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Serum adiponectin in a population sample of 64-year-old women in relation to glucose tolerance, family history of diabetes, autoimmunity, insulin sensitivity, C-peptide, and inflammation

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Abstract

The aim of the study was to describe serum adiponectin levels in a population-based sample of women with different degrees of glucose tolerance and to examine if the variability in serum adiponectin was explained by family history of diabetes, obesity, insulin resistance, glycemia, and inflammation. Repeated oral glucose tolerance tests were used in a screening procedure of a cohort of 64-year-old women to identify those with diabetes mellitus n = 210) and impaired glucose tolerance (n = 201). A random sample of women with normal glucose tolerance (NGT, n = 186) was also included. The examination included history of first-degree relatives with diabetes, anthropometry, measurement of circulating adiponectin, glutamic acid decarboxylase antibodies, blood glucose, HbA_{1c}, insulin, proinsulin, C-peptide, high-sensitivity C-reactive protein, and homeostasis model assessment. Serum adiponectin concentration was lowest among diabetic women, highest in the random-sample NGT group, and intermediate in the impaired glucose tolerance group. This difference was partly explained by homeostasis model assessment, C-peptide, family history, and high-sensitivity C-reactive protein (R^2 = 0.33, P < .001), but obesity and glycemia did not contribute to this variability in serum adiponectin. A family history of diabetes was associated with low serum adiponectin concentration independently of obesity, glycemia, or insulin sensitivity (P = .002). Glutamic acid decarboxylase–positive diabetic women (n = 17) had similar serum adiponectin as the NGT group in spite of hyperglycemia. In conclusion, serum adiponectin was lowered in women with type 2 diabetes mellitus, and this difference could only be partly explained by insulin resistance, insulin secretion, family history of diabetes, and inflammation. Family history of diabetes was independently associated with hypoadiponectinemia. Autoimmune diabetic women did not have low adiponectin levels.

1. Introduction

Adiponectin, one of the more recently described secretory proteins, is uniquely and abundantly expressed in the white adipose tissue. However, it has been shown that obese subjects have lower serum adiponectin levels than nonobese subjects [1]. This protein has important anti-inflammatory [2-4] and metabolic [5,6] effects. High serum adiponectin levels appear to play protective role in the development of the metabolic syndrome [7], type 2 diabetes mellitus (T2DM) [8-10], and cardiovascular [11-13] and cerebrovascular diseases [14]. Adiponectin knockout mice exhibit severe diet-induced insulin resistance [15,16], and recombinant adiponectin administered to lipoatrophic and obese rodents is followed by improvement of insulin sensitivity and glycemia [17]. This is related to a stimulatory effect of adiponectin on lipid oxidation and muscle [18] and hepatic insulin signaling [19]. In Asian Indians, low adiponectin levels were a strong predictor of the future development of diabetes [10]. In Pima Indians as well as in a Japanese population, a high serum concentration predicted a lower incidence of T2DM independent of obesity, and this seemed to be secondary to the association between low adiponectin and insulin resistance [20,21]. In a cross-sectional study of white men and women, it was concluded that adiponectin predicted increased insulin sensitivity [6]. Hence, it has been

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suggested that the reverse association between adiponectin and obesity, T2DM, or impaired glucose tolerance (IGT) may to a large extent be explained by the parallel occurrence of insulin resistance [6,22].

An alternative or additional explanation is that obesity is associated with an increased secretion of proinflammatory cytokines, which may reduce the production of adiponectin [23]. As we have previously shown, adiponectin and tumor necrosis factor α also have antagonistic associations with insulin sensitivity [24]. Thus, endogenous cytokines associated with diabetes may inhibit adiponectin synthesis and contribute to impaired insulin action. Family history of diabetes is associated with hypoadiponectinemia in some [25], but not all studies [6].

Taken together, it seems as if adiponectin may play an important role in the pandemic of the metabolic syndrome and T2DM. To our knowledge, there is a paucity of data regarding adiponectin levels in groups with different degrees of glucose tolerance in the general white population and relations to different types of diabetes, family history of diabetes, inflammation, and insulin peptides such as C-peptide. Women are of a particular interest as DM in women is associated with a higher relative risk for cardiovascular disease than for men [26].

Accordingly, the present study was undertaken in a population-based sample of middle-aged women to describe serum adiponectin levels in those with and without autoimmune diabetes, IGT, and normal glucose tolerance (NGT) and to examine to what degree the variability in adiponectin concentrations could be explained by family history of obesity or diabetes and measures of obesity, glycemia, insulin resistance, insulin secretion as assessed by C-peptide levels, and inflammation.

2. Subjects and methods

The Diabetes, Impaired Glucose Tolerance in Women and Atherosclerosis study was designed to examine subclinical atherosclerosis in the carotid and femoral arteries in a population sample of 64-year-old women. Briefly, 2602 women identified through the County Register were contacted and screened with a questionnaire, measurement of weight, height, waist, hip circumference, and an oral glucose tolerance test (OGTT). DM, IGT, and NGT were defined according to the World Health Organization (WHO) [27] classification. The diabetes and IGT diagnoses were confirmed with repeated testing. The diagnosis of IGT was based on 2 OGTTs fulfilling the IGT criteria. Women who had findings corresponding to IGT at the first OGTT and NGT at the second test were excluded from the present analysis. The aim was to compare strictly defined groups with diabetes (n = 210), IGT (n = 201), and NGT. The latter group consisted of such a large group of women that a random sample was drawn (NGTr, n = 101). A group of women with NGT but who were body mass index (BMI)– and waist-to-hip ratio (WHR)–matched to the IGT group were also recruited (NGTm, n = 97). Twelve women were included in both NGT groups. These women were placed in the NGTm group in comparisons, including all groups. The rationale for including an NGT group that was BMI- and WHR-matched to the IGT group was the possibility to compare the groups without the confounding effect of general or abdominal obesity.

The exclusion criteria were for all subjects malignant or inflammatory disease, high-sensitivity C-reactive protein (hsCRP) of 10 mg/L or higher, severe psychiatric disorders, or other circumstances making participation not feasible. For subjects with NGT, additional exclusion criteria were coronary heart disease, intermittent claudication, previous stroke or transient ischemic attack, treatment or need of treatment of hypertension, and dyslipidemia. Women with inflammatory disease were excluded as this may have confounded any association between insulin sensitivity and adiponectin.

The subjects were first invited to a screening examination with an OGTT, which was repeated within 2 weeks if IGT or diabetes were found. The included women participated in a baseline examination as described below.

The subjects received both written and oral information before they gave their consent to participate. The study was approved by the ethics committee at the Sahlgrenska University Hospital.

2.1. Measurements

A questionnaire was used to obtain information on previous and present diseases, smoking, medication, family history of DM, or obesity. Body weight was measured with the subject dressed in underwear at screening and after inclusion by using a balance scale, and height was measured at the screening examination. Body mass index was calculated for the 2 separate visits, and the mean value of these examinations was used. Waist and hip circumferences were also measured twice, and the mean values were used in the analyses. Systolic and diastolic blood pressures were assessed in duplicate after 5 minutes of supine rest. The mean values were used in the analysis.

At screening, capillary blood glucose was measured without delay with the glucose oxidase technique. At the examination after inclusion, venous blood samples were drawn, and serum and plasma were frozen in aliquots at −70°C within 4 hours. We determined HbA_{1c} with high-performance liquid chromatography on a Mono S HR 5/5 column (Amersham Biosciences, Piscataway, NJ). hsCRP was measured by an ultrasensitive method using particle-enhanced immunoturbidimetry (Orion Diagnostica, Espoo, Finland) [28]. All analyses were performed on a Konelab 20 autoanalyzer (Thermo Clinical Labsystems, Espoo, Finland). Serum levels of adiponectin were determined by an enzyme-linked immunosorbent assay kit (R&D Systems Europe, Abingdon, UK). The analyses were performed at the Wallenberg Laboratory. Cholesterol and triglyceride levels were determined by fully enzymatic

techniques (Thermo Clinical Labsystems). High-density lipoprotein (HDL) was determined after precipitation of apolipoprotein B–containing lipoproteins with magnesium sulfate and dextran sulfate (Thermo Clinical Labsystems). Low-density lipoprotein (LDL) cholesterol was calculated as described by Friedewald et al [29]. Insulin, intact proinsulin, and C-peptide were assayed at the Department of Clinical Biochemistry, Addenbrookes NHS Trust, Cambridge, UK, on a 1235 AutoDELFIA automatic immunoassay system using a 2-step time-resolved fluorometric assay. The kits for the insulin and C-peptide assays were manufactured for Wallac Oy, Turku, Finland, by DAKO, Ely, Cambridgeshire, UK. For the insulin assay, the calibrators are referenced to WHO First IRP 66/304. The labeled antibodies for intact proinsulin were those previously described [30].

Antibodies against glutamic acid decarboxylase (GAD) were measured by an autoantibody enzyme-linked immunosorbent assay kit (RSR, Cardiff, UK) according to WHO standard [31].

2.2. Definitions and derived variables

At the screening examinations, glucose tolerance was assessed according to the revised WHO and American Diabetes Association criteria [27]. DM was diagnosed as either or both fasting blood glucose (FBG) of 6.1 mmol/L or higher or 2-hour blood glucose of 10 mmol/L or higher during an OGTT observed at 2 separate occasions. IGT was defined as blood glucose of less than 6.1 mmol/L and 2-hour blood glucose of 6.7 to less than 10.0 mmol/L after an oral glucose load at 2 occasions 1 to 2 weeks apart. Subjects with FBG of less than 5.5 mmol/L and 2-hour blood glucose of less than 6.7 mmol/L were considered having an NGT.

2.3. Statistical analysis

All statistics were analyzed using SPSS for Windows 11.0 (Chicago, IL). The results are presented as mean (SD) and numbers (percentages), if nothing else is indicated. Skewed variables are presented as geometric mean (SD) and were log transformed before parametric analyses. Unpaired Student t tests were used for comparison of continuous variables. Pearson correlation coefficient was calculated in the univariate correlation analyses. Multiple regression was used in a covariate analysis exploring whether the association between the glucose tolerance groups and adiponectin concentrations was independent of other covariates, that is, measures of insulin secretion and sensitivity (C-peptide, homeostasis model assessment [HOMA]), glycemia (HbA_{1c}), obesity (BMI, WHR), family history of diabetes, and inflammation (CRP). The glucose tolerance groups were entered as categorical variables (1 = yes, 0 = no): diabetes, IGT, and NGTm, with NGTr as reference group. In another approach, stepwise multiple regression was used to examine independent covariates to log adiponectin in the diabetes, IGT, and NGTr groups taken together with blood glucose as measure of glycemia. Confidence intervals (95%) were calculated, and 2-sided $P < .05$ was considered statistically significant.

3. Results

As shown in Table 1, there was a statistically significant trend in all measured variables between women with DM, IGT, NGTm, and NGTr groups. Thus, the diabetic women were most obese, had the highest serum triglyceride, FBG, HbA_{1c}, plasma insulin, proinsulin, C-peptide, HOMA index, and hsCRP concentrations, whereas HDL and LDL cholesterol were lowest. Hence, mean adiponectin concentration was lowest among diabetic women and highest in the randomly selected NGT group.

The NGTm group was well matched to the IGT group regarding BMI and WHR (Table 1). However, adiponectin was lower in the IGT group (Table 1, $P < .002$), whereas C-peptide and HOMA were higher than in the NGTm group (Table 1 and $P < .001$ for both analyses).

3.1. Family history of DM or obesity

History of DM in a first-degree relative was found in 169 women (29%). In comparison to those with no such

Table 1
Characteristics of the population sample

	Diabetes (n = 210)	IGT (n = 201)	NGTm (n = 97)	NGTr (n = 89)	P (for trend)
BMI (kg/m^2)	29.2 ± 4.8	27.6 ± 4.9	27.5 ± 2.7	24.7 ± 3.1	<.001
WHR	0.91 ± 0.064	0.87 ± 0.059	0.87 ± 0.035	0.84 ± 0.068	<.001
HDL (mmol/L)	1.53 ± 0.42	1.62 ± 0.42	1.74 ± 0.39	1.84 ± 0.43	<.001
LDL (mmol/L)	3.17 ± 1.05	3.66 ± 0.89	3.80 ± 0.86	3.67 ± 0.98	<.001
Triglyceride (mmol/L)[a]	1.52 ± 1.0	1.35 ± 0.73	1.18 ± 0.50	1.14 ± 0.64	<.001
Fasting glucose (mmol/L)[a]	7.43 ± 2.7	5.02 ± 0.62	4.77 ± 0.51	4.6 ± 0.57	<.001
HbA_{1c} (%)	5.78 ± 1.39	4.65 ± 0.36	4.47 ± 0.31	4.47 ± 0.26	<.001
P-insulin (pmol/L)[a]	64.8 ± 67.0	44.6 ± 34.0	35.6 ± 17.6	31.4 ± 18.0	<.001
P-proinsulin (pmol/L)[a]	6.30 ± 8.24	3.91 ± 4.25	3.30 ± 1.84	2.73 ± 1.99	<.001
P–C-peptide (pmol/L)[a]	672 ± 440	671 ± 307	560 ± 207	499 ± 225	<.001
hsCRP (mg/L)[a]	1.50 ± 1.97	1.16 ± 1.81	1.43 ± 1.67	0.96 ± 1.61	.005
Serum adiponectin (μg/mL)[a]	10.8 ± 8.0	12.9 ± 6.6	15.1 ± 6.3	18.1 ± 7.9	<.001
HOMA index[a]	2.92 ± 4.47	1.42 ± 1.18	1.06 ± 0.59	0.91 ± 0.57	<.001

Values are presented as mean ± SD (geometric mean for skewed variables).
[a] Skewed variables.

family history (n = 408), mean adiponectin was lower (11.4 ± 7.3 vs 13.9 ± 7.5, $P < .001$), whereas blood glucose, plasma insulin, and HOMA were higher (data not shown). There were no statistically significant differences in BMI, WHR, total body fat, serum hsCRP, plasma C-peptide, or proinsulin between women with and without family history (data not shown). As shown in the covariance and multiple regression analyses below, the statistically significant difference in adiponectin concentration between those with and without family history of diabetes remained after adjustment for BMI, WHR, C-peptide, HOMA, CRP, and glycemia. Family history of diabetes was found in 37% of those with diabetes, in 32% in the IGT group, 33% in the NGTr group, and in 6% among the NGTm women who consisted of a selected group ($P < .01$).

Obesity in a first-degree relative was not associated with different serum adiponectin levels in comparison with the group of women with no such family history (data not shown).

3.2. Adiponectin by glucose tolerance group in covariance analysis

A covariance analysis was performed with log serum adiponectin as dependent variable and glucose tolerance groups, family history of diabetes, BMI, WHR, log HOMA, log C-peptide, HbA_{1c}, and log hsCRP as covariates. All these variables, except BMI, WHR, and HbA_{1c}, contributed with statistical significance to the total variability in log adiponectin ($R^2 = 0.33$, $P < .001$). As shown in Fig. 1, the diabetes, IGT, and NGTm groups had lower log adiponectin values than the NGTr group independently of all the other covariates in the model. These findings remained when women with previous myocardial infarction were excluded (data not shown).

3.3. Covariates to adiponectin

In this analysis, covariates to adiponectin were examined in the groups with diabetes, IGT, and NGTr taken together.

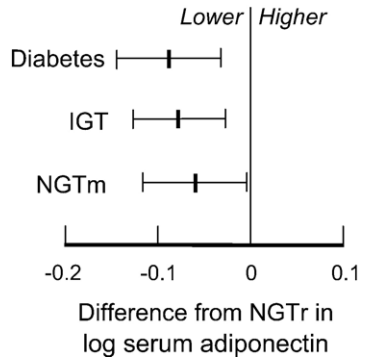

Fig. 1. Differences in log serum adiponectin concentrations in women with diabetes, IGT, or NGT who were BMI-matched to the IGT group (NGTm), in comparison with randomly selected healthy women with NGT (NGTr) (mean and 95% CI). Adjustments were made for history of first-degree relative with diabetes, body fat mass, WHR, log HOMA, log C-peptide, and log hsCRP.

Table 2
GAD-positive diabetic women and BMI-matched GAD-negative diabetic control women

	GAD-negative diabetic patients (n = 36)	GAD-positive diabetic patients (n = 18)
BMI (kg/m^2)	25.9 ± 4.0	26.1 ± 5.1
WHR	0.88 ± 0.04	0.88 ± 0.06
HDL (mmol/L)	1.56 ± 0.37	1.86 ± 0.57
LDL (mmol/L)	3.18 ± 1.04	2.93 ± 0.88
TG (mmol/L)[a]	1.41 ± 0.95	1.15 ± 0.57
Serum adiponectin (μg/mL)[a]	11.7 ± 5.1	17.3 ± 15.2*
hsCRP (mg/L)[a]	1.70 ± 1.94	1.46 ± 2.48
HbA_{1c} (%)	5.53 ± 1.09	6.69 ± 1.55*
Fasting glucose (mmol/L)	6.85 ± 2.16	9.14 ± 4.42
P-insulin (pmol/L)[a]	56.1 ± 74.2	62.6 ± 114.6
P-proinsulin (pmol/L)[a]	5.72 ± 9.98	3.93 ± 4.22
P–C-peptide (pmol/L)[a]	745 ± 407	148 ± 445*
HOMA	2.28 ± 4.19	3.22 ± 6.88

Values are presented as mean ± SD. Geometric means ± SD are shown for skewed variables.

[a] Skewed variables.

* $P < .05$ when the GAD-positive DM group is compared with the GAD-negative DM group.

The NGTm group was excluded in this analysis because it did not represent a random sample of NGT women. Adiponectin correlated negatively to BMI ($r = -0.33$), WHR ($r = -0.34$), blood glucose ($r = -0.34$), HbA_{1c} ($r = -0.17$), insulin ($r = -0.47$), proinsulin ($r = -0.46$), C-peptide ($r = -0.41$), HOMA ($r = -0.46$), and family history of diabetes ($r = -0.16$) (all $P < .01$). Similar correlations were observed within each glucose tolerance group with the exceptions of blood glucose and HbA_{1c}, which showed no consistent correlations to adiponectin.

A forward stepwise multiple regression model with log adiponectin as dependent variable was performed. Independent variables were WHR, BMI, log C-peptide, log HOMA, log hsCRP, family history of diabetes, and log blood glucose. All these variables except BMI, WHR, and log blood glucose were included in the model ($R^2 = 0.34$,

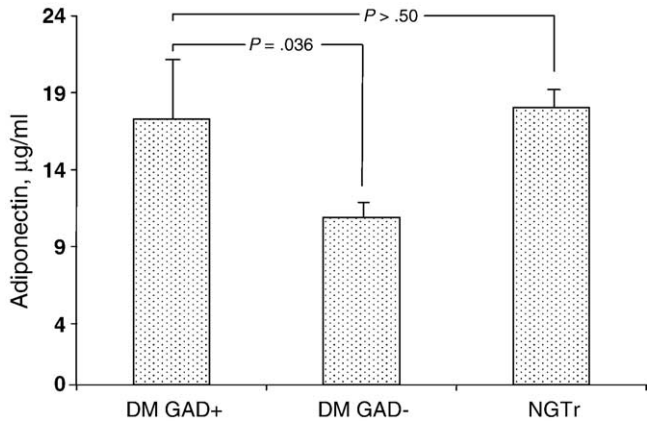

Fig. 2. Comparison of circulating adiponectin concentrations (geometric mean ± SEM) between women with GAD-positive diabetes (DM GAD+, n = 17), BMI-matched women with GAD-negative diabetes (DM GAD−, n = 34), and randomly selected healthy women with NGT (NGTr, n = 89).

$P < .001$). The statistically significant partial correlation coefficients were highest for log C-peptide ($r_{part} = -0.35$) and log HOMA ($r_{part} = -0.34$), whereas CRP and family history of diabetes were lower ($r_{part} = -0.12$ for both).

3.4. GAD-positive vs GAD-negative diabetes

The GAD-positive diabetic women (n = 17) were compared with a group of GAD-negative women with diabetes who were matched for BMI (n = 34). The former group showed similar WHR as the BMI-matched GAD-negative women (Table 2). The women with GAD-positive diabetes, in comparison with those without antibodies, had higher HbA_{1c}, lower C-peptide, but there was no statistical difference in HOMA, insulin, proinsulin, HDL cholesterol, triglycerides, or hsCRP. As shown in Fig. 2, mean adiponectin concentration in the GAD-positive group was higher than that in the GAD-negative group and comparable to the mean concentration in the NGTr group.

4. Discussion

We have shown in this population sample of 64-year-old Swedish women that serum adiponectin concentrations were as expected lowest among diabetic women, highest in the NGT group, and intermediate in the IGT group. This variability in adiponectin concentrations could partly be explained by insulin sensitivity as assessed by HOMA, C-peptide, hsCRP, and family history of diabetes in a first-degree relative, whereas the degree of obesity and glycemia measured as HbA_{1c} had no impact. Still, and in contrast to other findings in Pima Indians [22], a difference in adiponectin concentrations between the glucose tolerance groups remained after adjustment for insulin sensitivity and the other covariates, indicating other mechanisms related to adiponectin secretion or turnover. The strongest independent covariates to adiponectin levels in multivariate analyses were HOMA and C-peptide, representing both insulin sensitivity and insulin secretion. To our knowledge, the association between C-peptide and adiponectin has not been described before. Several observations indicated that the degree of glycemia did not seem to affect circulating adiponectin levels. First, in the covariance analysis, HbA_{1c} was not related to the difference in adiponectin levels between the glucose tolerance groups independently of insulin sensitivity. Second, in the multiple regression analysis of diabetes, in IGT and NGTr groups taken together, blood glucose was not associated with adiponectin after adjustment for other variables. Third, GAD-positive diabetic women had hyperglycemia, but similar adiponectin concentrations as the randomly selected women with NGT. In addition, although the glucose control was worse in the GAD-positive group in comparison with the BMI-matched GAD-negative diabetic women, still the latter group had the lowest serum adiponectin concentrations. GAD-positive diabetic women had lower C-peptide concentrations, which may be related to the adiponectin levels. We measured C-peptide that is co-secreted with insulin, but has a negligible hepatic removal, and thus can be used as a measure of insulin secretion [32]. Peripheral insulin measurements are not accurate indicators of insulin production because varying proportions are removed in the liver during the first pass through the portal circulation. In addition, this removal varies with the degree of obesity and insulin resistance [33]. We observed that HOMA, as a measure of insulin sensitivity, and C-peptide, as indicator of insulin secretion, were independently associated with the adiponectin concentration. Previous studies have shown that adiponectin may have multiple effects on insulin signaling in muscle and liver and on lipid oxidation [18,19]. The association with C-peptide is more unclear. It is not known whether C-peptide has any direct effect on the adipocyte production of adiponectin. One interesting observation is that adiponectin was associated with C-peptide and/or HOMA in all glucose tolerance groups, for example, both in the diabetes and NGT groups. This indicates that there might be a normal physiological mechanism linking adiponectin to insulin action, operating both in healthy individuals and in diabetic patients. Insulin has been reported to inhibit adiponectin secretion by some authors [34,35] and to stimulate according to others [36].

Adiponectin is known to form multimers, from trimers to low-molecular-weight hexamers and high-molecular-weight multimers. There are mutations related to diabetes and hypoadiponectinemia that are associated with impaired multimerization [37]. High-molecular-weight concentration is reported to be lowered by insulin [38] and increased by weight loss [39]. The biological effect of different multimers is controversial. Data indicate, however, that the ratio between the low- and high-molecular-weight forms, not the absolute amounts of adiponectin, is critical in determining insulin sensitivity [40]. Taken together, these aspects also have to be considered in the evaluation of the mechanisms relating adiponectin to insulin resistance and diabetes. There is yet no easily available method to measure the different multimers.

Similar with another report we observed that adiponectin was associated with hsCRP [41], and this remained after adjustment for body fat mass, glucose tolerance, and insulin sensitivity. There are data supporting the concept that adipocytes secrete proinflammatory cytokines that may inhibit adiponectin production [41,42].

We observed that a family history of diabetes in a first-degree relative was associated with adiponectin concentrations independently of other covariates to adiponectin such as obesity, insulin resistance, or inflammation. One may speculate that heredity for T2DM may be related to adiponectin and associated mechanisms. Single nucleotide polymorphisms (SNPs) in the adiponectin gene have been associated with IGT and decreased serum levels of adiponectin [43]. An association to SNPs has also been seen in coronary artery disease in T2DM (SNP +45) [44] in the Japanese population and in younger subjects (SNP

+276) [45]. According to a recent study by Ohashi et al [46], the I164T mutation in the adiponectin gene was a common genetic background associated with the metabolic syndrome and coronary artery disease in the Japanese subjects. Thus, SNPs could, at least partly, be an explanation of the variability in adiponectin concentrations seen in subjects with a family history of diabetes in this study. However, Salmenniemi et al [47] did not see any association of SNP +45 or SNP +76 with the lower adiponectin levels seen in offspring of patients with T2DM.

Coronary heart disease has been reported to be associated with lower adiponectin levels in diabetic patients [11]. In the present study, there was no indication that this confounded our findings.

The limitation of the present study is that only 64-year-old women were examined. However, the advantage was that confounders such as sex and age [48] could be minimized. Furthermore, this study is cross-sectional and cannot be used to show causality. However, population-based epidemiological studies are important to investigate the associations between different metabolic variables in well-defined populations, in this case, women with different stages of glucose tolerance.

In conclusion, among population-representative 64-year-old women, serum adiponectin concentration was as expected lowest in those with diabetes and gradually increased in parallel with improving glucose tolerance. The difference in adiponectin concentration was only partly explained by a history of a first-degree relative with diabetes, insulin sensitivity, insulin secretion as measured by C-peptide, and inflammation. The association between adiponectin and C-peptide or insulin sensitivity was observed within all glucose tolerance groups. Autoimmune diabetes did not show reduced adiponectin levels. Family history of diabetes was independently associated with hypoadiponectinemia.

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References

[1] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.

[2] Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 2000;96:1723-32.

[3] Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003;107:671-4.

[4] Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, et al. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem 2002;277:37487-91.

[5] Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Weyer C, Lindsay RS, et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes 2002;51:1884-8.

[6] Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S, et al. Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. Diabetes 2003;52:239-43.

[7] Choi KM, Lee J, Lee KW, Seo JA, Oh JH, Kim SG, et al. Serum adiponectin concentrations predict the developments of type 2 diabetes and the metabolic syndrome in elderly Koreans. Clin Endocrinol (Oxf) 2004;61:75-80.

[8] Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, et al. Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2004;53:2473-8.

[9] Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, et al. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003;361:226-8.

[10] Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner SM, Ramachandran A. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. Diabetes Care 2003;26:3226-9.

[11] Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.

[12] Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730-7.

[13] Zoccali C, Mallamaci F, Tripepi G. Inflammatory proteins as predictors of cardiovascular disease in patients with end-stage renal disease. Nephrol Dial Transplant 2004;19(Suppl 5):V67-V72.

[14] Chen MP, Tsai JC, Chung FM, Yang SS, Hsing LL, Shin SJ, et al. Hypoadiponectinemia is associated with ischemic cerebrovascular disease. Arterioscler Thromb Vasc Biol 2005.

[15] Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 2002;8:731-7.

[16] Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 2002;277:25863-6.

[17] Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-6.

[18] Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, et al. Proteolytic cleavage product of 30-kDa adipocyte complement–related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci U S A 2001;98:2005-10.

[19] Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001;7:947-53.

[20] Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002;360:57-8.

[21] Daimon M, Oizumi T, Saitoh T, Kameda W, Hirata A, Yamaguchi H, et al. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese population: the Funagata Study. Diabetes Care 2003;26:2015-20.

[22] Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.

[23] Bruun JM, Lihn AS, Verdich C, Pedersen SB, Toubro S, Astrup A, et al. Regulation of adiponectin by adipose tissue–derived cytokines: in vivo and in vitro investigations in humans. Am J Physiol Endocrinol Metab 2003;285:E527-33.

[24] Behre CJ, Fagerberg B, Mattsson Hultén L, Hulthe J. The reciprocal association of adipocytokines with insulin resistance and CRP in clinically healthy men. Metabolism 2005;54:439-44.
[25] Pellme F, Smith U, Funahashi T, Matsuzawa Y, Brekke H, Wiklund O, et al. Circulating adiponectin levels are reduced in nonobese but insulin-resistant first-degree relatives of type 2 diabetic patients. Diabetes 2003;52:1182-6.
[26] Niskanen L, Turpeinen A, Penttila I, Uusitupa MI. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. Diabetes Care 1998;21:1861-9.
[27] WHO. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.
[28] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 1998;97:425-8.
[29] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
[30] Sobey WJ, Beer SF, Carrington CA, Clark PM, Frank BH, Gray IP, et al. Sensitive and specific two-site immunoradiometric assays for human insulin, proinsulin, 65-66 split and 32-33 split proinsulins. Biochem J 1989;260:535-41.
[31] Bingley PJ, Bonifacio E, Mueller PW. Diabetes antibody standardization program: first assay proficiency evaluation. Diabetes 2003; 52:1128-36.
[32] Kuhl C, Faber OK, Hornnes P, Jensen SL. C-peptide metabolism and the liver. Diabetes 1978;27(Suppl 1):197-200.
[33] Faber OK, Christensen K, Kehlet H, Madsbad S, Binder C. Decreased insulin removal contributes to hyperinsulinemia in obesity. J Clin Endocrinol Metab 1981;53:618-21.
[34] Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. Diabetes 2002;51: 2968-74.
[35] Fasshauer M, Klein J, Neumann S, Eszlinger M, Paschke R. Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. Biochem Biophys Res Commun 2002;290:1084-9.
[36] Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746-9.
[37] Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, et al. Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. J Biol Chem 2003;278:40352-63.
[38] Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, et al. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073-85.
[39] Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res 2004;94:e27-e31.
[40] Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, et al. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem 2004;279:12152-62.
[41] Schulze MB, Rimm EB, Shai I, Rifai N, Hu FB. Relationship between adiponectin and glycemic control, blood lipids, and inflammatory markers in men with type 2 diabetes. Diabetes Care 2004;27: 1680-7.
[42] Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes 2003;52:1779-85.
[43] Gonzalez-Sanchez JL, Zabena CA, Martinez-Larrad MT, Fernandez-Perez C, Perez-Barba M, Laakso M, et al. An SNP in the adiponectin gene is associated with decreased serum adiponectin levels and risk for impaired glucose tolerance. Obes Res 2005;13:807-12.
[44] Lacquemant C, Froguel P, Lobbens S, Izzo P, Dina C, Ruiz J. The adiponectin gene SNP+45 is associated with coronary artery disease in type 2 (non–insulin-dependent) diabetes mellitus. Diabet Med 2004;21:776-81.
[45] Filippi E, Sentinelli F, Romeo S, Arca M, Berni A, Tiberti C, et al. The adiponectin gene SNP+276G>T associates with early-onset coronary artery disease and with lower levels of adiponectin in younger coronary artery disease patients (age ≤50 years). J Mol Med 2005;83:711-9.
[46] Ohashi K, Ouchi N, Kihara S, Funahashi T, Nakamura T, Sumitsuji S, et al. Adiponectin I164T mutation is associated with the metabolic syndrome and coronary artery disease. J Am Coll Cardiol 2004;43: 1195-200.
[47] Salmenniemi U, Zacharova J, Ruotsalainen E, Vauhkonen I, Pihlajamaki J, Kainulainen S, et al. Association of adiponectin level and variants in the adiponectin gene with glucose metabolism, energy expenditure and cytokines in offspring of type 2 diabetic patients. J Clin Endocrinol Metab 2005;90:4216-23.
[48] Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003;46:459-69.