

## CLINICAL STUDY

# Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity

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## Abstract

**Objective:** Metabolic control often deteriorates during puberty in children with type 1 diabetes. The aim of the present study was to investigate whether addition of metformin for 3 months improves metabolic control and insulin sensitivity.

**Design:** Twenty-six of 30 randomised adolescents with type 1 diabetes (18 females, eight males) completed a double-blind placebo-controlled trial. Their mean age was  $16.9 \pm 1.6$  (s.d.) years, mean glycosylated haemoglobin (HbA<sub>1c</sub>)  $9.5 \pm 1.1\%$  and daily insulin dosage  $1.2 \pm 0.3$  U/kg. The participants were randomised to receive oral metformin or placebo for 3 months. HbA<sub>1c</sub> was measured monthly, and peripheral insulin sensitivity was assessed by a euglycaemic hyperinsulinaemic clamp at baseline and at the end of the study.

**Results:** HbA<sub>1c</sub> decreased significantly in the group treated with metformin, from 9.6 to 8.7% ( $P < 0.05$ ), but was unchanged in the placebo group (9.5 vs 9.2%). Peripheral glucose uptake divided by mean plasma insulin concentration was increased in the metformin group ( $P < 0.05$ ) but not in the placebo group. Initial insulin sensitivity was inversely correlated to changes in HbA<sub>1c</sub> ( $r = -0.62$ ;  $P < 0.05$ ) and positively correlated to changes in insulin sensitivity ( $r = 0.77$ ;  $P < 0.01$ ).

**Conclusions:** In this double-blind placebo-controlled study we found that metformin improves metabolic control in adolescents with type 1 diabetes. The effect seems to be associated with an increased insulin-induced glucose uptake.

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## Introduction

Puberty is associated with marked insulin resistance (1), mainly affecting peripheral glucose utilisation (2), with less effect on fat metabolism (3). Weight gain is prevalent in adolescent females with type 1 diabetes after attainment of final height (4), which might further impair insulin sensitivity (5). Insulin dosages are often increased to overcome the resistance to insulin, but the metabolic control, however, often deteriorates during the later stages of pubertal development (6).

Thus, there is a great need for alternative therapeutic strategies in adolescents with type 1 diabetes. One possibility could be the addition of a drug that improves insulin sensitivity. A candidate for this is metformin, the effect of which regarding insulin sensitivity has been documented. This effect is mainly mediated through suppression of hepatic glucose production and increased insulin-mediated peripheral glucose utilisation. It has also been proposed that metformin

decreases fatty acid oxidation and intestinal glucose absorption, but the contributions of these effects to the total antihyperglycaemic action is considered to be small (7). Metformin has mainly been used in adult patients with type 2 diabetes and several studies have shown beneficial effects on body weight, blood lipid levels and metabolic control (8–10). Recently, Jones *et al.* (11) reported on a randomised double-blind placebo-controlled trial with metformin in adolescents with type 2 diabetes, where they noted an improvement in fasting plasma glucose. There have also been reports from studies in adolescents with type 1 diabetes demonstrating a reduction of glycosylated haemoglobin (HbA<sub>1c</sub>) during 6 month trials (12), although the effect was transient in one of them (13).

The aim of the present study was to determine whether the addition of metformin for 3 months had positive effects on glycaemic control and insulin sensitivity in a randomised double-blind placebo-controlled trial in adolescents with poorly controlled type 1 diabetes.

## Subjects and methods

### Subjects

Participants were recruited in five different Departments of Paediatrics in central Sweden (Eskilstuna, Falun, Karlstad, Västerås and Örebro), an area consisting of 1.5 million inhabitants, during the period from November 1998 to March 2001. Girls aged 14–20 years and boys aged 16–20 years, with an HbA<sub>1c</sub> level above 8% and a daily dosage of insulin >0.9 U/kg were asked if they would participate in the study. In the centre of Örebro, a total of 51 eligible adolescents were identified, and 20 of them (39%) fulfilled the inclusion criteria. Twelve accepted to be included in the study. The main reason for non-participation was the invasive parts of the study. The non-participating adolescents did not differ from those who did participate regarding age, daily dosage of insulin, body mass index (BMI) or HbA<sub>1c</sub>. In the other centres, which had a comparable number of patients, treatment guidelines and mean HbA<sub>1c</sub> (14), the participation rates were lower due to the need for travelling by car or train to the centre in Örebro.

A total of 30 adolescents were recruited, according to the defined criteria. There were 12 from Örebro, and five, four, five and four from Eskilstuna, Falun, Karlstad and Västerås respectively. All patients were Caucasian with a clinical history of typical diabetes symptoms and ketosis at onset and all of them required insulin treatment from onset of diabetes. Their mean age was 17.0±1.6 (S.D.) years and 21 (70%) of the patients were females. All were in the late stages of pubertal development (Tanner 4–5). Twenty-five patients were being treated with multiple insulin injection therapy (three to five preprandial doses and one or two doses of basal insulin) and five used insulin pumps. The mean daily dosage of insulin was 1.2±0.3 U/kg and the mean HbA<sub>1c</sub> was 9.3±1.2%. There was no significant gender difference in HbA<sub>1c</sub> or daily insulin

dosages. The BMI, waist circumference and waist/hip (W/H) ratio were significantly higher in females than in males. Clinical characteristics of all randomised subjects are presented in Table 1. All patients attended the outpatient departments for medical advice at least every third month in accordance with the Swedish national treatment guidelines. The metabolic control had been on the same level for at least 1 year prior to inclusion. Besides type 1 diabetes, no participant had any other disease or medication except for contraceptives. None had persistent nephropathy (defined as microalbuminuria >20 µg/min and antihypertensive treatment) and none had had diabetic ketoacidosis during the last year.

All subjects and their parents gave informed consent. The study was approved by the Ethics Committee of Örebro County Council and the Swedish Medical Products Agency.

### Study design

Adolescents who fulfilled the inclusion criteria were asked verbally about participation and were given written information about the study. After a run-in period of at least 1 month, all patients were admitted to the Department of Paediatrics in Örebro. The patients arrived in the late afternoon and their body weight, height, waist and hip circumferences were measured. The waist circumference was measured at the umbilicus and the hip at its widest point. Two indwelling catheters were inserted, one in the antecubital vein for i.v. insulin infusion and the other in a dorsal hand vein for blood sampling. The patients fasted from 2000 h that evening. During the night the patients received a variable insulin infusion, and their blood glucose was measured each hour, with the aim of achieving normoglycaemia during the night. At 0700–0800 h in the morning, fasting blood samples were drawn and a hyperinsulinaemic euglycaemic clamp procedure was initiated.

The included patients were randomised to receive oral treatment with metformin or placebo for 3 months. The randomisation procedure was stratified according to gender, so that the same sex distribution was obtained in both groups. The study was double-blinded and the study medicine was delivered from the Pharmacy Department at the hospital. Throughout the study, all patients and investigators were unaware of the treatment assignment.

The participants were instructed to take the medicine during the middle of the breakfast meal in the morning and during dinner at 1700–1800 h. All participants received a dosette (pill box), which they loaded with metformin or placebo. The initial study dose was 500 mg daily in the morning for 1 week, and this was followed by 500 mg twice daily for 3 weeks, and subsequently 1000 mg twice daily for the rest of the study period. The participants were asked to perform

**Table 1** Clinical characteristics at baseline (all randomised subjects). Data are numbers or means±S.D., unless otherwise indicated. BMI was calculated from all but one subject, who was later excluded. The groups did not differ significantly in any of the displayed variables.

	Metformin (n = 16)	Placebo (n = 14)
Sex (F/M)	11/5	10/4
Age (years)	17.2±1.7	16.9±1.4
Weight (kg)		
Median	68.8	66.6
Range	56.0–90.0	53.0–89.6
BMI (kg/m <sup>2</sup> )		
Median	26.2	23.9
Range	18.6–35.4	17.0–29.2
Diabetes duration (years)	9.1±5.0	7.1±3.0
Daily dosage of insulin (U/kg)	1.2±0.4	1.2±0.2
HbA <sub>1c</sub> (%)	9.3±1.1	9.3±1.4

at least twice daily preprandial home blood glucose measurements and were encouraged to adjust their doses of insulin according to the Swedish national guidelines, aiming at preprandial blood glucose levels between 4 and 8 mmol/l.

All patients were seen each month after the initiation of the study. They were asked about their current insulin dosage, any missed tablet doses and any side-effects. Any episodes of severe hypoglycaemia and diabetic ketoacidosis were recorded. After 3 months all patients were readmitted to the Department of Paediatrics in Örebro, according to the same procedure as during the initial visit.

HbA<sub>1c</sub>, the primary outcome measure, was assessed on inclusion in the study and thereafter every month during the study period. The secondary outcome measures, namely insulin sensitivity, insulin-like growth factor I (IGF-I), IGF-binding protein-1 (IGFBP-1), daily insulin dosage, BMI, waist circumference and blood lipid concentrations, were measured on inclusion and at the end of the study period.

Safety assessments, including examination of blood samples for renal and hepatic function indices, were carried out on inclusion and monthly thereafter during the study period. Physical measurements (height, weight and blood pressure) were made at each visit.

### Assays

For measuring HbA<sub>1c</sub>, HPLC with the Mono-S standard was used (15). The intra- and interassay coefficients of variations for HbA<sub>1c</sub> were 1.3 and 1.1% respectively. The reference level for healthy persons is 3.5–5.3% and the method gives values that are approximately 1% lower than the Diabetes Control and Complications Trial standard (normal reference range: 4.05–6.05%). Serum insulin was measured by a fluoroimmuno-metric assay using two separate monoclonal antibodies against separate antigenic determinants on the insulin molecule (Insulin kit for AutoDELFIA; Wallac Oy, Turku, Finland). Blood lipids were analysed from fasting blood samples using a dry chemistry method (Vitros 950 and/or a Vitros 250 instrument; Johnson & Johnson Clinical Diagnostics, Rochester, NY, USA). Both the cholesterol and the triglyceride slides were determined by enzymatic methods (Johnson & Johnson Clinical Diagnostics). IGF-I was assayed with an IRMA technique (Nichols Institute Diagnostics, San Clemente, CA, USA) and IGFBP-1 with a two-step IRMA technique (Diagnostic Systems Laboratories, Inc., Webster, CA, USA).

Blood glucose was measured by glucose dehydrogenase technique (Hemocue AB, Ängelholm, Sweden).

### Evaluation of insulin sensitivity

The hyperinsulinaemic euglycaemic clamp was used, with the technique described by DeFronzo *et al.* (16).

A primed infusion of human soluble insulin (Actrapid; Novo Nordisk, Copenhagen, Denmark) was given at a rate of 40 mU/m<sup>2</sup> per min for at least 60 min to achieve a steady-state. During the insulin infusion, the blood glucose was kept constant at 5.0 mmol/l by a variable infusion of 20% glucose. The rate of glucose infusion was adjusted manually according to the blood glucose levels, which were measured every 5 min. If the blood glucose was unstable after 60 min, the insulin infusion was prolonged for 15–30 min until a steady-state was achieved. Blood samples for serum insulin measurements were taken at the beginning of the steady-state and then after 20, 40 and 60 min. Samples for blood glucose and insulin were taken from a heated superficial hand vein, to obtain arterialised samples (17).

The amount of glucose infused during the last 60 min after a steady-state was achieved was calculated (M) and was related to the mean insulin concentration for the estimation of insulin sensitivity (M/I) (16, 18). Both M and M/I are estimations of the total peripheral insulin sensitivity regarding the glucose metabolism, based on the assumption that the hyperinsulinaemic level totally inhibits glucose production from the liver (19).

### Statistical analysis

We estimated that with an s.d. of 1.0% for HbA<sub>1c</sub>, a two-sided 0.05 significance level and a power of 80%, overall sample sizes of 18 and 34 subjects would be sufficient to detect true treatment differences of 1.5 and 1.0% respectively.

For presentation of baseline characteristics, data from all randomised subjects were used. Data for insulin sensitivity, BMI, weight and IGFBP-1 were not normally distributed and were therefore analysed with a non-parametric test. A paired Student's *t*-test or Wilcoxon signed-rank sum test was used to estimate the difference between baseline and the end of study. An unpaired *t*-test or Mann–Whitney U test was used to test differences between the two groups. A 95% confidence interval (CI) and/or the *P* value was calculated when appropriate.

Pearson's product moment correlation coefficient and Fisher's *r* to *z* was calculated to estimate associations between change in HbA<sub>1c</sub>, change in insulin sensitivity and different variables. For all statistical analyses, StatView version 5.0.1 was used. A *P* value less than 0.05 was accepted as significant.

### Results

We designed the study to include 40 patients, but due to problems in recruiting subjects we had to end the randomisation when we had included 30 patients.

Two patients were excluded on account of a low HbA<sub>1c</sub> at randomisation (one in the metformin and one in the placebo group). These two patients had

significantly improved their HbA<sub>1c</sub> during the run-in period. One patient left the study after 2 months because of low motivation. She was randomised to metformin and had no side-effects but forgot many tablets and was therefore excluded. Another girl, who was also randomised to metformin, stopped after 1.5 weeks because of nausea and low motivation. The remaining 26 adolescents completed the 3 month trial. In one patient the insulin sensitivity measurement failed because of technical problems and in another patient the clamp procedure was excluded for practical reasons. They were both randomised to metformin and were followed up regarding all other parts of the study (Fig. 1).

### Glycaemic control and insulin dosage

There was no significant difference between the metformin and placebo group regarding mean HbA<sub>1c</sub> on inclusion. During the study period the mean HbA<sub>1c</sub> value decreased from  $9.6 \pm 1.0$  to  $8.7 \pm 1.5\%$  (CI for the change:  $-1.6$  to  $-0.1$ ;  $P < 0.05$ ) in the metformin group, but remained unchanged ( $9.5 \pm 1.2$  vs  $9.2 \pm 1.3\%$ ; ns) in the placebo group. There was no significant difference between the metformin and placebo group regarding daily insulin dosage at baseline or after 3 months of therapy. In neither of the groups did the daily insulin dosage change significantly

during the 3 month trial (Table 2). There were no significant gender differences in improvement in HbA<sub>1c</sub> or change in insulin dose.

In the metformin group, change in HbA<sub>1c</sub> showed no association with the initial values for HbA<sub>1c</sub>, insulin dosage or change in insulin sensitivity. However, there was an inverse correlation between initial M/I on inclusion and change in HbA<sub>1c</sub> ( $r = -0.62$ ;  $P < 0.05$ ), indicating that patients with decreased initial insulin sensitivity benefited most from metformin.

### Compliance and side-effects

Poor compliance, defined by the number of missed doses ( $>10\%$  of the total doses during the study period or more than 7 consecutive days without treatment) was seen in two patients receiving placebo but in none of the metformin group. There was no correlation between the number of missed doses and change in HbA<sub>1c</sub> or daily dosage of insulin during the study period.

Side-effects were observed in two adolescents who were randomised to metformin. One of them had nausea and mild abdominal pain during the study period and the other had only mild discomfort from the abdomen at the last visit. Five adolescents who were randomised to placebo experienced gastrointestinal symptoms during the first weeks but subsequently

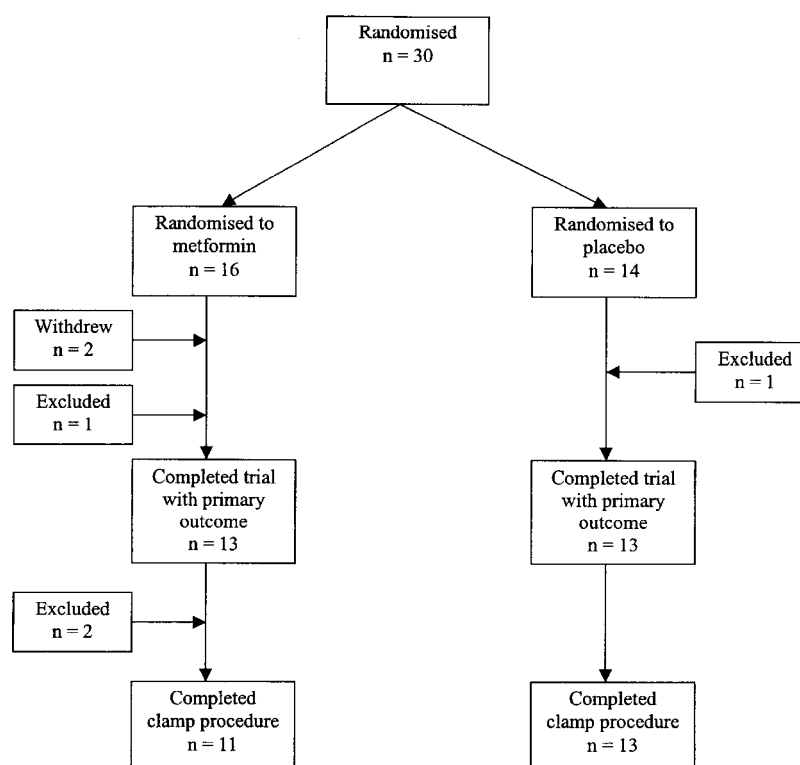


Figure 1 Flow diagram of participants throughout the study.

**Table 2** Treatment effects during the study. Data are numbers or means  $\pm$  s.d., unless otherwise indicated.

	Metformin		Placebo	
	0 month	3 months	0 month	3 months
Number	13	13	13	13
HbA <sub>1c</sub> (%)	9.6 $\pm$ 1.0	8.7 $\pm$ 1.5*	9.5 $\pm$ 1.2	9.2 $\pm$ 1.3
Daily dosage of insulin (U/kg)	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	1.2 $\pm$ 0.2	1.3 $\pm$ 0.2
Weight (kg)				
Median	66.0	67.0	65.0	66.0
Range	56.0–90.0	58.0–86.9	53.0–89.6	55.4–89.5
BMI (kg/m <sup>2</sup> )				
Median	23.5	23.3	23.9	23.3
Range	18.6–35.4	18.4–34.4	17.0–29.2	17.7–29.4
Waist circumference (cm)	84.2 $\pm$ 11.6	81.6 $\pm$ 7.2	82.3 $\pm$ 8.6	83.3 $\pm$ 9.4
IGF-I ( $\mu$ g/l)	203 $\pm$ 46	212 $\pm$ 55	248 $\pm$ 62	229 $\pm$ 62
IGFBP-1 ( $\mu$ g/l)				
Median	87	48	42	67
Range	8–394	12–117	13–183	6–219

\*  $P < 0.05$  comparing the metformin group before and after metformin therapy (Student's *t*-test).

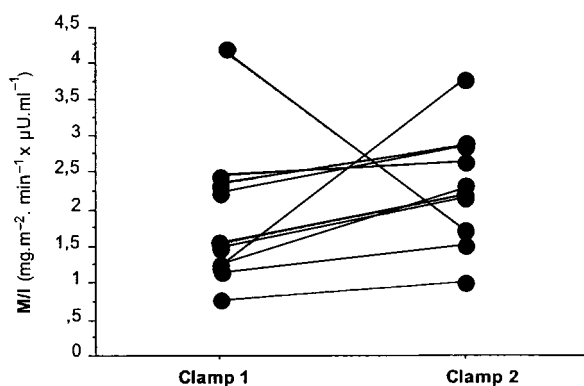
felt well. One subject with placebo treatment had stomach pain throughout the study. None of the participants in the metformin group had to decrease the dosage of metformin. No case of diabetic ketoacidosis, lactic acidosis or severe hypoglycaemia occurred

during the study period in either the metformin or placebo group.

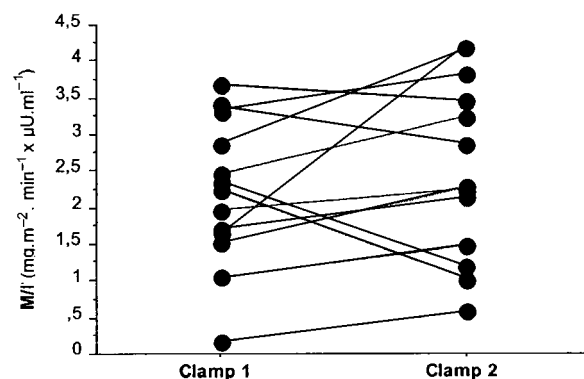
### Insulin sensitivity

Mean glucose and insulin concentrations during the steady-state are displayed in Table 3. There were no significant differences between the groups in either of the two clamps. Neither the M/I values nor the M values were significantly different between the groups at baseline or after 3 months. The M values were unchanged in both groups. M/I, however, increased significantly in the metformin group during the study ( $P < 0.05$ ), but was unchanged in the placebo group (Fig. 2, Table 3). In the metformin group, change in insulin sensitivity (M/I) showed no association with initial HbA<sub>1c</sub>, insulin dosage or change in insulin dose. However, there was a significant positive association between change in insulin sensitivity and initial M/I ( $r = 0.77$ ;  $P < 0.01$ ), indicating that patients with lower initial insulin sensitivity benefited most from metformin treatment.

A.



B.



**Figure 2** Individual values for change in insulin sensitivity (M/I) in the metformin (A) and placebo group (B).

### Body composition

Waist and hip circumference values were obtained from 23 patients on inclusion and 21 patients (10 placebo; 11 metformin) at the end of the study period. We found no significant changes in BMI, weight, waist circumference or W/H ratio (metformin:  $0.83 \pm 0.06$  to  $0.79 \pm 0.04$ ; placebo:  $0.83 \pm 0.08$  to  $0.83 \pm 0.06$ ) during the study period (Table 2). There was no significant gender difference in change in body weight.

### Other metabolic effects

The IGF-I and IGFBP-1 values did not change during the study and showed no significant difference between

**Table 3** Measurements from the hyperinsulinaemic euglycaemic clamp. Data are numbers or means  $\pm$  S.D., unless otherwise indicated.

	Metformin		Placebo	
	0 month	3 months	0 month	3 months
Number	11	11	13	13
Mean glucose concentration during steady state (mmol/l)	5.0 $\pm$ 0.2	5.0 $\pm$ 0.1	4.9 $\pm$ 0.2	4.9 $\pm$ 0.2
Mean insulin concentration during steady state ( $\mu$ U/ml)				
Median	62.4	60.1	67.2	60.9
Range	37.7–147.3	20.9–111.1	35.1–115.9	34.1–94.5
M (mg/m <sup>2</sup> per min)				
Median	101	110	135	143
Range	48–226	76–246	11–200	48–321
M/I (mg/m <sup>2</sup> per min $\times$ $\mu$ U/ml)				
Median	1.5	2.2*	2.0	2.3
Range	0.8–4.2	1.0–3.8	0.2–3.7	0.6–4.2

\*  $P < 0.05$  comparing the metformin group before and after metformin therapy (Wilcoxon signed-rank sum test).

M = amount of glucose infused during steady-state. M/I = the M value divided by mean insulin concentration during steady-state.

the groups either on inclusion or at the end of the study. The median IGFBP-1 seemed to decrease in the metformin group but this change did not reach statistical significance (Table 2).

No differences in blood lipid values were found between the two groups. Nor was there any significant change in lipid levels in either group during the study.

## Discussion

In this randomised placebo-controlled trial of adolescents with poorly controlled type 1 diabetes we found a significant improvement of the mean HbA<sub>1c</sub> from 9.6 to 8.7% with increased peripheral insulin sensitivity in the group receiving metformin, whereas no significant changes were observed in the placebo group. The daily dosage of insulin, weight and blood lipid levels did not, however, change during the study. The majority of adolescents were able to complete the trial without any disturbing side-effects.

Several studies have been undertaken to assess the effects of additional metformin therapy in patients with type 1 diabetes (reviewed by Daniel & Hagmeyer (20)). Most of these studies, however, were conducted before the introduction of HbA<sub>1c</sub> with small samples of mainly adult patients. Recently Hamilton *et al.* (21) reported a 3 month study of metformin in adolescents with poorly controlled type 1 diabetes, and found a significant reduction of HbA<sub>1c</sub> and decreased dosage of insulin. Our findings thus confirm previous observations regarding the effect of metformin on metabolic control.

The insulin-sparing effect during metformin therapy in patients with type 1 diabetes has been reported to be around 25% (22). This is in contrast to our results, where we did not find any reduced need for insulin. This might be explained by the fact that our population was selected from adolescents with poorly controlled type 1 diabetes. A reduction of the insulin dosage was not the primary goal. On the other hand, if the study

had been longer and the effect on metabolic control sustained, we might also have observed effects on the daily dosage of insulin.

The IGF-I/growth hormone (GH) axis is disturbed in adolescents with type 1 diabetes, leading to elevated GH levels (23), contributing to an insulin resistance which is mainly due to impaired peripheral insulin sensitivity (3). It is reasonable to speculate that the main effect of metformin in adolescents with type 1 diabetes is associated with improved peripheral insulin sensitivity. This is in contrast to patients with type 2 diabetes where the effect is mainly mediated by decreased hepatic glucose output (24).

Previous attempts to unravel the mechanism behind the improved metabolic control in metformin-treated adolescents with type 1 diabetes are few. Hamilton *et al.* (21) used the frequently sampled i.v. glucose tolerance test (FSIGT), which was originally designed for subjects with residual pancreatic insulin secretion. Although they used an insulin-modified FSIGT they experienced major methodological problems and their patients were not kept normoglycaemic overnight. Fasting blood glucose levels were thus negatively correlated to insulin sensitivity ( $S_I$ ), and glucose levels tended to increase during the end of the test resulting in a false high  $S_I$ .

Our study is the first to investigate the mechanism behind the metformin effect in adolescents with type 1 diabetes using the euglycaemic hyperinsulinaemic clamp technique. We estimated the peripheral glucose uptake but not the hepatic glucose production and found an improved glucose uptake in the patients treated with metformin but not in the placebo group. We also observed that more insulin-resistant patients benefited most from metformin treatment, as there was an association between initial M/I and both change in HbA<sub>1c</sub> and change in insulin sensitivity. These results emphasise that the metformin effect on peripheral insulin sensitivity seems to be of importance for the obtained metabolic effect in insulin-resistant adolescents with

type 1 diabetes, although simultaneous effects on hepatic glucose production can not be excluded.

In summary, this randomised double-blind placebo-controlled study has shown that adjunctive therapy with metformin in adolescents with type 1 diabetes is efficacious and safe. The effect was associated with an increased peripheral glucose uptake. Metformin might be used in clinical practice but further, larger studies, carried out over longer time periods, are recommended.

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