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Association between adipocytokines and insulin resistance in Indian hypertensive patients

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KEYWORDS

Adipocytokines
Hypertension
Indian population
Insulin resistance
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.

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≤25 kg/m^2) and (2) obese hypertensive (n=19) (BMI≥25 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 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 ≥25 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 mmol/L and 2 hours glucose <7.8 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 formula[26]:

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