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Plasma leptin level is positively associated with blood pressure measures independent of gender and BMI

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ABSTRACT

Background: Since the introduction of leptin, many studies suggest an important role for this hormone in obesity-related hypertension. However, in non-obese patients, there are controversial results regarding the possible role of leptin in essential hypertension especially in both sexes and different groups of body mass index (BMI). We aimed to evaluate the association of leptin and hypertension in both female and male gender.

Materials and Methods: This cross-sectional study was conducted, recruiting 80 essential hypertensive patients and 80 healthy normotensive volunteers using convenience sampling method. Subjects without history of diabetes mellitus, hyperlipidemia, smoking, thyroid disease and insulin or corticosteroid use were included in two groups of normotensive and hypertensive subjects who were matched for age, sex and BMI. Systolic and diastolic blood pressure (SBP and DBP), weight and height were measured for all subjects and a blood sample was obtained for measurement of leptin, fasting blood sugar and lipid profiles.

Results: Leptin was significantly higher in hypertensive patients as compared to normotensive subjects in all study population and both male and female subgroups ($p < 0.001$). Statistically significant correlation was also found between leptin and both SBP and DBP in above-mentioned subgroups. In comparison of controlled and uncontrolled hypertensive patients, leptin was significantly higher in uncontrolled hypertensive patients ($p < 0.001$).

Conclusion: Comparing two groups of hypertensive and normotensive subjects, leptin is found to be positively correlated with hypertension in both genders. Leptin level also tends to be higher in uncontrolled hypertensive patients which may indicate a possible role for leptin in mechanism of uncontrolled hypertension.

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KEYWORDS

Leptin; hypertension; BMI; uncontrolled hypertension

Background

Hypertension is considered as a major health problem with significant morbidity and mortality especially due to its vascular complications in multiple critical organs (1,2). The majority of hypertensive patients have essential hypertension with unknown etiology (3). Many of patients with essential hypertension, suffered from obesity or overweight (4). Obesity-related hypertension is multifactorial with several neurohormonal pathways involved including hormones of adipose tissue or adipokines (5). The role of adipokines such as leptin, adiponectin, resistin, etc. in pathogenesis of obesity-induced hypertension is increasingly highlighted during recent decade (5). Leptin has been introduced from 1994 as the product of *ob* gene with signaling potential from adipose tissue to brain (6). Leptin has a significant correlation with amount of adipose tissue and it have been shown to be higher in hypertensive obese patients (7). Although the mechanism of leptin-induced hypertension in obesity is not completely known, it is generally appreciated that the excitatory

effect of leptin on sympathetic nervous system along with resistance to acute peripheral depressor effect of leptin in overweight patients play the most important role in this regard (5,7,8).

With introduction of leptin as a key molecule in obesity-related hypertension, some studies suggested a possible role of this hormone in non-obese hypertensive patients as well (9). However, there are conflicting data regarding the presence of association between leptin and hypertension in normal-weight patients especially in different subgroups of sexes and ages (10–14). On the other hand, most of these studies included patients with new-onset or uncontrolled hypertension and it is not well evaluated in controlled hypertension. This study aimed to assess the association of leptin in two groups of normotensive and hypertensive patients in subgroups of genders and body mass index (BMI) in addition to assess the role of leptin in uncontrolled and controlled hypertensive patients.

Methods

Study population and data collection

This cross-sectional study was designed with a control group. The present study included 80 essential hypertensive patients selected among those who referred to our out-patient center and 80 healthy normotensive volunteers, recruited from the hospital staff as control group by convenience sampling method.

According to the pilot study, considering $\alpha = 0.05$, $\beta = 0.2$, $SD_1 = 14.6$, $SD_2 = 16.5$, $mean_1 = 16.2$ and $mean_2 = 23.2$, sample size was calculated as 80 subjects for each group.

The two groups were matched according to sex, age (within ± 1 year) and BMI (within ± 1 kg/m²) by individual matching. Patients with history of diabetes mellitus or fasting blood sugar (FBS) >126 mg/dl, hyperlipidemia, smoking, thyroid, liver or renal disease and insulin or corticosteroid use were excluded.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured for all patients in office after patient remained seated for at least 5 minutes. A mercury manometer was used with a standard-size cuff which positioned around right arm at the level of heart and blood pressure was measured for 3 times with 5-minute interval. The mean SBP and DBP of all 3 measurements were used as SBP and DBP in analyses. Patients with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and patients with history of hypertension receiving antihypertensive drugs were included in hypertensive group. After height and weight measurement for calculation of BMI, all patients and volunteers were asked to fill an informed consent form approved by the local ethic committee. Then 5 cc blood was obtained in fasting state for each individuals and centrifuged with 3000 r and froze in -30°C . When all samples were collected, plasma leptin level was measured simultaneously for all patients and control group by a leptin kit and ELIZA method with antibody sandwich. The minimum detectable concentration was 0.05 ng/ml leptin in serum. LDL (Low Density Lipoprotein) with direct method, HDL (High Density Lipoprotein) and total cholesterol were also measured.

Statistical analysis

Normality of data distribution was assessed by Kolmogorov-Smirnov test. The quantitative continuous variables are expressed as mean \pm standard deviation, and the categorical variables are presented by numbers (or percentages). Paired sample t-test was used for comparison of leptin, SBP, DBP, BMI and age between the normotensive and hypertensive subjects and in male and female subgroups. MacNemar test was used for comparison the frequency of sex between matched groups. We applied independent t-test for comparison of leptin, SBP, DBP, BMI and age between controlled and uncontrolled hypertensive patients. Correlation of SBP and DBP with leptin was calculated by Pearson's correlation test. The level of significance was set to 0.05.

The study was registered by the ethical committee of the Jiroft University of Medical Sciences (Ethical code: IR.JMU.REC.1394.36).

Table 1. Comparison of basic characteristics between normotensive and hypertensive groups.

	Normotensive group (n = 80)	Hypertensive group (n = 80)	P value ^a
Age(year)	52.10 \pm 10.7	52.35 \pm 10.8	0.070
F/M	53/27	53/27	1
BMI(kg/m ²)	27.23 \pm 3.5	27.50 \pm 3.8	0.077
SBP(mmHg)	116.12 \pm 10.4	142.62 \pm 16.3	<0.001
DBP(mmHg)	75.12 \pm 6.1	88.25 \pm 8.8	<0.001
Leptin(ng/ml)	14.28 \pm 13.5	26.09 \pm 16.4	<0.001
Cholesterol(mg/dl)	184.37 \pm 33.1	182.35 \pm 44.2	0.741
HDL(mg/dl)	40.11 \pm 8.8	47.91 \pm 11.1	<0.001
LDL(mg/dl)	110.75 \pm 27.0	119.77 \pm 34.2	0.053
FBS(mg/dl)	93.23 \pm 9.8	100.95 \pm 8.1	<0.001

^aP value < 0.05 is significant.

F/M, female/male; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure, HDL, high density lipoprotein; LDL, low density lipoprotein; FBS, fasting blood sugar.

Results

One hundred and sixty people were included as normotensive and hypertensive patients while each group consisted 80 individuals. Baseline characteristics of each group were presented in Table 1. There was significant difference between normotensive and hypertensive subjects about SBP, DBP, HDL, and FBS ($p < 0.001$). Plasma leptin level is significantly higher in the hypertensive patients as compared to normotensive cases ($p < 0.001$). Age ($p = 0.070$), sex ($p = 1$), BMI ($p = 0.077$), cholesterol ($p = 0.741$) and LDL ($p = 0.053$) were not significantly difference between two groups.

In comparison of females and males, there is significantly higher leptin level (25.28 vs 9.29 ng/ml, p value <0.001) and BMI (28.03 vs 25.62 kg/m², p value <0.001) in females. This statistically significant difference was also seen in separate analysis of normotensive and hypertensive groups. Normotensive and hypertensive groups were further compared in males and females, separately (Table 2). In both groups of males and females, plasma leptin was significantly higher in hypertensive group ($p < 0.001$). (Table 2).

Pearson's correlation coefficient of leptin with SBP and DBP in subgroups of males and females are presented in Table 3 which shows statistically significant but moderate correlation of leptin and blood pressure in both genders.

Hypertensive patients were also compared on the basis of blood pressure measures indicating controlled (SBP < 140 mmHg and DBP < 90 mmHg) or uncontrolled hypertension (Table 4). Patients with uncontrolled hypertension revealed significantly

Table 2. Comparison of blood pressure measures and leptin between normotensive and hypertensive groups in male and female, separately.

	Normotensive group n = 27	Hypertensive group n = 27	P value ^a
Male			
Age(year)	52.03 \pm 9.9	52.03 \pm 9.8	1
BMI(kg/m ²)	25.74 \pm 3.4	26.11 \pm 3.8	0.239
SBP(mmHg)	116.48 \pm 10.4	137.77 \pm 15.1	<0.001
DBP(mmHg)	74.81 \pm 6.4	86.48 \pm 8.5	<0.001
Leptin(ng/ml)	4.98 \pm 4.4	12.83 \pm 9.9	<0.001
Female			
Age(year)	52.50 \pm 11.4	52.13 \pm 11.3	0.150
BMI(kg/m ²)	28.01 \pm 3.4	28.20 \pm 3.7	0.194
SBP(mmHg)	115.94 \pm 10.5	145.09 \pm 16.5	<0.001
DBP(mmHg)	72.28 \pm 5.9	89.15 \pm 8.8	<0.001
Leptin(ng/ml)	18.60 \pm 13.79	32.34 \pm 15.28	<0.001

^aP value < 0.05 is significant.

F/M, female/male; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Correlation coefficient of leptin with blood pressure measures in males and females, separately.

	Leptin(ng/ml)			
	Males		Females	
	Pearson correlation (r)	P value ^a	Pearson correlation (r)	P value ^a
SBP(mmHg)	0.570	<0.001	0.581	<0.001
DBP(mmHg)	0.559	<0.001	0.541	<0.001

^aP value < 0.05 is significant.

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 4. Comparison of blood pressure measures and leptin between controlled and uncontrolled hypertensive groups.

	Uncontrolled Hypertension (n = 46)	Controlled Hypertension (n = 34)	P value ^a
Age(year)	52.13 ± 10.9	52.64 ± 10.7	0.834
F/M	33/13	20/14	0.227
BMI(kg/m ²)	27.78 ± 3.9	27.11 ± 3.7	0.446
SBP(mmHg)	154.13 ± 10.2	127.05 ± 8.1	<0.001
DBP(mmHg)	93.58 ± 7.2	81.1 ± 4.6	<0.001
Leptin(ng/ml)	31.18 ± 16.41	19.21 ± 13.87	<0.001

^aP value < 0.05 is significant.

F/M, female/male; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

higher leptin level ($p < 0.001$). The most widely used drugs by the hypertensive patients were metoral, triamterene H and amlodipine.

Discussion

This study which evaluate the association of blood pressure and leptin in two selected matched groups of normotensive and hypertensive patients, suggests that plasma leptin level is positively associated with blood pressure independent of age, sex and BMI.

Since 1994, when leptin introduced as a product of *ob* gene which secreted from adipose tissue (6), many animal studies were designed and performed to assess the various mechanism of actions and effects of this hormone on different aspects of metabolism and homeostasis including reproduction, body weight homeostasis, immune function and cardiovascular system (8). By activation of sympathetic nervous system and also central effect on hypothalamus in addition to resistance against its depressor effect on peripheral vasculature in obese patients, leptin is considered as a culprit molecule in pathogenesis of hypertension in obesity (8,15). However, human studies with chronic leptin administration in patients with lipodystrophy (16) or congenital leptin deficiency (17), were unable to confirm a significant direct relationship between increased leptin level and hypertension in these patients. Brown et al. showed that despite significant increase in plasma leptin level after one-year administration of leptin in lipodystrophy patients, no significant change occurred in blood pressure (16). Whereas these experimental studies have questioned the role of leptin in regulation of blood pressure in human, several epidemiologic cross-sectional and prospective cohort studies favored the positive correlation of leptin and blood pressure in both obese and non-obese patients. Studying a large cohort of United States population, Allison et al. have shown a significant relationship between leptin and blood pressure measures independent of other

risk factors, age and BMI (18). Another cross-sectional study with a considerable sample size of 5599 US adults, revealed a positive relationship between leptin and hypertension in both men and women independent of age, BMI, race/ethnicity, smoking, diabetes mellitus, C-reactive protein and cholesterol (9). A large prospective study by Asferg et al. also indicates higher baseline leptin level is associated with new-onset hypertension in different models of baseline adjustments (19). Since the leptin should be considered as a mediator in overweight-related hypertension and not a confounder, Jeppesen et al. stated that adjustment for BMI in evaluation of overweight-related hypertension is not appropriate and can be the reason for non-significant association between leptin and hypertension in some previous prospective studies (20). Thus, Seven et al. have recently found a significant association between leptin and both prevalent and incident hypertension in different categories of BMI in a large prospective study of Danish population, but stated that adjustment of leptin for BMI as a continuous variable, made the correlation insignificant (21).

Galletti et al. compared two groups of men with high and low leptin level (defined as more or less as 2.97 ng/ml) who were matched for age and BMI (11). They found significant difference between high leptin and low leptin group in prevalence of hypertension. When they excluded subjects on medical therapy, significant association was found between hyperleptinemia and hypertension in overweight subjects but not in normal-weight cases. Our study, in which cases were categorized on the basis of blood pressure measures instead of plasma leptin level, revealed that the association between leptin and hypertension is not dependent on BMI in both genders. Even in normal-weight patients, leptin is significantly higher in hypertensive patients and has a significant correlation with both SBP and DBP. Another recent study by Smith et al. has also showed a positive relationship between leptin and hypertension in underweight but not normal-weight African men (22).

Gender differences for plasma leptin level has well documented in many previous studies (23). Although several factors such as higher fat mass and sympathetic activity have been suggested, the underlying mechanism of this gender difference is still unclear (12,24–26). Earlier studies had revealed conflicting results regarding the positive association of leptin and hypertension in only men or women, however, others suggest a significant relationship in both genders (19). By comparison of two matched groups of normotensive and hypertensive subjects, Mallamaci et al. found a statistically significant different leptin level only in men (27). The current study also suggests a significant difference of plasma leptin level between males and females while significant association of leptin and hypertension was still seen in both genders.

In addition, our study also indicates that patients with controlled hypertension have lower plasma leptin levels as compared to uncontrolled hypertensive patients. Several studies have also illustrated the lowering effect of antihypertensive drugs on plasma leptin level (28–30). This finding not only is in favor of the positive association between leptin and essential hypertension but also suggests leptin as a potential factor in uncontrolled hypertension and maybe as a marker for qualification of hypertension management. In a recent study by Moraes et al. on 111 overweight patients, leptin level was compared between 3 groups of uncontrolled resistant hypertension ($n = 41$), controlled

resistant hypertension ($n = 39$) and well-controlled hypertensive patients (31). They found that leptin is significantly higher in the uncontrolled resistant hypertension as compared to controlled hypertension and resulted that leptin may contribute to BP control difficulty in resistant hypertension (31). Nevertheless, some previous studies showed different effects of various anti-hypertensive drugs on plasma leptin levels (28) and further dedicated studies are needed to evaluate the role of leptin in patients monitoring especially after therapy.

While we have tried to carefully match two groups on the basis of other risk factors like DM and hyperlipidemia, the baseline levels of FBS and HDL were different between two groups. However, for all subjects these values were within the normal limits. Recently, positive association of HDL and hypertension has been suggested by some authors (32). Further studies, however, reported a significant positive correlation only in a special age group (33) or in the presence of high circulating endothelial progenitor cell (CD34-positive cells) number (34). In our study, the higher level of HDL in hypertensive patients in the absence of other major cardiovascular risk factors as compared to a matched normotensive group, can be an additional evidence to strengthen this positive association. As another limitation, almost all hypertensive cases in our study were on at least one hypertensive drug. Since the results significantly different in hypertensive and normotensive patients, it seems that impact of antihypertensive drugs does not result in significant bias. Finally, the cross-sectional nature of our study warrants further prospective studies to confirm the results.

Conclusion

Comparing two groups of hypertensive and normotensive subjects, leptin is found to be positively correlated with hypertension in both gender. Leptin level also tends to be higher in uncontrolled hypertensive patients may indicate a possible role for leptin in mechanism of resistant hypertension or patients monitoring.

Disclosure statement

Authors declare that they have no conflict of interest

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