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Plasma Adiponectin and Insulin Resistance in New Onset Hypertension

Teoman Dogru,[1] Alper Sonmez,[1] Ilker Tasci,[1] M. Ilker Yilmaz,[2] Selim Kilic,[3] Taner Ozgurtas,[4] Tayfun Eyileten,[2] M. Kemal Erbil[4] and I. Hakki Kocar[1]

Gulhane School of Medicine, Departments of [1]Internal Medicine, [2]Nephrology, [3]Epidemiology, and [4]Biochemistry, Etlik, Ankara, Turkey

Objective: The data related to association among hypertension, insulin resistance, and plasma adiponectin concentration is controversial. We aimed to evaluate the relationships among these factors in a young hypertensive group who had no confounding factors. Design and methods: Thirty newly diagnosed and formerly untreated hypertensive males (mean age 23.4 ± 4.0 yr; body mass index: 24.9 ± 2.2 kg/m^2), and 60 healthy control subjects (mean age 22.5 ± 3.2 yr; body mass index: 24.6 ± 1.6 kg/m^2) were enrolled. Insulin resistance was calculated by homeostasis model assessment (HOMA). Results: The two groups were similar in terms of age, body mass index, fasting glucose, total cholesterol, HDL and LDL cholesterol, adiponectin, insulin, HOMA, and hsCRP levels. Mean triglyceride levels in hypertensive patients were significantly higher than the controls ($p = 0.02$). Conclusions: These results indicate that young, newly diagnosed, uncomplicated patients with hypertension have similar plasma adiponectin levels and insulin sensitivities when compared to healthy controls. We suggest that high blood pressure itself may not be associated with insulin resistance or low adiponectin levels in patients with new onset, uncomplicated hypertension.

Key Words: Adiponectin; insulin resistance; hypertension.

Introduction

Hypertension and insulin resistance are among the main risk factors for cardiovascular diseases (CVD) *(1)*. Insulin resistance, which is prevalent in established hypertension *(2,3)*, may even precede elevation in blood pressure *(4–6)*. However, the data regarding physiological relevance of such an association is not clear *(7,8)*. At least half of the patients with hypertension are insulin sensitive *(9)* and those who are insulin resistant frequently have common disorders such as obesity, unhealthy diet, and physical inactivity that mostly accompany both conditions.

Adiponectin is a novel adipocytokine with important roles in regulating energy homeostasis, improving insulin sensitivity, and preventing inflammation and atherogenesis *(10)*. Adiponectin levels were found to be negatively associated with increased insulin resistance and elevated inflammatory markers *(11,12)*. Hypoadiponectinemia is usually present in insulin-resistant states such as diabetes mellitus, obesity, dyslipidemia, and smoking *(11–14)*. However, the data from clinical trials concerning plasma adiponectin concentrations in hypertensive patients is controversial as both high *(15)* and low *(16,17)* levels have been reported so far. In addition, reduction in adiponectin was reported to accompany hypertension if only the patient is insulin resistant *(18)*. Finally, whether hypoadiponectinemia in hypertensive patients is the result of an increase in blood pressure itself or the accompanying conditions should be further investigated. Therefore, we designed a clinical study to answer the following questions: (1) Are plasma adiponectin concentration and insulin resistance in young, newly diagnosed and uncomplicated hypertensive men different from healthy controls? (2) Is there any relation between blood pressure and plasma adiponectin or insulin levels in such a group of patients? In order to assess the inflammatory state of both the patients and the controls plasma high-sensitive C-reactive protein (hsCRP) levels were also determined.

Results

The characteristics of the study group and the controls are described in Table 1. Mean systolic and diastolic blood pressures ($p < 0.001$, for both) and triglyceride ($p = 0.02$) levels were significantly higher in patients compared to controls. Total, HDL, and LDL cholesterol, fasting glucose, HOMA index, plasma insulin, adiponectin, and hsCRP levels in the two groups were similar. Insulin, HOMA, and adiponectin levels did not correlate with each other or the blood pressures. For all group, the correlation coefficients were between –0.08 and –0.20 ($p > 0.05$).

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Author to whom all correspondence and reprint requests should be addressed: Teoman Dogru, MD, Gulhane Medical School, Department of Internal Medicine, Etlik, 06018, Ankara, Turkey. E-mail: teomandogru@yahoo.com

Table 1
Characteristics of Hypertensive Patients and Normotensive Controls

	Hypertensive patients (n = 30)	Normotensive controls (n = 60)	p
Age (yr)	23.7 ± 4.4	22.5 ± 3.2	0.35
BMI (kg/m^2)	24.9 ± 2.2	24.6 ± 1.6	0.46
Systolic BP (mmHg)	146.8 ± 8.7	112.1 ± 7.7	<0.001
Diastolic BP (mmHg)	92.8 ± 9.3	73.4 ± 7.7	<0.001
Total Cholesterol (mg/dL)	153.4 ± 23.3	148.0 ± 25.8	0.34
LDL cholesterol (mg/dL)	88.6 ± 20.3	96.4 ± 27.3	0.24
HDL cholesterol (mg/dL)	38.1 ± 7.7 (38)	39.6 ± 8.5 (38)	0.77*
Triglyceride (mg/dL)	122.1 ± 51.6 (106)	95.6 ± 35.5 (96.5)	0.02*
Insulin (μU/mL)	6.6 ± 3.0	4.9 ± 4.4	0.15
Fasting glucose (mg/dL)	77.8 ± 14.6	78.1 ± 10.4	0.93
HOMA	1.33 ± 0.36 (1.04)	0.98 ± 0.21 (0.75)	0.21*
Adiponectin (μg/mL)	18.4 ± 9.2 (17.01)	18.9 ± 8.2 (18.42)	0.47*
hsCRP (mg/L)	1.0 ± 0.9 (0.83)	0.97 ± 0.93 (0.50)	0.72*

The tests were performed by independent samples t test, and *Mann–Whitney U test. Data is expressed as mean ± SD (median). BP: Blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA: homeostasis model assessment of insulin sensitivity; hsCRP: high-sensitive C-reactive protein.

The power of the study, calculated according to alpha errors for adiponectin, HOMA, and CRP were 0.42, 0.57, and 0.81, respectively.

Discussion

This study was designed to investigate the insulin sensitivity and adiponectin levels in a young, newly diagnosed, uncomplicated hypertensive male population. Criteria for patient selection were quite relevant because no patient with inciting factors for insulin resistance such as obesity, hyperglycemia, or dyslipidemia was included in the study group. We found that plasma insulin, HOMA, and adiponectin levels of patients were similar to those of healthy controls (Table 1). No correlation was observed between blood pressure and other parameters as well.

Insulin resistance is a physiological abnormality associated with increased likelihood of several disorders including type II diabetes, hypertension, cardiovascular diseases, polycystic ovary syndrome, nonalcoholic fatty liver disease, and certain forms of cancer *(19)*. Although the association between insulin resistance and hypertension was reported long ago *(20)*, the causal link between these two disorders is still not clear. In population-based studies, hyperinsulinemia and insulin resistance were reported to predict the eventual development of hypertension *(4–6)*. There is evidence that normotensive kindred of hypertensive patients are insulin resistant when compared to matched controls without a family history of hypertension *(21–23)*. Hyperinsulinemia may cause high blood pressure through several mechanisms including increased renal sodium retention *(24)* and activation of sympathetic system *(25)*. These data imply that insulin resistance and hyperinsulinemia may be involved in the pathogenesis of primary hypertension. However, as in our study, not all hypertensive patients are insulin resistant *(9)*. There are also studies concluded with no relation between hypertension and hyperinsulinemia or insulin resistance *(26,27)*. Likewise, in our study group, HOMA and insulin levels were not altered and there was no correlation between the blood pressures and the above parameters. Therefore, clearer evidence is needed to establish a causal relationship between hypertension and insulin resistance.

The data so far imply that adiponectin is a crucial fat tissue–derived hormone, which has remarkable anti-inflammatory, anti-atherosclerotic, and insulin-sensitizing functions *(10)*. It stimulates nitric oxide secretion, inhibits vascular smooth muscle cell proliferation, intracellular adhesion molecule expression, and accumulation of lipids in human monocyte-derived macrophages *(28–31)*. It also acts as an insulin sensitizer and decreases hepatic glucose output *(32)*. The elevation of inflammatory mediators such as hsCRP and interleukin-6 is associated with reduced plasma adiponectin levels *(33)*. Hypoadiponectinemia was reported to accompany the conditions associated with insulin resistance *(11–14)*. However, the data concerning patients with hypertension are controversial *(15–17)*. The earliest report, which was performed on patients with low glomerular filtration rates, concluded with high adiponectin levels in hypertensive patients *(15)*. In a subsequent study, however, patients with hypertension were found to have reduced adiponectin concentrations, but that work did not include determination of insulin resistance in the study group *(16)*. Murakami et al. reported that low adiponectin levels are present in hypertension if only the patients are insulin resistant *(18)*. Later on, Iwashima et al. reported low adiponectin levels in a large group of hypertensive patients *(17)*. However, the

population in their study was aged with several confounders such as type II diabetes mellitus and dyslipidemia, and past diseases of the patients were not determined. As we also previously reported that adiponectin levels in patients with hypertension correlate well with the extend of vascular disturbances *(34)*, hypoadiponectinemia in hypertensive patients seems to result from accompanying conditions rather than elevated blood pressure itself.

From the overall data it is likely that the presence of insulin resistance and hypoadiponectinemia in hypertension necessitates an underlying mechanism other than high blood pressure. Recently, normotensive young kindred of patients with hypertension were reported to have impaired insulin sensitivity and low adiponectin levels *(21)*. From this report it can be inferred that the role of genetic factors may be important in the presence of hypoadiponectinemia. Another probable mechanism of low adiponectin levels in hypertension may be inflammation. Inflammation predicts future generation of high blood pressure in otherwise healthy people and takes part in the hypertension-induced vascular changes *(35–38)*. Proinflammatory biomarkers are known to correlate strongly with the associates of hypertension such as insulin resistance, abdominal obesity and dyslipidemia, and hypoadiponectinemia *(33,39,40)*. Indeed, our study group had similar hsCRP levels when compared to healthy controls, which might explain the unaltered adiponectin concentrations and insulin levels in our patients.

The study, however, has several limitations. Because of narrow selection criteria, number of patients was hardly enough to make clearer estimations. In addition, as the study was performed in a group of primarily young men, generalization of the results simply to other patient groups may not be appropriate. Significantly higher triglyceride levels in the patient group compared to controls might seem to be confounding, however, all triglyceride values were within the normal ranges.

In conclusion, these data imply that young patients with uncomplicated hypertension have similar insulin sensitivity and plasma adiponectin concentrations when compared to healthy controls. We suggest that, in patients with hypertension, high blood pressure itself may not be the cause of insulin resistance and hypoadiponectinemia. Future prospective studies with larger populations may provide clear-cut results for the role of inflammation as a link between hypertension and these conditions.

Material and Methods

Subjects

Among the hypertensive patients who were referred to Gulhane Medical School over a period of 12 mo, a total number of 30 male subjects [mean age 23.4 ± 4.0 yr, body mass index (BMI): 24.9 ± 2.2 kg/m^2] were enrolled. The inclusion criteria for patients were as follows: new onset hypertension, no previous hypertensive medication, with no family history of diabetes mellitus, BMI <30 kg/m^2, fasting blood glucose <100 mg/dL, triglyceride <150 mg/dL, total cholesterol <200 mg/dL, normal renal, hepatic, and cardiac functions without any electrocardiographic sign of ventricular hypertrophy and ischemia. Also, in order to avoid the sexual dimorphism present for circulating adiponectin levels *(41)*, we did not enroll female patients and controls. Secondary causes of hypertension were eliminated by medical history, physical examination, and laboratory measurements where necessary.

Blood pressure was measured with an appropriate arm cuff and a mercury column sphygmomanometer after a resting period of at least 5 min. Two measurements within 5 min were averaged as the systolic and diastolic blood pressures. Patients were considered as hypertensive if their blood pressures measured on three separate occasions exceeded 140/90 mmHg.

One hundred and fifty healthy volunteers were evaluated for the control group. After medical consultation and laboratory work, 60 normotensive (<130/85 mmHg) male subjects (mean age 22.5 ± 3.2 yr, body mass index 24.6 ± 1.6 kg/m^2) with no family history of hypertension and diabetes mellitus, normal fasting glucose, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol levels were enrolled as controls. The Ethical Committee of Gulhane Medical School approved the study protocol, and both patients and controls gave informed consent to participate in the study.

Biochemical Parameters

After an overnight fast, venous blood samples were drawn and promptly centrifuged, and the plasma was stored at –80°C until adiponectin assay was performed. All samples were run in the same assay. Glucose was enzymatically determined by the hexokinase method *(42)*. Total cholesterol, HDL cholesterol, and triglycerides were determined by an enzymatic colorimetric method with an Olympus AU 600 auto analyzer using reagents from Olympus Diagnostics, GmbH (Hamburg, Germany). LDL cholesterol was calculated by the Friedwald's formula *(43)*. Fasting insulin levels were measured by the coated tube method (DPC-USA). Homeostasis Model Assessment Model (HOMA) was used to determine the insulin sensitivity index with formula: HOMA-IR= Fasting insulin (μU/mL) × Fasting glucose (mg/dL)/405 *(17)*.

Measurement of High-Sensitivity C-Reactive Protein and Adiponectin

Serum hsCRP was determined by turbidimetric fixed rate method *(44)* by an automated analyzer (Olympus AU-2700, Mishima, Japan). Plasma adiponectin concentrations were measured by radioimmunoassay (RIA; Human adiponectin RIA kit; Linco Research, Inc., St. Charles, MO, USA) [sensitivity 1 ng/mL; intraassay coefficient of variation (CV) 1.78–6.21%; interassay CV, 6.9–9.25%]. All assays were

performed in duplicate. Subjects with hsCRP levels above 10 mg/L were excluded from the study to prevent any interference by an acute infectious state or occult disease.

Statistical Analyses

Results are reported as the mean ± SD. One-sample Kolmogorov–Smirnov test was used to evaluate the distribution characteristics of variables. The differences between the groups were tested for significance by independent-samples *t*-test or Mann–Whitney *U* test. The relationship between variables was analyzed by Pearson's correlation or Spearman's rho correlation tests as appropriate. Differences and correlations were considered significant at $p < 0.05$. As there was no previous data about the adiponectin and insulin levels in young, uncomplicated, new onset hypertension, the sample size was not calculated before the study.

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