Original article

Hypoadiponectinemia predicts impaired endothelium-independent vasodilation in newly diagnosed type 2 diabetic patients: an 8-year prospective study

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Keywords: type 2 diabetes; endothelium; vasodilation; adiponectin

Cardiovascular disease (CVD) is the leading cause of mortality in type 2 diabetes. It is therefore important to identify predictors of cardiovascular disease risk. Endothelial dysfunction, occurring early before any overt vascular disease, is demonstrated a surrogate marker for cardiovascular disease. Endothelial function is damaged by traditional risk factor “burden” including obesity, hypercholesterolemia, diabetes, insulin resistance, hypertension and ageing. The molecular basis for the link between metabolic “burden” and vascular endothelial dysfunction, however, remains poorly clarified.

Adiponectin, an adipocyte-specific plasma protein, plays a key role in the integration of metabolic, inflammatory responses and the subsequent atherosclerosis. Recent studies have demonstrated not only the association of hypoadiponectinemia with metabolic diseases such as obesity, diabetes, hypertension, and dyslipidemia, but also its correlation with major cardiovascular diseases including atherosclerosis and cardiac hypertrophy. In tissue cultures, adiponectin protects endothelial function from expression of adhesion molecules or the attachment of monocytes involved in early atherosclerotic events. Adiponectin also increases production of nitric oxide (NO) in endothelial cells, which plays a pivotal role in endothelium-mediated vasodilation. In animal studies, endothelial function is impaired in adiponectin knockout mice, whereas treatment with globular domain of adiponectin improves endothelial function by attenuation of oxidative/nitrative stress and differential regulation of endothelial nitric oxide synthase (eNOS)/inducible NOS (iNOS) activity in hyperlipidemic rats.

Adiponectin is an adipokine with insulin-sensitising and anti-atherogenic properties. The aim of this study was to investigate whether low adiponectin levels predict the impairment of endothelial function in newly diagnosed type 2 diabetic patients in an 8-year prospective study.

Methods In the prospective study, we enrolled 133 newly diagnosed type 2 diabetic patients without subclinical atherosclerosis and gave them intensive therapy; the mean treatment period was 8 years. Intensive treatment was a stepwise implementation of behavior modification and pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidaemia and obesity. We measured baseline circulating adiponectin with an enzyme-linked immunosorbent assay, endothelium-dependent and -independent vasodilation by high-resolution vascular ultrasound. At year 8, 102 patients were reexamined for endothelium-dependent and -independent vasodilation.

Results Sex-adjusted adiponectin level was positively correlated with endothelium-independent vasodilation both at baseline ($r=0.150, P=0.043$) and at year 8 ($r=0.339, P=0.001$), whereas no association was found between adiponectin and endothelium-dependent vasodilation. In a stepwise multivariate linear regression model, adiponectin was an independent predictor for impaired endothelium-independent vasodilation at year 8 ($P=0.001$).

Conclusions Plasma adiponectin concentration was associated with endothelium-independent vasodilation and hypoadiponectinemia predicted the impairment of endothelium-independent vasodilation in newly diagnosed type 2 diabetic patients under multifactorial intervention. These data support the causative link of impairment of endothelium-independent vasodilation with hypoadiponectinemia.


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In humans, a close correlation of hyoadiponecinemia with impaired endothelial function has been reported in patients with hypertension, type 2 diabetes mellitus and in healthy individuals. However, at present, there are no prospective data regarding this association in individuals with type 2 diabetes, in whom a complex array of metabolic abnormalities most likely contributes to the deteriorating endothelial function. The aim of this study was to investigate the predictive power of adiponectin for endothelial function in a cohort of 133 newly diagnosed type 2 diabetic patients under multifactorial intervention who had just completed their 8-year follow-up.

**METHODS**

**Patients**

One hundred and thirty-three newly diagnosed type 2 diabetic patients without subclinical atherosclerosis according to World Health Organization criteria were recruited from the Diabetes Clinics at the Second Xiangya Hospital and were given multifactorial interventions for 8 years, including intensive control of blood glucose, blood pressure (BP), blood lipids and body weight. At year 8, 31 patients withdrew (21 patients withdrew because of personal reasons, five patients for protocol violation, and five patients for side effects). One hundred and two patients were reexamined for endothelium-dependent and -independent vasodilation. Study exclusion criteria were body-mass index (BMI) ≥35 kg/m², overt macrovascular disease, elevated liver enzymes (alanineaminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥40 U/L), manifest chronic kidney disease (CKD; serum creatinine levels ≥115 µmol/L), or any other serious chronic or acute comorbidity requiring continuous pharmacological therapy or hospital treatment. Subjects were excluded if they were prescribed one or more of the following medications at enrollment: exogenous insulin, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), statins, thiazolidinedione, glucocorticoids, α- or β-adrenergic receptor agonists. All patients accepted intensive multifactorial intervention. Strict treatment goals were achieved through behavior modification and a stepwise introduction of pharmacologic therapy directed by doctors at the Diabetes Center, the Second Xiangya Hospital, Central South University. On average, the patients were offered individual consultations every three months during the eight-year follow-up. Clinical data were obtained from medical records. The study protocol was approved by the Institutional Review Board (IRB) of Second Xiangya Hospital, Central South University. All study subjects provided written informed consent.

Intervention methods were as follows: diabetic diet and light-to-moderate exercise were recommended. If patients were unable to maintain glycosylated hemoglobin values below 6.5% by means of diet and increased physical activity alone after three months, an oral hypoglycemic agent was started. As the initial step, overweight patients (defined as those with BMI above 25) received metformin (maximum, 1 g twice daily); lean patients, or overweight patients who had contraindications to metformin therapy, received glipizide (maximum, 10 mg three times daily). As the second step, metformin was added to the regimen of lean patients and glipizide to that of overweight patients if hyperglycemia was not controlled. If the glycated hemoglobin (HbA1c) value exceeded 7.0% despite maximal doses of oral agents, the addition of neutral protamine hagedorn (NPH) insulin at bedtime was recommended. The insulin dose was adjusted on the basis of the morning fasting blood glucose concentration. If there was no decrease in the HbA1c value, patients were switched to regimens in which premixed insulin was given twice a day.

Arterial hypertension was also treated with a stepwise approach. For patient with hypertension, an ACEI (captopril, with a maximum of 25 mg three times daily, or the equivalent) or, if such a drug was contraindicated, an angiotensin II-receptor antagonist (valsartan, with a maximum of 80 mg twice daily, or the equivalent) was given according to the BP level. If the BP was still abnormal, thiazides, calcium-channel blockers, and beta-blockers were added as needed. Isolated cases of hyperglycemia were treated with statins (simvastatin, with a maximum of 40 mg daily, or the equivalent). Fibrates were used for isolated cases of hypertriglycerideremia, or were added to statin treatment if the fasting serum triglyceride concentration was also elevated. Fifty milligram of aspirin per day was given as secondary prevention to all patients (unless there were contraindications).

**Assessments**

Patient informations, including age, gender, smoking history and medication history were recorded. The details of anthropometric measurements (height, weight, and BP) were assessed after overnight fasting for at least 10 hours. Subjects were fasted for at least 10 hours prior to blood collection, and blood routine, urine routine, serum concentrations of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose, ALT, creatinine, blood urea nitrogen (BUN) were determined using standard laboratory procedures. HbA1c was measured in whole blood using ion-exchange high-performance liquid chromatography with the Bio-Rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, Inc., USA). Insulin resistance was estimated using homeostasis model assessment index (HOMA-IR). Plasma adiponectin level was determined by an in-house sandwich enzyme-linked immunosorbent assay (ELISA) established in our laboratory (5%–6% intraassay and 6%–8% interassay coefficient of variation). Endothelium-dependent and endothelium-independent
vasodilation of the brachial artery was assessed by a 7.0 MHz linear array transducer and a standard 128XP/10 system (Acuson, Mountain View, USA). In brief, diameter measurements of the right brachial artery were taken at rest and during reactive hyperemia after occlusion by inflation of a pneumatic tourniquet to a pressure of 300 mmHg for 4.5 minutes. Twenty minutes were allowed for vessel recovery, and a resting scan was repeated. Sublingual glyceryl trinitrate (500 µg) was then administered and diameter measurement was taken after 5 minutes. Endothelium-dependent and endothelium-independent vasodilation was calculated as the percentage change in diameter compared with baseline.

The diameter of the target artery was measured as well. Subclinical atherosclerosis was defined as intima-media thickness (IMT) >1.0 mm and/or with plaque on each of common carotid artery, femoral artery and common iliac artery but without clinical manifestations.

Statistical analysis
Results are presented as mean±standard deviation (SD) or median with interquartile range as appropriate. Data that were not normally distributed, as determined with the Kolmogorov-Smirnov test, were logistically transformed to obtain near normality before analysis. Adiponectin levels were adjusted for sex in all analyses because of the higher levels in women.26 Comparisons between two different groups were done using independent sample Student’s t test. One-way analysis of variance (ANOVA) analysis (LSD test) was used for comparison of multiple groups. Pearson’s correlations were used to test the relationship between variables. Baseline adiponectin levels of the entire cohort with 8-year follow-up data of endothelium-independent vasodilation (n=102) were grouped into tertiles. Stepwise linear regression analysis was used to examine the association of baseline adiponectin and other parameters with endothelium-independent vasodilation at baseline and at year 8 respectively. Two-sided values of P <0.05 were considered significant. All analyses were performed using SPSS16.0 (SPSS Inc., USA).

RESULTS
Baseline characteristics
The baseline demographic and clinical characteristics of the cohort are shown in Table 1. There are significant differences between male and female subjects in Waist/hip ratio (WHR), TG, HDL-C, systolic BP, endothelium-dependent vasodilation, endothelium-independent vasodilation and adiponectin. Consistent with previous studies, plasma adiponectin concentrations, endothelium-dependent and -independent vasodilation in female subjects were higher than that in male subjects (P <0.001, P=0.004, P=0.002, respectively). No significant differences were found in other demographic and biochemical characteristics between male and female subjects.

As shown in Table 2, endothelium-independent vasodilation in tertile 1 was worse than that in tertile 3 both at baseline and at year 8 (P=0.013, P=0.037, respectively). Subjects with rising tertiles of baseline adiponectin had a trend of progressively better endothelium-independent vasodilation at baseline and at year 8.

Table 1. Demographic and clinical characteristics at baseline according to gender

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>133</td>
<td>73</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.4±8.6</td>
<td>52.9±9.6</td>
<td>54.0±6.8</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2±2.5</td>
<td>24.4±2.5</td>
<td>23.8±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
<td>0.8±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4±2.3</td>
<td>7.6±2.0</td>
<td>7.2±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.3±1.1</td>
<td>5.2±1.3</td>
<td>5.3±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.7 (1.2–2.6)</td>
<td>1.5 (1.2–2.2)</td>
<td>2.2 (1.3–3.8)</td>
<td>0.035</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.3±0.3</td>
<td>1.2±0.2</td>
<td>1.4±0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.0±1.0</td>
<td>2.9±1.1</td>
<td>3.0±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.9 (2.6–5.6)</td>
<td>3.8 (2.6–5.5)</td>
<td>4.1 (2.7–5.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>118.0±17.0</td>
<td>117±15.5</td>
<td>119.0±18.9</td>
<td>0.049</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76.5±10.2</td>
<td>77.4±9.7</td>
<td>75.7±10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>7.2±3.0</td>
<td>5.8±1.3</td>
<td>9.5±2.3</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Table 2. Demographic and clinical characteristics at baseline by tertile of adiponectin

As shown in Table 2, endothelium-independent vasodilation in tertile 1 was worse than that in tertile 3 both at baseline and at year 8.

Relation of endothelium-independent vasodilation with plasma adiponectin at baseline
Sex-adjusted associations of adiponectin with endothelium-dependent vasodilation, endothelium-independent vasodilation and other clinical characteristics at baseline were analyzed (Table 3). Adiponectin level was positively related to age (r=0.197, P=0.049), HDL-C (r=0.206, P=0.040) and inversely related to WHR (r=-0.259, P=0.009), TG (r=-0.212, P=0.036) and HOMA-IR (r=-0.199, P=0.047). Adiponectin was positively associated with endothelium-independent vasodilation at baseline (r=0.150, P=0.043), but no correlation was found between adiponectin and endothelium-dependent vasodilation. Then according to gender we further investigated the correlation of adiponectin with clinical characteristics at baseline. In male subjects, the concentration of adiponectin was positively associated with endothelium-independent vasodilation (r=0.28, P=0.03) and age (r=0.27, P=0.04), and negatively associated with BMI (r=-0.258, P=0.049) and TC (r=-0.304, P=0.023). In female subjects, no associations were found between adiponectin and
Table 3. The correlation of adiponectin with clinical characteristics at baseline of the cohort according to gender

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P value</td>
<td>r</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.197</td>
<td>0.049</td>
<td>0.270</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.121</td>
<td>0.231</td>
<td>-0.258</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>-0.259</td>
<td>0.060</td>
<td>-0.230</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.130</td>
<td>0.198</td>
<td>-0.250</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>-0.141</td>
<td>0.443</td>
<td>-0.304</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>-0.212</td>
<td>0.036</td>
<td>0.044</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.206</td>
<td>0.040</td>
<td>0.120</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>0.193</td>
<td>0.297</td>
<td>0.199</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>0.010</td>
<td>0.924</td>
<td>0.014</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>-0.096</td>
<td>0.344</td>
<td>-0.111</td>
</tr>
<tr>
<td>Endothelium-dependent vasodilation</td>
<td>0.158</td>
<td>0.116</td>
<td>0.160</td>
</tr>
<tr>
<td>Endothelium-independent vasodilation</td>
<td>0.150</td>
<td>0.043</td>
<td>0.280</td>
</tr>
<tr>
<td>HOMA-IR¹</td>
<td>-0.199</td>
<td>0.047</td>
<td>-0.131</td>
</tr>
</tbody>
</table>

BMI: body mass index. Hba1c: hemoglobin A1c. TC: total cholesterol. TG: triglycerides. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. HOMA-IR: homeostasis model assessment index. Values are presented as mean±SD or median (interquartile range). ¹Log transformed before analysis.

endothelium vasodilation function. The concentration of adiponectin was negatively associated with WHR ($r=-0.306$, $P<0.001$).

To find the important determinants of endothelial function, we set up a general linear model. Adiponectin and gender was independent variables associated with endothelium-independent vasodilation in our linear regression model including age, gender, BMI, systolic BP, Hba1c, HOMA-IR, TC, TG, HDL-C, LDL-C at baseline ($P=0.041$, $P=0.037$, respectively). In male patients, adiponectin was the only independent variable associated with endothelium-independent vasodilation in our linear regression model including age, BMI, systolic BP, Hba1c, HOMA-IR, TC, TG, HDL-C, LDL-C at baseline ($P=0.033$).

Adiponectin predicts endothelium-independent vasodilation at year 8

Sex-adjusted adiponectin level was positively correlated to endothelium-independent vasodilation at year 8 ($r=0.339$, $P=0.001$), whereas no association was found between adiponectin and endothelium-dependent vasodilation. On linear regression model including age, gender, BMI, Hba1c, HOMA-IR, TC, TG, HDL-C, LDL-C and adiponectin, adiponectin, gender and age was independent predictors for impaired endothelium-independent vasodilation at year 8 ($P<0.001$, $P<0.001$, $P=0.001$, respectively).

DISCUSSION

The major finding in this study is that low plasma adiponectin levels predict impaired endothelium-independent vasodilation in a prospective cohort with 133 newly diagnosed type 2 diabetic patients who were followed up and given intensive intervention for 8 years. Our study provided novel information to the concept of adiponectin being a protective factor of vascular function and indicated that adiponectin might be used to identify populations at risk for targeted therapy as well as to monitor the effects of interventions. The results in the present study are consistent with adiponectin playing a direct antiatherogenic role in cardiovascular disease, in part, by improving endothelial function.⁴⁻⁸

The protective effects of adiponectin on endothelial function in both mice and human have been well demonstrated. In adiponectin-knockout (KO) mice, neointimal thickening and increased proliferation of vascular smooth muscle cells were observed compared with wild-type mice in response to external vascular cuff injury, and adenosine-mediating re-expression of adiponectin attenuates neointimal proliferation in adiponectin KO mice.⁶ Consistently, treatment with adiponectin-expressing adenoviruses decreased 30% of lesion formation in apolipo-proteinE (apoE)-deficient mice which develop early atherosclerosis as compared to control mice expressing β-galactosidase.⁶ In line with these results, in cross-sectional studies, adiponectin has been demonstrated associated with endothelial dysfunction in patients with hypertension, type 2 diabetes mellitus, healthy young men.¹⁷²⁴ Our findings are consistent with previous studies in human and animals. However, the evidences in the association of adiponection with endothelium vasodilation are inconsistent. Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation rather than endothelium-independent vasodilation in type 2 diabetic patients.²⁴ In apparently healthy humans and obese children, serum adiponectin concentration is demonstrated significantly associated with endothelium-independent vasodilation, but not with endothelium-dependent vasodilation.¹⁸²⁶ In the present study, we found that adiponectin was associated with endothelium-independent vasodilation rather than endothelium-dependent vasodilation in newly diagnosed type 2 diabetic patients without subclinical atherosclerosis. One potential explanation for this is that the association between adiponectin and endothelium-independent vasodilation may vary with age, duration of diabetes and additional cardiovascular risk factors. Consistent with previous studies,¹⁸²⁶ we also found that plasma adiponectin concentrations, endothelium-dependent and -independent vasodilation in female subjects were higher than that in male subjects. Besides that, adiponectin associations with endothelium-independent vasodilation were also affected by gender. In male group, but not in female group, we found association of sex-adjusted adiponectin with endothelium-independent vasodilation, and this different sex distribution may be due to lower adiponectin and lower endothelium-independent vasodilation in male than in female.

Nitroglycerin (NTG) is an exogenous NO donor. NTG-induced endothelium-independent vasodilation can
reflect vascular smooth muscle function, which is independent of impaired endothelium-dependent vasodilation.16 Dilation induced by NTG is mediated by smooth muscle cell, of which migration and proliferation are important components of atherosclerosis. The underlying mechanism of link between adiponectin and endothelium-independent vasodilatation remains unknown. We postulated several possible mechanisms. Firstly, adiponectin may affect endothelium-independent vasodilatation via direct effect on vascular wall. Circulating adiponectin accumulates in the sub-endothelial space of injured vascular wall containing smooth muscle cells and may inhibit proliferation and migration of smooth muscle cells in the development and progression of vascular lesions.7 Deletion of adiponectin gene in mice cause thickened neointimal and increased proliferation of vascular smooth muscle cells, which can be reversed via adenovirus-mediated adiponectin expression.27 In addition, adiponectin binds various growth factors including platelet-derived growth factor BB, basic fibroblast growth factor, and heparin-binding epidermal growth factor-like growth factor, and activates receptor-mediated cellular responses to inhibit vascular smooth muscle cell (VSMC) proliferation.28 Secondly, hypoadiponectinemia may cause impaired endothelium-independent vasodilation by its regulation on insulin resistance. Insulin has a number of biological vascular actions, and may lose its ability to maintain VSMC quiescence and instead promote VSMC migration in insulin resistance status.30 Changes in insulin resistance signaling lead to a decrease in p27Kip1, accelerating VSMC proliferation and migration.31 The insulin-sensitizing effects of adiponectin have been well demonstrated. Plasma adiponectin levels were decreased in KKAY mice (KK mice overexpressing the agouti protein) fed a high-fat diet, and its supplement can significantly improve high-fat diet-induced insulin resistance.4 In human studies, plasma adiponectin levels have been found correlated inversely with insulin resistance and a variety of insulin resistance-related states such as metabolic syndrome, hypertension, cardiovascular disease.17,24

In the present study, adiponectin was positively related to age, HDL-C and inversely related to WHR, TG and HOMA-IR in type 2 diabetic patients without subclinical atherosclerosis. These data suggest adiponectin was extensively involved in modulation of metabolic states. These results were consistent with previous studies that adiponectin had insulin-sensitizing effect and regulated lipid metabolism.4

One limitation of the present study is the relatively small number of subjects enrolled in our study. In addition, the power of evaluating predictive ability of adiponectin in endothelium-dependent vasodilatation will be more convincing if confirmed in a larger cohort or in other ethnic populations with different genetic and environmental backgrounds. Another limitation is that we only measured total adiponectin instead of high and lower molecular weight isomers although total adiponectin has been confirmed to be closely correlated to high molecule adiponectin and demonstrated a sensitive biomarker of CVD.

In conclusion, hypoadiponectinemia predicts the impairment of endothelium-independent vasodilation in a cohort of newly diagnosed type 2 diabetic patients in Chinese. These data support the causative link of endothelial dysfunction with hypoadiponectinemia and further confirmed the predictive value of adiponectin for cardiovascular diseases.

REFERENCES


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