Effects of Metformin on Body Weight and Body Composition in Obese Insulin-Resistant Children

A Randomized Clinical Trial

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OBJECTIVE—Metformin can decrease adiposity and ameliorate obesity-related comorbid conditions, including abnormalities in glucose homeostasis in adolescents, but there are few data evaluating the efficacy of metformin among younger children. Our objective was to determine whether metformin treatment causes weight loss and improves obesity-related comorbidities in obese children, who are insulin-resistant.

RESEARCH DESIGN AND METHODS—This study was a randomized double-blind placebo-controlled trial consisting of 100 severely obese (mean BMI 34.6 ± 6.6 kg/m^2) insulin-resistant children aged 6–12 years, randomized to 1,000 mg metformin (n = 53) or placebo (n = 47) twice daily for 6 months, followed by open-label metformin treatment for 6 months. All children and their parents participated in a monthly dietitian-administered weight-reduction program.

RESULTS—Eighty-five percent completed the 6-month randomized phase. Children prescribed metformin had significantly greater decreases in BMI (difference −1.09 kg/m^2, CI −1.87 to −0.31, P = 0.006), body weight (difference −3.38 kg, CI −5.2 to −1.57, $P < 0.001$), BMI Z score (difference between metformin and placebo groups −0.07, CI −0.12 to −0.01, P = 0.02), and fat mass (difference −1.40 kg, CI −2.74 to −0.06, P = 0.04). Fasting plasma glucose (P = 0.007) and homeostasis model assessment (HOMA) insulin resistance index (P = 0.006) also improved more in metformin-treated children than in placebo-treated children. Gastrointestinal symptoms were significantly more prevalent in metformin-treated children, which limited maximal tolerated dosage in 17%. During the 6-month open-label phase, children treated previously with placebo decreased their BMI Z score; those treated continuously with metformin did not significantly change BMI Z score further.

CONCLUSIONS—Metformin had modest but favorable effects on body weight, body composition, and glucose homeostasis in obese insulin-resistant children participating in a low-intensity weight-reduction program. ***Diabetes*** **60:477–485, 2011**

The prevalence of pediatric obesity has increased substantially since the 1970s; 19.6% of children 6–11 years of age are now considered obese (BMI ≥95th percentile standard for age and sex) (1). Excess body fat in children is associated with insulin resistance and dysglycemia (2) and predicts development of the metabolic syndrome in adulthood (3). Insulin resistance is of particular concern because it is independently associated with metabolic abnormalities during childhood (2,4) and development of type 2 diabetes (5–7).

Intensive behavioral treatments, which may reduce adiposity among children with moderately increased body weight (8), have limited efficacy among individuals most severely affected (9–12), leading to interest in developing other effective approaches. There have been few controlled pediatric trials of antiobesity agents. There are currently no medications that are approved by the U.S. Food and Drug Administration (FDA) to treat obesity in children <12 years of age.

Metformin recently received attention for its potential to assist in pediatric weight control efforts (13). Metformin is FDA-approved for treatment of type 2 diabetes in children age ≥10 years; it suppresses hepatic glucose production (14) and, at high concentrations, improves peripheral insulin sensitivity (15). Metformin induces weight stabilization or small weight losses in diabetic (16–19) and nondiabetic (20–23) adults. Case series involving obese children (24–26) and relatively small randomized trials in obese adolescents (27–33), including one 48-week multicenter trial (33), also suggest that metformin may induce small BMI/weight reductions, averaging ~1.4 kg/m^2 (3 kg) over 6 months (34,35) and 1.1 kg/m^2 over 1 year (33). Small trials also suggest that metformin has a positive impact on insulin resistance and hyperandrogenism in patients with polycystic ovary syndrome (36,37) or precocious pubarche (38,39). However, no randomized controlled trials have evaluated the effect of metformin on body weight and body composition in severely obese children age 6–12 years. Studies involving this age-group are important because some research suggests that obesity may be more tractable when treated during childhood (40).

We studied the effects of metformin in obese children aged 6–12 years who were believed to be at particular risk because they manifested a significant degree of insulin resistance. We hypothesized that, in the context of a weight-reduction program, metformin would decrease

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children's body weight, BMI, and fat mass; improve insulin sensitivity; and ameliorate aspects of the metabolic syndrome.

RESEARCH DESIGN AND METHODS

Study sample. Obese children, aged 6–12 years, recruited through newspaper advertisements and letters to physicians, were eligible if they had BMI ≥95th percentile according to the Centers for Disease Control and Prevention 2000 growth charts for the United States; were prepubertal or early pubertal (defined as breast Tanner stage I–III for girls; testes <8 mL for boys); and had fasting hyperinsulinemia, defined as fasting insulin ≥15 μU/mL, the 99th percentile for fasting insulin among 224 nonobese 6- to 12-year-old children studied as outpatients at the National Institutes of Health (NIH) with the same insulin assay (unpublished data). This cut point is also consistent with some prior adult data (41). Children were excluded if they had impaired fasting glucose, were diabetic, or reported a diagnosed renal, cardiac, endocrine, pulmonary, or hepatic disease that might alter body weight. Subjects were excluded for baseline creatinine >1 mg/dL and for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) that exceeded 1.5 times the upper limit of the laboratory normal range. The study was approved by the Institutional Review Boards of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIH, and the Phoenix Area Indian Health Service. Written assent and consent were obtained from children and their parents. The study was overseen by a Data and Safety Monitoring Board convened by NICHD.

Design overview. We conducted a single-center trial from September 2000 to August 2008. After an outpatient screening visit, participants were admitted as inpatients to the NIH Clinical Research Center (CRC) for assessment and then entered a 6-month randomized placebo-controlled double-blind treatment period and were then readmitted for reassessment. Participants who completed the randomized phase were offered an additional 6 months of open-label metformin.

Randomization and interventions. We randomly assigned participants in a 1:1 randomization ratio to receive metformin hydrochloride or placebo, twice daily with meals. Investigators assigned consecutive code numbers to participants from prespecified lists stratified by race/ethnicity, sex, and degree of pubertal development. The CRC Pharmaceutical Development Section used permuted blocks with stratification to generate allocations that translated code numbers into study group assignments by using a pseudo-random number program and prepared identically appearing placebo and metformin (U.S.P. Grade; SST Corporation, Clifton, NJ) capsules (250 mg/capsule). Pharmacy personnel not involved with the conduct of the study dispensed study capsules in containers that differed only by participant code number. No participant, investigator, or other medical or nursing staff interacting with participants was aware of study group assignments during the trial.

Once baseline assessments were completed, subject's study medication dose was progressively increased according to a prespecified algorithm over a 3-week period, starting with 500 mg twice daily and increasing to a maximum dose of 1,000 mg twice daily. The typical adult maximum dose was selected as the goal because the weight of the severely obese participants to be enrolled (Table 1) was anticipated to be similar to that of adults. We decreased the dose by 250 mg/dose for 1 week when participants reported difficulty tolerating study medication and then attempted to increase it. Study medication dose was progressively lowered by 250 mg/day if a prescribed dosage could not be tolerated after a 7-day trial. Once a tolerated dose was found, attempts were made to increase the dosage prescribed. Study medication was discontinued if 250 mg/day was not tolerated. A daily chewable multivitamin (Flintstones Complete) containing 6 μg cyanocobalamin was also prescribed. After conclusion of the randomized phase, participants were prescribed increasing doses of commercially available metformin in two divided doses with a maximum dose of 2,000 mg/day plus a daily multivitamin for an additional 6 months.

During both study phases, each participant and a parent/guardian met monthly with a dietitian who administered a weight-reduction lifestyle modification program that promoted a reduced-energy diet, increased physical activity, and decreased inactivity. Participants were trained to complete a baseline 7-day food diary that was reviewed by a registered dietitian. These data were used to offer individualized prescriptions for a "traffic light" style (42) 500 kcal/day–deficit diet that reduced fat and energy intake. The exercise prescription consisted of encouraging 30 min of aerobic exercise every day and inclusion of lifestyle exercise whenever possible and was monitored by pedometer readings recorded by parents. Adherence was gauged through self-monitoring of medication taken, food eaten, activity performed, amount of inactive time, and pedometer readings recorded in a progress book that was reviewed monthly.

Initial assessment. Subjects who met inclusion criteria were admitted as inpatients to the CRC for the following measurements: weight in a hospital gown using a calibrated digital scale (Life Measurement Instruments, Concord, CA); height in triplicate using a stadiometer (Holtain, Crymych, U.K.) calibrated before each measurement; abdominal and hip circumferences (assessed in triplicate) and triceps skinfold thickness (Lange calipers; Cambridge Scientific Industries, Cambridge, MD) by trained research dietitians (C.G.S. and N.G.S.); blood pressure using an automated sphygmomanometer (Dinamap-Plus; Critikon, Tampa, FL) measured in the seated position after at least 5 min rest; a hand roentgenogram for determination of skeletal age; whole-body fat mass by dual-energy X-ray absorptiometry (DEXA) (4500A; Hologic, Bedford, MA; software version 11.2) and by air displacement plethysmography; and intra-abdominal and subcutaneous abdominal adipose tissue by magnetic resonance imaging at L2–L3 and L4–L5 (T1-weighted spin-echo images, 0.5 T, relaxation time 400 ms, time of excitation 10 ms, number of repetitions of excitations 10). A 2-h hyperglycemic (200 mg/dL) clamp was also performed at baseline and follow-up admissions to estimate insulin sensitivity and first-phase insulin secretion as previously described (43). First-phase insulin was calculated as the mean of measurements obtained during the first 15 min. Whole-body glucose uptake (metabolic rate: M) was defined as the infusion rate of exogenous glucose administered, corrected for urinary glucose losses and the glucose space correction. As a measure of insulin sensitivity (SI_{clamp}) the ratio of metabolic rate to steady-state insulin (M/I) was calculated.

At baseline and follow-up, samples obtained in the fasted state were collected for measurement of ALT, AST, total and HDL cholesterol, direct LDL cholesterol, and triglycerides (Synchron LX20; Beckman Coulter, Fullerton, CA). Plasma for glucose was collected in tubes containing powdered sodium fluoride and measured by the NIH CRC clinical laboratory using a Roche Diagnostics (Indianapolis, IN) analyzer. C-reactive protein was measured by a high-sensitivity assay (IMMAGE Immunochemistry Systems; Beckman Coulter) with sensitivity of 0.020 mg/dL. Vitamin B_{12} and insulin were measured by chemiluminescent immunoassays using Siemens Healthcare Diagnostics (Los Angeles, CA) Immulite instruments. Fasting samples were used to estimate insulin resistance by the homeostasis model assessment–insulin resistance (HOMA-IR) index = insulin (μU/mL) × [glucose (mmol/L)/22.5]. Diagnosis of pediatric metabolic syndrome was made when three or more components were present from among the following: waist circumference, blood pressure, and triglycerides ≥90th percentile for age and sex; HDL cholesterol ≤10th percentile for age and sex; and fasting glucose ≥100 mg/dL (44).

Subjects and parents were also interviewed by a clinical pharmacist who used a structured questionnaire containing a comprehensive list of symptoms designed to identify potential adverse drug reactions (45).

Outcomes and follow-up measures. The prespecified primary study end point was change in BMI SD score (BMI *Z*), as determined at the end of the 6-month randomized treatment phase. Secondary outcomes were changes in BMI, body weight, and fat mass at the conclusion of the randomized phase. Tertiary outcomes included changes in skinfold thickness, body circumferences, visceral adipose tissue, insulin resistance, and laboratory components of the metabolic syndrome.

Participants were seen monthly and exchanged their unused study medication for a new supply at each visit. We used the tally of returned capsules to assess adherence. Measurements of BMI, blood pressure, liver function, plasma lactate, and serum vitamin B_{12} were obtained at each visit, along with an interim history obtained using a structured list of queries. After 6 months of treatment, subjects were re-evaluated and then offered open-label metformin for a second 6-month treatment period with continued monthly visits.

Statistical analysis. Power was based on prior data we collected examining BMI change over 6 months in obese 6- to 11-year-old children with hyperinsulinemia. We calculated that among severely obese children, a total sample size of 60 participants would detect a between-group difference of 0.09 BMI SD score units (approximately equivalent to a 2 kg/m^2 difference) with 80% power. Participant accrual was set at 100 participants to allow as much as 40% loss to follow-up (46). The reported primary data analyses were prespecified and analyzed using SPSS for Windows, version 14.0 (SPSS, Chicago, IL). Interim analyses for efficacy were performed by the Data Safety Monitoring Board when 40 and 70 subjects had been enrolled for 6 months of randomized phase treatment. Using the Lan-DeMets implementation of the O'Brien-Fleming method, the critical two-tailed α values were defined for each look, such that a *P* value of 0.04515 was considered significant at the end of the study. We assessed efficacy in the intention-to-treat sample of all randomly assigned participants using a multiple imputation model for missing data under a missing-at-random assumption. By using NORM, version 2.03 (Pennsylvania State University, State University Park, PA), we included all available baseline and follow-up measures in an imputation model. The imputation datasets were obtained using a sequential chain of 1,200 iterations using initial parameter estimates supplied by running the expectation-maximization (EM) algorithm. Starting after the first 200 iterations, data were sampled with 50 iterations between successive imputations. Each of the imputation-completed datasets was then analyzed separately using the prespecified ANCOVA model with SPSS for Windows, version 14.0. BMI *Z* change (or change in each secondary

TABLE 1
Baseline participant characteristics

	Metformin	Placebo
N	53	47
Age (years)	10.1 ± 1.6	10.4 ± 1.4
Female sex (%)	57	64
Race/ethnicity (%)		
Non-Hispanic white	42	49
Non-Hispanic black	42	38
Hispanic white	11	11
Other (Native American, Asian, or Pacific Islander)	5	2
Family history of type 2 diabetes (%)	81	72
Parent with type 2 diabetes (%)	34	28
Pubertal status		
Percentage prepubertal (%)	35.8	34.0
Boys' testis volume (cc)	3.9 ± 1.9	4.2 ± 1.5
Girls' breast stage [median (range)]	II (I–III)	II (I–III)
Skeletal age (years)*	11.6 ± 1.9	11.9 ± 1.4
Weight (kg)	76.4 ± 23.1	80.1 ± 20.5
BMI (kg/m^2)	34.2 ± 6.8	34.6 ± 6.2
BMI range (kg/m^2)	23.0–55.0	24.7–57.5
BMI SD score for age and sex	2.56 ± 0.27	2.58 ± 0.24
Fat mass by DEXA (kg)‡	33.9 ± 11.8	35.2 ± 10.0
Fat mass by air displacement plethysmography (kg)	39.0 ± 16.9	39.1 ± 14.2
Waist circumference (cm)	105.4 ± 15.1	106.1 ± 14.2
Presence of acanthosis nigricans (%)	64	68
Systolic blood pressure (mmHg)	115.5 ± 15.1	116.8 ± 1.5
SD score for age, sex, and height	0.76 ± 2.03	1.02 ± 1.28
Diastolic blood pressure (mmHg)	65.6 ± 9.8	64.3 ± 10.2
SD score for age, sex, and height	0.17 ± 1.17	0.13 ± 0.92
Fasting plasma glucose (mg/dL)	92 ± 8	92 ± 8
Fasting serum insulin (mIU/mL)	19.8 ± 8.9	21.7 ± 13.5
HOMA-IR index†	4.5 ± 2.2	4.9 ± 3.3
Insulin sensitivity (from hyperglycemic clamp) (mg/kg/min per μIU/mL)	4.9 ± 3.2	4.4 ± 2.4
Serum triglycerides (mg/dL)	97.2 ± 44.6	93.5 ± 42.8
Total cholesterol (mg/dL)	162.8 ± 30.1	151.1 ± 34.9
LDL/HDL cholesterol ratio	2.92 ± 0.96	2.78 ± 0.75
HDL cholesterol (mg/dL)	40.2 ± 9.0	40.2 ± 7.8
LDL/HDL cholesterol ratio	2.92 ± 0.96	2.78 ± 0.75
Diagnosis of pediatric metabolic syndrome (%)§	26.4	31.9
AST (U/L)	23.8 ± 8.3	26.0 ± 12.5
ALT (U/L)	24.8 ± 5.5	24.7 ± 6.3
High-sensitivity C-reactive protein (mg/dL)	0.56 ± 0.43	0.74 ± 1.03
Serum vitamin B_{12} (pg/mL)	683 ± 270	694 ± 265

Data are means ± SD unless otherwise indicated. At baseline, there were no significant differences between treatment groups (all $P > 0.32$). Race and ethnicity were self-reported. *Skeletal age according to Greulich and Pyle method. †HOMA-estimated insulin resistance. ‡Two subjects, one from each group, weighed >136 kg and could not be scanned using DEXA. §Diagnosis of pediatric metabolic syndrome was made when three or more components were present from among the following: waist circumference, blood pressure, and triglycerides ≥90th percentile for age and sex, HDL cholesterol ≤10th percentile for age and sex, and fasting glucose ≥100 mg/dL (44).

outcome variable) was the dependent variable; metformin treatment was the independent variable; and age, sex, and race/ethnicity were covariates. We then combined the coefficients from analyses of the 20 imputed datasets into a single set of estimates according to Rubin's rules for scalar estimands. To assess sensitivity of the results to the missing-at-random assumption, we conducted three additional analyses: assuming that all participants who withdrew from the study had major weight gain (≥2.27 kg [≥5 lb]); that those who received metformin had no weight gain, whereas those who received placebo had major weight gain; and that those who received placebo had no weight gain, whereas those who received metformin had major weight gain. We used multiple imputations to impute the missing 6-month weight measurements by using the same imputation model used for the main analysis. For the three scenarios, we added fixed amounts to the imputed values, reanalyzed the results by using ANCOVA, and combined them by using the Rubin rules for scalar estimands. An additional confirmatory analysis used the last-observation-carried-forward method for individuals who did not complete the study. Unadjusted analyses were also run both for the imputation and the last-observation-carried-forward models. Because all of these models yielded similar results, only the primary efficacy model is presented. We examined baseline characteristics by simple *t* tests or, in the case of categorical data, with exact tests. Reports of adverse events were also examined by exact tests.

Funding and role of the sponsor. The intramural research programs of NICHD and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, and the National Center on Minority Health and Health Disparities (NCMHD), NIH, which funded the study, had no role in study design, data accrual, data analysis, or manuscript preparation. The authors designed the study, wrote and made the decision to submit the manuscript for publication, and affirmed the completeness, accuracy, and integrity of the data and data analyses. Monitoring of the study, measurement and adjudication of study end points, and statistical analyses were performed by the authors without sponsor involvement. The manuscript was drafted by the principal investigator and revised by the coauthors.

RESULTS

A total of 100 children were randomly assigned to the two study groups (Fig. 1). There were no significant

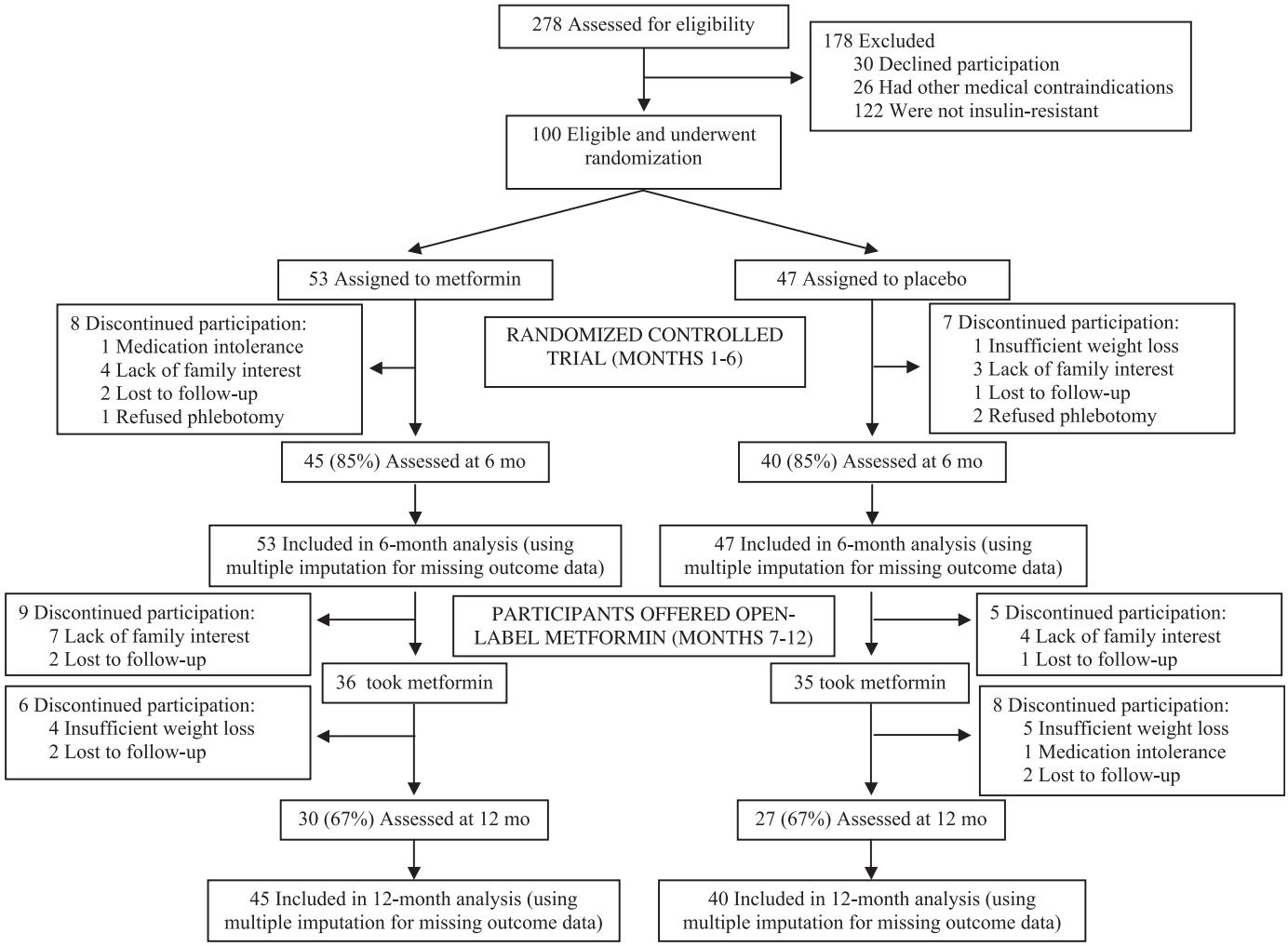

FIG. 1. Flow of participants throughout the trial.

demographic differences between subjects who participated and subjects who declined. Participants had evidence of significant insulin resistance; a family history of type 2 diabetes was also frequently reported (Table 1). When separated into prepubertal subjects and subjects who had evidence for pubertal onset (i.e., in boys, testes >3 mL; in girls Tanner II or greater breast stage), there were no significant differences between groups in demographic, historical, or laboratory data (all $P > 0.46$), including degree of insulin resistance (HOMA-IR metformin prepubertal: 4.3 ± 2.0, pubertal: 4.6 ± 2.3; placebo prepubertal: 4.5 ± 4.1, pubertal: 5.0 ± 2.9).

Of the participants, 85% completed the 6-month randomized trial (85% metformin; 85% placebo, $P = 0.98$). Among the 85 offered open-label metformin, 67% completed the second 6-month study phase (Fig. 1). Sociodemographic and baseline anthropometric or laboratory indexes did not significantly differ between participants who did and did not complete either phase of the study (all $P > 0.65$).

Changes in body weight and body composition. During the placebo-controlled randomized phase (Table 2 and Fig. 2), both metformin-treated and placebo-treated children significantly reduced BMI *Z* (P values <0.01); however, children given metformin had significantly greater decreases in BMI *Z* (difference between metformin and placebo groups −0.07, 95th CI −0.12 to −0.01, $P = 0.02$), BMI (difference −1.09 kg/m^2, CI −1.87 to −0.31, $P = 0.006$), body weight (difference −3.38 kg, CI −5.2 to −1.57, $P < 0.001$), and total-body fat mass ($P < 0.05$). Three metformin-treated versus 0 placebo-treated children lost sufficient weight to reach a BMI <97th percentile after 6 month of treatment ($P = 0.25$). Body circumference and skinfold thickness measurements decreased to a significantly greater extent in the metformin-treated children, although changes in intra-abdominal fat did not differ significantly between groups (Table 2). During the open-label phase, subjects who previously received placebo significantly decreased BMI *Z*; subjects treated continuously with metformin had nonsignificant increases in BMI *Z* (Fig. 2) compared with their 6-month values and increases in absolute BMI consistent with those expected to occur as children mature. Subjects examined at the end of the open-label phase had significantly lower BMI *Z* at the end of the 12-month treatment period when compared with their BMI *Z* values at baseline (−0.091, CI −0.183 to −0.001, $P = 0.05$). Additional analyses that included an interaction term for race × treatment group found non-Hispanic black participants decreased body mass less than non-Hispanic or Hispanic whites during the randomized treatment phase (BMI *Z* −0.035 ± 0.021 vs. −0.108 ± 0.017, difference 0.073, CI 0.020–0.127, $P = 0.008$), but the interaction between race and treatment group was not

TABLE 2
Changes in anthropometric variables at conclusion of the randomized phase

Characteristic	Metformin	Placebo	Difference	*P*
N	53	47		
BMI SD score	−0.11 (−0.16 to −0.05)	−0.04 (−0.1 to 0.02)	−0.07 (−0.12 to −0.01)	0.02
BMI (kg/m^2)	−0.78 (−1.54 to −0.01)	0.32 (−0.54 to 1.18)	−1.09 (−1.87 to −0.31)	0.006
Weight (kg)	1.47 (−0.31 to 3.24)	4.85 (2.84 to 6.85)	−3.38 (−5.2 to −1.57)	<0.001
Fat mass by DEXA (kg)	0.48 (−0.80 to 1.76)	1.88 (0.44 to 3.31)	−1.40 (−2.74 to −0.06)	0.04
Fat mass by air displacement plethysmography (kg)	−1.51 (−4.56 to 1.54)	1.81 (−1.64 to 5.25	−3.32 (−6.49 to −0.14)	0.04
Abdominal circumference (cm)	1.84 (−1 to 4.69)	4.38 (1.23 to 7.53)	−2.54 (−4.57 to −0.5)	0.02
Hip circumference (cm)	−0.44 (−2.76 to 1.87)	1.84 (−0.72 to 4.41)	−2.29 (−3.97 to −0.6)	0.009
Triceps skinfold thickness (mm)	−2.64 (−6.79 to 1.5)	1.65 (−2.94 to 6.24)	−4.29 (−7.28 to −1.3)	0.006
Abdominal adipose tissue (cc)				
L2–3 subcutaneous	7.4 (−25.7 to 40.5)	22.7 (−13.7 to 59.1)	−15.3 (−37.6 to 7.1)	0.18
L4–5 subcutaneous	−21.6 (−55 to 11.7)	1.0 (−35.6 to 37.7)	−22.7 (−45.1 to −0.2)	0.05
L2–3 intra-abdominal	2.5 (−26.1 to 31.0)	8.5 (−23.0 to 40.0)	−5.9 (−25.3 to 13.4)	0.54
L4–5 intra-abdominal	2.1 (−19.7 to 23.8)	4.4 (−19.5 to 28.3)	−2.3 (−17 to 2.4)	0.76
Systolic blood pressure SD score	0.20 (−0.88 to 1.28)	−0.17 (−1.38 to 1.05)	0.37 (−0.54 to 1.28)	0.42
Diastolic blood pressure SD score	−0.02 (−0.67 to 0.62)	−0.19 (−0.91 to 0.54)	0.16 (−0.38 to 0.7)	0.56

Estimated marginal means (95% CIs), adjusted for covariates, were reported from multiple imputation analyses.

significantly different (P = 0.064). When severity of insulin resistance or pubertal status at baseline was included in the statistical model for the primary or secondary body composition outcomes, no significant impact for severity of insulin resistance or puberty on treatment success was identified, even after race was removed from the analysis (all $P \geq 0.20$).

Changes in insulin resistance and metabolic consequences of obesity. Fasting serum insulin (P = 0.02), plasma glucose (P = 0.02), and HOMA-IR index

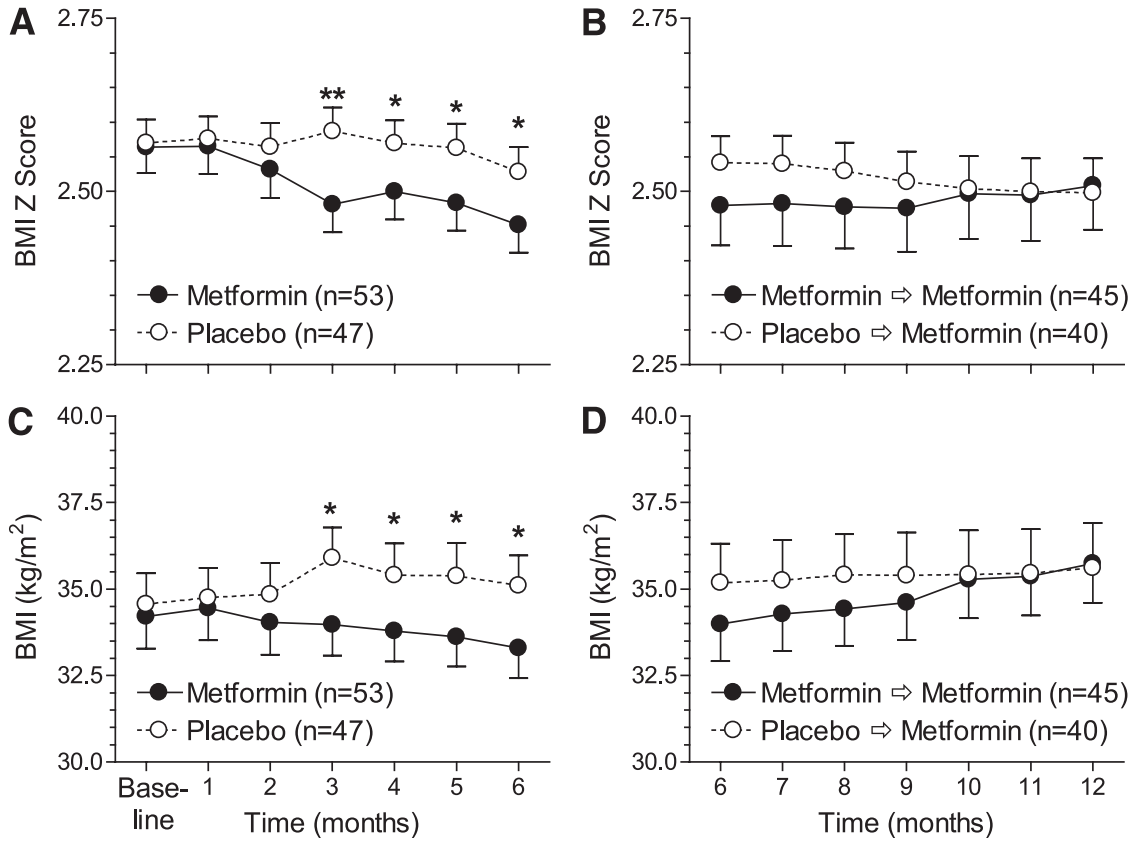

FIG. 2. Changes in BMI during the study. Mean ± SEM for BMI SD score (BMI *Z*) and BMI during the randomized placebo-controlled phase (*A* and *C*) and the open-label phase when all participants were offered metformin (*B* and *D*). *A*: BMI Z score, randomized phase. *B*: BMI Z score, open-label phase. *C*: BMI, randomized phase. *D*: BMI, open-label phase. Intent-to-treat imputed data analyses are shown. There were significant group by time interactions ($P < 0.001$) during each phase for both BMI *Z* and BMI. *$P < 0.05$; **$P < 0.01$ for comparison of children randomized to metformin and placebo at each time point.

(P = 0.006) improved more in metformin-treated than in placebo-treated children (Table 3). However, neither first-phase insulin secretion (P = 0.34) nor insulin sensitivity (P = 0.52) estimated from the hyperglycemic clamp study differed significantly between groups. Changes in other laboratory values commonly observed to improve with significant weight reduction did not differ significantly between the groups (Table 3). The prevalence of metabolic syndrome was not altered significantly by metformin treatment (P = 0.71).

Adverse events and adherence. No serious or life-threatening adverse events were reported. No subject developed abnormal AST or ALT concentrations or acidosis. Serum vitamin B_{12} remained within the normal range (220–960 pg/mL) in all subjects throughout the 12-month study, but decreased in the metformin-treated group, compared with the increase observed in placebo-treated children during the randomized phase (−57 ± 58 vs. 173 ± 67 pg/mL, $P < 0.001$). No metformin-associated difference in hemoglobin concentrations was observed (P = 0.53). Gastrointestinal complaints were significantly more prevalent among subjects treated with metformin. More metformin- than placebo-treated subjects reported at least one episode of liquid or loose stools (41.5%, CI 30.1–55.9% vs. 17%, CI 7.6–30.8%, P = 0.01) and vomiting (41.5%, CI 29.1–55.9% vs. 21.3%, CI 10.7–32.7%, P = 0.05). Fatigue was also significantly more likely to be reported (P = 0.02) among metformin-treated (37.7%, CI 24.8–52.1%) than placebo-treated (14.9%, CI 6.2–28.3%) children. One metformin-treated child lost interest in usual pleasurable activities that resolved with medication discontinuation, but this adverse event did not recur during a rechallenge. Reported metformin-associated symptomatology was most prevalent in the first month of treatment and then decreased such that no reported symptom was significantly different in prevalence between the two groups at the end of the placebo-controlled phase (Fig. 3) or during the open-label phase.

A total of nine metformin-treated children (17.0 vs. 2.1% placebo-treated, P = 0.03) were unable to take the highest dose (2,000 mg/day) and were prescribed doses ranging from 500 to 1,500 mg/day at conclusion of the randomized phase; however, only one subject discontinued the trial because of medication intolerance. Children for whom the full metformin dose could not be prescribed were younger (8.8 ± 1.9 vs. 10.3 ± 1.4 years, P = 0.01) but did not differ in BMI or fat mass from those who tolerated it. Adherence to the prescribed study medication regimen did not differ significantly among the groups during the randomized phase (93.2 ± 1.3 vs. 92.2 ± 2.3%).

DISCUSSION

Childhood-onset obesity presages the development of disorders that predispose to cardiovascular disease in later life (47,48). Prevention of the complications of obesity, including type 2 diabetes, thus is a primary medical goal for weight-reduction therapy in children. On the basis of evidence suggesting that adolescents given metformin have salutary changes in adiposity and obesity-related comorbid conditions (27–33) and data from adults suggesting that metformin can delay the incidence of type 2 diabetes (22,23), we tested the hypothesis that metformin could improve glucose homeostasis and decrease the weight and body fat gained by obese insulin-resistant 6- to 12-year-old children who participated in a low-intensity clinic-based weight-reduction program.

Metformin produced modest differences in BMI Z that, as found for adolescents (33), largely persisted during 1 year of treatment. Compared with placebo treatment, metformin improved several other measures of body fatness, although consistent with some (33) but not all (29,39) studies, metformin did not significantly change intra-abdominal adipose tissue. As might be anticipated because of its major effect to suppress hepatic gluconeogenesis (14), metformin improved fasting insulin, glucose, and the HOMA-IR index, measures of insulin sensitivity that appear principally to reflect hepatic sensitivity to insulin's actions (49), but metformin did not greatly alter whole-body (primarily muscle) insulin sensitivity. Among young adult Israeli army recruits, individuals with fasting glucose concentrations >86 mg/dL had monotonically increasing risks for developing diabetes during ~6 years of follow-up

TABLE 3
Changes in laboratory variables at conclusion of the randomized phase

	Metformin	Placebo	Difference	P
N	53	47		
Serum insulin (μIU/mL)	3.24 (−1.36 to 7.84)	9.0 (3.84 to 14.15)	−5.75 (−10.45 to −1.06)	0.02
Plasma glucose (mg/dL)	−0.88 (−3.81 to 2.05)	3.47 (0.13 to 6.82)	−4.35 (−7.51 to −1.19)	0.007
HOMA-IR index*	0.68 (−0.4 to 1.76)	2.23 (1.02 to 3.43)	−1.54 (−2.65 to −0.44)	0.006
First-phase insulin secretion (μIU/mL)	−7.26 (−31.4 to 16.88)	−24.7 (−52.8 to 3.4)	17.44 (−18.61 to 53.49)	0.34
Clamp insulin sensitivity (mg/kg · min/μU/mL)	0.53 (−0.77 to 1.83)	−0.19 (−1.64 to 1.27)	0.71 (−1.56 to 2.99)	0.52
Total cholesterol (mg/dL)	−9.05 (−16.64 to −1.47)	−4.52 (−13.03 to 4.00)	−4.54 (−12.53 to 3.46)	0.27
HDL cholesterol (mg/dL)	0.12 (−2.55 to 2.78)	−0.27 (−3.28 to 2.73)	0.39 (−2.49 to 3.28)	0.79
LDL cholesterol (mg/dL)	−6.57 (−14.09 to 0.95)	−2.78 (−11.34 to 5.78)	−3.79 (−12.02 to 4.43)	0.37
LDL/HDL cholesterol ratio	−0.15 (−0.43 to 0.12)	−0.003 (−0.27 to 0.27)	−0.12 (−0.40 to 0.15)	0.21
Triglycerides (mg/dL)	7.7 (−12.83 to 28.23)	3.79 (−19.39 to 26.96)	3.91 (−17.67 to 25.5)	0.72
AST (U/L)	−0.86 (−3.04 to 1.31)	−0.89 (−3.36 to 1.57)	0.03 (−2.27 to 2.33)	0.98
ALT (U/L)	3.01 (−0.71 to 6.73)	2.63 (−1.65 to 6.92)	0.38 (−3.72 to 4.48)	0.86
High-sensitivity C-reactive protein (mg/dL)	0.07 (−0.48 to 0.61)	0.33 (−0.33 to 0.98)	−0.26 (−0.95 to 0.43)	0.45
Vitamin B_{12} (pg/mL)	−57.1 (−170.3 to 56.1)	173.8 (42.6 to 305.1)	−230.9 (−356.9 to −105.0)	<0.001

Estimated marginal means (95% CIs), adjusted for covariates including age, race, and sex, were reported from multiple imputation analyses.
*HOMA-estimated insulin resistance.

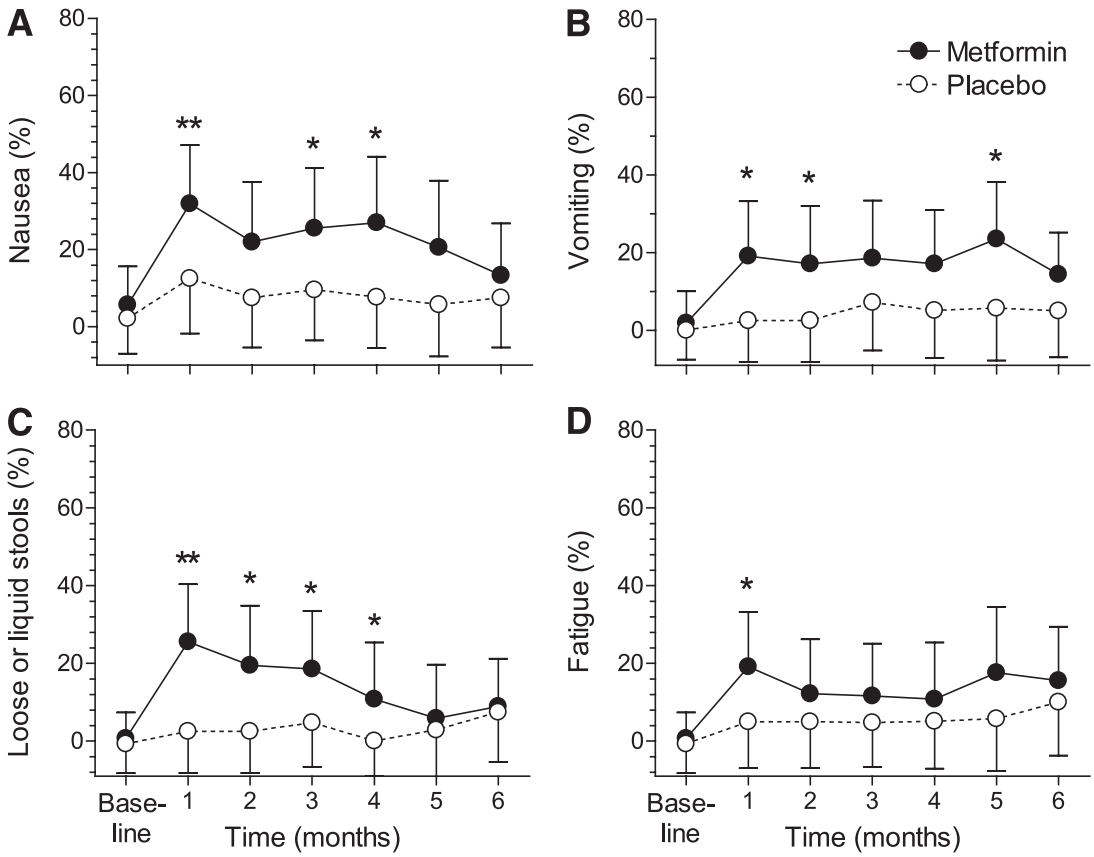

FIG. 3. Reports of symptoms during the placebo-controlled phase. *$P < 0.05$; **$P < 0.01$ for comparison of children randomized to metformin and placebo at each time point. *A*: Nausea. *B*: Vomiting. *C*: Loose or liquid stools. *D*: Fatigue.

(50). Our subjects' mean baseline plasma glucose was 92 mg/dL, decreasing slightly among metformin-treated children but increasing an additional 3.5 mg/dL in the placebo-treated group. The finding that metformin enabled study subjects to maintain fasting plasma glucose at a lower level suggests the possibility that metformin treatment might prevent or delay the onset of type 2 diabetes in children at high risk for this disorder. Other aspects of the insulin resistance–related metabolic syndrome did not change significantly with metformin treatment. The limited weight change observed, perhaps combined with the worsening of whole-body insulin resistance that commonly occurs as children enter adolescence, may account for the failure to find greater improvements in metabolism as a result of metformin treatment in this and prior studies conducted among adolescents (33,35).

Metformin therapy was associated with dose-limiting side effects in almost 17% of participants, particularly among younger subjects. Inability to tolerate 2,000 mg/day despite efforts made to reach the full dose may have limited the efficacy that could be observed. To some extent, the variability in the dose administered makes determination of metformin's efficacy more difficult. Our data suggest that a target total daily dose of 2,000 mg/day may not be achievable for all young children treated with metformin. Other studies report good toleration of lower doses (39) but a similar side effect profile among adolescents treated with 2,000 mg/day extended-release metformin (33). In addition to nausea and loose stools, we also observed fatigue symptomatology previously reported among children given metformin. Lastly, there was a relative diminution of serum vitamin B_{12} despite provision of a cyanocobalamin-containing multivitamin. B_{12} deficiency is unlikely to be reported among children treated with metformin because a long period of inadequate dietary B_{12} intake is required before clinical deficiency becomes manifest, but metformin has been reported to diminish serum B_{12} by 14–30% in adults, with the greatest effects observed among individuals treated with metformin for the longest time at the highest dosage (51). Our data reinforce the importance of monitoring potential adverse events among patients treated chronically with metformin.

Although this study is among the largest randomized controlled trials to date of a pharmacotherapeutic agent conducted for amelioration of obesity among young children, a limitation of this study is that only 100 children were studied; thus, there may have been insufficient power to detect differences between placebo- and metformin-treated groups for some obesity-related comorbid conditions examined. The placebo-controlled interval was only 6 months in duration and the maximal treatment duration was 1 year; thus, the study did not explore the efficacy of metformin in the longer term, which is required for a chronic condition like obesity. The study's generalizability is also somewhat limited by the fact that only severely obese insulin-resistant children were enrolled; it remains unclear how efficacious metformin is among children who are less obese and insulin resistant. Wilson et al. (33) have found quite similar results among adolescents who were not required to have insulin resistance. Finally, because the weight loss intervention was intended to model to some extent what might be available in clinical

practice, it consisted solely of monthly visits with a dietitian, and the magnitude of metformin-associated weight reduction that might occur among children treated with an intensified behavioral modification regimen is not established. Strengths include the recruitment of children who were racially and ethnically diverse, the use of intensive assessments of body composition and insulin sensitivity, the careful determination of adverse events using structured reporting tools, and the excellent subject retention rate.

We conclude that metformin treatment modestly reduces body weight and adiposity and improves measures of glucose homeostasis in obese insulin-resistant 6- to 12-year-old children. Although the weight loss produced is small, metformin treatment may hold promise as a method to prevent or delay the appearance of impaired glucose homeostasis in children at high risk for the development of type 2 diabetes.

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