Original Investigation

Effect of Metformin Added to Insulin on Glycemic Control Among Overweight/Obese Adolescents With Type 1 Diabetes
A Randomized Clinical Trial

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IMPORTANCE Previous studies assessing the effect of metformin on glycemic control in adolescents with type 1 diabetes have produced inconclusive results.

OBJECTIVE To assess the efficacy and safety of metformin as an adjunct to insulin in treating overweight adolescents with type 1 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Multicenter (26 pediatric endocrinology clinics), double-blind, placebo-controlled randomized clinical trial involving 140 adolescents aged 12.1 to 19.6 years (mean [SD] 15.3 [1.7] years) with mean type 1 diabetes duration 7.0 (3.3) years, mean body mass index (BMI) 94th (4) percentile, mean total daily insulin 1.1 (0.2) U/kg, and mean HbA_{1c} 8.8% (0.7%).

INTERVENTIONS Randomization to receive metformin (n = 71) (≤2000 mg/d) or placebo (n = 69).

MAIN OUTCOMES AND MEASURES Primary outcome was change in HbA_{1c} from baseline to 26 weeks adjusted for baseline HbA_{1c}. Secondary outcomes included change in blinded continuous glucose monitor indices, total daily insulin, BMI, waist circumference, body composition, blood pressure, and lipids.

RESULTS Between October 2013 and February 2014, 140 participants were enrolled. Baseline HbA_{1c} was 8.8% in each group. At 13-week follow-up, reduction in HbA_{1c} was greater with metformin (−0.2%) than placebo (0.1%; mean difference, −0.3% [95% CI, −0.6% to 0.0%]; $P = .02$). However, this differential effect was not sustained at 26-week follow up when mean change in HbA_{1c} from baseline was 0.2% in each group (mean difference, 0% [95% CI, −0.3% to 0.3%]; $P = .92$). At 26-week follow-up, total daily insulin per kg of body weight was reduced by at least 25% from baseline among 23% (16) of participants in the metformin group vs 1% (1) of participants in the placebo group (mean difference, 21% [95% CI, 11% to 32%]; $P = .003$), and 24% (17) of participants in the metformin group and 7% (5) of participants in the placebo group had a reduction in BMI z score of 10% or greater from baseline to 26 weeks (mean difference, 17% [95% CI, 5% to 29%]; $P = .01$). Gastrointestinal adverse events were reported by more participants in the metformin group than in the placebo group (mean difference, 36% [95% CI, 19% to 51%]; $P < .001$).

CONCLUSIONS AND RELEVANCE Among overweight adolescents with type 1 diabetes, the addition of metformin to insulin did not improve glycemic control after 6 months. Of multiple secondary end points, findings favored metformin only for insulin dose and measures of adiposity; conversely, use of metformin resulted in an increased risk for gastrointestinal adverse events. These results do not support prescribing metformin to overweight adolescents with type 1 diabetes to improve glycemic control.

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Despite the traditional phenotype of individuals with type 1 diabetes as having normal weight or being underweight, observational studies show, similar to the general population, increasing numbers of overweight and obese individuals with type 1 diabetes.[1] Recent data from the T1D (type 1 diabetes) Exchange Clinic registry indicated that in more than 11 000 US children and adolescents with type 1 diabetes, 24% were overweight and an additional 15% were obese.[2] For youth with type 1 diabetes, being overweight or obese potentially has serious metabolic consequences, especially during adolescence. Among these individuals, the high doses of insulin required to overcome the insulin resistance of obesity and puberty contribute to difficulties in glycemic control[3-7] and may promote further weight gain. In addition, among adolescents with type 1 diabetes, insulin resistance has been associated with increases in cardiovascular risk factors.[8]

Metformin is an oral glucose-lowering agent commonly used in treating type 2 diabetes. It improves glycemia in type 2 diabetes by several mechanisms including lowering hepatic glucose output and increasing peripheral uptake of glucose, especially in the muscle.[9] A meta-analysis[10] showed that metformin treatment was associated with significantly low insulin doses but had no effect on hemoglobin A_{1c} (HbA_{1c}) levels in adults with type 1 diabetes. However, studies in adolescents have been small, of short duration, or used nonstandard doses of metformin and have produced inconclusive results.[11-14] We designed a 6-month, multicenter, placebo-controlled, randomized trial to assess the effect of the addition of metformin, 2000 mg per day, to basal-bolus insulin treatment in overweight and obese adolescents with type 1 diabetes.

Methods

The trial was conducted at 26 clinical sites of the T1D Exchange Clinic Network. The protocol and Health Insurance Portability and Accountability Act (HIPAA)-compliant informed consent forms were approved by local institutional review boards. Written informed consent was obtained from participants aged 18 years and older or from a parent or guardian for younger participants who also assented. Study oversight was provided by an independent data and safety monitoring committee. The complete study protocol and statistical analysis plan are available in Supplement 1.

Study Participants

Major inclusion criteria included presumed autoimmune type 1 diabetes (as indicated by age of diagnosis <10 years or documented positive diabetes-related autoantibodies) for at least 1 year treated with either an insulin pump or at least 3 daily injections of insulin, age of 12 to less than 20 years, HbA_{1c} level of 7.5% to 9.9% from point-of-care measurement or local laboratory, body mass index (BMI, calculated using reference tables from the Centers for Disease Control and Prevention [CDC])[15] in the 85th percentile or greater for age and sex, total daily insulin dose of at least 0.8 units per kg per day, and frequency of self-monitoring of blood glucose at least 3 times per day (eTable 1 in Supplement 2 for a complete listing of eligibility and exclusion criteria). Race/ethnicity and socioeconomic status were determined from clinician report in order to characterize the study cohort.

Treatment

Following verification of eligibility from data entered on the study website, each participant was assigned randomly using a computer-generated sequence to either metformin or placebo with equal probability using a permuted block design stratified by screening HbA_{1c} (7.5%-8.9% and 9.0%-9.9%). A central pharmacy compounded the placebo to match the 500 mg metformin tablets.

The daily dose of study drug was increased over 4 weeks as follows: 1 tablet in the evening for 7 days, 1 tablet twice daily for 7 days, 1 tablet in the morning and 2 tablets at night for 7 days, and then 2 tablets in the morning and 2 tablets at night daily (2000 mg) for the remainder of the 26-week treatment period. A dose of 2000 mg of metformin was used without regard to each participant's weight because weight-based dosing is not common practice for metformin therapy, and a daily dose of 2000 mg is the standard dose used in managing type 2 diabetes in adolescent patients. Study drug dosage could be titrated at a slower rate and/or adjusted due to adverse effects per investigator discretion. Clinician judgment was used to adjust insulin doses. Pill counts of bottles returned by study participants were used to assess the amount of study drug taken.

Follow-up Visits

During the first 4 weeks after randomization, participants received weekly phone calls about adjustment of the study drug and their insulin dosages and assessment for adverse events. Office visits were conducted after 6, 13, and 26 weeks, and an additional phone contact was made at 20 weeks. The study drug was discontinued following the 26-week wearing of a continuous glucose monitor and a final visit was conducted 4 to 6 weeks later (eFigure 1 in Supplement 2).

Study Procedures and Assessments

At baseline, 13 weeks, and 26 weeks, each participant's height, weight, blood pressure, and waist circumference were measured; fasting blood was drawn for measurement at a central laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle) of HbA_{1c} (automated glycohemoglobin analyzer HLC-723G8, Tosoh Bioscience), serum lipids (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglycerides), liver enzymes (alanine aminotransferase and aspartate aminotransferase), creatinine, and C-peptide. Each participant was asked to wear a blinded continuous glucose monitor sensor (iPro2 digital recorder with Enlite sensor, Medtronic Diabetes) for 3 to 7 days at baseline, 13 weeks, and 26 weeks. Tanner staging was performed at randomization and again at 26 weeks if a participant had not developed to stage 5 (adult quantity and type

of pubic hair for both sexes, adult breasts for adolescent girls, and adult genitalia for adolescent boys) at randomization; dual-energy x-ray absorptiometry (DXA) scans were performed to assess body composition. Participants with detectable C-peptide (≥0.51 ng/mL; to convert to nmol/L, multiply by 0.331) at screening had a mixed-meal tolerance test performed at baseline and 26 weeks. Insulin use was determined by downloading the insulin pump (for pump users) at each visit or by reviewing the log of insulin injections (kept by injection users) for 1 week before each visit.

All adverse events were reported regardless of whether the event was considered treatment-related and coded using the *Medical Dictionary for Regulatory Activities*. Reportable severe hypoglycemia was defined as an event characterized by low blood glucose that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions to treat altered consciousness. The occurrence of diabetic ketoacidosis was defined by criteria from the Diabetes Control and Complications Trial.[16] Serum lactate was not routinely measured and was assessed only if deemed clinically indicated.

Outcomes

Primary Outcome

The primary efficacy outcome was the change in HbA_{1c} level (assessed at the central laboratory) from baseline to 26 weeks. Prespecified secondary HbA_{1c} outcomes (HbA_{1c} <7.5%, absolute decrease by ≥0.5%, and absolute increase by ≥0.5%) also were assessed.

Other Secondary and Exploratory Outcomes

Prespecified secondary and exploratory outcomes included continuous glucose monitor indices; total daily insulin per kg of body weight; total basal insulin per kg of body weight; BMI percentiles (analysis using z score also performed) adjusted for age and sex[15]; waist circumference; body composition measured by DXA; blood pressure percentiles adjusted for age, sex, and height (calculated using CDC reference tables); serum lipid levels; adipocytokines; inflammatory markers; and C-peptide levels. Posthoc binary variables were analyzed for total daily insulin, BMI, and weight change.

Safety Outcomes

All reported adverse events were tabulated. The primary safety outcomes included gastrointestinal events, occurrences of lactic acidosis, severe hypoglycemia, and diabetic ketoacidosis. Changes in serum creatinine and liver enzymes also were assessed.

Statistical Analysis

A sample size of 136 participants was planned to have 90% power to detect a difference in change in HbA_{1c} between treatment groups and assuming a population difference of 0.5%, standard deviation of 26-week values of 1.0%, correlation between baseline and 26-week values of 0.56, type I error rate of 5% (2-sided), and no more than a 15% loss to follow-up.

Analyses followed the intent-to-treat principle. Participants who discontinued use of the study drug remained in the study to complete follow-up and were analyzed according to the randomized treatment assignment.

Treatment group comparisons for continuous outcomes were conducted using a linear mixed model adjusted for baseline level of the outcome variable and random center effects. Treatment group differences in binary outcomes were evaluated in logistic regression models adjusted for baseline level of the outcome variable.

The proportions of participants experiencing any adverse event, any related adverse event, any gastrointestinal event, any event other than a gastrointestinal event, at least 1 severe hypoglycemic event, and at least 1 diabetic ketoacidosis event in each treatment group were compared using the Fisher exact test. The number of adverse events, new adverse events, serious adverse events, and nonserious adverse events were compared between groups using a Wilcoxon rank sum test.

Analyses were conducted using SAS version 9.4 (SAS Institute). A 95% CI was reported with each mean value. All *P* values were 2-sided. The primary analysis test of significance was conducted with a threshold of .05. *P* values for secondary analyses were unadjusted for multiple comparisons and should be considered exploratory. The Rubin method was used to impute missing HbA_{1c} data for the primary analysis.[17] Analyses of secondary outcomes were performed for the available measurements (without imputation for missing data). Analyses were performed on all efficacy outcomes obtained at 13 weeks by methods similar to those used at 26 weeks. Sensitivity analyses adjusting for potential confounders and including only eligible participants who were taking at least 1500 mg of the study drug at the 26-week visit (per-protocol analysis) were performed.

Results

Between October 2013 and February 2014, 140 participants were randomized to the metformin (n = 71) or placebo (n = 69) group (**Figure**). The mean (SD) age of participants was 15.3 (1.7) years (range, 12.1 to 19.6 years); 92 participants (66%) were female and 103 (74%) were white. Mean HbA_{1c} was 8.8% (0.7%), mean BMI z score was 1.6 (0.3), and mean total daily insulin was 1.1 (0.2) U/kg per day. **Table 1** lists baseline characteristics according to treatment group.

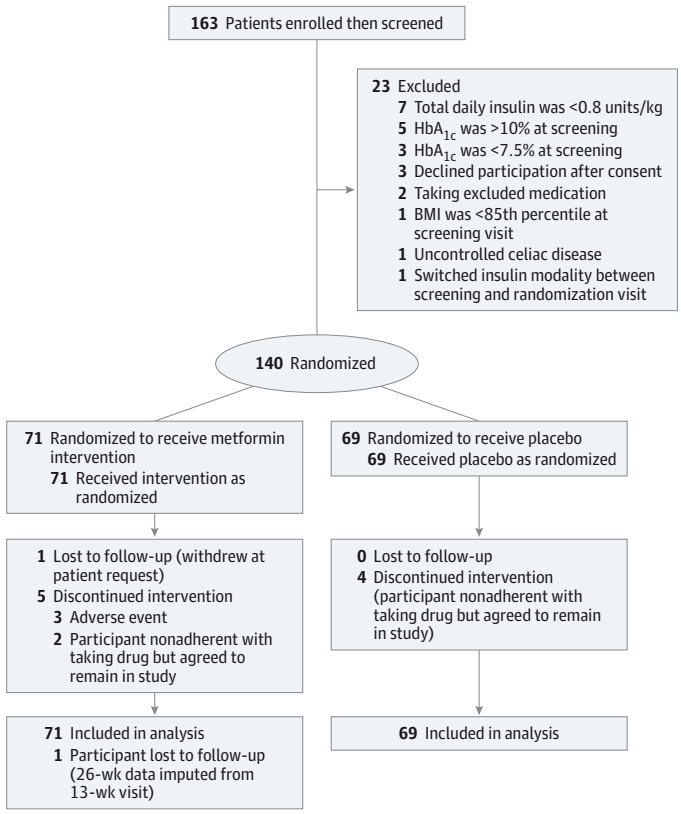
Visit Completion

The 26-week primary outcome visit was completed by 70 of 71 (99%) participants in the metformin group and by all 69 (100%) participants in the placebo group (Figure and eFigure 1 in Supplement 2). Telephone call and other visit completion rates were similar between treatment groups (eFigure 1 in Supplement 2).

Treatment

Five participants (7%) in the metformin group and 4 (6%) in the placebo group discontinued treatment prior to the

Figure. Flow of Study Participants: Metformin for Adolescents With Type 1 Diabetes



HbA1c indicates hemoglobin A1c; BMI, body mass index.

26-week follow-up. Of these, 3 participants (4%) in the metformin group discontinued the drug because of an adverse event (0 in the placebo group). At 13 weeks, 60 participants (84%) in the metformin group and 66 (96%) in the placebo group reported taking 2000 mg/d; at 26 weeks, 57 participants (80%) in the metformin group and 65 (94%) in the placebo group reported taking 2000 mg/d. Based on pill counts and the expected dose, mean (SD) medication adherence over the 26 weeks was 83% (24%) in the metformin group and 88% (23%) in the placebo group, and the mean of each participant's mean daily dose was 1699 (358) mg in the metformin group and 1793 (283) mg, in the placebo group (eTable 2 in Supplement 2).

Efficacy Analyses

Glycemic Control

Baseline HbA_{1c} was 8.8% (0.7%) in each group. At 13 weeks, mean change in HbA_{1c} from baseline was −0.2% in the metformin group and 0.1% in the placebo group (mean difference adjusted for baseline, −0.3% [95% CI, −0.6% to 0.0%]; $P = .02$). However, this difference was not sustained at the 26-week primary outcome visit in which the mean change in HbA_{1c} from baseline was 0.2% in the metformin group and 0.2% in the placebo group (mean adjusted difference, 0.0% [95% CI, −0.3% to 0.3%]; $P = .92$) (eFigure 2 in Supplement 2). Other HbA_{1c} outcomes are shown in **Table 2**. The sensitivity analyses showed no significant treatment group differences for the change in HbA_{1c} at 26 weeks (eTable 3 in Supplement 2). Continuous glucose monitoring outcomes showed no significant differences (eTable 4 in Supplement 2).

Total Daily Insulin

At 26 weeks, mean total daily insulin dose per kg was lower in the metformin group (−0.1 U/kg per day) vs in the placebo group (0.0 U/kg per day; mean difference, −0.1 [95% CI, −0.2 to −0.0]; $P < .001$; **Table 3**); 16 participants (23%) in the metformin group vs 1 (1%) in the placebo group had a reduction in total daily insulin of 25% or greater from baseline to 26 weeks (mean difference, 21% [95% CI, 11% to 32%]; $P = .003$).

Measures of Adiposity

From baseline to 26 weeks, less weight gain occurred in the metformin group (0 kg) compared with the placebo group (2 kg; mean difference, −2 [95% CI, −3 to −1]; $P = .003$; Table 3). More participants in the metformin group (12 [17%]) than in the placebo group (5 [7%]) had a reduction in body weight of at least 5% from baseline to 26 weeks (mean difference, 10% [95% CI, −1% to 21%]; $P = .09$). An increase in weight of more than 5% from baseline to 26 weeks was experienced by 17 participants (24%) in the metformin group vs 28 (41%) in the placebo group (mean difference, −16% [95% CI, −32% to −1%]; $P = .04$). There also was a greater reduction from baseline in BMI z score in the metformin group (0.0 [95% CI, −0.1 to 0.0]) vs the placebo group (0.1 [95% CI,

Table 1. Baseline Characteristics

	Metformin (n = 71)	Placebo (n = 69)
Female sex, No. (%)	44 (62)	48 (70)
Age, mean (SD), y	15.4 (1.7)	15.1 (1.8)
12-15 y, No. (%)	43 (61)	47 (68)
16-19 y, No. (%)	28 (39)	22 (32)
Race/ethnicity, No. (%)		
White	51 (72)	52 (75)
Black	4 (6)	5 (7)
Hispanic or Latino	13 (18)	11 (16)
Asian	2 (3)	0
Biracial or multiracial	1 (<1)	1 (<1)
Duration of diabetes, mean (SD), y	7.5 (3.6)	6.4 (3.0)
Duration by age group, No. (%)		
1-2 y	5 (7)	9 (13)
3-5 y	23 (32)	25 (36)
6-8 y	19 (27)	22 (32)
≥9 y	24 (34)	13 (19)
BMI[a]		
Z score, mean (SD)	1.6 (0.4)	1.7 (0.3)
Percentile, mean (SD)[b]	93.7 (4.1)	94.3 (3.8)
Overweight, 85th-<95th percentile, No. (%)	36 (51)	26 (38)
Obese, ≥95th percentile, No. (%)	33 (46)	41 (59)
Tanner staging, No. (%)[c]		
Pubic hair		
Stage 1	1 (<1)	1 (<1)
Stage 2	1 (<1)	3 (4)
Stage 3	5 (7)	7 (10)
Stage 4	16 (23)	9 (13)
Stage 5	48 (68)	49 (71)
Breasts or genitals		
Stage 1	1 (<1)	1 (<1)
Stage 2	0	2 (3)
Stage 3	5 (7)	6 (9)
Stage 4	12 (17)	9 (13)
Stage 5	53 (75)	51 (74)
Highest parental education level, No. (%)		
≤High school diploma or GED	22 (31)	20 (29)
Associate's degree	10 (14)	12 (17)
Bachelor's degree	18 (25)	15 (22)
Master's degree	12 (17)	13 (19)
Professional	5 (7)	7 (10)
Unknown or unanswered	4 (6)	2 (3)
Annual household income, No. (%), $		
<35 000	5 (7)	7 (10)
35 000 to <50 000	3 (4)	7 (10)
50 000 to <75 000	10 (14)	13 (19)
75 000 to <100 000	11 (15)	6 (9)
100 000 to <200 000	14 (20)	12 (17)
≥200 000	5 (7)	6 (9)
Unknown or unanswered	23 (32)	18 (26)
Insurance, No. (%)		
Private	53 (75)	48 (70)
Other	14 (20)	15 (22)
None	0	2 (3)
Unknown or unanswered	4 (6)	4 (6)

(continued)

Table 1. Baseline Characteristics (continued)

	Metformin (n = 71)	Placebo (n = 69)
Severe hypoglycemia episodes/events since diagnosis of type 1 diabetes, No. (%)[d]		
None	52 (73)	52 (75)
1-2	14 (20)	10 (14)
3-4	3 (4)	2 (3)
≥5	2 (3)	5 (7)
Diabetic ketoacidosis episodes/events since diagnosis of type 1 diabetes, No. (%)[e]		
None	53 (75)	48 (70)
1-2	15 (21)	13 (19)
3-4	2 (3)	6 (9)
≥5	1 (<1)	2 (3)
HbA_{1c} level, mean (SD), % of total hemoglobin	8.8 (0.8)	8.8 (0.7)
HbA_{1c}, No. (%), grouped by level		
<8.5%	25 (35)	24 (35)
8.5%-9.4%	32 (45)	26 (38)
≥9.5%	14 (20)	19 (28)
Sensor glucose, mean (SD), mg/dL	206 (35)	208 (34)
Insulin pump use, No. (%)	50 (70)	49 (71)
Continuous glucose monitor use, No. (%)	2 (3)	2 (3)
Self-monitoring of blood glucose/d, mean (SD)[f]	4.5 (1.2)	4.6 (1.6)
Self-monitoring blood glucose group, No. (%)		
3	13 (18)	14 (20)
4-5	44 (62)	43 (62)
≥6	14 (20)	12 (17)
Total daily insulin, mean (SD), U/kg per d	1.1 (0.2)	1.1 (0.2)
Total daily insulin, No. (%), grouped by level		
<1.0	33 (46)	26 (38)
1.0-1.4	33 (46)	39 (57)
≥1.5	5 (7)	4 (6)
Total basal/long-acting insulin, mean (SD), U/kg per d	0.5 (0.1)	0.5 (0.1)

Abbreviations: BMI, body mass index; GED, General Educational Development.

SI conversion factor: to convert glucose from mg/dL to mmol/L, multiply by 0.0555.

[a] Calculated from height and weight and adjusted for age and sex using growth chart tables from the Centers for Disease Control and Prevention.

[b] Two participants in the metformin group and 2 in the placebo group met the criteria for BMI (>85th percentile) at the screening visit that changed (<85th percentile) at the baseline/randomization visit.

[c] For pubic hair: stage 1, none; 2, initial hair is straight and fine; 3, curly, coarse, and dark; 4, like adult hair but limited in area; 5, adult distribution with spread to medial thighs. For female breasts: stage 1, none; 2, breast buds begin; 3, breasts and areolas grow; 4, nipples and areolas form separate mound protruding from breast; 5, areola rejoins breast contour. Male genitalia: stage 1 is preadolescent—testes, scrotum, and penis are approximately the same size and proportion as in early childhood; 2, scrotum and testes have enlarged and skin is changed in texture with reddening of scrotal skin; 3, initial growth of penis in length and breadth with further growth of the testes and scrotum; 4, further enlargement of the penis, testes, and scrotum, development of the glans, and the scrotal skin has further darkened; 5, genitalia are adult with regard to size and shape.

[d] Defined as cognitive impairment that required assistance to treat.

[e] Excludes diabetic ketoacidosis at diagnosis.

[f] Obtained from download of study-provided meter.

Table 2. Hemoglobin A_{1c} Outcomes

	Metformin (n = 71)	Placebo (n = 69)	Mean Difference (95% CI)	*P* Value[a]
Baseline				
HbA_{1c}, mean % (95% CI)	8.8 (8.6 to 9.0)	8.8 (8.6 to 9.0)		
13 Weeks[b]				
HbA_{1c}, mean % (95% CI)	8.7 (8.4 to 8.9)	8.9 (8.6 to 9.1)		
Change from baseline to 13 weeks, mean % (95% CI)	−0.2 (−0.4 to 0.0)	0.1 (−0.1 to 0.3)	−0.3 (−0.6 to 0.0)	.02
HbA_{1c}, No. (%) [95% CI]				
Decrease ≥0.5%	20 (29) [18 to 41]	20 (29) [18 to 41]	0 (−17 to 17)	.94
Increase ≥0.5%	12 (18) [8 to 27]	19 (28) [17 to 39]	−10 (−27 to 7)	.13
<7.5%	7 (10) [3 to 18]	0	10 (−7 to 27)	.01
26 Weeks[b]				
HbA_{1c}, mean % (95% CI)	9.0 (8.8 to 9.2)	8.9 (8.7 to 9.2)		
Change from baseline to 26 weeks, mean % (95% CI)	0.2 (0.0 to 0.4)	0.2 (−0.1 to 0.4)	0.0 (−0.3 to 0.3)	.92
HbA_{1c}, No. (%) [95% CI]				
Decrease ≥0.5%	13 (19) [8 to 28]	18 (26) [15 to 37]	−8 (−24 to 9)	.22
Increase ≥0.5%	31 (44) [32 to 56]	24 (35) [23 to 46]	10 (−7 to 26)	.22
<7.5%	2 (3) [<1 to 7]	3 (4) [<1 to 9]	−1 (−18 to 15)	.68

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

[a] *P* values for change in HbA_{1c} were obtained from linear mixed models adjusted for baseline HbA_{1c} and random center effects. *P* values for binary outcomes were obtained from logistic regression models adjusted for baseline HbA_{1c} and random center effects.

[b] HbA_{1c} values for 4 participants missing a level at 13 weeks and for 1 participant missing a level at 26 weeks were imputed using the Rubin method of multiple imputation.

0.0 to 0.1]) at 26 weeks (mean difference, −0.1 [95% CI, −0.2 to −0.1]; *P* < .001; Table 3); 17 participants (24%) in the metformin group and 5 (7%) in the placebo group had a BMI reduction at least 10% from baseline to 26 weeks (mean difference, 17% [95% CI, 5% to 29%]; *P* = .01).

Mean change from baseline to 26 weeks in DXA-measured total mass was 0 kg (95% CI, −1 to 1) in the metformin group vs 2 kg (95% CI, 1 to 3) in the placebo group (mean difference, −2 [95% CI, −4 to −1]; *P* < .001; Table 3), and change in % of body fat was 0% (95% CI, −1% to 1%) in the metformin group vs 1% (95% CI, 0% to 1%) in the placebo group (mean difference, −1% [95% CI, −2% to 0%]; *P* = .04). There was a reduction in DXA-measured total fat kg (mean difference, −2 kg [95% CI, −3 to −1]; *P* < .001) in the metformin group compared with the placebo group.

Other Exploratory Outcomes

No significant differences between groups were observed in change in blood pressure percentiles or lipid levels (Table 3) or inflammatory markers, C-reactive protein, or C peptide (eTable 5 in Supplement 2).

Safety Analyses

At least 1 adverse event was reported for 57 (80%) of the 71 participants in the metformin group and 39 (57%) of the 69 participants in the placebo group (mean difference, 24% [95% CI, 7% to 39%]; *P* = .003; **Table 4**). Gastrointestinal events were the most frequent type of adverse event with 50 events in the metformin group (70% [95% CI, 60% to 81%]) and 24 events in the placebo group (35% [95% CI, 23% to 46%]; *P* < .001; Table 4) (mean difference, 36% [95% CI, 19% to 51%]; *P* < .001). Excluding gastrointestinal events, at least 1 other adverse event was reported by 7 participants (10%) in the metformin group (95% CI, 3% to 17%) vs 15 (22%) in the placebo group (95% CI, 12% to 32%) (mean difference, −12% [95% CI, −28% to 4%]; *P* = .06). However, no system organ class other than gastrointestinal showed a significant treatment group difference. Lactic acidosis was not reported for any participant. There were no significant increases in serum creatinine or liver enzyme levels.

Diabetic ketoacidosis occurred in 3 (4% [95% CI, 1% to 9%]) participants in the metformin group vs 2 (3% [95% CI, 1% to 7%]) participants in the placebo group (mean difference, 1% [95% CI, −16% to 18%]; *P* ≥ .99). Severe hypoglycemia occurred in 5 (7% [95% CI, 1% to 13%]) participants in the metformin group and 0 in the placebo group (mean difference, 7% [95% CI, −9% to 23%]; *P* = .06). At 6 months, using blinded continuous glucose monitoring, mean (SD) time of less than 70 mg/dL was 5% (6%) in the metformin group vs 6% (8%) in the placebo group (mean difference, 0.0%, [95% CI, 0.0% to 0.0%]; *P* = .76).

Discussion

This multicenter placebo-controlled study of overweight and obese adolescents with type 1 diabetes failed to show a sustained effect of metformin as an adjunct to basal-bolus

Table 3. Secondary Outcomes

	Metformin, Mean (95% CI)			Placebo, Mean (95% CI)			Metformin vs Placebo, Mean Adjusted Difference (95% CI)			
	Baseline (n = 71)	13 Weeks (n = 68)	26 Weeks (n = 70)	Baseline (n = 69)	13 Weeks (n = 68)	26 Weeks (n = 69)	Baseline to 13 Weeks	*P* Value	Baseline to 26 Weeks	*P* Value
Daily insulin doses[a]										
Total daily insulin per kg	1.1 (1.0 to 1.1)	1.0 (0.9 1.0)	0.9 (0.9 to 1.0)	1.1 (1.1 to 1.2)	1.1 (1.0 to 1.1)	1.1 (1.0 to 1.1)				
Change in total daily Insulin per kg		−0.1 (−0.1 to −0.1)	−0.1 (−0.2 to −0.1)		0.0 (−0.1 to 0.0)	0.0 (−0.1 to 0.0)	−0.1 (−0.2 to 0.0)	.005	−0.1 (−0.2 to 0.0)	<.001
Body mass index[b]										
BMI percentile	94 (93 to 95)	93 (92 to 94)	93 (92 to 94)	94 (93 to 95)	95 (94 to 96)	95 (94 to 96)				
Change in BMI percentile		−1 (−1 to 0)	−1 (−2 to 0)		0 (0 to 1)	1 (0 to 1)	−1 (−2 to 0)	.001	−1 (−2 to −1)	.004
BMI z score	1.6 (1.5 to 1.7)	1.6 (1.5 to 1.7)	1.6 (1.5 to 1.7)	1.7 (1.6 to 1.7)	1.7 (1.6 to 1.8)	1.7 (1.7 to 1.8)				
Change in BMI z score		0.0 (−0.1 to 0.0)	0.0 (−0.1 to 0.0)		0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	−0.1 (−0.1 to 0.0)	<.001	−0.1 (−0.2 to −0.1)	<.001
Weight, kg	77 (74 to 80)	77 (74 to 79)	78 (75 to 80)	76 (74 to 79)	77 (75 to 80)	78 (76 to 81)				
Change in weight, kg		0 (−1 to 0)	0 (0 to 0)		2 (1 to 2)	2 (2 to 3)	−2 (−3 to −1)	<.001	−2 (−3 to −1)	.003
Waist circumference, cm[c]	91 (88 to 93)		90 (87 to 93)	92 (90 to 94)		93 (90 to 96)				
Change in waist circumference			0 (−2 to 1)			1 (−1 to 3)			−2 (−4 to 0)	.10
Body composition[d]										
Percent body fat	36 (34 to 38)		36 (34 to 38)	38 (37 to 40)		40 (40 to 41)				
Change in % body fat			0 (−1 to 1)			1 (0 to 1)			−1 (−2 to 0)	.04
Total mass, kg	76 (73 to 79)		75 (73 to 78)	75 (72 to 77)		77 (74 to 80)				
Change in total mass, kg			0 (−1 to 1)			2 (1 to 3)			−2 (−4 to −1)	<.001
Fat, kg	27 (25 to 29)		27 (25 to 29)	28 (27 to 30)		30 (28 to 32)				
Change in fat, kg			0 (−1 to 1)			2 (1 to 2)			−2 (−3 to −1)	<.001
Lean, kg	47 (45 to 49)		46 (44 to 49)	44 (43 to 46)		45 (43 to 46)				
Change in lean, kg			0 (0 to 0)			1 (0 to 1)			−1 (−2 to 0)	.12
Fat to lean ratio	0.6 (0.6 to 0.7)		0.6 (0.6 to 0.7)	0.7 (0.6 to 0.7)		0.7 (0.6 to 0.7)				
Change in fat to lean ratio			0.0 (0.0 to 0.0)			0.0 (0.0 to 0.0)			0.0 (−0.1 to 0.0)	.08

(continued)

Table 3. Secondary Outcomes (continued)

	Metformin, Mean (95% CI)			Placebo, Mean (95% CI)			Metformin vs Placebo, Mean Adjusted Difference (95% CI)			
	Baseline (n = 71)	13 Weeks (n = 68)	26 Weeks (n = 70)	Baseline (n = 69)	13 Weeks (n = 68)	26 Weeks (n = 69)	Baseline to 13 Weeks	*P* Value	Baseline to 26 Weeks	*P* Value
Blood pressure[e]										
Systolic percentile	61 (50 to 70)	63 (60 to 70)	62 (60 to 70)	61 (60 to 70)	65 (60 to 70)	57 (50 to 60)				
Change in systolic percentile		0 (0 to 0)	0 (0 to 0)		0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	.70	0 (0 to 0)	.15
Diastolic percentile	57 (50 to 60)	59 (50 to 60)	63 (60 to 70)	58 (50 to 60)	62 (60 to 70)	60 (50 to 70)				
Change in diastolic percentile		0 (0 to 0)	0 (0 to 0)		0 (0 to 0)	0.0 (0 to 0)	0 (0 to 0)	.61	0 (0 to 0)	.36
Serum lipids[f]										
LDL, mg/dL	106 (99 to 113)	101 (95 to 107)	100 (93 to 107)	98 (93 to 103)	99 (94 to 105)	100 (93 to 106)				
Change in LDL, mg/dL		−5 (−10 to −1)	−6 (−11 to 0)		2 (−2 to 6)	2 (−3 to 7)	−4 (−10 to 1)	.13	−6 (−13 to 1)	.10
VLDL, mg/dL	18 (16 to 20)	18 (16 to 21)	19 (16 to 22)	19 (15 to 23)	18 (16 to 21)	20 (16 to 24)				
Change in VLDL, mg/dL		0 (−3 to 2)	0 (−1 to 3)		0 (−3 to 2)	1 (−1 to 3)	0 (−3 to 3)	.87	0 (−3 to 2)	.74
HDL, mg/dL	52 (48 to 54)	51 (49 to 53)	51 (49 to 54)	51 (48 to 54)	53 (50 to 56)	51 (48 to 54)				
Change in HDL, mg/dL		−1 (−3 to 1)	0 (−2 to 2)		1 (−1 to 3)	−1 (−2 to 1)	−2 (−4 to 0)	.10	0 (−2 to 3)	.87
Triglycerides, mg/dL	90 (78 to 102)	90 (77 to 102)	94 (81 to 107)	94 (76 to 113)	92 (78 to 105)	100 (82 to 117)				
Change in triglycerides, mg/dL		−1 (−14 to 12)	4 (−5 to 13)		−2 (−14 to 10)	6 (−5 to 17)	1 (−13 to 15)	.90	−2 (−16 to 11)	.73
Total cholesterol, mg/dL	176 (167 to 185)	170 (162 to 178)	171 (162 to 179)	168 (160 to 176)	170 (163 to 178)	171 (163 to 179)				
Change in total cholesterol, mg/dL		−6 (−12 to −0)	−5 (−11 to 1)		2 (−3 to 8)	3 (−3 to 8)	−6 (−13 to 1)	.11	−6 (−13 to 2)	.13

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; DXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

SI conversion factors: to convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; for triglycerides from mg/dL to mmol/L, multiply by 0.0113.

[a] Insulin use was determined by insulin pump download for pump users at each visit. Injection users kept a log of insulin injections for one week before each visit. Linear mixed models for change from baseline were adjusted for random center effects and the baseline value of the outcome measure.

[b] BMI percentiles and z scores were calculated (weight in kilograms divided by height in meters squared) and adjusted for age and sex using national CDC reference tables. Linear mixed models for change from baseline were adjusted for random center effects and the baseline value of the outcome measure.

[c] Assessed at baseline and 26 weeks: linear mixed models for change from baseline were adjusted for random center effects and the baseline value of the outcome measure.

[d] Assessed at baseline and 26 weeks: linear mixed models for change from baseline were adjusted for random center effects and the baseline value of the outcome measure; 7 participants in the metformin group and 5 in the placebo group did not have a DXA at baseline or the 26-week visit; and 1 participant in the metformin group and 2 in the placebo group did not undergo waist circumference measurement at 26 weeks.

[e] Blood pressure percentiles were calculated from the average of 3 blood pressure measurements and adjusted for age, sex, and height using national CDC reference tables. Linear mixed models for change from baseline were adjusted for the baseline value of the outcome measure.

[f] Three lipid values in the metformin group and 11 in the placebo group were from nonfasting samples. Two participants in the metformin group and 1 in the placebo group did not have lipids measured at baseline or the 26-week visit. Linear mixed models for change from baseline were adjusted for random center effects and the baseline value of the outcome measure.

Table 4. Safety Outcomes

	Metformin (n = 71)	Placebo (n = 69)	*P* Value[a]
No. of adverse events[b]	184	78	
No. per participant[b]			
Mean (SD)	3 (2)	2 (2)	.005
Median (IQR)	3 (2-5)	2 (1-3)	
No. of serious adverse events[c]	3	3	
No. per participant[c]			
Mean (SD)	0 (0)	0 (0)	.66
Median (IQR)	0 (0-0)	0 (0-0)	
No. of nonserious adverse events	181	75	
No. per participant			
Mean (SD)	3 (2)	2 (2)	.002
Median (range)	3 (1-8)	2 (1-3)	
Participants with adverse events, No. (%) [95% CI]			
≥1 Adverse event	57 (80) [71-90]	39 (57) [45-69]	.003
≥1 Related adverse event[d]	46 (65) [53-76]		<.001
≥1 Gastrointestinal adverse event	50 (70) [60-81]	24 (35) [23-46]	<.001
≥1 Adverse event other than gastrointestinal events	7 (10) [3-17]	15 (22) [12-32]	.06
≥1 Diabetic ketoacidosis event	3 (4) [<1-9]	2 (3) [<1-7]	>.99
≥1 Severe hypoglycemic event	5 (7) [1-13]	0	.06
Biochemical hypoglycemia at 6 months[e]			
Percentage of time <70 mg/dL			
Mean (SD)	5 (6)	6 (8)	.76
Median (IQR)	2 (1-8)	4 (1-7)	
Percentage of time <50 mg/dL			
Mean (SD)	2 (4)	2 (5)	.51
Median (IQR)	0 (0-2)	0 (0-1)	

Abbreviation: IQR, interquartile range.

[a] *P* values were calculated using the Wilcoxon rank sum test for continuous safety outcomes and the Fisher exact test for binary outcomes unless otherwise specified.

[b] Adverse events from the same system class or underlying condition that occurred within 7 days were counted as the same event.

[c] All serious adverse events were for diabetic ketoacidosis except for 1 hospitalization for a suicide attempt in the placebo group.

[d] Related adverse events are any event thought by the investigator to be associated with the study drug.

[e] Biochemical hypoglycemia was measured with blinded continuous glucose monitor. A ranked transformation for the change in the outcome measure was used in a linear mixed model adjusted for the rank transformation of the baseline outcome measure and random center effect.

insulin therapy on glycemic control after 26 weeks. Despite a small decrease in HbA_{1c} favoring the metformin group at 13 weeks, mean HbA_{1c} levels increased by ≈ 0.2% from baseline values of 8.8% in each treatment group at 26 weeks. There also were no statistically or clinically significant differences from baseline to 26 weeks in continuous glucose monitor glucose profiles between treatment groups. The lack of benefit on glycemic control at 6 months is unlikely from bias because study completion was nearly 100%, the treatment discontinuation rate was low, and blinding of treatment assignment was maintained. It does not seem likely that different glycemic control results would have been achieved with a longer treatment period.

Although a benefit at 6 months on glycemic control was not observed, in hypothesis-generating analyses, metformin compared with placebo was associated with reductions in weight gain, BMI, body fat, and total daily insulin dose. The clinical relevance of these treatment group differences is uncertain. Other studies also have shown a decrease in BMI and total daily insulin dose with metformin.[10,12]

Although the changes in body weight composition and insulin requirements may have improved insulin sensitivity, there were no concomitant improvements in cardiovascular risk factors. Metformin treatment failed to improve a number of clinical and biochemical risk factors for future cardiovascular disease including blood pressure, plasma lipid concentrations, and adipocytokines. However, the 6-month study period may have been too short to show beneficial effects on these surrogate markers of future cardiovascular disease. In this regard, it is noteworthy that in the study of Lund et al,[18,19] metformin treatment in adults with type 1 diabetes lowered total and LDL-C after 1 year.

Metformin generally was well-tolerated, although the frequency of gastrointestinal adverse effects was greater than with placebo. Severe hypoglycemia occurred in 5 participants in the metformin group and did not occur in any participant in the placebo group. In 4 of the 5 of the participants who experienced severe hypoglycemia, the event occurred within the first 6 weeks of starting metformin (when the insulin dose was still being adjusted). This is noteworthy and suggests careful monitoring during the first few weeks following initiation of any noninsulin drug prescribed for glycemic control. There were no episodes of lactic acidosis, which is consistent with other reports of metformin use in the pediatric population.[10]

The primary limitation in interpretation of the results is uncertainty as to whether a more standardized approach to insulin management could have produced different results.

Because changes in the insulin regimen in this study were left to the discretion of treating clinicians, it is difficult to determine to what extent the greater reductions in total daily insulin doses in metformin-treated participants affected our ability to show treatment-group differences in changes in HbA_{1c} levels. This difficulty is compounded by the fact that there are so many other factors that affect the changes in HbA_{1c} levels—especially in adolescents. Another limitation is that adherence was measured by pill counts, which may or may not have been accurate.

Conclusions

Among overweight adolescents with type 1 diabetes, the addition of metformin to insulin did not improve glycemic control after 6 months. Of multiple secondary end points, findings favored metformin only for insulin dose and measures of adiposity; conversely, metformin resulted in an increased risk for gastrointestinal adverse events. These results do not support prescribing metformin to adolescents to improve glycemic control.

ARTICLE INFORMATION

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