# Beneficial Effects of Metformin in Normoglycemic Morbidly Obese Adolescents

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**Hyperinsulinemia and insulin resistance are common features of obesity in humans and experimental animals. It has been demonstrated that metformin, an antihyperglycemic agent, decreases hyperinsulinemia and insulin resistance leading to decreased adiposity in obese and non–insulin-dependent diabetes mellitus (NIDDM) adults. To evaluate the antiobesity effect of metformin, we conducted a randomized double-blind placebo controlled trial in 24 hyperinsulinemic nondiabetic obese adolescents (body mass index [BMI] >30 kg/m$^2$). All subjects were placed on a low-calorie (1,500 kcal for women and 1,800 kcal for men) meal plan. After an initial 1-week lead-in period, 12 subjects (mean ± SE for age and BMI, 15.6 ± 0.4 and 41.2 ± 1.8, respectively) received metformin (850 mg twice daily) for 8 weeks, and 12 subjects (mean ± SE for age and BMI, 15.7 ± 0.5 and 40.8 ± 1.4, respectively) received placebo. Compared to the placebo group, the metformin group had greater weight loss (6.5% ± 0.8% *v* 3.8 ± 0.4%, *P* < .01), greater decrease in body fat (*P* < .001), greater increase in fat-free mass to body fat ratio (*P* < .005), and greater attenuation of area under the curve (AUC) insulin response to an oral glucose tolerance test (*P* < .001). This was associated with enhanced insulin sensitivity, as determined by the fasting plasma glucose:insulin, 2-hour glucose:insulin, and AUC glucose:AUC insulin ratios, in the metformin group compared to controls (*P* < .01). This corresponded to a significant reduction in plasma leptin (*P* < .005), cholesterol, triglycerides, and free fatty acid (FFA) levels (*P* < .05) only in the metformin-treated subjects. Combined metformin treatment and low-calorie diet had a significant antiobesity effect in hyperinsulinemic obese adolescents compared to a low-calorie diet alone.**


HYPERINSULINEMIA and insulin resistance are common features of obesity in both humans and experimental animals.[1,2] Although it is frequently assumed that the increased insulin secretion is a result of insulin resistance, there appears to be some evidence that hyperinsulinemia may precede the development of insulin resistence, which can play a role in the pathogenesis of obesity.[3-6] The strong lipogenic effect of hyperinsulinism results in a positive energy balance with only a moderate intake and causes an elevation of the set point for body weight regulation.[7] As obesity increases to a severe level, a vicious cycle of increasing hyperinsulinism and positive energy balance is established.[8] With the exception of severely reducing food intake or exerting enormous amounts of energy, this process is very difficult to reverse once the elevated set point is established.

It is generally assumed that since fat deposition persists, an obese individual's insulin-stimulated lipogenesis remains unimpaired, despite the resistance to carbohydrate metabolism. Hyperinsulinemic subjects demonstrate marked resistance to glucoregulatory action of insulin, but minimal resistance to the antilipolytic action of insulin during euglycemic hyperinsulinemic clamp studies.[9] It seems that this selective antilipolytic action of insulin is an important factor in the maintenance of fat deposition in obese individuals. Therefore, theoretically, if circulating insulin levels are lowered, then the tendency for lipogenesis and weight gain in obese subjects should be also be decreased.

Metformin (dimethylbiguanide) is an insulin-sensitizing and antihyperglycemic agent used in the treatment of non–insulin-dependent diabetes mellitus (NIDDM). The exact mechanism of metformin is unknown, but one of its suggested actions is increased peripheral glucose disposal at lower insulin concentrations.[10-12] It has been shown that metformin treatment of obese adults with type 2 diabetes results in weight loss and improved glucose tolerance and lipid profiles.[13-16] Furthermore, the use of metformin in nondiabetic obese adults has been demonstrated to cause reduced food intake and weight loss with reduction in fasting plasma glucose, cholesterol, and insulin concentrations.[17,18] On the other hand, short-term metformin treatment in women with polycystic ovary syndrome and insulin resistance has been shown to improve insulin sensitivity without a significant effect on body weight.[19,20] Lutjens and Smit demonstrated that a 3-month trial of metformin (500 mg thrice daily), in a group of 7 nondiabetic obese children ages 9 to 14 years, resulted in weight loss and improved insulin sensitivity compared a control group.[21] However, the study was not placebo-controlled or double-blind. In order to evaluate the antiobesity and metabolic effects of metformin independent of its anorectic effect, we conducted an 8-week double-blind and placebo-controlled trial of metformin in nondiabetic hyperinsulinemic obese adolescents maintained on a low-calorie diet.

## SUBJECTS AND METHODS

### *Study Subjects and Design*

Subjects consisted of 24 Caucasian obese adolescents with a body mass index (BMI) greater than 30 kg/m$^2$. Subjects with a history of glucose intolerance, diabetes, renal disorders, previously identified endocrine disorders, and cardiovascular disease were excluded, as well as those with a fasting glucose greater than 120 mg/dL and/or a glycosylated hemoglobin ($HgbA_{1c}$) ≥ 7.0%. Our study subjects did not have impaired glucose tolerance and/or diabetes based on American Diabetes Association Criteria[22] with normal $HgbA_{1c}$ (Table 1). Each subject underwent a complete physical examination, body weight being measured on a standard electronic scale (Seca delta model 707, Quick

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**Table 1. Clinical Characteristics of Placebo and Metformin Groups**

| | Placebo | Metformin |
|---|---|---|
| No. | 12 | 12 |
| Age (yr) | 15.7 ± 0.5 | 15.6 ± 0.4 |
| Sex (females/males) | 8/4 | 7/5 |
| Weight (kg) | 113.4 ± 5.0 | 116.0 ± 5.1 |
| BMI (kg/m$^2$) | 40.8 ± 1.4 | 41.2 ± 1.8 |
| Reported caloric intake (kcal/d) | 1,859 ± 98 | 1,936 ± 64 |
| Caloric intake (%RDA) | 78 ± 4 | 83 ± 3 |
| $HgbA_{1c}$ (%) | 5.1 ± 0.1 | 5.2 ± 0.1 |

NOTE. Data are mean ± SE. There are no significant differences in age, weight, BMI, or reported caloric intake between the 2 groups.
Abbreviation: RDA, recommended daily allowance.

Medical, North Bend, WA). All female subjects were advised to use contraception during the trial, if they were sexually active. Subjects and their guardians provided informed consent according to the guidelines approved by the University of Tennessee Institutional Review Board. Table 1 summarizes the clinical characteristics of the 2 groups of subjects participating in the study.

Before beginning the study, all participants were placed on a hypocaloric diet and the placebo medication for a 1-week lead-in period to exclude individuals unlikely to be compliant with the study and ensure a stable body weight before randomization. Subjects were randomly assigned to 2 double-blind treatment groups: 12 subjects received metformin for 8 weeks and 12 subjects received a placebo (Table 1). All study subjects were initially started on metformin 850 mg or placebo once daily. After 1 week, metformin 850 mg or placebo dose was increased to twice daily for the remainder of the study. Subjects were seen weekly to assess their weight, blood pressure, and any side effects or concurrent illnesses. Unused tablets were counted when the patients were given a refill of the drug. The compliance rates for the metformin- and placebo-treated groups were comparable (81% ± 2% *v* 85% ± 3%).

### *Nutritional Assessment*

Each study subject underwent a comprehensive nutritional evaluation by a registered dietitian. All subjects were instructed to keep a 3-day food record prior to the start of the study. The dietary recalls were analyzed using a standard computer software program (Nutritionist IV, N-Squared Computing, Salem, OR). The assessment included a review of the food record for clarification of content as well as the individual's eating and exercise habits. Each subject was instructed to follow a calorie-controlled meal plan with caloric restrictions of 1,500 and 1,800 calories for females and males, respectively. Meal plans were based on the 1995 Exchange Lists for Meal Planning booklet by The American Diabetes Association and The American Dietetic Association.[23] Subjects were given 5 days of sample menus that included 3 meals and 1 snack. Food models were used to increase comprehension of portion control, and information regarding nutrient content of fast food and label reading was provided to each individual. Subjects were instructed to complete 24-hour food records for each of the nine weeks of the study. These records were collected at each weekly weight check.

### *Methods*

Initial laboratory studies consisted of routine chemistry profile, serum thyrotropin, glycosylated hemoglobin ($HgbA_{1c}$), and urinalysis. Before commencing, and after completion of the study, the following laboratory tests were obtained: fasting plasma glucose, insulin, leptin, cholesterol, triglycerides, and free fatty acids (FFA). Glucose was determined in plasma, by the glucose oxidase method (Sigma Chemical, St Louis, MO). Insulin concentration was analyzed by radioimmunoassay (RIA) using a double-antibody kit (ICN Pharmaceuticals, Costa Mesa, CA). Leptin concentration was analyzed by RIA using a double-antibody kit (LINCO Research, St Louis, MO). Cholesterol and triglyceride concentrations were measured by an enzymatic method (Sigma Diagnostics, St. Louis, MO), and plasma FFA was determined by an enzymatic colorimetric method (Wako Chemicals, Richmond, VA).

Glucose-stimulated insulin response and insulin sensitivity were determined both before and after completing the study by an oral glucose tolerance test (OGTT). After an ovenight fast, an oral glucose bolus of 75 g was administered. Blood for determination of glucose and insulin was obtained at -10, 0, 30, 60, 90, and 120 minutes. The integrated area under the curve (AUC) analysis for glucose and insulin was determined according to the formula of Tai.[24] Fasting glucose: insulin, 2-hour glucose:insulin ratio, areas under the curve (AUC) for glucose and insulin and their ratio (AUC glucose:AUC insulin) were utilized for assessment of insulin sensitivity.[25]

Body composition was measured by bioelectrical impedance analysis (BIA) using the Valhalla 1990B bioresistance body composition analyzer (San Diego, CA) before and at the completion of the study. The body composition was determined within an hour after lunch in all subject. The resistance index (RI = height$^2$/resistance) and weight were used ($0.61 \times RI + 0.25 \times weight + 1.31$) for estimation of fat-free mass and body fat as previously cross-validated by deuterium dilution in children ages 10 to 19 years.[26] Body water was calculated utilizing a deuterium dilution validated equation (body water= $0.35 \times RI + 0.27 \times age + 0.14 \times weight - 0.12$) for obese children and adolescents.[27]

### *Statistical Analysis*

The reported values represent the mean ± SE. The change in measurements (ie, weight, lipids, glucose:insulin ratio, body fat, and fat-free mass) from the lead-in period to the end of the study for the metformin group were compared with those of the placebo group, using a unpaired Student's *t* test. $P < .05$ was considered significant.

## RESULTS

The clinical characteristics of the two groups are summarized in Table 1. There were no significant differences in age, weight, BMI, or reported caloric intake between the 2 groups. Similarly, there were no significant differences in baseline fat-free mass, body fat, body water, and fat-free mass:body fat ratio between the 2 groups.

No significant changes in body weight were observed during the initial lead-in period. After 8 weeks, some weight loss was observed in both placebo group and the metformin group. However, the weight loss was greater in the metformin group (-6.1 ± 0.8 kg) than in the placebo group (-3.2 ± 2.0 kg, $P < .01$). The percent weight loss difference between metformin and placebo groups reached statistical significance from the 4th week to the completion of the study (6.5 ± 0.8 *v* 3.8 ± 0.4, $P < .01$) (Fig 1). The weight loss was associated with greater loss in body fat in the metformin group than in the placebo group (-6.0 ± 0.62 kg *v* –2.7 ± 0.51 kg, $P < .001$), whereas fat-free mass loss was similar in both groups (-1.6 ± 0.6 *v* -1.8 ± 0.32 kg; not significant), resulting in a greater increase in the fat-free mass:body fat ratio in the metformin group than in the placebo group ($P < .005$). There was no significant difference in body water change between the groups (Table 2).

Table 3 documents fasting plasma concentrations of glucose,

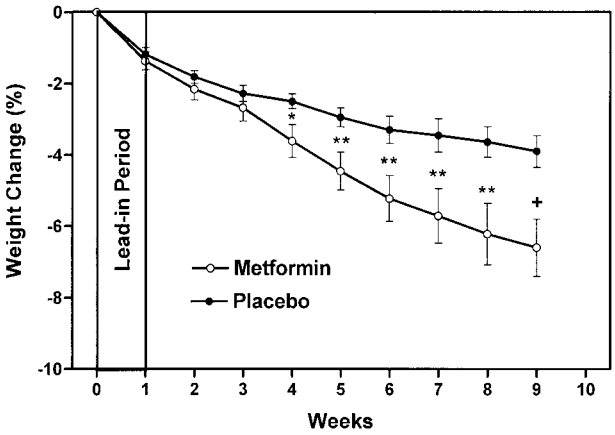


**Fig 1. Percent body weight difference (mean ± SE) between metformin and placebo groups (n = 12 for each group). *$P < .05$, **$P < .025$, †$P < .01$.**

insulin, leptin, cholesterol, triglycerides, and FFA at baseline and after 8 weeks therapy. There was no significant differences in glucose, insulin, leptin, and lipids between the 2 groups at the beginning of the study. After treatment, the decrease in fasting insulin ($P < .025$) and leptin concentrations ($P < .005$) were greater in the metformin group than in the placebo group, without a significant change in fasting glucose. This was accompanied by a significant reduction in plasma cholesterol, triglycerides, and FFA only in the metformin group ($P < .05$)

The AUCs for glucose and insulin, as measured by the response to OGTT, were similar in both groups before treatment. Metformin treatment resulted in a marked decrease in the AUC for insulin as compared with control subjects ($P < .001$), without a signficant change in AUCs for glucose in either group. However, this was associated with a significant increase in the AUC glucose:AUC insulin ratio and the 2-hour glucose: insulin ratio ($P < .01$) following metformin treatment without a significant change in the placebo group.

### *Adverse Effects*

Metformin administration caused minimal side effects in five of 12 subjects. These patients complained of mild nausea during the first week of treatment that resolved. No patient discontinued the study because of these effects. Two patients complained of dizziness, which resolved with eating. Two patients experienced loose stools for 2 days that resolved without modification of the dose.

## DISCUSSION

The present study demonstrated that metformin treatment leads to significant weight loss and decrease in body fat in hyperinsulinemic obese adolescents. Metformin treatment also resulted in enhanced insulin sensitivity and decreased hyperinsulinism with significant reduction in plasma leptin and lipid profiles. These findings were consistent with previous observations in obese adults in whom metformin therapy resulted in improved insulin sensitivity and weight loss.[17]

It is believed that hyperinsulinemia and insulin resistance might contribute to the development and maintenance of obesity by preferential shunting of substrates toward the adipose tissue leading to adipose hypertrophy and the conversion of preadipocytes to adipocytes.[28] These changes lead to a persistent lipogenic state. In our study, enhancement of insulin sensitivity by metformin led to reduction in hyperinsulinemia. Attenuation of hyperinsulinemia was accompanied by a significant amount of weight loss among metformin-treated subjects compared to controls. These findings are consistent with our previous observations that attenuation of hyperinsulinemia by diazoxide, an inhibitor of insulin secretion, in obese adults on a hypocaloric diet resulted in significant weight loss.[29] Since metformin-treated patients demonstrated a significant reduction in body fat, it is likely that attenuation of hyperinsulinemia by metformin exerted its antiobesity effect by reducing insulin-stimulated lipogenesis.

Previous studies have demonstrated that metformin treatment reduces food intake in both humans and experimental animals.[30,31] In our study, we controlled the level of caloric intake by maintaining both treatment groups on a hypocaloric diet. While the use of dietary recalls may be of limited value in obese patients who usually underreport their caloric intake,[32] the observed significant difference in weight loss between the 2 groups strongly suggests that metformin exerts its antiobesity effect independent of its anorectic effect. Recently, Oleandri et al demonstrated that 3-month trial of metformin treatment, in a

**Table 2. Change in Clinical Parameters in Placebo and Metformin Groups**

| | Placebo | | | Metformin | | |
|---|---|---|---|---|---|---|
| Parameter | Pre | Post | Pre-Post | Pre | Post | Pre-Post |
| Weight (kg) | | | | | | |
| Lead-in week | 113.4 ± 5.0 | 112.1 ± 5.0 | −1.3 ± 0.20 | 116.0 ± 5.1 | 114.5 ± 5.1 | −1.5 ± 0.31 |
| Metformin *v* placebo | 112.1 ± 5.0 | 108.9 ± 4.9 | −3.2 ± 0.50 | 114.5 ± 5.1 | 108.4 ± 5.0 | −6.1 ± 0.72* |
| Fat-free mass (kg) | 62.4 ± 2.7 | 60.6 ± 2.6 | −1.8 ± 0.32 | 65.8 ± 3.1 | 64.2 ± 3.0 | −1.6 ± 0.56 |
| Body fat (kg) | 50.7 ± 3.8 | 48.0 ± 3.6 | −2.7 ± 0.51 | 50.1 ± 3.7 | 44.1 ± 3.4 | −6.0 ± 0.60‡ |
| Body water (%) | 35.2 ± 1.6 | 35.5 ± 1.5 | 0.30 ± 0.22 | 36.3 ± 1.0 | 36.5 ± 0.90 | 0.20 ± 0.30 |
| Fat-free mass:body fat ratio | 1.32 ± 0.13 | 1.35 ± 0.12 | 0.03 ± 0.02 | 1.39 ± 0.31 | 1.55 ± 0.15 | 0.16 ± 0.03† |

NOTE. Data are the mean ± SE and were analyzed by unpaired Student's *t* test.

Abbreviations: Pre, pretreatment; Post, post-treatment.

* Significantly different from pre-post placebo group, $P < .01$.

† Significantly different from pre-post placebo group, $P < .005$.

‡ Significantly different from pre-post placebo group, $P < .001$.

**Table 3. Change in Biochemical Parameters in Placebo and Metformin Groups**

| Parameters | Placebo | | | Metformin | | |
|---|---|---|---|---|---|---|
| | Pre | Post | Pre-Post | Pre | Post | Pre-Post |
| Fasting | | | | | | |
| Glucose (mg/dL) | 79 ± 4 | 77 ± 3 | −2.0 ± 2.0 | 75 ± 3 | 73 ± 3 | −2.0 ± 2.0 |
| Insulin ($\mu$U/mL) | 37 ± 6 | 26 ± 3 | 11 ± 5 | 43 ± 7 | 22 ± 3† | −21 ± 6* |
| Glucose:insulin ratio (mg/$10^{-4}$ U) | 2.6 ± 0.30 | 3.5 ± 0.50 | 0.9 ± 0.40 | 2.4 ± 0.40 | 4.4 ± 0.50§ | 2.0 ± 0.40 |
| Leptin (ng/mL) | 51 ± 7 | 40 ± 6 | −11 ± 3.0 | 44 ± 10 | 29 ± 4§ | −16 ± 2 |
| Cholesterol (mg/dL) | 175 ± 12 | 171 ± 15 | −4 ± 7 | 179 ± 24 | 157 ± 6* | −22 ± 5* |
| Triglycerides (mg/dL) | 177 ± 24 | 164 ± 28 | −13 ± 9 | 156 ± 16 | 117 ± 10* | −39 ± 9* |
| FFA (mmol/L) | 0.83 ± 0.07 | 0.76 ± 0.05 | −0.07 ± 0.06 | 0.86 ± 0.05 | 0.69 ± 0.03* | −0.17 ± 0.03 |
| OGTT | | | | | | |
| AUC glucose | 16,328 ± 750 | 15,420 ± 610 | −908 ± 340 | 15,061 ± 844 | 13,956 ± 543 | −1,107 ± 563 |
| AUC insulin | 21,390 ± 2,022 | 17,171 ± 1,577 | −4,219 ± 1,967 | 21,973 ± 2,778 | 10,436 ± 1,077¶ | −11,537 ± 2,323† |
| AUC glucose:AUC insulin ratio (mg/$10^{-4}$ U) | 0.83 ± 0.07 | 0.99 ± 0.07 | 0.16 ± 0.09 | 0.76 ± 0.06 | 1.41 ± 0.14‡ | 0.65 ± 0.14‡ |
| 2-hour glucose:insulin ratio (mg/$10^{-4}$ U) | 0.85 ± 0.10 | 1.0 ± 0.06 | 0.15 ± 0.10 | 0.77 ± 0.11 | 1.41 ± 0.13‡ | 0.64 ± 0.14‡ |

NOTE. Data are mean ± SE and were analyzed by unpaired Student's *t* test.

* Significantly different from pretreatment or placebo group, $P < .05$.

† Significantly different from pretreatment or placebo group, $P < .025$.

‡ Significantly different from pretreatment or placebo group, $P < .01$.

§ Significantly different from pretreatment or placebo group, $P < .005$.

¶ Significantly different from pretreatment or placebo group, $P < .001$.

group of obese adults on hypocaloric diet, caused similar reduction in weight and BMI compared to placebo and dexfenfluramine treatment groups.[33] However, these investigators used a lower dose of metformin (500 mg twice daily) and did not achieve a significant attenuation of hyperinsulinemia in their patients. Consistent with our findings, Pasquali et al recently reported a significant antiobesity effect of long-term metformin treatment in abdominally obese women with or without polycystic ovary syndrome who were maintained on a hypocaloric diet.[34]

Other studies have proposed that weight loss associated with metformin treatment involves a loss of both fat-free mass and body fat,[35,36] while one study suggested that there was a preferential loss of adipose tissue.[30] In our study, we observed a significant loss of body fat in the metformin group compared with the placebo group without a significant difference in fat-free mass loss in either group. This was associated with a significant increase in the fat-fee mass:body fat ratio without a significant change in body water in either group. While the BIA helps assess short-term changes in total body water within individuals with high level of precision,[37] it should be pointed out that BIA may have methodological limitations in estimating body fat and fat-free mass with highest degree of accuracy in individuals or groups of children during periods of changing fluid states. Thus, the estimated body composition data should be interpreted cautiously.

In our study, there was a significant increase in insulin sensitivity in metformin-treated subjects without a significant change in glycemia and lipid profile in the metformin group. While the precise mechanism of action of metformin remains unknown, it is believed to increase insulin sensitivity and glucose uptake in individuals with type 2 diabetes mellitus (DM).[16] It has been suggested that metformin primarily exerts its antihyperglycemic effect by decreasing hepatic glucose output through inhibition of gluconeogenesis.[30] Recently, Abbasi et al demonstrated that the insulin-sensitizing effects of metformin treatment of adults with type 2 DM was accompanied by decreased tissue FFA release and increased glucose uptake implying that metformin increases the antilipolytic effect of insulin and may enhance lipogenesis in subjects with type 2 DM.[16] However, in our study, metformin treatment caused significant loss of body fat with a significant reduction in fasting plasma concentrations of cholesterol, triglycerides, and FFA.

A positive correlation between circulating leptin (product of *ob* gene) concentrations and body fat has been demonstrated in children and adolescents.[38] Also, it has been shown that plasma leptin levels tend to parallel plasma insulin levels.[39] Metformin treatment resulted in a significant suppression of circulating leptin, presumably as a result of decreased adiposity. Since *ob* gene expression has previously been shown to be increased by insulin,[40] it is also likely that significant reduction in circulating leptin levels in metformin-treated obese subjects is a consequence of decreased *ob* gene transcription after decreased insulinemia and decreased adiposity.

This preliminary study demonstrates that metformin-induced attenuation of hyperinsulinemia in obese adolescents results in a significant decrease in body fat and plasma lipid levels, presumably caused by a decrease in antilipolytic action of insulin. This antiobesity effect of metformin may be therapeutically beneficial in the management of obese hyperinsulinemic patients. However, larger and long-term studies may be needed to evaluate metabolic and anti-obesity effects of metformin in hyperinsulinemic obese adolescents.

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