Thiazolidinediones improve β-cell function in type 2 diabetic patients

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We studied 11 normal glucose-tolerant and 53 type 2 diabetic (T2DM) subjects. Subjects received 4 mo of treatment with pioglitazone (64) or placebo. Pioglitazone improved OGTT, Hb A1c, and insulin-mediated total body glucose disposal (Rd) (26). Pioglitazone has been shown to augment insulin secretion in obese subjects with combined impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) (12, 32). Similarly, both pioglitazone (10, 63) and pioglitazone (64) reduce the development of diabetes in Latino women with a history of gestational diabetes mellitus by improving insulin sensitivity and preventing the progressive deterioration of β-cell function, as assessed by the acute insulin response to intravenous glucose. We (52) have shown that pioglitazone enhances insulin secretion in type 2 diabetic patients, as assessed by the ΔI/ΔG ratio during the oral glucose tolerance test. Most recently, pioglitazone has been shown to augment insulin secretion in obese subjects with combined impaired fasting glucose (IFG)/IGT (26), whereas rosiglitazone reduced the insulin secretory rate during graded glucose infusion in normal glucose-tolerant (NGT), insulin-resistant individuals (39). Despite this mounting evidence, suggesting an important effect of TZDs on insulin secretion, a systematic examination of β-cell function in type 2 diabetic patients using state-of-the-art techniques has not yet been performed.

In the present study, we report the first comprehensive assessment of β-cell function in type 2 diabetic individuals using state-of-the-art methods to quantitate both insulin secretion and insulin sensitivity in the same individual.

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METHODS

Experimental Design

We examined insulin secretion during the oral glucose tolerance test (OGTT) in 53 type 2 diabetic and 11 NGT subjects matched for age, sex, ethnicity, and body mass index (BMI) while simultaneously taking into account changes in insulin sensitivity. Only diabetic subjects who were healthy, as assessed by medical history, physical examination, routine screening blood tests, urinalysis, and electrocardiogram, were studied. Other than sulfonylureas, no subject was taking any medication known to affect glucose or lipid metabolism. Body weight was stable for ≥3 mo prior to study, and no subject was participating in a heavy exercise program prior to study. Subjects were asked to consume a weight-maintaining diet containing 50% carbohydrate, 30% fat, and 20% protein for 3 days prior to each study.

During the 7- to 10-day period prior to randomization, all subjects had the following: (1) determination of Hb A1c, fasting plasma glucose (FPG), insulin, FFA, and lipid concentrations; (2) OGTT with tritiated H2O to measure fat mass and fat-free mass; and (3) two-step euglycemic hormone (40 and 160 mU·m−2·min−1) clamp with [3-3H]glucose. Diabetic subjects then were randomized to the following protocols: (1) nine drug-naïve subjects were treated with pioglitazone, 45 mg/day; (2) 20 diabetic subjects previously treated with a sulfonylurea were randomized in double-blind fashion to receive pioglitazone, 45 mg/day; (3) nine drug-naïve subjects were treated with pioglitazone, 45 mg/day; (3) 20 diabetic subjects previously treated with a sulfonylurea were randomized in double-blind fashion to receive pioglitazone, 45 mg/day; (4) 12 subjects (n = 10) or placebo (n = 12), with unchanged sulfonylurea dose; and (5) 24 diabetic patients discontinued their sulfonylurea for 6 wk and were then randomized in double-blind fashion to receive rosiglitazone, 8 mg/day (n = 12), or placebo (n = 12). During the 4- to 6-wk period following sulfonylurea withdrawal, the FPG concentration changed by <10% in all diabetic subjects. Following initiation of treatment, subjects returned to the Clinical Research Center every 2 wk for 4 mo. During each visit an interim medical history, pill count, body weight, and FPG concentration were obtained. Hb A1c was determined every 4 wk. After 4 mo of treatment with pioglitazone, rosiglitazone, or placebo, all of the above studies were repeated. All studies were performed on the Clinical Research Center at 8 AM following a 10- to 12-h overnight fast. For subjects who were taking a sulfonylurea, the medication was omitted on the morning of the OGTT and the insulin clamp study.

OGTT

At 8 AM, a catheter was placed into an antecubital vein for the withdrawal of all blood samples. Blood for fasting plasma glucose, FFA, insulin, and C-peptide determinations was obtained at −30, −15, and 0 min. At time 0, subjects ingested 75 g of glucose in an orange-flavored solution, and an intravenous bolus of tritiated water (100 uCi) was given. Following glucose ingestion, blood samples for measurement of plasma glucose, FFA, insulin, and C-peptide concentrations were obtained every 15 min for 2 h. Samples for determination of [3-3H]H2O radioactivity were obtained at 90, 105, and 120 min.

Euglycemic Insulin Clamp

At 8 AM, catheters were inserted into an antecubital vein for the infusion of all test substances and retrogradely into a vein on the dorsum of the hand for withdrawal of all blood samples. The hand was then inserted into a heated box (65°C) for arterIALIZATION of the venous blood. At ~180 min (~120 for nondiabetic subjects) a prime (25 uCi × FPG/100)-continuous (0.25 uCi/min) infusion of [3-3H]glucose (New England Nuclear, Boston, MA) was begun. Blood samples for determination of plasma insulin, glucose, and C-peptide concentrations and tritiated glucose radioactivity were obtained at −30, −20, −10, −5, and 0 min. At time 0, a prime-continuous insulin (40 mU·m−2·min−1) infusion was begun, and the plasma glucose concentration was measured every 5 min for 2 h. After 2 h, the insulin infusion rate was increased to 160 mU·m−2·min−1 for 100 min. In nondiabetic subjects the plasma glucose concentration was maintained at the fasting level by the periodic adjustment of a 20% glucose infusion that was based upon the negative feedback principle (16). In diabetics, after the start of insulin infusion, no glucose was infused until the plasma glucose concentration declined to 100 mg/dl, the level at which it was maintained. During the insulin clamp, plasma samples for determination of tritiated glucose radioactivity were obtained every 15 min from 0 to 90 min, every 5–10 min from 90 to 120 min, every 15 min from 120 to 190 min, and every 5–10 min from 220 to 240 min.

The study protocol was approved by the Institutional Review Board of the University of Texas Health Science Center, and all subjects gave their informed written consent prior to participation.

Analytical Techniques

Plasma glucose was measured by the glucose oxidase reaction (Beckman Glucose Analyzer; Beckman, Fullerton, CA). Plasma insulin was measured by affinity chromatography (Biochemical Methodology, Dower 4350; Isolab, Akron, OH). Plasma FFA was measured by enzymatic calorimetric quantitation (Wako Chemicals, Neuss, Germany). Plasma total cholesterol and triglycerides were measured enzymatically (Roche Molecular Biochemicals, Indianapolis, IN) on a Hitachi 704 autoanalyzer. HDL cholesterol was measured enzymatically on a Hitachi 704 autoanalyzer after precipitation of chylomicrons and very low-density lipoprotein and LDL cholesterol by phosphotungstic acid. LDL cholesterol was calculated from the Friedewald equation. Plasma [3-3H]glucose radioactivity was measured on Somogyi precipitates.

Data Analysis

During the baseline period, both the plasma glucose concentration and plasma [3-3H]glucose specific activity were stable during the last 30 min of tracer infusion in all subjects. Therefore, the rate of endogenous glucose production (EGP) was calculated as the ratio of the [3-3H]glucose infusion rate (DPM/min) to [3-3H]glucose-specific activity (DPM/mg; mean of 5 determinations). Under postabsorptive conditions, the rate of EGP equals the rate of glucose disposal by all tissues in the body. During the insulin clamp, non-steady-state conditions prevail, and the rate of glucose appearance (Ra) was calculated by adding the rate of residual EGP to the exogenous glucose infusion rate during the last 30 min of the insulin clamp and was expressed per kilogram of fat-free mass. The basal hepatic insulin resistance index was calculated as the product of basal rate of EGP and the fasting plasma insulin concentration. Over the range of plasma insulin concentrations that are typically seen under basal conditions (55 ± 3 to 75 ± 4 to 110 ± 4 pmol/l), there is a linear relationship between the increase in the plasma insulin concentration and the decrease in hepatic glucose production (r = 0.92, P < 0.001) (27). Insulin secretion rate (ISR) was calculated from the plasma C-peptide concentrations by deconvolution, as previously described (60). Because the β-cell responds to an increment in plasma glucose concentration by an increment in insulin secretion rate (DPM/mg; mean of 5 determinations). Under postabsorptive conditions, the rate of EGP equals the rate of glucose disposal by all tissues in the body. During the insulin clamp, non-steady-state conditions prevail, and the rate of glucose appearance (Ra) was calculated by adding the rate of residual EGP to the exogenous glucose infusion rate during the last 30 min of the insulin clamp and was expressed per kilogram of fat-free mass. The basal hepatic insulin resistance index was calculated as the product of basal rate of EGP and the fasting plasma insulin concentration. Over the range of plasma insulin concentrations that are typically seen under basal conditions (55 ± 3 to 75 ± 4 to 110 ± 4 pmol/l), there is a linear relationship between the increase in the plasma insulin concentration and the decrease in hepatic glucose production (r = 0.92, P < 0.001) (27). Insulin secretion rate (ISR) was calculated from the plasma C-peptide concentrations by deconvolution, as previously described (60). Because the β-cell responds to an increment in plasma glucose concentration by an increment in plasma insulin concentration, we calculated ΔISR/ΔG and ΔISR/ΔG (23). Since the severity of insulin resistance also influences β-cell function (9, 17, 56), we calculated the insulin secretion/insulin resistance (disposition) index as ΔISR/ΔG + 1/TGD, where TGD equals the rate of insulin-mediated glucose disposal during the euglycemic clamp (23). Parameters of β-cell function (3) were derived from mathematical analysis of plasma glucose and C-peptide concentrations during the OGTT, according to a previously developed model (45, 46). According to this approach,

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glucose-stimulated insulin secretion is the sum of two components. The first is proportional to the rate of change of plasma glucose concentration during the OGTT and is denoted as rate sensitivity. The second component, which represents the dependence of insulin secretion on the absolute glucose concentration at any time point and is characterized by a dose-response relationship, is denoted as glucose sensitivity. The dose-response relationship is modulated by a third factor, called the potentiation factor, that incorporates glucose-mediated and non-glucose-mediated potentiation, i.e., by nonglucose substrates and gastrointestinal hormones (2, 45, 46). Potentiation is a time-dependent phenomenon (3, 45, 46), and the potentiation parameter used for the present analysis is the ratio of the potentiation factor on the absolute glucose concentration at any time point and is characterized by a dose-response relationship, is denoted as glucose sensitivity. The dose-response relationship is modulated by a third factor, called the potentiation factor, that incorporates glucose-mediated and non-glucose-mediated potentiation, i.e., by nonglucose substrates and gastrointestinal hormones (2, 45, 46).

**RESULTS**

**Clinical Characteristics**

*Subjects.* Clinical and laboratory characteristics are shown in Table 1. NGT subjects were well matched to the diabetic groups with respect to age, sex, ethnicity, and BMI. Among the diabetic groups there were no significant differences, with the exception of Hb A1c, which was slightly lower in pioglitazone drug-naïve diabetic group. Within the two sulfonylurea-treated groups there were slightly more males. NGT subjects had higher HDL concentrations but similar values of total cholesterol and triglycerides. All other clinical and laboratory parameters were similar.

*Body weight and composition.* After 4 mo there were no significant changes in body weight, BMI, or fat mass from baseline in either of the placebo groups. In contrast, in the diabetic patients who received TZD treatment for 4 mo (i.e., drug-naïve diabetics treated with pioglitazone, sulfonylurea-treated diabetics receiving pioglitazone, sulfonylurea-withdrawn diabetics treated with rosiglitazone), body weight and BMI increased by 3.5 ± 0.6 kg and 1.22 ± 0.20 kg/m², respectively. In placebo-treated diabetics, neither body weight (+0.2 ± 0.4 kg) nor BMI (+0.08 ± 0.14 kg/m²) changed significantly (P < 0.001, TZD vs. placebo for both body weight and BMI). The increase in body weight was primarily accounted for by an increase in fat mass (3.1 ± 0.5 kg vs. 0.1 ± 0.3 kg in TZD- and placebo-treated groups, respectively, P < 0.0001).

*Glycemic control.* In both placebo-treated groups, the Hb A1c increased by a mean of 1.0 ± 0.3% (P < 0.0001). In the three TZD-treated groups there was a significant decrease in Hb A1c vs. baseline (P < 0.01–0.001) and vs. the respective placebo groups (P < 0.001). The mean Hb A1c decrease in the three TZD-treated groups was 1.6 ± 0.2%. The change in FPG (Table 2) paralleled the change in Hb A1c in all groups.

*Plasma lipids.* Plasma HDL cholesterol was significantly lower at baseline in type 2 diabetes mellitus compared with NGT subjects, and there was a tendency for the HDL cholesterol to increase in the three TZD-treated groups compared in the three TZD-treated groups.
Table 2. Metabolic characteristics during OGTT and insulin clamp

<table>
<thead>
<tr>
<th></th>
<th>NGT subjects</th>
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<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
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<td>FPG, mmol/l</td>
<td>5.1±0.1</td>
<td>9.4±0.6</td>
<td>8.2±0.7*</td>
<td>10.5±0.9</td>
<td>8.0±0.6*</td>
<td>8.9±0.8</td>
<td>10.5±1.2</td>
<td>11.2±0.7</td>
<td>8.4±0.4*</td>
<td>10.3±0.5</td>
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<td>AUC_G, mmol·l⁻¹·h⁻¹</td>
<td>0.87±0.04</td>
<td>1.83±0.11</td>
<td>1.63±0.13†</td>
<td>1.96±0.10</td>
<td>1.59±0.08*</td>
<td>1.71±0.11</td>
<td>1.90±0.14</td>
<td>2.00±0.09</td>
<td>1.58±0.06†</td>
<td>1.93±0.08</td>
<td>1.96±0.09</td>
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<td>FFA, μmol/l</td>
<td>741±75</td>
<td>637±74</td>
<td>590±27</td>
<td>656±45</td>
<td>477±35*</td>
<td>653±51</td>
<td>669±60</td>
<td>736±62</td>
<td>584±61*</td>
<td>682±38</td>
<td>761±63</td>
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<td>FFA (AUC), mmol·l⁻¹·h⁻¹</td>
<td>52±5</td>
<td>60±5</td>
<td>49±3</td>
<td>59±3</td>
<td>41±3*</td>
<td>55±3</td>
<td>61±5</td>
<td>68±4</td>
<td>51±5*</td>
<td>63±5</td>
<td>74±6</td>
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<tr>
<td>FPI, pmol/l</td>
<td>43±6</td>
<td>83±11</td>
<td>70±11</td>
<td>91±20</td>
<td>86±28</td>
<td>105±13</td>
<td>94±12</td>
<td>105±18</td>
<td>73±7</td>
<td>99±21</td>
<td>91±17</td>
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<tr>
<td>AUC_A, mmol·l⁻¹·h⁻¹</td>
<td>43±5</td>
<td>22±5</td>
<td>24±5</td>
<td>24±6</td>
<td>25±7</td>
<td>28±4</td>
<td>26±5</td>
<td>25±6</td>
<td>25±5</td>
<td>22±3</td>
<td>20±3</td>
</tr>
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<td>FCP, pmol/l</td>
<td>560±130</td>
<td>853±81</td>
<td>682±86</td>
<td>803±124</td>
<td>806±93</td>
<td>758±93</td>
<td>844±176</td>
<td>836±87</td>
<td>659±76</td>
<td>899±131</td>
<td>715±146</td>
</tr>
<tr>
<td>CP (AUC), mmol·l⁻¹·h⁻¹</td>
<td>283±30</td>
<td>150±15</td>
<td>168±19</td>
<td>150±22</td>
<td>178±50</td>
<td>152±19</td>
<td>170±43</td>
<td>169±23</td>
<td>165±26</td>
<td>175±22</td>
<td>142±26</td>
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<tr>
<td>Basal R_d = EGP, μmol·min⁻¹·kgFFM⁻¹</td>
<td>15.3±0.6</td>
<td>15.0±1.0</td>
<td>14.8±0.8</td>
<td>16.1±0.8</td>
<td>15.1±0.4</td>
<td>14.2±0.4</td>
<td>15.2±0.6</td>
<td>17.4±0.8</td>
<td>15.4±0.7</td>
<td>16.6±0.5</td>
<td>17.3±0.9</td>
</tr>
<tr>
<td>Clamp R_d (step 1), μmol·min⁻¹·kgFFM⁻¹</td>
<td>51.9±9.9</td>
<td>22.6±2.0</td>
<td>31.9±3.0*</td>
<td>20.5±1.9</td>
<td>21.6±2.4</td>
<td>21.1±1.6</td>
<td>21.6±1.1</td>
<td>16.1±0.9</td>
<td>18.2±1.1</td>
<td>20.5±2.4</td>
<td>20.9±2.1</td>
</tr>
<tr>
<td>Clamp GC (step 1), μmol·min⁻¹·kgFFM⁻¹</td>
<td>7.6±0.9</td>
<td>2.8±0.2</td>
<td>3.9±0.3*</td>
<td>2.5±0.4†</td>
<td>2.9±0.4</td>
<td>2.8±0.3</td>
<td>2.5±0.2</td>
<td>1.7±0.1</td>
<td>2.2±0.2*</td>
<td>2.6±0.4</td>
<td>2.4±0.3</td>
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<tr>
<td>Clamp R_d (step 2), μmol·min⁻¹·kgFFM⁻¹</td>
<td>108.5±7.7</td>
<td>54.0±4.6</td>
<td>74.6±7.0*</td>
<td>38.1±6.4</td>
<td>49.6±6.8*</td>
<td>49.5±3.2</td>
<td>41.8±3.4*</td>
<td>34.0±3.6</td>
<td>47.3±3.6*</td>
<td>43.6±5.7</td>
<td>39.2±5.6</td>
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<tr>
<td>Hepatic IR, pmol/l × μmol·min⁻¹·kgFFM⁻¹</td>
<td>733±74</td>
<td>1,101±151</td>
<td>773±104†</td>
<td>1,558±335</td>
<td>951±147†</td>
<td>1,221±189</td>
<td>1,311±244</td>
<td>1,587±289</td>
<td>1,019±102†</td>
<td>1,175±186</td>
<td>1,477±226</td>
</tr>
</tbody>
</table>

Values are means ± SE. OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; FFA, free fatty acid; AUC, area under curve; FPI, fasting plasma insulin; AUC_G, insulin area under curve; CP, C-peptide; EGP, endogenous glucose production; R_d, insulin-stimulated rate of glucose disappearance; GC, insulin-stimulated rate of glucose clearance; IR, insulin resistance. *P < 0.001–0.0001, post vs. pre and thiazolidinediones (TZD) vs. placebo; †P < 0.05–0.01, post vs. pre and TZD vs. placebo.
with the placebo-treated groups (0.04 ± 0.03 vs. −0.03 ± 0.03 mM, P = 0.08). In the two pioglitazone-treated groups there was a significant decrease in plasma triglyceride concentration (P < 0.01). Rosiglitazone did not alter the plasma triglyceride concentration. Total and LDL cholesterol decreased slightly, but not significantly, in the pioglitazone-treated groups and increased slightly but not significantly in the rosiglitazone-treated groups.

Metabolic Characteristics

OGTT. Before treatment, the fasting plasma glucose, insulin, C-peptide, and FFA concentrations during the OGTT were similar in the two placebo and three thiazolidinedione-treated groups (Fig. 1 and Table 2). After 4 mo of TZD treatment, the fasting plasma glucose concentration declined significantly in all three TZD groups compared with placebo (Δ = −2.3 ± 0.4 vs. Δ = 1.1 ± 0.7 mM, P < 0.001–0.0001 for TZD vs. placebo and vs. baseline). The incremental area under the plasma glucose curve (AUC) also decreased significantly in the TZD-treated groups (Δ = −0.07 ± 0. mol·L⁻¹·120 min⁻¹, P < 0.001 vs. baseline) and rose slightly in the two placebo-treated groups (Δ = 0.01 ± 0.03 mol·L⁻¹·120 min⁻¹, P < 0.05 vs. TZD groups).

There were no significant changes in fasting plasma insulin or C-peptide concentrations in any group. There were also no significant changes in the mean plasma insulin or C-peptide concentrations or the incremental areas under the plasma insulin or C-peptide curves in any of the five treatment (TZDs or placebo) groups.

Fig. 1. Plasma glucose (left), insulin (middle), and free fatty acid (FFA; right) concentrations during the oral glucose tolerance test (OGTT) performed before and after 4 mo in drug-naïve diabetic patients treated with pioglitazone (PIO; A), sulfonylurea (SU)-treated diabetic patients receiving pioglitazone (B), SU-treated diabetic patients receiving placebo (PLC; C), SU-withdrawn diabetic patients receiving rosiglitazone (ROSI; D), and SU-withdrawn diabetic patients receiving PLC (E).
Table 3. Parameters of β-cell function

<table>
<thead>
<tr>
<th></th>
<th>Drug-Naive T2DM</th>
<th>SU-Treated T2DM</th>
<th>SU-Diabetes Withdrawn</th>
<th>Pioglitazone</th>
<th>Placebo</th>
<th>Rosiglitazone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ISR, pmol/min^{-1} m^{-2}</td>
<td></td>
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<tr>
<td>NGT Subjects</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Post</td>
</tr>
<tr>
<td>73 ± 13</td>
<td>114 ± 11</td>
<td>89 ± 11</td>
<td>106 ± 15</td>
<td>112 ± 36</td>
<td>111 ± 19</td>
<td>106 ± 21</td>
<td>103 ± 12</td>
</tr>
</tbody>
</table>

Total ISR, nmol/m^{-2}:

|                         |                |                |                       |              |         |                |         |
|-------------------------|----------------|----------------|                       |              |         |                |         |
| 42 ± 5                  | 23 ± 2         | 28 ± 3         | 25 ± 3                | 28 ± 6       | 29 ± 5  | 28 ± 6        | 27 ± 4  |

ΔISR (AUC)/ΔG (AUC): [ΔISR (AUC)/ΔG (AUC)]

|                         |                |                |                       |              |         |                |         |
|-------------------------|----------------|----------------|                       |              |         |                |         |
| 234 ± 48                | 34 ± 11        | 40 ± 11        | 33 ± 9                | 37 ± 29      | 45 ± 58 | 42 ± 9        | 39 ± 9  |

β-Cell glucose sensitivity, pmol/min^{-1} m^{-2} m^{-1}:

|                         |                |                |                       |              |         |                |         |
|-------------------------|----------------|----------------|                       |              |         |                |         |
| 118 ± 22                | 14 ± 3         | 28 ± 6*        | 17 ± 4                | 25 ± 5*      | 21 ± 5  | 19 ± 8        | 17 ± 5  |

β-Cell rate sensitivity, pmol/m^{-2} m^{-1}:

|                         |                |                |                       |              |         |                |         |
|-------------------------|----------------|----------------|                       |              |         |                |         |
| 1,400 ± 370             | 23 ± 48        | 485 ± 136      | 102 ± 49              | 384 ± 101*   | 269 ± 92| 224 ± 78      | 413 ± 106|

Potentiation factor:

|                         |                |                |                       |              |         |                |         |
|-------------------------|----------------|----------------|                       |              |         |                |         |
| 2.0 ± 0.4               | 1.0 ± 0.1      | 1.2 ± 0.1      | 1.0 ± 0.1             | 1.0 ± 0.1    | 0.9 ± 0.1| 1.0 ± 0.2     | 0.9 ± 0.1|

Values are means ± SE. ISR, insulin secretion rate; I, insulin; G, glucose. *P < 0.01–0.001 pre vs. post and TZD vs. placebo.

The fasting plasma FFA concentration did not change significantly in either placebo group (mean Δ = +34 ± 46 μmol/l), whereas the fasting FFA declined in all three TZD treated groups (mean Δ = −139 ± 32 μmol/l). The mean plasma FFA concentration (AUC) decreased significantly in all three TZD-treated groups (mean Δ = −15.0 ± 2.7 mol·1^{-1} · 120 min^{-1}, P < 0.0001 vs. baseline) and increased slightly in the two placebo-treated groups (Δ = +7.6 ± 4.1 mol·1^{-1} · 120 min^{-1}, P < 0.0001 vs. TZD group).

Basal and insulin-stimulated glucose disposal (Rd). Prior to treatment, the basal rate of tissue glucose uptake (which equals the rate of EGP) and the insulin-stimulated Rd during the insulin clamp were similar in all five diabetic groups. Compared with NGT subjects, all diabetic subjects in the present study were very resistant to the action of insulin (P < 0.001). In all three TZD-treated groups, insulin sensitivity during the insulin clamp improved significantly, especially during second insulin step clamp (P < 0.05–0.001). No change in insulin sensitivity was observed in either placebo-treated group.

Basal EGP was unchanged in the two placebo groups and declined slightly, although not significantly, in the three TZD-treated groups. The basal hepatic insulin resistance index (EGP × fasting plasma insulin) improved significantly (P < 0.05–0.01) in all three TZD-treated groups.

β-Cell Function

During the OGTT, the ratio of the incremental AUC of insulin to the incremental AUC of plasma glucose concentration increased significantly in all three TZD-treated groups and did not change significantly in the two placebo groups (5.9 ± 2.9 vs. −3.8 ± 2.0, P < 0.03, for TZD vs. placebo and vs. baseline; Table 3). Similarly, the incremental AUC of ISR to the incremental AUC of plasma glucose concentration increased significantly (P < 0.01–0.001 for TZD vs. baseline and vs. respective placebo control). Because insulin secretion increases progressively with worsening severity of insulin resistance (IR) (23, 32, 52, 60, 63, 64), we also calculated in secretion/IR (disposition) index ΔI(AUC)/ΔG(AUC) ÷ IR and ΔISR(AUC)/ΔG(AUC) ÷ IR, where IR = 1/(Rd/I) and Rd is the insulin-mediated rate of glucose disposal measured during the first-step euglycemic insulin clamp and I is the steady-state plasma insulin concentration during the insulin clamp. When insulin secretion is accessed using ΔISR (AUC)/ΔG (AUC) ÷ IR or ΔI(AUC)/ΔG(AUC) ÷ IR, TZD therapy markedly increased β-cell function in drug-naïve (placebo), sulfonylurea-treated (pioglitazone), and sulfonylurea-withdrawn, diet-treated (rosiglitazone) diabetic subjects (P < 0.001 for TZD vs. baseline and vs. respective control placebo control group; Fig. 2). Placebo treatment had no effect on ΔISR (AUC)/ΔG (AUC) ÷ IR or ΔI(AUC)/ΔG(AUC) ÷ IR (Fig. 2).

Using a previously validated model of β-cell function (45, 46), we examined the effect of TZD therapy on the three major dynamic parameters of β-cell function: β-cell glucose sensitivity, β-cell rate sensitivity, and potentiation. At baseline, all parameters of β-cell function were markedly and significantly reduced in diabetics compared with NGT subjects. Both pioglitazone and rosiglitazone increased β-cell glucose sensitivity.

![TYPE 2 DIABETES MELLITUS](http://ajpendo.physiology.org/ by 10.20.33.3 on July 7, 2017)
1.5- to twofold in drug-naïve diabetic subjects (P < 0.001 vs. baseline and respective placebo control). The increase in β-cell glucose sensitivity when pioglitazone was added to sulfonylurea-treated diabetics (P < 0.001 vs. baseline and vs. respective control group) was virtually identical to that observed in drug-naïve patients. Placebo treatment had no significant effect on β-cell glucose sensitivity. Similarly, rate sensitivity increased two- to threefold in both pioglitazone-treated groups, whereas no effect was observed in the placebo groups. Rosiglitazone-treated diabetic subjects did not show any change in rate sensitivity. However, prior to the start of rosiglitazone, this parameter was significantly higher than the baseline value of rate sensitivity in the two pioglitazone-treated groups. Following 4 mo of pioglitazone, the value for rate sensitivity had increased to the baseline value observed in the rosiglitazone group. Neither TZD nor placebo treatment had any effect on β-cell potentiation.

**Correlation Analyses Between Metabolic and Clinical Parameters**

Prior to TZD/placebo treatment, ΔISR (AUC)/ΔG (AUC) ÷ IR was related to the fasting plasma glucose concentration and to the 2-h plasma glucose concentration during the OGTT, and the typical hyperbolic plot was observed (Table 4). Log transformation of the variables yielded a strong linear relationship between ΔISR (AUC)/ΔG (AUC) ÷ IR and both the FPG concentration (r = 0.83, P < 0.0001) and the 2-h plasma glucose concentration during the OGTT (r = 0.89, P < 0.00001; Fig. 3). This strong correlation indicates that glucose tolerance is a direct and linear function of β-cell function. Significant correlations were observed between the change, after TZD/placebo treatment, in ΔISR (AUC)/ΔG (AUC) ÷ IR and the changes in body weight and percent fat mass as well as with the change in plasma FFA concentration (AUC) during OGTT (r = −0.33, P < 0.01; Fig. 6).

None of the β-cell indexes, determined from the model of β-cell function, were correlated with changes in clinical parameters such as body weight or percent fat mass. When the dynamic parameter of β-cell glucose sensitivity (45, 46) is plotted against the 2-h plasma glucose concentration during the OGTT and against ΔISR (AUC)/ΔG (AUC) ÷ IR, a strong linear relationship is observed (Fig. 4). The improvements in β-cell glucose sensitivity and rate sensitivity were correlated

### Table 4. Correlation coefficients of regression analysis between changes in insulin secretion indexes, insulin sensitivity, and clinical and metabolic parameters after 4 months of TZD treatment

<table>
<thead>
<tr>
<th>Change in</th>
<th>[ΔISR(AUC)/ΔG(AUC)]</th>
<th>R0-s1</th>
<th>R0-s2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, kg</td>
<td>0.31</td>
<td>&lt;0.03</td>
<td>0.28</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>0.30</td>
<td>&lt;0.04</td>
<td>0.29</td>
</tr>
<tr>
<td>FPG, mM</td>
<td>−0.41</td>
<td>&lt;0.005</td>
<td>−0.32</td>
</tr>
<tr>
<td>PG120, mM</td>
<td>−0.51</td>
<td>&lt;0.0002</td>
<td>−0.40</td>
</tr>
<tr>
<td>Fasting FFA, mM</td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mean FFA0–120, mM</td>
<td>−0.36</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>FFA (ΔAUC), mM</td>
<td>NS</td>
<td>−0.27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>R0-s1, μmol/min⁻¹kg⁻¹FFM⁻¹</td>
<td>0.40</td>
<td>&lt;0.005</td>
<td>NS</td>
</tr>
<tr>
<td>R0-s2, μmol/min⁻¹kg⁻¹FFM⁻¹</td>
<td>0.40</td>
<td>&lt;0.004</td>
<td>NS</td>
</tr>
<tr>
<td>ISR (ΔAUC), pmol/m⁻²</td>
<td>0.45</td>
<td>&lt;0.002</td>
<td>0.43</td>
</tr>
<tr>
<td>Glucose sensitivity*</td>
<td>0.63</td>
<td>&lt;0.0001</td>
<td>0.28</td>
</tr>
<tr>
<td>Rate sensitivity*</td>
<td>0.41</td>
<td>&lt;0.004</td>
<td>NS</td>
</tr>
<tr>
<td>Potentiation*</td>
<td>0.31</td>
<td>&lt;0.03</td>
<td>NS</td>
</tr>
</tbody>
</table>

BW, body weight; PG120, plasma glucose concentration at 120 min during the OGTT; R0-s1 and R0-s2, insulin-mediated rate of glucose disposal during the first and second steps of the insulin clamp; NS, not significant. *Model-derived parameters of β-cell function (36, 37).
with the reduction in FPG concentration and with the improvement in insulin secretion, insulin sensitivity, and $\Delta\text{ISR}/\Delta \text{G} / \Delta \text{IR}$ (Fig. 5).

**DISCUSSION**

The TZDs were developed as insulin sensitizers, and they have proven to be very efficacious in improving glycemic control and reducing the Hb A1c (8, 13, 40, 44, 48–50, 53). Although the primary insulin-sensitizing action of the TZDs was believed to be exerted on muscle, they also have been shown to improve hepatic sensitivity to insulin (5, 6, 50) and to inhibit hepatic gluconeogenesis (24, 25). Most recently, evidence has accumulated to suggest that the TZDs also may enhance β-cell function. In rodent models of type 2 diabetes, improved insulin secretion and β-cell histology have been demonstrated following chronic TZD treatment (18, 29, 31, 36, 47). In humans with type 2 diabetes mellitus (40, 44, 48–50, 52) and impaired glucose tolerance (10, 12, 41, 63), TZD treatment has been associated with either no change or a modest reduction in the plasma insulin response to both oral
and intravenous glucose. The decline in plasma insulin response has generally been interpreted to represent the normal β-cell response to improved insulin sensitivity and/or reduced plasma glucose concentration (9, 14, 17, 33, 34, 56). However, several studies in man suggest that the TZDs exert beneficial effects on β-cell function. Using a graded glucose infusion in individuals with impaired glucose tolerance, Cavanagh et al. (12) demonstrated that troglitazone did not change or increased slightly the slope of the line relating the plasma insulin response to the increment in plasma glucose concentration. In a more recent study from the same laboratory (39), the investigators reported a decrease (rightward shift) in the slope of the line relating the ISR to the increase in plasma glucose concentration during a stepped intravenous glucose infusion in NGT insulin-resistant subjects. The authors interpreted the difference between their most recent results (39) and their previous report (12) to the different study populations. Thus, in the NGT insulin-resistant subjects, β-cell function is intact and the improvement in insulin sensitivity unloads the β-cell, leading to a reduction in the elevated ISR. In their previous study (12) of IGT subjects, β-cell function was more severely compromised at the start of TZD therapy, and the improvement in insulin sensitivity was accompanied with no change or a slight increase in ISR. Troglitazone has also been shown (12) to normalize the abnormal oscillatory insulin secretory response to glucose that was present in subjects with IGT.

Because TZDs improve insulin sensitivity and lower the plasma glucose concentration, both of which would be expected to reduce the plasma insulin response, one cannot utilize the absolute plasma insulin concentration to access the β-cells’ response to a hyperglycemic challenge. Moreover, the β-cell responds to an increment in plasma glucose concentration (ΔG) with an increment in plasma insulin response (ΔI) (3). In a recent study, we (52) evaluated ΔI/ΔG from 0 to 120 min in poorly controlled type 2 diabetics who were treated with pioglitazone for 4 mo. A highly significant, dose response (15 to 30 to 45 mg/day of pioglitazone)-related increase in ΔI/ΔG from 0 to 120 min was observed in diabetic patients treated with pioglitazone compared with placebo. Because insulin sensitivity was not assessed independently in this previous study, the complete impact of pioglitazone on β-cell function could not be evaluated. In fact, no previous study in type 2 diabetic subjects has examined the effect of TZDs on the ISR while simultaneously taking into account the glucose stimulus (ΔG) and the severity of insulin resistance.

In the present study we have examined the effect of two different TZDs, pioglitazone and rosiglitazone, on β-cell function during an OGTT by using two independent methods. The first approach used ΔI/ΔG and ΔISR/ΔG from 0 to 120 min of the OGTT and related ΔI/ΔG and ΔISR/ΔG to the change in insulin sensitivity, which was quantitated on a separate day using the euglycemic insulin clamp technique. The second approach employed a mathematical model of β-cell function (45, 46) to provide quantitative information about the three dynamic parameters, glucose sensitivity, rate sensitivity, and potentiation, that determine β-cell function (3). To examine whether prior treatment influenced the response to TZD treatment, we studied drug-naïve, sulfonylurea-treated, and sulfonylurea-withdrawn type 2 diabetic patients. Using both approaches (ΔI/ΔG0–120 +IR and the model of β-cell function), we observed that both pioglitazone and rosiglitazone significantly improved β-cell function in drug naïve, sulfonylurea-treated, and sulfonylurea-withdrawn type 2 diabetic subjects.

Following 4 mo of treatment, insulin sensitivity improved similarly in all TZD-treated groups and remained unchanged in both placebo-treated groups (Table 2). When the incremental insulin secretory response (AUC) per incremental plasma glucose response (AUC) from 0 to 120 min was expressed in relationship to the severity of insulin resistance (ΔISR/ΔG0–120 × IR), both pioglitazone and rosiglitazone were found to enhance β-cell function by a similar amount in drug-naïve and sulfonylurea-withdrawn diabetic subjects, respectively (Fig. 2). The magnitude of improvement in ΔISR/ΔG × IR following pioglitazone treatment in drug naïve diabetics was about twofold greater (Δ = 1.4 vs. 0.7, P < 0.05) than in sulfonylurea-treated patients (Fig. 2). It is noteworthy that the duration of diabetes in the sulfonylurea-treated diabetics was significantly longer than in the drug naïve group (6 vs. 2 yr, P < 0.01). Sulfonylurea-treated diabetic patients also had a higher starting Hb A1c (Table 2). These observations suggest that the beneficial effects of pioglitazone on β-cell function may diminish as a function of diabetes duration and severity of hyperglycemia or, more likely, some combination of the two. Nonetheless, a beneficial effect of the TZDs on β-cell function was observed in diabetic subjects with moderately poor to very poor glycemic control (Hb A1c ranging from 7.9 ± 0.4% in drug naïve patients to 9.1 ± 0.3% in sulfonylurea-treated diabetics; Table 1). Since the duration of the present study was only 4 mo, it remains to be determined whether this beneficial effect on β-cell function will be maintained after several years of TZD therapy.

We also evaluated the effect of TZD treatment on β-cell function, utilizing a novel β-cell model (45, 46) that allows quantitation of the three major dynamic parameters that influence insulin secretion (3). Following 4 mo of pioglitazone or rosiglitazone treatment, β-cell glucose sensitivity, i.e., the ability of the β-cell to respond to a given change in plasma glucose concentration, improved ~2- to 2.8-fold in drug naïve, sulfonylurea-treated, and sulfonylurea-withdrawn diabetic patients (Fig. 2). To the best of our knowledge, this represents the first demonstration that, in type 2 diabetic individuals, TZDs enhance β-cell sensitivity to glucose. β-Cell rate sensitivity, i.e., the ability of the β-cell to respond to the rate of change in plasma glucose concentration, increased two- to threefold in both pioglitazone-treated groups. Although rosiglitazone did not increase rate sensitivity, the starting value in this group (113 pmol·m·s–2·mM–1) was similar to the posttreatment values in both pioglitazone-treated diabetic groups (Table 3). β-Cell potentiation, i.e., the ability of the β-cell to respond to nonglucose stimuli, was not influenced by TZD treatment. The insulin secretion/insulin resistance index (ΔISR/ΔG × IR) provides the same basic information as the glucose sensitivity parameter derived from the β-cell model. We found a very strong correlation between ΔISR/ΔG × IR and glucose sensitivity (r = 0.78, P < 0.0001; Fig. 4), providing further validation of the model (45, 46) employed to examine the dynamic parameters of β-cell function.

PPARγ receptors have been found to be expressed in human β-cells, but their expression is low (19, 42). Although a direct effect of the TZDs to enhance insulin secretion by pancreatic β-cells cannot be excluded, the paucity of pancreatic PPARγ receptors suggests an indirect effect of the TZDs to enhance...
insulin secretion. Studies in rodent models of type 2 diabetes (21, 29, 55, 59) have demonstrated that accumulation of triglycerides and metabolites of FFA within the β-cells plays a causal role in the development of impaired insulin secretion. Conversely, treatment with TZDs has been shown to mobilize fat out of the β-cells and enhance β-cell function in these animal models of type 2 diabetes (18, 21, 29, 31, 36, 47, 55, 59). Recent studies in humans who are genetically predisposed to develop type 2 diabetes (11, 34) have demonstrated that lipid infusion to increase the plasma FFA concentration impairs insulin secretion. Conversely, a reduction in plasma FFA concentration with acipimox in these genetically predisposed individuals improves both first- and second-phase insulin release (35, 55). Consistent with these in vivo observations, prolonged exposure of human pancreatic islets in vitro has been shown to have cytostatic and proapoptotic effects that can be prevented completely by inhibition of upstream caspases and prevented partially by inhibition of ceramide synthesis or serine protease activity (43). In the present study we observed an inverse correlation between the change in ΔISR/ΔG ÷ IR and the decrement in plasma FFA (ΔAUC) during the OGTT (r = −0.33, P < 0.01; Fig. 6). This observation suggests that part of the beneficial effect of TZDs on β-cell function may be related to reversal of lipotoxicity (7, 59). The reductions in fasting plasma FFA (r = 0.42, P < 0.001) and mean FFA during the OGTT (r = 0.49, P < 0.0002) were also correlated with the decrement in Hb A1c.

TZD treatment usually is associated with weight gain (8, 13, 53). Nonetheless, glycemic control improves, and the greater the weight gain, the greater the decrease in Hb A1c (7, 40, 44, 48–50). This apparent paradox is explained by the TZD-induced alteration in fat topography, which is characterized by a reduction in visceral, hepatic, and muscle fat and an increase in subcutaneous fat (5–7, 48, 50). In the present study, tissue fat distribution was not assessed. However, body weight and fat mass increased following TZD treatment (Table 1) and, as in previous studies (49, 50) the increases in body weight (r = −0.57, P < 0.0001) and fat mass (r = −0.56, P < 0.0001) were correlated inversely with the decrement in Hb A1c. The changes in body weight (r = 0.38, P < 0.01) and fat mass (r = 0.37, P < 0.01) were also positively correlated with the improvement in β-cell function, as assessed by the change in ΔISR/ΔG ÷ IR. Because the increases in body weight and fat mass parallel the remodeling of fat, one could hypothesize that a similar redistribution of fat out of the β-cell contributes to TZD-related improvement in β-cell function.

We also observed significant correlations between the change in ΔISR (AUC)/ΔG (AUC) ÷ IR following TZD treatment and the decreases in Hb A1c (r = 0.27, P < 0.05), FPG (r = −0.47, P < 0.001), and 2-h plasma glucose concentration during the OGTT (r = −0.51, P < 0.001). These observations can be interpreted in one of two ways. In these insulin-resistant type 2 diabetic subjects, β-cell function, i.e., ISR, is an important determinant of glycemic control. Conversely, it could be argued that hyperglycemia inhibits β-cell function, i.e., glucotoxicity (58), and that the TZD-induced reduction in day-long plasma glucose concentration that results from enhanced tissue sensitivity to insulin is responsible for the improvement in β-cell function.

Diabetic subjects in all five treatment groups were markedly resistant to insulin-stimulated glucose disposal (Table 2). Following TZD treatment, a significant increase in Rd was observed in all TZD-treated groups. Changes in insulin secretion, both ΔISR (AUC)/ΔG (AUC) (r = 0.34, P < 0.02 vs. Rd-s1, r = 0.38, P < 0.006 vs. Rd-s2) and β-cell glucose sensitivity (r = 0.31, P < 0.03 vs. Rd-s1, r = 0.32, P < 0.03 vs. Rd-s2), were correlated to the changes in insulin sensitivity following TZD treatment. The mechanism via which the improvement in insulin sensitivity results in or is associated with an improvement in β-cell function remains to be determined. It commonly is stated that insulin resistance, by placing an increased demand on the β-cell to augment its insulin secretion, leads to an acceleration of β-cell failure. However, this descriptive explanation does not address the causality of the association. Our results suggest two potential explanations that are not mutually exclusive. First, TZD treatment leads to enhanced adipocyte sensitivity to the antilipolytic effect of insulin (7, 48, 49), and the resultant decline in plasma FFA concentration (Table 1), in combination with altered (reduced) tissue fat content (5–7, 48, 50), leads to improvements in both β-cell function and tissue sensitivity to insulin, i.e., amelioration of lipotoxicity (7, 59). Second, the reduction in mean plasma glucose concentration following TZD treatment leads simultaneously to enhanced β-cell function and to increased insulin sensitivity, i.e., ame-

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**Fig. 6.** Top: relationship between the insulin secretion/insulin resistance index [ΔISR (AUC)/ΔG (AUC) ÷ IR] and the log of the plasma FFA (AUC) during the OGTT in type 2 diabetic patients before (○) and after (●) treatment with PLC or TZDs. Bottom: relationship between the change in the insulin secretion/insulin resistance index [ΔISR(AUC)/ΔG(AUC) ÷ IR] and change in FFA (AUC) in type 2 diabetic patients treated with TZDs (●) and PLC (○).
loration glucotoxicity (58). Alternative explanations also can be invoked. Thus it is possible that TZDs alter the release of inflammatory and insulin-sensitizing adipocytokines (i.e., TNF-α, adiponectin, resistin, IL-6, and others) from fat cells and that alterations in these adipocytokines simultaneously influence both β-cell function and tissue sensitivity to insulin in a positive manner (reviewed in Ref. 7). TZD treatment has been shown to decrease plasma TNF-α and resistin concentrations and to increase plasma adiponectin levels in association with enhanced muscle and hepatic insulin sensitivity (5, 6, 51).

It also is possible that TZDs exert a direct effect on the pancreatic β-cells to enhance insulin secretion. PPARγ is expressed in all three human pancreatic endocrine cell types: β, α, and δ (42). However, exposure of these non-diabetic human islets to rosiglitazone had no effect on either basal or glucose-stimulated insulin secretion. Nonetheless, these short-term TZD incubation studies would not exclude an anti-apoptotic effect, which has been observed with chronic in vivo rosiglitazone treatment of Zucker diabetic fatty rats (21). Consistent with this possibility, addition of troglitazone to cultured islets from Zucker fatty rats improves glucose-stimulated insulin secretion (59), and PPARγ activation directly induces the expression of the GLUT2 glucose transporter and glucokinase, critical regulators of glucose-stimulated insulin secretion in cultured primary rat islets and insulinoma cell lines (37, 38). Although targeted elimination of PPARγ in β-cells does not inhibit the in vivo response to intravenous glucose or lead to an impairment in glucose homeostasis in insulin-resistant mice, the stimulatory effect of troglitazone on isolated islets is completely eliminated in these PPARγ deficient β-cell mice (57). Thus a direct effect of the TZDs on the β-cell, directed via the PPARγ receptor, to augment insulin secretion and prevent β-cell apoptosis cannot be excluded.

It should be noted that, although the improvement in glycemic control (ΔHb A1c = 1.3–2.3%) was considerable, the increase in β-cell function (to 15–20% of values in healthy controls; Table 3) was relatively small. This is explained by the observation that the improvement in glycemic control (FPG and 2-h plasma glucose during OGTT) and insulin secretory response are log related. Therefore, even a small increase in β-cell function would be expected to exert a major beneficial effect on blood glucose levels, and this effect would be further amplified in the presence of only mild to modest increments in insulin sensitivity (Table 2). The log relationship between plasma glucose concentration and both insulin secretion and insulin sensitivity predicts that, especially at extremes of β-cell function and insulin resistance, small (beneficial) changes in either parameter will exert a profound effect (reduction) on the plasma glucose concentration.

Recently, several studies (22, 30) have demonstrated that certain sulfonylureas (glimepiride > glyburide) possess PPARγ activity, and one could question what impact this might have on the present observations. Several comments are warranted. First, the PPARγ agonistic effects of both glimepiride and glyburide (34) were observed only at concentrations that were more than 10- to 20-fold greater than the plasma levels required to exert a glucose-lowering effect in man. Second, the PPARγ effects were not seen or were quite weak with other sulfonylureas. In the present study we observed a similar beneficial effect of pioglitazone on β-cell function in drug-naïve, sulfonylurea-withdrawn, and sulfonylurea-treated type 2 diabetic patients. This argues strongly that the presence or absence of the sulfonylurea (along with any associated PPARγ activity of the sulfonylurea) could not have any impact on the TZD-mediated improvement in β-cell function. Moreover, within the 10 sulfonylurea-treated subjects who received pioglitazone, eight were on glyburide, 10 were on glipizide, and two were on chlorpropamide. The improvement in β-cell function (ΔISR/ΔG ÷ IR) was observed in all 10 diabetic subjects and was of similar magnitude in each individual despite the different sulfonylureas that were ingested. Since the PPARγ effect was described only with pharmacological concentrations of glimepiride and glyburide, this further argues against any influence of the sulfonylurea in the present results.

Last, we observed a significant improvement in β-cell function (ΔISR/ΔG ÷ IR) in the present study, whereas most (10, 39, 41, 63) but not all (12, 26) previous studies have reported a decrease in insulin secretion following TZD treatment. Previous investigators (10, 63) have attributed the decline in insulin secretion to the improvement in insulin sensitivity and “unloading” or “rest” of the β-cell. Two comments are warranted. First, most of these previous studies did not express the insulin secretory response as a function of the glycemically stimulated insulin response (21, 29, 31, 36, 47, 54, 55). Second, one needs to take into account where the individual is on the β-cell function curve at the time of initiation of the TZD therapy. We (1, 15, 20, 23) have shown previously that relationship between insulin secretion and plasma glucose concentration resembles an inverted U-shaped curve. If one starts with insulin resistance and normal or only slightly impaired glucose tolerance (implying relatively well-preserved β-cell function), one might expect an improvement in insulin sensitivity to be associated with a decline in the elevated plasma insulin response, which represents a compensatory response to the underlying insulin resistance. On the other hand, if one has tipped over the top of Starling’s curve of the pancreas (35) and β-cell function is significantly reduced, one might expect the TZD-induced improvement in insulin sensitivity to be associated with an increase in β-cell function, especially if the TZD exerted a direct effect on the β-cell to enhance insulin secretion (21, 29, 31, 36, 47, 54, 55).

In summary, the present results demonstrate that chronic treatment of suboptimally controlled type 2 diabetic individuals with both pioglitazone and rosiglitazone improves glycemic control by enhancing insulin sensitivity and augmenting β-cell function. The improvement in β-cell function is primarily related to increased β-cell sensitivity to glucose and was documented by two independent measures, the insulin secretion/insulin resistance index [ΔISR(AUC)/ΔG (AUC) ÷ IR] and glucose sensitivity derived from a novel model of β-cell function. The increment in insulin secretion was the major determinant of the decrement in 2-h plasma glucose concentration during the OGTT and was correlated with the reduction in Hb A1c, the decrement in plasma FFA concentration during the OGTT, and the improvement in insulin sensitivity.
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