

# Effects of Metformin in Patients with Poorly Controlled, Insulin-Treated Type 2 Diabetes Mellitus

## A Randomized, Double-Blind, Placebo-Controlled Trial

Larissa Avilés-Santa, MD; Joyce Sinding, MSN, RN; and Philip Raskin, MD

**Background:** Patients with type 2 diabetes are often obese and require large doses of insulin to achieve glycemic control. Weight gain often accompanies insulin therapy and results in increasing insulin requirements.

**Objective:** To evaluate the efficacy of metformin in combination with insulin in patients with type 2 diabetes poorly controlled with insulin therapy alone.

**Design:** Randomized, double-blind, placebo-controlled trial.

**Setting:** Outpatient diabetes clinic at a university medical center.

**Patients:** 43 patients with poorly controlled type 2 diabetes who were receiving insulin therapy.

**Intervention:** Patients were randomly assigned to receive placebo or metformin in combination with insulin for 24 weeks.

**Results:** Hemoglobin A<sub>1c</sub> levels decreased by 2.5 percentage points (95% CI, 1.8 to 3.1 percentage points) in the metformin group, a significantly greater change ( $P = 0.04$ ) than the decrease of 1.6 percentage points in the placebo group. Average final hemoglobin A<sub>1c</sub> levels were 6.5% in the metformin group and 7.6% in the placebo group (difference, 11%). For patients who received placebo, the insulin dose increased 22.8 units (CI, 11 to 44 units) or 29% more than did the dose for patients who received metformin ( $P = 0.002$ ); for these patients, the insulin dose decreased slightly. Patients in the placebo group gained an average of 3.2 kg of body weight (CI, 1.2 to 5.1 kg); patients in the metformin group gained an average of 0.5 kg of body weight ( $P = 0.07$ ). Total cholesterol and low-density lipoprotein cholesterol levels decreased in both groups. High-density lipoprotein cholesterol and triglyceride levels did not change.

**Conclusions:** The addition of metformin to insulin therapy resulted in hemoglobin A<sub>1c</sub> concentrations that were 10% lower than those achieved by insulin therapy alone. This improvement in glycemic control occurred with the use of 29% less insulin and without significant weight gain. Metformin is an effective adjunct to insulin therapy in patients with type 2 diabetes.

Type 2 diabetes mellitus is more prevalent among persons and populations in which obesity or a family history of the disease is present. Modification of dietary habits and subsequent weight loss (important steps in the management of both obesity and diabetes) improve glycemic control. However, glycemic goals are usually not achieved by dietary restriction alone, and pharmacologic intervention is often necessary. Until 1995, sulfonylurea compounds were the only oral antihyperglycemic agents available in the United States for initial drug therapy for type 2 diabetes (1–3). These agents have a high rate of secondary failure (1–3), however, and the addition of other oral agents or insulin is often necessary.

Because many persons with type 2 diabetes are overweight and insulin resistant, high doses of insulin are often required to achieve adequate glycemic control. However, insulin therapy is associated with weight gain, which could somewhat vitiate the expected improvement in glycemic control. It is now common to combine therapeutic agents that have complementary mechanisms of action, such as sulfonylurea compounds and insulin (1–5). With the development of new oral medications—such as biguanides,  $\alpha$ -glucosidase inhibitors, and thiazolidinediones—that have different modes of action designed to improve diabetes control, combination therapy has become even more common (1–6).

Metformin, a biguanide, has been approved in the United States for use alone or in combination with sulfonylurea compounds since 1995. Its main mechanisms of action are to decrease hepatic glucose output (3, 7–12) and improve peripheral insulin sensitivity (1–3, 7, 8). The use of metformin alone or in combination with sulfonylurea compounds has been shown to improve glycemic control in patients with type 2 diabetes (1, 2, 10, 12). Blood lipid abnormalities, particularly hypertriglyceridemia, have also improved with metformin use (1–3, 7, 10, 12–14), and weight loss has been reported in many persons (1–3, 7, 10, 15, 16). Some physicians recommend metformin as the first drug of choice in the treatment of obese patients with type 2 diabetes (9, 17); this recommendation has been supported by the recent findings of the United Kingdom Prospective Diabetes Study (UKPDS) (16, 18).

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From University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. For current author addresses, see end of text.

Metformin–insulin therapy has been used successfully in Europe (13), but few reports of this potentially useful combination have been published. The probable clinical importance of the combination of metformin and insulin includes improvements in glycemic control and insulin sensitivity and avoidance of the weight gain that often accompanies improved glycemic control.

We evaluated the effect of metformin on glycemic control and exogenous insulin requirements when given in combination with insulin to patients with type 2 diabetes that was poorly controlled by insulin alone.

## Methods

### Patients

Study patients were required to meet the following criteria: type 2 diabetes diagnosed after 30 years of age and treated for at least 2 years with at least 50 units of insulin per day, age at enrollment younger than 70 years, and a hemoglobin A<sub>1c</sub> level greater than or equal to 8.0%. We excluded pregnant women; women trying to become pregnant; patients with a serum creatinine concentration greater than 132.6 mmol/L (1.5 mg/dL) or hepatic enzyme levels greater than twice the upper limit of normal; and patients with medical conditions that could promote lactic acidosis, such as renal or hepatic disease, congestive heart failure, or chronic obstructive pulmonary disease. All patients provided written informed consent before study entrance. The institutional review board of the University of Texas Southwestern Medical Center at Dallas approved the study protocol.

### Follow-up

Patients who met the inclusion criteria were randomly assigned in a double-blind fashion to receive metformin or placebo in addition to their current insulin therapy. Glycemic control, insulin dose requirements, study drug tolerance, body weight, and blood pressure changes were assessed at weeks 2, 4, 8, 12, 16, and 24.

### Evaluation of Other Study End Points

Body weight and blood pressure were measured at every office visit. Patients were weighed while wearing street clothes, and blood pressure was measured when the patient was in a sitting position. Complete medical histories, physical examinations, fasting lipid and lipoprotein profiles, C-peptide concentrations, and serum chemistries were determined at the beginning and end of the study.

## Intervention

Metformin was administered as 500-mg tablets. Metformin and placebo tablets had a similar appearance, thereby preventing identification of the tablets by the investigators or the patients. During the first 2 weeks of the study, patients were instructed to ingest one tablet of the study drug with breakfast and one tablet with supper in addition to their current insulin therapy. At week 2, the dosage of the study drug was increased to 1500 mg/d (one tablet three times daily with meals). At week 4, the dosage of the study drug was increased to 2000 mg/d, and the insulin dose was adjusted accordingly. At week 8, the dosage was increased to the maximum dose of 2500 mg/d (five tablets per day). Compliance was assessed by pill count, which was performed at each office visit. During the titration phase, drug tolerance was assessed at every visit. Hypoglycemic episodes and such symptoms as nausea, vomiting, abdominal pain, bloating, flatulence, diarrhea, and anorexia were also assessed at each visit. The dose of the study drug was adjusted when necessary to prevent adverse effects. The patients continued to receive the maximum tolerated dosage from weeks 8 to 24.

### *Assessment of Glycemic Control and Insulin Dose Adjustments*

The goal of therapy was to achieve normoglycemia in the absence of serious hypoglycemia. The patients were asked to perform blood glucose monitoring at least twice per day (before breakfast and before supper) and as necessary (that is, when symptoms of hypoglycemia occurred). Postprandial blood glucose monitoring was not done. Daily self-monitoring records and fasting plasma glucose concentrations were reviewed at every visit. A patient-directed insulin dose algorithm was not used. At every visit, the insulin dose was adjusted in amount or frequency depending on the patient's monitoring results, meal schedule, daily schedule, and reported symptoms of hypoglycemia. The insulin dose was decreased if the fasting plasma glucose concentrations were consistently equal to or less than 5.55 mmol/L (100 mg/dL) or if the patient reported symptomatic or asymptomatic hypoglycemia (blood glucose concentrations  $\leq$  2.78 mmol/L [50 mg/dL]). All changes in insulin dose were made by study personnel.

Hemoglobin A<sub>1c</sub> levels were measured by using high-pressure liquid chromatography at baseline and at weeks 8, 16, and 24. Levels within the range of persons without diabetes ( $\leq$ 5.6%) were the goal for both groups.

**Table 1. Baseline Characteristics of Study Patients**

Characteristic	Metformin Group (n = 21)	Placebo Group (n = 22)	P Value
Mean age ± SD (median [minimum, maximum]), y	53.1 ± 9.4 (55 [35, 69])	54.6 ± 7.8 (55 [36, 70])	>0.2
Men/women, n/n	6/15	10/12	>0.2
Ethnicity, n			
Non-Hispanic white	10	15	
African American	5	4	>0.2
Hispanics	5	3	
Other	1	0	
Mean duration of diabetes ± SD (median [minimum, maximum]), y	9.2 ± 6.4 (8.5 [1.5, 22])	10.1 ± 4.7 (10 [1, 16])	>0.2
Mean duration of insulin therapy ± SD (median [minimum, maximum]), y	5.4 ± 5.0 (5 [0.2, 16])	3.5 ± 4.2 (1.5 [0.2, 16])	>0.2

### Diet

Dietary counseling was offered to every patient at screening and at subsequent visits as needed. General guidelines regarding portion sizes from all food groups were given without calculated caloric plans. Changes in daily caloric intake were assessed through review of a 3-day food record at baseline and at the end of the study. Patients were encouraged to maintain baseline levels of physical activity throughout the study.

### Analytical Determinations

Plasma glucose concentrations were determined by using an automated glucose oxidase method (Glucose Analyser 2, Beckman Instruments, Fullerton, California). C-peptide concentrations were measured by radioimmunoassay using polyclonal antisera. Fasting lipid and lipoprotein concentrations were assessed by using standard laboratory methods.

### Statistical Analysis

The efficacy analysis included all patients who met inclusion criteria and had a baseline hemoglobin A<sub>1c</sub> measurement and at least one postbaseline

hemoglobin A<sub>1c</sub> measurement. Baseline characteristics and incidences of various events between groups were examined by using contingency-table analysis and Wilcoxon rank-sum tests. Paired *t*-tests with 95% CIs were used to compare baseline and post-treatment body weight, fasting plasma glucose concentrations, hemoglobin A<sub>1c</sub> concentrations, daily insulin dose, fasting C-peptide level, fasting lipid profile, and daily caloric intake within and between groups. The Fisher exact test was used to compare the incidence of side effects between groups. A *P* value less than 0.05 was considered statistically significant. All analyses were conducted by using SPSS software, version 9.0 (SPSS, Inc., Chicago, Illinois). All results are reported as the mean ± SD. Skewed data are shown as the mean ± SD (median [minimum, maximum]).

### Role of the Funding Source

Funding for this study was provided in part by a grant from Bristol-Myers Squibb. The study protocol was developed and implemented by the authors. Other than a preliminary statistical evaluation, the analysis and reporting were done by the authors

**Table 2. Comparison of Changes from Baseline\***

Characteristic	Metformin Group (n = 21)		Placebo Group (n = 22)	
	Baseline	Change from Baseline (95% CI)	Baseline	Change from Baseline (95% CI)
Body weight, kg	103.9 ± 25.2	0.5 (−1.9 to 2.8)	106.6 ± 23.2	3.2 (1.2 to 5.1)†
Insulin dosage, U/d	96.2 ± 44.9	−4.5 (−17.0 to 7.9)	96.9 ± 43.4	22.8 (11.1 to 34.6)‡
Fasting plasma glucose level, mg/dL§	197.2 ± 74.0	−63.1 (−94.5 to −31.7)‡	218.5 ± 69.4	−64.8 (−99.0 to −30.5)‡
Hemoglobin A <sub>1c</sub> level	9.0% ± 1.4%	−2.5 percentage points (−3.1 to −1.8)‡	9.1% ± 1.5%	−1.6 percentage points (−2.1 to −1.1)‡
Fasting C-peptide concentration, ng/mL	2.1 ± 1.2	1.0 (−0.1 to 2.1)	2.2 ± 1.5	0.3 (−0.7 to 1.3)
Total cholesterol level, mg/dL	215.1 ± 40.5	−19.6 (−35.0 to −4.2)¶	218.6 ± 58.4	−20.3 (−29.5 to −11.1)‡
High-density lipoprotein cholesterol level, mg/dL**	35.8 ± 10.1	−4.0 (−8.5 to 0.5)	33.7 ± 10.1	−4.1 (−10.6 to 2.4)
Low-density lipoprotein cholesterol level, mg/dL**	121.8 ± 31.7	−14.7 (−24.9 to −4.5)†	136.4 ± 41.2	−20.6 (−32.4 to −8.8)†
Triglyceride level, mg/dL††	202.3 ± 114.2 (167 [62, 474])	−6.1 (−39.7 to 27.4)	222.5 ± 191.3 (167 [62, 829])	−39.2 (−111.4 to 32.9)
Total daily caloric intake, kcal/d	1804 ± 443	−330 (−488 to −172)‡	1775 ± 504	−119 (−485 to 247)

\* Baseline values are the mean ± SD.

† *P* < 0.01 from baseline.

‡ *P* < 0.001 from baseline.

§ To convert mg/dL to mmol/L, multiply by 0.0555.

|| To convert mg/dL to mmol/L, multiply by 0.0259.

¶ *P* < 0.05 from baseline.

\*\* To convert mg/dL to mmol/L, multiply by 0.02586.

†† Mean ± SD (median [minimum, maximum]).

independently of Bristol-Myers Squibb. Dr. Raskin is a member of the Bristol-Myers Squibb speaker's bureau.

## Results

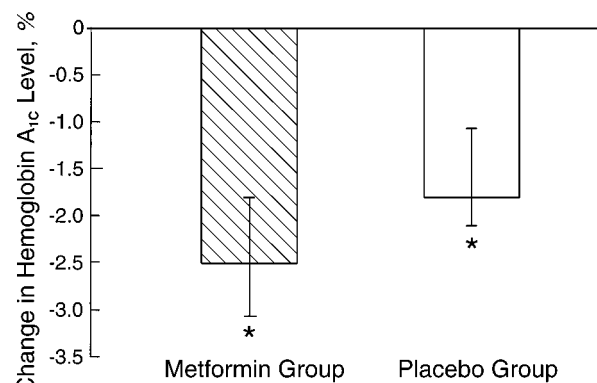
### Baseline Patient Characteristics

Fifty-four patients gave informed consent and were randomly assigned to receive placebo or metformin. Forty-three patients (21 assigned to receive metformin and 22 assigned to receive placebo) met the entrance criteria and were followed for the entire 24 weeks. Baseline characteristics of the study patients are presented in **Tables 1** and **2**. Both groups were comparable in age, body weight, sex, ethnicity, duration of diabetes, duration of insulin therapy, daily insulin dose, mean hemoglobin A<sub>1c</sub> levels, and all of the analyzed study variables.

Eleven patients did not complete the study. Eight patients were screened but did not return for follow-up and were therefore not randomly assigned to a treatment group. One patient developed acute congestive heart failure before randomization and withdrew from the study. Two patients—1 from the metformin group and 1 from the placebo group—were lost to follow-up after week 16.

### Glycemic Control

**Table 2** shows changes from baseline within each group and a comparison of changes from baseline between groups. An overall improvement in glycemic control, which was significant after week 16 and persisted throughout the study period, was observed in both groups. At the end of the study, both groups showed a significant decrease in mean hemoglobin



**Figure 1.** Change in hemoglobin A<sub>1c</sub> level from baseline to 24 weeks. Error bars represent the standard deviation. \*  $P < 0.001$  compared with baseline.

A<sub>1c</sub> level. However, the hemoglobin A<sub>1c</sub> levels in the metformin-treated patients were 11% lower than those achieved by the placebo recipients ( $P = 0.04$ ) (**Figure 1**).

Mean fasting plasma glucose concentrations decreased in both groups. The mean reduction in fasting plasma glucose concentrations was significant within each group ( $P < 0.001$ ) but not between groups ( $P > 0.2$ ).

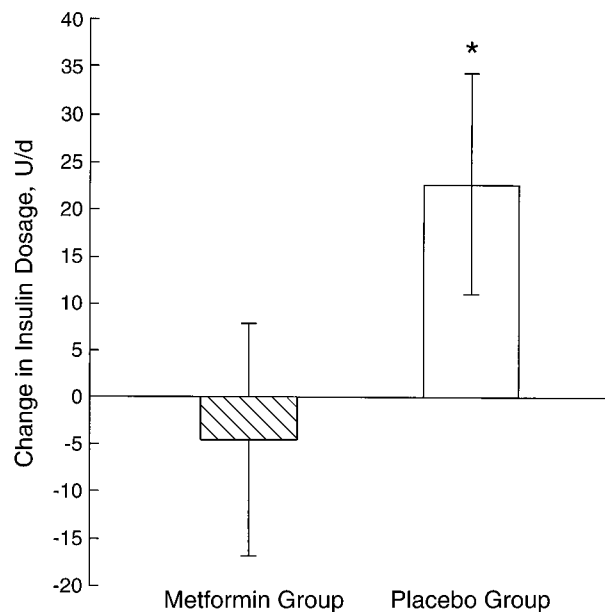
### Daily Insulin Requirements

All patients received at least two daily insulin injections, although some patients received two daily injections of 70/30 insulin and others received intermediate-acting insulin twice per day in combination with three or four injections of short-acting insulin per day. At baseline, total daily insulin dose was comparable between the two groups. The daily insulin dosage in patients treated with metformin decreased by 4.5 U/d (95% CI, -17.0 to 7.9 U/d;  $P > 0.2$ ); insulin dosages in patients treated with placebo increased by 22.8 U/d (CI, 11.1 to 34.6 U/d;  $P < 0.001$ ). The daily insulin dose taken by placebo recipients at the end of the study was 29% higher than that taken by metformin-treated patients; that is, the placebo recipients had a significant change from baseline (27.3 U [CI, 10.8 to 43.9 U];  $P = 0.002$ ) when compared with the patients who received metformin (**Figure 2**).

Insulin therapy had to be modified throughout the study in patients from both groups to achieve better glycemic control. Two of the 21 patients receiving metformin and 6 of the 22 patients receiving placebo required an increase in frequency of insulin injections ( $P > 0.2$ ; Fisher exact test). In addition, 4 patients receiving metformin and 4 patients receiving placebo required a change in both the type of insulin and the frequency of its administration ( $P > 0.2$ ; Fisher exact test).

**Table 2—Continued**

Difference in Change from Baseline between Groups (95% CI)	P Value for Difference between Groups
2.7 (-0.2 to 5.6)	0.07
27.3 (10.8 to 43.9)	0.002
-1.7 (-46.9 to 43.6)	>0.2
0.9 percentage points (0.04 to 1.7)	0.04
-0.7 (-2.1 to 0.8)	>0.2
-0.7 (-17.9 to 16.5)	>0.2
-0.1 (-8.2 to 7.9)	>0.2
-5.9 (-21.3 to 9.4)	>0.2
-33.1 (-111.5 to 45.4)	>0.2
221 (-178 to 601)	>0.2



**Figure 2.** Change in daily insulin dosage from baseline to 24 weeks. Error bars represent SDs. \*  $P < 0.001$  compared with baseline.

### Fasting C-Peptide Concentrations

Fasting C-peptide concentrations increased slightly in both groups but were not significant within each group or between groups.

### Body Weight and Daily Caloric Intake

Both groups had similar body weight and body mass indexes at baseline. Body weight in the group taking metformin increased by 0.5 kg from baseline (CI, -1.9 to 2.7 kg;  $P > 0.2$ ), whereas body weight in the group taking placebo increased by 3.2 kg (CI, 1.2 to 5.1 kg;  $P = 0.003$ ). However, the statistical evidence for the difference in changes between groups was not strong ( $P = 0.07$ ).

Both treatment groups exhibited an overall reduction in caloric intake at the completion of the study without a change in the percentage of intake from the major food groups. The daily caloric intake decreased by 119 kcal/d (CI, -485 to 247 kcal/d;  $P > 0.2$ ) in placebo recipients and by 330 kcal/d (CI, -488 to -172 kcal/d;  $P < 0.001$ ) in metformin-treated patients. Although at study end the caloric intake of metformin-treated patients was 18% lower than at baseline, the difference in reduction from baseline between groups was not statistically different ( $P > 0.2$ ).

### Plasma Lipid and Lipoprotein Levels

Plasma lipid and lipoprotein concentrations were similar at baseline in both groups. Total cholesterol level decreased by 0.51 (CI, -0.91 to -0.11) mmol/L (19.6 [CI, -35.0 to -4.2] mg/dL;  $P = 0.02$ ) in the metformin group and 0.53 (CI, -0.76 to -0.29) mmol/L (20.3 [CI, -29.5 to -11.1] mg/dL;

$P < 0.001$ ) in the placebo group. The difference between changes from baseline was not statistically significant ( $P > 0.2$ ). Low-density lipoprotein cholesterol levels decreased by 0.38 (CI, -0.64 to -0.12) mmol/L (14.7 [CI, -24.9 to -4.5] mg/dL;  $P = 0.008$ ) in the metformin group and 0.53 (CI, -0.84 to -0.23) mmol/L (20.6 [CI, -32.4 to -8.8] mg/dL;  $P = 0.002$ ) in the placebo group. However, the difference between changes from baseline was not significant ( $P > 0.2$ ). High-density lipoprotein cholesterol and triglyceride levels decreased in both groups, but the changes from baseline and the difference between changes were not statistically significant.

### Dosage of the Study Drug

Because both patients and investigators were blinded to drug identity, the administration of metformin and placebo did not differ. The mean metformin dosage was 4.2 tablets (2100 mg) per day, and the mean placebo dosage was 3.8 tablets per day ( $P > 0.2$ ). Eighteen of the 21 patients receiving metformin were receiving the maximum dosage of five tablets per day, 2 patients were receiving four tablets per day, and 1 patient was receiving three tablets per day.

### Side Effects

Table 3 shows a comparison of the incidence and type of gastrointestinal side effects most commonly reported by the study patients. Seven patients receiving metformin reported nausea, 5 of them at initiation of therapy (500 mg twice daily). These symptoms lasted from 2 to 28 days and resolved spontaneously without requiring adjustments of the dose of the study drug. Three of these patients experienced these symptoms again during week 4 when the dosage was increased to 1500 mg/d. One patient receiving metformin reported diarrhea during week 8 at a dosage of 2000 mg/d, requiring a decrease to and maintenance of the dosage at 1500 mg/d throughout the rest of the study without report of further symptoms. Two patients receiving metformin reported nausea, bloating, abdominal

**Table 3.** Incidence of Adverse Events

Side Effect	Metformin Group (n = 21)	Placebo Group (n = 22)
	n	
Nausea	7	4
Abdominal pain	1	0
Diarrhea	9	4
Hypoglycemia	3	3
Other		
Hunger	1	1
Bloating	1	1
Anorexia	1	0

discomfort, and diarrhea during week 8 after the dosage was increased to 2500 mg/d. The dosage was decreased to 2000 mg/d and increased to 2500 mg/d after 2 weeks (week 10). Symptoms recurred, and the dosage was subsequently decreased to and maintained at 2000 mg/d for the remainder of the study period. Only 3 patients receiving metformin did not tolerate the maximum dosage of 2500 mg/d.

Anorexia was reported by 1 patient receiving metformin. The incidence of hypoglycemia and other adverse events was also similar between groups. Hypoglycemic episodes were reported only once in 3 persons taking metformin. Blood glucose levels in patients who had hypoglycemic episodes ranged from 3.05 to 3.89 mmol/L (55 to 70 mg/dL). Patients were always able to treat themselves, and the symptoms resolved quickly. Although metformin therapy seems to have been safe, the small size of the study group provided a limited opportunity for study.

## Discussion

Several reports have discussed the effects of metformin on insulin action and peripheral insulin sensitivity in persons with type 1 diabetes mellitus (14) or type 2 diabetes mellitus (1, 7, 8, 10, 11, 19). However, the clinical effect of metformin has been more substantial in patients with type 2 diabetes. Metformin is approved in the United States for use alone or in combination with sulfonylurea compounds in patients with type 2 diabetes; however, its use in combination with insulin for the treatment of these patients is not uncommon. This combination has recently been approved by the Food and Drug Administration.

Our study reinforces several observations about the use of metformin. First, glycemic control improved significantly in both placebo recipients and metformin recipients. Placebo recipients had a 1.6–percentage point decrease in hemoglobin A<sub>1c</sub> concentrations from baseline, and metformin-treated patients had a 2.5–percentage point decrease. This reduction in hemoglobin A<sub>1c</sub> concentrations was greater than that reported by Giugliano and colleagues (11), who saw a reduction of 1.84 percentage points in hemoglobin A<sub>1c</sub> levels in a similar group of patients. However, in our study, hemoglobin A<sub>1c</sub> levels in metformin-treated patients were 10% lower than those in placebo recipients. This was both a statistically and clinically significant difference.

Although hemoglobin A<sub>1c</sub> levels in both groups did not reach target levels ( $\leq 5.6\%$ ), metformin as an adjunct to insulin therapy seems to improve glycemic control. The most reasonable explanation for

our inability to achieve target hemoglobin A<sub>1c</sub> concentrations is that our study lasted for only 6 months.

In placebo recipients, daily insulin requirements increased by 24% (22.8 U/d) from baseline, but insulin dosage did not change in metformin-treated patients. The difference between the change in insulin dosage between the two groups was statistically significant. Pagano and coworkers (14) reported a 25.8% reduction in daily insulin requirements in patients with type 1 diabetes when metformin was added to their insulin regimen. Giugliano and colleagues (11) reported a 25% reduction in insulin dosage with the addition of metformin in patients with type 2 diabetes; however, glycemic control did not improve in every patient in the metformin group, and no responders or nonresponders had mean hemoglobin A<sub>1c</sub> levels less than 7.0%. In our study, glycemic control improved in both the placebo and metformin groups. With no change in daily insulin requirements, mean hemoglobin A<sub>1c</sub> levels decreased by 2.5 percentage points in metformin-treated patients. Placebo recipients required a considerably higher dose of insulin and a more complex regimen than metformin recipients.

Increased endogenous insulin levels have been associated with increased risk for developing cardiovascular disease. Although many physicians have presumed that exogenous insulin administration could be associated with this risk, this has not been confirmed (16, 20). The clinical benefits of adding metformin to an insulin regimen are not related to the daily amount of insulin administered but rather to an improvement in glycemic control, the possible simplification of the insulin regimen, and the avoidance of weight gain.

Weight gain associated with improved glycemic control is common and often occurs when hemoglobin A<sub>1c</sub> levels are significantly reduced. This effect has been reported in the intensively treated cohorts of the Diabetes Control and Complications Trial (21) and the UKPDS (16) and in patients who received insulin combination therapy with sulfonylurea compounds (4, 5) or troglitazone (1, 6). The significant increase in daily insulin dose in the placebo group was associated with a 3.2-kg increase in average body weight compared with a 0.5-kg increase in average body weight in metformin-treated patients. Therefore, patients receiving metformin tended to gain less weight than patients receiving placebo. At study end, metformin-treated patients reported a daily caloric intake that was 18% lower than at baseline and placebo recipients reported a daily caloric intake that was 6.7% lower than at baseline. However, the total caloric daily intake at the end of the study and the change from baseline were similar between groups. The lower daily ca-

loric intake reported by metformin-treated patients may be attributed to gastrointestinal side effects associated with the use of metformin. However, the gastrointestinal side effects were transient and occurred at the initiation of therapy or during titration to a higher dose. Anorexia, a side effect sometimes associated with the use of metformin, was reported by only 1 metformin-treated patient. However, side effects could have been underestimated, and study patients could have underreported food intake.

The incidence of gastrointestinal symptoms and hypoglycemic episodes was similar in both treatment groups. Therefore, metformin was generally well tolerated and the incidence of side effects associated with its use was similar to that associated with placebo.

Aggressive insulin therapy can improve glycemic control in patients with type 2 diabetes mellitus. The addition of metformin to an intensified insulin regimen results in a hemoglobin A<sub>1c</sub> level 11% lower than that achieved by insulin therapy alone. This improvement in glycemic control occurs with the use of 29% less insulin, a less complicated insulin regimen, and no increase in the incidence of hypoglycemia or weight gain.

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*Requests for Reprints:* Philip Raskin, MD, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard G5.238, Dallas, TX 75235-8858.

*Current Author Addresses:* Drs. Avilés-Santa and Ms. Sinding: University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard G4.100, Dallas, TX 75235-8858. Dr. Raskin: University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard G5.238, Dallas, TX 75235-8858.

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