Original Article

Low Adiponectin Level in Young Normotensive Men with a Family History of Essential Hypertension

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Circulating level of adiponectin, an adipocyte-derived protein, is reduced in states of insulin resistance such as obesity and type 2 diabetes. We have previously shown that hypoadiponectinemia is related to insulin resistance in essential hypertension. Recent studies have shown that normotensive subjects with a positive family history of essential hypertension (FH+) have decreased insulin sensitivity compared to subjects with a negative family history of essential hypertension (FH−). We here examined the association between adiponectin concentration and insulin sensitivity in FH+ and FH−. Thirty young, non-obese and normotensive men without a family history of diabetes mellitus were enrolled. A total of 15 subjects were FH+, and the remaining 15 subjects were FH−. Insulin sensitivity index (ISI) was evaluated by the euglycemic hyperinsulinemic glucose clamp technique. Concentrations of adiponectin and other metabolic variables were measured. The FH+ group had significantly lower levels of ISI and adiponectin than did the FH− group. In all of the subjects, ISI was positively correlated with adiponectin concentration and high-density lipoprotein (HDL) cholesterol level and was negatively correlated with insulin level. Adiponectin concentration was the only independent determinant of ISI in a multiple regression analysis. Our results showed that adiponectin level was significantly decreased and that this was accompanied by reduced insulin sensitivity in young, non-obese and normotensive men with a family history of essential hypertension. Phenotype of reduced adiponectin level as an earlier penetrance may be especially useful in genetic analyses of insulin resistance and essential hypertension. (*Hypertens Res* 2005; 28: 141–146)

***Key Words*: adiponectin, essential hypertension, family history, insulin resistance**

Introduction

Adipose tissue was once thought to be simply a depot for fuel storage in the form of triglyceride. However, it is now known that adipocytes secrete a variety of proteins that are implicated in a wide range of biological effects. Adiponectin, an adipocyte-derived protein, has been independently identified and characterized by several groups (*1*–*5*). In humans, adiponectin is one of the most abundant gene transcript proteins in adipocytes, corresponding to 0.01% of all proteins (*2*). In contrast with other adipocyte-derived proteins, the circulating adiponectin level is reduced in patients with coronary artery disease and in states of insulin resistance such as obesity and type 2 diabetes (*6*–*8*). It has also been suggested that patients with type 2 diabetes not only have a decreased adiponectin level in the basal state but also impaired utilization of adiponectin in the tissue (*9*). Moreover, we have previously

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Table 1. Basal Characteristics and Metabolic Variables of the Studied 30 Normotensive Men

Variables	Family history of hypertension	
	–	+
n	15	15
Age (years)	23.5±0.9 (19–32)	23.7±1.1 (18–32)
Body mass index (kg/m^2)	24.3±0.9 (19.4–29.4)	24.6±0.8 (20.3–29.5)
SBP (mmHg)	113.6±3.3 (96–138)	116.5±3.5 (96–138)
DBP (mmHg)	74.7±2.0 (58–86)	76.4±1.9 (62–86)
Mean blood pressure (mmHg)	87.7±2.5 (70.7–105.0)	89.8±2.4 (73.3–106.7)
High-normal blood pressure	4	4
Pulse rate (beats/min)	59.7±1.6 (52–72)	60.7±2.3 (46–76)
Fasting plasma glucose (mmol/l)	4.6±0.1 (4.1–5.1)	4.8±0.1 (4.1–5.3)
Fasting plasma insulin (pmol/l)	22.2±1.5 (18.0–36.0)	25.7±2.3 (16.8–45.0)
Total cholesterol (mmol/l)	4.2±0.2 (3.0–5.5)	4.1±0.2 (3.0–5.5)
HDL cholesterol (mmol/l)	1.0±0.1 (0.7–1.3)	0.9±0.1 (0.7–1.4)
Triglyceride (mmol/l)	0.9±0.2 (0.3–2.3)	1.2±0.1 (0.4–2.3)
Free fatty acid (mmol/l)	0.4±0.1 (0.1–0.7)	0.4±0.1 (0.1–0.8)

Values are *n* or the means±SEM (range). SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein.

shown that hypoadiponectinemia is related to insulin resistance in essential hypertension, and that blockade of the renin-angiotensin system increases adiponectin levels with improvement in insulin sensitivity, at least in part *via* a decrease in adipocyte size (*10*, *11*). Adiponectin has also been suggested to enhance insulin sensitivity and prevent atherosclerosis in animal experiments (*12*, *13*). In fact, it has been reported that adiponectin concentration is negatively correlated with pulse wave velocity (PWV), which is measured as an index of atherosclerosis, and that adiponectin was a significant determinant of PWV in a multiple regression analysis (*14*).

In recent years, growing attention has been paid to the role of genetic factors in linking insulin resistance and essential hypertension. Essential hypertension has a familial predisposition, but the phenotype of elevated blood pressure has delayed penetrance. Insulin resistance sometimes exists before the onset of hypertension, and genetically and environmentally determined insulin resistance and/or compensated hyperinsulinemia might contribute to the development of hypertension (*15–18*). It has been shown that approximately 40% of essential hypertensives are insulin-resistant (*18*, *19*). Recent studies have shown that normotensive offspring of patients with essential hypertension have decreased insulin-stimulated glucose uptake compared to subjects with no family history of hypertension, suggesting that low insulin sensitivity may be a primary factor in the development of hypertension (*18*, *20–25*).

Although it has been demonstrated that adiponectin level is significantly reduced in non-obese relatives of type 2 diabetic subjects with a high propensity for type 2 diabetes (*26*), there have been no studies dealing with the relationship between adiponectin concentration and insulin sensitivity in relation to the family history of essential hypertension. We therefore examined the association between adiponectin concentration and insulin sensitivity assessed by the euglycemic hyperinsulinemic glucose clamp technique in young, non-obese and normotensive men with and without a family history of hypertension.

Methods

Thirty young normotensive men (mean age: 23.6±0.7 years) from the student body of our university were enrolled as volunteers in this study. All subjects were 18–32 years of age, had a body mass index (BMI) of <30 kg/m^2 and blood pressure of $<140/90$ mmHg, and were not taking any drugs. A total of 15 subjects had a positive family history of essential hypertension (FH+), and the remaining 15 subjects had a negative family history of essential hypertension (FH–). Family history was ascertained by a self-report questionnaire sent to the parents and by records of the parents' physicians. Subjects whose parents were both being treated with antihypertensive medication for essential hypertension were classified as FH+, whereas those without such a history and whose blood pressure was $<140/90$ mmHg at any recent health check on an annual basis were classified as FH–. Using records of parents' physicians or annual health checkups, parental blood pressure was evaluated on the basis of at least three measurements by a sphygmomanometer performed on different days. Subjects for whom a family history of hypertension was not certain and those with a family history of diabetes mellitus in any relatives were excluded. All of the subjects were hospitalized and were put on a regular diet (2,000 kcal/day) that included 310 g of carbohydrate, 50 g of fat, 80 g of protein, 120 mmol of sodium, and 75 mmol of potassium. Insulin sensitivity was evaluated by the euglycemic hyperinsulinemic glucose clamp technique. Before the clamp study, blood pres-

Table 2. Multiple Regression Analysis

Independent variables	Insulin sensitivity index		Adiponectin	
	β	p	β	p
Adiponectin	0.509	0.010	—	—
Family history of hypertension	−0.215	0.18	−0.102	0.51
Body mass index	0.124	0.44	−0.321	0.028
HDL cholesterol	0.110	0.49	0.092	0.55
Fasting insulin	−0.193	0.22	—	—
Insulin sensitivity index	—	—	0.519	0.003

Data are expressed as standardized regression coefficient (β) and p value. HDL, high-density lipoprotein.

sure and pulse rate were measured and blood samples were obtained from all subjects. Systolic blood pressure of 130–139 mmHg or diastolic blood pressure of 85–89 mmHg was defined as high-normal blood pressure. The concentrations of adiponectin, glucose, insulin, and lipid variables were measured. There were no dropout subjects. This study was performed with the approval of the ethics committee of our institution, and informed consent was obtained from all of the subjects.

Euglycemic Hyperinsulinemic Glucose Clamp Technique

A 2-h euglycemic hyperinsulinemic glucose clamp was performed according to the method described by DeFronzo *et al*. (*27*). A vein in a forearm was cannulated for blood glucose monitoring. During the glucose clamp, blood was continuously drawn at 2.0 ml/h through a catheter. In addition, a contralateral antecubital vein was cannulated with a plastic cannula for the infusion of insulin and glucose. Continuous insulin infusion, monitoring of glucose concentration, and infusion of various amounts of glucose in order to clamp glucose levels in the basal state were performed with a model STG-22 artificial endocrine pancreas (Nikkiso Corp., Tokyo, Japan). The infusion rate of insulin (humalin R U-40; Shionogi Pharmaceutical Co., Osaka, Japan) was 40 mU/m^2/min. During insulin infusion, euglycemia was maintained by infusion of a 20% glucose solution. The mean rate of glucose infusion for the last 30 min of the clamp was used as the M value (mg/kg/min). The insulin sensitivity index (ISI, mg/kg/min per μU/ml) was taken as the M value divided by the steady state plasma insulin concentration during the clamp.

Laboratory Investigations

Serum adiponectin level was measured using a commercially available sandwich enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals Co., Ltd., Tokushima, Japan) as previously reported (*5*). Fasting plasma glucose was determined by the glucose oxidase method. Fasting plasma insulin was measured by a radioimmunoassay method (Insulin RIA bead; Dianabot, Tokyo, Japan). Serum lipid profiles, including total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride and free fatty acid, were estimated by enzymatic methods.

Statistical Analysis

Numeric variables are expressed as the means±SEM. The Mann-Whitney U test was used for comparisons between two unpaired variables. Spearman's rank correlation test was used for analysis of correlations between two variables. Multiple linear regression analysis was performed using ISI and adiponectin level as dependent variables and using family history of hypertension (yes: 1; no: 0) and the variables with a significant correlation or a tendency of correlation in univariate regression analysis as independent predictors. Stepwise regression analysis was also performed in a forward direction with F for the entry set to 4, showing the percentage of variance in the adiponectin concentration that significantly independent variables explained (r^2). A p value of <0.05 was considered statistically significant.

Results

As shown in Table 1, the two groups were well matched for age and BMI. There were no significant intergroup differences in blood pressure, number of subjects with high-normal blood pressure, pulse rate, or the levels of glucose, total cholesterol, HDL cholesterol, triglyceride, or free fatty acid. The insulin level in the FH+ group was higher, but not significantly higher, than that in the FH− group. The FH+ group had significantly lower levels of ISI and adiponectin than did the FH− group (Fig. 1).

In all of the subjects, the ISI was positively correlated with adiponectin concentration ($r=0.64$, $p=0.0006$) and HDL cholesterol level ($r=0.39$, $p=0.038$) and negatively correlated with fasting insulin level ($r=-0.34$, $p=0.034$). BMI was not significantly correlated with ISI ($r=-0.19$, $p=0.19$). Multiple regression analysis showed that adiponectin concentration was independently related to ISI (Table 2). Stepwise regression analysis also revealed that adiponectin was the only independent predictor of ISI, explaining a total of 43% of the variance in this measure ($r^2 = 0.43$).

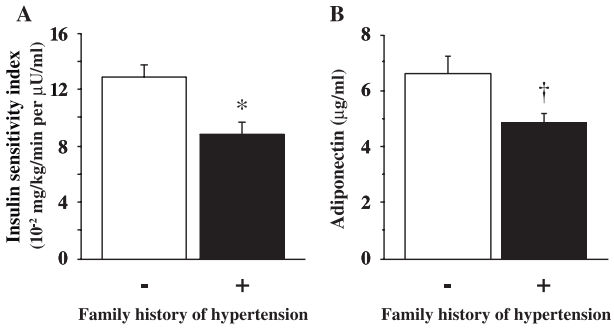

Fig. 1. *Bar graphs show the insulin sensitivity index (ISI) (A) and adiponectin level (B) in young normotensive men without (open bars) and with (closed bars) a family history of essential hypertension. Values are presented as the means±SEM.* *$p < 0.01$, †$p < 0.05$.

On the other hand, the adiponectin concentration was positively correlated with ISI ($r=0.64$, $p=0.0006$), as stated above, and HDL cholesterol level ($r=0.38$, $p=0.041$) and negatively correlated with BMI ($r=-0.48$, $p=0.0096$) and insulin level ($r=-0.42$, $p=0.0097$). Multiple regression analysis showed that ISI and BMI were independently related to adiponectin concentration (Table 2). Stepwise regression analysis also revealed that ISI and BMI were independent determinants of adiponectin concentration, explaining a total of 53% of the variance in this measure ($r^2 = 0.53$).

Discussion

Three notable findings were obtained in the present study. First, in normotensive offspring of essential hypertensives who had not yet developed high blood pressure, insulin sensitivity was already impaired. This result is in accordance with previous findings (*18*, *20–25*). Second, adiponectin level was significantly correlated with degree of insulin sensitivity in the whole body estimated by the glucose clamp study. In multiple regression analyses, adiponectin was the only determinant of ISI, and the ISI was also a predictor of adiponectin concentration independently of BMI even in young, non-obese and normotensive men, although it has been well established that adiponectin level is decreased in insulin-resistant states such as obesity, type 2 diabetes, and essential hypertension (*7–10*). The third and most important finding in the present study is that serum adiponectin concentration was significantly lower in the group of young normotensive men with a family history of essential hypertension than in the control group of age- and BMI-matched normotensive men with no family history of hypertension. Although it has been demonstrated that adiponectin level is significantly reduced in insulin-resistant first-degree relatives of type 2 diabetic subjects (*26*), this is the first report, to the best of our knowledge, on the relationship between adiponectin concentration and insulin sensitivity in relation to genetic predispositions for the development of essential hypertension.

Decreased adiponectin concentration and reduced insulin sensitivity might be early-penetrance phenotypes in the course of development of human genetic hypertension, because they are already present even in still-normotensive offspring of essential hypertensives. The early appearance of these phenotypes in still-normotensive FH+ subjects suggests that adiponectin concentration and insulin resistance play pathophysiological roles in the later response to high blood pressure.

Since obesity influences insulin sensitivity and adiponectin level (*5*, *15–17*), we enrolled non-obese subjects in the present study. In fact, there was no significant difference in BMI between the two groups. Therefore, the differences in ISIs and adiponectin concentrations between the two groups cannot be explained by a difference in the degree of obesity. Moreover, the subjects were selected so as to exclude the potentially confounding impact of other factors known to influence insulin sensitivity and adiponectin concentration, namely, family history of diabetes mellitus (*26*) and treatment with drugs such as thiazolidinedions (*28*, *29*) and renin-angiotensin system-blocking agents (*10*). Age-matching is also considered very important when comparing groups with positive and negative family histories of essential hypertension, since not only blood pressure but also insulin sensitivity is influenced by phenomena related to the aging process (*30*). The two groups in the present study were well matched for age, and the selected subjects were young (aged 18–32 years). In addition, there was no significant difference in blood pressure or the number of subjects with high-normal blood pressure between the two groups, although it has been reported that young men with high-normal blood pressure have lower serum adiponectin concentrations (*31*).

The precise mechanisms underlying reduced adiponectin levels in normotensive men with a family history of hypertension are unclear. It has been reported that insulin infusion during a glucose clamp study leads to a decrease in adiponectin concentration (*32*), suggesting that chronic hyperinsulinemia associated with an insulin-resistant state leads to a decrease in adiponectin concentration. The decrease in serum adiponectin level could be the result of impaired insulin sensitivity. However, the insulin level, but not ISI, in the FH+ group was not significantly higher than that in the FH− group in the present study as previously reported (*18*, *21–23*), although some previous studies showed significant fasting hyperinsulinemia in the offspring of hypertensive patients (*24*, *25*). Since the subjects in the present study were young, it is possible that insulin sensitivity evaluated by the euglycemic hyperinsulinemic glucose clamp method was decreased but that compensated hyperinsulinemia due to insulin resistance had not yet developed. Even at this time, adiponectin level had already decreased significantly. These findings support the idea that adiponectin primarily influences insulin sensitivity and that decreased insulin sensitivity results in compensated hyperinsulinemia.

Decreased adiponectin concentration may simply be an indicator of insulin resistance, as demonstrated by the direct association of adiponectin with ISI. Alternatively, the observation of decreased adiponectin level in still-normotensive individuals at genetic risk of hypertension is consistent with an early, perhaps pathogenic, role in the subsequent development of hypertension and may point to a logical target, in appropriately stratified patients, for early intervention in the pathogenesis of the disease.

One limitation of this study is the small number of subjects enrolled. Prospective studies using larger numbers of subjects are needed to determine whether adiponectin or a family history of hypertension is a major determinant in the subsequent development of hypertension. In addition, because we did not perform oral glucose tolerance tests in the present study, we could not investigate the presence and influence of impaired glucose tolerance in the subjects. Furthermore, it has been shown that adiponectin concentration is sex-related, being higher in females than in males (*8*, *33*). Although we enrolled only male subjects in the present study to adjust for confounding factors, it is important to confirm our findings by studies using female subjects.

In conclusion, our results showed that adiponectin level was significantly decreased and that this was accompanied by reduced insulin sensitivity in young, non-obese and normotensive men with a family history of hypertension. The reduction in insulin sensitivity coupled with a decrease in adiponectin concentration might precede the development of high blood pressure. Phenotype of reduced adiponectin level as an earlier penetrance may be especially useful in genetic analyses of insulin resistance and hypertension. Our findings might offer a new approach to identifying those at risk of hypertension in addition to novel metabolic strategies for early intervention.

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