Comparison of Glargine Insulin Versus Rosiglitazone Addition in Poorly Controlled Type 2 Diabetic Patients on Metformin Plus Sulfonylurea

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OBJECTIVE — We sought to examine the mechanisms by which the addition of glargine insulin or rosiglitazone improves glycemic control in type 2 diabetic subjects poorly controlled on maximally effective doses of metformin plus sulfonylurea.

RESEARCH DESIGN AND METHODS — Subjects (aged 47 ± 11 years, BMI 31 ± 5 kg/m^2, HbA_{1c} [A1C] 9.4 ± 1.3%) received bedtime glargine insulin (titrated based on the fasting plasma glucose [FPG], $n = 10$) or rosiglitazone (4 mg twice daily, $n = 10$). At baseline and after 4 months, A1C was measured and an oral glucose tolerance test and a 3-h euglycemic insulin (80 mU/m^2 per min) clamp with [3-^{3}H]glucose were performed.

RESULTS — A1C and FPG decreased similarly in the glargine insulin (9.1 ± 0.4 to 7.6 ± 0.3% and 212 ± 14 to 139 ± 5 mg/dl, respectively, both $P < 0.0001$) and rosiglitazone (9.4 ± 0.3 to 7.6 ± 0.4% and 223 ± 14 to 160 ± 19 mg/dl, respectively, both $P < 0.005$) groups. After 4 months, endogenous glucose production (EGP) declined similarly with glargine insulin (2.27 ± 0.10 to 1.73 ± 0.12 mg · kg^{-1} · min^{-1}, $P < 0.0001$) and rosiglitazone (2.21 ± 0.12 to 1.88 ± 0.12 mg · kg^{-1} · min^{-1}, $P = 0.01$). The hepatic insulin resistance index declined in the rosiglitazone group (32 ± 3 to 21 ± 1 mg · kg^{-1} · min^{-1} × μU/ml, $P = 0.03$ vs. baseline and $P < 0.05$ vs. glargine insulin) and did not change in the glargine group (22 ± 5 to 20 ± 3 mg · kg^{-1} · min^{-1} × μU/ml, P = NS). At 4 months, glargine insulin (3.6 ± 0.5 to 4.2 ± 0.4 mg · kg^{-1} · min^{-1}, $P < 0.01$) and rosiglitazone (2.7 ± 0.3 to 3.8 ± 0.3 mg · kg^{-1} · min^{-1}, $P < 0.0005$) increased R_d, but the increment was greater in the rosiglitazone group ($P < 0.05$). Diastolic blood pressure was reduced only by rosiglitazone ($P < 0.01$).

CONCLUSIONS — Triple therapy with glargine insulin or rosiglitazone similarly reduced A1C, primarily by suppressing basal EGP (hepatic). Glargine insulin reduced basal EGP by increasing plasma insulin levels, while rosiglitazone decreased basal hepatic glucose production by improving hepatic insulin sensitivity.

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It is well established that improved glycemic control decreases the risk of microvascular complications (1–3). In type 2 diabetic patients with baseline HbA_{1c} (A1C) 8.5–9.0%, monotherapy with metformin (4,5) or sulfonylureas (6,7) reduces the A1C by ~1.5–2%. Addition of metformin to a sulfonylurea or vice versa provides a completely additive effect and decreases the A1C to <7.0% in ~60–70% of patients (4,8,9). Mechanistically, optimal treatment in the remaining 30–40% of individuals who do not achieve adequate glycemic control on metformin/sulfonylurea therapy remains unclear (8,10). Two options have been commonly utilized: *1*) the addition of a third oral agent, i.e., a thiazolidinedione, or *2*) the addition of long-acting insulin at bedtime. Several studies have demonstrated the efficacy of thiazolidinedione addition (decrement in A1C = 0.9–1.5%) in patients with type 2 diabetes who have poor glycemic control and who are on maximally effective doses of metformin plus sulfonylurea (10–12). Studies in which bedtime insulin is added to a sulfonylurea alone (13) or to combined metformin/sulfonylurea treatment have also been shown to be effective (14,15).

No previous study has examined the mechanisms by which addition of a thiazolidinedione versus bedtime insulin improves glycemic control. Fasting hyperglycemia in type 2 diabetes results from hepatic insulin resistance and excessive production of glucose by the liver throughout the sleeping hours (8,16,17). In type 2 diabetic patients who are on the maximum dose of metformin/sulfonylurea therapy, yet remain in poor glycemic control, oral agents may be insufficient to overcome the hepatic resistance and normalize hepatic glucose output (8,16). Glargine insulin is a peakless, long-acting insulin analog that provides 24-h basal insulin replacement and causes less hypoglycemia than NPH insulin (18). The addition of bedtime glargine insulin, while maintaining the sulfonylurea plus metformin therapy, has a number of attributes that make it an efficacious and safe therapeutic option: *1*) nocturnal/early morning hyperinsulinemia will suppress the elevated rate of endogenous glucose production (EGP) throughout the sleeping hours, leading to a reduction in fasting plasma glucose (FPG) concentration; *2*) because glargine insulin has no

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Abbreviations: CRC, clinical research center; EGP, endogenous glucose production; FFA, free fatty acid; FPG, fasting plasma glucose; FPI, fasting plasma insulin; IRI, insulin resistance index; OGTT, oral glucose tolerance test; TGD, total glucose disposal.

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

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peak, hypoglycemia is minimized (19); and 3) since glargine insulin's duration of action is up to 24 h, glycemic control throughout the day should also be improved with a single bedtime injection (19). Two recent studies (10,11) have demonstrated that addition of a thiazolidinedione versus bedtime insulin are equally effective in reducing the A1C in poorly controlled type 2 diabetic subjects who are taking maximally effective doses of a sulfonylurea plus metformin. However, neither of these studies (10,11) examined the mechanism(s) by which thiazolidinediones and bedtime insulin produced beneficial effects on glucose homeostasis.

In the present study, we have compared the mechanism(s) of action of the addition of bedtime glargine insulin versus the addition of rosiglitazone in type 2 diabetic patients who are poorly controlled (A1C ≥9%) on maximally effective doses of sulfonylureas plus metformin.

RESEARCH DESIGN AND METHODS

— Twenty subjects (8 men, 12 women; aged 47 ± 11 years; BMI 31 ± 5 kg/m^2; A1C 9.4 ± 1.3%; 15 Mexican Americans, 4 Caucasians, 1 African American) with type 2 diabetes participated in the study. All subjects were taking stable, maximally effective doses of a sulfonylurea (≥20 mg/day of glyburide or glipizide) and metformin (≥2,000 mg/day). Patients who had ever received insulin or a thiazolidinedione were excluded. Entry criteria included age 30–70 years, stable body weight (±3 lb) for at least 3 months before the study, and A1C ≥9.0%. All patients were in good general health, without evidence of cardiac, hepatic, renal, or other chronic diseases as determined by history, physical examination, screening blood tests, urinalysis, and electrocardiogram. No subject participated in any heavy exercise, and no subject was taking any medication known to affect glucose metabolism. All subjects gave written, voluntary, informed consent before participation. The institutional review board of the University of Texas Health Science Center at San Antonio approved the protocol.

On screening, subjects had baseline blood studies to measure A1C, FPG concentration, and liver function. On the same visit (5–7 days before an oral glucose tolerance test [OGTT]), subjects met with a dietitian and were instructed to consume a weight-maintaining diet containing 50% carbohydrate, 30% fat, and 20% protein. On the evening before the OGTT, subjects were asked to refrain from eating or drinking anything except water after 8:00 P.M. At 7:30 A.M., subjects reported to the clinical research center (CRC) and a catheter was placed in an antecubital vein for all blood withdrawal. At −30, −15, and 0 min, blood for FPG, free fatty acids (FFAs), C-peptide, and insulin was obtained. At time zero, subjects ingested 75 g flavored glucose solution, and 100 μCi of ^3H_2O was given as an intravenous bolus. Plasma-tritiated water radioactivity was determined at 90, 105, and 120 min for determination of lean body mass and fat mass. Blood for plasma glucose, FFA, insulin, and C-peptide determination was obtained every 15 min after glucose ingestion. All oral antidiabetes medications were omitted on the morning of the OGTT.

Within 5–7 days following the OGTT, subjects returned to the CRC at 7:30 A.M., following a 10- to 12-h overnight fast, for a euglycemic insulin clamp (20). Catheters were inserted into an antecubital vein for infusion of all test substances and retrogradely into a vein on the dorsum of the hand for blood withdrawal. The hand was inserted into a heated box (70°C) to achieve arterialization of venous blood. At 8:00 A.M., baseline blood samples were drawn and a primed (25 μCi × FPG/100)-continuous (0.25 μCi/min) infusion of [3-^{3}H]glucose was started at −180 min via antecubital vein catheter. At −30, −20, −10, −5, and 0 min, blood was obtained for measurement of FPG, FFA, and insulin concentrations and tritiated glucose radioactivity. At time zero, a primed-continuous (80 mU/m^2 per min) infusion of regular insulin (Novolin; Novo Nordisk, Princeton, NJ) was started and continued for 180 min. Plasma glucose was allowed to drop until it reached 95 mg/dl, at which level it was maintained by a variable infusion of 20% dextrose. Plasma glucose levels were measured every 5 min throughout the insulin clamp. Plasma insulin and FFA concentrations and [3-^{3}H]glucose radioactivity were measured every 10–15 min after the start of insulin.

Following completion of the insulin clamp, subjects were randomized to receive rosiglitazone, 4 mg twice daily, or bedtime glargine insulin, 10 units/day, for 4 months. The dose of bedtime glargine insulin was increased on a weekly basis in an attempt to achieve a fasting glucose concentration <110 mg/dl. Each week, subjects were asked to perform home blood glucose monitoring four times per day: fasting, before lunch, before dinner, and at bedtime. Subjects maintained weekly telephone contact with the investigators and returned to the CRC every 2 weeks. At each 2-week visit, subjects had an interim history, measurement of blood pressure and body weight, and FPG determination. Every month, A1C and fasting plasma lipid profile were determined. After 4 months, OGTT and euglycemic insulin clamp were repeated as described above.

Analytical determinations

Plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin concentration (Diagnostic Products, Los Angeles, CA) was measured by radioimmunoassay. A1C was measured by affinity chromatography (Biochemical Methodology, Drower 4350; Isolab, Akron, OH). Plasma FFA concentration was measured by enzymatic colorimetric quantification (Waco Chemicals, Neuss, Germany). Plasma total cholesterol and triglyceride levels were measured enzymatically (Boehringer-Mannheim, Indianapolis, IN) on a Hitachi 704 autoanalyzer. HDL cholesterol was measured enzymatically on a Hitachi 704 autoanalyzer after precipitation of chylomicrons and VLDL. LDL cholesterol was calculated using the Friedwald equation. [3-^{3}H]glucose specific activity was determined on barium/zinc deproteinized plasma samples, as previously described (17).

Calculations

Under steady-state postabsorptive conditions, the rate of endogenous (primarily hepatic) glucose production (EGP) was calculated as the [3-^{3}H]glucose infusion rate (disintegrations per minute per minute) divided by steady-state plasma [3-^{3}H]glucose specific activity (disintegrations per minute per milligram). During the insulin clamp, the rate of glucose appearance (R_a) was calculated from Steele's equation (21), using a distribution volume of 250 ml/kg. EGP during the insulin clamp was calculated by subtracting the exogenous glucose infusion rate from the tracer-derived R_a. The basal hepatic insulin sensitivity index was determined as the product of EGP and fasting plasma insulin (FPI) concentration. Over the range of plasma insulin concentrations typically seen under basal condi-

Table 1—*Body weight, FPG and lipid levels, blood pressure, OGTT parameters, and hepatic insulin resistance before and after 4 months of treatment*

Parameter	Glargine insulin			Rosiglitazone			ΔRosiglitazone vs. Δglargine after 4 months
n	10			10			
Age (years)	54 ± 6			41 ± 11			
Sex (male/female)	4/6			4/6			
Ethnicity (MA/C/AA)	7/3/0			8/1/1			
	Baseline	After	*P* value	Baseline	After	*P* value	*P* value
Body weight (kg)	74.9 ± 5.4	77.9 ± 5.2	0.03	88.3 ± 4.1	91.9 ± 5.5	0.01	0.04
BMI (kg/m^2)	28.9 ± 1.7	32.3 ± 1.4	<0.01	31.4 ± 1.2	32.8 ± 1.2	0.05	NS
FPG (mg/dl)	212 ± 14	139 ± 5	<0.0001	223 ± 14	160 ± 19	0.0008	NS
A1C (%)	9.1 ± 0.4	7.6 ± 0.3	<0.0001	9.4 ± 0.3	7.6 ± 0.4	0.0025	NS
FPI (μU/ml)	9 ± 2	11 ± 2		15 ± 2	12 ± 1	0.05	<0.05
Fasting plasma FFA (μEq/l)	702 ± 56	646 ± 50		640 ± 34	441 ± 39	<0.01	0.004
Blood pressure (mmHg)							
Systolic	131 ± 4	129 ± 5		127 ± 4	129 ± 4		NS
Diastolic	69 ± 2	70 ± 3		67 ± 4	60 ± 4	<0.05	<0.01
Fasting plasma lipids (mg/dl)							
Total cholesterol	186 ± 12	170 ± 11	0.05	190 ± 11	219 ± 11	0.005	0.004
HDL cholesterol	43 ± 3	40 ± 5		38 ± 3	41 ± 2	0.02	NS
LDL cholesterol	119 ± 10	103 ± 7	0.03	103 ± 11	142 ± 9	0.03	0.003
Triglycerides	117 ± 13	136 ± 20		242 ± 59	184 ± 34		NS
75-g OGTT							
Mean plasma glucose (mg/dl)	350 ± 12	297 ± 16	0.005	321 ± 14	259 ± 16	0.02	NS
Mean plasma insulin (μU/ml)	18 ± 3	20 ± 3		27 ± 8	35 ± 7		NS
Mean plasma FFA (μEq/l)	534 ± 38	489 ± 66		478 ± 51	410 ± 56	<0.05	NS
Matsuda ISI	4.06 ± 0.89	4.22 ± 0.85		4.65 ± 1.6	6.21 ± 1.9	0.01	NS
Insulinogenic index (Δinsulin/Δglucose)	0.07 ± 0.01	0.12 ± 0.03		0.11 ± 0.03	0.17 ± 0.06		NS
Hepatic IRI*	22 ± 5	20 ± 3		32 ± 3	21 ± 1	0.03	<0.05

Data are means ± SE. *In mg · kg^{-1} · min^{-1} × μU/ml. AA, African American; C, Caucasian; MA, Mexican American; NS, not significant.

tions (8 ± 1 to 12 ± 1 to 20 ± 1 pmol/l), there is a linear relationship between the increase in plasma insulin concentration and the decrease in hepatic glucose production ($r = 0.92$, $P < 0.001$) (22). An index of adipocyte insulin resistance was calculated as the product of FPI and FFA concentrations (22). Total glucose disposal (TGD) equals the sum of residual EGP plus the exogenous glucose infusion rate.

Areas under the curve for plasma glucose, insulin, C-peptide, and FFA during the OGTT were determined using the trapezoidal rule. The mean plasma glucose, insulin, C-peptide, and FFA concentrations during the OGTT were calculated by dividing the area under the curve by 120 min. The Matsuda whole-body insulin sensitivity index during the OGTT was determined as follows (23):

$$\frac{10{,}000}{\sqrt{(\text{FPG} \times \text{FPI}) \times (\overline{\text{PG}} \times \overline{\text{PI}})}}$$

where FPG is in mg/dl, FPI is in μU/ml, and $\overline{\text{PG}}$ and $\overline{\text{PI}}$ equal the mean plasma glucose and insulin concentrations during the OGTT, respectively. The insulinogenic index during the OGTT was calculated as the incremental insulin response (0–120 min) divided by the incremental glucose response (0–120 min) divided by the severity of insulin resistance, where insulin resistance = steady-state plasma insulin/TGD during the insulin clamp.

Total-body water content was calculated from the mean plasma [^{3}H]water radioactivity at 90, 105, and 120 min after the bolus of ^3H_2O. Plasma-tritiated water specific activity was calculated assuming that plasma water represents 93% of total plasma volume. Fat-free mass equals total-body water divided by 0.73 (24).

Statistical analysis

Statistical calculations were performed with StatView for Windows, version 5.0 (SAS Institute, Cary, NC). Values before and after treatment (intragroup) were compared using the paired *t* test. Comparisons between groups (intergroup) were performed using ANOVA with Bonferroni/Dunn post hoc testing when appropriate. Data are presented as means ± SE. A *P* value <0.05 was considered statistically significant.

RESULTS — Other than fasting plasma triglyceride concentration, which was higher in the rosiglitazone group, there were no significant differences in baseline characteristics between the groups (Table 1). Baseline weight, FPI concentration, and hepatic insulin resistance index (IRI) were slightly, although not significantly, higher in the rosiglitazone group. All subjects in the rosiglitazone group took 4 mg rosiglitazone twice daily throughout the study. The average bedtime dose of glargine insulin was 17 ± 2 units/day at the conclusion of the trial. One subject in the rosiglitazone group required reduction of glipizide from 20 to 10 mg/day because of symptoms of hypoglycemia and capillary blood glucose readings <70 mg/dl at least twice per week.

Metabolic parameters

After 16 weeks of therapy, both A1C (glargine: 9.1 ± 0.4 to 7.6 ± 0.3%, Δ = 1.5 ± 0.2%; rosiglitazone: 9.4 ± 0.3 to 7.6 ± 0.4%, Δ = 1.8 ± 0.4%) and FPG concentration (glargine: 212 ± 14 to 139 ± 5 mg/dl, Δ = 74 ± 13 mg/dl; rosiglitazone: 223 ± 14 to 160 ± 19 mg/dl, Δ = 63 ± 12 mg/dl) were significantly reduced ($P < 0.001$); between-treatment differences for FPG and A1C were not significant. The FPI concentration increased slightly in the glargine group (9 ± 2 to 11 ± 2 μU/ml, P = NS) and decreased in the rosiglitazone group (15 ± 2 to 12 ± 1 μU/ml, $P < 0.05$; $P < 0.05$ glargine vs. rosiglitazone). Weight increased significantly in both groups, and the increment in body weight was slightly, although not significantly, higher in the rosiglitazone versus glargine insulin group (Δ = 4.7 ± 1.0 vs. 2.3 ± 1.0 kg, P = NS). In the rosiglitazone group, the change in A1C was correlated inversely with the changes in body weight ($r = -0.871$, $P < 0.0005$) and BMI ($r = -0.866$, $P = 0.0005$). In the glargine group, there was no correlation between the change in A1C and changes in body weight or BMI.

Systolic blood pressure did not change significantly with either glargine insulin or rosiglitazone therapy. There was a modest decline in diastolic blood pressure with the addition of rosiglitazone ($P < 0.05$ vs. baseline and vs. glargine insulin). From baseline, rosiglitazone significantly increased total cholesterol ($P = 0.005$), LDL cholesterol ($P = 0.03$), HDL cholesterol ($P = 0.02$), and tended to reduce triglycerides (P = NS), while glargine insulin reduced LDL cholesterol ($P = 0.03$) and total cholesterol ($P = 0.05$) (Table 1). After 4 months of treatment, rosiglitazone increased total and LDL cholesterol versus glargine insulin (both $P < 0.05$), whereas triglycerides and HDL cholesterol were not significantly different between the two groups. The fasting plasma FFA did not change in the glargine group and declined significantly in the rosiglitazone group ($P < 0.01$ vs. baseline and $P < 0.05$ vs. glargine insulin).

OGTT

Before treatment, mean plasma glucose, insulin, and FFA concentrations were similar in the rosiglitazone and glargine insulin groups (Table 1). After 4 months, the mean plasma glucose concentration (350 ± 12 to 297 ± 16 mg/dl, $P = 0.005$ and 321 ± 14 to 259 ± 16 mg/dl, $P = 0.02$) during the OGTT was reduced similarly in the glargine and rosiglitazone groups, respectively, without change in the mean plasma insulin concentration (Table 1). The mean plasma FFA concentration during the OGTT decreased similarly in both the rosiglitazone (478 ± 51 to 410 ± 56 μEq/l, $P < 0.05$) and glargine (534 ± 38 to 489 ± 66, $P < 0.10$) groups. After 4 months, the Matsuda whole-body insulin sensitivity index increased from 4.7 ± 1.6 to 6.2 ± 1.9 ($P < 0.05$) in the rosiglitazone group and remained unchanged in the glargine insulin group. The insulinogenic index (Δinsulin/Δglucose) increased slightly, but not significantly, in the rosiglitazone and glargine insulin groups (Table 1).

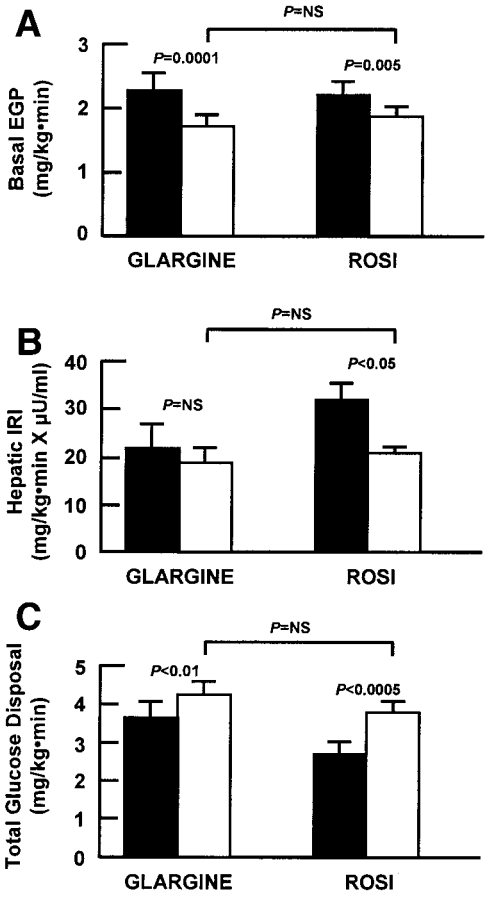

Figure 1— A: *Change in basal EGP before (■) and after (□) 4 months of treatment with glargine insulin or rosiglitazone (ROSI).* B: *Hepatic IRI before (■) and after (□) 4 months of glargine insulin and rosiglitazone treatment.* C: *Insulin-stimulated total-body glucose disposal (TGD) during the insulin clamp before (■) and after (□) 4 months of glargine insulin and rosiglitazone treatment.*

Euglycemic insulin clamp

After 4 months, glargine insulin and rosiglitazone similarly reduced basal EGP (2.27 ± 0.10 to 1.73 ± 0.12 mg · kg^{-1} · min^{-1}, $P < 0.0001$ and 2.21 ± 0.12 to 1.88 ± 0.12 mg · kg^{-1} · min^{-1}, $P = 0.01$, respectively) (Fig. 1*A*). The hepatic IRI (EGP × FPI) declined in the rosiglitazone group (32 ± 3 to 21 ± 1 mg · kg^{-1} · min^{-1} × μU/ml, $P < 0.05$ vs. baseline and vs. rosiglitazone) and did not change significantly in the glargine group (22 ± 5 to 20 ± 3 mg · kg^{-1} · min^{-1} × μU/ml, P = NS) (Table 1). The basal rate of EGP and FPG were positively correlated in the glargine and rosiglitazone groups before ($r = 0.76$, $P = 0.008$ and $r = 0.80$, $P = 0.01$, respectively) and after ($r = 0.66$, $P < 0.05$ and $r = 0.93$, $P = 0.0001$, respectively) 4 months of therapy.

During the insulin clamp studies before and after 4 months of therapy, the steady-state plasma insulin (100 ± 4 and 104 ± 6 μU/ml, respectively) and glucose (93 ± 1 and 91 ± 1 mg/dl, respectively) concentrations were similar in glargine insulin and rosiglitazone groups. Four months of treatment with glargine (3.6 ± 0.5 to 4.2 ± 0.4 mg · kg^{-1} · min^{-1}, $P < 0.01$) and rosiglitazone (2.7 ± 0.3 to 3.8 ± 0.3 mg · kg^{-1} · min^{-1}, $P < 0.0005$) increased insulin-mediated total-body glucose disposal (TGD) (Fig. 1*C*). The increment in TGD was significantly greater in the rosiglitazone versus glargine insulin groups (Δ = 1.14 ± 0.17 vs. 0.50 ± 0.15 mg · kg^{-1} · min^{-1}, $P < 0.05$, respectively). Suppression of EGP during the insulin clamp was virtually complete before

therapy in the rosiglitazone (90 ± 4%) and glargine (92 ± 3%) groups and improved slightly after 4 months of therapy (98 ± 1% in both groups). The decrement in fasting plasma FFA concentration correlated inversely with the increment in TGD in the rosiglitazone group ($r = -0.777$, $P < 0.01$), whereas no correlation was observed in the glargine insulin group. The basal adipocyte IRI (FPI × fasting plasma FFA) was reduced by rosiglitazone (9,191 ± 2,823 to 5,828 ± 1,299, $P < 0.05$) and unchanged by glargine insulin (7,320 ± 2,323 to 7,330 ± 1,447, P = NS vs. baseline and $P < 0.01$ vs. rosiglitazone).

Safety and tolerability

Other than one subject who developed hypoglycemia in the rosiglitazone group, neither therapy was associated with any adverse side effects. No rosiglitazone-treated patient developed edema, which was specifically looked for on each visit.

CONCLUSIONS — In the U.S., the most commonly utilized oral agent regimen is metformin plus a sulfonyurea (25). However, a significant number of diabetic patients fail to achieve an A1C <7.0% (26). In such individuals, the therapeutic options are addition of a thiazolidinedione or long-acting insulin given at bedtime (8). Most recently, exenatide (Byetta) was approved by the U.S. Food and Drug Administration and provides an additional option (27).

A few studies (10,11) have compared the efficacy of the addition of a thiazolidinedione versus the addition of a long-acting bedtime insulin with the therapeutic regimen of type 2 diabetic patients who are poorly controlled on combined sulfonylurea/metformin therapy, and no study has examined the mechanism(s) by which the addition of rosiglitazone or bedtime glargine insulin improve glucose homeostasis in such individuals. In the present study, 20 type 2 diabetic patients (A1C 9.4 ± 1.3%) on maximum doses of metformin plus sulfonylurea were randomly assigned to receive rosiglitazone, 4 mg twice daily, or glargine insulin, 10 units/day, at bedtime. The starting glargine dose was titrated up (by C.T. or L.G.) based upon each subject's home blood glucose monitoring results. At the end of 16 weeks, the mean bedtime dose of glargine was 17 ± 2 units, which was less than the dose (39–47 units) reached in previous studies (11,28). Although the targeted goal was an FPG concentration of 110 mg/dl, the physicians failed to achieve this goal, in part, because the home blood glucose monitoring results demonstrated reasonable glycemic control throughout the daytime and evening hours. With regard to this, it is noteworthy that the decrements in A1C in the glargine insulin (Δ = 1.5%) and rosiglitazone (Δ = 1.8%) were similar, as was the absolute level of A1C (7.6%) achieved after 4 months of therapy. Nonetheless, it is likely that a more aggressive titration of the glargine insulin could have achieved a greater decline in A1C, albeit with a greater incidence of hypoglycemia. In two previous studies (11,28) utilizing bedtime glargine insulin, the investigators also failed to achieve the targeted FPG goal. In the present study, the more conservative titration of bedtime glargine insulin had the safety advantage that no subject in the glargine group experienced hypoglycemia. This is in contrast to the treat-to-target study that reported 13.9 symptomatic hypoglycemic episodes per patient year in type 2 diabetic patients treated with glargine (28). The less aggressive titration of glargine insulin also allowed us to better compare the mechanism of action of each intervention, since both the decrements and absolute level of A1C achieved were similar in the glargine insulin and rosiglitazone groups. Since chronic hyperglycemia is known to cause insulin resistance, i.e., glucotoxicity (29), we were able to negate this confounding variable. Because rosiglitazone-treated subjects received the maximally effective dose, further titration would not have produced a greater reduction in A1C.

When comparing therapeutic options, it is important to consider the effect of the intervention on other metabolic/cardiovascular parameters and the mechanism(s) by which improved glycemic control is achieved. Rosiglitazone significantly reduced diastolic blood pressure and raised plasma HDL cholesterol (beneficial cardiovascular effects) but raised plasma total and LDL cholesterol levels. In contrast, glargine insulin had no effect on blood pressure, HDL cholesterol, or triglyceride levels but significantly reduced total and LDL cholesterol (Table 1). At present, it is not possible to assign a weighting value to the beneficial effects of glargine versus rosiglitazone on plasma lipid levels and blood pressure.

Although rosiglitazone and bedtime glargine insulin produced similar reductions in A1C (Δ = 1.5 vs. 1.8%, respectively) and FPG (Δ = 73 vs. 63 mg/dl, respectively), they did so via different mechanisms. The rate of EGP (primarily hepatic) is the primary determinant of FPG concentration (17). Consistent with this, the reduction in FPG following both rosiglitazone and glargine therapy was closely related to the decline in EGP. However, rosiglitazone reduced EGP by decreasing the basal hepatic IRI (by 35%), whereas glargine insulin had no effect on the basal hepatic IRI ($P < 0.05$ vs. rosiglitazone). The beneficial effect of glargine insulin to suppress EGP was related to nocturnal hyperinsulinemia, which overcame the hepatic insulin resistance, thereby reducing the elevated basal rate of hepatic glucose production. It should be noted that the basal hepatic IRI was modestly, although not significantly, higher in the rosiglitazone versus glargine insulin group before initiation of therapy. Whether rosiglitazone would have produced a similar improvement in type 2 diabetes with a lower starting hepatic IRI remains to be determined.

During the insulin clamp performed after 4 months of treatment, whole-body insulin sensitivity was improved with both rosiglitazone and glargine insulin, but the incremental increase observed with rosiglitazone was greater than ($P < 0.05$) that observed with glargine insulin. Consistent with this, insulin sensitivity (Matsuda index) during the OGTT improved significantly with rosiglitazone and only slightly with glargine insulin (Table 1). The improvement in insulin sensitivity with rosiglitazone is consistent with a recent review of the literature (30). Previous studies have demonstrated that improved insulin sensitivity following thiazolidinedione therapy is closely related to the reduction in plasma FFA (31,32) and an increase in body weight (32,34). In the present study, we also observed a strong inverse correlation between the improvement in insulin sensitivity during the insulin clamp and the decrease in fasting plasma FFA concentration ($r = -0.777$, $P < 0.01$). These relationships are explained as follows: peroxisome proliferator–activated receptor γ is primarily located in the vasculature and on adipocytes. When peroxisome proliferator–activated receptor γ agonists bind to subcutaneous adipocytes, fat cells are stimulated to divide and multiple genes involved in lipogenesis are induced (35). In addition, expression of genes involved in lipolysis are repressed (31). This leads to a net flux of

FFA into these newly formed fat cells and a reduction in the plasma FFA concentration, which results in improved tissue sensitivity to insulin (31,32,34). Redistribution of fat out of liver (33), muscle (34), and visceral adipose depots (32,34), as well as altered adipocytokine secretion by fat cells (34), also contribute to the improvement in insulin sensitivity. Glargine insulin also improved whole-body insulin-stimulated glucose disposal, but the increment was less than that observed with rosiglitazone ($\Delta = 0.50 \pm 0.15$ vs. 1.14 ± 0.17 mg · kg^{-1} · min^{-1}, $P < 0.05$). It is noteworthy that neither the fasting plasma FFA concentration nor the suppression of plasma FFA during the OGTT were significantly improved following glargine insulin therapy. Therefore, it is possible that the improvement in insulin sensitivity following glargine was secondary to the decline in plasma glucose concentration and reduced glucotoxicity (29). However, chronic hyperinsulinemia is known to cause insulin resistance (36), and this could have offset the beneficial effect of reduced plasma glucose levels to enhance insulin sensitivity. These offsetting effects of insulin therapy may explain the inconsistent effects of insulin therapy on insulin sensitivity, which have been observed in prior studies (16,37).

In summary, addition of glargine insulin or rosiglitazone in poorly controlled type 2 diabetic patients on metformin/sulfonylurea similarly reduced A1C, FPG, and mean plasma glucose concentration during an OGTT. Rosiglitazone produced these changes by enhancing hepatic and peripheral tissue (muscle) sensitivity to insulin, while the glucose-lowering action of glargine insulin was related to suppression of hepatic glucose production by nocturnal hyperinsulinemia. Peripheral, but not hepatic, tissue sensitivity to insulin was modestly improved by glargine insulin, most likely secondary to amelioration of glucotoxicity. Both therapeutic interventions have beneficial effects and, mechanistically, the addition of either glargine insulin or a thiazolidinedione are reasonable therapeutic options in poorly controlled type 2 diabetic patients who are on maximally effective doses of metformin plus sulfonylurea.

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