EFFICACY OF METFORMIN IN PATIENTS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS

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Abstract *Background. Sulfonylurea drugs have been the only oral therapy available for patients with non-insulin-dependent diabetes mellitus (NIDDM) in the United States. Recently, however, metformin has been approved for the treatment of NIDDM.*

Methods. We performed two large, randomized, parallel-group, double-blind, controlled studies in which metformin or another treatment was given for 29 weeks to moderately obese patients with NIDDM whose diabetes was inadequately controlled by diet (protocol 1: metformin vs. placebo; 289 patients), or diet plus glyburide (protocol 2: metformin and glyburide vs. metformin vs. glyburide; 632 patients). To determine efficacy we measured plasma glucose (while the patients were fasting and after the oral administration of glucose), lactate, lipids, insulin, and glycosylated hemoglobin before, during, and at the end of the study.

Results. In protocol 1, at the end of the study the 143 patients in the metformin group, as compared with the 146 patients in the placebo group, had lower mean (±SE) fasting plasma glucose concentrations (189±5 vs. 244±6 mg per deciliter [10.6±0.3 vs. 13.7±0.3 mmol per liter], P<0.001) and glycosylated hemoglobin values (7.1±0.1 percent vs. 8.6±0.2 percent, P<0.001). In protocol 2, the 213 patients given metformin and glyburide, as compared with the 209 patients treated with glyburide alone, had lower mean fasting plasma glucose concentrations (187±4 vs. 261±4 mg per deciliter [10.5±0.2 vs. 14.6±0.2 mmol per liter], P<0.001) and glycosylated hemoglobin values (7.1±0.1 percent vs. 8.7±0.1 percent, P<0.001). The effect of metformin alone was similar to that of glyburide alone. Eighteen percent of the patients given metformin and glyburide had symptoms compatible with hypoglycemia, as compared with 3 percent in the glyburide group and 2 percent in the metformin group.

In both protocols the patients given metformin had statistically significant decreases in plasma total and low-density lipoprotein cholesterol and triglyceride concentrations, whereas the values in the respective control groups did not change. There were no significant changes in fasting plasma lactate concentrations in any of the groups.

Conclusions. Metformin monotherapy and combination therapy with metformin and sulfonylurea are well tolerated and improve glycemic control and lipid concentrations in patients with NIDDM whose diabetes is poorly controlled with diet or sulfonylurea therapy alone. (N Engl J Med 1995;333:541-9.)

IN the United States patients with non-insulin-dependent diabetes mellitus (NIDDM) are usually treated with diet and a sulfonylurea drug.[1] However, approximately 30 percent of patients initially treated with a sulfonylurea drug have a poor response, and in the remaining 70 percent the subsequent failure rate is approximately 4 to 5 percent per year.[2] In most parts of the world, an alternative or additive approach to oral therapy is available in the form of metformin.[3,4] Clinical experience has proved metformin, either alone or in combination with a sulfonylurea, to be safe and efficacious in reducing plasma glucose concentrations in patients with NIDDM.[3-6] Metformin is believed to work by inhibiting hepatic glucose production[7-10] and increasing the sensitivity of peripheral tissue to insulin[8,9,11-13]; it does not stimulate insulin secretion, which explains the absence of hypoglycemia.[3,4,6,14,15] Metformin also has beneficial effects on plasma lipid concentrations[7,14-16] and promotes weight loss.[4] Because the primary action of sulfonylurea drugs is to enhance insulin secretion, whereas metformin exerts its beneficial effects on glycemic control by enhancing peripheral and hepatic sensitivity to insulin,[7-13] metformin should be equally effective when used as monotherapy and in patients receiving a sulfonylurea drug. This report describes the results of two randomized, placebo-controlled, multicenter trials in which moderately obese patients with NIDDM whose diabetes was poorly controlled with diet alone or with diet plus a sulfonylurea drug were treated with metformin for 29 weeks.

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METHODS

Subjects

Protocol 1

A total of 289 obese patients who were treated with diet alone were assigned to protocol 1. After an eight-week phase during which the patients were counseled about the consumption of a hypocaloric diet,[17] 143 patients were randomly assigned to receive metformin and 146 to receive placebo. The base-line characteristics of the two groups of patients are shown in Table 1.

Protocol 2

A total of 632 patients with NIDDM were assigned to protocol 2: 210 were assigned to receive metformin, 209 to receive glyburide, and 213 to receive both metformin and glyburide (combination therapy). The base-line characteristics of the three groups are also shown in Table 1.

The diagnosis of NIDDM was based on clinical history and the finding of a fasting plasma glucose concentration above 140 mg per deciliter (7.8 mmol per liter) on two occasions. To be included in the study all patients had to lack acceptable glycemic control (fasting plasma glucose, ≥140 mg per deciliter) after eight weeks of dietary therapy (protocol 1) or at least four weeks of dietary therapy plus 20 mg of glyburide per day (protocol 2). Other inclusion criteria included a weight that was 120 to 170 percent of ideal (on the basis of 1983 Metropolitan Life Insurance tables), an age of 40 to 70 years, normal renal function (serum creatinine, ≤1.4 mg per deciliter [124 μmol

per liter] in men and ≤1.3 mg per deciliter [115 μmol per liter] in women; and ≤2+ proteinuria), and normal liver function. Patients were excluded if they had any of the following: symptomatic diabetes (polyuria, polydipsia, and weight loss), symptomatic cardiovascular disease, diastolic blood pressure above 100 mm Hg during antihypertensive-drug treatment, or any concurrent medical illness. They were also excluded if they had received insulin therapy within the previous six months, used medications known to affect glucose metabolism, drank three or more alcoholic drinks per day (≥3 oz of alcohol per day), used illicit drugs, or had previously received metformin therapy. Therapy with estrogen and a progestin and chlorthalidone or a thiazide was permitted in patients already taking these drugs as long as the dosage was not changed during the study. The protocols were approved by the institutional review board of each participating center, and all patients gave written informed consent for the study.

Study Design

Protocol 1

Preenrollment dietary-therapy phase (phase I). Potential study patients initially provided a complete medical history and underwent a physical examination and screening laboratory tests (Fig. 1, top panel). On two occasions the patients kept a three-day dietary log; the patients were then instructed in a hypocaloric diet, which they were told to follow for eight weeks before undergoing randomization. The diet for each patient was designed to provide 20 percent fewer calories than the patient's calculated daily energy expenditure. Fasting plasma glucose concentrations were determined eight and four weeks before randomization and at base line (week 0). At the time of randomization (week 0), each patient again met with the dietitian to reinforce the dietary instructions.

Randomization. At the end of phase I, the patients were randomly assigned to treatment with metformin or placebo. Of the 535 patients who entered the preenrollment dietary-therapy phase, 289 went on to the active-treatment phase: 143 were assigned to metformin and 146 to placebo. Of the other 246 patients, 61 decided not to participate and 185 did not meet the entrance criteria, including 74 who were excluded because they had achieved glycemic control and 30 because they had a change in weight (loss or gain) of more than 3 percent.

Metformin-titration phase (phase II). After randomization, treatment was initiated with one 850-mg metformin tablet or one identical-appearing placebo tablet daily with the evening meal. After two weeks, the metformin (or placebo) dose was doubled, with one 850-mg tablet also taken with breakfast. After four weeks, the metformin (or placebo) dose was again increased by 850 mg, so that one additional tablet was taken with lunch. The metformin dose was increased in this fashion as long as the fasting plasma glucose concentration exceeded 140 mg per deciliter and the side effects were tolerable.

Active metformin-treatment phase (phase III). After the fifth week, the maximal dose of metformin (or placebo) (2550 mg per day) was continued unless side effects (primarily gastrointestinal) dictated a reduction in the dose. The patients were seen every 4 weeks thereafter for a total of 29 weeks.

At randomization the patients provided a medical history and underwent a physical examination (in which height and body weight were determined), routine blood chemical tests, urinalysis, electrocardiography, and a glucose-tolerance test in which 75 g of glucose was administered orally and plasma glucose, insulin, and C-peptide levels were measured at base line and one, two, and three hours later. In addition, a complete blood count was performed and glycosylated hemoglobin; fasting plasma glucose; fasting plasma lactate; fasting serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides; serum vitamin B_{12} and folic acid; and plasma metformin were measured.

At each follow-up visit, we obtained information about compliance, drug side effects, and intercurrent medical events; measured blood pressure; and obtained blood samples while the patients were fasting in order to measure glycosylated hemoglobin and plasma glucose and lactate. At week 29, oral glucose-tolerance tests were performed and plasma lipid and serum vitamin B_{12} and folic acid concentrations were measured; plasma metformin was measured at weeks 9, 21, and 29.

Protocol 2

Prerandomization phase (phase I). During a five-week prerandomization phase, 788 patients with NIDDM began (or continued) to take glyburide; patients taking another sulfonylurea drug were switched to glyburide. The dose of glyburide was 5 mg twice daily for the first week and then 10 mg twice daily for the remaining four weeks of phase I (Fig. 1, bottom panel). The patients also kept a three-day dietary log and then met with a dietitian who instructed the patients in a weight-maintaining diet.[17]

Randomization. Of the 788 diabetic patients who were enrolled in phase I, 632 entered the active-treatment phase. At week 0, open-label glyburide was discontinued and the patients were randomly assigned to treatment with glyburide plus metformin placebo (209 patients), metformin plus glyburide placebo (210 patients), or metformin plus glyburide (213 patients). Of the other 156 patients who completed phase I, 114 did not meet the randomization criteria (including 37 because they had achieved glycemic control) and 42 decided not to participate.

Metformin-titration phase (phase II). After randomization at week 0, the patients began taking one 500-mg tablet of metformin or one placebo tablet with their evening meal. After one week the metformin (or placebo) dose was increased to 1000 mg per day by adding a 500-mg tablet to the breakfast meal. After two weeks the metformin (or placebo) dose was increased to 1500 mg per day by adding a 500-mg tablet to be taken at lunch. After three weeks the dose was increased to 2000 mg per day by adding a second 500-mg tablet to be taken with the evening meal, and after four weeks the daily dose was increased to 2500 mg by adding a second 500-mg tablet to the breakfast dose. The daily dose was increased in this fashion to a maximum of 2500 mg of metformin (or five placebo tablets) as

*Table 1. Base-Line Characteristics of the Patients with NIDDM.**

Characteristic	Protocol 1		Protocol 2†		
	Placebo (N = 146)	Metformin (N = 143)	Glyburide (N = 209)	Metformin (N = 210)	Metformin + glyburide (N = 213)
Age (yr)	53±1	53±1	56±1	55±1	55±1
Sex (M/F)	62/84	62/81	103/106	96/114	98/115
Weight (kg)	92.2±1.2	94.4±1.1	92.6±1.0	92.6±1.0	92.1±1.1
Body-mass index‡	29.2±0.3	29.9±0.3	29.1±0.3	29.4±0.3	29.0±0.3
Duration of diabetes (yr)	6.0±0.6	6.0±0.5	8.7±0.4	8.4±0.4	7.8±0.4
Family history of diabetes (%)	70	80	72	72	75
Fasting plasma glucose (mg/dl)	238±6	241±5	247±3	254±4	251±4
2-hr plasma glucose (mg/dl)	368±8	383±8	399±6	398±6	391±6
Glycosylated hemoglobin (%)	8.2±0.2	8.4±0.1	8.5±0.1	8.9±0.1	8.8±0.1
Fasting plasma insulin (μU/ml)	15±1	13±1	16±1	18±1	17±1
Plasma C peptide (ng/ml)	2.7±0.1	2.7±0.1	2.8±0.1	2.9±0.1	2.8±0.1
Plasma total cholesterol (mg/dl)	212±4	211±3	215±3	212±3	216±3
Plasma LDL cholesterol (mg/dl)	138±3	136±3	136±3	134±3	137±3
Plasma HDL cholesterol (mg/dl)	41±1	39±1	37±1	37±1	39±1
Plasma triglycerides (mg/dl)	185±9	209±15	210±8	231±12	216±10

*Plus–minus values are means ±SE. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein. To convert values for glucose to millimoles per liter, multiply by 0.056; to convert values for total cholesterol, LDL cholesterol, and HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert values for triglycerides to millimoles per liter, multiply by 0.011; and to convert values for insulin to picomoles per liter, multiply by 6.

†Base-line measurements were made while all patients were taking 20 mg of glyburide per day.

‡Defined as the weight in kilograms divided by the square of the height in meters.

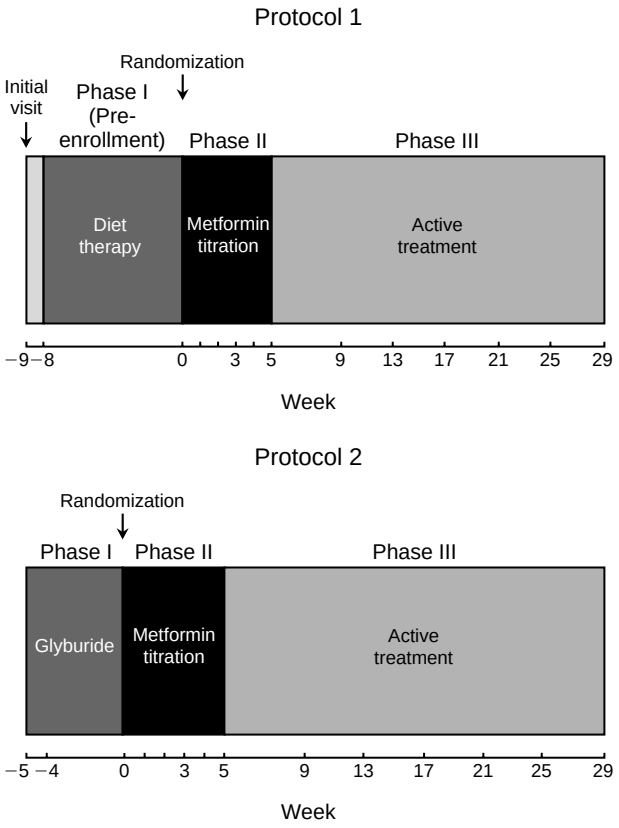

Figure 1. Design of Protocols 1 and 2.

long as the fasting plasma glucose concentration exceeded 140 mg per deciliter. Throughout this period and for the remainder of the study, the patients continued to take four tablets of glyburide (20 mg per day) or placebo per day, according to their treatment assignment.

Active metformin-treatment phase (phase III). After the fifth week, the patients took the maximal dose of metformin (2500 mg per day) unless side effects dictated a reduction in the dose. The patients were seen every 4 weeks thereafter for a total of 29 weeks. At these visits, the patients were questioned, examined, and studied as described in protocol 1.

Analytic Methods

Plasma glucose was measured enzymatically with a Hitachi Analyzer (model 736.50, Boehringer–Mannheim Diagnostics, Indianapolis). Glycosylated hemoglobin was measured by ion-exchange high-performance liquid chromatography with a Bio-Rad Diamat Analyzer (Bio-Rad, Hercules, Calif.) (range for normal subjects, 3.3 to 6.8 percent; mean value, 4.7 percent). Plasma free insulin (Coat-A-Count, Diagnostic Products Corporation, Los Angeles) and C peptide (C-peptide RAI Kit, Incstar, Stillwater, Minn.) were measured by radioimmunoassay after plasma was treated with polyethylene glycol. Plasma total cholesterol and triglycerides were measured enzymatically with a Cobas Fera analyzer (Boehringer–Mannheim Diagnostics). Plasma HDL cholesterol was measured enzymatically with a Cobas Fera analyzer after precipitation with dextran sulfate–manganese chloride. Plasma LDL cholesterol was calculated with the Friedwald equation. Serum folic acid and vitamin B_{12} were measured by radioimmunoassay (Bio-Rad Quantaphase B_{12}–Folate radioimmunoassay kit). Plasma lactate was measured enzymatically with a Cobas Mira analyzer (Sigma Diagnostics, St. Louis). Serum metformin was measured with modified high-performance liquid chromatography.[18]

Statistical Analysis

The primary analysis was an intention-to-treat analysis in which the final visit (week 29, or earlier for patients leaving the study) was the primary end point. For efficacy and safety analyses, any patient who took the study medication and completed at least one visit during the active-treatment phase was included. Absolute values, as well as changes from base-line values, for all efficacy measures were compared. Two analyses were performed: one in which only data available at each visit were analyzed and one in which the last available value was carried forward. In the latter analysis, missing values for evaluations during or at the end of treatment were replaced by the most recent previously recorded value. The results of the two analyses were similar. Statistical comparisons were performed with SAS software.[19] Comparisons within groups were made with a two-tailed paired t-test. For continuous variables, comparisons between groups were made with linear models that included contrasts (LS means in SAS) for pairwise comparisons between the treatment groups. These models included effects of treatment and center (analysis of variance),[20] with selected models including an effect of base-line values (analysis of covariance).[20] All values are given as means ±SE.

Results

Protocol 1

Metformin Dose

At the end of the five-week titration phase 78 percent of the patients assigned to metformin were taking the maximal dose (2550 mg per day), and 85 percent eventually took this dose. At week 29 the mean (±SE) fasting plasma metformin concentrations were 742±182 and 872±99 ng per milliliter in the patients taking 1700 and 2550 mg of metformin per day, respectively.

Body Weight and Blood Pressure

During the active-treatment phase, the patients in the metformin group lost 0.6±0.3 kg of weight and those in the placebo group lost 1.1±0.2 kg ($P=0.21$). The mean base-line blood pressure (supine) in the metformin and placebo groups was normal and did not change during treatment.

Fasting Plasma Glucose and Insulin Concentrations and Glycosylated Hemoglobin Values

By week 29 the fasting plasma glucose concentration had decreased by 52±5 mg per deciliter (2.9±0.3 mmol per liter) to 189±5 mg per deciliter (10.6±0.3 mmol per liter) in the metformin group and increased by 6±5 mg per deciliter (0.3±0.3 mmol per liter) to 244±6 mg per deciliter (13.7±0.3 mmol per liter) in the placebo group ($P<0.001$). The respective changes in glycosylated hemoglobin were −1.4±0.1 percent and 0.4±0.1 percent ($P<0.001$). At week 29, 22 percent of the patients treated with metformin had fasting plasma glucose concentrations of 140 mg per deciliter or less, as compared with 6 percent in the placebo group ($P=0.001$).

The fasting plasma glucose and glycosylated hemoglobin values during the active-treatment phase are shown in Figures 2 and 3, respectively. In the metformin group, the fasting plasma glucose concentration declined progressively during the metformin-titration phase, reaching a nadir that was about 55 mg per deciliter (3.1 mmol per liter) below base line between weeks 5 and 9, and remained at this level until the end of the study. The magnitude of the decline in fasting plasma glucose was correlated ($r=-0.551$, $P<0.001$)

with the base-line fasting plasma glucose concentration (Fig. 4). The declines in fasting plasma glucose and glycosylated hemoglobin values in the metformin group were independent of age (≥65 years or <65 years), race or ethnic group (white vs. black vs. Hispanic), duration of diabetes (≥10 years or <10 years), base-line body-mass index (the weight in kilograms divided by the square of the height in meters, ≥29 or <29), and base-line plasma lipid and insulin concentrations. The fasting plasma insulin and C-peptide concentrations did not change in either group.

Oral Glucose-Tolerance Tests

The plasma glucose and insulin concentrations (weighted mean of the values at 0, 1, 2, and 3 hours) before and after the oral administration of glucose at base line were similar in the metformin and placebo groups. At week 29 the mean plasma glucose concentration after glucose ingestion had not changed in the placebo group (337±10 vs. 337±7 mg per deciliter [18.9±0.6 vs. 18.9±0.4 mmol per liter]) but had decreased in the metformin group (from 347±7 to 275±7 mg per deciliter [19.3±0.4 to 15.3±0.4 mmol per liter],

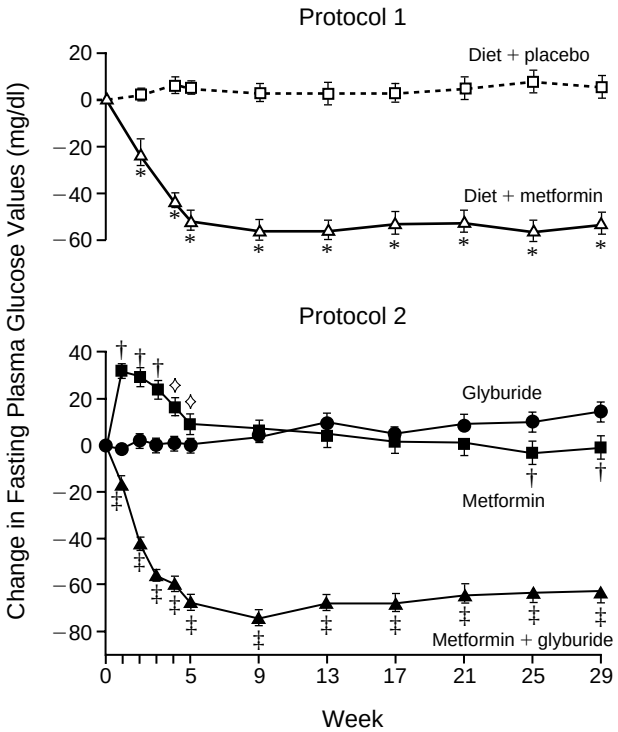

Figure 2. Mean (±SE) Changes in Fasting Plasma Glucose Concentrations in Patients with NIDDM Who Were Enrolled in Protocol 1 or 2.

The asterisks indicate significant differences (P<0.001) between the groups in Protocol 1, the daggers significant differences (P<0.001) between the metformin and glyburide groups, the diamonds significant differences (P<0.01) between the metformin and glyburide groups, and the double daggers significant differences (P<0.001) between the combination-therapy and glyburide groups. To convert values for glucose to millimoles per liter, multiply by 0.056.

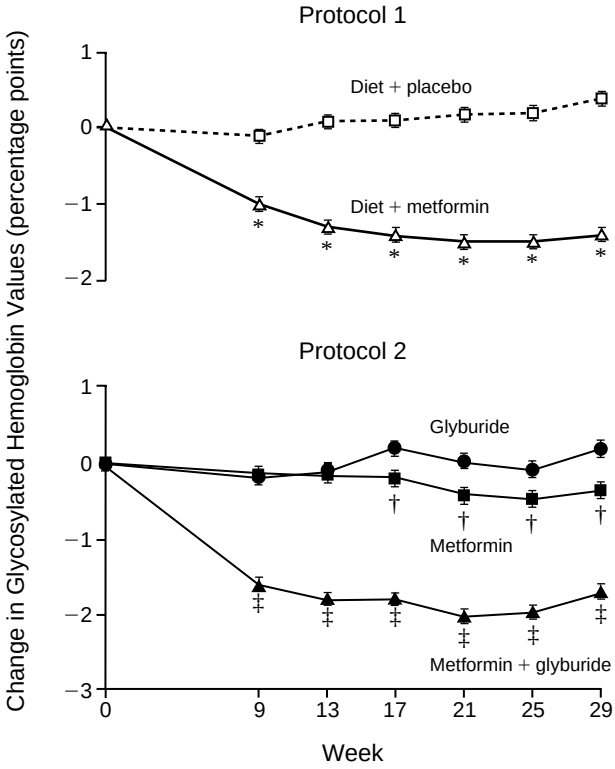

Figure 3. Mean (±SE) Changes in Glycosylated Hemoglobin Values in Patients with NIDDM Who Were Enrolled in Protocol 1 or 2.

The asterisks indicate significant differences (P<0.001) between the groups in Protocol 1, the daggers significant differences (P<0.01) between the metformin and glyburide groups, and the double daggers significant differences (P<0.001) between the combination-therapy and glyburide groups.

P<0.001 for the comparison with placebo); all of the decrease was the result of the decrease in the fasting plasma glucose concentration. The mean plasma insulin concentration did not change in the placebo group and rose slightly in the metformin group (to 36.2±2 from 29±2 μU per milliliter [216±12 from 174±12 pmol per liter], P = 0.001 for the comparisons with base line and with placebo). The plasma C-peptide concentrations closely paralleled the plasma insulin concentrations in both groups.

Plasma Lipids

Before treatment the fasting serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations were similar in the metformin and placebo groups (Table 2). There were no changes during treatment in the placebo group. By week 29 the serum total cholesterol, LDL cholesterol, and triglyceride concentrations in the metformin group had decreased and were significantly lower than in the placebo group (Table 2).

Fasting Plasma Lactate

The mean fasting plasma lactate concentrations at base line were slightly elevated in both groups (mean

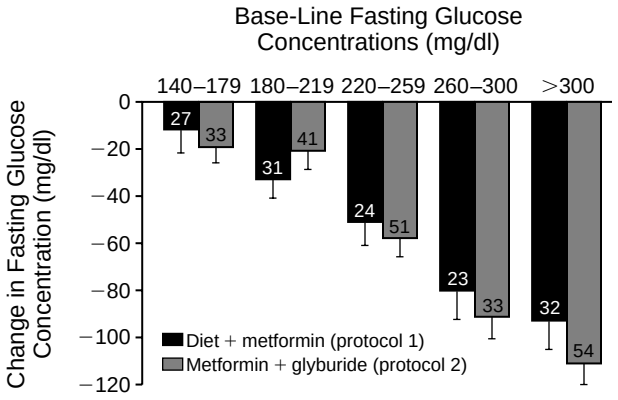

Figure 4. Relation between the Decrease in Fasting Plasma Glucose Concentrations at the End of Active Treatment and the Base-Line Concentrations in Patients with NIDDM.

The numbers of patients in each subgroup are indicated. Values are means ±SE. To convert values for glucose to millimoles per liter, multiply by 0.056.

in both groups, 1.41±0.10 mmol per liter; normal, <1.30 mmol per liter). The values were similar at all times during the active-treatment period in both groups.

Serum Vitamin B_{12} and Folate

Serum folate concentrations did not change in either the metformin or placebo groups. The serum vitamin B_{12} concentration at week 29 was lower in the metformin group (by 22 percent) but did not change in the placebo group. There were no changes in hematocrit or hemoglobin in either group.

Withdrawal of Patients and Adverse Effects

Thirty-one patients in the metformin group (22 percent) and 41 patients in the placebo group (28 percent) withdrew from the study before week 29 (Table 3). More patients in the placebo group than in the metformin group withdrew because of treatment failure (18 vs. 2 [12 percent vs. 1 percent], P<0.001). Adverse effects were limited to the digestive system. Diarrhea and nausea were more common in the group receiving metformin, but were characterized as severe in only 8 percent and 4 percent of patients, respectively. The frequency and severity of reported symptoms of hypoglycemia were similar in the metformin and placebo groups (<2 percent). No patient had biochemically documented hypoglycemia.

Protocol 2

Metformin and Glyburide Dose

At week 29, 90 percent of the patients in the metformin group and 70 percent in the group given metformin plus glyburide were receiving 2500 mg of metformin per day. The mean fasting plasma metformin concentrations in these two groups were 809±60 and 920±75 ng per milliliter, respectively, at this time.

Body Weight and Blood Pressure

There was no significant change in body weight at week 29 in the glyburide group (−0.3±0.2 kg). The

*Table 2. Plasma Lipid and Lactate Concentrations in the Five Groups before and after Treatment for 29 Weeks.**

Variable	Plasma Total Cholesterol	P Value	Plasma LDL Cholesterol	P Value	Plasma HDL Cholesterol	Plasma Triglycerides	P Value	Plasma Lactate
	mg/dl		*mg/dl*		*mg/dl*	*mg/dl*		*mmol/liter*
Protocol 1								
Before treatment								
Metformin	211±3		136±3		39±1	209±15		1.41±0.04
Placebo	212±4		138±3		41±1	185±9		1.40±0.04
After treatment								
Metformin	201±4		123±3		40±1	193±10		1.46±0.05
Placebo	213±4	0.005†	135±3	0.01†	41±1	191±10		1.41±0.04
Change								
Metformin	−11±3		−11±3		1±1	−17±12		0.04±0.05
Placebo	1±3	0.001†	−2±2	0.019†	−1±1	6±7		0.00±0.05
Protocol 2								
Before treatment								
Metformin	212±3		134±3		37±1	231±12		1.47±0.04
Glyburide	215±3		136±3		37±1	210±8		1.45±0.03
Metformin + glyburide	216±3		137±3		39±1	216±10		1.45±0.03
After treatment								
Metformin	208±3	0.003‡	129±3	0.001‡	39±1	221±13	0.004‡	1.54±0.04
Glyburide	220±4		141±3		38±1	227±11		1.42±0.04
Metformin + glyburide	206±3	0.001‡	128±3	0.001‡	40±1	194±9	0.001‡	1.51±0.04
Change								
Metformin	−4±2	0.011‡	−6±2	0.009‡	2±1	−16±7	0.001‡	0.08±0.04
Glyburide	5±2		3±2		<1±1	21±9		−0.01±0.03
Metformin + glyburide	−10±2	0.001‡	−8±2	0.001‡	1±1	−20±7	0.001‡	0.06±0.04

*To convert values for total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.0259, and to convert values for triglycerides to millimoles per liter, multiply by 0.011.

†For the comparison with metformin.

‡For the comparison with glyburide.

Table 3. Withdrawals from the Study, According to Treatment Group.

Reason for Withdrawal	Protocol 1		Protocol 2		
	Placebo (N = 146)	Metformin (N = 143)	Glyburide (N = 209)	Metformin (N = 210)	Metformin + Glyburide (N = 213)
			number (percent)		
All	41 (28)	31 (22)	35 (17)	53 (25)*	21 (10)
Adverse effects†	2 (1)	14 (10)	5 (2)	5 (2)	4 (2)
Treatment failure‡	18 (12)	2 (1)	6 (3)	21 (10)	1 (0.5)
Other§	21 (14)	15 (10)	24 (11)	27 (13)	16 (8)

*One patient in this group died of cardiac arrest, presumably caused by myocardial infarction.

†Adverse effects included digestive symptoms (principally diarrhea) in 11 metformin-treated patients in protocol 1 and 2 glyburide-treated patients, 3 metformin-treated patients, and 2 combination-therapy patients in protocol 2.

‡Treatment failure was defined as symptomatic diabetes including marked polyuria, polydipsia, and weight loss.

§Other reasons included intercurrent illness, abnormal laboratory results, patient's decision to withdraw, noncompliance, and loss to follow-up.

mean weight decreased by 3.8±0.2 kg in the metformin group, and it increased by 0.4±0.2 kg in the combination-therapy group ($P<0.001$). The mean base-line blood pressure was similar in the three groups and did not change in any group during the active-treatment period.

Fasting Plasma Glucose and Insulin Concentrations and Glycosylated Hemoglobin Values

At week 29 there were significant decreases in fasting plasma glucose (by 63±5 mg per deciliter [3.5±0.3 mmol per liter]) and glycosylated hemoglobin (by 1.7±0.1 percentage points) in the combination-therapy group. In contrast, in the glyburide group the fasting plasma glucose and glycosylated hemoglobin increased by 14±4 mg per deciliter (0.8±0.2 mmol per liter) and 0.2±0.1 percentage points, respectively, whereas in the metformin group the respective values decreased slightly, by 1±5 mg per deciliter (0.1±0.3 mmol per liter) and 0.4±0.1 percentage points, respectively ($P<0.001$ for the comparison of the combination-therapy group with the glyburide group and the metformin group). The fasting plasma glucose concentrations and glycosylated hemoglobin values during the active-treatment phase are shown in Figures 2 and 3, respectively. In the metformin group, the fasting plasma glucose concentration initially increased but then declined and remained near the base-line value. In the combination-therapy group, the fasting plasma glucose concentration declined progressively during the titration phase, reached a nadir that was 70 to 75 mg per deciliter (3.9 to 4.2 mmol per liter) below the base-line value between weeks 5 and 9, and remained at this level thereafter. The magnitude of the decline in the combination-therapy group was correlated ($r=0.591$, $P=0.001$) with the base-line fasting plasma glucose concentration (Fig. 4). The declines in fasting glucose and glycosylated hemoglobin values in this group were independent of age, race, duration of diabetes, body-mass index, and base-line plasma lipid and insulin concentrations. At week 29, 22 percent of the patients in the combination-therapy group had a fasting plasma glucose concentration of 140 mg per deciliter or less, as compared with 3 percent in the metformin group and 2 percent in the glyburide group. The fasting plasma insulin concentration did not change in either the glyburide group or the combination-therapy group and declined slightly in the metformin group (by 5±1 μU per milliliter [30±6 pmol per liter], $P=0.01$ for the comparison with the glyburide and combination-therapy groups).

Oral Glucose-Tolerance Tests

The mean plasma glucose and insulin concentrations before and after the oral administration of glucose at base line were similar in all three groups. The mean plasma glucose concentrations after oral glucose did not change in the glyburide or metformin group but decreased in the combination-therapy group (by 61±6 mg per deciliter [3.4±0.3 mmol per liter], $P=0.001$ for the comparison with the other two groups). All the improvement resulted from the decrease in the fasting plasma glucose concentration. The mean plasma insulin and C-peptide concentrations did not change in the glyburide and combination-therapy groups, but the mean plasma insulin concentration decreased slightly (by 5±2 μU per milliliter [30±12 pmol per liter]) in the metformin group ($P=0.05$ for the comparison with the other two groups).

Plasma Lipids

Before treatment the fasting plasma total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations were similar in the three groups (Table 2). In the metformin and combination-therapy groups, the plasma total cholesterol, LDL cholesterol, and triglyceride concentrations declined and were significantly lower than in the glyburide group at week 29 (Table 2). The magnitude of the changes was similar in the metformin and combination-therapy groups. Serum HDL cholesterol increased by 1.8±0.6 mg per deciliter (0.05±0.02 mmol per liter) and by 1.2±0.5 mg per deciliter (0.03±0.01 mmol per liter) in the metformin and combination-therapy groups, respectively, and did not change in the glyburide group.

Fasting Plasma Lactate

The mean fasting plasma lactate concentration at base line was slightly elevated in all three groups (combined mean, 1.46±0.30 mmol per liter) and did not change during treatment in any of the groups (Table 2).

Serum Vitamin B_{12} and Folate

Serum folate concentrations did not change after 29 weeks of treatment in any group. Serum vitamin B_{12} declined in the metformin group (by 29 percent) and

combination-therapy group (by 29 percent) but did not change in the glyburide group. There were no changes in hematocrit or hemoglobin in any of the groups.

Withdrawal of Patients and Adverse Effects

Thirty-five patients in the glyburide group (17 percent), 53 in the metformin group (25 percent), and 21 in the combination-therapy group (10 percent) withdrew from the study before week 29 (Table 3). Adverse effects were primarily limited to the digestive system. Nausea and diarrhea were more common in the groups receiving metformin and metformin plus glyburide, but in only ≤1 percent and 4 to 5 percent, respectively, were these symptoms characterized as severe. Symptoms compatible with hypoglycemia occurred at some time in 18 percent of the patients given metformin plus glyburide and in 3 percent and 2 percent of the glyburide and metformin groups, respectively. The episodes were almost always mild and limited to a single occurrence, and in no patient was there biochemical documentation of hypoglycemia. During the 15th week of the study, one patient in the metformin group died suddenly of cardiac arrest, presumably caused by an acute myocardial infarction.

DISCUSSION

Diet and exercise are the cornerstones of therapy for patients with NIDDM. When these fail, the patients are usually treated with a sulfonylurea drug. However, sulfonylurea therapy is often ineffective, and even if it is effective initially, its efficacy wanes with time. The results of the Diabetes Control and Complications Trial (DCCT)[21] have demonstrated conclusively that good glycemic control can prevent or ameliorate diabetic microvascular complications in patients with insulin-dependent diabetes. On the basis of epidemiologic evidence relating the microvascular complications of diabetes to plasma glucose concentrations[22,23] and evidence that good glycemic control may reduce microvascular complications in patients with NIDDM,[23] alternative hypoglycemic drugs are needed. Otherwise, insulin is the only option for patients with NIDDM, and in these patients good glycemic control usually requires doses in excess of 100 units per day.[24]

In protocol 2 the combination of metformin and glyburide lowered plasma glucose and glycosylated hemoglobin values in patients with NIDDM who had poor responses to maximal doses of a sulfonylurea alone. The substitution of metformin for glyburide resulted in little benefit, and the continuation of glyburide alone was associated with poor glycemic control. Thus, combination therapy with metformin and glyburide was superior to treatment with either drug alone. The decline in glycosylated hemoglobin values in the combination-therapy group was similar to the decline reported in the DCCT in patients with insulin-dependent diabetes who were treated with intensive insulin therapy.[21] In patients with NIDDM who had poor responses to diet alone (protocol 1), metformin caused a decline in plasma glucose that was similar to that in the combination-therapy group in protocol 2 (Fig. 2). These results indicate that the effect of metformin is additive to that of glyburide and, as a corollary, that the mechanism of action of metformin must differ from that of glyburide.

In protocol 1, 22 percent of the metformin-treated patients had an acceptable fasting plasma glucose concentration (<140 mg per deciliter) after treatment. In patients who did not respond to dietary therapy plus glyburide (protocol 2), the addition of metformin decreased the plasma glucose concentration and resulted in acceptable glycemic control in 22 percent. Although this represents an improvement over currently available therapy, an additional 70 to 80 percent of patients would still require further intervention. The addition of insulin at bedtime might be particularly efficacious in this group.[24]

Unlike sulfonylurea drugs, which augment insulin secretion,[2] metformin has no insulinotropic effect.[3,4,7-9,11,14] In protocol 2 fasting and glucose-stimulated plasma insulin concentrations did not increase in patients treated with metformin or metformin and glyburide. In protocol 1 metformin caused a small increase in plasma insulin during the oral glucose-tolerance tests, probably as a result of the amelioration of glucose toxicity.[25] Thus, the improvement in oral glucose tolerance in the combination-therapy group in protocol 2 and the metformin group in protocol 1 cannot be attributed to increased insulin secretion. All of the decrement in plasma glucose concentrations after oral glucose in the combination-therapy group in protocol 2 and in the metformin group in protocol 1 was explained by the decrement in fasting plasma glucose concentrations. This observation is consistent with the demonstrated ability of metformin to inhibit hepatic glucose production.[7-10] Since elevated basal hepatic glucose output is the primary factor responsible for increased fasting plasma glucose concentrations in patients with NIDDM,[26] our findings suggest that the chief beneficial effect of metformin is mediated through the inhibition of hepatic glucose production. In vitro, metformin inhibits hepatic gluconeogenesis,[27] but a recent study in patients with NIDDM demonstrated an inhibitory effect on glycogenolysis as well.[28]

When hyperglycemia persists despite maximal doses of a sulfonylurea, diabetic patients are considered to have no response to sulfonylurea therapy. However, this does not mean that the sulfonylurea has not exerted an important effect on glucose metabolism. In protocol 2, when glyburide was discontinued and patients were treated with metformin, the mean fasting plasma glucose concentration initially increased, suggesting that glyburide was still exerting an important glucose-lowering effect. However, as the dose of metformin was increased, fasting plasma glucose concentrations decreased. Thus, metformin as monotherapy primarily restored the glycemic control that was lost when the glyburide was stopped.

Another important action of metformin was its effect on plasma lipid concentrations. The improvement in

plasma lipid concentrations during combination therapy (protocol 2) was very similar to that in patients in the metformin group in protocol 1 and to that in patients in whom metformin was substituted for glyburide in protocol 2. In the latter group plasma lipid concentrations decreased despite the lack of change in plasma glucose concentrations, indicating that the beneficial effect of metformin on dyslipidemia was independent of improved glycemic control. Although we studied obese patients, similar qualitative and quantitative effects of metformin on lipid and glucose metabolism have been reported in lean patients with NIDDM.[4,7,8,10,11,14] Metformin has been reported to lower blood pressure in nondiabetic patients with essential hypertension,[29] but no change in blood pressure occurred in any group in our study.

The only clinically important adverse effects of metformin were nausea and diarrhea. These symptoms were usually mild and transient, and, even when more severe or persistent, they almost always subsided after the dose of metformin was reduced. Although the mean serum vitamin B_{12} concentrations decreased in all patients given metformin, no patient became anemic. Subjective symptoms compatible with mild hypoglycemia were reported by 18 percent of the patients in the combination-therapy group, but no patient had documented biochemical evidence of hypoglycemia.

Lactic acidosis has been reported with the biguanide phenformin, with an estimated incidence ranging from 0.25 to 1 case per 1000 patient-years.[3,30-32] The estimated incidence of metformin-related lactic acidosis is about 1/10 to 1/20 of that reported with phenformin, or 0.03 case per 1000 patient-years.[4,8,15,30-32] In our study fasting plasma lactate concentrations were not significantly higher in any of the groups given metformin than in any of the other groups. The absence of an increase in plasma lactate concentrations in this study and the low incidence of lactic acidosis reported in the literature in patients taking metformin,[4,8,15,30-32] as compared with phenformin, is consistent with known structural and functional differences between the two biguanides. Metformin, unlike phenformin, binds poorly to mitochondrial membranes and does not inhibit the electron-transport chain.[4] Consistent with these observations is the fact that metformin does not inhibit glucose oxidation[7,28] or alter lactate turnover[28] in patients with NIDDM. Metformin is not metabolized and is excreted unchanged in the urine; its plasma half-life is six hours.[3] In contrast, phenformin is, in part, metabolized to an inactive hydroxylated derivative. These pharmacologic differences may help explain why the reported incidence of lactic acidosis in patients taking metformin is very low. When lactic acidosis does occur, it is accompanied by a serious underlying medical disorder (i.e., impairment of renal function, cardiogenic or septic shock, or liver failure).[4] Because of this, diabetic patients with any degree of renal impairment, hepatic dysfunction, or cardiac disease should not be treated with metformin.

APPENDIX

The following persons and institutions participated in the Multicenter Metformin Study: W. Abelove, E. Reid, J. Pita, M. Callahan (Coral Gables, Fla.); D. Johnson, E. Pelayo, Arizona Health Science Center (Tucson); J. Pugh, M. Shank, P. Garza, Audie L. Murphy Veterans Affairs Hospital (San Antonio, Tex.); B. Haag, J. Korff, A. Angelo, B. Izenstein, M. Vanderleeden, H. Cathcart, M. Tierney, D. Biggs, Baystate Medical Center (Springfield, Mass.); J. Karam, M. Nolte, L. Gavin, M. Applegate Elder, J. Corboy, D. Thwaite, S. Wong, University of California (San Francisco); M. Davidson, A. Peters, Cedars–Sinai Medical Center (Los Angeles); T. Duncan, S. Kercher, Diabetes Education and Research Center (Philadelphia); J. Fischer, M. Kipnes, B.J. Radnick, Diabetes and Glandular Disease Clinic (San Antonio, Tex.); M. Roura, J. Roque, C. Montgomery, P. Collum, M. Rust, the Diabetes and Thyroid Center at Memorial Hospital (Jacksonville, Fla.); S. Pohl, M. Pfeifer, P. Allweiss, S. Leichter, P. Leach, Diabetes Research and Analysis Association (Lexington, Ky.); D. Gallina, V. Musey, K. Berkowitz, Emory University School of Medicine (Atlanta); R. Eastman, T. Taylor, M. Sainz de la Pena, J. Zawadski, P. Grimes, R. Tanenberg, R. Vigersky, G. Phillips, S. Browning, Georgetown University Hospital (Washington, D.C.); T. Flood, J. Flood, Georgia Center for Diabetics (Atlanta); H. Seltzer, J. Davidson, J. Rosenstock, V. Roberts, D. Flanders, Humana–Medical City Dallas Hospital (Dallas); C. Clark, C. Alexander, S. Steinkeler, C. Fisher, S. Fineberg, J. Bridges, V. Blevins, Indiana University School of Medicine (Indianapolis); C. Saudek, A. Georgopoulos, M. Monakil, Johns Hopkins University School of Medicine (Baltimore); R. Cooppan, R. Beaser, O. Ganda, J. Rosenzweig, J. Wolfsdorf, M. Wray, Joslin Diabetes Center (Boston); C. Kilo, J. Dudley, J. Ojile, M. Whitsett, Kilo Diabetes and Vascular Research Foundation (St. Louis); P.J. Palumbo, F. Kennedy, M. Kubly, Mayo Clinic (Rochester, Minn.); A. Garber, D. Huffman, S. Gandy, Methodist Hospital (Houston); L. Kelly, W. Tucker, E. Miller, H. Hinshaw, R. Kleinmann, J. Beck, Nalle Clinic (Charlotte, N.C.); L. Blonde, R. Zimmerman, J. Murray, S. Reddy, E. Miranda, J. Murray, V. Faessler, Ochsner Clinic (New Orleans); J. Falko, M. Rao, L. Jeffers, Ohio State University College of Medicine (Columbus); J. Brown, L. Larson, University of Iowa (Iowa City); J. Floyd, R. Knopf, S. Van Appledorn, University of Michigan Hospital–Clinical Research Center (Ann Arbor); J. Gerich, J. Johnston, R. Salata, A. Consoli, W. Evron, M. Korytkowski, M. Mokan, L. DeRiso, University of Pittsburgh–Presbyterian University Hospital (Pittsburgh); L. Vignati, H. Goldstein, M. Hudson, R. Sheehan, Waltham–Weston Hospital and Medical Center (Waltham, Mass.); and G. Grunberger, M. Vandenberg, Wayne State University School of Medicine (Detroit).

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