

# The Effect of Rosiglitazone on Overweight Subjects With Type 1 Diabetes

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**OBJECTIVE** — To evaluate the safety and effectiveness of rosiglitazone in the treatment of overweight subjects with type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — A total of 50 adult type 1 diabetic subjects with a baseline BMI  $\geq 27$  kg/m<sup>2</sup> were randomly assigned in a double-blind fashion to take insulin and placebo ( $n = 25$ ) or insulin and rosiglitazone 4 mg twice daily ( $n = 25$ ) for a period of 8 months. Insulin regimen and dosage were modified in all subjects to achieve near-normal glycemic control.

**RESULTS** — Both groups experienced a significant reduction in HbA<sub>1c</sub> (A1C) level (rosiglitazone:  $7.9 \pm 1.3$  to  $6.9 \pm 0.7\%$ ,  $P < 0.0001$ ; placebo:  $7.7 \pm 0.8$  to  $7.0 \pm 0.9\%$ ,  $P = 0.002$ ) and a significant increase in weight (rosiglitazone:  $97.2 \pm 11.8$  to  $100.6 \pm 16.0$  kg,  $P = 0.008$ ; placebo:  $96.4 \pm 12.2$  to  $99.1 \pm 15.0$ ,  $P = 0.016$ ). Baseline measures of BMI ( $P = 0.001$ ), total daily insulin dose ( $P = 0.002$ ), total cholesterol ( $P = 0.005$ ), HDL cholesterol ( $P = 0.001$ ), and LDL cholesterol ( $P = 0.02$ ) were predictors of improvement in A1C level only in the group treated with rosiglitazone. Total daily insulin dose increased in subjects taking placebo ( $74.0 \pm 33.8$  to  $82.0 \pm 48.9$  units,  $P < 0.05$  baseline vs. week 32), but it decreased slightly in subjects taking rosiglitazone ( $77.5 \pm 28.6$  to  $75.3 \pm 33.1$  units). Both systolic blood pressure ( $137.4 \pm 15.6$  vs.  $128.8 \pm 14.8$  mmHg, baseline vs. week 32,  $P < 0.02$ ) and diastolic blood pressure ( $87.2 \pm 9.4$  vs.  $79.4 \pm 7.2$  mmHg,  $P < 0.0001$ ) improved in the group treated with rosiglitazone. The total incidence of hypoglycemia did not differ between groups.

**CONCLUSIONS** — Rosiglitazone in combination with insulin resulted in improved glycemic control and blood pressure without an increase in insulin requirements, compared with insulin- and placebo-treated subjects, whose improved glycemic control required an 11% increase in insulin dose. Weight gain and hypoglycemia were similar in both groups at the end of the study. The greatest effect of rosiglitazone occurred in subjects with more pronounced markers of insulin resistance.

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**R**esearch in the past decade has conclusively demonstrated that improved blood glucose control is of benefit in preventing the microvascular complications of diabetes (1,2). Although new insulin analogs and intensive insulin treatment regimens are effective in im-

proving glycemic control, these treatments involve considerable effort and cost (3) and can result in weight gain and increased risk for severe and asymptomatic hypoglycemia (4). Faced with the challenge of balancing aggressive insulin replacement therapy against the risk for

the potentially serious consequences of excessive weight gain and insulin-induced hypoglycemia, investigators continue to search for treatments that address both the treatment of insulin deficiency as well as other metabolic abnormalities that are associated with diabetes (5).

Insulin resistance, a metabolic abnormality common in type 2 diabetes, appears to be present in individuals with type 1 diabetes, as well. Although insulin resistance in type 2 diabetes is generally associated with obesity, hypertension, dyslipidemia, and other metabolic disorders, studies have shown that overweight as well as normal-weight adults with type 1 diabetes can have peripheral and hepatic insulin resistance. Insulin clamp procedures performed on nonobese type 1 diabetic subjects under a variety of glycemic conditions demonstrated increased hepatic glucose production and reduced insulin clearance compared with nondiabetic subjects (6–10). Others have shown that type 1 diabetic subjects with a family history of type 2 diabetes who have undergone intensive insulin therapy have a greater tendency toward expressing the markers of insulin resistance, such as weight gain, increased insulin requirements, and dyslipidemia (11).

Insulin sensitizers such as biguanide, metformin, and the thiazolidinedione compounds troglitazone, rosiglitazone, and pioglitazone have significantly improved blood glucose levels in type 2 diabetic individuals by suppressing hepatic glucose output and enhancing insulin-mediated glucose disposal (12,13). Because insulin sensitizers have been effective in improving blood glucose control in type 2 diabetic individuals, for whom insulin resistance is a prevailing feature, it seems reasonable to consider the possibility that these agents would be of benefit in overweight subjects with type 1 diabetes, who are more likely to have a degree of insulin resistance. Studies have shown that the insulin sensitizer metformin significantly reduces the amount of insulin required to improve blood glucose levels in both adult and ad-

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

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olescent subjects with type 1 diabetes (14–17). No study, however, has investigated the potential benefit of a thiazolidinedione in the management of type 1 diabetes. Thus, this study was designed to examine the safety and efficacy of the thiazolidinedione rosiglitazone in the treatment of overweight adults with type 1 diabetes.

## RESEARCH DESIGN AND METHODS

Subjects entered the study based on the following criteria: age  $\geq 19$  years, medical history consistent with type 1 diabetes, HbA<sub>1c</sub> (A1C) level  $\geq 6.5\%$ , BMI  $\geq 27$  kg/m<sup>2</sup>, insulin dose  $> 35$  units per day, and normal hepatic, renal, and cardiac function. Subjects who met the inclusion criteria were randomly assigned in a double-blind fashion to rosiglitazone 4 mg twice daily or placebo one tablet twice daily. Tablets of rosiglitazone and placebo, identical in appearance, were dispensed by the pharmacist in the Clinical Trials Office at the University of Texas Southwestern Medical Center. The randomization codes were held in the Clinical Trials Office until the conclusion of the study. The insulin dose and/or regimen were changed as needed in all subjects in an attempt to achieve normal plasma glucose and A1C levels and to minimize episodes of hypoglycemia.

Subjects were seen biweekly the first month of treatment, once the second month of treatment, and bimonthly thereafter, for a total of 32 weeks of observation. Between-visit contacts with the health care team rarely occurred, and they were initiated by the subjects. Complete medical histories, physical examinations, waist and hip measurements, 3-day food records, and urine microalbumin levels were determined at the beginning and end of the study. Fasting lipid and lipoprotein levels, fasting plasma glucose levels, serum chemistries, hemoglobin and hematocrit levels, and C-peptide concentrations were obtained at baseline, week 16, and at the end of the study (week 32). Liver function tests, body weight, blood pressure, and A1C levels were obtained at each visit.

Subjects were asked to check their plasma glucose levels at least four times daily. Glycemic control, tolerance to the assigned treatment, and frequency of hypoglycemia were assessed at each visit. Subjects were encouraged to maintain baseline levels of dietary intake and phys-

ical activity throughout the study. Informed consent was obtained from all subjects after approval by the university's institutional review board.

## Intervention

At the randomization visit, subjects were given either placebo or rosiglitazone 4 mg twice daily. The insulin dose was modified as needed in all subjects in an attempt to achieve normal glycemic control. At each clinic visit, plasma glucose levels were downloaded from the patient's meter to the computer; all patients used a glucose meter that stored plasma glucose readings as well as the date and time the readings were obtained.

The frequency of hypoglycemia was determined by the number of plasma glucose readings stored in the patient's meter that were  $< 65$  mg/dl. Mild hypoglycemia was defined as a reading between 45 and 65 mg/dl. Moderate hypoglycemia was defined as the number of plasma glucose readings  $\leq 45$  mg/dl. Severe hypoglycemia, as in the DCCT (Diabetes Control and Complications Trial), was defined as any low plasma glucose level that patients were unable to treat themselves, and the patient's symptoms were reversed with oral carbohydrate, glucagon, or intravenous glucose. Edema was determined to be absent or present based on the patient's report of swelling combined with a physical examination.

## Analytical determinations

A1C levels were measured by high-pressure liquid chromatography (upper limit for nondiabetic individuals in this assay was 5.6%). An automated glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA) was used to measure plasma glucose concentrations. C-peptide concentrations were measured by radioimmunoassay using polyclonal antisera. Fasting lipid and lipoprotein concentrations were assessed by standard laboratory methods.

## Statistical analysis

Demographic and outcome variables were checked for normality across groups. A log transformation improved normality for BMI, total daily insulin dose, A1C, VLDL cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, VLDL triglyceride, alanine aminotransferase, aspartate aminotransferase, C-peptide, and urine albumin levels. A

one-way ANOVA assessed between-group differences, and a paired *t* test determined within-group differences. The Mann-Whitney *U* test was used to analyze categorical variables. A regression analysis was performed to identify predictors for change in A1C level and incidence of adverse events within each group. Pearson correlations were performed for all variables.

Two-tailed tests were performed for the analyses. A *P* value  $< 0.05$  was considered statistically significant. All analyses were conducted using SPSS software, version 12.0. Results are reported as the means  $\pm$  SD, unless otherwise indicated.

## RESULTS

A total of 52 subjects met the baseline criteria and were randomized to treatment. Two female subjects chose not to continue study participation after  $< 4$  weeks of treatment. One of these subjects had been assigned to rosiglitazone, and one had been assigned to placebo. The remaining 50 subjects completed the study. At baseline, the two groups were comparable in age, sex, ethnicity, duration of diabetes, weight, BMI, waist-to-hip ratio, total daily insulin dose, C-peptide, and A1C level. The group randomized to treatment with rosiglitazone had a higher baseline systolic blood pressure ( $P = 0.003$ ) and total cholesterol level ( $P = 0.02$ ) than the group randomized to placebo (Tables 1 and 2).

A1C improved to comparable levels in both groups after 32 weeks of treatment (rosiglitazone:  $7.9 \pm 1.3$  to  $6.9 \pm 0.7\%$ ,  $P < 0.0001$ ; placebo:  $7.7 \pm 0.8$  to  $7.0 \pm 0.9\%$ ,  $P < 0.0001$ ). An A1C level  $\leq 7.0\%$  was achieved by 68% of subjects assigned to rosiglitazone vs. 52% of subjects assigned to placebo ( $P = 0.3$ ). An A1C level between 6.0 and 6.5% was achieved by 36% of subjects assigned to rosiglitazone vs. 16% assigned to placebo ( $P < 0.05$ ).

Regression analysis showed that the only predictors of improvement in A1C level in the placebo-treated group were baseline A1C level ( $P < 0.0001$ ) and frequency of self-glucose testing ( $P = 0.003$ ,  $r^2 = 0.703$ ). Baseline A1C level was also the most significant predictor of improvement in A1C in the rosiglitazone-treated group. However, when baseline A1C level was removed from the model, the baseline BMI ( $P = 0.001$ ), total daily insulin dose ( $P = 0.001$ ), total cholesterol ( $P = 0.003$ ), HDL cholesterol ( $P = 0.001$ ),

**Table 1 — Baseline characteristics**

	Rosiglitazone + insulin	Placebo + insulin
n	25	25
Age (years)	43.7 ± 13.3	41.1 ± 9.2
Sex (M/F)	16/9	18/7
Ethnic group (n)	22 Caucasian, 3 African American	23 Caucasian, 1 African American, 1 Hispanic
Duration of diabetes (years)	20.7 ± 13.3	18.1 ± 9.3
Waist-to-hip ratio	0.91 ± 0.07	0.93 ± 0.06
Fasting C-peptide (ng/ml)	0.3 ± 0.3	0.3 ± 0.3

Data are means ± SD or n.

and LDL cholesterol ( $P = 0.03$ ) were significant predictors of improvement in A1C level in subjects treated with rosiglitazone ( $r^2 = 0.730$ ). This was not the case in the placebo group. Neither baseline waist-to-hip ratio nor systolic or diastolic blood pressures were associated with change in A1C level in either group. Frequency of self-glucose testing was also not a significant predictor for improved A1C in those treated with rosiglitazone.

Rosiglitazone-treated subjects with a BMI  $\geq 30$  kg/m<sup>2</sup> ( $n = 16$ , mean BMI  $35.2 \pm 5.4$  kg/m<sup>2</sup>) experienced significantly greater improvements in A1C ( $-1.4 \pm 1.2\%$ ) and total cholesterol ( $-18.2 \pm 31.6$  mg/dl) levels compared with rosiglitazone-treated subjects with a BMI  $< 30$  kg/m<sup>2</sup> (mean BMI  $28.4 \pm 0.7$  kg/m<sup>2</sup>; A1C  $-0.4 \pm 0.5\%$  and total cholesterol  $+13.8 \pm 31.6$  mg/dl,  $P < 0.05$ ,

vs. rosiglitazone subjects with a BMI  $\geq 30$  kg/m<sup>2</sup>) (Fig. 1). This did not occur in subjects taking placebo, even though baseline A1C levels were not different between groups (rosiglitazone  $8.1 \pm 1.5\%$  vs. placebo  $7.9 \pm 0.9\%$  when BMI  $\geq 30$  kg/m<sup>2</sup>). The A1C level improved by  $0.64 \pm 1.2\%$  in placebo-treated subjects with a BMI  $\geq 30$  kg/m<sup>2</sup> ( $n = 12$ ; mean BMI  $33.9 \pm 1.8$  kg/m<sup>2</sup>) compared with  $0.67 \pm 0.7\%$  in those with a BMI  $< 30$  kg/m<sup>2</sup> (mean BMI  $28.5 \pm 0.18$  kg/m<sup>2</sup>). Cholesterol levels were essentially unchanged in placebo-treated subjects, irrespective of baseline BMI.

Mean fasting blood glucose levels were somewhat more improved in the group treated with rosiglitazone midway through the study (week 16), approaching significance (rosiglitazone:  $172.6 \pm 68.3$  to  $139.3 \pm 67.9$  mg/dl baseline vs.

week 16; placebo:  $185.8 \pm 90.6$  to  $177.6 \pm 66.1$  mg/dl;  $P = 0.51$ ). However, by the end of the study, fasting plasma glucose levels were not significantly different from baseline, nor were they different between groups.

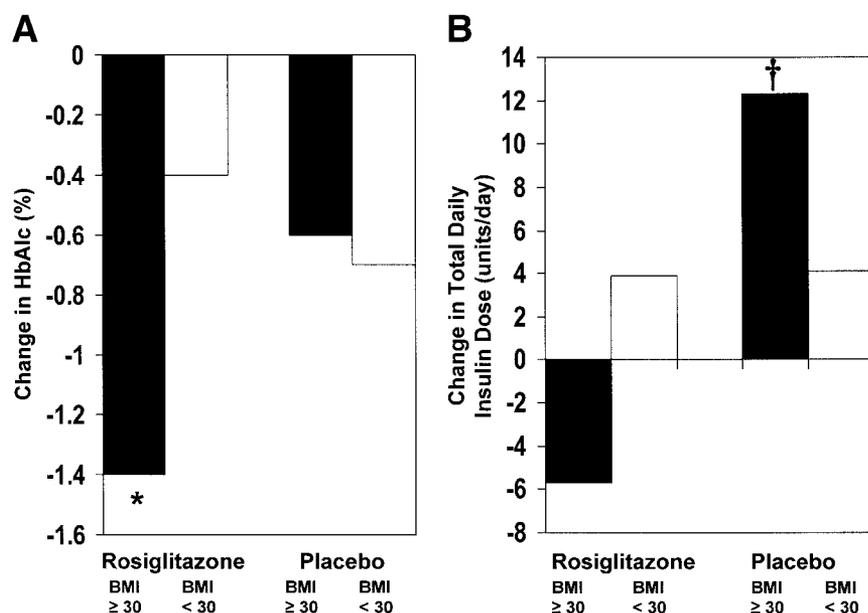
The insulin regimens used were not different between treatment groups at the beginning or the end of the study. At baseline, the rosiglitazone-treated group consisted of 10 subjects who used an insulin pump, 10 subjects who used three or four daily insulin injections of long- or intermediate-acting insulin in combination with rapid- or short-acting insulin, and 5 subjects who used twice-daily insulin. The group assigned to placebo consisted of 7 subjects who used an insulin pump, 15 subjects who used three to four daily insulin injections, and 3 who used twice-daily insulin. By the end of the study, none of the subjects used twice-daily insulin, and twice as many subjects in both groups were using insulin glargine to meet their basal insulin needs (32% of subjects). Also, ~60% of all subjects were using rapid-acting insulin at baseline (versus short-acting insulin), and ~80% were using rapid-acting insulin by the end of the study. Subjects using insulin pump therapy or multiple daily insulin injections at baseline remained on that treatment throughout the course of the study.

The total daily insulin dose increased in the group assigned to placebo ( $74.0 \pm 33.8$  units at baseline vs.  $82.0 \pm 48.9$  at

**Table 2—Results before and 32 weeks after treatment with rosiglitazone and insulin or placebo and insulin**

	Rosiglitazone and insulin		Placebo and insulin	
	Baseline	Week 32	Baseline	Week 32
Weight (kg)	97.2 ± 11.8	100.6 ± 16.0*	96.4 ± 12.2	99.1 ± 15.0*
BMI (kg/m <sup>2</sup> )	32.7 ± 5.4	34.0 ± 7.4*	31.1 ± 3.1	32.0 ± 4.2*
Systolic blood pressure (mmHg)	137.4 ± 15.6†	128.8 ± 14.8*	125.8 ± 10.0	127.5 ± 14.0
Diastolic blood pressure (mmHg)	87.2 ± 9.4	79.4 ± 7.2‡	84.7 ± 7.0	83.2 ± 7.1
Insulin dose (units/day)	77.5 ± 28.6	75.3 ± 33.1	74.0 ± 33.8	82.0 ± 48.9*
Fasting plasma glucose (mg/dl)	172.6 ± 68.3	153.3 ± 66.4	185.8 ± 90.6	173.4 ± 64.8
A1C (%)	7.9 ± 1.3	6.9 ± 0.7‡	7.7 ± 0.8	7.0 ± 0.9‡
Total cholesterol (mg/dl)	201.9 ± 37.6†	195.2 ± 37.5§	177.9 ± 33.1	175.1 ± 31.7
LDL cholesterol (mg/dl)	117.8 ± 32.0	120.1 ± 35.0	103.4 ± 25.2	102.6 ± 25.4
HDL cholesterol (mg/dl)	53.9 ± 20.5	53.6 ± 19.4	47.8 ± 15.0	49.1 ± 15.8
VLDL cholesterol (mg/dl)	15.8 ± 13.2	16.4 ± 9.8	13.8 ± 9.4	14.6 ± 15.6
Triglycerides (mg/dl)	108.1 ± 64.6	101.8 ± 53.8	92.8 ± 38.9	85.4 ± 39.7
VLDL triglycerides (mg/dl)	66.8 ± 57.6	61.9 ± 46.6	55.8 ± 31.6	48.8 ± 33.0
Hemoglobin (gm/dl)	14.4 ± 1.5	13.6 ± 1.9‡§	14.5 ± 1.0	14.5 ± 1.0
Hematocrit (%)	42.0 ± 3.9	39.8 ± 5.1‡§	42.3 ± 3.0	42.2 ± 2.9

Data are means ± SD. \* $P < 0.05$  vs. baseline; † $P < 0.05$  vs. placebo and insulin at baseline; ‡ $P < 0.0001$  vs. baseline; § $P < 0.05$  vs. placebo and insulin at week 32.



**Figure 1**—Change in mean A1C level (A) and total daily insulin dose (B) based on baseline BMI in type 1 diabetic subjects after 8 months of treatment with insulin and rosiglitazone or insulin and placebo. \* $P < 0.05$  vs. rosiglitazone-treated subjects with a BMI  $< 30$  kg/m<sup>2</sup>; † $P < 0.05$  vs. rosiglitazone-treated subjects with a BMI  $\geq 30$  kg/m<sup>2</sup>.

week 32,  $P < 0.05$ ), compared with a modest decline in the group treated with rosiglitazone ( $77.5 \pm 28.6$  units at baseline vs.  $75.3 \pm 33.1$  at week 32). Although the absolute values were not significantly different between groups, the change in insulin dose was significantly greater in the group treated with placebo (rosiglitazone:  $-2.2 \pm 17.8$  units; placebo:  $+8.1 \pm 17.9$ ;  $P < 0.05$ ). The significant change in total daily insulin dose in the placebo group was largely caused by the increase in insulin required by subjects with a baseline BMI  $\geq 30$  kg/m<sup>2</sup> ( $+12.3 \pm 24.2$  units/day), which significantly differed from the decrease in insulin requirements in rosiglitazone-treated subjects with a baseline BMI  $\geq 30$  kg/m<sup>2</sup> ( $-5.7 \pm 21.4$  units/day; rosiglitazone vs. placebo  $P < 0.05$ ) (Fig. 1). When examined as units per kilogram per day, rosiglitazone-treated subjects with a baseline BMI  $\geq 30$  kg/m<sup>2</sup> experienced a significant reduction in insulin requirements at week 32 ( $-0.10 \pm 0.16$  units  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup>) compared with rosiglitazone-treated subjects with a baseline BMI  $< 30$  kg/m<sup>2</sup> ( $+0.03 \pm 0.05$  units  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup>,  $P < 0.04$ ) and compared with placebo-treated subjects with a BMI  $\geq 30$  kg/m<sup>2</sup> ( $+0.07 \pm 0.19$  units  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup>,  $P = 0.02$ ).

Mean body weight and BMI signifi-

cantly increased in both treatment groups (rosiglitazone:  $+3.3 \pm 5.8$  kg,  $P = 0.008$ ; placebo:  $+2.7 \pm 5.2$  kg;  $P < 0.02$  vs. baseline), and an increase in weight was strongly associated with improvement in A1C level in both groups (rosiglitazone:  $r = -0.511$ ; placebo:  $r = -0.607$ ;  $P \leq 0.009$ ). An increase in weight was not associated with the presence of edema in the group treated with rosiglitazone ( $r = -0.244$ ,  $P = 0.20$ ). Mean caloric intake based on food records did not differ between groups (rosiglitazone:  $2,066.4 \pm 589.2$  and  $1,994.9 \pm 726.5$  calories/day for baseline and week 32, respectively; placebo:  $2,313.0 \pm 582.5$  and  $2,152.5 \pm 551.9$ ).

Lipid levels did not change in either group. Urine albumin levels significantly improved in both groups (rosiglitazone:  $54.7 \pm 127.7$  to  $23.3 \pm 42.7$  mg/24 h,  $P < 0.03$ ; placebo:  $37.7 \pm 68.1$  to  $25.2 \pm 35.2$  mg/24 h,  $P = 0.003$ , baseline vs. week 32). Both systolic blood pressure ( $137.4 \pm 15.6$  to  $128.8 \pm 14.8$  mmHg,  $P < 0.02$ , baseline vs. week 32) and diastolic blood pressure ( $87.2 \pm 9.4$  to  $79.4 \pm 7.2$  mmHg,  $P < 0.0001$ ) improved in the group treated with rosiglitazone. No change in blood pressure occurred in the placebo group. The change in systolic and diastolic blood pressure in the rosiglitazone-treated

group was significantly greater than in the placebo-treated group at the end of the study ( $P = 0.009$ ). Both groups were similar in terms of baseline history and treatment of hypertension and the number of subjects who were given additional doses and/or classes of antihypertensive medication during the course of the study.

### Adverse events

Rosiglitazone treatment was associated with an increased incidence of edema requiring diuretics compared with placebo (eight subjects versus one,  $P = 0.01$ ). One female subject reduced her study medication (rosiglitazone) to one tablet daily at week 18 because of significant edema in her extremities, despite the use of diuretic medication. Another female subject discontinued study medication at week 30 because of severe edema that resulted in hospitalization for congestive heart failure. There is a possibility, however, that this patient had exceeded the prescribed dose of rosiglitazone by mistake because the subject's bottle of diuretic medication was found to also contain study medication (rosiglitazone). None of the subjects treated with placebo reduced their dose of study medication. The incidence of mild anemia, as reflected in a significant decrease in hemoglobin (rosiglitazone:  $14.4 \pm 1.5$  vs.  $13.6 \pm 1.9$  g/dl) and hematocrit (rosiglitazone:  $42.0 \pm 3.9$  vs.  $39.8 \pm 5.1\%$ ;  $P < 0.0001$  baseline vs. week 32;  $P < 0.05$  rosiglitazone vs. placebo at week 32), was also associated with rosiglitazone. Regression analysis showed that female sex was the only significant predictor of the incidence of edema requiring diuretics ( $r = 0.736$ ,  $P < 0.0001$ ) and the incidence of anemia ( $r = 0.510$ ,  $P = 0.009$ ). There were no incidents of elevated alanine aminotransferase or aspartate aminotransferase levels in either group.

The total incidence of mild ( $P = 0.9$ ) and severe hypoglycemic episodes (rosiglitazone:  $n = 12$ ; placebo:  $n = 8$ ;  $P = 0.3$ ) was not different between groups. However, midway through the study, subjects treated with rosiglitazone had significantly more self-obtained plasma glucose readings  $\leq 45$  mg/dl ( $P < 0.05$ ). One male subject had to decrease his dose of study medication (rosiglitazone) to one tablet daily at week 8 because of frequent episodes of hypoglycemia.

**CONCLUSIONS**— These results demonstrated that overweight type 1 diabetic subjects taking rosiglitazone experienced significant and comparable improvements in A1C levels ( $-1.0\%$ ) as subjects taking insulin alone ( $-0.7\%$ ) when insulin therapy was adjusted in both groups in an attempt to achieve near-normal blood glucose levels. However, the placebo-treated group required 11% more insulin to achieve these results. Both groups also gained significant but comparable amounts of weight ( $\sim 3$  kg). This weight gain was not related to the presence of edema or change in insulin dose, and it was not associated with any increase in caloric intake based on 3-day food records. Rather, weight gain was strongly associated with improved A1C levels in both groups. By the end of the study, neither group had experienced any significant change in lipid levels, and the overall frequency of hypoglycemia was the same. The group treated with rosiglitazone experienced significantly more edema and anemia, with female sex being the only significant predictor of these events.

Differences between the groups emerged, however, when the subjects' baseline BMI was taken into consideration. Rosiglitazone-treated subjects with a baseline BMI  $\geq 30$  kg/m<sup>2</sup> experienced a significantly greater improvement in A1C ( $-1.4\%$ ) and total cholesterol level ( $-18.2$  mg/dl) and a significant decrease in insulin ( $-1.0$  units/kg) compared with rosiglitazone-treated subjects whose baseline BMI was  $< 30$  kg/m<sup>2</sup> (A1C:  $-0.4\%$ ; total cholesterol:  $+13.8$  mg/dl; insulin dose:  $+0.3$  units/kg). These outcomes were not influenced by BMI in subjects treated with placebo. In fact, placebo-treated subjects with a BMI  $\geq 30$  kg/m<sup>2</sup> accounted for the greatest increase in insulin dose in the placebo group ( $+12.3$  units/day), whereas subjects with a BMI  $\geq 30$  kg/m<sup>2</sup> taking rosiglitazone actually decreased their insulin requirements ( $-5.7$  units/day). This is more remarkable considering that the rosiglitazone-treated subjects with a BMI  $\geq 30$  kg/m<sup>2</sup> experienced a reduction in A1C of 1.4% compared with placebo-treated subjects with a BMI  $\geq 30$  kg/m<sup>2</sup>, whose A1C level improved by 0.6%. These results suggest that rosiglitazone had the greatest effect on subjects who may have had the most insulin resistance (BMI  $\geq 30$  kg/m<sup>2</sup>) because these subjects experi-

enced the greatest improvement in A1C and total cholesterol level while lowering their insulin dose. In addition, when baseline A1C level was removed from the model, baseline levels of BMI, total daily insulin dose, total cholesterol, HDL cholesterol, and LDL cholesterol (markers of insulin resistance) were significant predictors of improvement in A1C level in subjects treated with rosiglitazone. In contrast, baseline A1C level and frequency of blood glucose testing were the only predictors of a decrease in A1C in the group treated with placebo, suggesting that self-management behaviors were more important in improving A1C level in subjects who were not taking rosiglitazone.

Although the overweight type 1 diabetic subjects treated with rosiglitazone experienced a significant improvement in their mean A1C level while lowering their total daily insulin dose, the reductions in A1C level (from 7.9 to 6.9%) and total daily insulin dose ( $-3.0\%$ ) were not as pronounced as we have seen in previous studies involving type 2 diabetes. When we combined troglitazone with insulin therapy in type 2 diabetic subjects, A1C levels improved from 8.5 to 6.4% with a 13% reduction in insulin dose (18). The increased risk for hypoglycemia in type 1 diabetes may be the main obstacle preventing a more profound blood glucose-lowering effect of rosiglitazone in these individuals. In this study, type 1 diabetic subjects taking rosiglitazone had significantly more plasma glucose readings  $< 45$  mg/dl midway through the study (week 16) than subjects taking placebo. This may have precluded our taking a more aggressive approach to insulin therapy, or it may have prompted us to reduce the insulin dose. In addition, the patients may have altered their self-management behaviors in their effort to reduce the frequency of hypoglycemia and avoid episodes of severe hypoglycemia.

On the other hand, 68% of our rosiglitazone-treated subjects achieved an A1C level  $\leq 7.0\%$ . This is in contrast to results obtained in studies of type 2 diabetic subjects in whom insulin and thiazolidinedione treatment resulted in significantly lower A1C levels, but whose average A1C levels at the end of the study exceeded 7.8% (19–22). Because these type 2 diabetic studies did not allow for an increase in insulin dose, the simultaneous use of intensive insulin regimens with a thiazolidinedione, as was done in this

study, may be what is necessary to achieve target glycemic levels.

Our subjects gained comparable amounts of weight gain irrespective of treatment with rosiglitazone or placebo, reflecting the increase in weight that is associated with improved levels of glycemic control. Our subjects were encouraged to maintain baseline levels of dietary intake, and food records revealed no change in dietary intake at the end of the study. Other studies have shown, however, that with caloric restriction, weight gain can be avoided when glycemic control is improved with thiazolidinediones (23,24).

The insulin sensitizer metformin has resulted in improved glycemic control without weight gain in type 2 diabetic subjects, both as dual insulin and metformin therapy (18,25) and as triple therapy when metformin was added to insulin therapy and later combined with a thiazolidinedione (26). Studies of normal-weight type 1 diabetic subjects (BMI  $\leq 26$  kg/m<sup>2</sup>) given metformin resulted in no weight gain, but the subjects also experienced only small if any improvement in glycemic control (15–17). Therefore, it is not known whether metformin in combination with insulin in overweight (BMI  $\geq 30$  kg/m<sup>2</sup>) type 1 diabetic subjects would result in improved glycemic control without weight gain.

Rosiglitazone-treated subjects experienced a significant improvement in systolic and diastolic blood pressure over the course of the study. No change in blood pressure was observed in subjects taking placebo. Although the group assigned to treatment with rosiglitazone had a higher baseline systolic blood pressure than the group assigned to placebo, baseline diastolic blood pressures were similar between the groups. Thus, even though the study was not designed to evaluate the impact of rosiglitazone on blood pressure, it appears that rosiglitazone had a beneficial effect. Hypertension was aggressively treated in all subjects, and there were no differences between groups regarding history of hypertension at baseline, the number of subjects who were being treated for hypertension at baseline, or the number of subjects who were prescribed increased doses and/or additional classes of antihypertensive medication.

In summary, rosiglitazone may be an effective adjunct to insulin therapy in type 1 diabetic subjects with a BMI  $\geq 30$  kg/m<sup>2</sup>

who have markers of insulin resistance, such as high insulin requirements, hypertension, and hypercholesterolemia. Despite the variability seen among subjects with a BMI  $\geq 30$  kg/m<sup>2</sup> who took rosiglitazone, lower overall total daily insulin dosage and significant improvements in A1C, cholesterol, and blood pressure levels were observed. However, the potential benefit of rosiglitazone must be balanced against the potential risk for hypoglycemia, edema, and anemia, especially in women who appear to experience edema and anemia more profoundly with this drug. Because aggressive insulin therapy using increased doses of insulin led to overall improvements in glycemic control that were comparable to that which was achieved in the group treated with rosiglitazone, treatment with rosiglitazone should only be considered after efforts at improving glycemic control with intensive insulin treatment, increased blood glucose self-monitoring, and dietary management do not result in desired glycemic goals. More investigation into the long-term effects of rosiglitazone may provide more definitive evidence regarding the beneficial impact of rosiglitazone on glycemic control and cardiovascular risk factors in type 1 diabetic individuals who have features of insulin resistance.

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