Decreased Plasma Adiponectin Concentrations Are Closely Related to Hepatic Fat Content and Hepatic Insulin Resistance in Pioglitazone-Treated Type 2 Diabetic Patients

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The effect of pioglitazone (PIO) on plasma adiponectin concentration, endogenous glucose production (EGP), and hepatic fat content (HFC) was studied in 11 type 2 diabetic patients (age, 52 ± 2 yr; body mass index, 29.6 ± 1.1 kg/m²; HbA1c, 7.8 ± 0.4%). HFC (magnetic resonance spectroscopy) and basal plasma adiponectin concentration were quantitated before and after PIO (45 mg/d) for 16 wk. Subjects received a 3-h euglycemic insulin (100 mU/m² and after PIO (45 mg/d) for 16 wk. Subjects received a 3-h euglycemic insulin (100 mU/m² clamp combined with 3-[3H] glucose infusion to determine rates of EGP and tissue glucose disappearance (Rd) before and after PIO. PIO reduced fasting plasma glucose (10.0 ± 0.7 to 7.2 ± 0.6 mmol/liter, \( P < 0.01 \)) and HbA1c (7.8 ± 0.4 to 6.5 ± 0.3%, \( P < 0.01 \)) despite increased body weight (83.0 ± 3.0 to 86.4 ± 3.0 kg, \( P < 0.01 \)). PIO improved Rd (6.6 ± 0.6 vs. 5.2 ± 0.5 mg/kg/min, \( P < 0.005 \)) and reduced EGP (0.23 ± 0.04 to 0.05 ± 0.02 mg/kg/min, \( P < 0.01 \)) during the 3-h insulin clamp. After PIO treatment, HFC decreased from 21.3 ± 4.2 to 11.0 ± 2.4% (\( P < 0.01 \)), and plasma adiponectin increased from 7 ± 1 to 21 ± 2 µg/ml (\( P < 0.0001 \)). Plasma adiponectin concentration correlated negatively with HFC (\( r = -0.60, P < 0.05 \)) and EGP (\( r = -0.80, P < 0.004 \)) and positively with Rd before (\( r = 0.68, P < 0.02 \)) pioglitazone treatment; similar correlations were observed between plasma adiponectin levels and HFC (\( r = -0.65, P < 0.03 \)) and Rd after (\( r = 0.70, P = 0.01 \)) pioglitazone treatment. EGP was almost completely suppressed after pioglitazone treatment; taken collectively, plasma adiponectin concentration, before and after pioglitazone treatment, still correlated negatively with EGP during the insulin clamp (\( r = -0.65, P < 0.001 \)). In conclusion, PIO treatment in type 2 diabetes causes a 3-fold increase in plasma adiponectin concentration. The increase in plasma adiponectin is strongly associated with a decrease in hepatic fat content and improvements in hepatic and peripheral insulin sensitivity. The increase in plasma adiponectin concentration after thiazolidinedione therapy may play an important role in reversing the abnormality in hepatic fat mobilization and the hepatic/muscle insulin resistance in patients with type 2 diabetes. (J Clin Endocrinol Metab 89: 200–206, 2004)

Plasma levels of adiponectin, a glycoprotein secreted only by adipocytes (5), are reduced in obese rodents and humans (6, 7) as well as in humans with type 2 diabetes mellitus (7). It has been suggested that adiponectin might function as an adipostat in regulating energy balance and that its deficiency might contribute to the development of obesity and type 2 diabetes mellitus. Consistent with this hypothesis, Yamauchi et al. (8) have shown that high fat feeding in mice leads to a reduction in fat cell mRNA and circulating adiponectin levels in association with the development of insulin resistance and hyperglycemia. These investigators (8) speculated that adiponectin works primarily in the muscle to burn fat. In mice, Berg et al. (9) and Combs et al. (10) have shown in vivo and in isolated hepatocytes (9) that adiponectin sensitizes the liver to the antiluconeogenic effects of insulin without affecting peripheral glucose disposal (10). These observations are of considerable interest because recent studies from our laboratory (11) and others (12–15) have provided evidence that increased hepatic fat content is an important determinant of hepatic insulin resistance in type 2 diabetic patients. Fatty liver is common in type 2 diabetic patients (16). The mechanisms responsible for the increase in hepatic fat content are unclear. It has been suggested that fatty liver results...
from accelerated fatty acid mobilization from expanded visceral fat stores and their deposition in the liver (17) as well as decreased hepatic fatty acid oxidation (18). Thiazolidinediones have been shown to reduce hepatic fat content and improve hepatic insulin sensitivity in patients with type 2 diabetes (11). The thiazolidinediones initiate their action by binding the peroxisome proliferator activator receptors (PPARγ), which primarily are located on adipocytes (19). Treatment of insulin-resistant mice (20) as well as type 2 diabetic patients (20–23) with insulin sensitizing PPARY activators, such as thiazolidinediones, increases plasma adiponectin levels. Indirect evidence suggests that adiponectin might mediate some of the insulin-sensitizing effects of PPARγ agonists (20, 24). However, no previous study has examined whether the decrease in hepatic fat content and/or the improvement in hepatic insulin sensitivity is related to the thiazolidinedione-mediated increase in plasma adiponectin levels in type 2 diabetic patients.

The current study examined the relationship between plasma adiponectin levels and hepatic fat content as well as hepatic and peripheral tissue sensitivity to insulin in patients with type 2 diabetes mellitus treated with pioglitazone. No previous study has examined the effect of thiazolidinedione on the relationship between changes in plasma adiponectin levels and changes in hepatic insulin sensitivity/hepatic fat content in humans, and this is of great clinical importance when viewed in context of the recent studies by Combs et al. in mice (10).

Subjects and Methods

Subjects

Eleven type 2 diabetic patients [seven men, four women aged 52 ± 2 yr; duration of diabetes, 4 ± 1 yr; hemoglobin A1c (HbA1c), 7.8 ± 0.4%; fasting plasma glucose, 10.0 ± 0.7 mm] participated in the study. The insulin clamp and hepatic fat content data in these 11 subjects were reported in a previous publication (11). Three subjects were taking a stable dose of sulfonylurea drugs (one on chlorpropamide, two on glipizide) for at least 3 months before study, and these were continued during the study period. Eight subjects were treated with diet alone. Patients who ever had received insulin, metformin, or another thiazolidinedione were excluded. Entry criteria included age from 30–70 yr; stable body weight for at least 3 months before the study, and fasting plasma glucose between 7.0 and 14.5 mmol/liter. No subjects participated in any heavy exercise, and none were taking medications known to affect glucose metabolism, i.e. angiotensin-converting enzyme inhibitors, β-blockers, thiazide diuretics, corticosteroids. All patients were in good general health without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by history, physical examination, screening blood tests, and urinalysis. All subjects gave signed voluntary, informed consent before participation. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved the protocol.

Study design

Three weeks before study all subjects met with a dietitian and were instructed to consume a weight-maintaining diet containing 50% carbohydrate, 30% fat, and 20% protein. During the week before the start of pioglitazone treatment, all subjects received: 1) baseline measurement of fasting plasma glucose, free fatty acid (FFA), adiponectin, and insulin concentration, and at the same time blood samples were taken for liver function tests, fasting plasma lipids, and HbA1c; 2) a measurement of liver fat content using proton spectroscopy (25); and 3) a euglycemic insulin (100 mU/m2·min) clamp (26) in combination with 3-H glucose infusion to quantitate whole-body glucose disposal (Rd) and endo-

Euglycemic insulin clamp

Subjects were admitted to the GCRC at 1800 h on the evening before the study and a standard, weight-maintaining meal (50% carbohydrate, 30% fat, and 20% protein) was ingested between 1830 and 1900 h. After 2000 h subjects refrained from eating or drinking anything except water. At 2200 h a catheter was placed in the antecubital vein and a variable low-dose insulin infusion (8–12 μU/m2·min) was initiated to reduce and maintain the plasma glucose concentration to about 100 mg/dl (5.55 mmol/liter). At 0800 h on the following day, a second catheter was inserted retrogradely into a vein on the dorsum of the hand for blood sampling and the hand was placed in a heated box (60°C) for the duration of the study. A euglycemic insulin (100 μU/m2·min) clamp was begun and continued for 3 h. During the 180 min of the euglycemic insulin clamp, a primed (25 μg/min) continuous (0.25 μg/min) infusion of 3-H glucose (started with the onset of insulin infusion) was given to measure endogenous glucose production. Arterialized blood samples were collected every 5 min for plasma glucose determination and a 20% glucose infusion was adjusted to maintain the plasma glucose concentration at about 100 mg/dl (5.55 mmol/liter) (26). Insulin, glucose, and 3-H glucose were infused via the antecubital vein. Blood samples for determination of plasma insulin concentration were obtained every 15–30 min throughout the study. Plasma samples for the determination of 3-H glucose-specific activity were obtained every 5–10 min during the 150- to 180-min period of the euglycemic insulin clamp. During the 150- to 180-min time period of the insulin clamp, the exogenous glucose infusion rate required to maintain euglycemia was constant.

Liver fat content [proton magnetic resonance spectroscopy (MRS)]

Localized 3H nuclear magnetic resonance spectra of the liver were acquired on a 1.9 T magnetic resonance imaging scanner (Elscint Prestige Ltd., Elscint, Haifa, Israel), using a standard body coil in transmitter and receiver mode. An initial T1-weighted spin-echo anatomical magnetic resonance scan for liver MRS localization was performed with the following parameters: repetition time/echo time = 130 msec/15 msec; slice thickness = 7 mm; field of view = 44 cm × 45 cm; number of excitations = 1, and an image matrix = 100 × 256. The slice with the largest gross dimensions of the liver was chosen for the MRS study. MRS for water and fat quantification was accomplished by using a point resolved spectroscopy sequence (25). The imaging parameters for point resolved spectroscopy sequence were as follows: repetition time/echo time = 1500 msec/54 msec; number of averages = 2; and data points = 512. A 3 cm × 3 cm × 3 cm volume (voxel) was selected in the left, right anterior, and right posterior hepatic lobes for scanning to provide a more generalized distribution of fat within the liver. During the measurements, the subject lay supine within the bore of the magnet. The total scan time was approximately 60 min. During the MRS examinations, identical areas of the liver were scanned in the pre- and post-treatment MRS studies of the same subject by the use of anatomical landmarks visualizing images. After line broadening, phase and baseline correction, the peak area
of the water at 4.77 ppm, and fat resonance (Sf) at 1.4 ppm were measured. Quantification of the fat content was done by comparing the area of the Sf with that of the unsuppressed water. Spectroscopic data were processed using the Elscint operating system software. Hepatic fat percentage was calculated by dividing (100 × Sf) by the sum of SF and peak area of the water. This technique is highly reproducible, with a coefficient of variation less than 2% when the same subjects were studied on eight separate days.

**Analytical determinations**

Plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin concentration was measured by RIA (Diagnostic Products Corp., Los Angeles, CA). Tritiated glucose-specific activity was determined on deproteinized plasma by the sum of Sf and peak area of the water. This technique is highly reproducible, with a coefficient of variation less than 2% when the same subjects were studied on eight separate days.

**Statistical analysis**

Statistical calculations were performed with StatView for Windows, version 5.0 (SAS Institute, Cary, NC). Values before and after treatment were compared using paired t test. Linear or logarithmic (for nonlinearly distributed data) regression analysis was used to examine the relationships between hepatic insulin sensitivity, hepatic fat content, and the plasma adiponectin concentration. Statistical significance of the relationship was determined using the ANOVA regression table. Data are presented as mean ± SEM. P < 0.05 was considered to be statistically significant.

**Results**

**Metabolic parameters**

After 16 wk of pioglitazone treatment, body weight increased by 3.4 kg (Table 1). Nonetheless, the fasting plasma glucose concentration decreased significantly from 10 to 7.2 mmol/liter and the HbA1c declined from 7.8 to 6.5% (P < 0.01), in association with a 40% decline in the fasting plasma insulin concentration. Fasting plasma triglyceride (P < 0.05) and FFA (P < 0.01) concentrations decreased significantly after pioglitazone treatment. Total cholesterol, HDL cholesterol, and LDL cholesterol did not change significantly.

**Euglycemic insulin clamp: plasma glucose, insulin, and FFA concentrations**

The plasma glucose concentrations after the overnight insulin infusion were similar during the euglycemic insulin clamp studies performed before and after pioglitazone treatment (6.4 ± 0.2 vs. 6.5 ± 0.2 mmol/liter). During the 3-h euglycemic insulin clamp, the steady-state plasma glucose concentrations were similar before and after pioglitazone (5.5 ± 0.1 vs. 5.5 ± 0.1 mmol/liter). The plasma insulin concentrations did not differ significantly during the 180-min euglycemic insulin clamp performed before and after (1348 ± 115 vs. 1201 ± 109 pmol/liter) pioglitazone treatment. During the 150- to 180-min period of the insulin clamp, suppression of plasma FFA concentration was enhanced after pioglitazone treatment (127 ± 18 vs. 160 ± 18 μmol/liter, P < 0.05).

**Glucose metabolism during the insulin clamp**

After pioglitazone treatment, the insulin-mediated whole-body Rd was significantly increased (6.6 ± 0.6 vs. 5.2 ± 0.5 mg/kg/min, P < 0.005). Suppression of EGP, determined during the 150- to 180-min period of the euglycemic insulin clamp, was significantly enhanced after pioglitazone treatment (0.05 ± 0.02 vs. 0.23 ± 0.04 mg/kg/min, respectively, P < 0.01). Taken collectively, EGP during the 150- to 180-min period, before and after pioglitazone treatment correlated positively with the mean plasma FFA concentrations during the insulin clamp (r = 0.43, P < 0.05).

**Hepatic fat content**

Pioglitazone therapy resulted in a significant decrease (see Fig. 1) in hepatic fat content (21.3 ± 4.2 to 11.0 ± 2.4%, P < 0.01). Before pioglitazone treatment, hepatic fat content was positively correlated (r = 0.63, P < 0.05) with EGP during the euglycemic-insulin clamp. After pioglitazone therapy, EGP was near completely suppressed. Taken collectively, liver fat content, before and after pioglitazone treatment, correlated positively with EGP (see Fig. 3) during the insulin clamp (r = 0.61, P < 0.01).

**Plasma adiponectin concentration**

Pioglitazone therapy resulted in a significant increase (Fig. 1) in plasma adiponectin concentration (7 ± 1 to 21 ± 2 μg/ml, P < 0.0001). Before pioglitazone treatment, the plasma adiponectin concentration was negatively correlated (r = −0.60, P < 0.05) with hepatic fat content (Fig. 2) and with EGP (r = −0.80, P < 0.004) during the euglycemic-insulin clamp. After pioglitazone treatment, plasma adiponectin concentration correlated negatively (Fig. 2) with hepatic fat content (r = −0.65, P < 0.03). EGP was near completely suppressed after pioglitazone therapy. Taken collectively, plasma adiponectin concentration, before and after pioglitazone treatment, still correlated negatively with EGP (Fig. 3) during the insulin clamp (r = −0.65, P < 0.001). The plasma adiponectin concentration correlated positively with whole-

**TABLE 1.** Anthropometric and laboratory measurements before and after pioglitazone treatment for 16 wk

<table>
<thead>
<tr>
<th>Measure</th>
<th>Before</th>
<th>After</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>83.0 ± 3.0</td>
<td>86.4 ± 3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.6 ± 1.1</td>
<td>30.9 ± 1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HaA1c (%)</td>
<td>7.8 ± 0.4</td>
<td>6.5 ± 0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting plasma gluc (mm)</td>
<td>10.0 ± 0.7</td>
<td>7.2 ± 0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting plasma insulin (pm)</td>
<td>72 ± 12</td>
<td>43 ± 6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting plasma FFA (μmol/liter)</td>
<td>703 ± 73</td>
<td>540 ± 48</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>197 ± 8</td>
<td>188 ± 8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>125 ± 8</td>
<td>119 ± 7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>45 ± 3</td>
<td>47 ± 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>138 ± 16</td>
<td>107 ± 17</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.
body Rd during the insulin clamp before (r = 0.68, P < 0.02) and after (r = 0.70, P = 0.01) pioglitazone treatment. When pre- and postpioglitazone treatment results were analyzed collectively, plasma adiponectin concentration correlated with fasting plasma insulin (r = −0.50, P < 0.02), glucose (r = −0.59, P < 0.005), HbA1c (r = −0.61, P < 0.003), HDL cholesterol (r = 0.40, P = 0.06), and triglyceride (r = −0.49, P < 0.02) concentrations.

Discussion

In the present study, we employed the euglycemic insulin clamp technique and hepatic proton spectroscopy to examine the relationship between the plasma adiponectin concentration, hepatic/peripheral insulin sensitivity, and hepatic fat content in type 2 diabetic subjects before and after 16 wk of pioglitazone treatment. The results demonstrate that the marked increase in circulating plasma adiponectin levels after pioglitazone treatment is closely related to the decrease in hepatic fat content and the increase in hepatic insulin sensitivity. We believe that the present investigation is the first study to demonstrate a relationship between plasma adiponectin levels and hepatic insulin sensitivity and hepatic fat content in patients with type 2 diabetes. Furthermore, we show for the first time that the increase in plasma adiponectin concentration after pioglitazone treatment is associated with improvements in both hepatic fat content (decreased) and hepatic insulin sensitivity (increased). The correlation between the pioglitazone-induced increase in plasma adiponectin concentration and peripheral tissue (muscle) glucose disposal is consistent with a recently published paper (23) as well as previous publications demonstrating a relationship between insulin sensitivity and plasma adiponectin concentrations in nondiabetic obese and type 2 diabetic individuals (7). The clinical importance of the pioglitazone-induced increase in plasma adiponectin concentration is underscored by its strong correlation with the reduction in HbA1c (r = −0.61, P < 0.003), fasting plasma glucose (r = −0.59, P < 0.005), and fasting triglyceride concentrations (r = −0.49, P < 0.02).

Some insight into the mechanisms via which adiponectin influences lipid and glucose metabolism in liver and muscle has been gained from in vivo and in vitro studies in animals. Injection of recombinant adiponectin in mice increases fatty acid oxidation in muscle, reduces triglyceride content in
muscle, improves muscle sensitivity to insulin, and decreases basal hepatic glucose output (8–10, 30). In isolated hepatocytes, adiponectin increases the ability of subphysiological levels of insulin to suppress glucose production (9). At the molecular level, adiponectin increases fatty acid transport proteins in muscle and increases the activity of acyltransferase-coenzyme A oxidase and uncoupling protein-2 (8).

This results in an increase of FFA transport/oxidation in muscle and a reduction in plasma FFA and muscle triglyceride concentration (8). Elevated plasma FFA as well as increased triglyceride/fatty acyltransferase-coenzyme A content in muscle led to the development of muscle insulin resistance (31, 32). Adiponectin also has been shown to augment insulin-stimulated tyrosine phosphorylation of the insulin receptor substrate-1 and Akt in the skeletal muscle of mice (8) and a positive correlation between plasma adiponectin levels and insulin-stimulated tyrosine phosphorylation of the insulin receptor in the human skeletal muscle has been demonstrated (33). We previously have demonstrated that impaired insulin-stimulated tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 is a characteristic feature of obesity and type 2 diabetes mellitus (34). Other mechanisms that have been proposed to explain the metabolic effects of adiponectin include an increased expression of PPARα gene, leading to increased fat oxidation (8), and direct activation of AMP-activated protein kinase in the skeletal muscle and liver and subsequent increase in fatty acid oxidation, glucose uptake, and lactate production in the myocytes (35).

Thiazolidinediones initiate their metabolic effects by binding to and activating the PPARγ (36). PPARγ activation causes apoptosis of large fat cells in intraabdominal fat depots and the differentiation of preadipocytes into mature fat cells in sc fat depots along with the induction of key enzymes involved in lipogenesis (37, 38). These effects result in smaller, more insulin-sensitive peripheral adipocytes (37, 38), a shift in fat distribution from visceral to sc fat depots (39, 40), a reduction in circulating plasma FFA levels (39, 41), and an improvement in peripheral insulin sensitivity (41). Previous studies from our laboratory (42) have shown that the weight gain after pioglitazone treatment was associated with significant increases in both superficial and deep abdominal sc adipose depots. Both visceral and hepatic fat content decreased significantly during pioglitazone treatment, although the decrease in visceral fat did not correlate with the decrease in hepatic fat. Adiponectin secretion by visceral adipocytes is enhanced by thiazolidinediones; in contrast, adiponectin secretion by sc adipocytes is unaffected by thiazolidinedione treatment (43). These findings suggest that enhanced adiponectin secretion by visceral adipocytes in response to thiazolidinedione treatment may play a role in the systemic insulin-sensitizing effects of this class of drugs (43). Thiazolidinediones also have been shown to enhance the expression of adiponectin mRNA in cultured 3T3-L1 adipocytes (20), and this effect is believed to be mediated through activation of the adiponectin promoter (20). Although we did not investigate the expression of adiponectin in adipose tissue in the present study, it would be plausible to speculate that the increase in adiponectin levels and the associated decrease in hepatic fat content as well as the improvement in peripheral and hepatic insulin sensitivity after pioglitazone treatment are secondary to increased transcription of adiponectin gene, caused by activation of the transcription factor, PPARγ.

Consistent with in vitro and in vivo effects in animals (37, 38), pioglitazone therapy in the present study was associated with a decrease in fasting plasma FFA concentration in association with a decline in the fasting plasma insulin concentration and improved insulin-mediated suppression of plasma FFA concentrations during the insulin clamp, indicating enhanced sensitivity of adipocytes to insulin. Circulating substrate levels (FFA and glucose) play an important role in the regulation of hepatic triglyceride synthesis (44). Pioglitazone caused a marked reduction in both fasting plasma FFA and glucose concentrations, and this would be expected to result in a decrease in hepatic triglyceride synthesis. Consistent with this, diabetic patients treated with pioglitazone experienced a significant decline in fasting plasma triglyceride concentration (Table 1). Because the plasma adiponectin concentration was correlated inversely with the plasma triglyceride level, it is possible that adiponectin has a direct effect to inhibit hepatic triglyceride synthesis. Lastly, if adiponectin were to stimulate fat oxidation in the liver (35), this could contribute to the decrease in hepatic fat content.

Both before (r = −0.80, P < 0.004) and after pioglitazone (r = −0.65, P < 0.001) treatment, we observed a strong correlation between plasma adiponectin concentration and EGP determined during the 150- to 180-min period of the insulin clamp (Fig. 3). These observations are consistent with the recently demonstrated effect of adiponectin to enhance hepatic sensitivity to insulin (10). Previous studies that have shown impaired suppression of hepatic glucose production by insulin is strongly correlated with increased hepatic fat content in patients with type 2 diabetes (14). We also observed a similar relationship in the present study, i.e., hepatic fat content was correlated with EGP both before (r = 0.63, P < 0.05) and after (r = 0.61, P < 0.01) pioglitazone treatment. These results of the present study strongly suggest that the plasma adiponectin concentration may be the crucial link between hepatic fat content and hepatic insulin sensitivity. With regard to this, adiponectin in has been shown to increase AMP-activated protein kinase activity and reduce the expression of phosphoenolpyruvate carboxylase and glucose-6-phosphatase.

Adiponectin is an adipokine that, in animal models of diabetes, has been shown to have antiatherogenic and anti-inflammatory effects (45). In studies in man, low plasma adiponectin levels have been shown to be associated with peripheral insulin resistance and laboratory manifestations of metabolic syndrome, i.e., increased fasting plasma triglyceride, and plasma glucose concentrations and decreased HDL cholesterol concentration (7, 23). It remains to be investigated whether low plasma adiponectin levels contribute directly or indirectly (by aggravating the individual components of the metabolic syndrome) to accelerated atherosclerosis in patients with metabolic syndrome.

In summary, the present results demonstrate that pioglitazone treatment significantly increases the plasma adiponectin concentration in patients with type 2 diabetes. The
increase in plasma adiponectin levels is associated with a decrease in hepatic fat content and an improvement in hepatic insulin sensitivity. The marked increase in adiponectin concentration after thiazolidinedione therapy may play an important role in reversing the impairment in hepatic fat and glucose metabolism in patients with type 2 diabetes.

Acknowledgments

The authors thank the nurses on the General Clinical Research Center (GCRC) for their diligent care of our patients and especially Patricia Wolff, R.N.; Norma Diaz, B.S.N.; James King, R.N.; and John Kincade, R.N., for carrying out the insulin clamp studies. We gratefully acknowledge the technical assistance of Kathy Camp, Cindy Munoz, Richard Castillo, and Shiela Taylor. Ms. Lorrie Albarado and Ms. Elva Chapa provided skilled secretarial support in the preparation of this manuscript.

Received July 29, 2003. Accepted October 1, 2003.

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This work was supported in part by grants from Takeda America, National Institutes of Health Grant DK-24092, a Veterans Affairs Merit Award, and GCRC Grant MO1-RR01346.

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