Baseline Adiponectin Levels Do Not Influence the Response to Pioglitazone in ACT NOW

DOI: 10.2337/dc13-1745

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OBJECTIVE

Plasma adiponectin levels are reduced in type 2 diabetes mellitus (T2DM) and other insulin-resistant states. We examined whether plasma adiponectin levels at baseline and after pioglitazone treatment in impaired glucose tolerance (IGT) subjects were associated with improved insulin sensitivity (S_I) and glucose tolerance status.

RESEARCH DESIGN AND METHODS

A total of 602 high-risk IGT subjects in ACT NOW were randomized to receive pioglitazone or placebo with a median follow-up of 2.4 years.

RESULTS

Pioglitazone reduced IGT conversion to diabetes by 72% in association with improved β-cell function by 64% (insulin secretion/insulin resistance index) and increased tissue sensitivity by 88% (Matsuda index). In pioglitazone-treated subjects, plasma adiponectin concentration increased threefold from 13 ± 0.5 to 38 ± 2.5 μg/mL ($P < 0.001$) and was strongly correlated with the improvement in S_I ($r = 0.436$, $P < 0.001$) and modestly correlated with glucose area under the curve during oral glucose tolerance test ($r = 0.238$, $P < 0.005$) and insulin secretion/insulin resistance index ($r = 0.306$, $P < 0.005$). The increase in adiponectin was a strong predictor of reversion to normal glucose tolerance and prevention of T2DM. In the placebo group, plasma adiponectin did not change and was not correlated with changes in glucose levels. There was an inverse association between baseline plasma adiponectin concentration and progression to diabetes in the placebo group but not in the pioglitazone group.

CONCLUSIONS

Baseline adiponectin does not predict the response to pioglitazone. The increase in plasma adiponectin concentration after pioglitazone therapy in IGT subjects is strongly related to improved glucose tolerance status and enhanced tissue sensitivity to insulin.

Over 78 million persons in the U.S. have impaired glucose tolerance (IGT), with a rate of conversion to diabetes that varies from 3 to 11% per year (1). Therefore, interventional strategies that successfully reverse the metabolic abnormalities at this early stage of disease could have major benefits in preventing morbidity and mortality from diabetes. Adiponectin is a 244–amino acid collagen-like protein that is expressed by adipocytes and regulates energy homeostasis and glucose and lipid metabolism (2). Adiponectin levels are reduced in insulin-resistant states, such as

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Received 24 July 2013 and accepted 14 February 2014.

Clinical trial reg. no. NCT00220961.7, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-1745/-/DC1.

D.T. and S.C.C. contributed equally to this study.

type 2 diabetes (3,4), and are high in insulin-sensitive states, such as trained athletes (5). In animal models, adiponectin acts via specific receptors, ADIPOR1 and ADIPOR2, in muscle and liver and enhances fatty acid oxidation, mitochondrial function, and glucose uptake (6–8). Transgenic animals with increased adiponectin expression are resistant to diabetes, while animals with low adiponectin expression are prone to diabetes (9,10). Similarly, epidemiologic studies in humans demonstrate that higher fasting levels of adiponectin are associated with a lower risk of type 2 diabetes in a dose-response relationship (11). In the Diabetes Prevention Program (DPP), the ability of lifestyle change or metformin to prevent the conversion of IGT to overt diabetes was related to the baseline adiponectin concentration, with success more likely to occur in subjects with higher baseline levels (11).

Pharmacologic interventions that enhance the secretion of adiponectin and/or adiponectin action may be beneficial in reversing the metabolic abnormalities of IGT and, therefore, be effective in preventing progression to type 2 diabetes. Pioglitazone, a peroxisome proliferator–activated receptor γ activator, markedly increases adiponectin levels (12,13) and increases the expression of genes involved in adiponectin signaling (6). The ACT NOW study demonstrated that treatment of IGT patients with pioglitazone markedly reduced the conversion rate of IGT to overt diabetes (14). In the current study, we explored the relationship between plasma adiponectin levels and changes in glucose tolerance status in the ACT NOW cohort.

RESEARCH DESIGN AND METHODS

Patients

A total of 602 individuals with IGT were followed for a mean of 2.4 years. The details of recruitment, inclusion and exclusion criteria, study design, and patient characteristics have previously been published (14). The study was approved by the institutional review board of the University of Texas Health Science Center. At baseline, all subjects received a 2-h oral glucose tolerance test (OGTT) at 8:00 A.M. after an overnight fast, and plasma samples were obtained every 15 min for 2 h for determination of glucose, insulin, free fatty acid, and C-peptide concentrations. Participants were randomized to pioglitazone (30 mg/day) or placebo. One month after randomization, pioglitazone was increased to 45 mg/day. Baseline measurements were repeated at study end (2 years after recruitment of the last subject), at the time of drop out or loss to follow-up (last observation carried forward), or at time of conversion to type 2 diabetes mellitus (T2DM). Participants at four centers (n = 376) had a frequently sampled intravenous glucose tolerance test (FSIVGTT) at baseline and at study end (15).

Measurements

Plasma glucose was measured by the glucose oxidase reaction, plasma insulin by radioimmunoassay (Diagnostic Products, Los Angeles, CA) (interassay and intra-assay coefficient of variation [CV] 7.1 and 5.1%, respectively), plasma C-peptide by radioimmunoassay (Diagnostic Systems, Webster, TX) (interassay and intra-assay CV 4.3 and 2.4%), and HbA_{1c} with a DCA 2000 Analyzer (Bayer, Leverkusen, Germany). Total plasma cholesterol and triacylglycerol and HDL cholesterol were measured using a commercially available assay (Stanbio Laboratory, Boerne, TX). LDL cholesterol was calculated using the Friedewald equation. Plasma adiponectin, leptin, hsCRP, plasminogen activator inhibitor-1, and other inflammatory cytokines (tumor necrosis factor α, interleukin-6, and macrophage chemotactic factor-1) were measured using a Multiplex assay (Milliplex Human Adipokine Panel, Millipore Corp., Billerica, MA). The interassay and intra-assay CVs for adiponectin were $<$15 and $<$10%, respectively.

Calculations

The incremental area under the curve (AUC) for plasma glucose and insulin during OGTT was calculated according to the trapezoidal rule. The primary stimulus for insulin secretion is the increment in plasma glucose concentration, and insulin section (insulinogenic index) was calculated as the change in plasma insulin concentration (ΔI) (AUC) divided by the change in plasma glucose concentration (ΔG) (AUC) from 0 to 30 min and from 0 to 120 min ($\Delta I/\Delta G$). During the FSIVGTT, first-phase insulin secretion was calculated as the increment in plasma insulin (AUC) from 0 to 10 min. Insulin sensitivity (S_I) was determined from the FSIVGTT. S_I during the OGTT was calculated from the Matsuda index (MI). β-Cell function was calculated as the insulin secretion/insulin resistance (disposition) index ($\Delta I_{0-120}/\Delta G_{0-120} \times$ MI) during OGTT.

Statistical Analysis

Statistical analysis was performed using SPSS, version 19 (Chicago, IL). The difference between values before and after treatment (within placebo and pioglitazone groups) was analyzed using paired Student t test. Spearman or Pearson correlation coefficient was used to examine the relationship between S_I and plasma adiponectin concentration at baseline and the change in S_I and the change in plasma adiponectin concentration after treatment. Study participants were categorized into tertiles of plasma adiponectin at baseline. The risk of development of diabetes based upon tertiles of adiponectin was analyzed by Cox proportional hazard regression. Comparison between the tertiles of adiponectin was performed using ANOVA with Bonferroni post hoc testing when appropriate. Data are presented as mean $\pm$ SEM. Trend analysis for progression to T2DM in both pioglitazone and placebo groups was carried out by the Cochrane-Armigate test.

RESULTS

Baseline Plasma Adiponectin Concentration

Of the entire cohort of 602 subjects, baseline and final adiponectin levels were available in 414 subjects. There was no difference in baseline anthropometric measures between placebo (n = 207) and pioglitazone (n = 207) subjects in whom adiponectin was measured (Table 1). The baseline plasma adiponectin concentrations ranged from 1.5 to 46.7 μg/mL with a median value of 10.0 μg/mL. As expected, women had a slightly higher plasma adiponectin concentration than men at baseline (12.9 $\pm$ 0.5 vs. 10.1 $\pm$ 0.5 μg/mL, respectively; $P < 0.005$). Baseline variables of the cohort, divided into three equal tertiles (138 per tertile) of baseline adiponectin levels, are shown in Table 2. In agreement with previous studies (11), we found positive associations between plasma adiponectin concentration at baseline and age (r = 0.230, $P <$ 0.005), MI (r = 0.277, $P < 0.005$), S_I (r =

Table 1—Baseline clinical, anthropometric, and laboratory data

	Pioglitazone	Placebo
n	207	207
Age (years)	54.2 ± 0.7	52 ± 0.7
BMI (kg/m^2)	33.4 ± 0.4	34.1 ± 0.4
Sex		
Male (*n*)	94	87
Female (*n*)	113	120
HbA_{1c}, % (mmol/mol)	5.52 ± 0.3 (37 ± 2)	5.46 ± 0.3 (36 ± 2)
FPG, mg/dL	105 ± 0.5	108 ± 0.5
2-h PG, mg/dL	109 ± 1.2	170 ± 1.3
FPI, mU/L	10.1 ± 0.6	10.2 ± 0.5
Total chol, mg/dL	170 ± 2.3	171 ± 7.2
LDL chol, mg/dL	105 ± 2.2	106 ± 2.0
TG, mg/dL	121 ± 4	120 ± 2
HDL chol, mg/dL	40.5 ± 7	40.9 ± 2
SBP, mmHg	127 ± 1.1	127 ± 0.2
DBP, mmHg	74 ± 0.6	73 ± 0.07
Adiponectin, μg/mL	11.5 ± 0.5	11.9 ± 0.5

Data are means ± SEM unless otherwise indicated. chol, cholesterol; DBP, diastolic blood pressure; FPI, fasting plasma insulin, PG, plasma glucose, SBP, systolic blood pressure; TG, triglyceride.

0.301, $P < 0.005$), and HDL cholesterol ($r = 0.307$, $P < 0.005$). Measures of adiposity (BMI, waist circumference) ($r = -0.124$, $P = 0.01$, and $r = -0.180$, $P < 0.005$), acute insulin response during FSIVGTT ($r = -0.176$, $P = 0.005$), and plasma triglycerides ($r = -0.176$, $P < 0.005$) were inversely associated with plasma adiponectin concentration at baseline. Of note, measures of glycemia (fasting plasma glucose [FPG], 2-h glucose, glucose $AUC_{0–120\ min}$) were not associated with plasma adiponectin levels at baseline.

Table 2—Clinical characteristics of IGT patients stratified according to tertile of plasma adiponectin concentration at baseline

	Adiponectin tertile		
	1	2	3
Adiponectin			
Mean	5.2 ± 0.1	10.2 ± 0.1	19.7 ± 0.6
Range	1.5–7.6	7.6–13.0	13.1–46.4
Age (years)	50.5 ± 0.9	53.6 ± 0.9	50.2 ± 0.9
Sex (*n*)			
Women	59	84	90
Men	79	53	47
BMI (kg/m^2)	34.4 ± 0.5	34.4 ± 0.5	32.5 ± 0.5
SBP (mmHg)	128 ± 1.3	129 ± 1.4	127 ± 1.4
DBP (mmHg)	74 ± 0.8	73.4 ± 0.8	73 ± 0.8
FPG (mg/dL)	105 ± 0.7	105 ± 0.6	104 ± 0.6
2-h PG (mg/dL)	171 ± 1.5	169 ± 1.5	167 ± 1.5
FPI (mU/L)	12.1 ± 0.7	10.7 ± 0.6	10.4 ± 0.6
Total chol (mg/dL)	167 ± 2.9	171 ± 2.9	173 ± 2.9
TG (mg/dL)	131 ± 5.3	125 ± 4.9	107 ± 9.0
LDL chol (mg/dL)	104 ± 2.0	106 ± 2.6	106 ± 2.6
HDL chol (mg/dL)	32.4 ± 0.8	40.2 ± 0.9	44.7 ± 0.9
MI	3.32 ± 6.2	3.65 ± 0.2	5.02 ± 0.3
$\Delta I_{0–120}/\Delta G_{0–120} \times MI$	3.15 ± 0.2	3.28 ± 0.1	3.33 ± 0.1

Data are means ± SEM unless otherwise indicated. chol, cholesterol; DBP, diastolic blood pressure; FPI, fasting plasma insulin, PG, plasma glucose, SBP, systolic blood pressure; TG, triglyceride.

Figure 1 shows the relationship between the plasma adiponectin concentration at baseline and final glycemic status in placebo and pioglitazone-treated subjects. We observed an inverse association between baseline plasma adiponectin concentration and progression to diabetes in the placebo group ($P < 0.0005$ for trend analysis [Fig. 2*A*]) but not in the pioglitazone group. Pioglitazone markedly reduced the risk of progression to diabetes, and the reduced risk was equal across all tertiles of adiponectin ($P = 0.10$ for trend analysis). Figure 2*B* shows the rate of regression of IGT to normal glucose tolerance (NGT). Reversion of IGT to NGT occurred in 48.3% of the individuals in the pioglitazone-treated group compared with 27.5% in the placebo group (Fig. 2*B*). Baseline adiponectin concentration was not associated with the rate of reversion to NGT in either group.

Change in Plasma Adiponectin Concentration

Treatment with pioglitazone was associated with a marked threefold increase in plasma adiponectin concentration (13 ± 0.5 to 38 ± 2.5 μg/mL, $P < 0.001$), while placebo had no effect on the plasma adiponectin concentration (12 ± 1 to 13 ± 1 μg/mL) (Fig. 2). Pioglitazone-treated subjects who reverted to NGT had higher final plasma adiponectin levels (45.7 ± 4.1 μg/mL) compared with pioglitazone-treated subjects who progressed to diabetes (22.6 ± 10.6 μg/mL). Pioglitazone -treated subjects who remained at IGT had plasma adiponectin levels intermediate between the NGT and diabetic groups (34.0 ± 3.2 μg/mL). There was no significant change in plasma adiponectin concentration in placebo, regardless of final glucose end point.

The change in plasma adiponectin concentration correlated with the improvement in final glucose AUC during the OGTT ($r = 0.238$, $P < 0.005$) and with the change in S_I, measured with the MI ($r = 0.436$, $P < 0.001$) (Supplementary Fig. 1). There was no correlation between final glucose AUC or S_I indices and change in plasma adiponectin concentration in placebo-treated patients.

Measures of β-cell function ($\Delta I/\Delta G$ and $\Delta I/\Delta G \times MI$) increased markedly

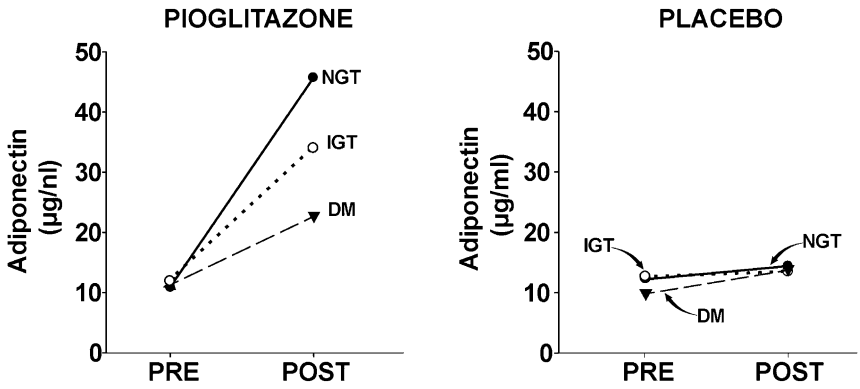

Figure 1—Relationship between the mean change in plasma adiponectin concentration and final glucose tolerance status in pioglitazone-treated and placebo IGT subjects. DM, diabetes mellitus; POST, posttreatment; PRE, pretreatment.

with pioglitazone treatment (5.38 ± 0.3 to 7.6 ± 0.3, $P < 0.005$) and did not change in the placebo-treated group (Fig. 3). However, there was no correlation between the change in plasma adiponectin concentration and β-cell function indices. Correlations between the change in plasma adiponectin concentration and change in measured variables in PIO-treated patients are shown in Supplementary Table 1.

Baseline and Change in Other Cytokines

Plasminogen activator inhibitor-1 levels decreased slightly with pioglitazone therapy (15.1 ± 0.7 to 12.5 ± 0.6 ng/mL, $P < 0.005$). Plasma tumor necrosis factor α, macrophage chemotactic factor-1, interleukin-6, hsCRP, and leptin levels did not change significantly after either pioglitazone treatment or placebo.

Baseline Adiponectin and Development of Diabetes

When subjects were stratified into tertiles of adiponectin at baseline, individuals in the lowest tertile of adiponectin had the highest risk of development of diabetes and those in the highest tertile of adiponectin had the lowest incidence of diabetes (Fig. 4). However, when the pioglitazone-treated and placebo groups were analyzed separately, baseline adiponectin no longer was a predictor of development of diabetes in pioglitazone-treated individuals. The rate of conversion of IGT to T2DM in tertiles 1, 2, and 3 in the placebo group was 29.6, 18.5, and 9.8%, respectively, compared with 5.9, 4.1, and 5.9% in the pioglitazone-treated group ($P < 0.005$, pioglitazone vs. placebo).

Change in Plasma Adiponectin Predicts Response to Pioglitazone Therapy

In pioglitazone-treated individuals, the change in plasma adiponectin was associated with reversion to NGT, as well as protection from development of diabetes. Only 0.5% of pioglitazone-treated individuals in the highest two tertiles of adiponectin response (Δadiponectin >16 ± 0.7 μg/mL) progressed to T2DM compared with 13.2% ($P < 0.005$) of individuals who had the lowest increase in plasma adiponectin (Δadiponectin <0.9 ± 0.37 μg/mL, tertile 1). Similarly, 34% of individuals with the lowest adiponectin response reverted to NGT compared with 61% of individuals with the highest adiponectin response.

CONCLUSIONS

The novel finding in the current study is the strong association between the increase in plasma adiponectin concentration and prevention of type 2 diabetes in high-risk IGT subjects after pioglitazone treatment. Previous studies have demonstrated that the baseline adiponectin concentration is an important predictor for future diabetes. In the DPP, both lifestyle (by 58%) and metformin (by 31%) significantly reduced the progression of IGT to diabetes (16). However, a substantial percent of IGT individuals in

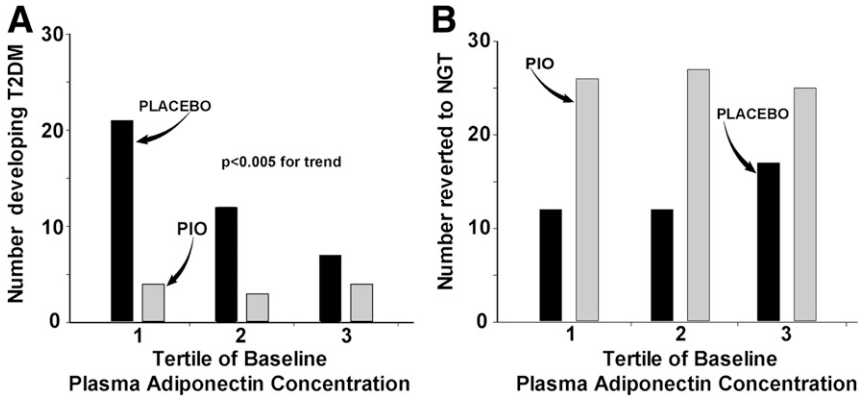

Figure 2—Number of IGT subjects who developed diabetes (*A*) or who reverted to NGT (*B*) after pioglitazone (PIO) treatment or placebo based upon the tertile of plasma adiponectin concentration at baseline. Tertile 3 represents IGT subjects with the highest plasma adiponectin concentration.

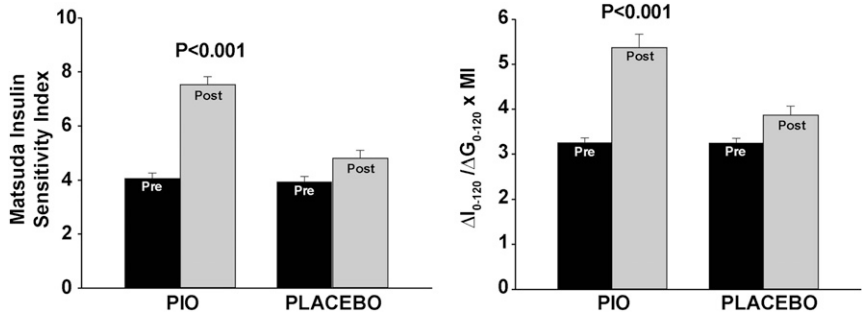

Figure 3—MI of S_I and insulin secretion/insulin resistance index in pioglitazone-treated (PIO) and placebo IGT subjects pretreatment (Pre) and posttreatment (Post).

both groups progressed despite treatment. Analysis of the plasma adiponectin levels in the DPP cohort (11) demonstrated a progressive increase in risk for progression of IGT to diabetes with both lifestyle and metformin treatment when the baseline adiponectin level was <11 μg/mL. This finding suggests that IGT patients with a low plasma adiponectin concentration are resistant to intervention with lifestyle and metformin. In contrast to the DPP study, we found no relationship between efficacy of treatment with pioglitazone (i.e., prevention of conversion of IGT to T2DM) and baseline adiponectin level. This finding implies that patients with a low adiponectin level have a pathophysiologic defect that, while unresponsive to lifestyle change or metformin treatment, is corrected by pioglitazone. Other medications currently available for diabetes treatment (i.e., glucagon-like peptide 1 agonists, dipeptidyl peptidase-4 inhibitors, SGLT-2 inhibitors) may or may not be effective in these IGT patients with low plasma adiponectin levels, and this question is worthy of future study.

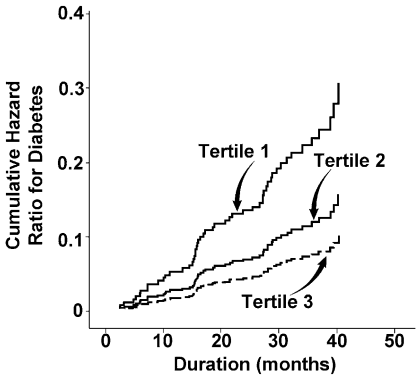

Figure 4—Cumulative hazard ratio for the development of diabetes in IGT subjects stratified according to tertile of plasma adiponectin concentration at baseline. All subjects with pretreatment and posttreatment measurements of plasma adiponectin are included in the analysis. Tertile 3 represents IGT subjects with the highest plasma adiponectin concentration.

Some comments are warranted about the failure to observe any correlation between baseline plasma adiponectin concentration and conversion to diabetes in the pioglitazone-treated group, whereas a significant correlation between these two variables was observed in the placebo group. This apparent discrepancy most likely is explained by multiple factors: *1*) uniformly reduced plasma adiponectin concentration at baseline, i.e., a very narrow range; *2*) the relatively small number of subjects, and *3*) most importantly, the institution of pioglitazone therapy that obliterated any potential relationship between the baseline plasma adiponectin concentration and final glucose tolerance status.

In the pioglitazone-treated group, we observed a strong correlation between the change in plasma adiponectin concentration and the improvement in final glucose tolerance status (Fig. 1). We also observed a significant correlation between the reduction in glucose AUC and the increase in plasma adiponectin concentration in pioglitazone-treated subjects. Previous studies have shown that thiazolidinediones increase adiponectin gene expression and augment plasma adiponectin levels (6,17). Several recent studies have shown that pioglitazone increases the plasma adiponectin concentration without increasing adiponectin gene expression in subcutaneous adipose tissue in subjects with IGT (18) and in cultured adipocytes (19). These results suggest that the peroxisome proliferator–activated receptor γ–mediated increase in adiponectin secretion is due to enhanced translation/posttranscriptional modification. The current findings are consistent with these in vivo and in vitro observations. Whether pioglitazone interferes with the clearance of adiponectin remains unknown.

Of the core defects in T2DM (20), pioglitazone improved both the MI of S_I and the insulin secretion/insulin resistance (disposition) index, which represents the gold standard for β-cell function (Fig. 4). With respect to improvement in these pathophysiologic abnormalities, the increment in plasma adiponectin concentration after pioglitazone therapy was strongly correlated with improvement in MI of S_I ($r = 0.469$, $P < 0.005$) and more modestly with improvement in indices of β-cell function: $\Delta I_{0-120}/\Delta G_{0-120} \times$ MI ($r = 0.306$, $P < 0.005$) and $\Delta I_{0-30}/\Delta G_{0-30} \times$ MI ($r = 0.273$, $P < 0.05$) (Supplementary Table 3). The increment in plasma adiponectin after pioglitazone also was correlated with the decrement in plasma glucose AUC during the OGTT ($r = 0.238$, $P < 0.001$). Although correlations do not prove causality, the strong relationship between improved glucose tolerance and increase in plasma adiponectin concentration suggests that, in part, pioglitazone exerts its beneficial effect on glucose homeostasis via an adiponectin-mediated insulin-sensitizing effect. This is consistent with in vitro and in vivo studies in rodents that have demonstrated that adiponectin enhances S_I in muscle (4,6–8,21,22). The effect of adiponectin on β-cell function has not previously been studied. In the current study, we observed a correlation, albeit weak, between the increment in plasma adiponectin concentration and the

improvement in insulin secretion/insulin resistance index of β-cell function. Whether adiponectin exerts a direct effect to improve β-cell function or an indirect effect secondary to unloading of the β-cell remains to be determined. Lastly, in addition to its effect to increase plasma adiponectin levels, pioglitazone has multiple mechanisms via which it improves S_I and β-cell function (rev. in 20), which could contribute to the marked reduction in the conversion rate of IGT to T2DM (14).

In conclusion, our results support previous observations that the baseline plasma adiponectin concentration is a strong predictor of future diabetes in subjects with IGT. The completely novel observation of the current study is that the increase in plasma adiponectin concentration after pioglitazone treatment correlates strongly with the prevention of T2DM and reversion to NGT in high-risk individuals with IGT. The potential success or failure of a specific medication or lifestyle intervention may be related to how effectively the therapy corrects the underlying pathophysiologic defect responsible for the low plasma adiponectin level.

Acknowledgments. The authors appreciate the enormous and expert help of their nurses and other technical staff without whom this study would not have been possible. The authors are also indebted to the 602 IGT patients who participated in this study. Lorrie Albarado and Amy Richardson of the University of Texas Health Science Center at San Antonio provided expert secretarial assistance in preparation of the manuscript.

Funding. This study was supported in part by General Clinical Research Center grant M01-RR-00221 at the University of Tennessee Health Science Center, Clinical and Translational Science Award grant UL1-TR-000130 to the University of Southern California, and the South Texas Veterans Health Care System–Audie Murphy Division. Part (five-eighths) of R.A.D.'s salary is supported by the Veterans Administration Health Care System. Takeda Pharmaceuticals North America provided the study drug.

Duality of Interest. The study was supported by an investigator initiated and unrestricted research grant from Takeda Pharmaceuticals North America, which also provided the study drug. D.T. reports receiving consultant fees from HDL Diagnostics, Inc. S.C.C. reports that he is a full-time employee of Merck and Co. D.C.S. reports receiving funding of the Phoenix Data Coordinating Center by a Takeda Grant. M.B. reports receiving consulting fees from Sanofi, Merck, Roche, and Boehringer Ingelheim, grants from Takeda and Merck, and fees for participation in review activities from Novartis and Bristol-Myers Squibb (BMS). T.A.B. reports receiving grant support from Allergan and Takeda, serving on an advisory panel for Takeda and speakers bureau for Takeda, and receiving stock options from Tethys Bioscience. A.G. reports receiving grant support from Amylin and Roche and is a consultant for Roche. R.R.H. reports receiving grant support from AstraZeneca, BMS, Eli Lilly, Sanofi, and Medtronic; is a consultant to Boehringer Ingelheim, Gilead, Intarcia, Isis, Eli Lilly, Novo Nordisk, Roche, and Medtronic; and is on the advisory board for Amgen, AstraZeneca, BMS, Gilead, Intarcia, Johnson & Johnson/Janssen, Eli Lilly, Merck, Novo Nordisk, Roche, Sanofi, Daiichi Sankyo, and Elcelyx. S.M. reports being a speaker for Takeda. R.E.R. reports receiving research support from Takeda. P.D.R. reports receiving research grants from BMS and Novo Nordisk and receiving speaker support through Amylin and is a consultant of BMS. R.A.D. reports receiving grants from Amylin, Takeda, and BMS; serves on the advisory board for Amylin, Takeda, BMS, Novo Nordisk, Janssen, and Boehringer Ingelheim; and is on the speakers bureau for Novo Nordisk, BMS, and Janssen. No other potential conflict of interest relevant to this article was reported.

Takeda played no role in the study design, data collection/analysis, or manuscript preparation/review.

Author Contributions. D.T., T.A.B., A.G., P.D.R., and R.A.D. all participated in writing and reviewing the first draft of the manuscript. S.C.C., D.C.S., M.A.B., G.A.B., R.R.H., A.E.K., S.M., R.E.R., F.B.S., and N.M. reviewed the manuscript prior to submission. R.A.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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