

EFFICACY AND METABOLIC EFFECTS OF METFORMIN AND TROGLITAZONE IN TYPE II DIABETES MELLITUS

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ABSTRACT

Background Combination therapy is logical for patients with non-insulin-dependent (type II) diabetes mellitus, because they often have poor responses to single-drug therapy. We studied the efficacy and physiologic effects of metformin and troglitazone alone and in combination in patients with type II diabetes.

Methods We randomly assigned 29 patients to receive either metformin or troglitazone for three months, after which they were given both drugs for another three months. Plasma glucose concentrations during fasting and postprandially and glycosylated hemoglobin values were measured periodically during both treatments. Endogenous glucose production and peripheral glucose disposal were measured at base line and after three and six months.

Results During metformin therapy, fasting and postprandial plasma glucose concentrations decreased by 20 percent (58 mg per deciliter [3.2 mmol per liter], $P < 0.001$) and 25 percent (87 mg per deciliter [4.8 mmol per liter], $P < 0.001$), respectively. The corresponding decreases during troglitazone therapy were 20 percent (54 mg per deciliter [2.9 mmol per liter], $P = 0.01$) and 25 percent (83 mg per deciliter [4.6 mmol per liter], $P < 0.001$). Endogenous glucose production decreased during metformin therapy by a mean of 19 percent ($P = 0.001$), whereas it was unchanged by troglitazone therapy ($P = 0.04$ for the comparison between groups). The mean rate of glucose disposal increased by 54 percent during troglitazone therapy ($P = 0.006$) and 13 percent during metformin therapy ($P = 0.03$ for the comparison within the group and between groups). In combination, metformin and troglitazone further lowered fasting and postprandial plasma glucose concentrations by 18 percent (41 mg per deciliter [2.3 mmol per liter], $P = 0.001$) and 21 percent (54 mg per deciliter [3.0 mmol per liter], $P < 0.001$), respectively, and the mean glycosylated hemoglobin value decreased 1.2 percentage points.

Conclusions Metformin and troglitazone have equal and additive beneficial effects on glycemic control in patients with type II diabetes. Metformin acts primarily by decreasing endogenous glucose production, and troglitazone by increasing the rate of peripheral glucose disposal. (N Engl J Med 1998; 338:867-72.)

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HYPERGLYCEMIA in patients with non-insulin-dependent (type II) diabetes mellitus is caused by peripheral insulin resistance, which results in decreased insulin-mediated glucose disposal; increased endogenous glucose production, chiefly from the liver; and inadequate pancreatic insulin secretion.¹ Reversal of these defects, either individually or in concert, improves glycemic control. New drugs are now available that affect each of these defects separately, and an understanding of their mechanisms of action is important for their proper use, especially when they are administered in combination.

Until recently in the United States, the only oral drugs available for patients with type II diabetes were sulfonylureas. These increase insulin secretion,² but they often lead to weight gain and may cause hypoglycemia. Recently, metformin became available. Its exact mechanisms of action are poorly understood, but they include suppression of endogenous glucose output³ and increased peripheral insulin sensitivity.⁴ In patients with diabetes, metformin lowers plasma glucose concentrations both alone^{5,6} and in combination with a sulfonylurea,⁶⁻⁸ while simultaneously decreasing plasma insulin concentrations. A third category of drug, α -glucosidase inhibitors, decreases postprandial plasma glucose concentrations by delaying the absorption of carbohydrates.⁹ Troglitazone, the drug that has become available most recently, acts by increasing overall insulin sensitivity,¹⁰ with evidence of effects in both the liver,^{11,12} the primary glucose-producing organ, and skeletal muscle,^{13,14} the main site of glucose disposal. Troglitazone is effective both when given alone¹⁵⁻¹⁷ and when given in combination with either a sulfonylurea^{18,19} or insulin.²⁰ Given that metformin and troglitazone may have different metabolic actions, both with the theoretical advantage of reducing hyperglycemia without increasing insulin secretion, they are attractive prospects for combination therapy in patients with type II diabetes.

In this study, we evaluated the efficacy and phys-

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iologic effects of these two drugs during three months of monotherapy in a group of patients with type II diabetes and then during three months of combination therapy.

METHODS

Study Subjects

We studied 29 patients with type II diabetes, as defined by the National Diabetes Data Group,²¹ who had a glycosylated hemoglobin value above the upper limit of normal and a plasma C-peptide concentration of at least 1.5 ng per milliliter (0.50 nmol per liter) while receiving dietary therapy or treatment with a sulfonylurea. Patients were excluded if they had abnormal renal or hepatic function or had had a recent atherosclerotic event. Fifteen patients (8 women and 7 men) were randomly assigned to receive metformin for three months, and 14 (8 women and 6 men) to receive troglitazone for three months. They then were treated with both drugs for an additional three months. Both the patients and the investigators were aware of the treatment. One patient assigned to receive troglitazone withdrew from the study after two weeks because of persistent hyperglycemia (plasma glucose concentrations, >350 mg per deciliter [19.4 mmol per liter]). One patient in each treatment group elected not to continue into the combination phase. Finally, two patients assigned to receive troglitazone completed the monotherapy period but not the period of combination therapy, because of intervening illnesses. The protocol was approved by the human-investigation committee of Yale University, and all the patients gave informed consent.

Study Design

Monotherapy: Months 0 to 3

After a two-week washout period during which any previous drug therapy was discontinued, the patients received either 1000 mg of metformin twice daily orally or 400 mg of troglitazone once daily orally for three months. Plasma glucose, glycosylated hemoglobin, and routine hematologic and chemical values were measured at base line and monthly thereafter. At base line and month 3, the patients underwent an eight-hour mixed-meal tolerance test and a hyperinsulinemic-euglycemic clamp study²² with [6,6-²H]glucose to measure endogenous glucose production and glucose disposal rate.

Combination Therapy: Months 4 to 6

After the initial three-month period, the patients were invited to continue therapy for a second three months, during which they took both the original drug and the other drug in combination. The patients were again followed monthly as described above, and at the end of the study period they underwent a final mixed-meal tolerance test and hyperinsulinemic-euglycemic clamp study. During the course of the study, the patients were prescribed a diet designed to maintain base-line body weight, with a composition of 50 percent carbohydrate, 34 percent fat, and 16 percent protein.

Meal-Tolerance Test

At approximately 7 a.m., with the patients in bed after a 12-hour fast, an intravenous catheter was inserted into an antecubital vein for blood sampling. At 8 a.m., the patients drank a liquid formula breakfast (Sustacal-HC) containing 33 percent of their total daily caloric intake, followed four hours later by an identical liquid lunch. Blood samples were drawn before the breakfast and then hourly for eight hours for measurements of plasma glucose, insulin, and C peptide. After completing the test, the patients received an evening meal and then fasted until the end of the clamp study, which was performed the next day. The mean of all plasma glucose values after the first test was taken as the postprandial value.

Hyperinsulinemic-Euglycemic Clamp Study

Beginning at 6 a.m., a primed (corrected for ambient fasting plasma glucose concentration) [6,6-²H]glucose solution (2 mg per square meter of body-surface area per minute) was infused into the antecubital vein continuously for four hours. During the third hour, a retrograde cannula was inserted into a warmed vein of the contralateral hand for sampling of arterialized venous blood. Blood samples were drawn at 10-minute intervals during the final 40 minutes of the 4-hour basal period for the measurement of plasma glucose, insulin, and [²H]glucose. Then, a two-step priming dose of insulin was administered for 10 minutes (480 mU per square meter per minute for 5 minutes, followed by 240 mU per square meter per minute for 5 minutes), followed by a continuous infusion of insulin (120 mU per square meter per minute) for a total of 5 hours. The plasma glucose concentration was allowed to fall to 100 mg per deciliter (5.6 mmol per liter) and then maintained at that concentration by the administration of glucose (20 g of dextrose per 100 ml enriched to approximately 2.5 percent with [6,6-²H]glucose). The basal isotope infusion was stopped when the exogenous glucose infusion was started. During the final hour of the clamp study, additional blood samples were drawn at 10-minute intervals for the measurement of plasma insulin and steady-state glucose isotope enrichment.

Substrate and Hormone Measurements

Plasma samples were shipped frozen to Corning Nichols Institute for chemical analysis. Plasma insulin was determined by radioimmunoassay, with an interassay coefficient of variation of 12.3 percent and an intraassay coefficient of variation of 7.4 percent. Plasma C peptide was also measured by radioimmunoassay, with an interassay coefficient of variation of 12.0 percent and an intraassay coefficient of variation of 6.5 percent. Glycosylated hemoglobin was measured by high-performance liquid chromatography (Bio-Rad), with a normal reference range of 4.5 to 5.9 percent; the assay was linear up to a value of 14 percent. Plasma glucose was measured at the bedside with a Beckman glucose analyzer.

Gas chromatography-mass spectrometry of the [6,6-²H]glucose concentration in plasma was carried out at the Yale Stable Isotope Core Facility, with the pentaacetate derivative of glucose as described previously.²³ Basal endogenous glucose production was calculated with the following equation:

$$\text{Basal endogenous glucose production} = (f/\text{BSA}) \times ([\text{enrichment}_{\text{inf}}/\text{enrichment}_{\text{plasma}}] - 1),$$

where *f* is the basal [6,6-²H]glucose infusate rate (in milligrams per minute), BSA is the body-surface area (in square meters), enrichment_{inf} is the percent enrichment of [6,6-²H]glucose infusate, and enrichment_{plasma} is the percentage of basal plasma [6,6-²H]glucose enrichment. The glucose disposal rate during clamping was calculated with the following equation:

$$\text{Glucose disposal rate} = \text{cEGP} + \text{GIR},$$

where GIR is the mean rate of infusion of exogenous glucose from minutes 260 to 300 of the clamping period (in milligrams per square meter per minute), and cEGP is endogenous glucose production during clamping, calculated as follows:

$$\text{Endogenous glucose production during clamping} = \text{GIR} \times ([\text{enrichment}_{\text{inf}}/\text{enrichment}_{\text{plasma}}] - 1),$$

where enrichment_{inf} is the percent [6,6-²H]glucose enrichment of infusate, and enrichment_{plasma} is the steady-state percentage of plasma [6,6-²H]glucose enrichment during clamping.

Statistical Analysis

Descriptive and inferential statistical analyses were performed with Systat, version 5.2.1. The actual results at each time were compared with repeated-measures analysis of variance. All statistical tests were two-sided.

RESULTS

Characteristics of the Patients

The patients in the two groups were evenly matched with respect to age; body-mass index; fasting plasma glucose, insulin, and C-peptide concentrations; and glycosylated hemoglobin values (Table 1).

Monotherapy

At three months, metformin and troglitazone lowered the mean fasting plasma glucose concentration by 58 mg per deciliter (3.2 mmol per liter) ($P < 0.001$) and 54 mg per deciliter (3.0 mmol per liter) ($P = 0.01$), respectively, a decrease of 20 percent in both groups (Fig. 1A). The glycosylated hemoglobin values did not change significantly in either group from the values obtained before the two-week period of washout from former therapy. During the meal-tolerance test, the mean postprandial plasma glucose concentration decreased by 87 mg per deciliter (4.8 mmol per liter) in the metformin group ($P < 0.001$) and by 83 mg per deciliter (4.6 mmol per liter) in the troglitazone group ($P < 0.001$), a decrease of 25 percent in both groups (Fig. 1B). The mean fasting and postprandial plasma insulin and C-peptide concentrations decreased slightly but not significantly in both groups.

After three months of metformin therapy, mean endogenous glucose production decreased by 19 percent, from 108 to 87 mg per square meter per minute (6.0 to 4.8 mmol per square meter per minute, $P = 0.001$). In contrast, there was no significant change (-3 percent) in the troglitazone group ($P = 0.04$). The mean glucose-disposal rate increased in the troglitazone group by 54 percent, from 172 to 265 mg per square meter per minute (9.5 to 14.7 mmol per square meter per minute, $P = 0.006$). The increase with metformin therapy was comparatively less (13 percent; from 240 to 272 mg per square meter per minute [13.3 to 15.1 mmol per square meter per minute]; $P = 0.03$).

When the data were analyzed according to the mean percent changes in these values within subjects, endogenous glucose production decreased by a mean of 18 percent after three months of metformin therapy but was not significantly changed (-0.1 percent) by troglitazone therapy (Fig. 2). The mean increase in the glucose-disposal rate within subjects was 97 percent in the troglitazone group and 27 percent in the metformin group (Fig. 2). The changes in these results were also significantly different between the groups ($P = 0.04$ for the change in endogenous glucose production, and $P = 0.03$ for change in glucose disposal).

Combination Therapy

During combination therapy, the mean fasting plasma glucose concentration decreased by an addi-

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS WITH TYPE II DIABETES MELLITUS WHO COMPLETED THE THREE-MONTH MONOTHERAPY PHASE OF THE STUDY.*

CHARACTERISTIC	METFORMIN GROUP (N = 15)	TROGLITAZONE GROUP (N = 13)
Age (yr)	51 ± 13	56 ± 12
Duration of diabetes (yr)	6 ± 6	4 ± 3
Weight (kg)	99 ± 15	96 ± 26
Body-mass index†	33.7 ± 6.8	34.0 ± 8.1
Fasting plasma glucose after wash-out period (mg/dl)	287 ± 84	275 ± 73
Glycosylated hemoglobin at screening (%)	9.8 ± 1.7	9.3 ± 1.9
Fasting plasma insulin (μU/ml)	24 ± 13	35 ± 25
Fasting plasma C peptide (ng/ml)	1.9 ± 0.5	2.3 ± 0.7

*Plus-minus values are means ± SD. There were no significant differences between groups. To convert values for glucose to millimoles per liter, multiply by 0.056. To convert values for insulin to picomoles per liter, multiply by 6. To convert values for C peptide to nanomoles per liter, multiply by 0.33.

†Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

tional 41 mg per deciliter (2.3 mmol per liter) ($P = 0.001$), a reduction of 18 percent, between three and six months (Fig. 1A). The total mean decrease in fasting plasma glucose concentration in all patients during the six-month treatment period was 98 mg per deciliter (5.4 mmol per liter) ($P = 0.001$), a 35 percent reduction. During combination therapy the mean postprandial plasma glucose concentration decreased an additional 54 mg per deciliter ($P < 0.001$), a reduction of 21 percent (Fig. 1B). During the entire six-month study period, the mean postprandial plasma glucose concentration decreased by 140 mg per deciliter (7.8 mmol per liter) ($P < 0.001$), a 41 percent reduction. The mean glycosylated hemoglobin value also decreased during the three months of combination therapy, with a mean absolute fall of 1.2 percent from base line ($P < 0.001$) (Fig. 3). The mean fasting and postprandial plasma insulin and C-peptide concentrations were lower at six months than at base line, although the changes were small and not statistically significant.

The addition of troglitazone to metformin resulted in no further decrease in basal endogenous glucose production. At six months in this group, mean endogenous glucose production was 90 mg per square meter per minute (5.0 mmol per square meter per minute), representing a decrease of 17 percent from base line ($P = 0.002$) and one not significantly different from the 19 percent decrease after three months of metformin alone. Similarly, in the group given metformin in addition to troglitazone, there was no decrease in endogenous glucose production at six months (92 mg per square meter per minute

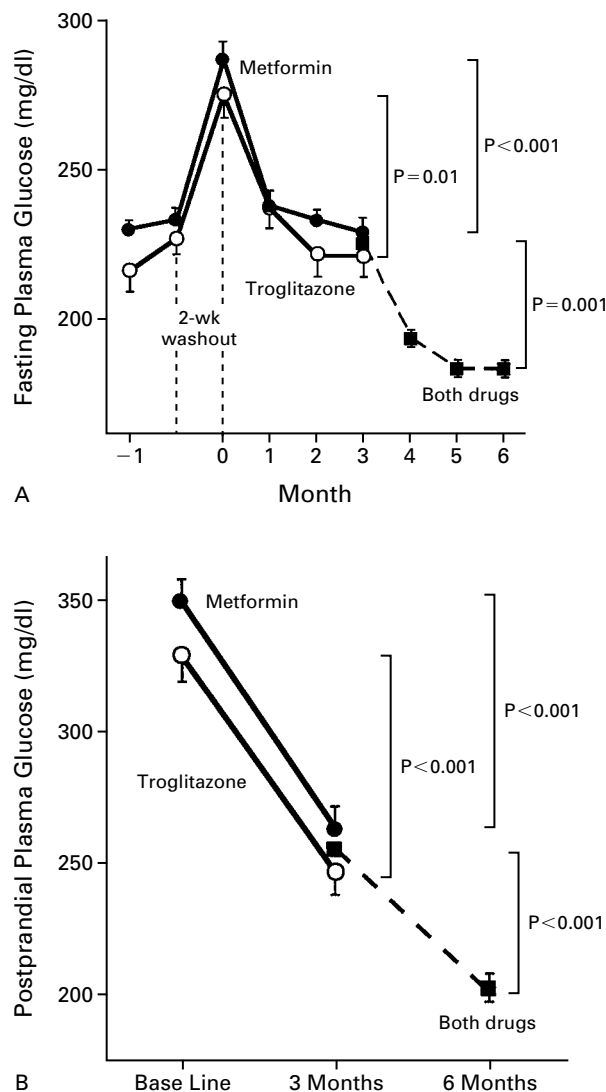


Figure 1. Mean (\pm SE) Changes in Fasting Plasma Glucose Concentrations (Panel A) and Postprandial Plasma Glucose Concentrations (Panel B) during Therapy with Metformin or Troglitazone for Three Months Followed by Combined Therapy with Metformin and Troglitazone for Three Months.

The postprandial plasma glucose values are the means of eight hourly measurements made during the meal-tolerance test. To convert values for glucose to millimoles per liter, multiply by 0.056.

[5.1 mmol per square meter per minute]) as compared with base line (92 mg per square meter per minute) or after three months of troglitazone alone (89 mg per square meter per minute [4.9 mmol per square meter per minute]).

Adding troglitazone to metformin significantly increased the rate of glucose disposal to 337 mg per square meter per minute (18.7 mmol per square meter per minute), a mean increase of 24 percent over the three-month value ($P=0.04$). In contradistinction, when metformin was added to troglitazone, the rate of glucose disposal increased to 304 mg per square meter per minute (16.9 mmol per square meter per minute), a mean increase of only 15 percent from three months ($P=0.30$). The mean increase in the rate of glucose disposal between base line and six months was 40 percent ($P<0.001$) in the patients who received metformin first, with troglitazone added for the second three months, and it was 77 percent ($P<0.001$) in those initially treated with troglitazone, with metformin added for the second three months.

Body Weight and Adverse Events

There were no significant changes in body weight during either monotherapy or combination therapy. Intermittent diarrhea developed in one patient soon after metformin was added to troglitazone. She subsequently withdrew from the study. No other adverse events were ascribed to either monotherapy or combination therapy. The mean plasma lactate concentration was normal at all times in both groups, and no patient had any abnormalities on liver-function tests during the study.

DISCUSSION

In this small group of patients with moderate type II diabetes, metformin and troglitazone had nearly identical efficacy in reducing plasma glucose concentrations. Their mechanisms of action, however, differed. Metformin primarily lowered endogenous glucose production, presumably at the level of the liver, whereas troglitazone increased insulin-mediated peripheral glucose disposal, which occurs predominantly in skeletal muscle. Peripheral glucose disposal was also increased by metformin, but the increase was less than one quarter of that associated with troglitazone. Whereas all the glucose-lowering effect of troglitazone at this dosage may be attributed to this peripheral effect, the action of metformin is more difficult to categorize. The effect of metformin on endogenous glucose production appears to be primary and substantial, with the 19 percent reduction translating to a correction of more than two thirds of the increase described in patients with type II diabetes.^{24,25} The beneficial effect of metformin on glucose disposal, on the other hand, is in the same range as that which occurs in patients treated

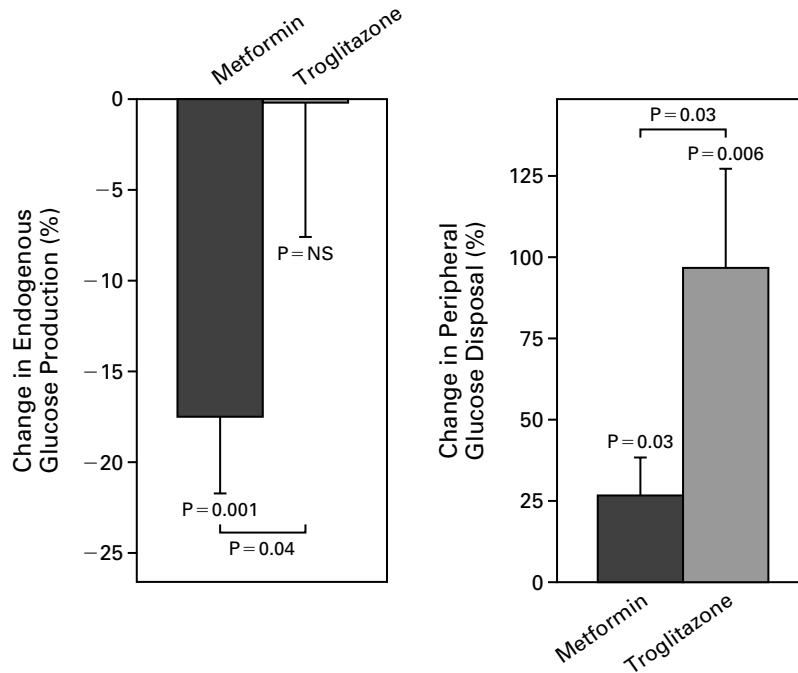


Figure 2. Mean (\pm SE) Percent Changes within Subjects in Endogenous Glucose Production and the Glucose Disposal Rate under Hyperinsulinemic-Clamp Conditions after Three Months of Therapy with Metformin or Troglitazone. NS denotes not significant.

with sulfonylurea drugs.^{26,27} Whether this is a direct effect of metformin or due to an overall decrease in glucose toxicity is not known.²⁸

The lack of effect of troglitazone at this dose on endogenous glucose production is in contrast to findings by others,^{10,12,13} but is in agreement with the results of a recently reported large, multicenter study.¹⁴ At higher doses (600 mg per day), troglitazone therapy does result in small decreases in hepatic glucose production.¹⁴

Although both drugs alone resulted in improved glycemc profiles, the mean fasting plasma glucose concentrations remained high in both groups at three months. In combination, these drugs further reduced both fasting and postprandial plasma glucose concentrations. The addition of troglitazone to metformin resulted in a significant further increase in peripheral glucose disposal. The small, insignificant increase in glucose disposal when metformin was added to troglitazone suggests that the peripheral action of metformin is minimal. By six months, peripheral glucose disposal had increased in both groups, but the increase was greater among the patients who were initially given troglitazone. This may reflect a delayed effect of troglitazone,²⁹ since the group with the greater increase had received troglitazone for a full six months.

When troglitazone was added to metformin, there

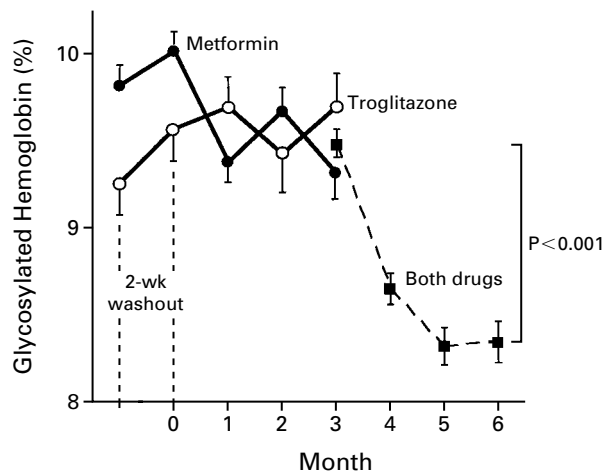


Figure 3. Mean (\pm SE) Changes in Glycosylated Hemoglobin Values during Therapy with Metformin or Troglitazone for Three Months Followed by Combined Therapy with Metformin and Troglitazone for Three Months.

was no further decrease in endogenous glucose production, in keeping with our finding that troglitazone alone had no significant effect on this variable. However, the lack of further lowering of endogenous glucose production when metformin was added to troglitazone is more difficult to explain, particularly because these patients had a significant improvement in glycemic control during combined treatment.

In conclusion, metformin and troglitazone have different mechanisms of action, yet are equally effective in lowering plasma glucose concentrations in patients with type II diabetes. Combination metformin and troglitazone therapy results in further improvement in glucose control, without stimulation of insulin secretion and with reversal of the two principal pathophysiological abnormalities in this disorder.

Supported in part by grants from the Public Health Service (RO1-DK49230, MO1-RR00125) and Warner-Lambert.

Drs. Inzucchi and Shulman serve as consultants to Parke-Davis (Warner-Lambert).

Presented in abstract form at the Annual Scientific Sessions of the American Diabetes Association, Boston, June 21–24, 1997.

We are indebted to David Silver for statistical guidance and to the nursing staff of the Yale–New Haven Hospital General Clinical Research Center for their skilled assistance in carrying out the metabolic studies.

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