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Treating young adults with type 2 diabetes or monogenic diabetes

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It is increasingly recognised that diabetes in young adults has a wide differential diagnosis. There are many monogenic causes, including monogenic beta-cell dysfunction, mitochondrial diabetes and severe insulin resistance. Type 2 diabetes in the young is becoming more prevalent, particularly after adolescence. It's important to understand the clinical features and diagnostic tools available to classify the different forms of young adult diabetes. Classic type 1 diabetes is characterised by positive β-cell antibodies and absence of endogenous insulin secretion. Young type 2 diabetes is accompanied by metabolic syndrome with obesity, hypertension and dyslipidaemia. Monogenic β-cell dysfunction is characterised by non-autoimmune, C-peptide positive diabetes with a strong family history, while mitochondrial diabetes features deafness and other neurological involvement. Severe insulin resistance involves a young-onset metabolic syndrome often with a disproportionately low BMI. A suspected diagnosis of monogenic diabetes is confirmed with genetic testing, which is widely available in specialist centres across the world.

Treatment of young adult diabetes is similarly diverse. Mutations in the transcription factors *HNF1A* and *HNF4A* and in the β-cell potassium ATP channel components cause diabetes which responds to low dose and high dose sulfonylurea agents, respectively, while

Abbreviations: CRP, C-reactive protein; HNF1A, hepatocyte nuclear factor 1 alpha; HNF4A, hepatocyte nuclear factor 4 alpha; HNF1B, hepatocyte nuclear factor 1 beta; GCK, glucokinase; IPSAD, International Society for Paediatric and Adolescent Diabetes; LADA, Latent Autoimmune Diabetes in Adults; MELAS, Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes; MIDD, Maternally Inherited Diabetes and Deafness; MODY, maturity-onset diabetes of the young; ND, neonatal diabetes; PNDM, Permanent Neonatal Diabetes; SGLT-2, sodium glucose co-transporter-2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TNDM, Transient Neonatal Diabetes; US, United States.

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glucokinase mutations require no treatment. Monogenic insulin resistance and young-onset type 2 diabetes are both challenging to treat, but first line management involves insulin sensitisers and aggressive management of cardiovascular risk. Outcomes are poor in young-onset type 2 diabetes compared to both older onset type 2 and type 1 diabetes diagnosed at a similar age.

The evidence base for treatments in monogenic and young-onset type 2 diabetes relies on studies of moderate quality at best and largely on extrapolation from work conducted in older type 2 diabetes subjects. Better quality, larger studies, particularly of newer agents would improve treatment prospects for young adults with diabetes.

Introduction

Classically, diabetes presenting in the young is assumed to be Type 1 diabetes mellitus (T1DM). While T1DM still represents the majority of cases of diabetes in young children in most countries, the increased awareness of monogenic forms of diabetes, plus the increasing prevalence of obesity leading to Type 2 diabetes mellitus (T2DM) presenting at a younger age, mean that those working with young adults should be familiar with the differential diagnosis and management of all forms of diabetes. This article reviews the range of presentation of different types of diabetes in young adults and discusses evidence-based recommendations for management strategies.

Background: epidemiology and clinical features

Monogenic diabetes

Monogenic diabetes comprises maturity-onset diabetes of the young (MODY), neonatal diabetes (ND), mitochondrial diabetes and the inherited causes of severe insulin resistance. MODY, ND and mitochondrial mutations predominantly lead to β-cell defects, whilst monogenic severe insulin resistance causes young onset metabolic syndrome and abnormalities of body fat distribution (often without obesity). Over recent years there has been a huge expansion in the number of genes known to cause diabetes, particularly those linked to ND [1], however most are rare. Good prevalence data is not available, but monogenic diabetes probably represents 3–5% of diabetes in those diagnosed <45 years [2,3], has a minimum population prevalence of around 1 in 10,000 [4–6], and arises in the first 6 months of life in approximately 1 in every 100,000 births [1].

MODY is characterised by autosomal dominant inheritance, age of onset in the 2nd–4th decade, absence of β-cell autoimmunity, lack of metabolic syndrome features, and sustained insulin secretion (C-peptide positivity) [7]. The commonest types of MODY are due to mutations in hepatic nuclear factor 1 alpha (*HNF1A*), glucokinase (*GCK*), hepatic nuclear factor 4 alpha (*HNF4A*) and hepatic nuclear factor 1 beta (*HNF1B*), representing 52%, 32%, 10% and 6%, respectively of known MODY cases in the UK [5].

Glucokinase MODY

This is the commonest form of monogenic diabetes in children. Glucokinase, known as the pancreatic β-cell glucose sensor, regulates the initiation of glucose-stimulated insulin secretion. Heterozygous inactivating *GCK* mutations cause a lifelong, non-progressive, fasting hyperglycaemia (fasting glucose 5.5–8.0 mmol/l, HbA_{1c} 40–60 mmol/mol) [8]. Unlike other forms of hyperglycaemia, insulin secretion remains intact in GCK-MODY and regulated, although the ambient blood glucose is shifted 2–3 mmol/l higher. This results in low post-prandial glucose excursions compared to other