Plasma Adiponectin Concentrations Predict Insulin Sensitivity of Both Glucose and Lipid Metabolism

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In animals, the adipocyte-derived hormone adiponectin has been shown to improve insulin sensitivity, a key factor in the pathogenesis of type 2 diabetes. In Pima Indians, high plasma adiponectin levels are associated with increased insulin sensitivity and reduced risk of type 2 diabetes. It is unclear whether this is also the case in white individuals and whether an additional beneficial effect on lipid metabolism exists. We therefore analyzed in nondiabetic individuals the associations between plasma adiponectin concentrations and insulin sensitivity measured by a euglycemic-hyperinsulinemic clamp (n = 262) and estimated by an oral glucose tolerance test (OGTT; n = 636) and serum lipid parameters using correlational analysis. Plasma adiponectin concentrations were positively correlated with insulin sensitivity, both measured with the clamp (r = 0.28, P = 0.0015 in women; r = 0.42, P < 0.0001 in men) and estimated from the OGTT (r = 0.37, P < 0.0001 in women; r = 0.41, P < 0.0001 in men) before and after adjusting for sex and percentage of body fat (all P < 0.001). Fasting triglycerides and the free fatty acid (FFA) concentrations during the OGTT (area under the curve) and at 120 min were negatively correlated in both women and men, whereas HDL was positively correlated with plasma adiponectin concentrations (all P < 0.004). Most notable, these relationships remained significant after adjusting for insulin sensitivity of glucose disposal in addition to sex and percentage of body fat (all P < 0.05). In conclusion, high adiponectin predicts increased insulin sensitivity. This relationship is independent of low body fat mass and affects not only insulin-stimulated glucose disposal but also lipoprotein metabolism and insulin-mediated suppression of postprandial FFA release. This suggests pleiotropic insulin sensitizing effects of adiponectin in humans. *Diabetes* 52:239–243, 2003

A number of hormone-like peptides released from the adipocyte, so-called adipocytokines, have been identified. For some, such as leptin, tumor necrosis factor-α, resistin, and adiponectin, a number of metabolic effects have been demonstrated, making these molecules candidate links between obesity and insulin resistance (1,2). Adiponectin, however, unlike other adipocytokines, is decreased in adiposity (3,4) and increases after weight reduction (5). In a nested case-control study in Pima Indians, high plasma adiponectin concentrations strongly predicted a lower incidence rate of type 2 diabetes independent of obesity (6). This seemed to be secondary to the association with increased insulin sensitivity in this population (3,7).

Despite the strong statistical correlation between circulating adiponectin and measures of adiposity, a high interindividual variability remains. In other words, for a given degree of fatness, adiponectin concentrations can vary considerably among individuals. It remains to be shown whether this remaining (or residual) variability in adiponectin concentrations is an independent predictor of insulin sensitivity in a large white population. Therefore, we studied the relationships between plasma adiponectin concentrations and insulin sensitivity of glucose disposal using both hyperinsulinemic-euglycemic clamp data (n = 262) and estimates from oral glucose tolerance tests (OGTTs) (n = 636) obtained from nondiabetic volunteers before and after adjusting for measures of adiposity. In addition, we analyzed relationships between plasma adiponectin concentrations and surrogate measures of insulin sensitivity of lipid metabolism using fasting free fatty acid (FFA), triglyceride, and HDL and LDL cholesterol concentrations and the decrease of plasma FFA concentrations during an OGTT.

RESEARCH DESIGN AND METHODS

Subjects. We analyzed data of 636 nondiabetic white volunteers who participated in the Tübingen Family Study for type 2 diabetes. The study protocol was approved by the Ethical Committee of the University of Tübingen School of Medicine, and informed written consent had been obtained before the studies. A total of 562 subjects had normal glucose tolerance (NGT), and 74 had impaired glucose tolerance (IGT) according to World Health Organization criteria (8). The participants did not take any medication known to affect glucose tolerance, insulin sensitivity, or insulin secretion. The characteristics of the subjects are shown in Table 1.

OGTT. After a 10-h overnight fast, the subjects ingested a solution containing 75 g dextrose, and venous blood samples were obtained at 0, 30, 60, 90, and 120 min for determination of plasma glucose, plasma insulin, and plasma FFA.

Hyperinsulinemic-euglycemic clamp. Subjects who underwent the hyperinsulinemic-euglycemic clamp had exclusively NGT. After the baseline period,

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AUC, area under the curve; FFA, free fatty acid; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PPAR-γ, peroxisome proliferator–activated receptor-γ; RQ, respiratory quotient; WHR, waist-to-hip ratio.

TABLE 1
Subject characteristics

	OGTT		Hyperinsulinemic-euglycemic clamp	
	Mean ± SE	Range	Mean ± SE	Range
n	636		262	
Sex (M/F)	229/407		137/125	
Family history of diabetes (first degree)	343 (55.8%)		160 (62.3 %)	
NGT/IGT	562/74		245/17	
Age (years)	35.4 ± 0.4	16–76	31.3 ± 0.5	16–61
BMI (kg/m^2)	26.3 ± 0.2	16.2–52.6	24.6 ± 0.3	17.4–49.0
WHR	0.85 ± 0.003	0.67–1.11	0.84 ± 0.005	0.67–1.07
Body fat (%)	28.1 ± 0.4	7.0–55.5	23.7 ± 0.6	7.0–48.0
Fasting plasma glucose (mmol/l)	4.97 ± 0.02	3.00–6.88	4.79 ± 0.03	3.00–6.67
Fasting plasma insulin (pmol/l)	54 ± 2	10–521	45 ± 2	10–313
HbA_{1c} (%)	5.1 ± 0.02	3.6–6.4	5.2 ± 0.02	4.1–6.1

subjects received a primed insulin infusion at a rate of 1.0 mU · kg^{-1} · min^{-1} for 2 h as previously described. Blood was drawn every 5–10 min for determination of blood glucose, and the infusion rate of exogenous glucose was adjusted appropriately to maintain the baseline glucose level. Indirect calorimetry was performed during a 30-min period before the clamp and at the end of the clamp

Indirect calorimetry. Oxygen consumption and carbon dioxide production was measured using a Deltatrac II Metabolic Monitor (Deltatrac, Helsinki, Finland). Basal measurements were performed during the 20 min preceding the clamp, and steady-state measurement was performed in the insulin-stimulated state during the last 30 min of the clamp. The respiratory quotient calculated as the ratio of CO_2 production divided by O_2 consumption was used as a measure of preferential carbohydrate or lipid oxidation.

Analytical procedures. Blood glucose was determined using a bedside glucose analyser (glucose-oxidase method; YSI, Yellow Springs Instruments, Yellow Springs, CO). Plasma insulin was determined by microparticle enzyme immunoassay (Abbott Laboratories, Tokyo, Japan), and serum FFA concentrations were determined with an enzymatic method (WAKO Chemicals, Neuss, Germany). Lipoprotein concentrations were measured with a standard colorimetric method using the Roche/Hitachi analyzer (Roche Diagnostics, Mannheim, Germany). Serum samples were frozen immediately and stored at −20°C for determination of adiponectin by radioimmunoassay (LINCO Research, St. Charles, MO). It has previously been shown that adiponectin remains stable in plasma samples stored at −20°C over many years; thus, detection by this radioimmunoassay is unaltered (6).

Calculations. The insulin sensitivity index (ISI; in μmol · kg^{-1} · min^{-1} · pmol^{-1} · l^{-1}) for systemic glucose uptake was calculated as mean infusion rate of exogenous glucose necessary to maintain euglycemia during the last 60 min of the euglycemic clamp divided by the steady-state insulin concentration. Insulin sensitivity from the OGTT was estimated as proposed by Matsuda et al. (9): $ISI_{est} = 10{,}000/\sqrt{(Gluc_0 \cdot Ins_0 \cdot Gluc_{mean} \cdot Ins_{mean})}$. The plasma insulin area under the curve (AUC) during the OGTT was calculated as $0.5 \times (0.5 \times Ins_0 + Ins_{30} + Ins_{60} + Ins_{90} + 0.5 \times Ins_{120})$, and that for plasma FFA was calculated analogously. To obtain a measure of suppression of lipolysis from the OGTT, which is independent of insulin sensitivity, we adjusted FFA AUC for the insulin AUC.

Statistical analyses. Unless otherwise stated, data are given as mean ± SE. Statistical comparison of normally distributed parameters between two groups was performed using Student's *t* test. Distribution was tested for normality using Shapiro-Wilk W test. For all analyses, nonnormally distributed parameters were logarithmically transformed to approximate a normal distribution. To adjust the effects of covariates and identify independent relationships, we performed multivariate linear regression analyses. $P < 0.05$ was considered to be statistically significant. The statistical software package JMP (SAS Institute, Cary, NC) was used.

RESULTS

Effect of gender, glucose tolerance status, and family history of type 2 diabetes. Plasma adiponectin concentrations were significantly higher in women (12.5 ± 0.3 μg/ml) than in men (8.7 ± 0.3 μg/ml; $P < 0.0001$). The inverse correlation between percentage of body fat and plasma adiponectin concentrations was displaced in parallel (Fig. 1), indicating that the sex difference was independent of the degree of adiposity. Plasma adiponectin concentrations were significantly higher in subjects with NGT (11.3 ± 0.2 μg/ml) than in subjects with IGT (9.9 ± 0.6 μg/ml; $P = 0.024$). However, because subjects with IGT were more obese (33.4 ± 1.1% body fat) than subjects with NGT (27.4 ± 0.4% body fat; $P < 0.0001$), this difference was no longer significant after adjusting for sex and percentage of body fat ($P = 0.07$ and $P = 0.23$ after additionally adjusting for waist-to-hip ratio [WHR]). In contrast, plasma adiponectin concentrations were not significantly different between subjects with (10.8 ± 0.3 μg/ml) and without family history of type 2 diabetes (11.4 ± 0.3 μg/ml; $P = 0.27$).

Univariate correlations. Plasma adiponectin concentration was negatively correlated with fasting and 2-h plasma glucose, fasting and 2-h plasma insulin, BMI, percentage of body fat, and WHR. Plasma adiponectin concentration was positively correlated with insulin sensitivity both measured with the clamp and estimated from the OGTT and with the insulin stimulated respiratory quotient (RQ). The 120-min FFA concentrations, FFA AUC, and triglycerides were negatively correlated, whereas HDL cholesterol concentrations were positively correlated with plasma adiponectin concentrations (Table 2).

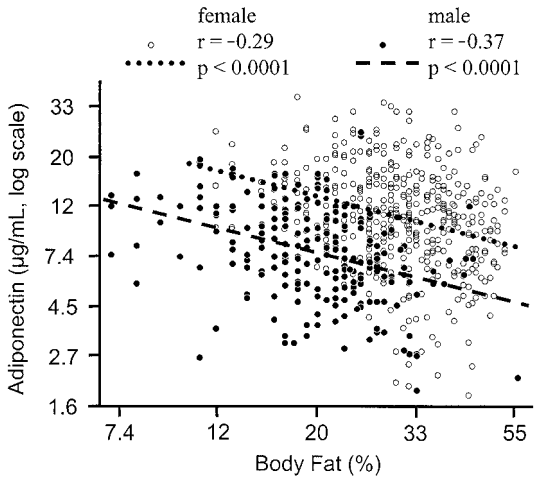

FIG. 1. Correlation between percentage of body fat and plasma adiponectin concentrations in women and men.

TABLE 2
Univariate correlations with plasma adiponectin concentration

	Women (n = 407)		Men (n = 229)	
	r	P	r	P
Fasting plasma glucose	−0.18	0.0003	−0.17	0.009
Plasma glucose 120 min (OGTT)	−0.22	<0.0001	−0.20	0.0028
Fasting plasma insulin	−0.35	<0.0001	−0.33	<0.0001
Plasma insulin 120 min (OGTT)	−0.32	<0.0001	−0.29	<0.0001
BMI	−0.33	<0.0001	−0.42	<0.0001
% Body fat	−0.29	<0.0001	−0.37	<0.0001
Age	−0.05	0.29	−0.08	0.21
WHR	−0.28	<0.0001	−0.27	<0.0001
Fasting FFA	−0.05	0.25	−0.08	0.23
FFAs 120 min (OGTT)	−0.24	<0.0001	−0.19	0.0038
Plasma triglycerides	−0.29	<0.0001	−0.38	<0.0001
Total plasma cholesterol	−0.002	0.97	−0.12	0.065
Plasma LDL cholesterol	−0.09	0.068	−0.09	0.17
Plasma HDL cholesterol	0.47	<0.0001	0.44	<0.0001
ISI (clamp)*	0.28	0.0015	0.42	<0.0001
RQ (basal)†	−0.01	0.69	0.08	0.48
RQ (end of clamp)†	0.14	0.19	0.40	0.0004
ISI (OGTT, Matsuda)	0.37	<0.0001	0.41	<0.0001

*Data from 125 women and 137 men; †data from 87 women and 76 men.

Multivariate correlations. Insulin sensitivity as determined by the hyperinsulinemic-euglycemic clamp remained significantly and positively correlated with plasma adiponectin concentrations after adjusting for sex and measures of obesity, such as BMI (P = 0.0003), percentage of body fat (P = 0.0002), or WHR (P < 0.0001). Similarly, insulin sensitivity as estimated from the OGTT also remained significantly and positively correlated with plasma adiponectin concentrations after adjusting for sex and BMI (P < 0.0001), percentage of body fat (P < 0.0001), or WHR (P < 0.0001). Figure 2 shows the correlation of plasma adiponectin concentrations with insulin sensitivity after adjusting for sex and percentage of body fat. In addition, plasma adiponectin concentrations were positively correlated with the insulin-stimulated RQ (r = 0.36, P < 0.0001), which remained highly significant after adjusting for sex, percentage of body fat, basal RQ, and ISI (P = 0.0012).

After adjusting for sex and percentage of body fat, the correlations between plasma adiponectin concentrations and 120-min FFA (P = 0.0009), FFA AUC (P = 0.002), triglyceride (P < 0.0001), and HDL concentrations (P < 0.0001) remained significant. It is interesting that additionally adjusting for insulin sensitivity of glucose disposal (Matsuda index or insulin sensitivity from the euglycemic-hyperinsulinemic clamp) did not also abolish these significant relationships (Fig. 3). To assess an insulin-regulated parameter of lipid metabolism, we analyzed the correlation between the FFA AUC and plasma adiponectin concentration. There was a negative correlation (r = −0.19, P < 0.0001), which remained significant after adjusting for sex, percentage of body fat, and the insulin AUC (P = 0.032).

DISCUSSION

The most important finding of the present analyses was the relationship between high plasma adiponectin concentrations and increased insulin sensitivity independent of measures of adiposity such as BMI, percentage of body fat, or WHR. These observations extend the work of Weyer et al. (3) and Stefan et al. (7) in Pima Indians to whites. They also provide a plausible explanation for the reduced incidence of type 2 diabetes in subjects with relatively high adiponectin shown not only in Pima Indians (6) but also in preliminary form in a German population (10). Moreover, the findings are highly consistent with animal studies

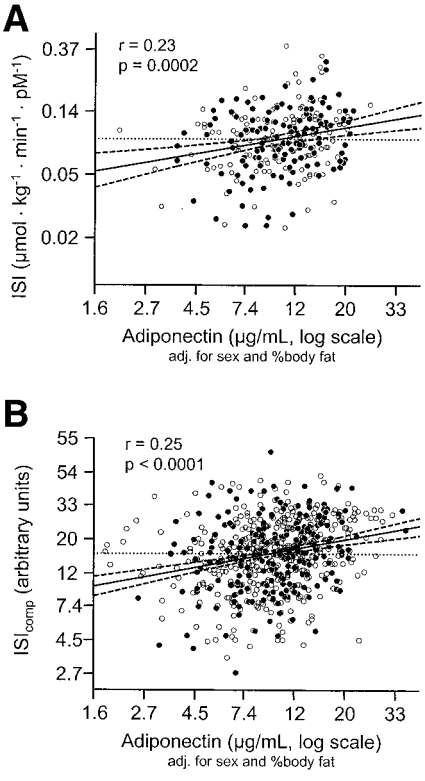

FIG. 2. Correlation between insulin sensitivity measured with the hyperinsulinemic-euglycemic clamp (*A*) or estimated from the OGTT (*B*) and plasma adiponectin concentration adjusted for percentage of body fat and sex (least-squares linear regression line with its 95% confidence intervals). ●, males; ○, females.

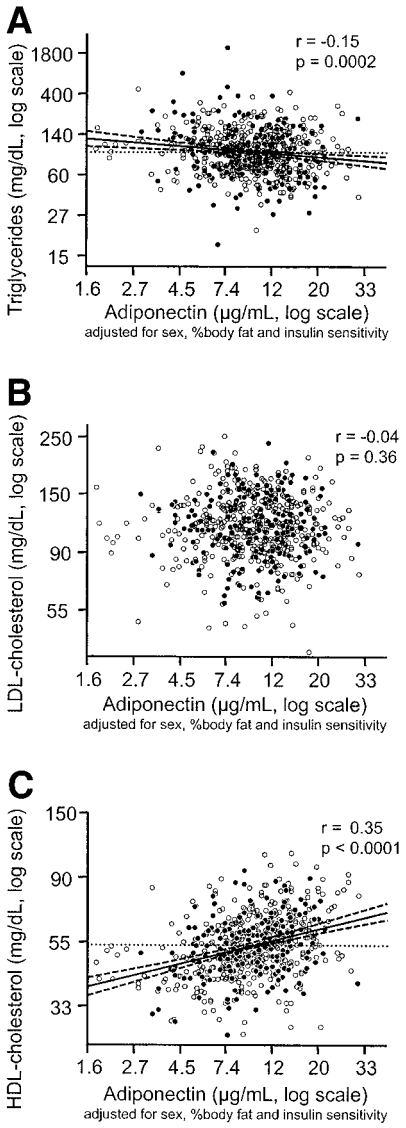

FIG. 3. Correlation between plasma triglyceride concentrations (*A*), plasma LDL cholesterol concentrations (*B*), or plasma HDL cholesterol concentrations (*C*) and plasma adiponectin concentrations adjusted for percentage of body fat and sex (least-squares linear regression line with its 95% confidence intervals). ●, males; ○, females.

showing that administration of recombinant adiponectin increases insulin sensitivity in both lipotrophic and obese murine models of insulin resistance (11) and studies demonstrating reduced insulin sensitivity in the adiponectin knockout mice (12).

It is interesting that we found a positive correlation between adiponectin concentrations and the insulin-stimulated RQ that was independent of the relationship with insulin sensitivity of glucose disposal. The increase in RQ during a hyperinsulinemic-euglycemic clamp indicates a shift in oxidative substrate preference from lipids to carbohydrates. Our observation therefore indicates that high adiponectin concentrations were associated with a relatively greater proportion of the glucose disposed of under the action of insulin being funneled into oxidative rather than nonoxidative pathways.

Lipid parameters also correlated with adiponectin in a manner compatible with increased insulin sensitivity of lipid metabolism, specifically lipoprotein synthesis. Our findings are generally consistent with observations in Japanese women also showing a strong positive association between plasma adiponectin concentrations and plasma HDL cholesterol concentrations (13). This relationship, like in our study, was independent of obesity, but measures of insulin sensitivity were not available in that study. Most notable in our study was that the association of high adiponectin with high HDL cholesterol and low triglycerides was independent of insulin sensitivity of glucose disposal, an observation highly suggestive of a direct insulin-sensitizing effect on hepatic lipoprotein metabolism (14). Clearly, a direct effect of adiponectin on lipoprotein metabolism is also possible.

Although it probably represents the weakest piece of evidence, because of the non–steady-state situation of the OGTT, it is noteworthy that postload FFA concentrations were lower with higher adiponectin. Because this was independent of insulin sensitivity (at least of glucose disposal), it cannot be excluded that, in addition to an insulin-sensitizing effect on lipolysis, adiponectin directly increased hepatic FFA extraction.

Combs et al. (15) showed that administration of recombinant adiponectin in rats enhanced suppression of hepatic gluconeogenesis and glucose-6-phosphatase activity, another key metabolic insulin-regulated pathway in the liver. In our study, without the use of a glucose tracer, insulin-stimulated glucose disposal and insulin-induced suppression of endogenous glucose production could not be assessed independently. Thus, although glucose production should be largely suppressed by the insulin infusion rate that we used, a residual contribution of glucose output to the variability in the glucose infusion rate cannot be excluded. It thus seems possible that muscle and liver are equally relevant sites of adiponectin action.

What determines the interindividual variability of plasma adiponectin concentration for any given degree of fatness? A number of hormonal (insulin and glucocorticoids) and other factors (cAMP, ionomycin, and tumor necrosis factor-α) have been shown to modulate adiponectin expression or secretion in vitro (rev. in 16). For example, thiazolidinediones have been shown to increase adiponectin secretion both in vitro (17) and in humans in vivo (18,19). This suggests that peroxisome proliferator–activated receptor-γ (PPAR-γ) activity is closely related to adiponectin expression and/or secretion. It is possible, therefore, that for a given fat mass, genetic variants affecting transcriptional activity of PPAR-γ influence adiponectin secretion. Indeed, carriers of the rare dominant negative mutations in the PPAR-γ gene have very low or undetectable plasma adiponectin concentrations (19). There is no conclusive evidence that common genetic variants in the adiponectin gene itself affect plasma adiponectin concentrations (4,20). Therefore, genes encoding other proteins involved in the regulation of adiponectin expression, secretion, and degradation will have to be investigated to answer the question conclusively.

In addition to improving insulin-sensitive metabolic processes, adiponectin seems to have a beneficial effect on the development of atherogenic lesions (12). This may have to do with improving insulin effects on endothelial function, tonus of the vasculature, and platelet coagulabil-

ity (21,22). Alternatively, adiponectin may modulate the plasma lipid profile in an antiatherogenic manner as suggested by the association with high HDL cholesterol concentrations and low triglyceride concentrations demonstrated in our analysis.

In conclusion, high adiponectin predicts increased insulin sensitivity. This relationship is independent of low body fat mass and affects not only insulin-stimulated glucose disposal but also insulin-mediated lipoprotein metabolism, especially insulin-mediated suppression of postprandial FFA release. That the latter association was independent of that with glucose metabolism suggests a nonspecific effect of adiponectin on insulin-regulated pathways in general, for example common upstream elements of the insulin-signaling cascade. The precise mechanisms that determine interindividual variability of adiponectin secretion relative for body fatness remain to be identified.

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