

The Effects of Metformin on Body Mass Index and Glucose Tolerance in Obese Adolescents With Fasting Hyperinsulinemia and a Family History of Type 2 Diabetes

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ABSTRACT. *Objectives.* The prevalence of type 2 diabetes in American adolescents has increased markedly during the past generation. Although the factors that contribute to the development of type 2 diabetes are complex and not wholly elucidated, the triad of severe obesity, hyperinsulinemia, and a family history of type 2 diabetes places a child at an increased risk for development of the disease. Current approaches to the prevention of type 2 diabetes, including dietary counseling and exercise, have had limited success. We reasoned that drugs that increase glucose tolerance in diabetic patients might prove useful in preventing the progression to glucose intolerance in high-risk patients. To that end, we conducted a double-blind, placebo-controlled study of the effects of metformin on body mass index (BMI), serum leptin, glucose tolerance, and serum lipids in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes.

Methods. The study population consisted of 29 white and black adolescents aged 12 to 19 years. All had BMIs exceeding 30 kg/m². Criteria for enrollment included: 1) a fasting insulin concentration exceeding 15 μ U/mL; and 2) at least 1 first- or second-degree relative with type 2 diabetes. All patients had fasting plasma glucose concentrations <110 mg% and hemoglobin A1c concentrations \leq 6.0%. All had normal linear growth and sexual development for age, with no marked hirsutism, severe acne, or menstrual irregularities characteristic of polycystic ovary syndrome. Eight participants had acanthosis nigricans. After baseline laboratory studies including a rapidly sampled intravenous glucose tolerance test, patients were randomized to receive metformin (500 mg twice daily) or a placebo for a total of 6 months. The effects of metformin on BMI standard deviation score, serum leptin, glucose tolerance, and serum lipids were analyzed. The study was double-blinded and included no specific dietary restrictions.

Results. Metformin caused a decline of 0.12 standard deviation in BMI in study participants (-1.3% from baseline), and a 5.5% reduction in serum leptin in girls. In contrast, BMI and serum leptin rose 0.23 standard deviation (2.3%) and 16.2%, respectively, in the placebo group during the treatment period. Metformin caused a progressive decline in fasting blood glucose (from a mean of 84.9 to 75.1 mg%) and a reduction in fasting insulin levels (from 31.3 to 19.3 μ U/mL). In contrast, fasting glucose levels in the placebo group rose slightly from 77.2 to 82.3

mg%, and fasting insulin levels did not change. Insulin sensitivity, as assessed by the ratio of fasting insulin to glucose concentrations and the quantitative insulin sensitivity check index ($1/[\log \text{fasting insulin} + \log \text{fasting glucose}]$) and homeostasis model assessment insulin resistance index ($\text{fasting insulin} \times \text{fasting glucose}/22.5$) indices, increased slightly in the metformin-treated participants. However, the insulin sensitivity measured using Bergman's minimal model did not change. There were also no significant changes in glucose effectiveness, hemoglobin A1c, serum lipids, or serum lactate in the metformin or placebo groups. Metformin was tolerated well by the majority of patients. Transient abdominal discomfort or diarrhea occurred in 40% of treated participants; there were no episodes of vomiting or lactic acidosis.

Conclusions. The treatment of obesity and insulin resistance in adults often proves ineffective because the vicious cycle leading to type 2 diabetes may have become entrenched and, to some extent, may be irreversible. Early detection and therapy of the obese adolescent with a family history of type 2 diabetes may interrupt the cycle of weight gain and insulin resistance that leads to glucose intolerance in adulthood. Through its ability to reduce fasting blood glucose and insulin concentrations and to moderate weight gain, metformin might complement the effects of dietary and exercise counseling and reduce the risk of type 2 diabetes in selected patients. *Pediatrics* 2001;107(4). URL: <http://www.pediatrics.org/cgi/content/full/107/4/e55>; obesity, type 2 diabetes, metformin, insulin, glucose.

ABBREVIATIONS. BMI, body mass index; HbA1c, hemoglobin A1c; RIA, radioimmunoassay; IGF-I, insulin-like growth factor I; SDS, standard deviation scores; SD, standard deviation; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostasis model assessment insulin resistance index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

The past generation has witnessed a striking increase in the prevalence of glucose intolerance and type 2 diabetes mellitus in adolescents in the United States.¹⁻⁸ The emergence of type 2 diabetes in childhood is related, at least in part, to the increased prevalence of obesity in American teenagers. Among obese adolescents, the risk for the development of type 2 diabetes is highest in black, Native American, and Hispanic American populations,¹⁻¹⁴ particularly in those individuals with a family history of the disease. Obesity is accompanied by a resistance to insulin action and by hyperinsulinemia, which often precede and likely play important roles in the development of glucose intoler-

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ance.^{15–24} Although the factors that contribute to the development of type 2 diabetes are complex and not wholly elucidated, the triad of severe obesity, hyperinsulinemia, and a family history of type 2 diabetes is known to place a child at an increased risk for subsequent development of the disease.^{8–10,14,16–22}

Current approaches to the prevention of type 2 diabetes in high-risk patients, including diet and exercise, have had limited success. We reasoned that drugs that increase glucose tolerance in diabetic patients might prove useful in preventing the progression to glucose intolerance in high-risk patients. To that end, we conducted a double-blind, placebo-controlled study of the effects of metformin on body mass index (BMI), serum leptin, glucose tolerance, and serum lipids in obese adolescents ($n = 29$) with fasting hyperinsulinemia and a family history of type 2 diabetes. Metformin reduces blood glucose, insulin, and hemoglobin A1c (HbA1c) levels in type 2 diabetic patients and in obese nondiabetic adults.^{25–31} Because the investigation was designed to assess the effects of metformin on glucose tolerance and weight gain in the absence of dietary intervention, we made no attempt to control the caloric intake or food selection of the patients.

METHODS

Participants

A total of 32 patients were enrolled in the study in a randomized, double-blinded manner. All were between 12 and 19 years old and had a BMI exceeding 30 kg/m². Criteria for enrollment included: 1) a fasting insulin concentration exceeding 15 μ U/mL and 2) at least 1 first- or second-degree relative (parent, sibling, or grandparent) with type 2 diabetes. All patients had normal fasting glucose concentrations (<110 mg%) and HbA1c concentrations ($\leq 6.0\%$), and none had glycosuria or ketonuria. Two placebo patients and a metformin-treated patient failed to complete the study for reasons unrelated to drug toxicity or to complications of the trial. These patients discontinued therapy in the first 4 to 6 weeks of the trial; thus, their auxologic and biochemical data were not included in the final analysis. The final analysis includes data from 14 metformin-treated participants and 15 placebo controls (Table 1).

No patients had renal, adrenal, hepatic or thyroid dysfunction, or galactorrhea, and none were taking medications chronically for systemic illness. All patients had normal linear growth and sexual development for age, with no marked hirsutism, severe acne, or menstrual irregularities characteristic of polycystic ovary syndrome. Eight of the participants had mild acanthosis nigricans (1 black male and 3 black females in the placebo group, 2 black males and 2 black females in the metformin group). The study was conducted only in adolescents who had reached Tanner stage III puberty because previous studies demonstrated significant reduc-

tions in insulin sensitivity during early puberty.³² Plasma lactate was normal in all cases. Baseline clinical characteristics of the patient population are shown in Table 1. Before participating in the study, each participant and his/her parent(s) or guardians gave written informed voluntary consent. The study was approved by the institutional review board of Duke University Medical Center.

Study Design

After the initial screening, each participant was admitted to the Duke Clinical Research Center for baseline metabolic studies. After admission, the patient had a standard dinner and bedtime snack and fasted overnight for 12 hours. On the following morning, intravenous catheters were inserted in both arms and blood was obtained for measurement of serum glucose, insulin, hemoglobin A1c, leptin, lactate, cholesterol, triglycerides and lipoproteins, serum insulin-like growth factor I levels, liver and renal function tests, and complete blood counts.

The patient then underwent a rapidly sampled intravenous glucose tolerance test.^{33–35} Each patient received an intravenous bolus of glucose (100 g) followed 20 minutes later by an intravenous bolus of tolbutamide (300 mg/1.73 m²). Aliquots of blood were obtained at times 0 (just before the glucose bolus), 2, 4, 8, 19, 22, 25, 30, 35, 40, 50, 70, 90, and 180 minutes for measurement of plasma glucose and insulin levels.

After the completion of the test, the patient was discharged with a coded vial of pills containing either metformin (500 mg) or placebo. Patients were instructed to take 1 pill at breakfast and 1 at supper each day. This dose of metformin was selected because it is comparable to that used in previous studies of obese nondiabetic men and women.^{33–35} Patients returned to the outpatient clinic to be measured and weighed. Blood was sampled under fasting conditions. The blood samples were used for measurements of serum glucose, insulin, liver and renal function tests, and lactate (all monthly) and HbA1c, cholesterol, triglycerides, lipoproteins, and leptin (all every other month). Six months after initiating the study, the patient was readmitted to the inpatient ward of the clinical research unit for repeat blood sampling and a frequently sampled intravenous glucose tolerance test. Therapy with metformin or placebo was continued throughout the study, with no washout period before repeating the intravenous glucose tolerance test at 6 months. Compliance with the medication was assessed by patient reports and by pill counts at each monthly visit.

Analytical Procedures and Statistical Analysis

Serum glucose was measured by a colorimetric assay, using glucokinase as a substrate, while serum insulin was measured using a human insulin radioimmunoassay (RIA) provided by Linco (St Charles, MO). Serum leptin was measured by RIA using the human leptin kit manufactured by Linco. Serum insulin-like growth factor I (IGF-I) was measured using a human IGF-I RIA kit manufactured by Diagnostic Systems Laboratory (Webster, TX). Serum chemistries, lactate, cholesterol and lipoproteins, and blood counts were measured using standard clinical assays. All biochemical assays were performed in duplicate. Serum leptin and lipoproteins and serum IGF-I levels were measured because morbid obesity and insulin resistance are commonly accompanied by hyperleptinemia and dyslipidemia and may be associated with increases in serum IGF-I concentrations.

The study group represented a heterogeneous mix of white and black boys and girls. Because BMI in the normal population varies according to age, gender, and ethnic background, we expressed absolute values of BMI as standard deviation scores (SDS) and changes in BMI as changes in SDS, using the norms for age, sex, and race defined by Rosner et al.³⁶ We calculated SDS as the number of standard deviations (SDs) by which a given value deviated from the mean for a child of the same age, gender, and ethnic background. Given the heterogeneity of the patient population, the use of SDS provides a more reliable means for comparison among participants than does the absolute values of BMI. Changes in blood glucose, insulin, and leptin were expressed as absolute values and as a percentage of each individual's baseline value.

Insulin sensitivity and glucose effectiveness were estimated using the Minimal Model,^{33–35} an analytical program developed to quantify in vivo glucose metabolism from the frequently sampled

TABLE 1. Study Population

	Placebo	Metformin
Age (y)	15.4 \pm 0.5	14.4 \pm 0.6
Gender (M/F)	8/7	3/11
Ethnicity (white/black)	7/8	9/5
BMI (kg/M ²)	38.7 \pm 1.3	41.5 \pm 0.9*
Glucose (fasting, mg%)	77.2 \pm 3.0	84.9 \pm 4.5
Insulin (fasting, μ U/mL)	28.0 \pm 3.2	31.5 \pm 3.4
HbA1c (%)	5.5 \pm 0.1	5.6 \pm 0.1
Leptin (ng/mL)		
Males	28.0 \pm 3.3	30.2 \pm 2.0
Females	47.7 \pm 7.4**	57.0 \pm 5.4**

Values are mean \pm standard error.

* $P < .05$, metformin versus placebo.

** $P < .02$, females versus males.

intravenous glucose tolerance test. Insulin sensitivity characterizes insulin action on glucose kinetics, whereas glucose effectiveness characterizes noninsulin-dependent glucose kinetics at basal concentrations of insulin. Glucose effectiveness is a measure of the ability of glucose itself to increase whole-body glucose uptake and to suppress hepatic glucose output independent of insulin. Minimal model analysis was performed using computer software purchased from Dr Richard Bergman, at the University of Southern California. Changes in insulin sensitivity were also assessed by quantifying changes in: 1) the ratio of fasting insulin to glucose concentrations; 2) the quantitative insulin sensitivity check index (QUICKI; $1/[\log \text{ fasting insulin} + \log \text{ fasting glucose}]^{37}$; and 3) the homeostasis model assessment insulin resistance index (HOMA-IR; $\text{fasting insulin} \times \text{fasting glucose}/22.5$).³⁸ QUICKI and HOMA-IR are calculated from the fasting concentrations of glucose and insulin. Statistical differences between sample groups were determined by analysis of variance, followed by the Newman-Keuls tests for group comparisons. A *P* value $<.05$ was considered statistically significant.

RESULTS

The baseline BMI of patients in the metformin treatment group was 7.2% ($P < .05$) greater than that of patients in the placebo group (Table 1). There were no statistical differences between the groups in baseline plasma glucose or insulin, calculated insulin sensitivity or glucose effectiveness, HbA1c, or serum cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), or leptin. Serum leptin levels in females in each group were significantly higher than were those in males ($P < .02$).

As shown in Fig 1, metformin caused a decline of 0.12 SD in BMI during the study, amounting to a mean decrease of 0.5 kg/m², or -1.3% from baseline. In contrast, BMI rose 0.23 SD, or 2.3% (mean + 0.9 kg/m²) in the placebo group. The differences in absolute and percent change in BMI SDS in the 2 groups were statistically significant ($P < .02$). Given the small number of patients in the study groups, it was impossible to perform extensive analysis of the effects of metformin on BMI in various subgroups matched for gender or race (Fig 1). Results in boys must be interpreted cautiously because only 3 males received the drug. Comparison among subgroups matched for gender and racial background revealed a statistically significant difference ($P < .05$) in BMI SDS between the metformin-treated ($n = 3$) and placebo-treated ($n = 3$) black girls (data not shown).

Metformin had no effect on serum leptin in males (Table 2). Serum leptin levels declined by 5.5% in

metformin-treated girls ($n = 7$) but rose 16.2% in placebo-treated girls ($n = 11$). The differences in percent change in serum leptin between the 2 groups of girls were statistically significant ($P < .05$; Table 2).

Metformin caused a progressive decline in fasting blood glucose levels (Fig 2), from 84.9 ± 2.2 mg% at the start of the study to 75.1 ± 1.6 mg% at the end of the 6-month trial ($P < .02$). In contrast, fasting blood glucose levels in the placebo group did not change significantly during the study (baseline: 77.2 ± 2.2 mg%; final: 82.3 ± 2.7 mg%). Fasting glucose levels at 6 months were 9.2 \pm 3.9% lower than baseline levels in the metformin group and 8.7 \pm 3.3% higher than baseline levels in the placebo group ($P < .01$, metformin vs placebo).

The reduction in plasma glucose levels was associated with a reduction in fasting insulin levels (Fig 3). Fasting insulin concentrations in the metformin group declined from 31.5 ± 3.3 $\mu\text{U}/\text{mL}$ at baseline to 19.2 ± 1.5 $\mu\text{U}/\text{mL}$ after 6 months of treatment ($P < .01$). In contrast, fasting insulin levels did not change in the placebo group. The response to metformin did not seem to vary according to gender or racial background (data not shown). Insulin sensitivity as assessed by the minimal model did not change significantly during the study. In contrast, metformin caused a significant ($P < .01$) albeit small increase in insulin sensitivity as assessed by: 1) the ratio of fasting insulin to glucose concentration; 2) QUICKI; and 3) HOMA-IR (Table 3). Despite the reductions in fasting glucose and insulin concentrations, there were no significant changes in HbA1c during the 6-month trial (Table 2). Moreover, there were no changes in glucose effectiveness or serum IGF I levels (Tables 2 and 3). Finally, there were no statistically significant changes in serum lipids; the only measure that approached statistical significance ($P = .1$) was the ratio of LDL to HDL.

Metformin was tolerated well by the majority of patients. One patient complained of intermittent nausea during the third and fourth months of therapy and reduced her intake of metformin to 500 mg per day for the final 3 months of the trial. A second metformin-treated patient had no complications but took only 40% to 50% of her pills during the final 2 months of treatment. Auxologic and biochemical data on these 2 patients were included in full in the final analysis. An additional 3 metformin-treated patients complained of transient abdominal discomfort or diarrhea that resolved within the first 1 to 2 weeks of therapy. A single patient in the placebo group had a similar complaint. One patient may have had an exacerbation of migraine, although she completed the study. Serum lactate and liver and renal function tests remained normal in all patients throughout the study, and there were no episodes of vomiting or lactic acidosis. As noted previously, 2 placebo patients and a metformin-treated patient failed to complete the study for reasons unrelated to drug toxicity or to complications of the trial. These patients discontinued therapy in the first 4 to 6 weeks of the trial; thus, their auxologic and biochemical data were not included in the final analysis.

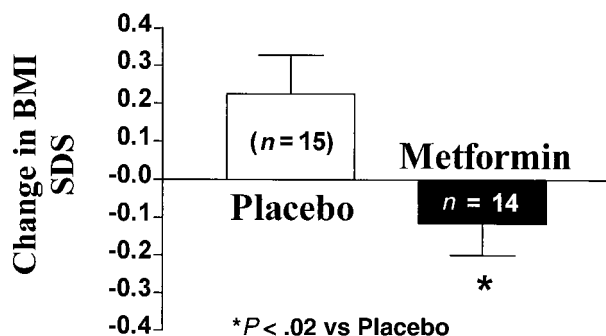


Fig 1. Change in BMI SDS in metformin- and placebo-treated patients during the 6-month trial. Values represent mean \pm standard error.

TABLE 2. Effects of Metformin on Various Biochemical Indices

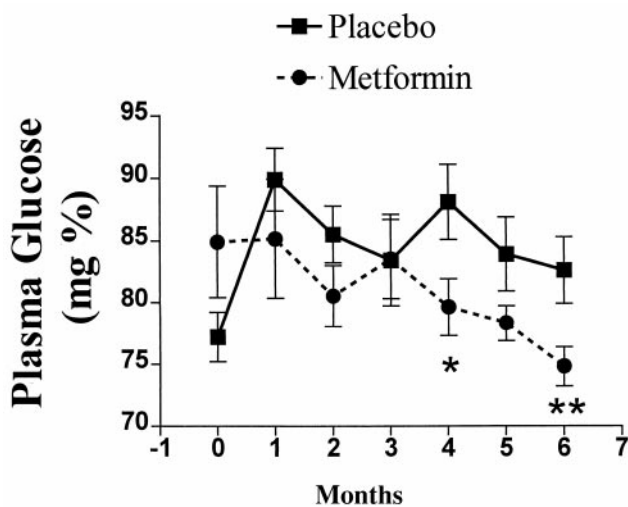
	Placebo		Metformin	
	Initial	Final	Initial	Final
Insulin ($\mu\text{U}/\text{mL}$)	28.0 \pm 3.2	26.4 \pm 7.7	31.5 \pm 3.4	19.2 \pm 1.5*
Glucose (mg%)	77.2 \pm 2.2	82.3 \pm 2.7	84.9 \pm 4.5	75.1 \pm 1.6*
Leptin (ng/mL)				
Males	28.0 \pm 3.3	24.7 \pm 3.4	30.2 \pm 2.0	31.6 \pm 6.2
Females	47.7 \pm 7.4**	55.3 \pm 10.9	57.0 \pm 5.4**	53.8 \pm 5.6
% change (females)		16.2 \pm 8.4		5.5 \pm 6.7***
HbA1c (%)	5.5 \pm 0.1	5.7 \pm 0.1	5.6 \pm 0.1	5.7 \pm 0.1
IGF-I (ng/mL)	453.3 \pm 30.3	461.6 \pm 46.0	406.8 \pm 43.7	411.1 \pm 31.9
Lactate (mg%)	1.3 \pm 0.1	1.3 \pm 0.1	1.3 \pm 0.1	1.3 \pm 0.1
Cholesterol (mg%)	161.1 \pm 10.4	154.3 \pm 9.8	149.5 \pm 6.0	142.4 \pm 5.2
LDL (mg%)	101.7 \pm 9.2	98.4 \pm 7.6	93.7 \pm 7.6	87.2 \pm 4.8
HDL (mg%)	38.3 \pm 1.7	36.9 \pm 1.6	37.6 \pm 2.4	38.4 \pm 2.4
LDL/HDL	2.7 \pm 0.2	2.7 \pm 0.2	2.5 \pm 0.2	2.3 \pm 0.2
Triglycerides (mg%)	109.4 \pm 20.0	95.6 \pm 21.6	86.4 \pm 11.2	84.9 \pm 9.9

Values are means \pm standard error.

* $P < .02$, metformin final versus metformin initial.

** $P < .02$, females versus males.

*** $P < .05$, metformin versus placebo.



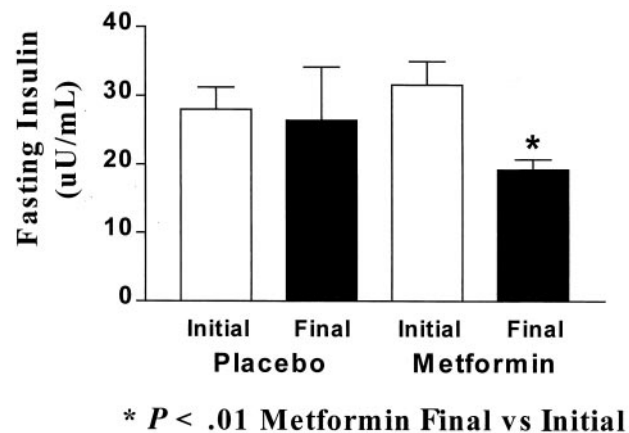
* $P < .05$ vs Placebo Controls

** $P < .02$ vs Placebo Controls

Fig 2. Changes in fasting plasma glucose concentrations in the metformin- and placebo-treated patients during the trial. Values represent mean \pm standard error.

DISCUSSION

Recent national surveys indicate that the prevalence of obesity in childhood and adolescence in the United States is rising sharply: ~15% to 20% of American teenagers are obese.³⁹⁻⁴¹ The risk of development of type 2 diabetes in an obese individual increases in proportion to the severity of the obesity, the number of parents and first-degree relatives with the disease, and the fasting and postprandial concentrations of insulin and glucose.¹⁶⁻²² As noted previously, certain minority populations are at particular risk. In high-risk obese patients, insulin resistance and hyperinsulinemia may be detected more than a decade before the development of glucose intolerance.^{16-22,42-56} Thus, sudden or progressive increases in BMI and/or plasma insulin concentrations in a child or adolescent may forewarn of impending metabolic decompensation.



* $P < .01$ Metformin Final vs Initial

Fig 3. Changes in fasting plasma insulin concentrations in the metformin- and placebo-treated patients during the 6-month trial. Values represent mean \pm standard error.

Our pilot study represents an attempt to explore new strategies to reduce the risk of type 2 diabetes in highly susceptible adolescent populations. Thus, the trial was conducted in markedly obese adolescents with a family history of type 2 diabetes and evidence of insulin resistance. Measures of fasting insulin levels and insulin sensitivity at baseline confirmed that our patients were insulin resistant. The initial insulin sensitivity index in our patient population approximated 1.0×10^{-4} per minute/ $(\mu\text{U}/\text{mL})$. This value is one half to one fifth that of normal weight adolescents in midpuberty,^{32,33} one fourth to one seventh that of healthy adult women and men, respectively, and one half that of obese nondiabetic men, but approximately twice as high as that of adults with frank type 2 diabetes.³³⁻³⁵ The degree of insulin resistance in our patients was comparable to that observed by other investigators in studies of markedly obese pubertal children.³² In contrast, baseline glucose effectiveness (glucose effectiveness: 0.02/minute) in our patients was comparable to values in normal and obese nondiabetic adults and higher than those of patients with type 2 diabetes. Previous investigations demonstrated that glucose effective-

TABLE 3. Effects of Metformin on Insulin Sensitivity

	Placebo		Metformin	
	Initial	Final	Initial	Final
Minimal model				
Insulin sensitivity†	1.0 ± 0.2	1.2 ± 0.2	0.9 ± 0.2	1.2 ± 0.4
Glucose disposal‡	0.018 ± 0.001	0.021 ± 0.002	0.022 ± 0.003	0.019 ± 0.001
Insulin/glucose ($\mu\text{U}/\text{mL}$)/mg%	0.35 ± 0.03	0.29 ± 0.07	0.38 ± 0.05	0.25 ± 0.02*
QUICKI (1/[log insulin + log glucose])	0.30 ± 0.004	0.31 ± 0.006	0.30 ± 0.004	0.32 ± 0.004*
HOMA-IR (insulin × glucose/22.5)	96.3 ± 11.7	94.9 ± 30.6	119.5 ± 14.1	64.0 ± 5.2*

* $P < .01$, metformin final versus metformin initial.

† Insulin sensitivity units = $\times 0.0001/\text{minute}/(\mu\text{U}/\text{mL})$.

‡ Glucose disposal units = /minute.

ness does not decline until obese patients develop frank glucose intolerance.^{33–35}

We did not restrict the amount or content of food ingested by any patient. This point differentiates our study from most previous metformin studies, in which patients were placed on a hypocaloric diet. Nevertheless, metformin therapy was accompanied by a small but statistically significant reduction in BMI SDS during the 6-month trial. In contrast, BMI SDS rose slightly in placebo-treated patients. The reduction in serum leptin levels in the metformin-treated girls suggests that the decrease in BMI may be associated with a reduction in body fat mass.⁵⁷ Our findings in this regard are consistent with previous studies of metformin in diabetic and obese nondiabetic adults. For example, metformin reduced slightly the rates of weight gain and body fat accumulation in diabetic and nondiabetic adults^{58–61} and in nondiabetic women with polycystic ovarian syndrome.⁶² Serum leptin levels declined ~10% to 15% in 2 studies of nondiabetic obese patients^{60,63}; in one of these studies the effect of metformin on serum leptin was transient, disappearing after 2 to 4 months of treatment. Preliminary short-term studies suggest that the effects of metformin on BMI and serum leptin may be mediated in part by reductions in food intake.⁶⁰ Metformin may have had more significant effects on serum leptin in our adolescent girls than in boys because leptin levels in females are higher than those in males at all developmental stages.⁵⁷

In our study metformin induced a progressive decline in fasting blood glucose levels and a 39% reduction in fasting insulin levels. Insulin sensitivity as assessed using the minimal model did not change during the study. However, there were small but significant increases in insulin sensitivity as assessed by other indices including the fasting insulin:glucose ratio, QUICKI, and HOMA-IR. There is considerable controversy regarding the optimal measure for assessing insulin sensitivity. The minimal model may be unreliable in diabetic patients^{37,64} and may fail to reveal small changes in insulin sensitivity in markedly obese participants. Preliminary studies suggest that simplified measures such as QUICKI and HOMA-IR, which are calculated indices derived from the fasting glucose and insulin concentrations, may prove useful in these respects.³⁷ The absence of a pronounced effect of metformin on insulin sensi-

tivity in our study group suggests that the reduction in fasting glucose and insulin concentrations may result from reductions in hepatic glucose output. Such effects have been recorded in studies of diabetic and nondiabetic adults. Reductions in fasting blood glucose levels in diabetic patients treated with metformin result primarily from a decline in hepatic glucose production that may be mediated by inhibition of gluconeogenesis or glycogenolysis.^{30,31} The effects of metformin on fasting insulin levels and insulin sensitivity are more variable; no effects on fasting plasma insulin concentrations or insulin sensitivity were detected in some investigations, whereas other studies showed small or moderate effects.^{30,31} In contrast, significant weight loss in type 2 diabetic and nondiabetic adults is associated with increases in insulin sensitivity and reductions in fasting insulin levels.⁶⁵

Like its effects on insulin sensitivity, the effects of metformin on plasma cholesterol and lipoproteins are inconsistent and depend in part on the nature of the underlying condition. In a study of adult participants with type 2 diabetes, metformin reduced total cholesterol, LDL, and triglyceride levels but had no effects on serum HDL.⁶⁶ Other studies of diabetic patients, however, found no independent effects of metformin on plasma lipids.⁶¹ In obese nondiabetic adults,^{58,67} metformin reduced plasma cholesterol and had inconsistent effects on plasma triglyceride and HDL levels. It may be relevant to note that the lipid-lowering effects of metformin were observed in studies of patients with preexisting dyslipidemia. We did not observe significant changes in serum lipids in our study patients, who had normal serum lipid levels at baseline. It is possible that the duration of our study was too short to detect small changes in serum lipids that might accrue with time.

There were only minor and transient side effects associated with metformin therapy in the majority of patients. Mild abdominal discomfort and diarrhea were observed in 7 patients and resolved shortly after initiation of therapy. However, persistent, although mild, nausea forced one of the patients to reduce her dose of metformin by 50%. One patient may have had an exacerbation of migraine, although she completed the study. Plasma lactate levels remained normal throughout the course of the trial, and there were no episodes of lactic acidosis. The risk of lactic acidosis in type 2 diabetic patients treated

with metformin approximates 0.03 per 1000 patient years.^{27,68,69} Nearly all cases of lactic acidosis have occurred in patients with underlying renal and/or atherosclerotic cardiovascular disease, liver disease, or alcohol abuse.^{27,68,69} Adherence to patient exclusion criteria has reduced the risk of lactic acidosis markedly; patients with ketosis-prone diabetes or with underlying renal, hepatic, or cardiopulmonary disease should not be given the medication. Long-term therapy with metformin is associated with decreased intestinal absorption of vitamin B₁₂ and folate. In adults, the reductions in plasma B₁₂ and folate are rarely clinically important and are reversed on discontinuation of the drug.²⁷ We did not measure serum B₁₂ and folate levels but found no decline in hemoglobin during therapy.

It must be noted that our trial has important limitations. First, the study involved a small number of patients and the results must be confirmed in a larger sample.

Second, the treatment and control groups were not matched precisely for ethnic background, gender, or initial BMI; this fact compels us to interpret the results with caution. However, the consequences of these differences among the treatment and control groups at baseline may have been negated in part because: 1) we expressed absolute values for BMI as SDS, thereby correcting in part for differences in ethnic background, age, and gender; and 2) we expressed changes in BMI in our patients as changes in SDS, and changes in plasma glucose, insulin, leptin, and lipids as a percentage of each individual's baseline value. This allowed us to use each patient as his or her own control during the study. Given the small number of patients in our study, we were unable to perform extensive analysis of the effects of metformin in various subgroups matched for sex and race. However, the available data identify significant effects of metformin on BMI and serum leptin in female participants. No clear-cut effects of race or gender were noted in our analysis of changes in plasma glucose or insulin concentrations. A previous study found that the effects of metformin on glucose tolerance were comparable among men and women and among individuals of various racial and ethnic groups.⁶⁶

Third, the study lasted only 6 months. It is unclear whether positive effects of metformin would be sustained over longer periods. Moreover, long-term drug safety in nondiabetic patients has not been established.

Fourth, the effects of metformin on BMI and fasting blood glucose and insulin levels, although statistically significant, were relatively small in magnitude. At the present time, it is unclear whether persistent, although small, reductions in BMI and glucose and insulin concentrations can forestall the progression to type 2 diabetes in the predisposed patient.

The treatment of obesity and insulin resistance in the adult often proves ineffective because the vicious cycle leading to type 2 diabetes may have become entrenched and, to some extent, may be irreversible. Early detection and therapy of the obese adolescent with a family history of type 2 diabetes may interrupt the cycle of weight gain and insulin resistance that lead to glucose intolerance in adulthood. The

obese patients at greatest risk for future development of type 2 diabetes are those with the highest fasting concentrations of glucose and insulin.^{19,21} Through its ability to reduce fasting blood glucose and insulin levels and to moderate weight gain, metformin therapy might complement the effects of dietary and exercise counseling and reduce the risk of type 2 diabetes in selected patients. Future studies, including the Diabetes Prevention Program in adults,⁷⁰ will provide a test of this hypothesis.

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