiomyocyte contraction is amplified by ceramide. Peptides 2006; 27: 1415-9.
18. Narkiewicz K, Somers VK, Mos L, et al. An independent relationship between plasma leptin and heart rate in untreated patients with essential hypertension. J Hypertens 1999; 17: 245-9.
19. Ren J. Leptin and hyperleptinemia – from friend to foe for cardiovascular function. J Endocrinol 2004; 181: 1-10.
20. Galderisi M, Tagliamonte MR, D'Errico A, et al. Independent association of plasma leptin levels and left ventricular isovolumic relaxation in uncomplicated hypertension. Am J Hypertens 2001; 14: 1019-24.