Paediatrics

Pioglitazone in adolescents

Krystyna Matyka, Senior Lecturer in Paediatrics, University of Warwick Medical School

Difficulties in adherence to intensive treatment strategies for diabetes are often believed to account for the deterioration in glycaemic control seen in adolescents with type 1 diabetes. However, there are also important contributions of the dramatic changes in the hormonal milieus that occur during this time of accelerated development. Supraphysiological concentrations of growth hormone and increases in sex steroid production contribute to the insulin resistance of puberty that necessitates increases in insulin dose – sometimes to almost double the dose prescribed for prepubescent children on a per kilogram basis. These high doses do not always result in improved glycaemic control but can lead to an increased risk of hypoglycaemia.

The 195 adolescents aged between 13 and 17 years who participated in the Diabetes Control and Complications Trial (DCCT; DCCT Research Group, 1994) found it more difficult to achieve a lower HbA_{1c} than their adult counterparts (8.06 % ± 0.13 % versus 7.12 % ± 0.03 %; $P < 0.001$), yet they had a greater tendency towards severe hypoglycaemia (85.7 events per 100 patient years versus 56.9 events in the adult cohort). Large doses of insulin can also lead to unwanted weight gain, which seems to be a greater problem for young women and can lead to an increased cardiovascular risk.

Insulin sensitising agents such as metformin are now being prescribed to people with type 1 diabetes who are also felt to have features of insulin resistance, although data on the effectiveness of such interventions are limited. The thiazolidinediones decrease insulin resistance, primarily through enhancing peripheral glucose utilisation, and are used in the management of type 2 diabetes. In this randomised controlled study by Zdravkovic et al (summarised on right), adolescents were selected on the basis of their HbA_{1c} and insulin dose to receive either pioglitazone (15 mg once a day for 4 weeks increasing to 30 mg if tolerated) or placebo. At the end of the 6-month study, there were no significant differences in glycated haemoglobin or insulin dose between the two groups. In addition, the pioglitazone group gained weight during the 6-month study period with a significant increase in BMI standard deviation score compared with those in the placebo group.

So, does this mean that pioglitazone is of no use? I am not sure that it does. The study group size was small: only 18 in the pioglitazone group and 17 in the placebo group. The groups were also quite heterogeneous with roughly 25 % in early puberty, but an equal ratio of females to males. With such small numbers, these variables may have had a significant effect on outcome. The definition of insulin resistance used to identify study participants also appears to be somewhat arbitrary: a range of HbA_{1c} from 7.5 % – 11 % and a mean dose of insulin greater than 0.9 U/kg/day.

It would be unwise to dismiss thiazolidinediones as a useful adjunct to the management of type 1 diabetes in adolescents. Further studies to examine the impact of thiazolidinediones and/or metformin on insulin resistance using hyperinsulinaemic euglycaemic clamp studies in homogeneous groups of adolescents both with and without diabetes would provide greater information on their potential benefits. These data could then inform the design of larger randomised controlled trials, which would help clinicians manage this challenging group.

The Diabetes Control and Complications Trial Research Group. (1994) Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *Journal of Pediatrics* **125**: 177–188

JOURNAL OF PEDIATRICS

Pioglitazone for glycaemic control in adolescents with type 1 diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Adolescents with type 1 diabetes were administered either pioglitazone (n=18) or placebo (n=17) along with their standard therapy to determine the effect of pioglitazone on metabolic control.

2 Inclusion criteria for this randomised, placebo-controlled trial were a mean insulin requirement of >0.9 U/kg/day and an HbA_{1c} of 7.5–11 %.

3 Along with HbA_{1c}, insulin dose, BMI, lipids and waist-to-hip ratio were taken as outcome measures.

4 At 6 months, all individuals had improved glycaemic control ($P=0.02$).

5 HbA_{1c} improvement was not significantly different between those receiving pioglitazone (0.4 ± 0.9 % from a mean of 8.8 at baseline) and those on placebo (0.5 ± 1.2 % from a mean of 8.9 at baseline; $P=0.67$).

6 There was, however, a significantly greater increase in BMI in the pioglitazone group compared with controls (0.3 kg/m^2 ± 0.3; $P=0.01$).

7 The authors concluded that pioglitazone does not improve glycaemic control in adolescents with type 1 diabetes and that the lower levels of HbA_{1c} in both groups was possibly due to better diet or insulin adherence.

8 There was a greater improvement in glycaemic control when only those with a BMI above 30 kg/m^2 were analysed, suggesting that pioglitazone had no effect here owing to the low BMI of this particular study group.

Zdravkovic V, Hamilton JK, Daneman D, Cummings EA (2006) Pioglitazone as adjunctive therapy in adolescents with type 1 diabetes. *Journal of Pediatrics* **149**: 845–9

"Measuring the degree of albumin excretion is a feasible option for identifying the risk of nephropathy, especially when combined with elevated HbA_{1c} value."

DIABETES CARE

Retinopathy screening in young people with diabetes

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Type 1 diabetes is associated with asymptomatic microvascular disease. Therefore, frequent screening for diabetic retinopathy in adolescents with diabetes is recommended.

2 Elevated HbA_{1c} levels are used as an indication that screening may be necessary. In the past, recorded HbA_{1c} levels were higher than those found in young people today. As a result of this and because many paediatric clinics do not have state-of-the-art equipment to perform eye screening, the authors aimed to compare clinical outcomes and cost–effectiveness of retinopathy screening with blood pressure and microalbuminuria screening.

3 The chart analysis included 130 people between 10 and 21 years of age who had a duration of type 1 diabetes of more than 3 years and had written reports from an examining opthalmologist or optometrist.

4 Mean HbA_{1c} was less than 8% and diabetic retinopathy had only been identified in three individuals, however one case was a misdiagnosis.

5 In contrast, hypertension was reported in 19 cases and microalbuminuria in seven.

6 The total cost of eye examinations if all 130 individuals had commenced screening after 3 or 5 years of diabetes (American Diabetes Association recommendations) would have been US$96 615 and US$67 170, respectively.

7 The authors conclude that screening for diabetic retinopathy should not be based solely on age and duration of diabetes as this would lead to large and unnecessary health costs.

8 Screening for youths with hypertension, microalbuminuria or elevated HbA_{1c} would be more cost effective.

Huo B, Steffen AT, Swan K et al (2007) Clinical outcomes and cost-effectiveness of retinopathy screening in youth with type 1 diabetes. *Diabetes Care* **30**: 362–3

DIABETIC MEDICINE

Insulin detemir and NPH insulin control of blood glucose

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 The ability of insulin detemir to control HbA_{1c} and fasting plasma glucose in children with type 1 diabetes was compared with that of Neutral Protamine Hagedorn human isophane (NPH) insulin.

2 Children aged 6–17 years were administered either insulin detemir (n=232) or NPH insulin (n=115), plus premeal insulin aspart.

3 HbA_{1c} improved by approximately 0.8% in each group.

4 Those on insulin detemir had a lower and more predictable fasting plasma glucose (8.4 versus 9.6 mmol//l for NPH insulin; $P<0.022$) and a 26% lower risk of nocturnal hypoglycaemia ($P=0.041$).

5 The mean BMI was also lower with insulin detemir ($P=0.001$), suggesting a clinical advantage.

Robertson KJ, Schoenle E, Gucev Z et al (2007) Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. *Diabetic Medicine* **24**: 27–34

DIABETIC MEDICINE

Albumin excretion can identify those at risk for nephropathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This study aimed to investigate whether or not there is an association between high albumin excretion in early puberty and the subsequent development of microalbuminuria and proteinuria.

2 Longitudinal data on the albumin: creatinine ratio in three early-morning annual samples were collected for 554 individuals from the Oxford Regional Prospective Study of Childhood Diabetes.

3 Each individual was assigned an albumin excretion phenotype defining deviation from the mean of regression models. Covariates included age, duration of diabetes and gender.

4 Tertiles of the albumin excretion phenotype significantly predicted the risk of developing microalbuminuria and all individuals who developed proteinuria had high albumin secretion or HbA_{1c} above 9% at 11–15 years of age.

5 The authors concluded that measuring the degree of albumin excretion is a feasible option for identifying the risk of nephropathy, especially when combined with elevated HbA_{1c} values.

Dunger DB, Schwarze CP, Cooper JD et al (2007) Can we identify adolescents at high risk for neuropathy before the development of microalbuminuria? *Diabetic Medicine* **24**: 131–6

NUTRICION HOSPITALARIA

Children with food insecurity develop diabetes in adulthood

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 Mexican children were studied to determine their perceptions of hunger and their risk of becoming overweight in adulthood.

2 Anthropometric status was measured in 1200 children and perception of hunger in 1452 between 2001 and 2003. Information on hunger was collected using a questionnaire.

3 The total prevalence and risk of becoming overweight did not differ over time for either gender.

4 Abdominal obesity had increased in the 2003 group among girls over 9 years old ($P<0.001$) and the risk of hunger was higher (58%) than in 2001 (46%).

5 The authors conclude that children suffering from food insecurities are more likely to develop diabetes and obesity in adulthood. If they show rapid catch-up fat following economic recession periods, the risk is increased.

Jimenez-Cruz A, Bacardi Gascon M (2007) Prevalence of overweight and hunger among Mexican children from migrant parents. *Nutricion Hospitalaria* **22**: 85–8

"Children suffering from food insecurity are more likely to develop diabetes and obesity in adulthood."