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Hypoadiponectinemia in Obesity and Type 2 Diabetes: Close Association with Insulin Resistance and Hyperinsulinemia

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ABSTRACT

Plasma concentrations of adiponectin, a novel adipose-specific protein with putative antiatherogenic and antiinflammatory effects, were found to be decreased in Japanese individuals with obesity, type 2 diabetes, and cardiovascular disease, conditions commonly associated with insulin resistance and hyperinsulinemia.

To further characterize the relationship between adiponectinemia and adiposity, insulin sensitivity, insulinemia, and glucose tolerance, we measured plasma adiponectin concentrations, body composition (dual-energy x-ray absorptiometry), insulin sensitivity (M, hyperinsulinemic clamp), and glucose tolerance (75-g oral glucose tolerance test) in 23 Caucasians and 121 Pima Indians, a population with a high propensity for obesity and type 2 diabetes.

Plasma adiponectin concentration was negatively correlated with percent body fat ($r = -0.43$), waist-to-thigh ratio ($r = -0.46$), fasting plasma insulin concentration ($r = -0.63$), and 2-h glucose concentration ($r = -0.38$), and positively correlated with M ($r = 0.59$) (all $P < 0.001$); all relations were evident in both ethnic groups. In a multivariate analysis, fasting plasma insulin concentration, M, and waist-to-thigh ratio, but not percent body fat or 2-h glucose concentration, were significant independent determinates of adiponectinemia, explaining 47% of the variance ($r^2 = 0.47$). Differences in adiponectinemia between Pima Indians and Caucasians (7.2 ± 2.6 *vs.* 10.2 ± 4.3 μg/ml, $P < 0.0001$) and between Pima Indians with normal, impaired, and diabetic glucose tolerance (7.5 ± 2.7, 6.1 ± 2.0, 5.5 ± 1.6 μg/ml, $P < 0.0001$) remained significant after adjustment for adiposity, but not after additional adjustment for M or fasting insulin concentration.

These results confirm that obesity and type 2 diabetes are associated with low plasma adiponectin concentrations in different ethnic groups and indicate that the degree of hypoadiponectinemia is more closely related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity and glucose intolerance. (*J Clin Endocrinol Metab* **86:** 1930–1935, 2001)

OBESITY IS COMMONLY associated with insulin resistance and hyperinsulinemia (1) and is a major risk factor for the development of type 2 diabetes and cardiovascular disease (2). Although adipose tissue is now known to express and secrete a variety of metabolites, hormones, and cytokines that have been implicated in the development of insulin resistance and atherosclerosis (3, 4), the molecular basis for the link between obesity, diabetes, and cardiovascular disease remains poorly understood. While free-fatty acids released from adipose tissue have long been implicated in the development of these obesity-related complications (5), there is growing evidence that adipocyte-derived cytokines such as tumor necrosis factor-α (TNFα) (6, 7), plasminogen activator inhibitor type 1 (8), interleukin 6 (9, 10), and complement C3 (11) may also have a role. This is in part based on experimental evidence that these adipocytokines have direct effects on the insulin signaling cascade (TNFα) (7), the fibrinolytic system (plasminogen activator inhibitor type 1) (8), and endothelial cell adhesion (interleukin 6) (9). Furthermore, clinical studies have shown that the plasma concentrations of several of these adipocytokines correlate with measures of adiposity, insulin sensitivity, and endothelial function in humans (8–11).

More recently, a novel adipose-specific protein, adiponectin, has been discovered (12–15). Adiponectin, the gene product of the adipose most abundant gene transcript-1 (*apM1*) gene which is exclusively and abundantly expressed in white adipose tissue, is a 244-amino acid protein with high structural homology to collagen VIII, X, and complement C1q (12–15) as well as TNFα (16). Although the physiological role of adiponectin is yet to be fully determined, experimental findings that this protein accumulates in injured vessel walls (17) and dose-dependently inhibits TNFα-induced cell adhesion in human aortic endothelial cells (18, 19), have led to the proposal that adiponectin may have an antiatherogenic effect. Moreover, adiponectin has recently been reported to have an inhibitory effect on the proliferation of myelomonocytic progenitors as well as on phagocytic activity and TNFα production by macrophages (20), findings consistent with an antiinflammatory effect of this protein. Finally, recent findings of markedly reduced adipose tissue *apM1* gene expression in ob/ob mice (14) and in obese Caucasians with type 2 diabetes (21) has led to the hypothesis that adiponectin may have a role in the pathogenesis of obesity and type 2 diabetes (21). Using an adiponectin-specific enzyme-linked immunosorbent assay, Arita *et al.* (22) have demonstrated that

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adiponectin is abundant in the circulation in humans, with plasma levels in the microgram per ml range, thus accounting for approximately 0.01% of total plasma protein. In contrast to all other adipocytokines known to date, plasma adiponectin concentrations were found to be decreased, not increased, in Japanese individuals with obesity (22), type 2 diabetes (23), and cardiovascular disease (18, 23), conditions commonly associated with insulin resistance and hyperinsulinemia.

To gain further insights into the anthropometric and metabolic determinants of adiponectinemia in humans, it would be useful to examine the relationship between the plasma adiponectin concentration and direct measures of adiposity, body fat distribution, insulin sensitivity, insulinemia, and glucose tolerance. Moreover, comparative studies of adiponectinemia in populations with different propensity for obesity, insulin resistance, type 2 diabetes, and atherosclerosis are warranted. The Pima Indians of Arizona are interesting in this respect, because they have among the highest reported prevalence rates of obesity, insulin resistance, and type 2 diabetes in the world (24, 25), but a relatively low incidence of cardiovascular disease (26).

In the present study, we examined the relationship between the plasma adiponectin concentration and adiposity, body fat distribution, insulin sensitivity, insulinemia, and glucose tolerance in a large group of Pima Indians and Caucasians covering a wide range of glucose tolerance.

Subjects and Methods

A total of 144 subjects (23 Caucasians and 121 Pima Indians; Table 1) who had participated in ongoing studies of the pathogenesis of obesity and type 2 diabetes (27, 28) and of whom frozen plasma samples had been stored were included in this analysis. All subjects were between 18 and 50 yr of age, nonsmokers at the time of the study, and, except for type 2 diabetes in 17 Pima Indians, healthy according to a physical examination and routine laboratory tests. No subject had clinical or laboratory signs of acute infection and none had a history of, or presence of, clinically evident cardiovascular disease. Subjects were admitted for 8–10 days to the NIH Clinical Research Unit in Phoenix, Arizona, where they were fed a weight-maintaining diet (50% of calories as carbohydrate, 30% as fat, and 20% as protein) and abstained from strenuous exercise. After at least 3 days on the diet, subjects underwent a series of tests for the assessment of body composition, glucose tolerance, and insulin sensitivity. The protocol was approved by the Tribal Council of the Gila River Indian Community and by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases and all subjects provided written informed consent before participation.

Anthropometric measurements

Body composition was estimated by total body dual energy x-ray absorptiometry (DPX-L; Lunar Corp., Madison, WI) with calculation of percent body fat, fat mass, and fat-free mass as described (29). Waist and thigh circumferences were measured at the level of umbilicus and the gluteal fold in the supine and standing position, respectively, and the waist-to-thigh ratio was calculated as an index of body fat distribution.

Oral glucose tolerance test (OGTT) and analytic procedures

After a 12-h overnight fast, subjects underwent a 75-g OGTT (30). Baseline blood samples were drawn for determination of the fasting plasma glucose, insulin, and adiponectin concentrations. Plasma glucose concentrations were determined by the glucose oxidase method (Beckman Coulter, Inc. Instruments, Fullerton, CA) and were also measured at 2 h after glucose ingestion for assessment of glucose tolerance according to the 1985 WHO diagnostic criteria (30). Plasma insulin concentrations were determined by an automated immunoassay (Access; Beckman Coulter, Inc.). The fasting plasma insulin concentration from the OGTT was averaged with two additional fasting plasma insulin concentrations determined on separate days during the same admission to obtain a more robust measure of fasting insulinemia. Blood samples for measurement of fasting plasma adiponectin concentrations were drawn with prechilled syringes, transferred into prechilled EDTA tubes, and immediately placed on ice. All tubes were cold-centrifuged (+4 C) within several minutes of collection and stored at −70 C until assay at the Department of Internal Medicine and Molecular Sciences, Osaka University (Osaka, Japan). Fasting plasma adiponectin concentrations were determined using a validated sandwich enzyme-linked immunosorbent assay employing an adiponectin-specific antibody (intraassay

TABLE 1. Physical and metabolic characteristics of the study population (mean ± SD)

	All	By ethnic group[a]		By glucose tolerance[b]		
		Caucasians	Pima Indians	NGT	IGT	Diabetic
No. (male/female)	144	23 (17/6)	104 (76/28)	79	25	17
Age (yr)	29 (18–47)	32 ± 7	28 ± 7[c]	27 ± 6^{A}	31 ± 8^{B}	31 ± 6^{B}
Height (cm)	169 (147–191)	172 ± 10	169 ± 8[c]	169 ± 8^{A}	167 ± 9^{A}	164 ± 8^{A}
Body weight (kg)	92.9 (49.5–147.7)	94.7 ± 25.9	91.4 ± 19.7	88.9 ± 19.5^{A}	99.3 ± 18.5^{B}	99.9 ± 14.0^{B}
BMI (kg/m^2)	32.7 (19.6–54.2)	31.9 ± 8.8	32.1 ± 6.7	31.1 ± 6.8^{A}	35.3 ± 5.3^{B}	37.2 ± 4.9^{B}
Body fat (%)	31 (12–50)	28 ± 10	30 ± 8	29 ± 8^{A}	35 ± 6^{B}	38 ± 7^{B}
Fat mass (kg)	29.6 (7.4–59.1)	28.8 ± 16.1	28.4 ± 11.6	26.5 ± 11.9^{A}	34.6 ± 8.4^{B}	38.1 ± 10.3^{B}
Fat-free mass (kg)	63.3 (39.5–97.8)	65.9 ± 13.2	63.0 ± 11.3	62.4 ± 10.7^{A}	64.7 ± 13.0^{A}	61.8 ± 10.6^{A}
Waist-to-thigh ratio	1.63 (1.26–2.04)	1.53 ± 0.13	1.65 ± 0.14[d]	1.64 ± 0.14^{A}	1.68 ± 0.12^{A}	1.67 ± 0.12^{A}
Fasting glucose (mmol/L)	4.8 (3.3–9.4)	4.6 ± 0.6	4.7 ± 0.6	4.6 ± 0.5^{A}	5.1 ± 0.6^{B}	6.1 ± 1.3^{C}
2-h glucose (mmol/L)	7.2 (2.5–17.4)	6.2 ± 1.8	6.3 ± 1.8	5.5 ± 1.3^{A}	8.8 ± 1.1^{B}	13.4 ± 2.1^{C}
Fasting insulin (pmol/L)	246 (66–720)	150 ± 78	252 ± 120[d]	228 ± 114^{A}	330 ± 120^{B}	348 ± 114^{B}
2-h insulin (pmol/L)	1146 (66–6606)	432 ± 312	1146 ± 1116[c]	810 ± 696^{A}	2208 ± 1494^{B}	2100 ± 1830^{B}
M-low (mg/kg EMBS per min)[e]	2.8 (1.4–8.2)	3.5 ± 1.3	2.7 ± 1.2[c]	3.0 ± 1.3^{A}	2.0 ± 0.3^{B}	1.9 ± 0.2^{B}
M-high (mg/kg EMBS per min)[e]	8.6 (2.4–16.3)	9.3 ± 2.4	8.8 ± 2.1	9.3 ± 2.1^{A}	7.4 ± 1.5^{B}	6.0 ± 1.8^{C}
Adiponectin (μg/ml)[f]	7.5 (3.1–19.8)	10.2 ± 4.3	7.2 ± 2.6[d]	7.5 ± 2.7^{A}	6.1 ± 2.0^{B}	5.5 ± 1.6^{B}

[a] Ethnic comparison (17 diabetic Pima Indians excluded).

[b] Comparison by glucose tolerance (23 Caucasians excluded); *values not sharing a common character* are significantly different (adjusted for age and sex).

[c] $P < 0.01$, adjusted for age and sex; significant differences between Caucasians and Pima Indians.

[d] $P < 0.001$, adjusted for age and sex; significant differences between Caucasians and Pima Indians.

[e] Assessed in 18 of the 23 Caucasians only.

[f] To convert adiponectin concentrations to micromoles per L, divide by 30.

and interassay coefficients of variation 3.3% and 7.4%, respectively) (16, 21, 22).

Two-step hyperinsulinemic euglycemic glucose clamp

Insulin sensitivity was assessed at physiologic and supraphysiologic insulin concentrations during a two-step hyperinsulinemic euglycemic glucose clamp as described (27, 28). In brief, after an overnight fast, a primed continuous iv insulin infusion was administered for 100 min at a constant rate of 240 nmol/m^2 body surface area per minute (low dose), followed by a second 100-min infusion at a rate of 2,400 nmol/m^2·min (high dose). These infusions achieved steady-state plasma insulin concentrations of 840 ± 4,252 pmol/L and 13,320 ± 3,480 pmol/L (mean ± SD), respectively. Plasma glucose concentrations were maintained at approximately 5.5 mmol/L with a variable infusion of a 20% glucose solution. The rate of total insulin-stimulated glucose disposal (M) was calculated for the last 40 min of the low-dose (M-low) and high-dose (M-high) insulin infusion. As described previously (27, 28), M-low was corrected for the rate of endogenous glucose output [measured by a primed (30 μCi), continuous (0.3 μCi/min) 3-^{3}H-glucose infusion, Refs. 27 and 28] and adjusted for the steady-state plasma glucose and insulin concentrations. M-low and M-high were normalized to estimated metabolic body size (EMBS = fat-free mass + 17.7 kg) (27, 28). Five of the 23 Caucasian subjects had no assessment of insulin sensitivity.

Statistical analyses

Statistical analyses were performed using the software of the SAS Institute, Inc. (Cary, NC). M-low and the fasting plasma insulin and adiponectin concentrations were all log-transformed to achieve a more normal distribution. General linear regression models with adjustment for age and sex were used to compare anthropometric and metabolic characteristics between Caucasians and Pima Indians and between subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes.

Adiponectinemia in relation to anthropometric and metabolic variables in nondiabetic Caucasians and Pima Indians

In a first analysis, we examined the relationship of the plasma adiponectin concentration to selected anthropometric and metabolic variables in Caucasians and Pima Indians carefully matched for body mass index (BMI) and glucose tolerance. Because no samples of diabetic Caucasians were available and to control for the confounding effect of frank hyperglycemia, results from the 17 diabetic Pima Indians were excluded from this analysis. Univariate linear regression models were used to examine the simple relationships of adiponectin to selected variables. Stepwise and general multivariate regression analyses were used to identify independent determinants of adiponectin and the percentage of variance in adiponectin that they explained (r^2).

Adiponectinemia in Pima Indians with NGT, IGT, and diabetes

In a second analysis, we compared the mean plasma adiponectin concentration between Pima Indians with NGT, IGT, and diabetes. General linear regression models with computation of least square means were used to compare the mean plasma adiponectin concentration between the three glucose tolerance groups after adjustment for covariates.

Results

As shown in Table 1, subjects covered a wide range of body size and composition, glucose tolerance, and insulin sensitivity. Despite having similar BMI and glucose tolerance, nondiabetic Pima Indians had a higher waist-to-thigh ratio and were markedly more insulin resistant and hyperinsulinemic than nondiabetic Caucasians. As expected, Pima Indians with IGT and diabetes were more obese, hyperinsulinemic, and insulin resistant than those with NGT (Table 1).

Adiponectinemia in relation to anthropometric and metabolic variables in nondiabetic Caucasians and Pima Indians

Figure 1 and Table 2 show the simple relationships between the plasma adiponectin concentration and selected anthropometric and metabolic variables for the entire study population (Fig. 1) and separately for the two ethnic groups (Table 2). The plasma adiponectin concentration was negatively correlated with BMI, percent body fat, waist-to-thigh ratio, and the fasting plasma insulin and 2-h plasma glucose concentrations in both Caucasians and Pima Indians (Fig. 1, A and B, and Table 2). In contrast, plasma adiponectin concentration was positively correlated with M-low and M-high (Fig. 1, C and D, and Table 2). In a multivariate analysis, the fasting plasma insulin concentration, M-low, and waist-to-thigh ratio, but not percent body fat or the 2-h glucose concentration, were significant independent determinants of the plasma adiponectin concentration, explaining a total of 47% of the variance in this measure ($r^2 = 0.47$). The mean plasma adiponectin concentration was lower in Pima Indians than in Caucasians, a difference that remained significant after adjustment for percent body fat, but not after additional adjustment for M and/or the fasting plasma insulin concentration (Fig. 1E). Although females had higher percent body fat than males (39% *vs.* 27%, $P < 0.001$), adiponectin levels did not differ between females (6.9 μg/ml) and males (7.7 μg/ml) ($P = 0.98$ and $P = 0.54$ with and without adjustment for the aforementioned determinants).

Adiponectinemia in Pima Indians with NGT, IGT, and diabetes

The plasma adiponectin concentration was negatively correlated with the 2-h plasma glucose concentration (Fig. 2A) and accordingly, was lower not only in individuals with diabetes, but also, to a similar extent, in individuals with IGT compared with those with NGT (Fig. 2B). As with the ethnic comparison, differences in mean plasma adiponectin concentration between glucose tolerance groups remained significant after adjustment for percent body fat, but not after additional adjustment for M and/or the fasting plasma insulin concentration (Fig. 2B).

Discussion

The present study revealed two important findings. First, it confirmed previous findings that obesity and type 2 diabetes are associated with low plasma adiponectin concentrations and indicated that this hypoadiponectinemia is evident across different ethnic groups with marked differences in the propensity for obesity, type 2 diabetes, and atherosclerosis. Second, the results show that the plasma adiponectin concentration is more closely related to insulin sensitivity and fasting insulinemia than to adiposity and glycemia, which suggests that the hypoadiponectinemia in people with obesity and type 2 diabetes is in large part attributable to insulin resistance and/or hyperinsulinemia.

Previous studies in Japanese individuals have shown that the plasma adiponectin concentration is negatively correlated with body mass index (BMI) and accordingly, lower in

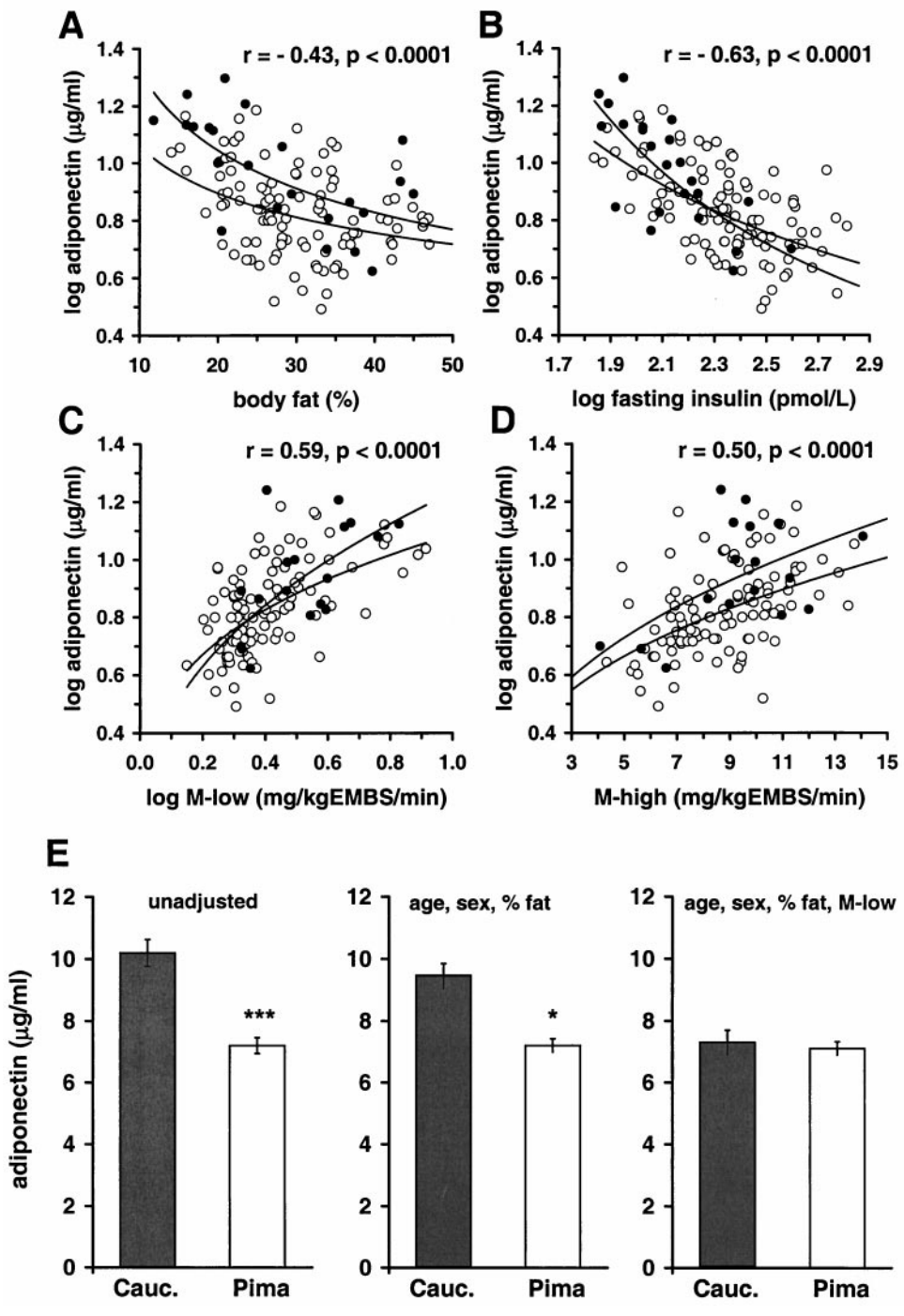

FIG. 1. Fasting plasma adiponectin concentration in relation to percent body fat (A), fasting insulinemia (B), and insulin-stimulated glucose disposal (M) as assessed under physiological (C) and supraphysiological (D) levels of hyperinsulinemia in nondiabetic Pima Indians (○) and Caucasians (●). E, Mean fasting plasma adiponectin concentration in nondiabetic Pima Indians *vs.* Caucasians with and without adjustment for age, sex, percent body fat, and/or insulin sensitivity. To convert adiponectin concentrations to micromoles per L, divide by 30.

obese than in lean subjects (18, 22, 23). The present results extend this finding by demonstrating that plasma adiponectin concentrations are inversely related to percent body fat, a direct measure of adiposity, and that this is consistent across different ethnic groups. Our results thus confirm that adiponectin is the only adipose-specific protein known to date that, despite its exclusive production in white adipose tissue, is negatively regulated in obesity. This agrees with findings in rodents where the murine homologue of adiponectin, adipoQ, is also down-regulated in obesity (14) and with a recent report of decreased *apM1* gene expression in sc and visceral adipose tissue of obese humans (21).

We also found that the mean plasma adiponectin concentration was lower in nondiabetic Pima Indians than in Caucasians and in subjects with IGT and diabetes compared with those with NGT. The fact that these differences were not explained by differences in percent body fat indicates that factors other than adiposity must play a role in determining adiponectinemia. Our finding that the plasma adiponectin concentration was more closely re-

lated to fasting insulinemia and to the rate of insulin-stimulated glucose disposal, a direct measure of insulin sensitivity, than to percent body fat and the 2-h glucose concentration suggested that hyperinsulinemia and/or insulin resistance might be major determinants of the hypoadiponectinemia in obesity and type 2 diabetes. This was supported by the finding that differences in adiponectinemia between Pima Indians and Caucasians and between glucose tolerance groups were almost completely explained by differences in insulin sensitivity and/or fasting insulinemia, but not by differences in percent body fat.

TABLE 2. Relationship between adiponectin and selected anthropometric and metabolic variables by ethnic group

	Caucasians	Pima Indians[a]
BMI	−0.65[b]	−0.37
Percent body fat	−0.63[b]	−0.33
Waist-to-thigh ratio	−0.45[c]	−0.39
2-h glucose	−0.48[c]	−0.37
Fasting insulin	−0.75[a]	−0.58
M-low	0.60[b]	0.56
M-high	0.49[c]	0.50

Pearson correlation coefficients. [a–c] Level of significance.
[a] $P < 0.0001$.
[b] $P < 0.01$.
[c] $P < 0.05$.

The mechanism underlying the observed close association between plasma adiponectin concentration and insulin sensitivity/insulinemia are presently unknown. A direct effect of hyperinsulinemia to down-regulate *apM1* gene expression in adipose tissue is an unlikely explanation, given that insulin appears to up-regulate *apM1* in rodents (13, 14) and that plasma adiponectin concentrations do not decrease postprandially in humans (23). Interestingly, two recent genomic scan studies have independently revealed linkage of insulinemia to a region on chromosome 3 that harbors the *apM1*

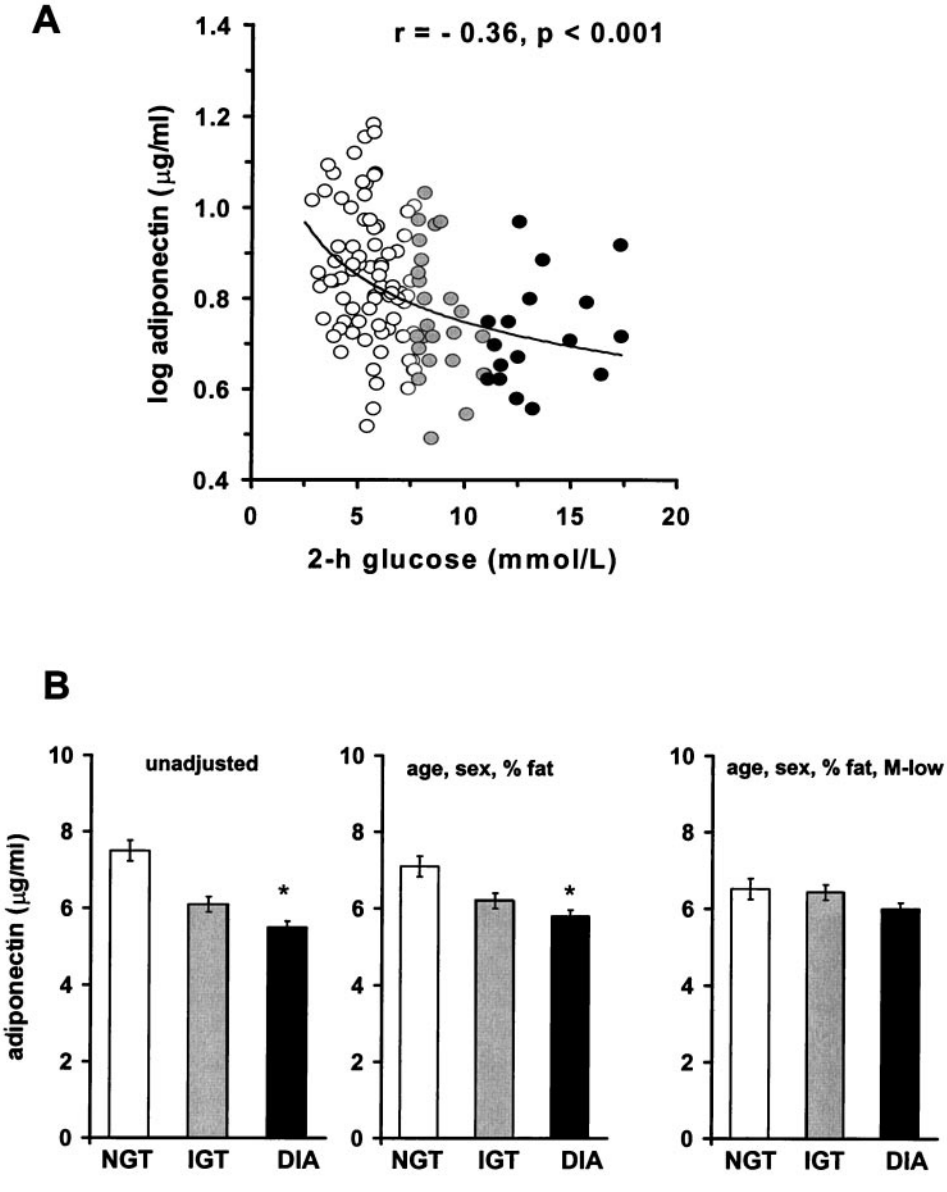

FIG. 2. A, Fasting plasma adiponectin concentration in relation to 2-h glucose concentration in Pima Indians with NGT (○), IGT (◍), or diabetes (●). B, Mean fasting plasma adiponectin concentration in Pima Indians with NGT, IGT, and diabetes (DIA) with and without adjustment for age, sex, percent body fat and/or insulin sensitivity. To convert adiponectin concentrations to micromoles per L, divide by 30.

gene (28, 31). Studies of the regulation of adiponectin gene expression are now warranted.

Although there is currently no experimental evidence to support this, it is at least possible that adiponectin itself may affect insulin sensitivity and/or insulinemia. For instance, adiponectin has recently been shown to inhibit both the production (in macrophages) and action (in endothelial cells) of TNFα (18, 20), a cytokine which has direct effects on the insulin signaling cascade and has long been implicated as a possible link between obesity and insulin resistance/hyperinsulinemia (6, 7). Alternatively, it has been suggested (14) that adiponectin, which also shares striking structural homology to collagens VII and X and is thus assumed to be a matrix-forming protein, may affect intermediate metabolism by forming matrixes in the interstitium of different tissues. Clearly, experimental studies of the *in vitro* and *in vivo* effects of adiponectin on insulin signaling and glucose metabolism are needed to establish the role of adiponectin, if any, as a molecular link between obesity, insulin resistance, hyperinsulinemia, type-2 diabetes, and atherosclerosis.

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