

Effects of valsartan treatment on serum ghrelin level and left ventricular mass index in patients with untreated primary hypertension

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ABSTRACT

Objective: In the present study, left ventricular hypertrophy and serum ghrelin concentration in patients with primary hypertension and effects of angiotensin receptor blocker valsartan on these parameters were determined.

Methods: Thirty-seven patients and 30 age and body mass index matched healthy controls were followed up prospectively. Serum ghrelin level was measured by enzyme immunoassay (EIA). Left ventricular mass was determined by transthoracic echocardiography. Left ventricular mass index (LVMI) was calculated by dividing the left ventricular mass to body surface area. All patients were started treatment with oral valsartan 80 mg. Follow-up visits were performed every 4 weeks, and the dosage was doubled in subjects with insufficient blood pressure reduction. At the end of the 12th week all measurements were repeated in the patient group. All data were recorded in the computer using SPSS for Windows software. Mann-Whitney U, Student t, Wilcoxon and t tests were used for statistical analyses.

Results: At baseline, mean serum ghrelin level was significantly lower in the patients group (14.9 ng/mL) compared to healthy controls (42.1 ng/mL) ($p<0.05$). After a 12-week antihypertensive treatment of patients, serum ghrelin concentration increased while LVMI decreased ($p<0.05$, for both). No significant correlation was found between Δ -ghrelin level and Δ -LVMI ($r=0.155$, $p=0.368$).

Conclusion: Low circulating level of ghrelin in patients with hypertension and its increase after antihypertensive treatment suggest that this peptide need to be explored in the mechanism and complications of hypertension. (*Anadolu Kardiyol Derg 2014; 14: 234-8*)

Key words: hypertension, left ventricular mass index, ghrelin, valsartan

Introduction

Ghrelin is a relatively newer peptide hormone suggested to be involved in the etiopathogenesis of the hypertension. This 28-amino acid peptide hormone is known to be produced primarily by the stomach and small intestine, but it was detected in many organs and tissues at varying concentrations (1-3). Ghrelin participates in energy homeostasis by improving energy balance through decreasing the use of fat; however, it is also involved in many steps of glucose homeostasis (4) and blood pressure control (5). The effects of ghrelin to decrease blood pressure have been reported in the animals with normal blood pressure (6), the healthy individuals (7), and the patients with heart failure (8). Most of these effects were accepted to be the acute effects of ghrelin. But also, effect of long-term treatment with ghrelin (10 nmol/kg, twice a day, intraperitoneally) was shown on Dahl salt sensitive hypertensive (DS) rats which had

hypertension induced by high salt (8.0% NaCl) diet. Ghrelin significantly increased urine volume and tended to increase urine Na⁺ excretion. Furthermore, ghrelin increased urine nitric oxide (NO) excretion and tended to increase renal nNOS mRNA expression. Furthermore, ghrelin prevented the high salt-induced increases in heart thickness and plasma ANP mRNA expression. These results demonstrate that long-term ghrelin treatment counteracts salt-induced hypertension in DS rats primarily through diuretic action associated with increased renal NO production. These data suggest the preventive and therapeutic abilities of long-term ghrelin treatment against salt-sensitive hypertension and cardiac hypertrophy (9).

Significant correlations of circulating ghrelin with left ventricular mass, left ventricular mass index and interventricular septum thickness was reported, all of which determining the left ventricular functions (10, 11). Ghrelin is thought to increase myocardial contractility through the effect of Ca-ATPase in the sarcoplasm (7). While it results in increased heart rate, ghrelin

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infusion lowers blood pressure by promoting vasodilatation in the periphery, directly or via nitric oxide (NO)-dependent mechanisms (7, 12). Accordingly, injection of ghrelin caused a substantial decrease in the mean arterial blood pressure in an animal model with heart failure (11).

Administration of ghrelin directly or potential therapeutic modalities that can increase the synthesis and secretion of ghrelin may be promising options in the treatment of severe heart failure and hypertension. The present study was designed to determine i) serum ghrelin level, ii) association of blood ghrelin and left ventricular hypertrophy and, iii) effects of angiotensin receptor blocker valsartan on serum level of ghrelin in subjects with primary hypertension.

Methods

Study design

The present case-control, prospective and interventional study enrolled only newly diagnosed hypertensive patients without any other systematic disease or medications. Patients and controls involved in this study were recruited from cases that were referred to our Internal Medicine Outpatient Department between December 2006 and May 2007.

Participants

Control group included age-, gender- and body mass index (BMI) matched volunteers who also did not have any disease condition or drug intake. The main inclusion criteria were having primary hypertension and being yet untreated, as well as absence of hypertensive complications, any type of cardiovascular disease, renal disease, diabetes mellitus, hypo-hyperthyroidism, medications, and other causes of secondary hypertension or confounders for elevated blood pressure. Subjects having signs and symptoms of severe hypertension suggestive of an underlying secondary etiology were also excluded at the beginning even though their initial evaluation including blood tests were normal.

Definition of hypertension

Following a 10-minute resting blood pressure readings were taken from the right arm in sitting position using a mercury sphygmomanometer. Mean of three blood pressure measurements done within 5-minute intervals was recorded as systolic and diastolic blood pressure and was classified according to JNC VII report (13). All subjects met the diagnostic criteria for hypertension in this guideline. Either stage 1 or stage 2 hypertensive individuals were included.

Study protocol and follow-up

After obtaining the complete medical history all subjects underwent detailed physical examination and routine blood analyses. BMI was calculated by dividing the body weight (kg) to the square of the height expressed as meters. All participants signed written, informed consent. The study was approved by the Ethical Committee of Gülhane School of Medicine.

The participants who were started antihypertensive treatment were followed-up for 12 weeks, with control visits every 4-week during the study period. The dose of medication was doubled in subjects with still high blood pressure. All subjects received oral valsartan 80 mg tablets initially, which was increased to 160 mg in individuals with a poor response. Subjects were recorded as completed the study when they were admitted for the final visit on the 12th week in which all measurements were repeated.

Echocardiographic measurements

Left ventricular mass (LVM) was evaluated by transthoracic echocardiography using Vivid 7 echocardiography device (GE Medical Systems, Norway, 3,5 MHz prob) by the same cardiologist. LVM was calculated using the equation of Devereux et al. (14). Left ventricular mass index (LVMI) was calculated by dividing LVM by the body surface area. $LVMI \geq 131$ gr/m² for men and $LVMI \geq 110$ gr/m² for women was considered as the threshold for the left ventricular hypertrophy (LVH) (15).

Ghrelin assay

For the measurement of circulating ghrelin concentration, following an overnight fasting venous blood samples were collected in the morning using EDTA aprotinin tubes. Plasma were separated by centrifuging at 5000/min for 15 minutes, and according to the manufacturer's instructions, plasma samples were acidified with HCl. Finally plasma samples were stored at -80°C until assayed. Ghrelin was measured in serum using commercially available ELISA kit (Human Acylated Ghrelin Enzyme Immunoassay Kit (SPI BIO, Cayman Chemical Company, Michigan, USA) and Bio-Tek reader. The minimum detectable concentration for ghrelin was 1.5 pg/mL. Intra-assay coefficient of variation (CV) ranged from 5.5% to 10.3%, while inter-assay CV ranged from 5.9% to 10.9% for ghrelin.

Statistical analysis

All data were recorded in the computer using SPSS for Windows (version 15, Chicago, IL, USA) software. Normality was tested using Kolmogorov-Smirnov goodness of fit test. Inter-group differences were evaluated using Mann-Whitney U test or Student t- test where applicable. In order to compare pre- and post-treatment values, T test or Wilcoxon test were used. The correlation between the variables was examined using Pearson or Spearman-Rho correlation tests. Data were calculated as mean±standard deviation, median (minimum-maximum), and obtained differences were considered significant at $p < 0.05$.

Results

A total of 37 patients with primary hypertension (16 male, 21 female) and 30 volunteer controls (13 male, 17 female) were finally analysed. Baseline characteristics and comparisons of the participants are given in Table 1. In the hypertensive group, as expected, systolic and diastolic blood pressures were significantly higher compared to the control group ($p < 0.001$).

Pre-treatment assessment

Before treatment mean serum ghrelin level was found to be markedly lower in hypertensive participants (14.9 ng/mL) compared to the controls (42.1 ng/mL) ($p < 0.05$) (Table 1, Fig. 1). Serum ghrelin level did not change according to gender [male: 19.4 (4.1-42.1) ng/mL, and female: 14.9 (3.5-44.3) ng/mL)] ($p > 0.05$).

Post-treatment assessment

By the end of a 12-week treatment drug dosage was doubled in 78.4% ($n=29$) of patients. Alterations in blood pressure, LVMI and serum ghrelin level following treatment are presented in Table 2, Figure 1. After medication, mean values of systolic and diastolic blood pressures showed a statistically significant decrease ($p < 0.001$) (Table 2, Fig. 1). Concomitantly, a 2-fold increase in blood ghrelin level ($p < 0.05$) and significant decrease in LVMI ($p < 0.001$) were observed following treatment (Table 2, Fig. 1). No significant correlation was detected between serum ghrelin level and LVMI ($r = -0.30$, $p = 0.872$). The magnitude, or Δ -decrease in LVMI was not associated to Δ -increase in ghrelin levels ($r = 0.155$, $p = 0.368$). Also, Δ -decrease in blood pressure was not associated to Δ -increase in ghrelin levels ($r = -0.113$, $p = 0.511$).

Discussion

In this study, while serum ghrelin level was found lower in hypertensive patients compared to healthy controls, it increased significantly upon efficient blood pressure lowering. As expected before the study, antihypertensive treatment resulted in a significant regression in LVMI. To our knowledge, the present study is the first human study to investigate how serum level of ghrelin is affected by the administration of an angiotensin receptor blocker in hypertensive patients. In the descriptive part of this work, circulating ghrelin concentration was significantly lower in hypertensive patients compared to non-hypertensive subjects. Besides, we found no gender difference with respect to blood ghrelin, which was also consistent with a number of previous reports (5, 16-18). Consistent with our results, several authors previously reported that blood level of ghrelin was reduced and there was an inverse correlation between blood pressure and ghrelin in hypertensive individuals (5, 7, 11, 19). Three different mechanisms have been proposed to explain the effects of ghrelin on blood pressure regulation: a direct effect of ghrelin on endothelium (20); a direct effect on smooth muscle cells (21); and the most probable explanation, a central action of ghrelin to decrease sympathetic outflow (22).

Ghrelin is among the major stimulators of growth hormone (GH) production. GH leads to growth and hypertrophy in several tissues by acting through insulin-like growth factor-1 (IGF-1). The stimulation of IGF-1 receptor by IGF-1 was shown to cause cardiomyocyte hypertrophy (5, 7, 11). Therefore, in a hypertensive individual, reduced synthesis and secretion of ghrelin might be an adaptive defense mechanism of the body, and increase in left ventricular mass may be prevented by inhibiting the growth

Table 1. Basic characteristics and comparison of patient and controls

Parameter	Patients (n=37)	Controls (n=30)	P* value
Gender, male/female	16/21	13/17	>0.05
Age, year	48.05±8.6	46.9±7.7	>0.05
Height, cm	165.9±6.8	166.2±7.6	>0.05
Weight, kg	76.5±13.1	76.8±10.4	>0.05
BMI, kg/m ²	27.8±5.0	27.2±4.8	>0.05
SBP, mm Hg	158.9±14.2	118.5±7.5	<0.001
DBP, mm Hg	99.3±7.6	70.8±6.7	<0.001
Ghrelin, ng/mL	14.9 (3.5-42.1)	42.1 (16.0-76.6)	<0.05

*Student t-test
BMI - body mass index; DBP - diastolic blood pressure; SBP - systolic blood pressure

Table 2. Serum ghrelin level, blood pressure and change of mean LVMI following treatment with valsartan in the patient group

Variable (n=37)	Pre-treatment	Post-treatment	P*
SBP, mm Hg	158.9±14.2	128.2±9.1	<0.001
DBP, mm Hg	99.3±7.6	83.5±6.2	<0.001
LVMI, g/m ²	129.8±26.1	103.9±18.6	<0.001
Ghrelin, ng/mL	14.9 (3.5-42.1)	30.7 (16.0-60.2)	<0.05

*Wilcoxon test
DBP - diastolic blood pressure; LVMI - left ventricular mass index; SBP - systolic blood pressure

and proliferation of cardiomyocytes. In favor of this concept, a previous study demonstrated a negative correlation between left ventricular mass index and serum ghrelin (23). Regression of LVMI as well as increased blood level of ghrelin following anti-hypertensive therapy in our study supports this notion. We detected, however, no significant correlation between LVMI and ghrelin blood level, possibly due to small sample size to test such a relation.

Effective blood pressure control resulted in increased serum ghrelin concentration in the present investigation. While ghrelin has been shown to display favorable actions on regulation of arterial pressure and increasing cardiac output, these hemodynamic effects were shown to be independent from the axis of GH/IGF-1/nitric oxide in experimental studies (7, 11, 12, 24). On the other hand, the precise mechanism of reduction in blood level of ghrelin upon increase in blood pressure is not known. Given that the pathophysiology of hypertension includes numerous mechanisms, it is likely that synthesis or secretion of peptide hormones such as ghrelin which possess critical actions in regulation of the metabolic events are impaired. Reversal of pathologic or adaptive alterations after adequately controlled blood pressure is not a marginal thought as well. As an example, blood level of adiponectin, which is probably the most well-known peptide that is involved in various metabolic functions, decreases when blood pressure is increased but suddenly increases upon appropriate treatment (25, 26). Existing evidences strongly suggest that uncontrolled blood pressure has profound influences on the metabolism of these proteins.

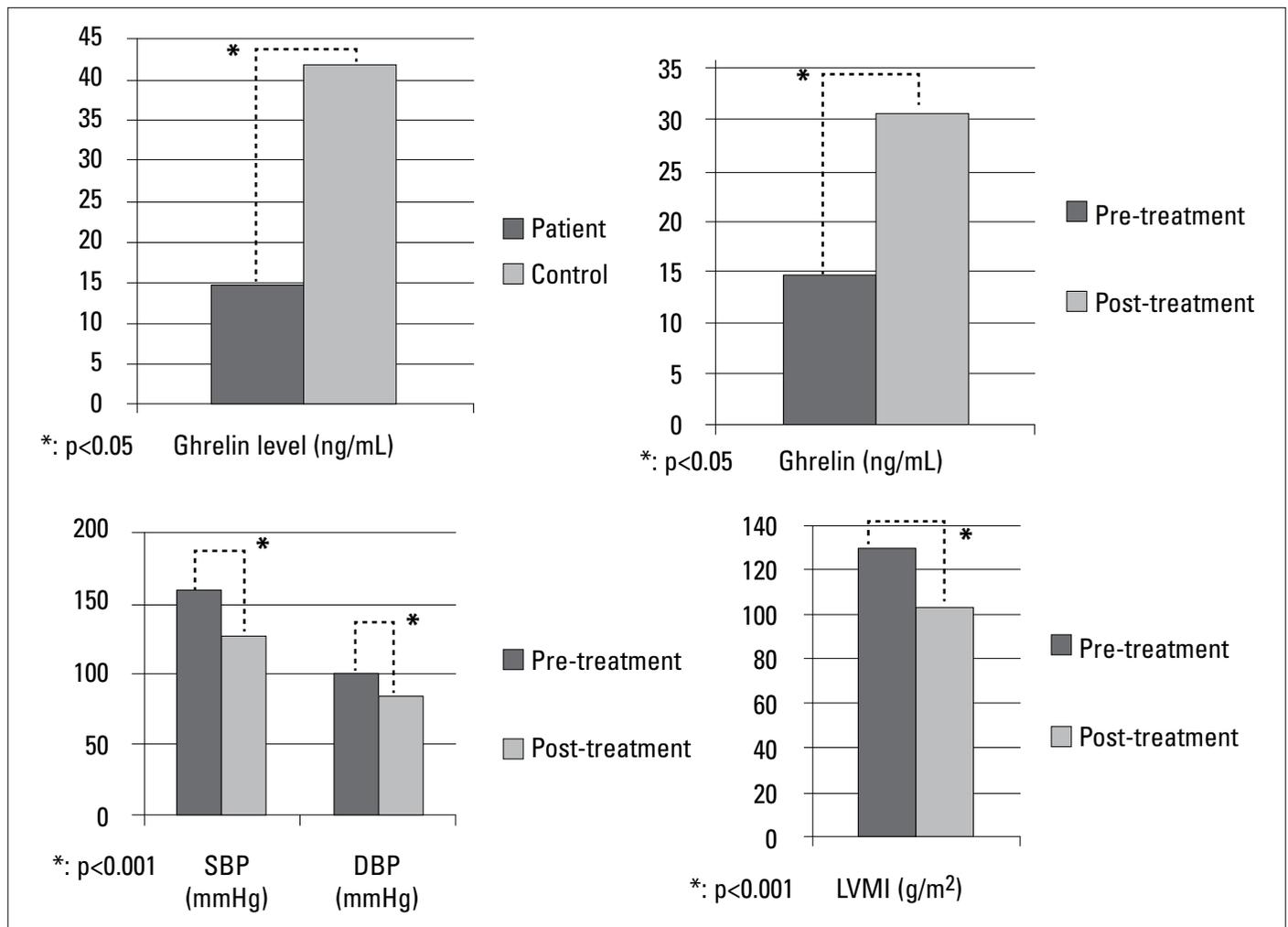


Figure 1. Comparisons of ghrelin levels of patients-controls, pre-treatment-post-treatment ghrelin levels, systolic-diastolic blood pressures and left ventricular mass index

DBP - diastolic blood pressure; LVMI - left ventricular mass index; SBP - systolic blood pressure

Skoczylas et al. (27) reported in a group of hypertensive patients that serum ghrelin level displayed different types of change after currently available antihypertensive medications. They showed that, blood ghrelin increased after a 6 wk treatment with cilazapril, decreased after bisoprolol and remained unchanged after amlodipine or indapamid. Although a 6 wk period seems inadequate to estimate long term changes, that study suggested for the first time the influences of different sorts of therapeutic agents on ghrelin could be independent from their antihypertensive effects. In the literature, however, there is no study on the effects of an angiotensin receptor blockers (i.e. valsartan) on circulating ghrelin except for the study showing effect of candesartan on ghrelin levels in hypertensive rats (28). The present work with a longer follow-up compared to previous ones showed that valsartan causes an increase in serum ghrelin level. Although angiotensin converting enzyme inhibitors (i.e., cilazapril) and receptor blockers share some similar pathways in their actions on vascular system, it became clear in recent years that these two classes of drugs are not entirely the same. However, in terms of possible actions on blood ghrelin these two drug class seem to have similar effects.

Study limitations

The present study has some limitations, one of which is the small number of participants. However, especially the patients are hard to find in the general population as many hypertensives have at least one comorbidity at the time of diagnosis. As seen in Table 1, serum levels of ghrelin show a wide range of distribution. This may not be related to the sample size or the type of assay because it seems to be a common issue (29-31). On the other hand, our study contributes to the literature as it is particularly the first to investigate the changes in circulating ghrelin after blood pressure control in treatment native hypertensive subjects without any complications.

Conclusion

In conclusion, the present study showed that patients with primary hypertension have decreased ghrelin level in peripheral blood, which increases significantly after appropriate blood pressure control. Prospective interventional studies may demonstrate detailed actions of this peptide on cardiac physiology and complications in subjects with hypertension.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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