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Low serum adiponectin level as a predictor of impaired glucose regulation and type 2 diabetes mellitus in a middle-aged Finnish population

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Abstract

Low levels of adiponectin are associated with obesity and type 2 diabetes mellitus (DM2). However, only few studies on this topic have used the most recent World Health Organization 1999 criteria, which include a definition of impaired glucose regulation (IGR). Our objective was to find out if a baseline low adiponectin level in initially normoglycemic subjects predicted IGR or DM2 during a mean follow-up period of 5.1 years. A population-based cohort study was carried out in Oulu, Northern Finland. Subjects born in 1935 and living in Oulu in 1990 were invited to participate in a follow-up study. At baseline, oral glucose tolerance tests and measurements of adiponectin, lipids, blood pressure, and body mass index were performed; and oral glucose tolerance tests were repeated at follow-up. Analyses were performed for 201 subjects who were normoglycemic at baseline. *Low adiponectin level* was defined as the lowest quartile of adiponectin levels. During the follow-up, 47 (23%) of the 201 subjects developed IGR or DM2. Impaired glucose regulation or DM2 developed in 15 of 41 (37%) subjects with low adiponectin level at baseline, whereas the corresponding proportion was 32 of 160 (20%) subjects with higher adiponectin levels (P = .025). In logistic regression analysis, the adjusted odds ratio for IGR or DM2 was 2.1 (95% confidence interval, 1.0-4.5) when adjustment was made for sex and body mass index. Low concentrations of adiponectin predicted subsequent development of IGR and DM2 in initially normoglycemic middle-aged Finnish subjects. Our findings support the hypothesis that adiponectin may play a role in the pathogenesis of abnormal glucose metabolism.

1. Introduction

Adiponectin is a hormone produced by adipocytes [1]; and it has been suggested to have antidiabetic, anti-inflammatory, and antiatherogenic effects [2,3]. Adiponectin levels are regulated by genetic and environmental factors [2,4,5]. The mechanism of the adiponectin effect is unclear, but some animal studies have suggested that adiponectin modulates glucose metabolism by having insulin-sensitizing effects [6,7].

In humans, several cross-sectional studies have shown that low adiponectin levels are associated with obesity and type 2 diabetes mellitus (DM2) [8-13]. There are reports showing that low adiponectin levels predict the development of DM2 in various ethnic groups [14-20]. So far, however, prospective studies among white populations are scarce [21-26]. Furthermore, in these studies, the diagnosis of diabetes has been based on self-report [21,23,26] or older definitions [22]. Only 2 studies have used the most recent World Health Organization (WHO) 1999 criteria [27], which also defined impaired glucose regulation (IGR) [24,25].

To further clarify whether a baseline low adiponectin level predicts IGR and DM2, as defined in the most recent WHO 1999 criteria [27], we analyzed our prospective population data.

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2. Subjects and methods

2.1. Subjects and clinical measurements

In 1990-1992, a population-based survey [28] was carried out in northern Finland; and a follow-up survey was performed in 1996-1998 [29]. The original study population consisted of the 1008 persons born in 1935 and living in the city of Oulu on October 1, 1990. Eight hundred thirty-one persons (369 men) attended the first phase. A standardized 75-g oral glucose tolerance test was performed according to the instructions of the WHO Study Group [30,31]. A venous blood sample was taken to measure fasting blood glucose (FBG), and a capillary blood sample was taken to determine postload blood glucose 2 hours after loading. According to the most recent WHO criteria [27], *diabetes* is defined as FBG ≥6.1 mmol/L or 2-hour blood glucose ≥11.1 mmol/L. *Impaired glucose tolerance* is defined as FBG <6.1 mmol/L and 2-hour blood glucose of 7.8 to 11.0 mmol/L. *Impaired fasting glucose* is defined as FBG of 5.6 to 6.0 mmol/L and 2-hour blood glucose ≤7.7 mmol/L. *Normoglycemia* is defined as FBG ≤5.5 mmol/L and 2-hour blood glucose ≤7.7 mmol/L. Seven hundred sixty-eight persons could be classified according to glucose status. Four hundred fifty-one of them (181 men) were normoglycemic according to the most recent WHO 1999 criteria [27], and they constituted the study population. Of these 451 subjects, 350 (78%; 132 men) participated in the second phase. In addition to the oral glucose tolerance tests, blood samples for measurements of adiponectin, cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were collected at both phases of the study. After collection, the blood samples were kept on ice and centrifuged within 1 hour without using anticoagulant; and the serum samples were stored at −74°C until the present adiponectin measurements in 2007.

Measurements of blood pressure, height, and weight were included in the clinical examination. Four measurements of blood pressure were made by the physician, using both upper limbs in sitting and recumbent positions. The mean value of these 4 measurements was used in the analyses. Height and weight in light clothing were measured in the clinical examination, and the body mass index (BMI; in kilograms per square meter) was calculated.

The serum adiponectin concentrations were measured with an enzyme-linked immunosorbent assay using a monoclonal anti–human adiponectin antibody (2 μg/mL) as a capture antibody and biotinylated monoclonal anti–human adiponectin antibody (2 μg/mL) as a detection antibody (R&D Systems, catalog MAB10651 and BAM1065, respectively). Biotin-labeled antibody was detected using 1:18 000 diluted alkaline phosphatase–labeled NeutrAvidin (Pierce, catalog 31002) and Lumiphos 530 (Lumigen, catalog P-501). Each individual microtiter plate had a standard curve (from 1.8 to 60 ng/mL) prepared from human recombinant adiponectin (Biovendor, catalog RD172023100). Serum samples were diluted 1:1000, and all the measurements were performed in triplicate. The intraassay variation of the measurements was 9.8%, and interassay variation was 17.0%.

At follow-up, glucose levels were used to classify the subjects according to the 1999 WHO criteria [27] into groups with normal glucose tolerance (NGT), IGR (impaired fasting glucose and/or impaired glucose tolerance), or DM2. *Low adiponectin level* was defined as the lowest quartile of adiponectin levels, and the cutoff point was calculated separately for men and women. Materials and methods have been described in more detail previously [28,29,31].

2.2. Statistical methods

In descriptions of the study population, means (standard deviations) and medians (interquartile ranges) were used for normally and non-normally distributed variables, respectively.

After bivariate analyses, multivariate generalized logistic regression analyses were performed to assess the effect of low adiponectin level on the development of IGR and DM2. The lowest adiponectin quartile was compared with the higher ones. The results were reported by using adjusted odds ratios (ORs) and their 95% confidence intervals (95% CIs). The statistical analyses were performed using the SAS 9.1.3 for Windows (SAS, Cary, NC).

3. Results

Among the 350 subjects who were normoglycemic at baseline and participated in the second phase, adiponectin level was measured for 201 (57%) subjects. There were no statistically significant differences in HDL cholesterol, triglycerides, systolic and diastolic blood pressures, or BMI in the subjects with or without measured adiponectin levels. Nor was there any statistically significant difference in the 2-hour glucose levels, but the mean fasting glucose levels were lower in the subjects with than in those without measured adiponectin levels (4.5 ± 0.6 vs 4.7 ± 0.4 mmol/L, $P = .043$).

During the mean follow-up of 5.1 years (SD, 0.7), 47 (23.4%) of the 201 subjects developed IGR or DM2 (IGR, 41; DM2, 6). The baseline characteristics of the subjects who developed IGR or DM2 compared with those who remained normoglycemic are shown in Table 1. The mean serum adiponectin level was 33.5 μg/mL (SD, 16.2) in the subjects who remained normoglycemic, whereas the corresponding level was 28.9 μg/mL (SD, 11.6) in those who progressed to IGR or DM2 ($P = .073$). The subjects who remained NGT had significantly lower levels of triglycerides and 2-hour glucose, and tended to have lower BMI, lower systolic and diastolic blood pressures, and higher HDL cholesterol than the other group at baseline.

Impaired glucose regulation or DM2 developed in 15 of 41 (37%) subjects with low adiponectin level at baseline, whereas the corresponding proportion was 32 of 160 (20%)

Table 1
The baseline characteristics of the 55-year–old subjects who remained NGT and those who progressed to DM2 or IGR at follow-up

	NGT (n = 154)	DM2 or IGR (n = 47)	*P* value
S-Adiponectin (μg/mL)	33.5 (16.2)	28.9 (11.6)	.073
Weight (kg)	70.3 (12.8)	71.2 (13.2)	.694
BMI (kg/m^2)	25.7 (3.9)	26.9 (4.1)	.066
S-Cholesterol (mmol/L)	5.7 (1.3)	5.8 (1.2)	.526
HDL (mmol/L)	1.4 (0.5)	1.3 (0.4)	.067
LDL (mmol/L)	3.8 (1.3)	4.0 (1.2)	.430
Triglycerides (mmol/L)	0.79 (0.63-1.10)	1.00 (0.69-1.50)	.005
Systolic BP (mm Hg)	136 (18)	142 (18)	.069
Diastolic BP (mm Hg)	87 (11)	91 (13)	.081
FBG (mmol/L)	4.5 (0.6)	4.5 (0.7)	.865
2-h Blood glucose (mmol/L)	5.8 (1.2)	6.5 (1.0)	<.001

Data are means (SD), except those for triglycerides, which are median (interquartile range). NGT indicates normal glucose tolerance; DM2, type 2 diabetes; IGR, impaired glucose regulation; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure.

subjects with higher adiponectin levels ($P = .025$). When the subjects with low adiponectin level and those with higher adiponectin levels at baseline were compared, the OR for the development of IGR or DM2 was 2.3 (95% CI, 1.1-4.9). In logistic regression analysis, the adjusted OR for IGR or DM2 was 2.1 (95% CI, 1.0-4.5) when adjustment was made for sex and BMI.

4. Discussion

Our main finding was that a baseline low adiponectin level was associated with a more than 2-fold risk for developing IGR or DM2 after a mean follow-up of 5.1 years (SD, 0.7) in a group of middle-aged Finnish subjects who were initially normoglycemic according to the most recent WHO 1999 criteria [27]. So far, prospective studies among white populations are scarce [21-26]; and to our knowledge, there are only 2 other studies in which IGR has been taken into account besides DM2 [24,25].

Snijder et al [25], who conducted the Hoorn Study, investigated the association between baseline adiponectin levels and subsequent 6.4-year incidence of IGR and DM2 in a population-based cohort of 1264 white people aged 50 to 75 years. One of the main findings was that a high baseline adiponectin level protected especially women from the development of IGR and DM2. Adjusted ORs comparing women in the highest quartile with the lowest adiponectin quartile were 0.28 for IGR and 0.15 for DM2. However, no corresponding association was found in men. Schwarz et al [24] studied the association of baseline adiponectin level with progression toward IGR and DM2 in 550 German subjects with mean age of 57 years and a family history of DM2. Adiponectin levels were highest in patients who remained normoglycemic or presented with regression of the disease. Thus, our findings are in line with these 2 earlier studies [24,25] with a focus on both IGR and DM2.

Besides having low adiponectin level at baseline, those of our study subjects who progressed to IGR or DM2 tended to have a worse metabolic profile for all components of the metabolic syndrome (MetS) than those who remained normoglycemic. In previous studies, low plasma adiponectin levels have been associated with the MetS [11,12,32-34]; and it has even been suggested that adiponectin could be the best marker of the MetS [11,32,33,35-37].

As regards the beneficial influence of adiponectin, it has several effects on insulin sensitivity [6]. It activates glucose utilization in muscle and decreases the triglycerides content of muscle and liver by inducing fatty acid oxidation. Adiponectin also decreases hepatic glucose production. Adiponectin is an important contributor to peroxisome proliferator–activated receptor γ–mediated improvements in glucose tolerance through mechanisms that involve activation of the protein kinase (AMPK) pathway in both muscle and liver [7].

Adiponectin levels were measured in 57% of our normoglycemic subjects at baseline. Concerning the components of the MetS, the only difference between the subjects with and without measured adiponectin levels was fasting glucose, which was lower in the former group. Therefore, the normoglycemic subjects with measured adiponectin levels were not in a less favorable situation concerning glucose metabolism; and in our opinion, the results can be generalized to apply to the whole group. To our knowledge, until now, only one previous study on this topic has had a representative population-based sample of white subjects [25].

One limitation of the present study was the fairly small number of subjects, which prevented stratified analyses according to sex and BMI, for example. As regards sex, some previous studies have suggested that the association between adiponectin and DM2 is stronger in women than men [21,25]. Furthermore, there is some evidence that the association of adiponectin with DM2 would be stronger in obese than leaner subjects [26]. Another limitation of the study was that we were able to measure only total adiponectin instead of its different fractions. Recent work has shown that adiponectin exists in different isoforms, low-molecular-weight and high-molecular-weight (HMW) complexes [32]; and the HMW adiponectin complex is possibly the active form of this protein. Women have more HMW adiponectin than men [38], which may partly explain the stronger association in women than in men. Finally, we did not measure insulin levels at baseline. Therefore, we could not include assessment of insulin resistance and/or insulin secretion into the analyses.

In conclusion, we found that low concentrations of adiponectin predicted subsequent development of IGR and DM2 in initially normoglycemic middle-aged Finnish subjects. Our findings support the hypothesis that adiponectin may play an important role in the pathogenesis of abnormal glucose metabolism. However, further studies

focusing on the adiponectin isomer distribution and stratification by sex and obesity are needed to further clarify this association.

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