The care of adolescents with type 2 diabetes in primary care

Julian Shield

Diagnosing a new case of childhood-onset diabetes is still a relatively infrequent occurrence in primary care. It is estimated that in a large UK general practice, a new case of likely type 1 diabetes will be seen once every 2 years (Ali et al, 2011). However, there has been recent concern that accompanying the increased prevalence of childhood obesity, both primary and secondary care will be faced with a new phenomenon: childhood-onset type 2 diabetes. This article explores these concerns and reviews the evidence on the likelihood of encountering this condition as a GP, the risk factors, diagnostic issues and role of primary care in prevention and treatment.

Article points

1. Adolescents are presenting with polyuria and polydypsia associated with significant obesity, signs of insulin resistance, such as acanthosis nigricans, and negative auto-antibody screening for type 1 diabetes.
2. The prevention of adolescent (and early adult) onset type 2 diabetes will need to include the treatment of childhood obesity.
3. A greater emphasis on developing effective, primary care weight management interventions for obese children and adolescents is urgently required.

Key words

- Adolescence
- Insulin resistance
- Obesity
- Prevention

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While there are no national data for England on levels of overweight and obesity in adolescence, there are good quality data from children in year 6 of primary school (roughly aged 11 years). Although the prevalence may be levelling off, recent figures suggest that one in five children at this age is obese (NHS Information Centre, 2009). In the USA, a rising prevalence of type 2 diabetes in adolescence has mirrored the rise in obesity prevalence. A study by the Writing Group for the SEARCH for Diabetes in Youth Study Group et al (2007) suggested that type 2 diabetes was now almost as likely as type 1 diabetes in those newly diagnosed between the ages of 15 and 19 years.

Until the beginning of this century, many paediatricians in the UK never really considered type 2 diabetes in those presenting to their diabetes practice. However, in 2002 it was reported that adolescents were presenting with polyuria and polydypsia associated with significant obesity, signs of insulin resistance, such as acanthosis nigricans, and negative auto-antibody screening for type 1 diabetes (Drake et al, 2002).

Given the apparent increase in prevalence of obesity among children and further anecdotal reports of type 2 diabetes presenting to paediatricians, a surveillance study in the UK was undertaken through the British Paediatric Surveillance Unit (BPSU) in 2004. This aimed to accurately describe the incidence and presenting features of type 2 diabetes in children and adolescents under the age of 17 years (Haines et al, 2007).

Overall, this study was relatively reassuring as an incidence for the UK was estimated at 0.6

cases per 100 000 per year, a figure far less than that described for type 1 diabetes in approximately the same age population (around 23 cases per 100 000 person years) (Imkampe and Gulliford, 2011). However, there were significant effects on incidence by ethnicity: for the black population the incidence was much higher at 3.9 cases per 100 000 per year and the south Asian population had an intermediate level of 1.25 cases per 100 000 per year. When taken in isolation, the incidence in the white population was very low at 0.35 cases per 100 000 per year. These figures have been borne out by the recent National Diabetes Audit showing that for the white population around 1% of cases being treated in paediatric clinics have type 2 diabetes but that in south Asian people, type 2 diabetes accounts for almost 10% of cases and for the black population the figure stands at around 6% (NHS Information Centre, 2010).

Risk factors for type 2 diabetes

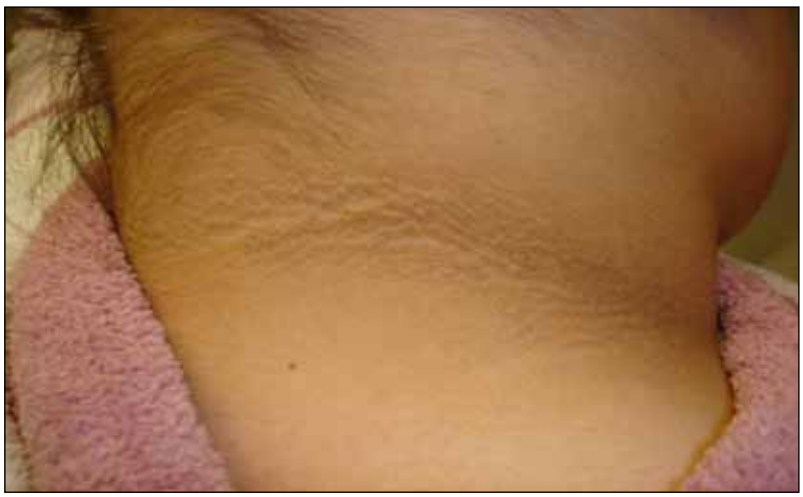
The BPSU study (Haines et al, 2007) identified certain risk factors that should alert clinicians to the possibility of overt or sub-clinical type 2 diabetes. Ninety-four per cent of cases in the survey were overweight with 75% being classified as obese. The average BMI for this cohort was 32.5 kg/m^2 (BMI Standard Deviation [SD] score of +2.9) and average age at presentation was 13.6 years. There was a slight excess of females (55%). In two thirds of cases, a first degree relative (usually a parent) also had a diagnosis of type 2 diabetes. Over 50% had the clinical features of acanthosis nigricans at presentation (*Figure 1*). Acanthosis nigricans is a brown velvety rash often seen under the arms, on the knuckles and around the neck, which has a well recognised association with insulin resistance and type 2 diabetes (Stoddart et al, 2002). Around 25% of females at diagnosis had clinical and/or biochemical evidence of polycystic ovary syndrome (Shield et al, 2009). While some cases were asymptomatic at diagnosis, and diabetes was identified during investigation for obesity often with documented acanthosis nigricans, most presented with the classic features of polyuria, polydypsia and lethargy with or without recent evidence of weight loss. In addition, a significant number of females were diagnosed having primarily presented with recurrent vaginal Candida infections or perineal abscesses, an association recently reported in another case series from Canada (Curran et al, 2011) (*Box 1*).

Screening and diagnosis

Identifying obese adolescents with established impaired glucose tolerance

Screening of asymptomatic, at-risk, obese adolescents in primary care is more likely to identify impaired glucose

Figure 1. Acanthosis nigricans on the neck of an adolescent with significant insulin resistance.



Box 1. Case report.

Presentation
A 15-year-old girl presented to an accident and emergency department with a 3-day history of lower back pain. She had been seeing her GP for oligomenorrhoea associated with a weight of 129 kg and BMI of 44.6 kg/m^2.

History and investigation
There was no history of parental diabetes. The back pain was due to a pilonidal abscess with a degree of added cellulitis. There was no history of polyuria or polydypsia but a routine fasting glucose level was 6.1 mmol/L (impaired fasting glucose) and her HbA_{1c} level was 6.2% (44 mmol/mol). Over the next 2.5 months the pilonidal lesion did not completely resolve and required multiple courses of oral antibiotics. Surgical review identified a sinus requiring drainage.

Diagnosis
A fasting blood glucose level on this admission was 8.0 mmol/L with an HbA_{1c} level of 6.7% (50 mmol/mol). An oral glucose tolerance test confirmed the diagnosis of diabetes with a 2-hour glucose level of 16.1 mmol/L. An elevated C-peptide level and absent type 1 diabetes auto-antibodies confirmed the diagnosis of type 2 diabetes. At no stage did the individual report polyuria or polydypsia, lethargy or weight loss. Testing for glycosuria on these admissions had proven negative.

Box 2. Obese or overweight adolescents that should be considered at additional risk for type 2 diabetes.

- A first-generation family history of type 2 diabetes.
- At-risk ethnicity: in the UK this includes people of south Asian and black ethnic origin.
- Clinical features of acanthosis nigricans or polycystic ovary syndrome.
- A history of recurrent perineal infections.

tolerance (IGT) or impaired fasting glucose than frank type 2 diabetes. *Box 2* describes which people are at additional risk of type 2 diabetes. In an unselected hospital cohort of obese children, IGT was identified in around 10% of children (Sabin et al, 2006). A population-based study of school children aged 8–19 years from Europe identified that only 3 out of 1000 children had IGT but all were obese and the prevalence in the obese group of children was around 7% (Mazur et al, 2007).

A series of large well-designed trials in adults with IGT has established that combined dietary and activity lifestyle modification programmes can significantly reduce the risk of progression to overt type 2 diabetes in adults (Lindström et al, 2006; Li et al, 2008; Diabetes Prevention Program Research Group et al, 2009). Similar evidence is currently unavailable for adolescents but observational evidence has suggested that continual weight gain with IGT is associated with a greater risk of progression to diabetes while weight loss is more likely to cause reversion to normal glucose tolerance (Weiss et al, 2005; Kleber et al, 2010).

Diagnosis of type 2 diabetes

While those with classic symptoms of type 2 diabetes will likely have glycosuria or a high blood glucose level on random testing in primary care, detecting those with asymptomatic, sub-clinical diabetes is more difficult.

Recently, there has been a concerted move to using HbA_{1c} as a diagnostic screening tool for diabetes with a value of ≥6.5% (≥48 mmol/mol) being diagnostic with symptoms or after a repeat without symptoms (NHS Health Checks Programme, 2009; American Diabetes Association [ADA], 2011). However, this has not been confirmed by the Department of Health for use in the UK. Caution should be used when applying this to the diagnosis in adolescents – recent studies have suggested this test to be less sensitive and specific in this age group (Lee et al, 2011; Nowicka et al, 2011) and it is still probably advisable to arrange for a true, fasting plasma glucose measurement (diagnostic level ≥7.0 mmol/L) or an oral glucose tolerance test when screening for type 2 diabetes.

Differentiating between type 1 and type 2 diabetes

For those presenting acutely with clinical symptoms, it is worth noting that some people with later proven type 2 diabetes do present initially with a degree of ketosis and some with evidence of ketoacidosis (Grinstein et al, 2003; Haines et al, 2007; Amed et al, 2010). Body mass indices in the obese range are no use in differentiating between type 1 and type 2 diabetes – with the increased prevalence of obesity in childhood, a significant minority of those with type 1 diabetes are identified in primary care before weight loss is severe (Scott et al, 1997). For this reason, it is still advisable to arrange for an urgent, same-day review by the local paediatric diabetes team, as is recommended for type 1 diabetes (Ali et al, 2011) whenever a case of diabetes is identified in an adolescent, even if they have significant obesity.

Preventative interventions and treatment of type 2 diabetes in adolescents

The prevention of adolescent (and early adult) onset type 2 diabetes will need to include the treatment of childhood obesity. In the longer-term this requires a number of population-based, obesity prevention programmes, although effective interventions to prevent childhood obesity have proven difficult to identify and much more work is needed in this area (Summerbell et al, 2005).

For those children and adolescents who are already overweight and obese, interventions concentrating on weight reduction through a combination of improved eating behaviours and increased activity should be first-line therapy. The NICE guidelines on obesity (NICE, 2006) identified primary care as a key site in the management of child obesity, and the Department of Health (2006) published a primary care pathway for obese children. Research among primary care practitioners, however, has identified a degree of ambivalence as to whether primary care has the resources or expertise to deal with this problem (Turner et al, 2009). This reluctance to engage is perhaps understandable given the dearth of effective interventions currently described in the latest Cochrane review (Oude Luttikhuis et al, 2009) and results from a recent large randomised trial in general practice in Australia (Wake et al, 2009), which again demonstrated disappointing results. The Cochrane review did suggest that behavioural interventions in which therapists aim at "changing thinking patterns and actions, especially in relation to dietary intake and eating, physical activity and sedentary behaviours, and the family's food and physical environment" were more likely to be successful than those simply addressing lifestyle through dietary or activity interventions alone. However, the pooled meta-analysis of behavioural interventions at 12 months (two studies) only displayed a modest BMI SD

Page points

1. There are a number of more intensive management options that might aid weight loss in obese adolescents at high risk of type 2 diabetes. Among the interventions that might be considered in primary care with some secondary care advice, as suggested by NICE, is orlistat.
2. For adolescents with profound obesity (BMI >35 kg/m^2) and evidence of impaired glucose tolerance it is worth considering a referral for bariatric surgery.
3. Few centres in the UK (Bristol, Sheffield and London) currently offer consideration of surgery for weight loss in adolescence but there is evidence of effectiveness.

score improvement of –0.14 (95% confidence interval, –0.18 to –0.10) (Oude Luttikhuis et al, 2009), a level which is unlikely to reflect a significant impact on actual adiposity (Hunt et al, 2007).

A Research for Patient Benefit study has recently been completed in Bristol, examining the transfer of a multidisciplinary obesity service for children from hospital to secondary care with practice nurses as the clinic lead as opposed to hospital staff. The study did identify a favourable individual and family opinion of the service and equivalence in terms of weight improvement (slightly better than the BMI SD score improvement described in the Cochrane meta-analysis); however, patient engagement and retention remains unsatisfactory and the overall levels of BMI SD score improvement are still under-achieving in terms of what is needed to improve metabolic health in most people (Banks et al, 2011).

Intensive interventions for obesity

If it is accepted that "broad stroke", simple interventions are unlikely to benefit many obese adolescents, what strategies could be adopted to target those at greatest risk of the early development of type 2 diabetes? There are a number of more intensive management options that might aid weight loss in obese adolescents at high risk of type 2 diabetes. Among the interventions that might be considered in primary care with some secondary care advice, as suggested by NICE, is orlistat.

Orlistat is a potent pancreatic lipase inhibitor effectively reducing fat absorption in the gut. A randomised trial in adolescence, with additional significant dietary and lifestyle input, did demonstrate useful weight loss (Chanoine et al, 2005). However, the rather inconvenient side-effects of orlistat when a strict low-fat diet is not followed, result in many people giving up the medication. In practice, NICE recommendations for adults using orlistat is to continue therapy after 3 months only if body weight has reduced by at least 5% (NICE, 2006). For adolescents who may often still be gaining height, this is not appropriate and estimation of changes in BMI provides a better reflection of efficacy. Changes in BMI should be reviewed after 6 months' therapy and orlistat stopped if there is little or no improvement. In Bristol the standard practice is to prescribe multivitamin drops before bed in all people to provide supplementary fat soluble vitamins.

There is currently considerable research interest in the potential effectiveness of the insulin-sensitising agent metformin on adolescent obesity when used in combination with lifestyle modification. Only small, preliminary studies have yet reported and it is possible (Park et al, 2009) although not certain (Park and Kinra, 2010), that metformin may produce modest improvements in adiposity above that achieved with lifestyle modification alone (Rogovik et al, 2010). While a number of larger studies are currently addressing this issue in adolescents with simple obesity and adolescents with obesity with IGT (Wilson et al, 2009; Garnett et al, 2010), there is currently insufficient evidence to recommend this therapy for primary care management.

For adolescents with profound obesity (BMI >35 kg/m^2) and evidence of IGT it is worth considering a referral for bariatric surgery. NICE guidelines suggest that obesity surgery is not generally recommended for children and young people (NICE, 2006); however, in exceptional circumstances, and in those people who have reached near physiological maturity (a reasonable definition being height velocity <2 cm per year), surgery might be considered if the individual has tried all non-surgical methods to lose weight without benefit in a specialised obesity service and a comprehensive assessment has been undertaken of the education, psychology and social background.

Few centres in the UK (Bristol, Sheffield and London) currently offer consideration of surgery for weight loss in adolescence but there is evidence of effectiveness (Shield et al, 2008; O'Brien et al, 2010). Surgical interventions need very close scrutiny and such cases need a multidisciplinary team evaluation to ensure the family and, more importantly, the adolescent understand the full implications of this course of action and the requirement for lifelong follow-up.

Recent work in Bristol has specifically targeted speed of eating to reduce food consumption, thus augmenting simple behavioural lifestyle modifications. The Mandometer study used a computer device to train obese adolescents to eat their main meal of the day more slowly while also addressing food choices and encouraging more activity (Ford et al, 2009). At 12 months, average BMI SD score improvement was –0.4 in the intervention arm compared with –0.14 with standard care, which included healthy eating and greater activity (mean difference at 12 months with baseline adjustment, 0.27; 95% CI 0.14 to 0.41; $P<0.001$). This improvement was associated with significant reductions in self-determined portion size and speed of food consumption in the intervention arm. More importantly, the improvement and difference persisted 6 months after active intervention, suggesting that this behavioural modification produced sustained benefit. While the mandometer was originally tested in secondary care, the main components of such an intervention could, in theory, be transferred to primary care and this is currently subject to a large randomised trial beginning in 2012.

Treatment options for type 2 diabetes

In obese adolescents presenting with symptomatic diabetes and evidence of ketosis it is advisable to initiate insulin therapy until a more concrete confirmation of type 2 diabetes can be made. In those without ketosis and in whom type 2 diabetes is the likely diagnosis due to obesity with associated features such as acanthosis nigricans, dietary management plus metformin is first-line therapy (ADA, 2000; Rosenbloom et al, 2008). Due to the previously described diagnostic complexities and need to promptly and effectively treat type 1 diabetes in obese adolescents, it is advisable to seek secondary care review as a matter of urgency.

Outcomes for people with type 2 diabetes diagnosed in adolescence

It is undoubtedly the case that the treatment of type 2 diabetes in adolescence is unsatisfactory in the UK and many other areas. While lifestyle modification to improve body composition is central to type 2 diabetes management (Gahagan et al, 2003), the mean change in weight in the BPSU cohort 1 year after diagnosis was a gain of 3 kg with only 15% improving their BMI SD score by >0.5, a level at which metabolic health parameters are likely to improve (Reinehr and Andler, 2004). Furthermore, engagement in continued care can be very poor for adolescents with this form of diabetes: a recent study from Germany (Reinehr et al, 2008) reported a 60% drop-out from diabetes clinics within 7 months of diagnosis – a feature also noted in the present author's clinical practice. This degree of disengagement is worrying as type 2 diabetes in the young is associated with significant comorbidity. Over a third of the BPSU cohort had hypertension at 1 year and only 58% had achieved an HbA_{1c} level of ≤7.0% (≤53 mmol/mol) (Shield et al, 2009).

Studies from the USA have demonstrated significant diabetic nephropathy ranging from 16 to 28% within approximately 1 year of diagnosis (Eppens et al, 2006; Maahs et al, 2007). Perhaps the most worrying data, albeit limited to minority populations (such as Pima Indians), is mortality: the age- and sex-adjusted death rate from natural causes in participants with adolescent-onset type 2 diabetes was three-times higher than in individuals without diabetes (Pavkov et al, 2006).

Conclusion

Type 2 diabetes should now be part of differential diagnosis in overweight or obese adolescents presenting in primary care with symptomatic diabetes. However, type 2 diabetes is still a relatively rare condition in this age group when compared with type 1 diabetes. In the obese adolescent, non-symptomatic, silent diabetes can occur and should be screened for. Certain social (ethnicity and family history) and clinical features (acanthosis nigricans and polycystic ovary syndrome) should prompt a lower threshold for diabetes screening in these individuals in primary care.

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3. In the obese adolescent, non-symptomatic, silent diabetes can occur and should be screened for.

Type 2 diabetes developing in adolescence will undoubtedly carry a high burden of early morbidity and mortality. Lifestyle modification, addressing eating behaviours and activity are likely to be the best preventative strategies for obese, at-risk adolescents, but many current interventions lack efficacy. A greater emphasis on developing effective, primary care weight management interventions for obese children and adolescents is urgently required. ■

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