Original article

Association between adipocytokines and insulin resistance in Indian hypertensive patients

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KEYWORDS

Adipocytokines
Hypertension
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Obesity

ABSTRACT

Objective: Although the relationship between obesity, hypertension (HT), and insulin resistance is well-recognised, the pathophysiological mechanism involved is relatively poorly understood. The present study aims in examining the relationship between adipocytokines and insulin resistance in Indian hypertensive patients to better understand the pathogenesis of HT.

Methods: A total of 124 subjects including 41 controls, 41 obese, and 42 hypertensive patients were recruited in this cross-sectional study. Fasting adipocytokines (leptin, adiponectin, resistin) and highly sensitive C-reactive protein (hsCRP) levels were measured by enzyme-linked immunosorbent assay (ELISA). Insulin resistance (IR) index was calculated by the homeostasis model assessment (HOMA). The relation between these variables was studied by univariate and multiple logistic regression analysis.

Results: Among the hypertensive patients, obese hypertensive patients exhibited significantly increased HOMA-IR and altered adipocytokine profile compared to the non-obese control subjects. In a stepwise multiple linear regression analysis with IR as a dependant variable, the study shows leptin as a significant predictor in hypertensive patients. Multiple logistic regression analysis revealed that among the adipocytokines, leptin had a strong association with HT in our population.

Conclusion: Among the adipocytokine, serum leptin levels were significantly increased in hypertensive patients and were also associated with IR and HT. Thus, our findings suggest that leptin may be playing an important role in the development of HT in our population.

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Introduction

Hypertension (HT) as a component of the metabolic syndrome results from complex and multifactorial mechanism including obesity-induced metabolic and hormonal disturbances. Insulin resistance (IR) is often associated with obesity, glucose intolerance, and dyslipidaemia. Recently, IR has also been linked to essential HT.^{1–4} Hyperinsulinemia which compensates for IR, is thought to cause and maintain high blood pressure (BP) by stimulating sympathetic nervous activity, proliferation of vascular smooth muscle cells, altered cation transport, and increased sodium reabsorption.^{3,4} Obesity is defined as an increased mass of adipose tissue and is also a common background of the typical lifestyle-related disease, such as HT. Although the relationship between obesity, IR, and HT is

well-recognised, the pathophysiological mechanism involved remains relatively poorly understood.

In the past, adipose tissue was thought to be a passive depot for the storage of excess energy. However, recent studies have demonstrated that the adipocyte synthesises and secretes biologically active molecule. These molecules collectively known as adipocytokines, which include adiponectin, resistin, leptin, tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), and free fatty acids, appears to be important in the development of IR^{5,6} and other related diseases including HT.

The association between obesity and HT suggests that adipose mass and adipocytokines secreted by them may be important in the regulation of BP or in the pathogenesis of HT, although the mechanism underlying this are not yet evident.^{7–11}

Among the adipocytokines, leptin is a hormone which is predominantly secreted by the adipose tissue. Recent studies have shown that leptin increases arterial BP. Although data from available animal studies clearly indicate an association

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between leptin and HT, results of human studies have been less definitive.^{9–15} Though several studies have shown that adiponectin correlates negatively with BP, the results of studies on the relation between adiponectin and HT have been inconsistent.^{7,8,16,17} Resistin, a novel cysteine-rich protein secreted by adipocytes, has been proposed to serve as a link between obesity and IR in rodents, but this has remained controversial.^{18–21} Very few studies have been carried out to find the role of resistin in essential HT, but results are inconsistent.¹¹ All these adipocytokines such as leptin, adiponectin, and resistin have been associated with HT in either cross-sectional or longitudinal studies. However, few studies directly compared the relative association of these cytokines with BP or with the presence of HT.

Thus, the role of individual adipocytokine in HT in relation to IR is still controversial. The Indian population is relatively more IR due to the high percentage of body fat and higher abdominal obesity at low body mass index (BMI) though the exact cause of increased abdominal obesity and IR in Asian Indian has not been clear.²² According to our recent study adipocytokine may play an important role in the development of IR in Indian diabetic patients.⁵ In addition, we also reported that almost 40% of the essential hypertensive patients were insulin resistant. Thus, with the increasing prevalence of IR, HT is also becoming a major health problem in India. Hence, in the present study we would like to elucidate the role of adipocytokine in relation to IR in Indian hypertensive patients.

Methods

Subjects

A total of 124 subjects aged between 30 years and 70 years comprising 41 controls, 41 obese, and 42 hypertensive patients were taken up for the study after an overnight fast. Hypertensive patients were further divided into 2 subgroups based on their BMI: (1) non-obese hypertensive ($n=23$) ($BMI \leq 25 \text{ kg/m}^2$) and (2) obese hypertensive ($n=19$) ($BMI \geq 25 \text{ kg/m}^2$).

Past medical history and clinical data were collected and anthropometrics measurements such as height, weight, and waist circumference were taken. Waist circumference was measured around the abdomen just above the hip bone. Body mass index was calculated from the ratio of body weight in kilograms (kg) to height in square meters and expressed as kg/m^2 units. Blood pressure was measured in the seated position using mercury sphygmomanometer. Average of two consecutive readings taken 5 minutes apart was recorded. All the subjects gave their informed consent after the procedure was explained to them. The Ethics Committee of Our Hospital approved the project.

Study design

Each subject's venous blood was collected after 12–14 hours fast for estimating fasting glucose, lipid profile, insulin, high

sensitive C-reactive protein (hsCRP), and adipocytokines including leptin, adiponectin, and resistin.

Inclusion and exclusion criteria for selection of subjects

Hypertensive patients

1. Hypertension was defined as systolic BP (SBP) to diastolic BP (DBP) $>140/90 \text{ mmHg}$ or the use of antihypertensive medication.²³
2. Hypertensive patients were not receiving treatment for diabetes or any other illness at the time of study.

Obese subjects

1. Obesity was defined if their $BMI \geq 25 \text{ kg/m}^2$ according to the cut-off suggested for Asian Indians.^{24,25}

Control subjects

1. Controls were classified as having normal glucose tolerance (fasting plasma glucose $<6.1 \text{ mmol/L}$ and 2 hours glucose $<7.8 \text{ mmol/L}$).²⁴
2. They were non-hypertensive and non-obese.
3. They were confirmed to have no known disease condition including cardiac, thyroid disease or any other acute and chronic disease in the past or any current infection/condition.

They were never symptomatic.

Biochemical analysis

Fasting plasma glucose was measured by the glucose peroxidase method (Randox, USA). Serum cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride levels were measured by the enzymatic method (Randox USA). Fasting serum insulin was assayed by radioimmunoassay using RIA kit (BRIT Mumbai, India) incorporating ^{125}I -labelled porcine insulin as the tracer and guinea pig antiserum. Serum hsCRP levels were measured by a highly sensitive enzyme-linked immunosorbent assay (ELISA) (DSL, USA) which has the lower detection limit of 1.6 ng/mL with intra-assay coefficient of variation 4.25% and inter-assay coefficient of variation 5.95%. Serum leptin, adiponectin, and resistin levels were measured by ELISA (Linco Res, USA). Intra-assay and inter-assay coefficient of variation are as follows: for leptin (1.4%, 4.6%), for adiponectin (4.4%, 6.6%), for resistin (2.75%, 6.7%).

Calculation and data analysis

Insulin resistance measured as homeostasis model assessment-IR (HOMA-IR) using following formula²⁶:

$$\text{IR (HOMA-IR)} = \frac{\text{Fasting insulin (U/mL)} \times \text{Fasting glucose (mmol/L)}}{22.5}$$

Statistical analysis

Data are presented as mean $\pm$ SD (standard deviation) or median and inter-quartile range. Group means were compared using unpaired 't' test or the Mann-Whitney rank sum test. Univariate and linear regression analysis were performed for determining the relationship between serum hsCRP and other variables like different adipocytokines and IR. Pearson's correlation coefficient was obtained and $P < 0.05$ was considered statistically significant. Logistic regression analysis was carried out using HT as the dependent variable and biomarkers as independent variables. All analysis was performed using SPSS (version 15).

Results

Clinical characteristics

Table 1 presents the anthropometrical and biochemical characteristics of 41 non-obese control, 41 obese, 23 non-obese hypertensive, and 19 obese hypertensive patients. Mean levels of BMI, waist size, SBP, and triglyceride levels were significantly increased and HDL cholesterol levels were significantly reduced in obese patients compared to non-obese control subjects. As expected elevated SBP and DBP levels were found in non-obese and obese hypertensive patients. In addition, obese hypertensive patients also exhibit increased BMI, waist circumference, and triglyceride levels.

Table 1
Anthropometric and biochemical characteristics of study subjects.

Parameter	Non-obese control (n=41)	Obese (n=41)	Non-obese HT (n=23)	Obese HT (n=19)
M:F	21:20	20:21	13:10	8:11
Age (yr)	47.2 $\pm$ 1.31	47.2 $\pm$ 1.09	47.96 $\pm$ 1.45	49.5 $\pm$ 1.92
BMI (kg/m ²)	22.0 $\pm$ 0.30	29.1 $\pm$ 0.46 ^a	22.5 $\pm$ 0.33	28.72 $\pm$ 0.69 ^a
Waist (cm)	77.7 $\pm$ 1.19	91.5 $\pm$ 1.27 ^a	79.5 $\pm$ 1.65	91.1 $\pm$ 1.65 ^a
SBP (mmHg)	115.6 $\pm$ 2.45	120.2 $\pm$ 2.33 ^a	136.7 $\pm$ 4.19 ^a	131.1 $\pm$ 4.58 ^b
DBP (mmHg)	75.8 $\pm$ 1.21	79.0 $\pm$ 1.39	86.7 $\pm$ 2.91 ^c	84.2 $\pm$ 2.07 ^b
Glucose F (mmol/L)	4.53 $\pm$ 0.08	4.57 $\pm$ 0.09	4.59 $\pm$ 0.11	4.77 $\pm$ 0.13
Cholesterol (mmol/L)	5.06 $\pm$ 0.17	5.07 $\pm$ 0.14	4.71 $\pm$ 0.20	5.02 $\pm$ 0.29
Triglyceride (mmol/L)	1.23 $\pm$ 0.05	1.52 $\pm$ 0.09 ^c	1.44 $\pm$ 0.13	1.57 $\pm$ 0.12 ^c
HDL cholesterol (mmol/L)	1.32 $\pm$ 0.04	1.15 $\pm$ 0.02 ^c	1.24 $\pm$ 0.04	1.24 $\pm$ 0.05
WBC count	7.20 $\pm$ 0.24	7.27 $\pm$ 0.32	7.62 $\pm$ 0.3	8.09 $\pm$ 0.31

All values are given as mean $\pm$ SE (standard error). ^a $P < 0.001$, ^b $P < 0.05$, ^c $P < 0.01$ compared to controls. BMI: body mass index, DBP: diastolic blood pressure, Glucose F: fasting, HDL: high-density lipoprotein, HT: hypertension, SBP: systolic blood pressure, WBC: white blood cell.

Table 2
Metabolic characteristics of study subjects.

Parameter	Control (n=41)	Obese (n=41)	Non-obese HT (n=23)	Obese HT (n=19)
HOMA-IR	4.1 (3.02–5.3)	5.05 (3.9–8.2)	4.6 (3.26–6.44)	6.16 (4.25–8.9)
Serum insulin levels (uU/mL)	20 (16–25)	25 (20–38.5) ^a	23 (17–30)	26.5 (21–44) ^b
Serum leptin levels (ng/mL)	11.5 (6.35–20)	22 (13.5–44) ^a	16 (8–22)	43 (21.5–65) ^a
Serum adiponectin levels (mg/L)	9 (7–11.5)	6.5 (5.2–9.5) ^a	9.0 (6.75–11)	7.0 (5.7–8.25) ^b
Serum resistin levels (ng/mL)	10.5 (7.2–13)	10.5 (6.1–13)	9.6 (6.8–13)	8.8 (8–13)
Serum hsCRP levels (mg/L)	1.8 (0.6–4.8)	3.2 (1.38–7.2)	3.3 (1.0–6.1)	5 (2.15–11.2) ^a

Values are given as median and inter-quartile range. ^a $P < 0.001$, ^b $P < 0.01$, compared to controls. HOMA-IR: homeostasis model assessment-insulin resistance, hsCRP: high sensitive C-reactive protein, HT: hypertension.

Metabolic characteristics

Serum insulin levels, HOMA-IR measure of IR, leptin, and hsCRP levels increased significantly and serum adiponectin levels decreased significantly in obese and obese hypertensive patients compared to non-obese control subjects. No difference was found in insulin HOMA-IR, hsCRP, and adipocytokine levels between non-obese control and non-obese hypertensive patients (Table 2).

Correlation and regression analysis

Pearson bivariate correlation analysis was carried out to find out the association of adipocytokine with IR and other independent variables. In non-obese controls, leptin levels were significantly associated with resistin (0.651, $P < 0.001$) CRP (0.354, $P < 0.02$), BMI (0.541, $P < 0.001$) and DBP (0.408, $P < 0.01$). In obesity it is significantly associated only with BMI (0.784, $P < 0.001$) and hypertensives with insulin (0.409, $P < 0.01$), HOMA-IR (0.419, $P < 0.01$), CRP (0.32, $P < 0.05$) in addition to BMI (0.609, $P < 0.001$).

Serum adiponectin levels were significantly associated with only insulin (-0.407 , $P < 0.01$) and HOMA-IR (-0.395 , $P < 0.01$) in control subjects. In obese patients, serum adiponectin levels is not associated with any of the parameters while in obese hypertensive patients it is associated only with the obesity parameter, waist circumference (-0.338 , $P < 0.05$).

Serum resistin levels were significantly associated with leptin (0.651, $P < 0.001$), CRP (0.495, $P < 0.001$), BMI (0.333, $P < 0.05$), SBP (0.336, $P < 0.05$), and DBP (0.416, $P < 0.01$) in control subjects, while in obese patients it is associated only with waist circumference (0.379, $P < 0.01$), and in hypertensive patients it is associated with CRP (0.407, $P < 0.01$) and BMI (0.337, $P < 0.05$). Interestingly, serum resistin levels were significantly associated with HOMA-IR in non-obese hypertensive patients (0.485, $P < 0.02$).

Findings from the above bivariate correlation analysis were further explored using the stepwise multiple linear regression analysis with HOMA-IR as a dependent variable. It was found that only adiponectin is the significant predictor of IR in non-obese control subjects (β : -0.177, SE (β): 0.066, $P < 0.01$), and leptin in hypertensive patients (β : 0.037, SE (β): 0.018, $P < 0.04$). It was also observed that serum resistin levels are a significant predictor of SBP in non-obese control subjects (β : 1.306, SE (β): -0.585, $P < 0.03$).

Multiple logistic regression analysis using HT as the dependent variable revealed that among the adipocytokine, leptin had a strong association with HT in our population (odds ratio [OR] 1.048, confidence interval [CI] 1.016–1.081), $P < 0.003$.

Discussion

With an increasing prevalence of IR, HT is becoming a major health problem in India. According to our recent study adipocytokine may be playing an important role in the development of IR among Indian diabetic patients. Hence, in the present study we have elucidated the association of adipocytokines with IR in Indian hypertensive patients.

The main findings of the study are:

1. Hypertensive patients exhibit affected lipid metabolism with increased triglyceride levels.
2. Homeostasis model assessment-IR and serum leptin levels increased significantly and adiponectin levels decreased significantly in obese hypertensive patients even after normalising with BMI.
3. Interestingly in stepwise multiple linear regression analysis serum resistin levels were significantly associated with SBP in controls. In addition we also found that adiponectin is an important predictor of IR in controls and leptin in hypertensive patients. Multiple logistic regression analysis revealed leptin to be the important predictor of HT in our population.

Disturbances of glucose and lipid metabolism are known to be related to HT, since it has been suggested that hyperinsulinemia enhances hepatic very low-density lipoprotein (VLDL) synthesis and contribute to increased plasma triglyceride levels.⁷ Thus, our results are consistent with these previous reports, which suggest that essential hypertension often accompanies IR and resultant disturbances of lipid metabolism, increasing the risk of arteriovascular disease in essential HT.

Although till date several studies have been carried out to elucidate the role of different adipocytokines in hypertensives,

the results obtained from different studies were highly controversial.^{8–12,16} Among the adipocytokines an association between HT and adiponectin levels has been reported by several groups.^{7,8,16,17} Although no association of adiponectin was found with BP and IR in our hypertensives, it is significantly associated with IR in controls exhibiting a physiological relationship. We also found that among adipocytokines, adiponectin level decreased significantly independent of the changes in BMI in obese hypertensive patients. The mechanism by which adiponectin levels are lowered in patients remains to be clarified. Although there are several mechanisms that could account for the relationship, it is possible firstly, that the activation of rennin-angiotensin system (RAS) may be responsible, by hypo adiponectinemia resulting in an increase in fat mass and BP¹⁷ or secondly, inflammation may contribute to the pathogenesis of HT. Adiponectin is said to have beneficial and protective effects including antiatherogenic and anti-inflammatory properties.

Resistin is an adipocyte derived peptide that might play a role in obesity and IR; however, its role in humans is largely unknown. In our previous study, we found that it may be playing an indirect role in the pathogenesis of T2DM (type 2 diabetes mellitus) through its association with leptin in our population.⁵

Studies by Furuhashi¹¹ suggest that circulating resistin levels are not related to IR in essential hypertensive patients, although disturbances of lipid metabolism may be associated with IR. In our study we found that there was no difference in serum levels and no association with BP in hypertensives but are significantly associated with SBP in control subjects. Additional studies are needed to elucidate the regulatory and biological function of resistin in humans.

In this study, we have selected hypertensive patients randomly from the clinic and in addition the groups we examined are relatively small. It is likely that with a large number of subjects, the statistical analysis could show better significance; this was the limitation of the study.

The result of earlier studies on the role of leptin in human HT is not consistent. Some studies report significantly higher leptin levels in essential HT than in control^{26,27} or a significant correlation between HT and BP.^{26–28} However, these results were not confirmed by others.^{29,30}

In the present study, serum leptin levels increased significantly in obese hypertensive patients. This increase was independent of changes in BMI. Though leptin is not significantly associated with BP, in stepwise multiple linear regression analysis it is the only adipocytokine significantly associated with IR in our hypertensives. According to our previous study, 40% of the hypertensive patients exhibit IR. It can be speculated that insulin and leptin interact and modulate each other's effects and contribute to HT is an effect of tubular sodium handling.¹⁴ Leptin has several effects such as stimulation of the RAS and sympathetic nervous system which may affect BP levels in humans.^{12,13,31}

Moreover, in multiple logistic regression analysis leptin is an important predictor of HT in our population suggesting that leptin may be playing an important role in the development of HT in our population. Taken together, leptin does indeed

have peripheral physiological effects that suggest it may be a link in the triad of obesity, IR, and HT.

To summarise, findings from our study shows that a correlation exists between leptin and IR; moreover, in logistic regression analysis after adjusting for confounding variables, increasing leptin levels were associated with high-risk of the development of HT. Thus, leptin may be playing an important role in development of HT through its association with IR in our population. Detailed study on the role of adipocytokines may provide new insights into the development of safe and effective pharmaceutical treatment of essential hypertensive patients with IR.

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References

- Modan M, Halkin H, Almog S, et al. Hyperinsulinemia: a link between hypertension obesity and glucose tolerance. *J Clin Invest* 1985;75:809–17.
- Reaven GM. Banting lecture 1988: role of IR in human disease. *Diabetes* 1988;37:1595–1607.
- DeFronzo RA. IR: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173–92.
- Agata J, Miyazaki Y, Takada M, Masuda A, Miura T. Association of IR and hyperinsulinemia with disturbed lipid metabolism in patients with essential hypertension. *Hypertens Res* 1998;21:57–62.
- Mahadik SR, Deo SS, Mehtalia SD. Association of adiposity, inflammation and atherosclerosis: the role of adipocytokines and CRP in Asian Indian subjects. *Metab Syndr Relat Disord* 2008;6:121–8.
- Matsuzawa S. Therapy insight: adipocytokines in metabolic syndrome and related cardiovascular disease. *Nat Clin Pract Cardiovasc Med* 2006;3:35–42.
- Murakami H, Nobuyuki URA, Furuhashi M, Shimamoto K. Role of adiponectin in insulin resistant hypertension and atherosclerosis. *Hypertens Res* 2003;26:705–10.
- Sung SH, Chuang SY, Sheu WH, Lee WJ, Chou P, Chen CH. Adiponectin, but not leptin or high sensitivity C-reactive protein is associated with blood pressure independently of general and abdominal adiposity. *Hypertens Res* 2008;31:633–40.
- Imatoh T, Miyazaki M, Momose Y, et al. Hyperleptinemia is associated with hypertension in Japanese males. *Acta Med Okayama* 2008;62:169–74.
- Almeida-Pititto B, Gimeno SGA, Freire RD, Ribeiro-Filho FF, Ferreira SRG. Leptin is not associated independently with hypertension in Japanese-Brazilian women. *Brazilian J Med Biol Res* 2006;39:99–105.
- Furuhashi M, Ura N, Higashiura K, Murakami H, Shimamoto K. Circulating resistin levels in essential hypertension. *Clin Endocrinol* 2003;59:507–10.
- Haynes W. Role of leptin in obesity-related hypertension. *Exp Physiol Symp Rep* 2005;90:683–8.
- Bravo PE, Morse S, Borne DM, Aguilar EA, Reisin E. Leptin and hypertension in obesity. *Vascular health and risk management* 2006;2:163–9.
- Stenvinkel P. Leptin and blood pressure—is there a link? *Nephrol Dial Transplant* 2000;15:1115–7.
- Ogawa Y, Masuzaki H, Aizawa M, et al. Blood pressure elevation in transgenic mice overexpressing leptin, the obese gene product. *J Hypertens* 1998;16:7.
- Imatoh T, Miyazaki M, Momose Y, Une H, Tanihara S. Adiponectin levels associated with the development of hypertension: a prospective study. *Hypertens Res* 2008;31:229–33.
- Patel JV, Lim HS, Hughes EA, Lip GYH. Adiponectin and hypertension: a putative link between adipocyte function and atherosclerotic risk? *J Hum Hypertens* 2007;21:1–4.
- Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. *Nature* 2001;409:307–12.
- Nagaev I, Smith U. IR and Type 2 diabetes are not related to resistin expression in human fat cell or skeletal muscle. *Biochem Biophys Res Commun* 2001;295:561–4.
- Janke J, Engeli S, Gorzellniate K, et al. Resistin gene expression in human adipocytes is not related to IR. *Obes Res* 2002;10:1–5.
- Savage DB, Sewter CP, Klenk ES, et al. Resistin/Fizz3 expression in relation to obesity and Peroxisome proliferator activated receptor γ action in humans. *Diabetes* 2001;50:2199–202.
- Mahadik SR, Deo SS, Mehatalia SD. Increased prevalence of metabolic syndrome in non-obese Asian Indian: an urban-rural comparison. *Metab Syndr Relat Disord* 2007;5:140–50.
- Chobanian AV, George L, Bakris GL, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.
- World Health Organization (1999). Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus (WHO/NCD/CS/99.2) World Health Organization, Geneva.
- World Health Organization. The Asia-Pacific perspective: redefining obesity and its treatment. Geneva, Switzerland: World Health Organization 2000.
- Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: IR and beta cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
- Agata J, Masuda A, Takada M, Murakami H, Higashiura K, Miyazaki Y. High plasma immunoreactive leptin level in essential hypertension. *Am J Hypertens* 1997;10:1171–4.
- Sheu WH, Lee WJ, Chen YT. High plasma leptin concentrations in hypertensive men but not in hypertensive women. *J Hypertens* 1999;17:1289–95.
- Hirose H, Saito I, Tsujioka M, et al. The obese gene product, leptin: possible role in obesity-related hypertension in adolescents. *J Hypertens* 1998;16:2007–12.
- Kokot F, Adamczak M, Wiecek A, Cieplak J. Does leptin play a role in the pathogenesis of essential hypertension? *Kidney Blood Press Res* 1999;22:154–60.
- Uckaya G, Ozata M, Sonmez A, et al. Plasma leptin levels strongly correlate with plasma rennin activity in patients with essential hypertension. *Horm Metab Res* 1999;31:435–8.