Type 2 diabetes mellitus: incidence, management and prognosis

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Abstract

Type 2 diabetes mellitus in childhood emerged in the UK in about 2000, and now affects about 500 children or 2% of all childhood diabetes in the UK. It is an aggressive disease in children, with rapidly progressive pancreatic beta cell decline and early development of complications. It characteristically presents in an obese child, around the time of puberty, with osmotic symptoms or as a coincidental finding. A small proportion may present with metabolic decompensation and diabetic ketoacidosis. Acanthosis nigricans is a common feature. There is a significant female preponderance, with children from ethnic minorities disproportionately represented, and usually a history of type 2 diabetes mellitus in first degree relatives. In contrast to type 1 diabetes, children with type 2 may develop complications within 1–2 years of diagnosis. The differential diagnosis includes type 1 diabetes, usually distinguished by the presence of GAD65 autoantibodies; diabetes secondary to monogenic causes, transplant and immunosuppression. Management includes confirming the diagnosis of diabetes according to World Health Organisation criteria; screening for both microvascular complications and complications of metabolic syndrome; and initiating lifestyle, dietary and exercise advice to decrease calorie intake and increase energy expenditure. Children with osmotic symptoms or HbA1c greater than 69 mmol/mol (8.5%) should be commenced on insulin therapy then weaned off over 1–3 months. Metformin should also be instituted from diagnosis provided there is no ketoacidosis, and the dose increased to the maximum tolerated. Insulin is currently the only second line treatment licensed for use in the UK. A pragmatic approach is to offer once a day long acting insulin; and add in mealtime short acting insulin if insufficient response. The glycated haemoglobin target for optimal glycaemic control is less than 53 mmol/mol (7.0%). Future treatments under investigation for paediatric use drugs targeting the insulin resistance, the beta cell failure, and glucose availability. It is likely that these clinical trials will generate an evidence base for better treatments in future.

Keywords diabetes; youth

Introduction, definition and epidemiology

Diabetes mellitus is the name given to a wide spectrum group of disorders characterised by raised plasma glucose. In paediatric practice, type 1 diabetes accounts for about 96% of all affected children, and is characterised by an absolute insulin deficiency due to autoimmune destruction of insulin producing beta cells in the pancreas. Affected children will die unless insulin therapy is instituted. In contrast, most adults with diabetes have type 2, characterised by a relative insulin secretory defect, and target tissue resistance to the effects of insulin. There has been a dramatic rise in the prevalence of type 2 diabetes in adult populations since about the 1950s, and this has been related to the increased prevalence of obesity. It is likely that type 2 diabetes in children is now emerging for the same reasons. In the UK, type 2 diabetes in children began to appear in the late 1990s, particularly in ethnic minority children. These were of Pakistani, Middle East or African-Caribbean origin; 12–16 years of age; and characterised by severe insulin resistance as assessed by hyperinsulinaemia. A British Paediatric Surveillance Unit (BPSU) case finding survey in 2005 identified an incidence of 0.53 new cases per 100,000 per year. This compares to an incidence of 28 cases per 100,000 per year for children aged 0–14 years with type 1 diabetes in 2013. Although over 50% of affected children were of White UK origin, the likelihood of a newly diagnosed child having type 2 diabetes was 14 times higher for a child of African-Caribbean or South Asian origin. The National Paediatric Diabetes Audit for 2013/14 identified about 500 children and young people with type 2 diabetes, compared to over 26,000 with type 1 diabetes. A second BPSU survey was undertaken in 2015/16 and is likely to show a significant rise in incidence.

Pathology and course of the disease

Type 2 diabetes (T2DM) in children and young people is clearly different to type 1 diabetes, and the underlying pathology is similar to that in adults with type 2 diabetes; that is, insulin resistance and beta cell failure. However, we now know that childhood type 2 diabetes has unique features, including more rapid progression of pancreatic beta cell failure, poorer response to treatments, earlier onset of complications, and more rapid progression of complications. There may also exist subgroups of children who have different rates of progression of the disease. T2DM is also frequently associated with other features of the insulin resistance or metabolic syndrome. These include obesity, dyslipidaemia, hypertension, albuminuria, ovarian hyperandrogenism, non-alcoholic fatty liver disease (NAFLD), and obstructive sleep apnoea. There is also a component of systemic inflammation as estimated by elevated C-reactive protein, inflammatory cytokines and white blood cell counts.

The natural history in childhood starts with fasting hyperinsulinaemia, exacerbated by obesity. This is followed by postprandial hyperglycaemia, when the pancreatic beta cells are unable to maintain high enough circulating insulin levels to respond to a glucose load (impaired glucose tolerance on an oral glucose tolerance test). Due to a combination of lipid and glucose toxicity on beta cells, increasing tissue insulin resistance and hepatic glucose output, fasting hyperglycaemia follows. Early on in the natural history there is loss of the first phase insulin response. There is second phase hyperinsulinaemia in response to an oral glucose tolerance test, but a progressive loss such that many affected adults eventually become insulin dependent. Insulin resistance means an impaired response to the physiological actions of insulin on carbohydrate, lipid and protein metabolism and on endothelial function.

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The principal tissues affected by insulin resistance are liver, muscle and fat. In the liver this impaired insulin related inhibition of hepatic gluconeogenesis results in increased hepatic glucose output, exacerbating hyperglycaemia. In muscle, reduced transport of carbohydrates into muscle combined with lipid deposition in muscle cells leads to impaired exercise ability and lowered threshold for tiredness with exercise. In fat tissue, there is impaired insulin-mediated inhibition of hormone-dependent lipase, with breakdown of lipids to free fatty acids and glycerol, contributing to the dyslipidaemia.

The Treatment Options for type 2 diabetes in Adolescents and Youth (TODAY) was a landmark clinical trial that compared the effects of metformin, metformin plus rosiglitazone, and lifestyle interventions on the glucose control of 677 young people with type 2 diabetes. There was a rapid loss of glycaemic control in many of the participants, even though they only had a short (less than one year) duration of diabetes. The rate of loss of glycaemic control even on therapy was significantly faster than published rates in adults. In the same study, many of the participants had evidence of microvascular complications and risk factors for macrovascular complications present at diagnosis: 14% of participants had blood pressure at or above the 95th percentile, 13% had microalbuminuria, 80% had low HDL-cholesterol level, and 10% had raised triglycerides. These complications appear to progress faster in children than in adults: a study in First Nation Canadians with childhood type 2 diabetes showed that renal and neurological complications appeared within 5 years of diagnosis; and major complications such as dialysis, blindness or amputation, appear from 10 years after diagnosis.

Diagnosis including history and investigation

Diabetes is diagnosed according to World Health Organisation criteria (see box 1). Currently this requires a fasting or random capillary or venous glucose estimation; or measurement of glycated haemoglobin.

The classic features of type 2 diabetes in childhood include a presentation with symptoms during the second decade of life, with a mean age of diagnosis around 13 years. This corresponds roughly with the peak of the growth spurt and associated physiological insulin resistance. More girls are affected than boys in a ratio of about 2:1, and this may be related to gender differences in body fat mass. Type 2 diabetes affects children of all ethnic origins, but in the UK it disproportionately affects those of non-European descent, for instance children of South Asian origin (Pakistan, India, Bangladesh, Sri Lanka), or African-Caribbean children. Type 2 diabetes disproportionately affects families with lower socio-economic status. In about 85% there is a strong family history of type 2 diabetes or cardiovascular disease, often in a parent, sibling or grandparents. It is not unusual for children to be identified co-incidentally, apparently asymptomatic when screened either in primary care or on a glucose meter belonging to another family member with diabetes. However a minority present with metabolic decompensation and diabetic ketoacidosis. A further group may present with severe hyperosmolar non-ketotic dehydration, which has a high risk for fatality. Finally, type 2 diabetes is a non-autoimmune disease and not HLA-associated. The main differential diagnoses for type 2 diabetes are shown in Box 2. It cannot be stressed strongly enough

Diagnosis of diabetes

Diabetes is diagnosed when:

- A fasting plasma glucose is equal to or greater than 7.0 mmol/L (126 mg/dL)

OR:

- The post challenge plasma glucose is equal to or greater than 11.1 mmol/L (200 mg/dL). This must be undertaken as described by The World Health Organisation, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR:

- Symptoms of thirst, polyuria, tiredness and weight loss and a random plasma glucose equal to or greater than 11.1 mmol/L (200 mg/dL). This can be performed at any time of the day regardless of the time of the last meal.

OR:

- HbA1c greater than 6.5% using a DCCT aligned assay.

There is no need to undertake an oral glucose tolerance test if diabetes can be diagnosed using fasting or random criteria. Impaired fasting glycaemia and impaired glucose tolerance are intermediate stages in the pathogenesis of disordered carbohydrate metabolism, but are NOT diabetes mellitus.

Box 1

Differential diagnosis of Type 2 diabetes in children

- Type 1 diabetes. This is associated with diabetes autoantibodies in about 85% of affected children, and children have an absolute insulin requirement.
- Apparent type 2 diabetes with coexistent autoimmunity. About 10% of children with an apparent diagnosis of type 2 diabetes are found to have antibodies to Glutamate Decarboxylase (GAD65), islet cells (ICA), or insulin (IAA). Pancreatic beta cell function is significantly less in antibody positive children, and there is more rapid development of insulin dependence. It is likely that these children have type 1 diabetes with obesity.
- Flatbush diabetes. This is seen in some children of African-Caribbean origin, with a strong family history, sometimes autosomal dominant, and with a female preponderance, no HLA association and diabetes autoantibody negative. These children may present with ketoacidosis or ketosis and require insulin initially; but can be weaned off insulin while maintaining relatively good glycaemic control.
- Monogenic diabetes (formerly Maturity Onset Diabetes of the Young). This usually presents in families with autosomal dominant history; affects no more than 1% of children with diabetes; is not associated with obesity beyond the prevalence in the background population; and is not associated with insulin resistance.

Box 2