CLINICAL STUDY

Adiponectin and the development of diabetes in patients with coronary artery disease and impaired fasting glucose

Hilla Knobler, Michal Benderly1, Valentina Boyko1, Shlomo Behar1, Zipora Matas2, Ardon Rubinstein3, Itamar Raz4 and Julio Wainstein5

Metabolic Unit, Kaplan Medical Center, Rehovot, Israel, 1 BIP Study Group Coordinating Center, Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Tel-Aviv, Israel, 2 Biochemistry Laboratory, Wolfson Medical Center, Holon, Israel, 3 Metabolic Institute, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, 4 Israel Diabetes Center, Hadassah Medical Center, Jerusalem, Israel and 5 Diabetes Center, Wolfson Medical Center, Holon, Israel

(Correspondence should be addressed to H Knobler; Email: knobler@inter.net.il)

Abstract

Objectives: Adiponectin has insulin-sensitizing properties, and high adiponectin levels have been shown to be associated with reduced risk of developing diabetes. Patients with coronary artery disease (CAD) have relatively low adiponectin levels and high prevalence of glucose intolerance. The role of adiponectin in predicting the development of diabetes in this high-risk group has not been determined. The study aimed to determine whether baseline adiponectin levels predict the development of diabetes in a group of patients with CAD and impaired fasting glucose (IFG).

Methods: A total of 588 patients who participated in the Bezafibrate Infarction Prevention (BIP) study and who had at baseline fasting glucose of 100–125 mg/dl were included and followed for 6.2±1.3 years. Adiponectin was determined in frozen plasma samples taken at baseline.

Results: Of the patients with IFG at baseline, 256 (44%) developed diabetes during follow-up. The patients who developed diabetes had at baseline higher body-mass index, fasting glucose, C-reactive protein, triglycerides, homeostatic assessment of insulin resistance (HOMA-IR) and diastolic blood pressure than patients who did not develop diabetes. Adiponectin levels at baseline were significantly lower in patients who developed diabetes than in patients who did not develop diabetes (P=0.009, nonparametric Kruskall–Wallis test). An increase of 1 unit of natural logarithm of adiponectin level was associated with a hazard ratio of 0.77 (95% CI, 0.61–0.96) for diabetes development.

Conclusion: Patients with CAD and IFG have a very high rate of conversion to type 2 diabetes. Even in this high-risk group, high adiponectin levels are associated with reduced risk of developing diabetes.

European Journal of Endocrinology 154 87–92

Introduction

Patients with known coronary artery disease (CAD) have a high prevalence of undiagnosed diabetes mellitus (DM) and glucose intolerance (1–3). In previous study based on data from the Bezafibrate Infarction Prevention (BIP) study, a secondary prevention trial, 20% of the patients had fasting glucose levels of ≥110 mg/dl (4). These patients were characterized by a higher body-mass index (BMI) and fasting glucose levels, by a lipid profile typical of the metabolic syndrome and by a worse clinical outcome. Impaired fasting glucose (IFG) is a ‘prediabetes’ state with a high rate of conversion to type 2 DM (5). Recent epidemiologic data have shown that low levels of adiponectin, a cytokine exclusively synthesized in adipose tissue, were associated with higher risk of subsequently developing type 2 DM (6–8). The adiponectin gene is located on chromosome 3q27, where a susceptibility locus for diabetes and the metabolic syndrome has been mapped (9). Although the physiologic role of adiponectin is yet to be fully elucidated, numerous animal studies in recent years have shown that adiponectin increases insulin sensitivity (10–13). Adiponectin was shown to decrease hepatic glucose output and to enhance muscle fat oxidation and glucose transport. In man, adiponectin levels were shown to correlate negatively with BMI, C-reactive protein (CRP), and fasting level of glucose, insulin and triglycerides, and to correlate positively with high-density lipoprotein cholesterol (HDL-C) (10, 14, 15). Adiponectin levels are also significantly lower in patients with CAD than in control subjects (16), and adiponectin levels are inversely correlated with progression of coronary artery calcification in diabetic and nondiabetic patients (17). The antiatherogenic effects of adiponectin have been attributed partly to its anti-inflammatory properties (12). The low levels of adiponectin observed in
CAD patients may be linked to the high prevalence of glucose intolerance and increased risk of developing type 2 diabetes. Moreover, adiponectin insulin-sensitizing actions may be altered in CAD patients, many with proinflammatory state, a known risk factor also for type 2 DM development. The role of adiponectin in regulating glucose homeostasis in this high-risk group has not been determined. The aim of the current study was to assess in a group of CAD patients who participated in the BIP study, with IFG at baseline, whether adiponectin levels predict the development of subsequent type 2 DM.

Subjects and methods

Subjects and design

The BIP study, a secondary prevention, prospective, double-blind study comparing bezafibrate (400 mg daily) to placebo in patients with established CAD, was conducted in 18 cardiology departments in Israel. The BIP study design and results were previously described (18). Inclusion criteria included age of 45–74 years, history of myocardial infarction of 6 months to 5 years before enrollment, and/or stable angina pectoris confirmed by coronary angiography and/or radionuclear studies or standard exercise tests. A total of 3122 patients were included and followed for 6.2±1.3 years, with routine visits to the clinics, including blood testing for fasting glucose and lipid levels, every 4 months. Patients were diagnosed as having IFG when they had on two occasions during the pre-randomization period, fasting baseline glucose levels of 100–125 mg/dl (19), had no prior diagnosis of DM or were not receiving DM treatment. During follow-up, patients who had fasting blood glucose of >126 mg/dl on two occasions, or who started to receive DM treatment were diagnosed as having DM. A total of 617 patients were diagnosed with IFG by these criteria. In 29 patients (12 in the group who later developed DM and 17 in the group who did not develop DM), no plasma samples were available for adiponectin measurements. Thus, 588 patients (95%) were included in the final analysis.

Laboratory methods

Detailed data on laboratory methods were given in a previous report (18). Briefly, blood samples collected in the 18 participating centers were transported in cooled containers to a central laboratory. Blood samples were drawn after at least 12 h of fasting. Laboratory measurements of lipid, glucose and fibrinogen levels were made by standard automated procedures with commercially available kits (Roche). Fasting glucose levels were determined in baseline samples by the GOD-PAP method with a BM/Hitachi 717/911 analyzer. For the purpose of this study, plasma samples that had been taken at baseline and stored as frozen aliquots at −70°C were thawed and assayed for insulin and high-sensitive CRP with the Immulite 2000 analyzer (Diagnostics Products Corporation, Los Angeles, CA, USA). We used the manufacturer’s solid-phase chemiluminescent immunometric assay. Adiponectin in frozen baseline plasma aliquots was determined by commercial sandwich enzyme immunoassay (R&D Systems, Minneapolis, MN, USA). The following formula was used: homeostatic assessment of insulin resistance (HOMA-IR) = fasting insulin (U/l) × fasting glucose (mmol/l)/22.5.

Statistical analysis

Data were analyzed with SAS software, Version 8.2 (SAS Institute, Cary, NC, USA). Comparisons of dichotomous variables and normally distributed continuous variables were done by the chi-square test and Student’s t-test respectively. Geometric means were used for triglycerides, insulin, CRP and adiponectin to correct for their skewed distribution. Non-normally distributed variables were compared by the nonparametric Kruskal–Wallis test, and they were log transformed for further analysis. Spearman’s rank correlation coefficients were computed for the association between adiponectin levels and other clinical variables. In the correlation analysis, patients were stratified according to BMI of <30 kg/m² or ≥30 kg/m², on the basis of previous data showing that the relationship of adiponectin with other clinical variables is influenced by the coexistence of obesity (20). Age and multivariable adjusted hazard of developing diabetes were computed with the Cox proportional hazard model to account for differences in length of follow-up and correlation of covariates. The variables included in the analysis were chosen from previous data (10); they included age, adiponectin (log-transformed), BMI, glucose, HDL-C, triglycerides (log-transformed), HOMA-IR, CRP (log-transformed), and systolic and diastolic blood pressure. The variables were introduced into the models as continuous variables. Model performance was assessed with C-statistics, the area under the receiving operating curve.

Results

Of patients participating in the BIP study, 617 were found to have IFG, and 588 of them were included in the study. During the mean follow-up time of 6.2 years, DM developed in 256 (44%) of the patients included, while 332 (46%) remained without diabetes. The baseline characteristics of the patients who developed or did not develop DM are presented in Table 1. Patients who developed DM had higher BMI, higher fasting glucose levels and higher HOMA-IR than patients who did not develop DM. Patients who...
developed DM had significantly higher diastolic blood pressure than patients who did not develop DM and there was a borderline significant difference in systolic blood pressure between the groups. Triglycerides and total cholesterol levels were significantly higher in patients who developed DM than in patients who did not develop DM, but the differences in HDL-C and low-density lipoprotein cholesterol (LDL-C) levels were not statistically significant. Patients who developed DM also had significantly higher fibrinogen, white blood cell and CRP levels than patients who did not develop DM. Adiponectin levels were significantly lower at baseline in patients that developed DM: 4.1 (3.9–4.4) mg/l vs 4.6 (4.3–4.9) mg/l in the group that did not develop DM (P = 0.009). There were no significant differences between the groups in the following: previous history of myocardial infarction (78.5% vs 80.4%), peripheral artery disease (4.3% vs 3.3%) and smoking at entry (10.5% vs 8.4%). The usage of the following medications was similar in the two groups: beta blockers (41.8% vs 48.8%), angiotensin-converting enzyme inhibitors (12.9% vs 15.1%), antiplatelet aggregation agents (70.7% vs 70.5%), calcium antagonists (50.4% vs 53.0%), nitrates (52.7% vs 47.9%), diuretics (16.8% vs 17.8%) and bezafibrate (50.4% vs 52.7%). No difference in medication usage was statistically significant.

In a correlation analysis, adiponectin was positively associated with HDL-C and negatively associated with triglyceride levels (Table 2). There was also a significant but relatively weak negative correlation between adiponectin and measures of insulin sensitivity— that is, insulin and HOMA-IR. Interestingly, when we stratified patients by BMI (20), the correlation of adiponectin with insulin sensitivity was strengthened in the obese group and was no longer present in the nonobese group.

### Risk of subsequent DM according to baseline adiponectin quintiles

Figure 1 shows the association of baseline adiponectin quintiles with DM development. As shown, age-adjusted increasing baseline concentration of

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**Table 1** Clinical characteristics of patients with IFG at baseline who subsequently developed or did not develop DM.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Developed DM (n = 256)</th>
<th>Did not develop DM (n = 332)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.4±6.1</td>
<td>61.3±6.5</td>
<td>0.096</td>
</tr>
<tr>
<td>Male (%)</td>
<td>92.2</td>
<td>92.8</td>
<td>0.789</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3±3.6</td>
<td>26.7±3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>115.8±11.1</td>
<td>109.1±7.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>1.5 (0.9–2.4)</td>
<td>1.3 (0.8–2.0)</td>
<td>0.012</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83.2±9.3</td>
<td>81.2±8.6</td>
<td>0.006</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136.1±18.3</td>
<td>133.6±16.7</td>
<td>0.086</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>150.5 (144.1–157.3)</td>
<td>136.0 (131–141.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>214.5±18.3</td>
<td>211.1±17.0</td>
<td>0.023</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>33.6±5.3</td>
<td>34.4±5.6</td>
<td>0.094</td>
</tr>
<tr>
<td>WBC (10³/µl)*</td>
<td>7.3±3.0</td>
<td>6.9±1.55</td>
<td>0.045</td>
</tr>
<tr>
<td>CRP (mg/l)*</td>
<td>4.4 (3.9–4.9)</td>
<td>3.2 (2.9–3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adiponectin (mg/l)*</td>
<td>4.1 (3.9–4.4)</td>
<td>4.6 (4.3–4.9)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* Geometric mean (95% confidence interval). BMI, body-mass index; HOMA-IR, homeostatic assessment of insulin resistance; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell count; CRP, C-reactive protein.

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**Table 2** Pearson correlations between baseline adiponectin levels and baseline clinical parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 588)</th>
<th>P</th>
<th>BMI &lt;30 kg/m² (n = 481)</th>
<th>P</th>
<th>BMI &gt;30 kg/m² (n = 107)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.13</td>
<td>0.002</td>
<td>0.14</td>
<td>0.002</td>
<td>0.03</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.09</td>
<td>0.02</td>
<td>-0.09</td>
<td>0.09</td>
<td>-0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>0.29</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.24</td>
<td>&lt;0.001</td>
<td>-0.25</td>
<td>&lt;0.001</td>
<td>-0.17</td>
<td>0.07</td>
</tr>
<tr>
<td>Insulin</td>
<td>-0.09</td>
<td>0.02</td>
<td>-0.04</td>
<td>0.33</td>
<td>-0.29</td>
<td>0.002</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.09</td>
<td>0.03</td>
<td>-0.04</td>
<td>0.36</td>
<td>-0.30</td>
<td>0.002</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.05</td>
<td>0.30</td>
<td>-0.04</td>
<td>0.35</td>
<td>-0.04</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Triglycerides, insulin, HOMA-IR, CRP were log transformed. BMI, body-mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic assessment of insulin resistance; CRP, C-reactive protein.
adiponectin was associated with lower risk of subsequent type 2 DM. Patients in the highest quintile of adiponectin levels, compared with patients in the lowest quintile, had a hazard ratio (HR) of 0.65 (95% CI, 0.43–0.98). Increase of one unit (adiponectin quintile as an ordinal variable) was associated with $P = 0.02$, indicating a linear trend.

With adjustment for age, an increase of 1 unit of natural logarithm of adiponectin level was associated with reduced risk of developing DM, with HR of 0.77 (95% CI, 0.61–0.96). We tested several multivariate models for the association between diabetes development and baseline clinical variables (listed in Subjects and methods). The models that had the best performance, assessed by the goodness of fit (C-statistics), are presented in Table 3. After further adjustment for other variables, higher adiponectin levels were still associated with reduced risk to develop DM, but the statistical significance of the association was attenuated (Table 3). As can be seen in model 1, which included BMI and fasting glucose, higher adiponectin level was associated with HR of 0.83 (95% CI 0.65–1.05), and the C-statistic of the model was 0.696. In model 2, which included also CRP, triglycerides, HDL-C and HOMA-IR, higher adiponectin level was associated with HR of 0.84 (95% CI 0.65–1.08), and the C-statistic was similar to the previous model. As fasting glucose was an independent, strong predictor for developing DM in these two models, we performed model 3, which did not include fasting glucose. In this model, higher adiponectin level was associated with HR of 0.82 (95% CI 0.64–1.01), and CRP were found to be an independent predictor of DM development, but the C-statistic of this model was reduced to 0.623. The HR associated with adiponectin when both glucose and triglycerides were removed from the model was 0.79 (95% CI 0.62–1.01) with C-statistic of 0.620.

### Discussion

Previous data from the BIP study and other studies have demonstrated that patients with coronary heart disease have a high prevalence of diabetes and abnormal fasting glucose levels (1–4). In the present study, 44% of the patients diagnosed with IFG by the newer American Diabetes Association (ADA) criteria (19) subsequently developed DM during 6.2 years of follow-up. These data agree with the high conversion rate of IFG to diabetes reported by the Diabetes Prevention Program study (5). In this study, 3234 nondiabetic persons with elevated fasting and post-load plasma glucose levels were followed for 2.8 years, and the incidence of type 2 DM was 11 per 100 person-years in the control group. The high conversion rate observed in the current study suggests that patients with known coronary heart disease and IFG represent a very high-risk group for developing type 2 DM. High fasting glucose, triglycerides, CRP and BMI, were all independent risk factors for diabetes development, and these findings confirm previous studies (4, 5, 21, 22).

The most important finding of this study was that in patients with CAD and IFG, adiponectin levels inversely correlate with the risk of developing type 2 DM during a 6.2-year follow-up period. Patients in the highest quintile of adiponectin levels, compared with patients in the lowest quintile, had HR of 0.65 (95% CI, 0.43–0.98). These data suggest that even in this group of patients, who are especially prone to develop DM, adiponectin still has a protective effect of decreasing the high conversion rate to type 2 DM.

Our data as well as previous data show that low adiponectin levels are associated with features of the metabolic syndrome, a known prediabetes state (23).
Adiponectin levels inversely correlated with triglycerides and positively with HDL-C, and in the obese group, they correlated with insulin resistance as determined by fasting insulin and HOMA-IR. Correlation studies do not distinguish cause-and-effect relationships; however several studies in rodent models support the hypothesis that adiponectin has direct insulin-sensitizing properties (10–13). Adiponectin administration was found to increase insulin sensitivity and lower circulating levels of glucose, free fatty acids and triglycerides. Adiponectin decreases hepatic glucose output and enhances muscle fat oxidation and glucose transport; these effects are mediated by activation of AMP-activated protein kinase (AMPK) (12, 13). Furthermore, in a longitudinal study in man, low adiponectin level at baseline preceded a decrease in insulin sensitivity (24).

The negative association of adiponectin levels and risk of developing type 2 DM was shown previously in several populations (6–8). In a study of 91 Asian Indians with impaired glucose tolerance (IGT), low adiponectin level was an independent predictor of diabetes development in 1-year follow-up (25). In addition, polymorphism of the adiponectin gene predicted the conversion from IGT to type 2 diabetes in the STOP-NIDDM trial (26). These previous studies did not focus on patients with CAD. Our results not only confirm these findings but also extend them to CAD patients, a population known to have significantly lower adiponectin levels than subjects without CAD (16, 27). Mean and median adiponectin levels in our study group were lower than reported in previous studies (6–8, 10), but similar to the levels reported in a recent study of patients with acute myocardial infarction, many of whom were found to have IFG and previously undiagnosed DM (3). The low range of adiponectin levels in our study may also explain the relatively moderate magnitude of the association between adiponectin and DM development. The possibility that, in this low range, the direct role of adiponectin in improving insulin sensitivity is attenuated needs to be evaluated by further studies. In addition, recent data suggest that measuring total adiponectin levels, as performed in this study and most other clinical studies, does not provide data on adiponectin complexes, and that examining the low-molecular-weight and high-molecular-weight forms may provide better correlation between adiponectin and insulin sensitivity (12, 13).

In conclusion, in a group of patients with CAD and IFG at baseline, 44% developed type 2 DM during 6.2 years of follow-up. Patients who developed DM had higher BMI, fasting glucose triglyceride and CRP levels and lower adiponectin levels than patients who did not develop DM. Higher adiponectin levels were associated with a significantly reduced risk of DM development. These data suggest that even in this very high-risk group with relatively low adiponectin levels, higher adiponectin levels are still associated with reduced risk of type 2 DM development.

References


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