

# Type 2 diabetes in childhood

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## Article points

1. The prevalence of type 2 diabetes in childhood has increased considerably in recent years.
2. New evidence is emerging for a structured way forward in regard to the diagnosis and management of type 2 diabetes in children and young people.
3. The author concludes that efforts need to be focussed on increasing our understanding of the mechanisms of ethnic risk and tackling childhood obesity.

## Key words

- Childhood obesity
- Education
- Ethnic risk
- Management

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**Although the vast majority of children with diabetes have type 1 diabetes, there has been a considerable increase in the prevalence of type 2 diabetes in children over the past two decades, a trend that has been widely attributed to the obesity epidemic. Children most at risk appear to be those who are 10–20 years old with a strong family history of type 2 diabetes. Recent studies have also revealed striking differences in the incidence of type 2 diabetes among children with different ethnic backgrounds, in which children of south Asian origin in the UK are at a significantly greater risk of developing the condition. This article explores the current challenges involved with the diagnosis and management of type 2 diabetes in childhood, in view of the limited number of studies supporting an optimum approach, and evaluates the new body of evidence emerging for a more structured way forward.**

There have been concerns that the global epidemic of obesity would dramatically change the epidemiology of childhood diabetes with the emergence of type 2 diabetes as an important childhood disorder (Alberti et al, 2004). There is no doubt that type 2 diabetes is seen more commonly in paediatric practice than perhaps 10 or 20 years ago but it is not clear whether we are seeing the massive tide that was predicted (Pinhas-Hamiel and Zeitler, 2005). Nevertheless, the emergence of type 2 diabetes as an important differential in childhood diabetes and the pervasiveness of overweight and obesity even in those who have type 1 diabetes is leading to significant diagnostic dilemmas.

## Who is at risk?

The SEARCH for Diabetes in Youth Study is a national, multicentre study aimed at understanding more about diabetes among children and young people in North America. It has been running since 2000 and has provided a number of publications (Wake Forest University School of Medicine, 2012).

The most recent data suggest that between 2002 and 2005, 15 600 children and young people were newly diagnosed with type 1 diabetes annually and 3600 were diagnosed with type 2 diabetes annually (Centers for Disease Control and Prevention, 2011). There was a marked difference in age at diagnosis with type 2 diabetes as the rate of new cases was 0.4 per 100 000 for those under the age of 10 years and 8.5 per 100 000 for those aged 10–19 years. There were also striking ethnic differences. For Asian/Pacific Islander and American Indian children and young people aged 10–19 years, there were more cases of type 2 diabetes than type 1 diabetes. For non-Hispanic black and Hispanic children and young people, the rates of new cases of type 2 diabetes and type 1 diabetes were comparable. Data from the recent survey performed by the Royal College of Paediatrics and Child Health suggest that 1.5% of the 23 000 children reported as having diabetes in England were felt to have type 2 diabetes but there are no epidemiological data about ethnic risk in the UK (Royal College of Paediatrics and Child Health, 2009). Case series also highlight

the significant ethnic risk in the UK, mainly in people from south Asian or Middle Eastern backgrounds (Ehtisham et al, 2004).

### How do we make the diagnosis?

It can be difficult to be confident that a young child has type 2 diabetes, as the presence of ketonuria does not exclude the diagnosis of type 2 diabetes (Pinhas-Hamiel and Zeitler, 2007). Even though many will be overweight or obese, it would not be possible to make a confident diagnosis on weight alone. It should be stressed that if there is any significant doubt that the child may have type 1 diabetes, it is much safer to prescribe insulin and then review the diagnosis in subsequent months in the relative safety of the outpatient department.

Children and young people with type 2 diabetes are likely to be overweight or obese, originate from a particular ethnic background (mainly south Asian origin in the UK), have a strong family history of type 2 diabetes and may have evidence of other features of insulin resistance, such as dyslipidaemia, polycystic ovarian syndrome (PCOS), hypertension and acanthosis nigricans (Alberti et al, 2004). Antibody testing (islet cell and glutamic acid decarboxylase [GAD] antibodies) may be useful, but 10–40% of adults and young people with type 2 diabetes have been shown to have antibodies associated with type 1 diabetes and still not require insulin treatment 12 months post-diagnosis (Turner et al, 1997; Reinhard et al, 2006). Overlap in C-peptide concentrations occurs in people with type 1, type 2 and monogenic diabetes over the first 12 months. This is owing to changes in insulin secretion during the “honeymoon period” and variations in the effect of glucotoxicity or lipotoxicity on insulin secretion in type 1 and type 2 diabetes (International Diabetes Federation, 2011).

### Diabetes management

The majority of children and young people with type 2 diabetes in the UK will be overweight or obese at presentation (Ehtisham et al, 2004). However, data suggest that 30% of children in Japan and up to 50% of Asian Indian urban children are normal weight at diagnosis (Sugihara et al, 2005). It is likely that most people with

diabetes will benefit from improvements in lifestyle interventions. Indeed, the recent International Paediatric and Adolescent Diabetes (ISPAD) guidelines suggest that diet and exercise are the cornerstone of treatment for type 2 diabetes in children and young people, who are asymptomatic at presentation and can maintain their HbA<sub>1c</sub> levels at less than 53 mmol/mol (7%) and blood glucose levels at less than 7.2 mmol/L pre-prandially and 10 mmol/L post-prandially (International Diabetes Federation, 2011). There are few studies that have demonstrated significant benefit in terms of weight management in childhood obesity and there are currently no studies that have examined weight-loss interventions per se in children with type 2 diabetes (Oude Luttikhuis et al, 2009).

### Pharmacological intervention

The most recent guidelines from ISPAD and the International Diabetes Federation (IDF) for the management of type 2 diabetes in childhood provide a useful clinical algorithm (International Diabetes Federation, 2011). This algorithm is based on clinical consensus rather than a robust evidence base. Nevertheless, clinical data are accumulating, which will allow fine-tuning of this set of guidelines in time. The guidelines separate patients at presentation into those who are asymptomatic or mildly symptomatic with abnormal but not high glucose values, versus those who are symptomatic with high glucose values or with ketosis or ketoacidosis. The aim is to maintain pre-prandial blood glucose levels at less than 7.2 mmol/L and post-prandial levels less than 10 mmol/L with HbA<sub>1c</sub> levels at less than 53 mmol/mol (7%).

### Symptomatic at diagnosis (blood glucose >13.9 mmol/L) or with ketosis or ketoacidosis

Metformin alone is unlikely to be beneficial in those individuals with high random blood glucose concentrations or those who are unwell at presentation. These individuals will need insulin – either once-daily long-acting insulin or neutral protamine Hagedorn insulin (International Diabetes Federation, 2011). The aim would be to gradually reduce the insulin dosage as the blood glucose concentrations fall and move over to metformin. The subsequent management of

### Page points

1. Children and young people with type 2 diabetes are likely to be overweight or obese, originate from a particular ethnic background and have a strong family history of the condition.
2. It is likely that most individuals will benefit from lifestyle interventions aimed at weight reduction but few studies have so far emerged to support this strategy.
3. Recent guidelines for pharmacological intervention in diabetes management suggest separating individuals at presentation into those who are asymptomatic or mildly symptomatic with abnormal but not high glucose levels, and those who are symptomatic with high glucose values or with ketosis or ketoacidosis.

**“People with type 2 diabetes and their families are likely to benefit from a greater understanding of the aetiology of type 2 diabetes if they are to manage their condition well.”**

diabetes will follow the same path as for those who are asymptomatic or mildly symptomatic at diagnosis (see next section; International Diabetes Federation, 2011).

#### **Asymptomatic or mildly symptomatic at diagnosis**

Children and young people who have blood glucose levels at less than 13.9 mmol/L and are asymptomatic in terms of osmotic symptoms can be started on lifestyle interventions aimed at weight reduction. Their individual cases should be reviewed monthly with the aim of maintaining pre-prandial blood glucose levels at less than 7.2 mmol/L and post-prandial levels at less than 10 mmol/L with HbA<sub>1c</sub> levels at less than 53 mmol/mol (7%). If the blood glucose and HbA<sub>1c</sub> levels rise or there are osmotic symptoms at presentation, then the patient should be started on a low dose of metformin that can be titrated upwards. If diabetes control is not adequate the second-line treatment is to add in a sulphonylurea or to stop metformin and change to once-daily long-acting insulin such as glargine with a meglitinide. If diabetes control is still not adequate despite good compliance, then adding in metformin to a long-acting insulin analogue with meglitinide may be helpful. Those on a combination of metformin and sulphonylurea should be changed to an insulin analogue with meglitinide if control is not adequate. The addition of a glitazone may be necessary but not in combination with insulin (International Diabetes Federation, 2011). Experience of prescribing oral hypoglycaemic medication in children and young people under the age of 18 years is limited and should be initiated under specialist care. Glitazones, meglitinide and most sulphonylureas are not licensed for anyone under the age of 18 years.

There is little empirical evidence to support this clinical strategy yet it is likely that this plan is being followed by a number of paediatricians, who will develop their clinical skills as they see an increasing number of children with type 2 diabetes. There has been one very recent study published in the *New England Journal of Medicine* this year which deserves detailed mention in view of its size and treatment interventions.

Almost 700 young people aged 10–17 years were randomised to participate in the study, which compared metformin alone versus either metformin with rosiglitazone<sup>1</sup> or metformin with a lifestyle intervention programme (TODAY Study Group et al, 2012). The primary outcome was the time to treatment failure. Treatment failure was defined as a persistently raised HbA<sub>1c</sub> at more than 64 mmol/mol (8%) over a period of 6 months or persistent metabolic decompensation, which was considered as either the inability to wean off insulin within 3 months from starting it for a decompensation or a second episode of decompensation within 3 months of stopping insulin. Approximately 46% of participants achieved the primary outcome over an average follow-up of 3.86 years and a median time to treatment failure of 11.5 months. Rates of failure were high with 51.7% in the group treated with metformin alone, 38.6% in the group treated with a combination of metformin plus rosiglitazone, and 46.6% in the group treated with metformin combined with a lifestyle intervention programme. The combination of metformin plus rosiglitazone was associated with a 25.3% decrease in the primary outcome and was found to be superior to the other two groups. There was no significant difference between treatment with metformin alone or metformin with lifestyle intervention. Treatment adherence declined during the course of the study with an adherence rate of 84% at 8 months to 57% at 60 months, which did not differ across treatment groups (TODAY Study Group et al, 2012).

There were significant differences in BMI between the groups in which the greatest increase in BMI was observed in the metformin plus rosiglitazone group and the lowest in the metformin-only group. However, there was no impact of BMI on the rate of treatment failure. The group also found that the use of metformin alone was least effective in non-Hispanic black participants, suggesting that ethnicity may be an important consideration when choosing treatment regimen. It was also found that the combination of metformin and rosiglitazone appeared to be more effective in females than males.

<sup>1</sup>Rosiglitazone was withdrawn from clinical use in the UK in 2010

Finally, it was found that, for all the treatments, there was no significant benefit on cardiometabolic complications, as the number of cardiometabolic complications increased over time. Upon completion of the study, 33.8% of the study group had hypertension, 10.3% had high LDL, 28.2% had hypertriglyceridaemia and 16.6% had microalbuminuria (TODAY Study Group et al, 2012).

### Diabetes education

Diabetes education is an important component of diabetes management. People with type 2 diabetes and their families are likely to benefit from a greater understanding of the aetiology of type 2 diabetes if they are to manage their condition well. Information will need to address lifestyle issues (which are likely to benefit all members of the family) and provide a greater understanding of the treatments that are being offered. The latter is likely to be more challenging as the available treatments are so diverse. Currently, there are no evidence-based educational programmes for either type 1 or type 2 diabetes in childhood but common sense would suggest that multidisciplinary team involvement providing both structured and *ad hoc* education is necessary (International Diabetes Federation, 2011). The issue of weight management will need to be addressed and may prove challenging. A paper from North America has suggested that it can be difficult for children and families to understand the need for weight loss. The study has shown that among 104 adolescents with type 2 diabetes (mean BMI, 36.4 kg/m<sup>2</sup>), only 41% of parents and 35% of adolescents considered that the adolescent was “very overweight” (Skinner et al, 2008). Of those adolescents with a BMI of more than the 95th percentile, 40% of their parents felt that their child’s weight was “about right” and 55% of these adolescents were happy with their weight. The parents and adolescents observed to have underestimated the weight concerns had poorer dietary and physical activity behaviours than those who were observed to have greater insight (Skinner et al, 2008). Recent demographic shifts in the average weight of the childhood population may mean that peer group comparisons could provide a false sense of security. It is essential not to assume that all children and young people

with a weight problem and type 2 diabetes will recognise the need for weight management as a crucial step in the long-term management of their condition.

### Self-monitoring of blood glucose

The frequency of home blood glucose monitoring will vary according to the treatment regimen. Data from people with type 1 diabetes suggest that increased frequency of home blood glucose monitoring is linked to improved diabetes control although there are no data in children with type 2 diabetes (St John et al, 2010). Those being treated with metformin, meglitinide or glitazone would benefit from the measurement of fasting blood and 2-hour post-prandial glucose concentrations. The frequency of these estimations is difficult to judge but it would seem sensible to perform assessments more frequently when blood glucose concentrations are not well controlled and adjustments to treatment regimen are anticipated. ISPAD guidelines suggest that several fasting values are taken per week and once-daily post-prandial tests are completed after the largest meal of the day (International Diabetes Federation, 2011). Those who are being treated with insulin or sulphonylureas will need to check blood glucose concentrations more frequently to ensure that levels are achieving target ranges and avoid recurrent hypoglycaemia, which may lead to weight gain. Blood should be taken for HbA<sub>1c</sub> levels at least twice a year and more often if control is not good (International Diabetes Federation, 2011).

### Screening for complications

Data suggest that the prevalence of microvascular complications is greater in those with type 2 diabetes and that it leads to end-organ damage even before a diagnosis is made, which may reflect that this condition has a more insidious onset in childhood, as well as in adults (for review, see Pinhas-Hamiel and Zeitler, 2007). It has been shown that 22% of Pima Indians have evidence of microalbuminuria at presentation (Fagot-Campagna et al, 1998). In another study, persistent microalbuminuria has been found in 18% of children with type 2 diabetes compared with 11% of children with type 1 diabetes, despite the children with type 2 diabetes having had diabetes for a

### Page points

1. Information will need to address lifestyle issues (which are likely to benefit all members of the family) and provide a greater understanding of the treatments that are being offered.
2. A study has shown that increasing the frequency of home blood glucose monitoring is linked to improved diabetes control, but there are currently no data in children with type 2 diabetes.
3. Research suggests that complications, such as microalbuminuria and hypertension, appear to be more frequent in children with type 2 diabetes than in children with type 1 diabetes.

*“Although there have been few studies on the optimum approach to management, evidence is now emerging for a structured way forward.”*

shorter duration (Yoo et al, 2004). In contrast, the prevalence of retinopathy is lower among people with type 2 diabetes compared with those with type 1 diabetes (Eppens et al, 2006).

Screening for retinopathy, nephropathy and neuropathy, as well as insulin-resistant phenomena, should be performed annually in all children and young people with type 2 diabetes. Insulin-resistant phenomena include hypertension, dyslipidaemia, non-alcoholic fatty liver disease and symptoms of PCOS in girls. Hypertension has been reported in 10–32% of adolescents with type 2 diabetes and is eight times more frequent than in young people with type 1 diabetes at diagnosis (Zdravkovic et al, 2004). A study comparing children with type 2 diabetes (n=283) versus type 1 diabetes (n=1963) showed that 33% had elevated cholesterol levels, 24% had elevated LDL-cholesterol levels, 29% had high triglyceride concentrations and 44% had low concentrations of HDL-cholesterol (Kershner et al, 2006).

Children found to have hypertension should be treated with an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, as tolerated, which is also recommended for those with type 1 diabetes. Statins may be needed for high LDL or triglyceride levels and metformin may be useful for PCOS, although the benefits of weight loss should also be stressed to these individuals.

### Caution in girls

The risks of poorly controlled diabetes to a healthy pregnancy in both maternal and infant terms are well understood in data from adult women (Balsells et al, 2009). Young women with type 2 diabetes who have polycystic ovarian syndrome may well have difficulty getting pregnant. They may also run into problems not only with respect to high blood glucose concentrations, but also the medications that they are taking, as there are concerns of teratogenicity with statins and some anti-hypertensive medications. Hormonal contraception may be contraindicated in girls with type 2 diabetes who may need specialist advice for methods of birth control.

### Summary

The prevalence of type 2 diabetes in childhood has increased in recent years. Although there have been few studies on the optimum approach

to management, evidence is now emerging for a structured way forward. Current work does suggest that the prognosis for many of these individuals may be poor. Efforts to prevent the development of type 2 diabetes by increasing our understanding of the mechanisms of ethnic risk and tackling childhood obesity need to be paramount. ■

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