Original Article

Effect of Pioglitazone on Pancreatic β-Cell Function and Diabetes Risk in Hispanic Women With Prior Gestational Diabetes

Anny H. Xiang,[1] Ruth K. Peters,[1] Siri L. Kjos,[2] Aura Marroquin,[3] Jose Goico,[3] Cesar Ochoa,[3] Miwa Kawakubo,[1] and Thomas A. Buchanan[2,3]

The Pioglitazone In Prevention Of Diabetes (PIPOD) study was conducted to evaluate β-cell function, insulin resistance, and the incidence of diabetes during treatment with pioglitazone in Hispanic women with prior gestational diabetes who had completed participation in the Troglitazone In Prevention Of Diabetes (TRIPOD) study. Women who completed the TRIPOD study were offered participation in the PIPOD study for a planned 3 years of drug treatment and 6 months of postdrug washout. Oral glucose tolerance tests were performed annually on pioglitazone and at the end of the postdrug washout. Intravenous glucose tolerance tests (IVGTTs) for assessment of insulin sensitivity and β-cell function were conducted at baseline, after 1 year on pioglitazone, and at the end of the postdrug washout. Of 95 women who were not diabetic at the end of the TRIPOD study, 89 enrolled in the PIPOD study, 86 completed at least one follow-up visit, and 65 completed all study visits, including the postdrug tests. Comparison of changes in β-cell compensation for insulin resistance across the TRIPOD and PIPOD studies revealed that pioglitazone stopped the decline in β-cell function that occurred during placebo treatment in the TRIPOD study and maintained the stability of β-cell function that had occurred during troglitazone treatment in the TRIPOD study. The risk of diabetes, which occurred at an average rate of 4.6% per year, was lowest in women with the largest reduction in total IVGTT insulin area after 1 year of treatment. The similarity of findings between the PIPOD and TRIPOD studies support a class effect of thiazolidinedione drugs to enhance insulin sensitivity, reduce insulin secretory demands, and preserve pancreatic β-cell function, all in association with a relatively low rate of type 2 diabetes, in Hispanic women with prior gestational diabetes. *Diabetes* 55:517–522, 2006

From the [1]Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California; the [2]Department of Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles, California; and the [3]Department of Medicine, University of Southern California Keck School of Medicine, Los Angeles, California.

Address correspondence and reprint requests to Thomas A. Buchanan, MD, Room 6602 GNH, 1200 N. State St., Los Angeles CA, 90033. E-mail: buchanan@usc.edu.

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S.L.K. is currently affiliated with the Department of Obstetrics and Gynecology, Harbor-UCLA Medical Center, Torrance, California.

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AIR, acute insulin response; DI, disposition index; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; PIPOD, Pioglitazone In Prevention Of Diabetes; TRIPOD, Troglitazone In Prevention Of Diabetes.

Type 2 diabetes frequently results from progressive failure of pancreatic β-cells in a setting of chronic insulin resistance (1–6). In the Troglitazone In Prevention Of Diabetes (TRIPOD) study (7), we found that treatment of insulin resistance with the thiazolidinedione drug, troglitazone, improved insulin sensitivity and reduced the incidence of type 2 diabetes in Hispanic women with prior gestational diabetes. Protection from diabetes was closely related to the degree to which endogenous insulin requirements were reduced soon after initiation of troglitazone treatment. Moreover, women who were protected from diabetes during troglitazone treatment had stable β-cell function and insulin resistance for nearly 5 years. These findings provided evidence that reducing the secretory demands that are placed in pancreatic β-cells by chronic insulin resistance can preserve β-cell function and slow or stop progression to type 2 diabetes. Troglitazone was withdrawn from clinical use in 2000. The Pioglitazone In Prevention Of Diabetes (PIPOD) study was conducted to assess the effect of a currently available thiazolidinedione drug, pioglitazone, on pancreatic β-cell function and, secondarily, insulin resistance and diabetes rates in women who completed the TRIPOD study.

RESEARCH DESIGN AND METHODS

The PIPOD study was an open-label observational study to determine the effects of pioglitazone in women with prior gestational diabetes who had completed the TRIPOD study. The details of the TRIPOD study have been previously published (7,8). Briefly, Hispanic women of Mexican, Guatemalan, or Salvadoran descent with a recent history of gestational diabetes were randomized to 400 mg/day troglitazone or placebo between August 1995 and May 1998. Fasting glucose was measured at 3-month intervals, and oral glucose tolerance tests (OGTTs) were performed annually to detect diabetes using American Diabetes Association criteria (1). Treatment continued in each subject until she developed diabetes, at which time she was placed on open-label troglitazone, or until March 2000 (when troglitazone was withdrawn from human use), at which time all subjects stopped study medications. Subjects were asked to return for an OGTT ~8 months after study medications were stopped. Intravenous glucose tolerance tests (IVGTTs) to assess insulin resistance and pancreatic β-cell function were performed before randomization, 3 months later, and 8 months after study medications were stopped.

Women who completed the TRIPOD study and posttrial testing were eligible for participation in the PIPOD study if their HbA_{1c} (A1C) was <7%. The present report is based on 95 women who did not have diabetes at the end of the TRIPOD study, women for whom diabetes prevention remained relevant. All participants gave written informed consent for participation in the institutional review board–approved study.

Subjects who agreed to enroll in the PIPOD study received dietary advice

and were advised to walk for 30 min three times each week, as they had been at annual visits during the TRIPOD study. They were started on 30 mg/day pioglitazone for 2 months. Since there was no clinical evidence of fluid retention at this dose, the dose was increased to 45 mg/day for the remainder of a 3-year treatment period in each subject. Follow-up visits were scheduled every 2 months during the 1st year and every 3 months thereafter. Fasting glucose and A1C were measured at each visit, and OGTTs were performed annually. A frequently sampled IVGTT was performed at entry and after 1 year of treatment to assess insulin resistance and β-cell function. Subjects remained on treatment unless A1C exceeded 7%, at which time final testing was performed and they were referred for additional treatment of diabetes. In subjects who completed 3 years of treatment, pioglitazone was stopped and subjects were asked to return 3 months later for an A1C measurement. If A1C was >7%, final testing was performed immediately and patients were referred for diabetes care. If the 3-month postdrug A1C was ≤7%, subjects were asked to return for a final OGTT and IVGTT 3 months later (i.e., 6 months after stopping pioglitazone).

Clinical testing protocols. OGTTs and IVGTTs were performed on separate days and initiated between 7:00 and 9:00 A.M., after 8- to 12-h overnight fasts. For OGTTs, subjects drank 75 g dextrose. Venous blood was sampled from an indwelling catheter before and 30, 60, 90, and 120 min after the dextrose ingestion. For IVGTTs, dextrose (300 mg/kg body wt) was injected into an antecubital vein. Tolbutamide (125 mg/m^2 body surface area; Orinase Diagnostic, Pharmacia & Upjohn, Peapack, NJ) was injected 20 min later. Twenty-two arterialized venous blood samples were drawn and placed on ice before and up to 240 min after the dextrose injection. For both tests, plasma was separated within 20 min and stored at −80°C.

Laboratory methods. Glucose was measured by glucose oxidase (YSI Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH). Insulin was measured by a radioimmunoassay (Linco Research, St. Charles, MO) that provided <0.2% cross-reactivity with proinsulin. A1C was measured by high-pressure liquid chromatography (Biorad Diamat).

Data analysis. Whole-body insulin sensitivity (S_i) was calculated from IVGTTs using the Bergman minimal model (9). Areas under glucose and insulin curves were calculated using the trapezoid rule. Insulin concentrations during IVGTTs were analyzed in two ways. The total area under the insulin curve from 0 to 240 min was used to assess total posthepatic insulin output from β-cells. The acute insulin response to intravenous glucose (AIR_g; the incremental insulin area between 0 and 10 min after the glucose injection) was used as a combined measure of β-cell mass (10) and function (11). The product of AIR_g and S_i (the disposition index [DI]) was used as a measure of β-cell compensation for insulin resistance (12,13).

The average annual diabetes incidence rate was estimated by person-time, and the cumulative incidence rate was estimated by Kaplan Meier survival analysis. Baseline characteristics and 1-year change on treatment were compared between women who did not develop diabetes and women who did during follow-up by two methods: two-group *t* tests and Wilcoxon's rank-sum tests for medians. Continuous variables were checked for normal distribution before *t* tests, and baseline fasting insulin, OGTT insulin, S_i, AIR_g, DI, and IVGTT insulin were log transformed before the *t* tests. Consistent results were observed between *t* tests and Wilcoxon's rank-sum tests; only results from *t* tests are reported. Cox proportional hazard regression analysis was used to identify independent predictors of diabetes. Variables considered in the multivariate Cox regression analysis were all baseline characteristics listed in Table 1 and changes in OGTT and IVGTT variables and weight after 1 year on treatment. Changes in insulin sensitivity, β-cell function, and body weight were compared across two intervals, baseline of the TRIPOD to baseline of the PIPOD study and baseline of the PIPOD to end of the PIPOD study, by paired *t* tests and Wilcoxon's signed-rank tests. Consistent results were observed, and only *P* values from paired *t* tests are reported.

Data are presented in tables and text as means and SDs in their original scales. All reported *P* values are two sided. A *P* value of 0.05 was accepted as statistically significant.

TABLE 1
Baseline characteristics of 86 women who enrolled in the PIPOD study and completed at least one follow-up visit

Variable	Mean (range) ± SD
Age (years)	39 (25–54) ± 6.6
BMI (kg/m^2)	31 (21–48) ± 4.9
Waist-to-hip circumference ratio	0.86 (0.72–1.32) ± 0.07
OGTT fasting plasma glucose (mg/dl)*	99 (81–124) ± 9.7
OGTT 2-h plasma glucose (mg/dl)*	151 (97–199) ± 27.6
OGTT glucose area ($mg \cdot dl^{-1} \cdot min^{-1} \cdot 10^{-3}$)*	18.3 (12.0–24.7) ± 2.8
OGTT fasting plasma insulin (μU/ml)*	17.4 (5–64) ± 10.4
OGTT insulin area ($\mu U \cdot ml^{-1} \cdot min^{-1}$)*	11,058 (3,165–30,120) ± 6,662
A1C (% of hemoglobin)	5.7 (4.4–6.6) ± 0.5
S_i ($min \cdot \mu U^{-1} \cdot ml^{-1} \cdot 10^{-4}$)†	2.33 (0.37–10.90) ± 1.65
AIR_g ($\mu U \cdot ml^{-1} \cdot min^{-1}$)‡	408 (−3 to 1,342) ± 292
DI§	834 (−2 to 2,418) ± 583
IVGTT insulin area ($\mu U \cdot ml^{-1} \cdot min^{-1}$)¶	9,654 (2,503–36,172) ± 5,743

Data are means (range) ± SD. *75-g OGTT; areas are total calculated by trapezoid rule. †Minimal model analysis of IVGTT results. ‡Incremental insulin area during the first 10 min after glucose injection. §$S_i \times AIR_g$, a measure of β-cell compensation for insulin resistance. ¶Total area from 0 to 240 min. To convert values for glucose to mmol/l, multiply by 0.05551. To convert values for insulin to pmol/l, multiply by 6.0.

RESULTS

Subjects and follow-up. Of 95 women who did not have diabetes at posttrial testing in the TRIPOD study, 89 agreed to participate in the PIPOD study, had baseline tests, and were assigned to study medication. Three women failed to return for any follow-up, 7 dropped out during the 1st year of follow-up, 11 dropped out during the 2nd year, and 3 dropped out during the 3rd year, resulting in an average annual rate of loss to follow-up of 9.6%. Sixty-five women (30 from the active drug arm of the TRIPOD study) completed the entire study by developing an A1C >7% during treatment ($n = 1$) or completing treatment and postdrug testing ($n = 64$). For the 24 women who failed to complete the study, the median duration of follow-up was 12 months (range 0–33). Incomplete follow-up occurred in 19 women because they either moved away ($n = 9$) or withdrew consent for personal reasons ($n = 10$); none had diabetes as their reason for dropping out. Five women failed to come for scheduled appointments either immediately after enrollment ($n = 3$) or after a period of active participation ($n = 2$), and attempts to contact them failed, so their diabetes status at the time of drop out was unknown. Fasting glucose levels from three of these five women were found in the Los Angeles County clinical database and were <110 mg/dl. The 24 subjects who enrolled but failed to complete the study did not differ substantively or statistically at baseline from 65 women who completed the study with regard to age, BMI, waist-to-hip circumference ratio, OGTT glucose, or A1C ($P > 0.12$ for each). However, the women with incomplete participation had slightly lower S_i (1.86 ± 1.65 vs. 2.44 ± 1.63, $P = 0.03$) and DI (617 ± 517 v. 895 ± 590, $P = 0.06$) at baseline compared with women who completed the study.

Diabetes rates. Incidence rates of diabetes were calculated from 86 women (42 from the active treatment arm of the TRIPOD study) who had at least one follow-up visit after enrollment (Table 1). Overall, 11 of them had diabetes at one or more OGTTs during a median of 35.9 months (fourth versus first interquartile range 9.2 months) of pioglitazone treatment. No new cases of diabetes were observed during the postdrug washout, which lasted a median of 5.7 months. Average annual incidence rates of diabetes were 5.2% during pioglitazone treatment and 4.6% during the entire observation period, including the post-

TABLE 2
Baseline characteristics and changes after 1 year of treatment in women who did develop diabetes and women who did not during the PIPOD study

Variable*	No diabetes		Diabetes		*P* value†
Baseline					
n	75		11		
Age (years)	39.2 ± 6.5		41.2 ± 7.5		0.36
BMI (kg/m^2)	30.5 ± 4.9		31.0 ± 5.4		0.75
Waist-to-hip circumference ratio	0.86 ± 0.07		0.86 ± 0.06		0.90
OGTT glucose area (mg · dl^{-1} · min^{-1} · 10^{-3})	18.0 ± 2.7		20.4 ± 2.5		0.01
OGTT insulin area (μU · ml^{-1} · min^{-1})	11,579 ± 6,939		7,595 ± 2,551		0.08
IVGTT insulin area (μU · ml^{-1} · min^{-1})	9,954 ± 6,051		7,660 ± 2,249		0.37
S_i (min · μU^{-1} · ml^{-1} · 10^{-4})	2.32 ± 1.71		2.41 ± 1.31		0.60
AIR_g (μU · ml^{-1} · min^{-1})	432 ± 296		251 ± 220		0.05
DI	866 ± 571		627 ± 646		0.15
1-year change		*P*‡		*P*‡	
n	66		11		
Weight (kg)	2.1 ± 4.2	0.0001	4.8 ± 3.9	0.002	0.05
OGTT glucose area (mg · dl^{-1} · min^{-1} · 10^{-3})	−1.7 to 3.0	0.0001	−1.2 ± 2.5	0.15	0.57
OGTT insulin area (μU · ml^{-1} · min^{-1})	−3,077 to 6,211	0.0002	243 ± 2,970	0.79	0.01
IVGTT insulin area (μU · ml^{-1} · min^{-1})	−3,173 to 4,447	0.0001	1,493 ± 5,214	0.36	0.01
S_i (min · μU^{-1} · ml^{-1} · 10^{-4})	1.33 ± 2.62	0.0003	0.77 ± 2.73	0.37	0.52
AIR_g (μU · ml^{-1} · min^{-1})	23.0 ± 385	0.66	32.9 ± 447	0.81	0.93
DI	511 ± 1,033	0.0003	18 ± 1,057	0.96	0.15

Data are means ± SD from women who had baseline tests and returned for at least one follow-up visit. One-year change data are from the subset of 77 women who had both an OGTT and IVGTT after 1 year of pioglitazone treatment and at least one subsequent follow-up visit. *Definitions of variables and units appear in Table 1. †By two-group *t* test. ‡By paired *t* test within each group.

drug washout. The final cumulative incidence of diabetes during treatment and postdrug follow-up was 17%. These rates were similar to analogous rates observed during a median of 31 ± 8 months of troglitazone treatment and posttrial washout in the TRIPOD study (5.7 and 25% per year, respectively) and lower than rates observed during a median of 28 ± 8 months of placebo treatment and posttrial washout in the TRIPOD study (13.1 and 52% per year, respectively). Annual diabetes incidence rates during the PIPOD study were similar in women who had been randomized in the TRIPOD study to placebo or troglitazone (4.1 vs. 5.2% per year, respectively, $P = 0.67$).

Predictors of diabetes. Compared with women who developed diabetes, women who remained diabetes free entered the PIPOD study (Table 2, *top*) with lower glucose levels, higher acute insulin responses during IVGTTs, and marginally higher insulin levels on OGTTs. Baseline insulin sensitivity and DI did not differ significantly between the groups. After 1 year of treatment and based on data from the 77 women who had both an OGTT and IVGTT at 1 year (Table 2, *bottom*), both groups had gained weight, but the women who remained free of diabetes throughout the PIPOD study had gained less weight. The glucose area during OGTTs and total insulin areas during OGTTs and IVGTTs fell, and insulin sensitivity and DI rose significantly only in the women who remained free of diabetes. AIR_g did not change in either group. First-year changes in OGTT and IVGTT insulin areas were directionally opposite and statistically different between groups. Intergroup differences in the changes in OGTT glucose area, insulin sensitivity, and DI did not reach statistical significance.

Multivariate Cox regression analysis revealed two significant and independent predictors of developing diabetes during the study: the change in IVGTT total insulin area during the 1st year of treatment (fall = low risk, $P = 0.001$) and the baseline OGTT glucose area (low = low risk, $P = 0.02$). In separate analysis in which OGTT glucose area was not offered, OGTT fasting (low = low risk, $P = 0.01$) and 2-h (low = low-risk, $P = 0.02$) glucose levels were also predictive of development of diabetes after adjustment for the effects of changes in IVGTT insulin area.

Because an initial fall in IVGTT insulin area was also the strongest predictor of a low risk of diabetes in the troglitazone arm of the TRIPOD study (7), we compared the relationship between diabetes rates and initial changes in IVGTT insulin area between the two studies. Changes in the TRIPOD study were assessed 3 months after randomization, and changes in the PIPOD study were assessed 1 year after enrollment. The comparison (Fig. 1) revealed a greater range of change in IVGTT insulin area in the PIPOD study but a relationship between that change and the risk of diabetes that was virtually identical in slope to

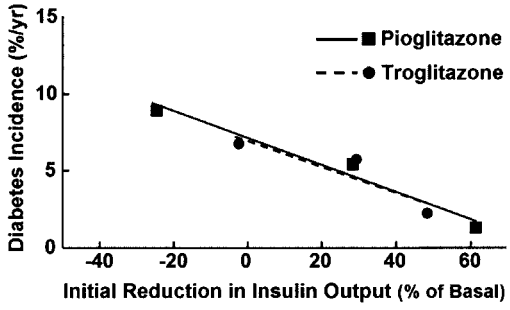

FIG. 1. Relationship between initial fractional reduction in IVGTT insulin area and corresponding diabetes incidence rates in the troglitazone arm of the TRIPOD study (●) and in the PIPOD study (■). Insulin output was assessed as the total area under the insulin curve during IVGTTs. Reductions in output were calculated between enrollment into each study and the initial on-treatment IVGTT, which occurred after 3 months in the TRIPOD study and after 1 year in the PIPOD study. Symbols represent the low, middle, and high tertile of change in each study. Lines represent best linear fits of data for each study.

TABLE 3
Insulin sensitivity, β-cell function, and body weight in the TRIPOD and PIPOD studies

Variable	Baseline TRIPOD (period 1)	Baseline PIPOD (period 2)	End PIPOD (period 3)	*P* value (2 vs. 1)*	*P* value (3 vs. 2)*
TRIPOD troglitazone group (n = 27)					
S_i ($min \cdot \mu U^{-1} \cdot ml^{-1} \cdot 10^{-4}$)	2.38 ± 1.52	2.81 ± 2.09	2.50 ± 2.56	0.23	0.57
AIR_g ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	453 ± 283	479 ± 309	392 ± 207	0.60	0.13
DI	913 ± 518	1,095 ± 607	878 ± 598	0.24	0.12
Weight (kg)	69.1 ± 10.9	73.0 ± 11.0	75.0 ± 11.2	<0.0001	0.006
TRIPOD placebo group (n = 32)					
S_i ($min \cdot \mu U^{-1} \cdot ml^{-1} \cdot 10^{-4}$)	2.79 ± 2.32	2.24 ± 1.24	2.16 ± 1.34	0.16	0.72
AIR_g ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	593 ± 554	382 ± 285	484 ± 357	0.03	0.13
DI	1125 ± 687	754 ± 542	953 ± 678	0.003	0.14
Weight (kg)	68.3 ± 8.8	69.4 ± 8.0	72.3 ± 9.6	0.15	0.0004

Data are means ± SD from 59 women who had IVGTTs performed at enrollment into to TRIPOD (period 1), at enrollment into PIPOD (period 2, equivalent to end of postdrug washout period for TRIPOD), and end of postdrug washout period in PIPOD (period 3), so that all results were obtained remote from any acute drug effects. *By paired t test.

the relationship observed with troglitazone treatment in the TRIPOD study.

Patterns of change in insulin sensitivity, β-cell function, and body weight. Fifty-nine subjects completed the PIPOD treatment period and postdrug IVGTTs (six other women had only OGTTs at postdrug testing). Data from those 59 subjects (Table 3) were used to assess patterns of change in insulin resistance, β-cell function, and body weight during pioglitazone treatment and postdrug washout (median 3.5 years) in relation to patterns that had already been observed during placebo or troglitazone treatment and posttrial washout in the TRIPOD study (median 4.6 years). Thus, all tests were performed remote from drug treatment and any acute drug effects, allowing assessment of the impact of treatment on the natural history of pre-diabetes. Women who had been randomized to troglitazone in the TRIPOD study manifested no significant change in insulin sensitivity (S_i), acute insulin secretion (AIR_g), or β-cell compensation (DI) across either study, despite average weight gains of ~4 and 2 kg in the TRIPOD and PIPOD studies, respectively. Women who had been randomized to placebo in the TRIPOD study also had no significant change in insulin sensitivity across either study. However, they had a significant fall in AIR_g and DI in the absence of significant weight gain during placebo treatment in the TRIPOD study. They then manifested stabilization of AIR_g and DI in the face of an average weight gain of ~3 kg across the PIPOD study.

DISCUSSION

There are three main findings in this report. The first and most robust is about stabilization of pancreatic β-cell function, an important determinant of deterioration to type 2 diabetes (2,6). Measurements obtained during placebo treatment in the TRIPOD study established a natural history of declining β-cell function, manifested as a 33% fall in β-cell compensation for insulin resistance over a median of 4.6 years. That decline was stopped when women were placed on pioglitazone for 3 years and then removed from any acute drug effects for 6 months. Parallel analysis of data from women who had been on troglitazone in the TRIPOD study revealed no significant change in β-cell function in either study. In both cases, insulin resistance was ameliorated during periods of thiazolidinedione treatment but returned to baseline values when medications were stopped. These findings support an action of pioglitazone to stabilize β-cell function, as we previously observed for troglitazone in the TRIPOD study (7,14).

The second main finding was the strong relationship between an initial reduction in insulin output and the risk of diabetes. As was true with troglitazone treatment in the TRIPOD study (7), multivariate Cox regression analysis identified the change in IVGTT total insulin area when first measured during treatment as the strongest predictor of diabetes during pioglitazone treatment in the PIPOD study. Also consistent with the TRIPOD study, diabetes incidence rates revealed that they were lowest in the third of women with the greatest reduction in insulin output after 1 year of treatment and highest in the third of women with the smallest reduction after 1 year. Comparison to the analogous relationship among troglitazone-treated patients from the TRIPOD study revealed the same change in diabetes incidence for any initial change in insulin output, although there was a wider range of change in insulin output in the PIPOD study. Whether this wider range was due to differences between effects of the two medications or to the fact that measurements were made after a longer period of treatment in the PIPOD study cannot be determined. However, the striking comparability of the slopes of relationships in Fig. 1, combined with the fact that insulin sensitivity increased significantly during treatment only in women who did not develop diabetes, supports the concept that reducing insulin secretory demands through amelioration of insulin resistance can reduce the risk of diabetes, at least in high-risk Hispanic women.

The third main finding was a diabetes rate of 4.6% per year during treatment with pioglitazone for 3 years, followed by 6 months of postdrug washout. This rate is much lower than the rate of 12.1% per year observed during placebo treatment in the TRIPOD study. However, the interpretation of this finding is complicated by two factors. First, there was no parallel control group in the PIPOD study from which we could ascertain the expected rate of diabetes in the absence of treatment. Observation at a later stage relative to the index pregnancy and prior treatment of many subjects with troglitazone could have modified their inherent diabetes risk compared with the TRIPOD study. Second, drop outs in this highly mobile recent immigrant population precluded complete follow-up to ascertain diabetes status of all individuals. Baseline characteristics of drop outs were similar to women who completed follow-up save for slightly greater insulin resistance and slightly worse β-cell function. Both characteris-

tics could indicate an increased risk of diabetes in the absence of treatment (15), although neither was an independent predictor of development of diabetes in this study. The baseline differences do not indicate a reduced likelihood of protection from diabetes during thiazolidinedione treatment (7), which could have been maintained in a standard clinical care setting in many subjects who dropped out of this study (e.g., subjects who moved away from the study site). We have no evidence to indicate that women dropped out because they developed diabetes. In the end, although we do not have strong evidence that incomplete follow-up biased our results in favor of apparent protection from diabetes, limitations in our study design limit the conclusions that we can draw about the impact of pioglitazone on the risk of diabetes in our high-risk patients.

Unlike β-cell function, which was preserved by treatment with both troglitazone (7,14) and pioglitazone, insulin sensitivity measured remote from any acute effects of medication did not consistently change across the TRIPOD or PIPOD studies, even during periods that were characterized by weight gain. Testing conducted remote from medication use (Table 3) allowed us to assess patterns of change independent of any acute drug effects. As expected, pioglitazone did increase insulin sensitivity while it was being taken (Table 2, 1-year change). In fact, the increase was twice as large in women who did not develop diabetes, an intergroup difference that did not approach statistical significance due to large variability of responses and the relatively small numbers of subjects. Changes in insulin sensitivity after 1 year of pioglitazone treatment were not independently predictive of diabetes. This finding was true in the TRIPOD study as well and was explained by a nonlinear relationship between insulin sensitization and reduced endogenous insulin requirements (7). In both the TRIPOD and PIPOD studies, the latter change occurred in the presence of improved insulin sensitivity and was the variable that was most closely associated with a low risk of diabetes.

The potential clinical implications of our findings rest in part on their relationship to findings in the TRIPOD study. In that study, which was randomized and double blind in design, we observed an unequivocal effect of troglitazone to alter the natural history of progression to type 2 diabetes that was closely related to initial β-cell "rest" (7). Both ethical and practical considerations led us to conduct the PIPOD study as an open-label follow-up study to the TRIPOD study. The well-characterized patterns of change in β-cell function that we observed during the TRIPOD study provided a robust outcome variable for an open-label follow-up study. Indeed, we view the stabilization of β-cell function in women who had been losing function during placebo treatment in the TRIPOD study to be the most important outcome of the PIPOD study. Continued stability of β-cell function in women from the troglitazone arm of the TRIPOD study is encouraging as well, although it is impossible to exclude a lingering effect of prior treatment with troglitazone. However, the fact that continued protection from new cases of diabetes was not observed after discontinuation of troglitazone in the Diabetes Prevention Program (16) speaks against a prolonged protective effect of that drug. That protection from diabetes in the PIPOD and TRIPOD studies occurred in the presence of improved insulin sensitivity while subjects were taking study medication, and the fact that protection was most closely associated with initial reductions in insulin output, speaks strongly of a similar protective mechanism for the two drugs. Thus, our results are most consistent with a class effect of thiazolidinediones to lower insulin secretory demands, preserve β-cell function, and slow or stop progression to type 2 diabetes in one high-risk group. Whether similar effects will occur in other groups and whether weight gain induced by pioglitazone will limit the duration of protection in some patients, as suggested by differences in weight gain between groups that did and did not develop diabetes in the PIPOD study, remain to be determined.

In summary, 3 years of pioglitazone treatment given to Hispanic women with prior gestational diabetes was associated with stable pancreatic β-cell function and a relatively low rate of diabetes. The lowest rate of diabetes occurred in association with the greatest reduction in insulin secretory demands during the 1st year of treatment. These patterns from an observational study with an available thiazolidinedione drug suggest an effect on the pathobiology of diabetes that is similar to the effect observed in our randomized trial of troglitazone treatment in the same study cohort. Taken together, findings from these two trials support a role for thiazolidinedione drugs to modify the natural history of progression to type 2 diabetes in high-risk Hispanic patients. The optimal timing of treatment and the generalizability to other high-risk groups will require additional studies, some of which are currently underway.

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