Metformin as an Adjunct Therapy in Adolescents With Type 1 Diabetes and Insulin Resistance

A randomized controlled trial

JILL HAMILTON, MD[1]
ELIZABETH CUMMINGS, MD[2]
VERA ZDRAVKOVIC, MD[1]
DIANE FINEGOOD, PHD[3]
DENIS DANEMAN, MB, BCH[1]

OBJECTIVE — To evaluate whether, in adolescents with type 1 diabetes, the addition of metformin to insulin and standard diabetes management results in *1*) higher insulin sensitivity and *2*) lower HbA_{1c}, fasting glucose, insulin dosage (units per kilogram per day) and BMI.

RESEARCH DESIGN AND METHODS — This was a randomized, placebo-controlled 3-month trial of metformin therapy in 27 adolescents with type 1 diabetes, high insulin dosage (>1 unit · kg^{-1} · day^{-1}), and HbA_{1c} >8%, with measurements of insulin sensitivity (by frequently sampled intravenous glucose tolerance test [FSIGT]), HbA_{1c}, insulin dosage, and BMI at the onset and end of treatment.

RESULTS — At $t = 0$, HbA_{1c} was 9.2 ± 0.9%, insulin dosage was 1.2 ± 0.2 units · kg^{-1} · day^{-1}, fasting glucose was 10.6 ± 2.4 mmol/l, and BMI was 24.2 ± 3.9 kg/m^2 (means ± SD), with no difference between the metformin and placebo groups. At the end of the study, HbA_{1c} was 0.6% lower in the metformin group than in the placebo group ($P < 0.05$). This was achieved at lower daily insulin dosages (metformin group −0.14 ± 0.1 vs. placebo group 0.02 ± 0.2 units · kg^{-1} · day^{-1}; $P < 0.05$), with no significant change in BMI. Fasting glucose levels improved significantly in the metformin group ($P < 0.05$). Change in insulin sensitivity, measured by FSIGT, was not significantly different between the two groups at study end. Mild hypoglycemia occurred more frequently in the metformin-treated than in the placebo subjects (1.75 ± 0.8 vs. 0.9 ± 0.4 events · $patient^{-1}$ · $week^{-1}$; $P = 0.03$). There were no differences in frequency of severe hypoglycemic episodes or gastrointestinal complaints between the two groups.

CONCLUSIONS — Metformin treatment lowered HbA_{1c} and decreased insulin dosage with no weight gain in teens with type 1 diabetes in poor metabolic control. Changes in insulin sensitivity were not documented in this study using the FSIGT. Long-term studies will determine whether these improvements are sustained and whether certain subgroups accrue greater benefit from this therapy.

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Insulin resistance of puberty is well documented in both nondiabetic and diabetic adolescents (1–4). In those with diabetes, it likely plays a role in the deterioration of metabolic control seen in this age group (3–6). In the Diabetes Control and Complications Trial (DCCT), adolescents achieved HbA_{1c} levels that were on average 1% higher than in adults in both the conventional and intensive treatment groups, despite receiving more insulin (units per kilogram body weight) and having increased weight gain (7). This triad of high HbA_{1c}, high insulin dosage, and weight gain suggests that the insulin administered was less effective in maintaining glycemic control (i.e., insulin resistance) in the adolescent cohort.

The increase in growth hormone (GH) secretion during puberty is exaggerated in teens with type 1 diabetes compared with their nondiabetic peers, and contributes to the greater insulin resistance in this population (4,8,9). Insulin given subcutaneously bypasses the portal circulation and decreases the intrahepatic insulin effect on GH binding protein (GHBP) synthesis (10). This decrease in GHBP leads to decreased GH action, lower IGF-I levels, and, because of the lack of feedback inhibition, exaggerated GH secretion, together resulting in insulin resistance (11,12). Sex steroids and the hyperglycemia associated with noncompliance may also contribute to insulin resistance in adolescents (3,14,15).

Oral agents used to treat type 2 diabetes may be useful adjunctive therapy in individuals with type 1 diabetes and insulin resistance. The biguanide, metformin, acts primarily to decrease hepatic glucose output, but also effects insulin sensitivity (S_I). Both mechanisms may benefit the insulin-resistant individual with type 1 diabetes (16). A few reports of metformin added to insulin therapy in type 1 diabetic adults documented that the subjects showed a reduction in insulin requirements and variable changes in glycemic

From the [1]Division of Endocrinology, Hospital for Sick Children, Toronto, Ontario; the [2]Department of Pediatrics, Izaak Walton Killam Health Centre, Halifax, Nova Scotia, Canada; and the [3]School of Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada

Address correspondence and reprint requests to Jill Hamilton, MD, Division of Endocrinology, Hospital for Sick Children, Toronto, Ontario, Canada. E-mail: jill.hamilton@sickkids.ca .

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Abbreviations: DCCT, Diabetes Control and Complications Trial; FSIGT, frequently sampled intravenous glucose tolerance test; GH, growth hormone; GHBP, GH binding protein; MINMOD, minimal model; S_I, insulin sensitivity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

control (17–19). Preliminary results of two studies of metformin use in teens with type 1 diabetes have yielded conflicting results (20,21). No studies have measured physiological changes in S_I in response to metformin in adolescents with type 1 diabetes. The purpose of this study was to determine if the addition of metformin to standard diabetes care in teens with type 1 diabetes and insulin resistance would improve S_I, as assessed by the frequently sampled intravenous glucose tolerance test (FSIGT) and by clinical outcomes of lowered HbA_{1c} and insulin dosage and lack of weight gain.

RESEARCH DESIGN AND METHODS

— This randomized, double-blind, placebo-controlled trial recruited adolescents with type 1 diabetes attending the diabetes clinic at The Hospital for Sick Children, Toronto, Canada. Inclusion criteria were the following: age 12–17 years; Tanner stage 2–5 (assessed by the method of Marshall and Tanner) (22,23); duration of diabetes of >3 years; suboptimal metabolic control, defined as a HbA_{1c} >8.0 but < 11.0% (nondiabetic range 4.0–6.0%) for the prior 6 months; and insulin dosage ≥1 unit · kg^{-1} · day^{-1}. Exclusion criteria included nephropathy (albumin excretion rate >200 μg/min), proliferative retinopathy, recurrent diabetic ketoacidosis (more than two episodes in the past year), recurrent severe hypoglycemia (more than two episodes of hypoglycemia with altered level of consciousness, requiring assistance to treat in the past year), renal or hepatic dysfunction, another serious medical illness, the presence of a known eating disorder, or, if female, being sexually active and unwilling to take birth control. The protocol was approved by the Research Ethics Board of The Hospital for Sick Children. Written informed consent was obtained from all participants and their parents. The primary outcome was change in S_I.

Protocol

Subjects underwent a 2-month run-in period to screen for complications and to update patient education, optimize insulin therapy, and assess the subjects' ability to comply with the protocol. At the end of the run-in, subjects were randomized to either placebo or metformin using a computer-generated block random number table by sex and pubertal status (Tanner 2–3 vs. Tanner 4–5). The investigators were masked to patient allocation. The subjects were assessed monthly during the 3-month active phase of the trial. Medication (metformin or placebo) was taken with meals to minimize gastrointestinal side effects. Starting dosage was 500 mg/day (at breakfast), and was increased by 500 mg/day each week to a maximum of 1,000 mg/day (500 mg twice daily) for those weighing <50 kg, 1,500 mg/day (one 1,000- and one 500-mg dose) for those weighing 50–75 kg, or 2,000 mg/day (1,000 mg twice daily) for those weighing >75 kg.

Subjects were asked to monitor home premeal glucose three to four times daily (and at other times if they experienced symptomatic hypoglycemia) and to record glucose levels and insulin dosage in a diary. Insulin dosage adjustments were made by the subjects following guidelines currently used in our practice (24). Briefly, fast acting insulin (insulin Lispro, Humalog; Lilly) was adjusted at each injection using a scale based on ambient blood glucose concentrations. Adjustments to the intermediate-acting insulin dosage (NPH insulin) were made in 10% increments or decrements when premeal blood sugars were above the target range (4–8 mmol/l) for 3 days in a row or below for 2 days in a row, respectively. Phone contact was made weekly with the study physician for review of side effects and to facilitate insulin dosage adjustment. Subjects were asked to return pill containers for pill counts at each monthly visit. Compliance was defined as acceptable if <25% of the prescribed pills were returned at each assessment.

At each visit, height, weight, BMI, and blood pressure were recorded, and screening blood work (hepatic alanine aminotransferase and aspartate aminotransferase, creatinine, complete blood count, lactate) was performed to monitor for adverse effects. The mean total daily insulin dosage (in units per kilogram per day) for the 7 days preceding each visit was calculated from the subjects' diaries. Mean fasting glucose was also calculated from the home readings for the 7 days before each monthly clinic visit. Subjects notified the study physician immediately about severe hypoglycemic episodes, defined according to DCCT criteria (25). All episodes of mild symptomatic hypoglycemia were recorded in the diaries. Only glucose concentrations <4.0 mmol/l were used to calculate the mild hypoglycemic event rate. All meter readings were downloaded to a computer to ensure reliability of blood glucose monitoring, and simultaneous laboratory and meter glucose measurements were compared at each visit to ensure accuracy of the meter (defined as the meter reading within 15% of the laboratory value).

HbA_{1c} (determined using Biorad Variant II; nondiabetic range 4.0–6.0%; intrassay coefficient of variation 1%), cholesterol, and triglyceride levels were measured at the start of the run-in period, randomization, and study end. Insulin sensitivity was measured using the insulin-modified FSIGT at randomization and study end (26). Individuals received their usual insulin dosage the night before the test and underwent the insulin-modified FSIGT in the fasting state the next morning. The FSIGT involved administration of 300 mg/kg of 50% dextrose followed by a 20-mU/kg insulin injection, according to the method of Finegood et al. (26). FSIGT samples were placed in potassium oxalate sodium fluoride tubes, centrifuged at 2,000 rpm for 10 min at 4° C, and stored at –20° C until assayed for insulin and glucose. Plasma glucose was measured by the Vitros 950 Chemistry System Analyzer. Plasma insulin was measured by the double-antibody radioimmunoassay technique (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden) with inter- and intra-assay coefficient of variations of 6.6–8.8% and 5.4–5.8%, respectively. The S_I (minutes per micro units per milliliter) was calculated according to minimal model (MINMOD) formulas (27) using MINMOD computer software.

Sample size calculation and statistical analysis

The planned sample size of 32 subjects (16 subjects per treatment) was estimated to provide 80% power to detect a difference of change in S_I of 0.6×10^{-4} min · μU^{-1} · ml^{-1} between metformin and placebo groups at a two-sided 0.05 significance level, assuming a SD of 0.6×10^{-4} min · μU^{-1} · ml^{-1}. This change represents a 30% improvement in insulin sensitivity, which has been reported in metformin therapy and is clinically important enough to justify larger, long-term trials if significant (16).

Statistical analysis was performed using SPSS 8.0 (SPSS, Inc.) software. The mean changes in S_I, HbA_{1c}, fasting blood

Table 1 —*Baseline demographic and clinical characteristics of each study group*

Characteristics	Metformin		Placebo	
	Run in	Randomization	Run in	Randomization
n	14		13	
Age (years)	15.7 ± 1.9	15.9 ± 1.9	15.9 ± 1.7	16 ± 1.7
Sex (F/M)	8/6		6/7	
Duration of diabetes (years)	9.7 ± 4.4	9.9 ± 4.4	6.9 ± 3.8	7 ± 3.8
Weight (kg)	62.9 ± 13.7	63.3 ± 13.6	71.2 ± 11.7	71.6 ± 11.7
BMI (kg/m^2)	22.7 ± 4.1	22.8 ± 4.2	25.4 ± 2.9	25.7 ± 2.9
Pubertal status (Tanner$_{2–3}$/Tanner$_{4–5}$)	5/9		5/8	
HbA$_{1c}$ (%)	9.4 ± 1	9.3 ± 1.4	8.9 ± 0.8	8.6 ± 0.8
Insulin dosage (units · kg^{-1} · day^{-1})	1.2 ± 0.2	1.21 ± 0.3	1.3 ± 0.2	1.28 ± 0.19
S_I ($\times 10^{-4}$ · min^{-1} · μU^{-1} · ml^{-1})	1.7 (CI 1.0–2.6)		1.1 (CI 0.6–2.2)	

Data are means ± SD, except S_I, which is expressed as geometric mean and 95% CI.

glucose, insulin dosage (units per kilogram per day), BMI, blood pressure, and lipids between the 0 and 12 week visits for each group along with their 95% CIs were compared using the unpaired Student's *t* test. Repeated-measures ANOVA was performed to assess the change in insulin dosage and fasting glucose concentration over the study period. The S_I data were not normative and were analyzed by the nonparametric Mann-Whitney *U* test. The S_I data were also log transformed, and the mean change in S_I was analyzed with an unpaired *t* test. $P < 0.05$ was considered statistically significant. Pearson's correlation was performed to identify parameters that significantly influenced S_I results. ANCOVA was performed with adjustment for the significant covariate of fasting glucose. The frequency of severe hypoglycemic episodes was compared in the two groups using a binomial test of two independent proportions. The proportion of subjects in each group experiencing all other adverse events was compared using Fisher's exact test.

RESULTS — In all, 85 subjects were eligible for the study, and 38 (45%) agreed to participate. Age, sex, and HbA$_{1c}$ were not different between those who consented and those who did not. During the run-in period, eight subjects withdrew because of their unwillingness to comply with the protocol. During the study period, three subjects dropped out or were withdrawn: one because of unwillingness to undergo a second FSIGT (placebo group), one because of gastrointestinal discomfort (metformin group), and the third because of an episode of acute hepatitis with an elevation of hepatic transaminases (placebo group). Age, sex, HbA$_{1c}$, BMI, and insulin dosage were similar in those who completed the study and those who withdrew. The remaining 27 subjects completed the study (14 in the metformin group and 13 in the placebo group). Of these, 11 (79%) of the metformin-treated subjects and 8 (62%) of the placebo-treated subjects were compliant with the tablets. All subjects received three daily injections of insulin as a mixture of NPH and Humalog at breakfast, Humalog at supper, and NPH at bedtime.

Table 1 shows baseline characteristics of all subjects. All subjects were Caucasian. Although adolescents in the placebo group had a slightly higher BMI and shorter duration of diabetes than those in the metformin group, these differences were not statistically significant.

Mean S_I (95% CI) at onset of intervention was 1.35 (CI 0.57–2.51) min · μU^{-1} · ml^{-1}, with no difference between the two groups (Table 1). At the end of the 12-week study period, the change in S_I was not statistically significantly different between the two groups using both parametric (*t*) and nonparametric (Mann-Whitney *U*) tests (Table 2). There was a significant negative correlation between fasting blood glucose at the onset of the FSIGT and S_I result ($r = -0.66$, $P = 0.003$). Adjustment for this variable resulted in an improvement of S_I in the metformin-treated compared with the placebo-treated group that approached statistical significance ($P = 0.07$).

HbA$_{1c}$ decreased in the entire group during the run-in period from 9.2 ± 0.9 to 8.9 ± 1.1%. Analysis of all subjects completing the trial demonstrated a significant improvement in HbA$_{1c}$ of 0.6% in the metformin group compared with placebo ($P < 0.035$) (Table 2 and Fig. 1). Separate analysis of the compliant subjects also showed significant improvement in HbA$_{1c}$ in the metformin group,

Table 2 —*Change from baseline after 3 months of treatment*

	Metformin	Placebo	*P*
n	14	13	—
Δ S_I ($\times 10^{-4}$ min^{-1} · μU^{-1} · ml^{-1})	2.6 (CI 1.0–4.1)	2.5 (CI 1.9–2.9)	0.26
Δ HbA$_{1c}$ (%)	–0.3 ± 0.7	0.3 ± 0.7*	0.03
Δ fasting glucose (mmol/l)	–0.9 ± 3.8	–0.5 ± 3.2*	0.04
Δ insulin dose (units · kg^{-1} · day^{-1})	–0.14 ± 0.1	0.02 ± 0.2*	0.01
Δ BMI (kg/m^2)	–0.05 ± 1.0	0.2 ± 0.5	0.35

Data are means ± SD, except for S_I, which is expressed as geometric mean and 95% CI. *$P < 0.05$ vs. metformin group.

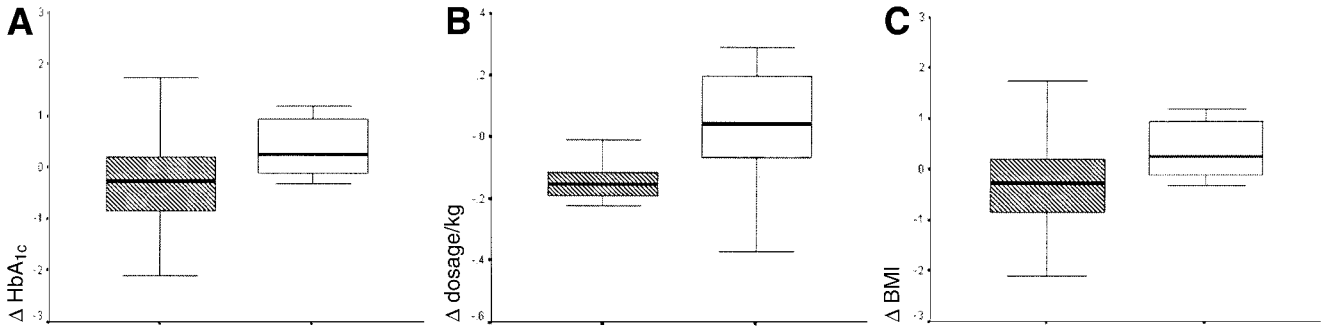

Figure 1—*Changes in HbA1c levels (A), insulin dosage (unit/kg; B), and BMI (C) in metformin (▨) and placebo (□) groups over 3-month active study period.*

with a decrease in HbA_{1c} of 0.5% in the metformin group and a difference of 0.7% between the two groups at study end ($P < 0.05$).

Metformin-treated subjects required significantly lower insulin dosages on a unit per kilogram basis compared with placebo-treated subjects ($P < 0.05$) (Table 2 and Fig. 1). Analysis of change in insulin dosage showed that only the NPH insulin was significantly lower in the metformin group ($P = 0.04$). There was a trend to lower BMI in the metformin group at study end ($P = 0.15$) (Table 2). There was a significant decrease in fasting glucose in the metformin group over the study period, with the effect being strongest at 2 months (-1.2 ± 2.0 [metformin] vs. 0.1 ± 2.5 mmol/l [placebo]; $P = 0.004$). Cholesterol and triglyceride levels did not change during the study period. There were no clinically detectable changes in puberty throughout the study period, and no subject reported a large change in physical activity over the 3-month active phase of the trial.

In all, 11 subjects complained of gastrointestinal discomfort (6 from the metformin group, 5 from the placebo group), with no significant differences between the groups. In addition, two subjects experienced brief episodes of vomiting (both metformin group; one withdrew from the study), and three subjects (two metformin group, one placebo group) experienced severe hypoglycemic events (two had seizures and one experienced an altered level of consciousness). In all, the events were clearly related to missing meals. During the run-in period, there was a mean of 1.0 ± 0.6 mild hypoglycemic episodes · patient^{-1} · week^{-1}. Over the 3-month treatment period, the number of mild hypoglycemic events in the metformin group increased compared with the placebo group (1.75 ± 0.8 vs. 0.9 ± 0.4 events · patient^{-1} · week^{-1}; $P = 0.03$).

CONCLUSIONS — In this study, we demonstrated that adolescents with type 1 diabetes and insulin resistance receiving metformin had a lower HbA_{1c}, decreased their insulin requirements by ~10%, and had no significant weight gain over the 3-month study period, compared with those in the placebo group. These changes suggest a clinical improvement in S_I and overall diabetes control in the metformin-treated subjects. All subject received standardized advice regarding insulin dosage adjustment in response to glucose monitoring, yet only the metformin group improved metabolic control significantly. Metformin may have lowered HbA_{1c} by smoothing out glycemic excursions over a 24-h period, perhaps by decreasing hepatic glucose output. Two findings support this view: first, the decrease in insulin requirement was significant only for NPH, and, secondly, a significantly lowered fasting glucose was documented in the metformin group. S_I, as measured by FSIGT, was not improved, although S_I did show a trend toward improvement in the metformin group after adjustment for ambient glucose. Within the metformin group, there were three girls with BMI >28 kg/m^2 (all Tanner stage 4) who responded particularly well; two had decreases in HbA_{1c} of 1.2 and 0.4% with concurrent decreased daily insulin dosages of 10–15 units (−0.15 units/kg) and stable or decreased BMI (from 28.5 to 27.2 kg/m^2). The third subject had no change in her HbA_{1c}, but decreased her daily insulin dosage by 22 units (−0.22 units/kg) and her BMI from 30 to 27.9 kg/m^2. In contrast, two females in the placebo arm, who had similar BMI and Tanner stage, experienced improved HbA_{1c} (1 and 0.1%) at the expense of increased insulin dosage requirements (0.13 and 0.17 units/kg, respectively) and increased BMI (both 0.8 kg/m^2). Although the number of subjects in this study was too small to perform subgroup analysis, there may have been certain subjects (e.g., females in advanced puberty with BMI >28 kg/m^2) who responded particularly well to the addition of metformin to their usual insulin therapy.

The inclusion criteria for this study were set out to minimize the likelihood of recruiting subjects with type 2 diabetes. All subjects were Caucasian, had diabetes onset between ages 1.5 and 12.0 years, and had a diabetes duration of 8.3 ± 4.3 years. Their mean BMI was 24.2 kg/m^2 (range 17–30 kg/m^2), much lower than that reported in studies of teens with type 2 diabetes (28,29). Patients were stratified at randomization by early and late pubertal development, and pubertal stage did not change appreciably over the 3-month study period. GH secretion or IGF-I levels, which are believed to be responsible for the insulin resistance of puberty, were not measured (4,8,9). The short study duration and lack of clinical pubertal progression make it highly unlikely that changes in GH alone could account for the benefits accrued in the metformin-treated, but not placebo-treated subjects. Exercise has been shown to improve insulin sensitivity and could theoretically have resulted in improved metabolic control (30). Subjects' activity was not restricted; however, they were asked to keep a detailed log of blood glucose recordings, insulin dosages, and comments related to changes in diet and activity. In

addition, during weekly phone contact, a review of blood glucose excursions and a specific discussion about physical activity as one factor that may modify blood glucose levels took place. None of the subjects reported an increase in his or her activity during the study period.

Preliminary results of two studies examining metformin treatment in teens with type 1 diabetes have been presented (20,21). The first, an open-label, nonrandomized study of five adolescents taking 500–1,000 mg metformin daily found no improvement in HbA_{1c} or decrease in insulin dosage after 6 months (21). This study was limited because it was small, uncontrolled, and used low metformin dosages. The second was a larger randomized controlled trial, with metformin administered as 500 mg twice daily for 6 months in 80 adolescents with poor metabolic control and type 1 diabetes (20). After 3 months, there was a beneficial effect on HbA_{1c} in the metformin group (decrease from 9.6 to 8.7% compared with a decrease of 9.6 to 9.4% in those taking placebo), but by 6 months the former group's HbA_{1c} had returned to baseline. Weight and insulin dosage also decreased (males only) in the metformin group at 3 months. In the current study, we have also demonstrated a beneficial effect of metformin over a 3-month study period; whether this will be sustained in the longer term at the higher dosages of metformin that we used remains to be tested.

Technical issues related to the performance of FSIGT in individuals with type 1 diabetes without residual pancreatic insulin secretion may have interfered with our ability to show significant differences in S_I between our study groups. The SD in our population was much wider than anticipated and likely was related to difficulties in calculating S_I in this population by the MINMOD analysis method. Ambient glucose at the start of the study correlated with S_I; thus, for this test to be improved upon in type 1 diabetes, strict stabilization of blood glucose at the onset may be necessary. The original protocol modified for type 1 diabetes by Finegood et al. (26) has only been tested in individuals with diabetes within the first year of diagnosis, with a much narrower range of fasting glucose, reflecting residual insulin secretion. The most significant issue we detected related to a significant and continuing increase in glucose level at the end of the 180-min test that interferes with the ability of the MINMOD program to accurately calculate parameters, as the model assumes the 180-min glucose level to be at steady state. In those subjects with a rise in glucose beyond 80–100 min, this results in a false "undershoot" of glucose in response to insulin earlier in the test. Consequently, the calculated S_I may be falsely high. Further work to determine the most appropriate modifications of this technique in type 1 diabetes may make it a more reliable tool in this setting (31,32).

Although we could not document improved S_I by FSIGT, clinical indicators such as decreased insulin dosage, decreased BMI, and lowered HbA_{1c} suggested an improvement in S_I in those receiving metformin. This improvement may have been attributable to the direct impact of metformin on peripheral tissues, but more likely was secondary to metformin's effects on decreased hepatic glucose output or, possibly, as a consequence of weight loss subsequent to a decreased appetite. The potential therapeutic benefit of potent insulin sensitizers, such as the thiazolidinediones, should also be investigated. This pilot study demonstrated that targeting insulin resistance with metformin, traditionally used to treat type 2 diabetes, improves metabolic control in teens with type 1 diabetes and represents a novel adjunctive therapy worthy of further investigation.

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