Response of Pancreatic β-Cells to Improved Insulin Sensitivity in Women at High Risk for Type 2 Diabetes

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The purpose of this study was to examine the response of pancreatic β-cells to changes in insulin sensitivity in women at high risk for type 2 diabetes. Oral glucose tolerance tests (OGTTs) and frequently sampled intravenous glucose tolerance tests (FSIGTs) were conducted on Latino women with impaired glucose tolerance and a history of gestational diabetes before and after 12 weeks of treatment with 400 mg/day troglitazone (n = 13) or placebo (n = 12). Insulin sensitivity was assessed by minimal model analysis, and β-cell insulin release was assessed as acute insulin responses to glucose (AIR_g) and tolbutamide (AIR_t) during FSIGTs and as the 30-min incremental insulin response (30-min dINS) during OGTTs. β-Cell compensation for insulin resistance was assessed as the product (disposition index) of minimal model insulin sensitivity and each of the 3 measures of β-cell insulin release. In the placebo group, there was no significant change in insulin sensitivity or in any measure of insulin release, β-cell compensation for insulin resistance, or glucose tolerance. Troglitazone treatment resulted in a significant increase in insulin sensitivity, as reported previously. In response, AIR_g did not change significantly, so that the disposition index for AIR_g increased significantly from baseline (P = 0.004) and compared with placebo (P = 0.02). AIR_t (P = 0.001) and 30-min dINS (P = 0.02) fell with improved insulin sensitivity during troglitazone treatment, so that the disposition index for each of these measures of β-cell function did not change significantly from baseline (P > 0.20) or compared with placebo (P > 0.3). Minimal model analysis revealed that 89% of the change from baseline in insulin sensitivity during troglitazone treatment was accounted for by lowered plasma insulin concentrations. Neither oral nor intravenous glucose tolerance changed significantly from baseline or compared with placebo during troglitazone treatment. The predominant response of β-cells to improved insulin sensitivity in women at high risk for type 2 diabetes was a reduction in insulin release to maintain nearly constant glucose tolerance. *Diabetes* 49:782–788, 2000

There is mounting evidence that quantitative and qualitative defects in pancreatic β-cell function precede the onset of type 2 diabetes. Cross-sectional comparisons between groups at low and high risk for the disease have revealed insulin responses to nutrients that are inappropriately low for the degree of insulin resistance frequently encountered in the high-risk groups (1,2). Longitudinal studies in high-risk ethnic groups (3–6) and in women with gestational diabetes mellitus (GDM) (7–9) have identified poor insulin responses to oral glucose to be predictive of the development of diabetes. At present, the extent to which chronic insulin resistance contributes to the development or worsening of these early defects in β-cell function is not known.

Three groups (10–12) have reported small (12–15%) but statistically significant improvements in glucose tolerance in association with relatively larger (28–100%) improvements in insulin sensitivity in people with impaired glucose tolerance who were treated with the insulin-sensitizing drug troglitazone. Approaches to and results of β-cell function testing varied among the studies. Insulin levels during oral glucose tolerance tests (OGTTs) fell by 34–114% (10–12). Acute insulin responses to intravenous glucose remained constant (11) or increased (12) despite improved insulin sensitivity, leading to the conclusion that β-cell compensation for insulin resistance had improved. Entrainment of insulin secretion by oscillatory glucose infusions also improved in the 2 studies in which it was assessed (11,12).

We (13) recently found no significant improvement in oral or intravenous glucose tolerance despite significant improvement in insulin sensitivity during 12 weeks of troglitazone treatment in a group of Latino women with a history of GDM. In the present report, we examine changes in several quantitative aspects of β-cell function in relation to insulin sensitivity in those high-risk women to address the discrepancy between amelioration of insulin resistance and changes in glucose levels.

RESEARCH DESIGN AND METHODS

Subjects. Subjects whose data were analyzed for this report participated in a 12-week randomized trial (13) of troglitazone treatment in Latino women with impaired glucose tolerance and a recent history of GDM, characteristics that carry an 80% risk of developing type 2 diabetes within 5 years (14). Details of subject recruitment have been published previously (13). Briefly, the women were >18 years of age; they had had GDM (15) within the prior 4 years; they had impaired glucose tolerance by World Health Organization criteria (16) when not pregnant; they were using a reliable method of contraception; and they had no evidence for medical problems that could be detected from a medical history, physical examination, serum chemistries, urinalysis, and a hemogram. There were 14 women assigned to treatment with 400 mg/day troglitazone, and 14 were assigned to placebo. Data for the present report are from the 13 women in the former group and 12 women in the latter group who completed 12 weeks of treatment. All participants gave written informed consent for participation in the study, which was approved by the Institutional Review Board of the Los Angeles County and the University of Southern California Medical Center.

Study design. Participants had baseline OGTTs and frequently sampled intravenous glucose tolerance tests (FSIGTs) at the General Clinical Research Center (GCRC). The tests were conducted <10 days apart and after 10- to 12-h overnight fasts. Subjects were then randomized to receive troglitazone or placebo for 12 weeks. Compliance with study medication, assessed by monthly pill counts, was >90% in each group. During the 12th week of treatment, women returned to the GCRC at least 24 h after the most recent dose of study medication and after a 10- to 12-h overnight fast for an OGTT. They returned 3–5 days later and 24 h after the final dose of study medication for an FSIGT.

Clinical testing. OGTTs were performed according to National Diabetes Data Group guidelines for nonpregnant individuals (17). Subjects were kept to bed rest during the test, and blood samples were obtained from an indwelling antecubital venous catheter before and 30, 60, 90, and 120 min after ingestion of 75 g D-glucose. Samples were placed on ice and centrifuged immediately, and plasma was stored at –20°C.

For FSIGTs, D-glucose (300 mg/kg as a 50% solution in water) was given in an antecubital vein over 1 min, followed by an injection of tolbutamide 20 min later (Orinase Diagnostic; Upjohn, Kalamazoo, MI) at 125 mg/m^2 body surface area. Blood samples were obtained from a heated hand vein in the contralateral hand at –15, –5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, 180, 210, and 240 min relative to the start of the glucose injection. Samples were placed on ice and plasma was separated within 20 min and stored at –20°C.

Laboratory analyses. Glucose was measured by glucose oxidase (Beckman Glucose Analyzer II; Beckman Instruments, Brea, CA). Insulin was measured by a radioimmunoassay (Linco Research, St. Charles, MO), which provided <0.2% cross-reactivity with proinsulin. Glucose and insulin concentrations from baseline and 12-week tests for each subject were run in the same assay to eliminate the effects of interassay variation.

Data analysis. Insulin sensitivity (S_I) was calculated from FSIGT insulin and glucose results using a minimal model analysis program, MINMOD (18), provided by Dr. Richard Bergman. Areas below glucose and insulin curves were calculated by the trapezoid method. Total and incremental areas were calculated for OGTT glucose. Incremental areas above the plasma insulin value immediately before the stimulus (glucose or tolbutamide) were calculated for FSIGTs. Glucose tolerance during selected intervals of FSIGTs was calculated as the slope of the line relating the natural log of the plasma glucose concentrations to time (K_g) during the period of interest.

The relationship between first-phase insulin responses to intravenous glucose and insulin sensitivity has been shown to be hyperbolic in cross-sectional studies, allowing the use of the insulin sensitivity-secretion product (the "disposition index" [19–21]) to assess β-cell compensation for insulin resistance. For the present study, 3 measures of β-cell insulin release were tested for their relationship to S_I using pretreatment data from all 25 subjects: *1*) the acute insulin response to intravenous glucose (AIR$_g$) (incremental plasma insulin area during the first 10 min after the glucose injection), *2*) the acute insulin response to intravenous tolbutamide (AIR$_t$) during FSIGTs (incremental plasma insulin area during the first 20 min after the tolbutamide injection), and *3*) the early insulin response to oral glucose (30-min incremental insulin response [30-min dINS]) (rise in plasma insulin concentration above basal 30 min after glucose ingestion). In each case, the relationship between the log of the measure of insulin release and the log of S_I was evaluated by least squares regression analysis. The slope of each relationship was tested for a difference from –1 using the method of perpendicular least squares with proper weighting (22) and our published coefficients of variation for S_I and AIR$_g$ (23) to account for variability in independent as well as dependent variables.

For normally distributed variables, within-group comparisons of pre- and posttreatment variables were made by paired *t* tests, and between-group comparisons of changes from baseline were made by nonpaired *t* tests. OGTT fasting and 0- to 30-min incremental insulin concentrations were not normally distributed. Medians for those variables were compared by Wilcoxon signed-rank test within groups and Wilcoxon ranked sum test between groups.

Changes in ambient plasma glucose and free fatty acid (FFA) concentrations can alter insulin responses to glucose (24–26). Accordingly, data from the placebo group were analyzed by linear regression to identify relationships between changes from baseline in glucose or FFA concentrations and changes from baseline in relevant β-cell response parameters. Changes in β-cell responses during troglitazone treatment were then analyzed before and after adjustment for any relationships observed in the placebo group to account for any impact of ambient nutrient concentrations per se on the β-cell responses. For AIR$_g$, which represents an acute release of insulin from the pancreas in response to a maximal glucose stimulus (27), changes in FSIGT fasting glucose concentrations were used for the adjustment. For AIR$_t$, changes in the mean of the 19- to 40-min FSIGT glucose concentrations were used, since β-cells were exposed to tolbutamide for a finite period after the tolbutamide injection. For the OGTT 30-min incremental insulin response, changes in the OGTT fasting and 30-min glucose concentrations and the OGTT fasting and 30-min FFA concentrations were used, since β-cells were exposed to these nutrients during the 0- to 30-min period.

Data are presented as mean ± SD in text and mean ± SE in figures. All reported *P* values are 2-sided. Adjustment for small intergroup differences in age and BMI did not alter the results in any important way, so the unadjusted data are presented.

RESULTS

Women who completed 12 weeks of troglitazone or placebo treatment were similar with regard to age (35 ± 7 vs. 33 ± 5 years, *P* > 0.20) and BMI (30.9 ± 6.7 vs. 32.3 ± 6.4 kg/m^2, *P* > 0.60). BMI did not change significantly during 12 weeks of treatment in either group (*P* > 0.30).

Relationships between each of the 3 β-cell response parameters and S_I are shown in Fig. 1. In each case, there was a significant linear correlation between the log of the β-cell measure and the log of S_I (log AIR$_g$ vs. log S_I: *r* = –0.57, *P* = 0.003; log AIR$_t$ vs. log S_I: *r* = –0.68, *P* = 0.0002; log OGTT 30-min dINS vs. log S_I: *r* = –0.55, *P* = 0.006). None of the slopes of these relationships was significantly different from –1 (log AIR$_g$ vs. log S_I: slope = –1.03, *P* = 0.92; log AIR$_t$ vs. log S_I: slope = –0.95, *P* = 0.82; log OGTT 30-min dINS vs. log S_I: slope = –0.86, *P* = 0.61). These findings support the existence of hyperbolic relationships and the use of sensitivity-secretion products (disposition indexes [19–21]) to assess β-cell compensation for insulin resistance.

Insulin sensitivity increased significantly during 12 weeks of troglitazone treatment, but did not change significantly from baseline in women who received placebo (Table 1). The change in S_I was significantly greater in the troglitazone group (Table 1), as reported previously (13). AIR$_g$ did not change significantly in either group or differently between groups (Table 1). Fasting plasma insulin concentrations and AIR$_t$ fell significantly (by 38 and 31%, respectively) in association with increased insulin sensitivity during troglitazone treatment (Table 1). Neither of these parameters changed significantly from baseline in the placebo group (Table 1). The difference between groups in the degree of change from baseline was highly significant for AIR$_t$ but of borderline significance for fasting insulin (Table 1). Adjustments for changes in fasting and 19- to 40-min plasma glucose concentrations during troglitazone treatment confirmed the lack of change in AIR$_g$ (*P* = 0.74) and the significant reduction in AIR$_t$ (*P* = 0.0001) during troglitazone treatment.

Plots of individual relationships between insulin sensitivity and AIR$_g$ (Fig. 2*A*) revealed a tendency for patients in the
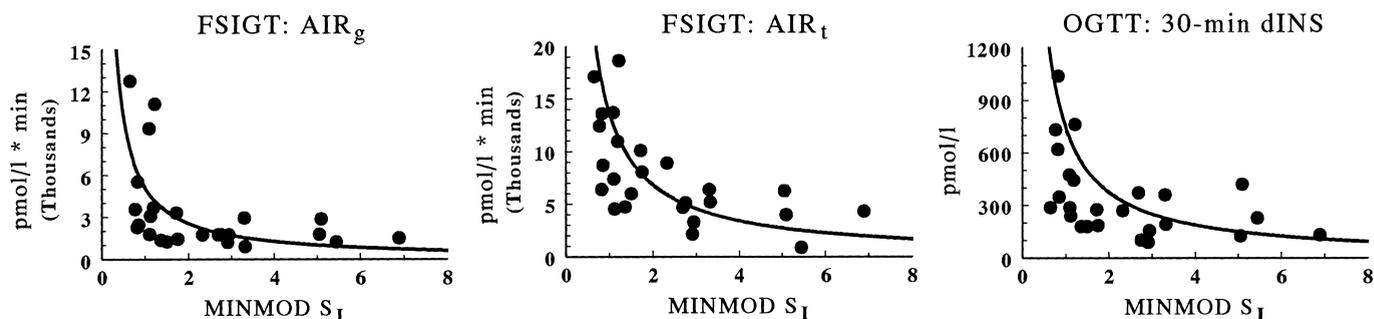
FIG. 1. Relationships between 3 measures of insulin release (AIR$_g$, AIR$_t$, and OGTT 30-min dINS, as defined in text) and minimal model S_I at baseline. Data are from all 25 women who participated in the study. Solid lines are hyperbolae described by the equation $y \times x = k$, where k is a constant. Regression analysis of log-log plots for each pair of sensitivity-secretion measures revealed significant correlations ($P < 0.007$ for each) and slopes that were not significantly different from –1 ($P > 0.60$ for each).

troglitazone group to cross their baseline hyperbolae to more favorable sensitivity-secretion relationships. This tendency was confirmed by a 54% increase in the disposition index for AIR$_g$ ($P = 0.004$; Table 1). No improvement in sensitivity-secretion relationships (Fig. 2B) or the disposition index for AIR$_g$ (Table 1) was observed in the placebo group. The intergroup difference in change from baseline in the disposition index for AIR$_g$ was highly significant (Table 1).

Plots of relationships between insulin sensitivity and AIR$_t$ (Fig. 3) revealed a tendency to change in parallel with the baseline hyperbola in each treatment group. Movement was down and to the right in the troglitazone group but was in no specific direction in the placebo group. These tendencies were confirmed by calculation of the disposition index for AIR$_t$, which did not change significantly in either group or to a degree that differed between groups (Table 1).

The changes in β-cell compensation observed for AIR$_g$ and AIR$_t$ in the troglitazone group translated into slight (13.6 and

7.4%, respectively) and statistically nonsignificant changes in the glucose fractional disappearance rates between 10–19 and 19–40 min of the FSIGTs (Table 1). Even smaller changes (2.1 and 3.4%, respectively) were observed in the placebo group. Intergroup differences in the magnitude of change from baseline in K_g values did not approach statistical significance (Table 1).

Minimal model analysis using each troglitazone-treated subject's baseline FSIGT glucose concentrations with her 12-week insulin concentrations revealed an S_I value of $3.62 \pm 2.27 \times 10^{-4}$ min^{-1} per µU/ml. Thus, of the total increase in S_I observed during troglitazone treatment (from 2.29 to 3.80×10^{-4} min^{-1} per µU/ml), 89% (from 2.29 to 3.62×10^{-4} min^{-1} per µU/ml) could be attributed to changes in plasma insulin per se (Fig. 4). Analysis using each troglitazone-treated subject's baseline insulin and 12-week glucose values revealed an S_I of $2.46 \pm 2.16 \times 10^{-4}$ min^{-1} per µU/ml, indicating that only 11% (i.e., from 2.29 to 2.46 min^{-1} per µU/ml $\times 10^{-4}$) of the total

TABLE 1
Parameters from FSIGTs at baseline and after 12 weeks of study

Variable	Troglitazone group			Placebo group			Intergroup P†
	Baseline	12 weeks	P*	Baseline	12 weeks	P*	
Insulin sensitivity							
S_I (min^{-1} per µU/ml $\times 10^{-4}$)‡	2.29 ± 1.91	3.80 ± 0.64	0.002	2.41 ± 1.53	2.04 ± 0.79	0.24	0.0007
β-Cell function							
Fasting insulin (pmol/l)	109 ± 72	67 ± 32	0.001	98 ± 41	86 ± 16	0.29	0.08
AIR$_g$ (pmol/l × min)§	3,504 ± 3,228	3,540 ± 3,198	0.90	3,078 ± 3,168	3,306 ± 2,334	0.58	0.70
AIR$_t$ (pmol/l × min)‖	8,604 ± 4,788	5,904 ± 4,626	0.0001	6,816 ± 4,224	7,350 ± 4,314	0.42	0.0004
Glucose and glucose tolerance							
Fasting glucose (mmol/l)	5.4 ± 0.5	5.1 ± 0.4	0.002	5.4 ± 0.3	5.3 ± 0.3	0.21	0.06
Average glucose, 19–40 min (mmol/l)¶	11.1 ± 1.1	10.4 ± 1.0	0.001	11.1 ± 0.8	11.0 ± 0.6	0.54	0.06
K_{g10-19} (min^{-1} × 100)#	1.32 ± 0.44	1.50 ± 0.41	0.10	1.42 ± 0.30	1.45 ± 0.33	0.77	0.31
K_{g19-40} (min^{-1} × 100)**	1.47 ± 0.58	1.58 ± 0.56	0.40	1.45 ± 0.48	1.50 ± 0.52	0.76	0.77
S_g (min^{-1} × 100)††	1.41 ± 0.34	1.49 ± 0.39	0.94	1.44 ± 0.20	1.51 ± 0.36	0.56	0.90
β-Cell compensation for insulin resistance							
$S_I \times$ AIR$_g$	5,784 ± 3,954	8,880 ± 3,780	0.004	5,478 ± 3,618	5,718 ± 2,466	0.76	0.02
$S_I \times$ AIR$_t$	14,268 ± 7,446	16,014 ± 7,356	0.22	13,200 ± 7,590	12,996 ± 5,910	0.90	0.35

Data are means ± SD. *By paired t test within a group; †by between-group comparison of change from baseline using nonpaired t test; ‡minimal model insulin sensitivity index; §AIR$_g$: incremental area under plasma insulin curve during first 10 min after glucose injection; ‖AIR$_t$: incremental insulin area during 20 min after tolbutamide injection, calculated relative to 19-min plasma insulin concentration; ¶average of 19-, 22-, 24-, 25-, 27-, 30-, and 40-min plasma glucose concentrations; #fractional glucose disappearance rate (× 100) between 10 and 19 min after glucose injection; **fractional glucose disappearance rate (× 100) between 19 and 40 min after glucose injection; ††minimal model glucose effectiveness (fractional glucose disappearance at basal insulin) (S_g).
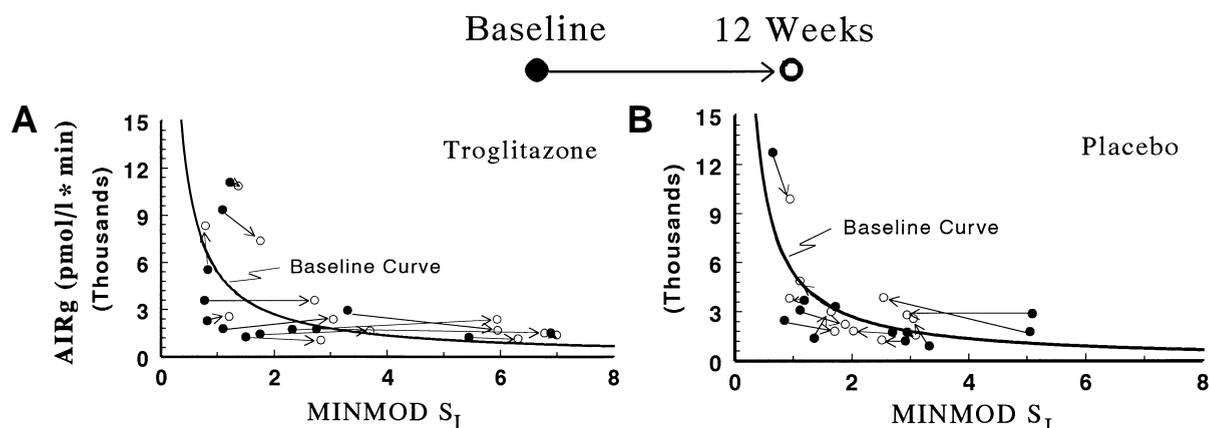
FIG. 2. Individual changes in insulin sensitivity-secretion relationships for S_I and AIR_g during 12 weeks of treatment with 400 mg/day troglitazone (*A*) or placebo (*B*). Solid curves represents product of minimal model $S_I \times AIR_g$ at baseline in each group. Arrows connect pre- and posttreatment values in individual patients. See Table 1 for statistical analysis of changes in β-cell compensation (sensitivity-secretion products).

increase in S_I in that group could be attributed to changes in glucose disappearance (Fig. 4).

During OGTTs (Table 2), fasting plasma insulin and the 30-min incremental insulin response in troglitazone-treated patients fell by 37 and 35%, respectively (Table 2). These variables increased slightly, but not significantly, in the placebo group (Table 2). The intergroup difference in the change from baseline was of borderline statistical significance for each variable. Fasting and 30-min glucose concentrations did not change significantly in either group or between groups (Table 2). Fasting and 30-min plasma FFA concentrations were lowered to a greater degree during troglitazone than during placebo treatment (Table 2), but differences between groups in the changes from baseline were not statistically significant. The reduction in the 30-min dINS in the troglitazone group remained significant ($P = 0.02$) after adjustment for individual changes from baseline in fasting and 30-min plasma glucose and FFA concentrations.

Plots of individual relationships between the OGTT 30-min dINS and S_I (Fig. 5) revealed a tendency for patients in the troglitazone group to move down and to the right in parallel with the baseline hyperbola. No systematic change was observed in the placebo group. These patterns were confirmed by a lack of significant change in the disposition index for the 30-min dINS in both groups and lack of a significant difference in change from baseline between groups (Table 2). Similar results were

obtained when the OGTT 30-min incremental plasma insulin:glucose ratio was used in place of the OGTT 30-min dINS to calculate a disposition index ($P = 0.61$ for change from baseline in the placebo group and $P = 0.86$ in the troglitazone group; $P = 0.44$ for difference in change between groups).

Consistent with the lack of change in the β-cell compensation for insulin resistance during the OGTT, neither the total nor the incremental plasma glucose area during OGTTs changed significantly in either treatment group or differently between groups (Table 2).

DISCUSSION

In response to a relatively short-term improvement in whole-body insulin sensitivity, Latino women with impaired glucose tolerance and a recent history of GDM maintained AIR_g at a constant level but exhibited significant reductions in AIR_t during FSIGTs (by 31%) and 30-min insulin responses during OGTTs (by 35%). Plots of insulin sensitivity-secretion relationships at baseline revealed hyperbolic relationships for each of the 3 β-cell parameters. Calculation of disposition indexes revealed a significant improvement in β-cell compensation during troglitazone treatment in the case of AIR_g but only very small and nonsignificant changes in β-cell compensation in the case of the other two measures of β-cell function. Tolerance to oral and intravenous glucose did not improve significantly during the study, suggesting that the
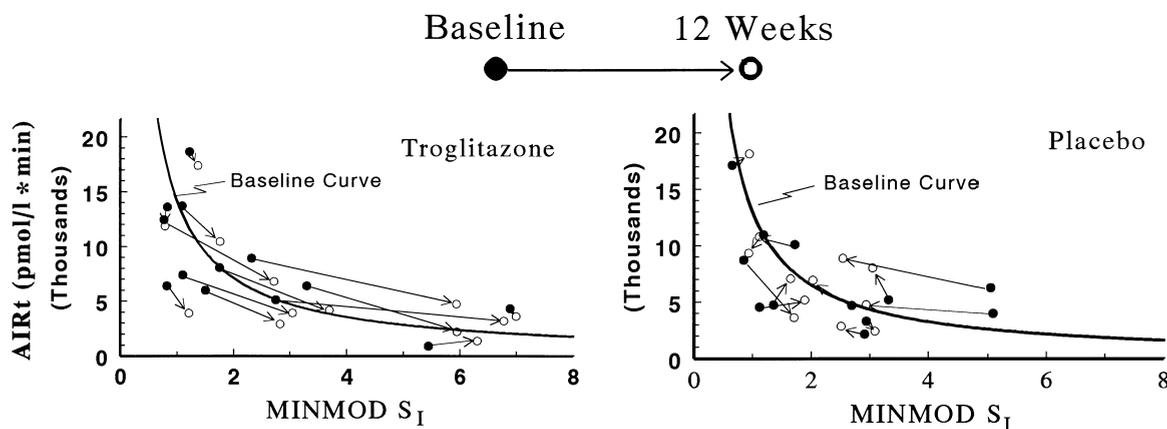

FIG. 3. Plots of insulin sensitivity-secretion relationships for S_I and AIR_t. Format is identical to Fig. 2.
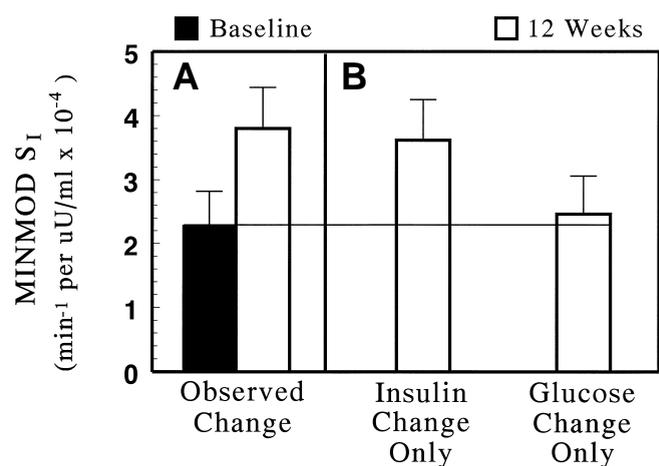
FIG. 4. Components of increased S_I in the troglitazone-treated group. A: S_I values obtained by modeling baseline insulin and glucose (■) or 12-week insulin and glucose (□) together. B: S_I values that were obtained when 1) 12-week insulin values were modeled with baseline glucose values in each subject to assess the contribution of change in plasma insulin patterns to the total change in S_I (Insulin Change Only), and 2) 12-week glucose values were modeled with baseline insulin to assess the contribution of changes in glucose patterns (Glucose Change Only). Horizontal solid line represents mean of S_I at baseline. Changes in insulin accounted for 89% of the observed change in S_I; changes in glucose accounted for only 11%.

dominant β-cell response was a reduction in insulin release that was nearly reciprocal to the improvement in insulin sensitivity. Indeed, minimal model analysis of FSIGT data revealed that reduced insulin responses accounted for 89% of the overall increase in S_I, whereas improvements in intravenous glucose tolerance accounted for only 11% of the increase in S_I during troglitazone treatment. Glucose effectiveness did not change significantly during treatment. These findings suggest that components of β-cell function that were critical for the determination of glucose tolerance were set to

operate on an insulin sensitivity-secretion curve that maintained impaired glucose tolerance, at least during short-term changes in insulin sensitivity.

Our results reveal some similarities and some differences when compared with other reports (10–12) in which troglitazone was given for 12 weeks at a dose of 400 mg/day to groups of 12–18 insulin-resistant subjects, most of whom had impaired glucose tolerance. In those studies, insulin sensitivity improved by 28–100%. That improvement was associated with small or no reductions in fasting (0–12%) and 2-h (12–15%) plasma glucose concentrations and much larger reductions in fasting (34–48%) and 2-h (44–114%) plasma insulin concentrations during 75-g OGTTs. We observed a 66% improvement in mean S_I, along with small reductions in fasting (4%) and 2-h (14%) glucose and larger reductions in fasting (37%) and 2-h (38%) insulin levels during OGTTs. Like Cavaghan et al. (11) and Ehrmann et al. (12), we found that the disposition index for AIR_g improved >50% during troglitazone treatment. However, the very small changes in glucose disappearance rates that accompanied the large improvement in the disposition index for AIR_g in our patients led us to examine 2 other characteristics of β-cell function: the AIR_t and the OGTT 30-min dINS. The fact that these parameters maintained nearly constant compensation for insulin resistance was consistent with the very small changes in glucose tolerance that we (13) and others (10–12) had observed during troglitazone treatment in patients with impaired glucose tolerance. The observed patterns suggest a predominance of β-cell downregulation in response to improved insulin sensitivity. That suggestion is strongly supported by the demonstration that nearly all of the increase in S_I was accounted for by reductions in the plasma insulin profile in the face of relatively constant rates of glucose disposition during FSIGTs.

The different patterns of response for different β-cell measures may provide important clues into the regulation of glucose tolerance in patients with impaired glucose tolerance. AIR_g has been reported to be a relatively early defect in the

TABLE 2
Parameters from OGTTs at baseline and after 12 weeks of study

Variable	Troglitazone group			Placebo group			Intergroup
	Baseline	12 weeks	P^*	Baseline	12 weeks	P^*	$P†$
β-Cell function							
Fasting insulin (pmol/l)	102 ± 88	64 ± 30	0.05	83 ± 20	88 ± 23	0.47	0.07
30-Min dINS (pmol/l)‡	396 ± 294	258 ± 198	0.02	264 ± 114	288 ± 162	0.45	0.06
Glucose and glucose tolerance							
Fasting glucose (mmol/l)	5.3 ± 0.5	5.1 ± 0.5	0.15	5.6 ± 0.5	5.4 ± 0.4	0.29	0.76
30-Min glucose (mmol/l)	7.9 ± 1.1	8.0 ± 1.0	0.80	8.4 ± 1.1	8.1 ± 1.0	0.44	0.53
Total glucose area (mmol/l × min × 10^{-2})§	10.6 ± 0.9	9.8 ± 1.4	0.14	10.9 ± 1.2	10.3 ± 1.2	0.23	0.78
Incremental glucose area (mmol/l × min × 10^{-2})‖	4.2 ± 0.9	3.8 ± 1.1	0.24	4.3 ± 0.9	3.9 ± 1.2	0.39	0.85
FFAs							
Fasting (μmol/l)	659 ± 164	515 ± 219	0.07	595 ± 215	484 ± 166	0.20	0.76
30-Min (μmol/l)	569 ± 136	415 ± 168	0.02	488 ± 201	441 ± 110	0.50	0.24
β-Cell compensation							
S_I × 30-min dINS	672 ± 348	738 ± 246	0.60	594 ± 540	540 ± 306	0.65	0.49

Data are means ± SD. *By paired t test or Wilcoxon signed-rank test within a group; †from between-group comparison of change from baseline using nonpaired t test or Wilcoxon ranked sum test; ‡incremental plasma insulin 30 min after start of glucose ingestion, calculated relative to fasting insulin concentration; §total plasma glucose area 0–120 min after glucose ingestion; ‖incremental plasma glucose area, calculated relative to fasting plasma glucose concentration.
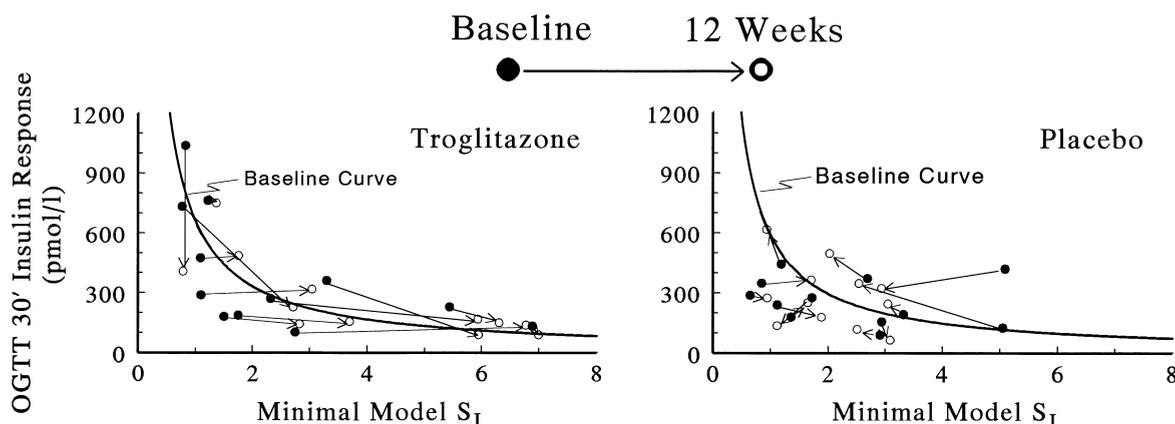
FIG. 5. Plots of insulin sensitivity-secretion relationships for minimal model S_I and OGTT 30-min dINS. Format is identical to Fig. 2.

development of hyperglycemic disorders (28,29). On that basis, we speculate that the capacity to generate AIR_g was so deficient relative to the demands placed on β-cells by insulin resistance that the improved S_I values achieved with troglitazone were still low enough to exceed the maximal capacity for compensation by AIR_g. Thus, AIR_g remained constant but lower than would be expected for normal individuals with similar insulin resistance (2). In contrast to AIR_g, AIR_t and the OGTT 30-min dINS fell when S_I increased. That finding suggests that the latter 2 measures for β-cell function were not so deranged relative to the change in insulin sensitivity that was achieved with troglitazone. The net result of treatment was a large reduction in the amount of insulin made by β-cells relative to the improvement in glucose tolerance—a finding confirmed by analysis of the components of the improved S_I values during FSIGTs.

Insulin responses to glucose and other secretogogues may be modified by ambient concentrations of glucose (24) and FFAs (25,26). Therefore, we assessed the potential impact of changes in glucose and FFAs per se on the insulin response parameters. In the case of glucose, we observed small but statistically significant reductions in fasting and 19-to 40-min plasma glucose concentrations during FSIGTs and a nonsignificant reduction in fasting glucose during OGTTs in the troglitazone group. The range of change in each measure of glycemia was similar to the range observed in the placebo group. This similarity allowed us to quantify the effect of changing glycemia per se on insulin release in the placebo group, then adjust for any such effect in the troglitazone group. Conclusions about the change in insulin release during troglitazone treatment were not altered by this adjustment or by an analogous adjustment for changes in plasma FFA concentrations. Thus, the slightly lower glucose and FFA concentrations after 12 weeks of troglitazone treatment were not acutely responsible for the reduced insulin responses to tolbutamide or to oral glucose. We cannot exclude the possibility that levels of one or both of these metabolic signals for insulin release were reduced early in the course of treatment, resulting in a chronic downregulation of AIR_t and the OGTT 30-min dINS. We also cannot exclude a direct effect of troglitazone to reduce insulin secretion, although an in vitro study by Masuda et al. (30) suggests that any direct effect of the drug would augment rather than reduce

insulin secretion. Thus, we speculate that the reductions in AIR_t during FSIGTs and 30-min insulin responses during OGTTs occurred in response to improved insulin sensitivity and were mediated by a yet unidentified signal from peripheral tissues to the β-cell.

In summary, insulin resistance was partially reversed with troglitazone treatment for 3 months in Latino women with impaired glucose tolerance and a recent history of GDM. Examination of patterns of change in β-cell function revealed that AIR_g did not change significantly in troglitazone-treated patients, while AIR_t during FSIGTs and to oral glucose during OGTTS was reduced during troglitazone treatment. According to the hyperbolic relationship between insulin responses and β-cell function proposed by Bergman and colleagues (19,20) and demonstrated by Kahn et al. (21) and in our own patients (Fig. 1), these changes imply improved compensation for insulin resistance on the part of AIR_g. On the other hand, compensation by AIR_t and the OGTT 30-min dINS remained essentially constant during troglitazone treatment. The net result was maintenance of nearly constant glucose tolerance, as reported previously (13), despite a >60% increase in insulin sensitivity. These findings highlight the utility of insulin sensitivity-secretion relationships in the assessment of β-cell function (19–21). The results also suggest a functional "resetting" of β-cell compensation for insulin resistance, at least in the case of acute responses to tolbutamide and to oral glucose in our high-risk patients.

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