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Original Article

The addition of rosiglitazone to insulin in adolescents with type 1 diabetes and poor glycaemic control: a randomized-controlled trial

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Objective: To evaluate the effect of rosiglitazone, an insulin sensitizer, on glycaemic control and insulin resistance in adolescents with type 1 diabetes mellitus (T1DM)
Research design and methods: Randomized, double-blind, placebo-controlled crossover trial of rosiglitazone (4 mg twice daily) vs. placebo (24 wk each, with a 4 wk washout period). Entry criteria were diabetes duration >1 yr, age 10–18 yr, puberty (≥Tanner breast stage 2 or testicular volume >4 mL), insulin dose ≥1.1 units/kg/day, and haemoglobin A1c (HbA1c) >8%. Responses to rosiglitazone were compared with placebo using paired *t*-tests.
Results: Of 36 adolescents recruited (17 males), 28 completed the trial. At baseline, age was 13.6 ± 1.8 yr, HbA1c 8.9 ± 0.96%, body mass index standard deviation scores (BMI-SDS) 0.94 ± 0.74 and insulin dose 1.5 ± 0.3 units/kg/day. Compared with placebo, rosiglitazone resulted in decreased insulin dose (5.8% decrease vs. 9.4% increase, $p = 0.02$), increased serum adiponectin (84.8% increase vs. 26.0% decrease, $p < 0.01$), increased cholesterol (+0.5 mmol/L vs. no change, $p = 0.02$), but no significant change in HbA1c (−0.3 vs. −0.1, $p = 0.57$) or BMI-SDS (0.08 vs. 0.04, $p = 0.31$). Insulin sensitivity was highly variable in the seven subjects who consented to euglycaemic hyperinsulinaemic clamps. There were no major adverse effects attributable to rosiglitazone.
Conclusion: The addition of rosiglitazone to insulin did not improve HbA1c in this group of normal weight adolescents with T1DM.

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Key words: Type 1 Diabetes – insulin resistance – poor glycaemic control

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In type 1 diabetes mellitus (T1DM), achieving optimal glycaemic control during adolescence is difficult because of physical, social and psychological factors (1). Physical factors include increased insulin requirement with growth, increased carbohydrate consumption and insulin resistance. Insulin resistance is a feature

of T1DM, particularly with poor glycaemic control (2–4), and of puberty (5, 6). Furthermore, adolescents with obesity and/or a family history of type 2 diabetes have additional risk factors for insulin resistance (7, 8).

Increased insulin doses to overcome insulin resistance, particularly when delivered in a non-physiological way, can lead to excessive weight gain, increased hypoglycaemia (9) and may play a role in polycystic ovarian syndrome (10). Furthermore, intensive insulin therapy may be unacceptable for some patients (9, 11). The use of an oral insulin sensitizer has potential benefits in overcoming insulin resistance without an increased insulin dose, being less intrusive on a young person's lifestyle and reducing the risk of long-term atherosclerotic complications. Metformin has been used in conjunction with insulin in adolescents (12) and adults (13–15) with T1DM resulting in some improvement in glycaemic control. The thiazolidindiones (TZDs) might offer additional advantages over metformin as they also reduce hepatic lipid content (16), inflammatory markers (17), blood pressure (18), microalbuminuria (19) and have less gastrointestinal side effects.

Our aims were (i) to determine whether rosiglitazone, in addition to insulin, would improve the glycaemic control of adolescents with T1DM by ameliorating insulin resistance and (ii) to examine the impact of rosiglitazone on markers of insulin resistance – insulin sensitivity (measured by euglycaemic hyperinsulinaemic clamp), insulin dose and serum adiponectin.

Research design and methods

This was a multicentred, randomized, double-blind placebo-controlled crossover trial involving adolescents with T1DM from the three children's hospitals in New South Wales.

Recruitment

Patients were invited to participate if they met the enrolment criteria: age 10–18 yr, breast development $\geq$Tanner stage 2 or testicular volume >4 mL, insulin dose ≥ 1.1 units/kg/day and haemoglobin A1c (HbA1c) $> 8\%$. These criteria were established to select a group of patients that was likely to be insulin resistant and therefore more likely to respond to an oral insulin sensitizer. Patients with an established history of poor compliance, recurrent diabetic ketoacidosis or hypoglycaemic seizures were excluded. Patients who agreed to participate in the study were asked if they would also undergo the euglycaemic hyperinsulinaemic clamps in addition to the main study protocol. Approval for the study was granted from the institutional ethics committees of Sydney Children's Hospital, John Hunter Children's Hospital and The Children's Hospital at Westmead. Participation was voluntary. Fully informed written consent was obtained from the subjects and their parents.

Thirty-six subjects volunteered to participate and 28 completed the trial. Four subjects whose HbA1c improved to 7–8% between enrolling and commencing treatment, were retained. The investigators withdrew three patients because of non-compliance with insulin and diet resulting in recurrent ketoacidosis or severe hypoglycaemia. Two patients were withdrawn because of change in insulin type and regimen. Three patients withdrew because of reluctance to continue participation in the trial.

Randomization

To ensure a similar number of subjects with each pubertal stage in the treatment arms, subjects enrolled in the study were stratified into two groups, either early or late puberty. Late puberty was defined in girls as postmenarche or $\geq$Tanner IV breast development, and in boys as testicular volume ≥ 10 mL. Randomization of permuted blocks was performed by the Prince of Wales Hospital clinical trials pharmacy. Clinicians and subjects were blinded to the treatment arm. A placebo identical in appearance to 4 mg rosiglitazone tablets was provided by GlaxoSmithKline (Boronia, Australia).

Treatment

The subjects received rosiglitazone then placebo (group B) or reverse order (group A) with a 4-wk washout period between treatments (Fig. 1). The rosiglitazone dose was 2 mg twice daily for 4 wk then 4 mg twice daily for 20 wk. Subjects were reviewed at baseline, then every 12 wk, with an extra visit 4 wk after the commencement of each treatment period to monitor for side effects. Routine diabetes care was provided, including ready access to the study co-ordinator and regular telephone contact to monitor compliance. Subjects were requested to perform at least four blood glucose readings each day.

Each patient remained on the same insulin type and regimen for the duration of the trial. Insulin adjustments were made with the aim of achieving preprandial blood glucose values of 4–8 mmol/L. In general, dose adjustments were 10% of the total daily dose, except when there was recurrent symptomatic hypoglycaemia or persistent elevation of blood glucose level (BGL) above target range when adjustments of up to 20% of the total daily dose were made. Subjects were followed by weekly calls after any dose adjustment to assess their progress and were encouraged to ring the investigator prior to any insulin adjustments.

Outcomes

The primary outcome was improvement in glycaemic control. This was assessed by HbA1c and by the average fasting blood glucose level over the 2 wk preceding

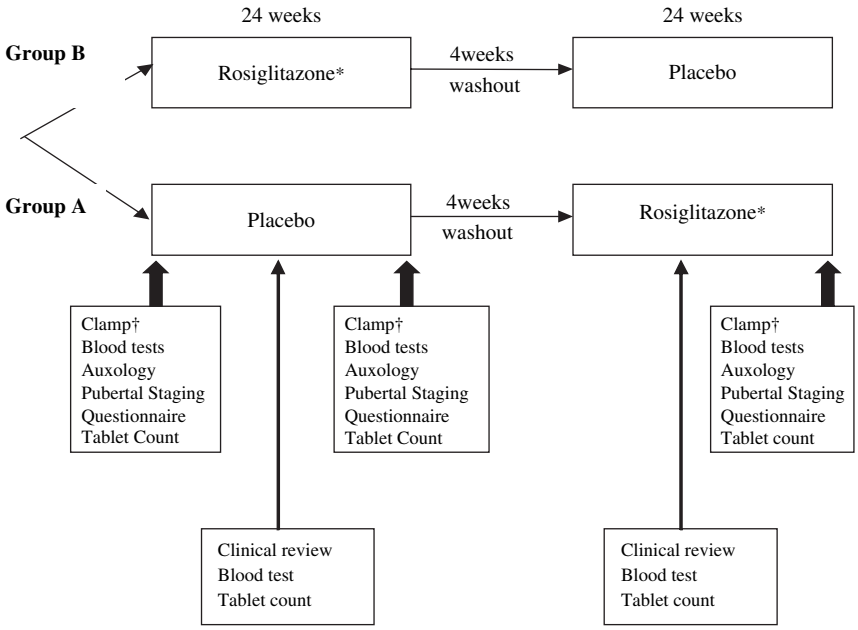

Fig. 1. Flow diagram illustrating the study protocol. *The dose of rosiglitazone was 2 mg twice daily for 4 wk then 4 mg twice daily. †Clamps were performed in a subset.

each visit. We also invited a group of patients to have continuous glucose monitoring (CGMS Gold; Medtronic, Northridge, CA, USA) at baseline and at the end of each arm, but the data could not be analysed because only one subject completed all three CGMS recordings.

Secondary outcome measures included: (i) markers of insulin sensitivity: euglycaemic hyperinsulinaemic clamps (in seven patients), insulin dose and serum adiponectin; (ii) body composition: height measured by stadiometer, weight by electronic scales, skinfold thickness (triceps, subscapular and suprailiac measured by Harpenden callipers in duplicate and averaged), waist circumference measured at the level of the umbilicus (5), and body mass index standard deviation scores (BMI-SDS) calculated using age- and sex-specific data from the Centre of Disease Control (CDC) (20); (iii) adverse events and biochemical parameters to monitor safety: number of episodes of severe hypoglycaemia (defined as hypoglycaemic seizure or decreased conscious state requiring glucagon treatment), non-fasting total and high-density lipoprotein cholesterol and triglycerides, electrolytes, liver function tests and full blood count and (iv) quality of life measured by the child health questionnaire (21, 22).

All measurements and insulin dose adjustments were performed by a single physician (M. L. S.) who attended each study centre during the trial. Compliance with the study medication was estimated by tablet count. Carbohydrate consumption was estimated by a 3-d food diary to estimate the extent to which any changes in insulin dose were because of changes in carbohydrate consumption. Reported hours of exercise per week were recorded at each clinic visit.

Euglycaemic hyperinsulinaemic clamp studies

This technique for measuring insulin sensitivity has been described previously (23). In brief, patients were admitted to a day stay ward in the hospital after an overnight fast. Two intravenous cannulae were inserted. The sampling arm was kept warm with a thermostatically controlled heat pad. The blood glucose level was lowered to less than 10 mmol/L by intravenous insulin infusion prior to commencing the clamp. The insulin infusion was then increased to 40 mU/m^2/h and the blood glucose level maintained at 5 mmol/L by adjusting the rate of an infusion of 25% glucose. The blood glucose level was monitored every 10 min using a YSI glucose analyzer, (Yellow Springs Instruments, Yellow Springs, OH, USA). The insulin sensitivity was calculated according to the volume of 25% glucose infused during a 40-min period during which the blood glucose level was maintained at 5 mmol/L $\pm$ 10%. To check that an appropriate level of hyperinsulinaemia was achieved, serum insulin was measured at least twice during the period of euglycaemia.

Assays

HbA1c was measured by high pressure liquid chromatography (Variant; Bio-Rad Laboratories, Munich, Germany). Cholesterol and triglycerides were measured by an automated enzymatic colorimetric assay (Beckman Synchron LXi; Beckman Coulter Inc, Fullerton, CA, USA). Adiponectin was measured by radioimmunoassay (Linco, St Louis, MO, USA) with intraassay coefficient of variations (CV) 1.8%. dehydroepiandrosterone

(DHEAS) was measured as a marker of adrenarche by chemiluminescent immunometric assay (Immulite 2000). Insulin like growth factor (IGF-1) was measured as a marker of growth hormone secretion by a two-site chemiluminescent immunoassay (Nichols Advantage, San Clemente, CA, USA) with intraassay CV 5.2%. Insulin was measured by radioimmunoassay (Linco) after washing the serum with 15% polyethylene glycol to precipitate insulin antibodies (24).

Statistics

Baseline statistics are reported using mean and SDS for normally distributed data and median and range for skewed data. The difference in study parameters during treatment with placebo and rosiglitazone was assessed using paired *t*-tests or the Wilcoxon test for skewed data. Subjects who did not complete the study were not included in this analysis. For parameters with large variation between subjects, the percentage change from baseline parameters was also used. A sample size of 33 patients was estimated based on 80% power to detect a difference in HbA1c of 0.5 and 95% significance. Of 36 patients enrolled, 28 completed the trial, which gives 80% power to detect a difference in HbA1c of 0.55.

Results

Patients

Twenty-eight subjects completed the trial. The two groups had comparable baseline characteristics and both groups had more subjects in late than early puberty (Table 1). Four patients were treated with an angiotensin converting enzyme (ACE) inhibitor, three for hypertension and one for persistent microalbuminuria.

Effect on glycaemic control

The mean of all HbA1c values measured during the trial was 8.7 ± 0.62%. The reduction in HbA1c during treatment with rosiglitazone was not significantly different from that during placebo. There was no significant change in fasting blood glucose (Table 2).

Effect on insulin sensitivity

The subgroup of seven patients who had euglycaemic hyperinsulinaemic clamps had a significantly lower HbA1c (8.1 ± 0.8% vs. 9.1 ± 0.9%, p = 0.01) than the remaining subjects but otherwise comparable clinical characteristics. The insulin sensitivity was highly variable between individuals at baseline, and there was no consistent change during the trial. Only two of the seven subjects had an improvement in insulin sensitivity of greater than 10% on rosiglitazone. The improvement in these subjects could not be predicted by initial HbA1c, age, BMI-SDS, pubertal stage or compliance.

Insulin dose decreased during treatment with rosiglitazone compared with placebo (Table 2). This could not be explained by any significant change in

Table 1. Baseline clinical characteristics of the two randomized groups

	A (n = 18)	B (n = 18)
Male	10	7
Age (yr)	13.6 ± 1.6	13.6 ± 2
Puberty		
Tanner 2–3	6	6
Tanner 4–5	12	12
BMI (kg/m^2)	22.3 ± 3.9	23.8 ± 4.0
BMI-SDS	0.87 (−0.03 to 1.5)	1.1 (0.5–1.7)
BMI-SDS >2.0	2	2
Waist circumference (cm)	74.8 ± 10.5	75.9 ± 8.7
HbA1c (%)	8.8 ± 0.92	9.0 ± 1.0
Fasting glucose (mmol/L)	11.2 ± 2.3	10.7 ± 4.3
Number of daily insulin injections		
2	3	3
3	9	9
4	6	6
Insulin dose (units/kg/day)	1.5 ± 0.26	1.5 ± 0.4
Cholesterol (mmol/L)	4.6 ± 0.83	4.3 ± 1.4
HDL cholesterol (mmol/L)	1.3 ± 0.47	1.3 ± 0.49
Triglycerides (mmol/L)	0.85 (0.6–2.5)	1 (0.5–1.8)
Adiponectin (ng/mL)	19.5 ± 6.5	15.5 ± 4.4
DHEAS (mmol/L)	3.8 ± 2.2	3.1 ± 1.3
IGF-1 (ng/mL)	285 (240.8–409.9)	305.0 (252.6–323.4)

HbA1c, haemoglobin A1c; BMI-SDS, body mass index standard deviation scores; HDL, high-density lipoprotein.The table summarizes the baseline clinical characteristics of the two randomized groups. Group A received placebo followed by rosiglitazone. Group B received rosiglitazone followed by placebo. The number, mean ± SD or median (interquartile range) are reported.

Table 2. Changes in outcome parameters during treatment arms

	Placebo			Rosiglitazone			
	Pre	Post	Change in parameters†	Pre	Post	Change in parameters†	p
HbA1c (%)	8.7 ± 1.0	8.5 ± 1.5	−0.1 ± 1.1	8.6 ± 1.0	8.4 ± 1.0	−0.3 ± 1.1	0.57
Fasting blood glucose (mmol/L)	11.12 ± 1.2	11.17 ± 2.2	−0.8 (−5.2, 5.4)	10.37 ± 2.9	11.1 ± 2.1	0.8 (−5.6, 5)	0.78
Insulin dose (units/kg/day)	1.5 ± 0.36	1.6 ± 0.43	0.12 ± 0.3	1.57 ± 0.39	1.52 ± 1.51	−0.11 ± 0.4*	0.01
% change in insulin dose			9.4 ± 0.22			−5.8 ± 0.25*	0.02
BMI-SDS	1.1 (−0.6 to 2.6)	1.1 (−0.8 to 2.6)	0.04 ± 0.22	1.0 (−0.1 to 2.4)	1.1 (−0.4 to 2.6)	0.08 ± 0.33	0.5
Waist circumference (cm)	75.4 ± 9.7	77.44 ± 10.3	2.5 (−8 to 7.2)	78.35 ± 10.49	80.7 ± 9.67	1.7 (−9.5 to 15)	0.78
Sum skinfolds (cm)	20.8 ± 12.87	20.39 ± 10.39	−0.76 ± 6.2	20.44 ± 10.39	23.46 ± 14.19	3.5 ± 9.7	0.05
Cholesterol (mmol/L)	4.57 ± 0.79	4.53 ± 0.86	0 ± 0.6	4.43 ± 0.86	4.46 ± 1.57	0.5 ± 0.9*	0.02
HDL (mmol/L)	1.29 ± 0.48	1.25 ± 0.42	−0.05 ± 0.3	1.24 ± 0.45	1.30 ± 0.41	0.05 ± 0.3	0.2
LDL (mmol/L)	2.44 ± 0.87	2.79 ± 1.08	−0.08 ± 0.5	2.68 ± 0.76	2.55 ± 0.88	0.34 ± 0.6*	0.01
Triglycerides (mmol/L)	2.68 ± 0.76	2.55 ± 0.88	0.0 ± 1.0	2.44 ± 0.87	2.79 ± 1.08	0.1 ± 0.6	0.9
Adiponectin (ng/L)	23.5 ± 9.0	16.6 ± 6.1	−5.2 ± 9.7	16.0 ± 5.7	27.9 ± 9.6	11.9 ± 10	<0.01
% change in adiponectin			−25 (−77 to 16)			84.8 (6.6 to 423)	<0.01
IGF-1	309.2 (142.1–496.5)	315.1 (152.5–506.2)	27.1 ± 79.5	339.5 (193.7–472.6)	344.9 (138–489)	−5.6 ± 126.2	
% change in IGF-1			4 (−22.8 to 58.6)			0 (−40.4 to 40.4)	0.9

Raw data includes the mean and SD before and after each arm of the trial.
HbA1c, haemoglobin A1c; BMI-SDS, body mass index standard deviation scores; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*$p < 0.05$ for difference between means.
†Data are mean ± SD or median (range) of the difference in outcome during treatment with rosiglitazone (for group A week 52 compared with 24, for group B week 24 compared with week 0) and placebo (for group A week 24 compared with week 0, for group B week 52 compared with week 24). Paired *t*-tests, (or sign rank test for skewed data) were used to test the statistical significance between changes in parameters during treatment with rosiglitazone or placebo.

carbohydrate consumption (assessed by food diary) or the number of hours of exercise per week.

Serum adiponectin increased during treatment with rosiglitazone in 23 of the 28 subjects (Table 2). The median increase in adiponectin on rosiglitazone compared with placebo was 8.9 ng/mL (range −1.5 to 36 ng/mL). There was no correlation between change in adiponectin level and changes in HbA1c or insulin dose. We could not detect a significant correlation between change in serum adiponectin with rosiglitazone and compliance ($r = 0.37$, $p = 0.09$).

Effect on body composition and biochemical parameters

There was no significant change in BMI-SDS or waist circumference on rosiglitazone compared with placebo. The average of sum of skinfold thickness increased slightly during treatment with rosiglitazone, although this was of borderline statistical significance ($p = 0.05$; Table 2). Total and low-density lipoprotein (LDL) cholesterol increased during treatment with rosiglitazone (Table 2). There was no significant change in DHEAS or IGF-1.

Compliance

Compliance with the study medication (estimated by tablet count in those who returned their tablet bottles) was 70% (median), range 20–80%. Seventy-five per cent of subjects returned at least one tablet bottle, the median number of bottles returned was 1, range 0–5. There was no significant improvement in HbA1c on rosiglitazone in those whose compliance was estimated to be greater than 50% ($n = 26$) or greater than 80% ($n = 15$).

Adverse events

There were no serious adverse events attributable to rosiglitazone. Two subjects had multiple episodes of severe hypoglycaemia, both in the placebo arm. Factors contributing to these episodes included exercise without insulin adjustment or extra carbohydrate intake and delayed food intake after insulin administration. Diabetic ketoacidosis (DKA) occurred in three subjects during rosiglitazone and two subjects during placebo arms. Insulin omission was responsible for all episodes of DKA. Two subjects experienced nausea, both in the placebo arm. No subjects experienced oedema. There were no abnormalities in liver function tests, haemoglobin, leucocyte count or electrolytes. There was no change in quality-of-life scores.

Conclusions

In this cohort of adolescents with T1DM, the addition of rosiglitazone to insulin was not effective in improving glycaemic control. However, there was a relative increase in serum adiponectin and decrease in insulin dose after 24 wk of rosiglitazone, suggesting improvement in insulin sensitivity.

Poor compliance with study medication, and possibly also insulin, diet and blood glucose testing, may also have limited our study's ability to detect a significant improvement in HbA1c. Our study population was certainly less compliant than is ideal for a clinical trial, but was representative of adolescents in a clinic setting who need to improve their glycaemic control. Furthermore, compliance with the study medication was sufficient to achieve a substantial change in adiponectin level. HbA1c is, however, a crude estimate of glycaemic control as it averages the swings in blood glucose levels. Continuous glucose monitoring may have detected a difference and we did attempt to measure this; however, only one subject tolerated monitoring at baseline, 24 wk and 52 wk.

Our results are consistent with those of a randomized-controlled trial of pioglitazone in a similar group of adolescents (25). A trial of rosiglitazone in obese adults with T1DM found a greater decrease in insulin dose than in our patients (26). Both groups in the adult study had a fall in HbA1c but there was no significant difference between rosiglitazone and placebo, similar to our results. Within the rosiglitazone group, the adult T1DM subjects with BMI > 30 kg/m^2 had significantly greater improvement in HbA1c, suggesting that an obese subgroup may benefit. We could not identify a benefit in an obese subgroup, but our study had only four subjects with BMI-SDS >2. A clinical trial of pioglitazone in normal weight adults with T1DM (BMI: 18–24.9 kg/m^2 and HbA1c $< 8\%$) found a greater improvement in HbA1c in the pioglitazone group compared with placebo, without any significant weight gain (27).

Our clamp data did not find the improvement in insulin sensitivity after treatment with rosiglitazone that others have found in T2DM (16, 28). This may either be because rosiglitazone was not effective at improving insulin sensitivity in this population, or that we were unable to identify the change in insulin sensitivity because of the many other confounding factors that operate simultaneously and were unable to be controlled for. In general, euglycaemic hyperinsulinaemic clamps are highly reproducible. Our data would have been improved had we been able to have the subjects on an insulin infusion for 12 h prior to the clamp to ensure a period of euglycaemia at the onset of the clamp. The interindividual variability in insulin sensitivity at the start of the study is interesting and highlights the difficulties predicting insulin sensitivity based on clinical criteria.

The majority of our patients had the expected increase in serum adiponectin during treatment with rosiglitazone. This is consistent with studies in adults

treated with TZDs and this effect correlates with changes in hepatic fat and hepatic glucose production (16, 29, 30). We could not demonstrate any significant correlation between the change in adiponectin and HbA1c, insulin dose or compliance with rosiglitazone. Previous studies in non-diabetic and type 2 diabetic populations have shown that low levels of adiponectin are associated with insulin resistance and adiposity (31–36). In contrast, adiponectin levels are reported to be normal or elevated in T1DM, with inconsistent relationships with insulin treatment, glycaemic control and BMI (37–39).

There were no major adverse effects directly attributable to rosiglitazone. Unlike studies in adults (40), we did not find significant weight gain (assessed by BMI-SDS) or increased waist circumference during treatment with rosiglitazone as compared with the placebo, although there was a small increase in skinfold thickness of borderline significance. A more comprehensive assessment of body composition and abdominal adiposity, such as by dual energy X-ray absorptiometry (DEXA) and CT scan, would have been interesting. The absence of weight gain in our patients may reflect the absence of coexistent cardiac and renal impairment that is common in adults with T2DM and thus our patients may be less sensitive to the fluid retention (41) that the TZDs can cause. A redistribution of fat from the periphery has been described with TZDs and may be responsible for the increased skinfold measurements that we observed. We found increased total and LDL cholesterol, consistent with previous reports in adults (40, 42). Despite the increase in cholesterol, rosiglitazone is reported to have other antiatherogenic effects of uncertain mechanism, and to reduce intrahepatic fat.

Our results do not support the use of rosiglitazone as an adjunct treatment for adolescents with T1DM during puberty. Optimal glycaemic control in adolescents with T1DM requires adequate doses of insulin given in the most physiological way possible. For some adolescents, intensification of the treatment using multiple daily injections or an insulin pump is effective at improving glycaemic control. For others, improving self-management competency (43), reducing family conflict, enhancing motivation (44) or increasing the frequency of blood glucose testing is required before any benefit can be obtained from intensive insulin therapy. Although we did not find any serious adverse effects attributable to rosiglitazone after 24 wk of treatment, recent concerns about the effect of rosiglitazone on cardiovascular function (45) and bone metabolism (46–48) have been raised and require further study.

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