**Effect of Rosiglitazone Versus Insulin on the Pancreatic β-Cell Function of Subjects With Type 2 Diabetes**

**Fernando Ovalle, MD, FACE**

**David S.H. Bell, MB, FACE**

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**OBJECTIVE** — In a previous study, we found observational evidence of improvement in β-cell function when rosiglitazone was added to a failing oral antihyperglycemic regimen consisting of sulfonylureas and metformin. To confirm our previous observations, we designed and performed a prospective, randomized, and controlled study.

**RESEARCH DESIGN AND METHODS** — A total of 17 subjects with type 2 diabetes, inadequately controlled on a maximized oral antihyperglycemic double regimen of glimepiride and metformin, were randomized to the addition of rosiglitazone or insulin to their treatment regimens for a period of 6 months. At baseline and at 6 months, the following were performed: measurement of fasting plasma glucose, fasting proinsulin, and insulin levels; frequently sampled intravenous glucose tolerance test; and glucagon stimulation test for C-peptide.

**RESULTS** — Nine subjects were randomized to the addition of 8 mg rosiglitazone, and eight subjects were randomized to the addition of one injection of insulin (premixed 70/30) before their evening meal. The treatment groups were well matched for age, duration of diabetes, and BMI. Most important, the HbA1c was well matched between groups before treatment (8.7 ± 0.3 and 9.0 ± 0.3%; NS) and at the end of the 6 months (7.8 ± 0.5 and 7.8 ± 0.3%; NS). After 6 months, at the end of the study, there was a significant improvement in acute insulin response to glucose in the rosiglitzone group (+15.3 μU·mL⁻¹·min⁻¹; P < 0.001) that led to an increase in the disposition index from 0.18 at baseline to 4.18 at 6 months (P = 0.02). Furthermore, at the end of the study, the proinsulin-to-insulin ratio had decreased in the rosiglitzone group by 36% (P = 0.03) but did not change significantly in the insulin treatment group.

**CONCLUSIONS** — Rosiglitazone, but not insulin, induced a recovery of pancreatic β-cell function, as evidenced by the restoration of the first-phase insulin response to glucose, improvement in the disposition index, and a decrease in the proinsulin-to-insulin ratio in subjects with type 2 diabetes in whom oral antihyperglycemic therapy failed. This improvement was independent of the correction of glucotoxicity.

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From the Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, The University of Alabama at Birmingham School of Medicine, Birmingham, Alabama.

Address correspondence and reprint requests to David S.H. Bell, MB, 510 S. 20th St., Rm. 702, Birmingham, AL 35294. E-mail: dshbell@uab.edu.

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**Abbreviations:** A1C, acute insulin response to glucose; AUCab, area under the curve above the baseline; FFA, free fatty acid; fsIVGTT, frequently sampled intravenous glucose tolerance test; HOMA, homeostasis model assessment; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Pancreatic \( \beta \)-cell function in type 2 diabetes

Table 1—Baseline characteristics of treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Insulin</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 ( \pm ) 4</td>
<td>56 ( \pm ) 5</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7.6 ( \pm ) 2.1</td>
<td>7.6 ( \pm ) 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>31.5 ( \pm ) 2.3</td>
<td>30.8 ( \pm ) 1.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means \( \pm \) SE.

Proinsulin was measured by enzyme-linked immunosorbent immunoassay (Nichols Institute, San Clemente, CA). At baseline and after 6 months of therapy, an intravenous glucose tolerance test (ISIVGTT) was performed to determine the acute insulin response to glucose (AIRg) as a way to evaluate first-phase insulin response to glucose. Additionally, a glucagon stimulation test for C-peptide was performed 1 week after the ISIVGTT. C-peptide was measured using a double-antibody C-peptide kit (reference range 1.0–5.0 ng/ml). All tests were performed 1 week after the ISIVGTT, venous blood samples for measurement of serum insulin were collected at baseline (average of 10 and \( \pm \)4 min samples) and at +2, +3, +4, +5, +6, +8, and +10 min after an intravenous bolus of glucose calculated at a dose of 300 mg/kg of body weight given over 60 s starting at time 0. The AIRg was calculated as the area under the curve above the baseline (AUC\(_{\text{ab}}\)) as a way to evaluate first-phase insulin sensitivity and calculating the disposition index, which was calculated as the product of AIRg and the disposition index.

Insulin resistance was calculated at baseline and at 6 months using the following homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) formula: (insulin [micro–International Units/milliliter] \( \times \) glucose [millimoles/liter])/22.5. For calculation purposes, the reciprocal of IR (1/IR) was used as the insulin sensitivity index (\( S_i \)).

\( S_i \) function was determined by the disposition index, which was calculated as the product of AIRg and \( S_i \). Statistical analysis was performed using two-tailed Student’s \( t \) tests for most comparisons except for the ISIVGTT, which was analyzed using a one-way ANOVA and performed using GraphPad Prism Version 4.00 for Windows (GraphPad Software, San Diego, CA). Data are shown as means \( \pm \) SE. \( P \) values <0.05 were considered statistically significant.

**RESULTS** — As shown in Table 1, the groups were well matched for age, BMI, and duration of diabetes. Furthermore, and most importantly, HbA1c was well matched among study groups before the start of the study and decreased to the same level after treatment in both groups (Table 2, Fig. 1).

The AIRg increased significantly, from a baseline of 1.42 to 16.71 \( \mu \text{U} \cdot \text{ml}^{-1} \cdot 10 \text{ min}^{-1} \) at 6 months (+15.3 \( \mu \text{U} \cdot \text{ml}^{-1} \cdot 10 \text{ min}^{-1} \) [AUC\(_{\text{ab}}\)]; \( P \leq 0.001 \)), in the rosiglitazone group but not in the insulin group, in which there was a nonsignificant decrease from a baseline of 8.43 to 7.23 \( \mu \text{U} \cdot \text{ml}^{-1} \cdot 10 \text{ min}^{-1} \) at 6 months (—1.2 \( \mu \text{U} \cdot \text{ml}^{-1} \cdot 10 \text{ min}^{-1} \) [AUC\(_{\text{ab}}\)]; NS) (Fig. 2).

As expected, rosiglitazone induced a significant improvement (92.3% increase) in insulin sensitivity (Table 3). \( S_i \) was calculated using the reciprocal of the HOMA method as described above.

Furthermore, the disposition index increased significantly in the rosiglitazone-treated group from a baseline of 0.18 to 4.18 at 6 months (\( P = 0.02 \)); meanwhile, the insulin-treated group experienced a nonsignificant decrease from a baseline of 1.86 to 1.23 at 6 months (NS) (Fig. 3).

Although no differences between groups were observed when looking at the raw C-peptide data obtained during the glucagon-stimulated C-peptide tests, we found significant differences when adjusting for the differences in insulin sensitivity and calculating the disposition index. The rosiglitazone-treated group demonstrated a significant (+43%) increase in the disposition index compared with a nonsignificant decrease (—9.4%) in the insulin group after 6 months of therapy (Table 4).

Furthermore, the proinsulin-to-insulin ratio, which was equally elevated

Table 2—Mean HbA1c and FPG at baseline and end of study

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Insulin</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HbA1c (%)</td>
<td>8.7</td>
<td>9.0</td>
<td>NS</td>
</tr>
<tr>
<td>6-month HbA1c (%)</td>
<td>7.8</td>
<td>7.8</td>
<td>NS</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Baseline FPG (mg/dl)</td>
<td>186.3</td>
<td>171.7</td>
<td>NS</td>
</tr>
<tr>
<td>6-month FPG (mg/dl)</td>
<td>142.6</td>
<td>145.3</td>
<td>NS</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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**Figure 1**—Insulin and rosiglitazone both reduce HbA1c levels. Insulin (INS) and rosiglitazone (RSG) therapy achieve similar levels of glycemic control. Values are means \( \pm \) SE.
Rosiglitazone group 0.13 0.25 0.038
Insulin group 0.22 0.17 0.049
HOMA-IR (1/HOMA).
and development of diabetes is avoided (8). The damage to the β-cell is caused by elevated FFA, its metabolite ceramide, nitric oxide, and peroxinitrite levels, leading to accelerated β-cell apoptosis (9,10). In addition, increased FFA levels decrease the expression of the IDX-1 gene, which is responsible for the formation of new β-cells from stem cells in the pancreatic duct (11). Rosiglitazone has been shown in animal studies to decrease islet cell triglyceride levels and increase stainable insulin in both the db/db mouse and the Zucker diabetic fatty rat models (12,13).

Autopsy studies of human β-cells have shown that with aging, more fat accumulates in the pancreatic β-cells of the islets of Langherhans than in the α-cells or the pancreatic duct cells and that apoptosis rather than decreased formation of β-cells is responsible for the decreasing β-cell mass seen in type 2 diabetes (14,15). Therefore, in the absence of unethical pancreatic biopsy studies in type 2 diabetic patients, we must assume that the mechanism of pancreatic β-cell destruction and its correction with rosiglitazone is similar to that seen in animal models.

Because rosiglitazone and perhaps other TZDs differ from the currently available therapies for type 2 diabetes in their ability to rejuvenate pancreatic β-cells, these drugs should be used at the earliest possible opportunity in the course of type 2 diabetes and not withheld until the later stages of the disease (16). In this study, the average duration of diabetes was 7.6 years. It should be noted that determining the exact date of onset of type 2 diabetes may be a difficult task and, in general, type 2 diabetes goes unrecognized for several years before being diagnosed. In this study, the time of onset was determined by patient recollection and review of medical records.

There are potential limitations of this study that need to be discussed. One of these is the difference (9 years) in the mean age between the two treatment groups; although this difference was not statistically different, a negative effect of aging on β-cell function has been shown by some investigators (17). Nonetheless, the fact that the baseline AIRg was better in the insulin group and that both groups had similar proinsulin-to-insulin ratios at baseline seems to make this age difference irrelevant. Another potential limitation of this study is the lack of determination of hepatic insulin extraction, which can potentially account for differences in proinsulin-to-insulin ratio (18).

In conclusion, this study demonstrates that rosiglitazone, but not insulin, helps to induce a recovery of pancreatic β-cell function, as evidenced by the restoration of the first-phase insulin response to glucose. This effect was in independent of the correction of glucose toxicity.

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