Type 2 diabetes in the young: why we should worry

Gaya Thanabalasingham, Katharine R Owen

Type 2 diabetes has traditionally been considered a disease affecting older age groups. In recent years, however, type 2 diabetes has become increasingly common in children, adolescents and young adults, particularly associated with obesity and in ethnic minority groups. In this article we discuss the rising prevalence of young type 2 diabetes and the mounting evidence for poor outcomes in this group. We also highlight the need for evidence-based strategies to optimally manage these high-risk patients.

**Young-onset type 2 diabetes is increasing in prevalence**

Evidence for increasing rates of type 2 diabetes in the young has largely originated from paediatric epidemiological studies in the USA. The SEARCH study reported that the prevalence of type 2 diabetes in youths aged 10–19 years in the USA was 0.46/1000 in 2009, an increase of 35% over the prevalence of 0.34/1000 in 2001.1 This indicated that there are at least 20 000 cases of type 2 diabetes in this age group in the USA. The prevalence was particularly high in youth from ethnic minority backgrounds. Statistically-modelled projections suggest that the prevalence of type 2 diabetes in the USA in those under 20 years will increase four-fold to over 80 000 in 2050.2

Fortunately, type 2 diabetes in childhood and adolescence is much less common in the UK than in the USA, although there is evidence that cases have increased over the last 15 years. In 2000, a postal survey of all UK consultant paediatricians detected 25 children (aged under 16 years) with type 2 diabetes, which equated to a crude minimum prevalence of 0.21/100 000 under 16 years of age.3 The prevalence was much higher in South Asian children (1.42/100 000) than white children (0.10/100 000). A survey organised by the Royal College of Paediatrics and Child Health in 2009 reported 328 children in England with type 2 diabetes diagnosed before the age of 18 years (www.rcpch.ac.uk). This represented 1.5% of all diabetes cases in this age group, and equated to a minimum prevalence of type 2 diabetes of 3.0/100 000. The most recent data come from the National Paediatric Diabetes Audit (NPDA) 2011–12,4 which reported that in UK children with diabetes aged up to 19 years, 1.1% of boys and 3.6% of girls have type 2 diabetes, about 450 cases in total. The relative proportion was higher in children from ethnic minority backgrounds (2.1% of Asian children and 8.7% of black children with diabetes). Most cases arise in adolescents over the age of 15, and so there might be incomplete ascertainment of cases through older teenagers being followed up in primary care.

Data for the adult population from the National Diabetes Audit (NDA) are recognised to have limitations due to incomplete participation by GP practices. With these limitations in mind, in 2011–12, the NDA reported 10 409 cases of type 2 diabetes in the 20–29 year age group, and 58 601 in the 30–39 year age group (www.hscic.gov.uk/nda). This accounted for approximately 0.5% and 2.7% respectively of all cases of type 2 diabetes, and represented 25% and 63% respectively of all the diabetes in these age groups. Therefore, there appears to be a marked increase in those affected with type 2 diabetes during the transition from childhood to young adulthood.

Published data also suggest that type 2 diabetes is common and increasing in young adults in the UK. A population-based registry of West Yorkshire residents from 1991–2006 reported that the incidence of type 2 diabetes was 2.5/100 000/year in individuals aged under 30 years.5 Incidence rates of type 2 diabetes were much higher in South Asians (6.9/100 000/year) than non-South Asians (1.8/100 000/year). Type 2 diabetes represented 12% of all diabetes cases in this age group. There was an 18% rise in the incidence of type 2 diabetes in the 15–29 year age range over the period studied.

Holden and colleagues retrospectively examined the UK Clinical Practice Datalink (a database of primary care daily records across the UK) from 1991 to 2010.6 Over this 20-year period, there was a marked increase in the incidence of type 2 diabetes in patients aged under 40 years at diagnosis. Furthermore, these cases accounted for a higher proportion of all diabetes cases in more recent years: 5.9% (642 cases of type 2 diabetes diagnosed <40 years) in 1991–1995 compared with 12.4% (15 326 cases) in 2006–2010.

Therefore, young-onset type 2 diabetes is an increasingly common diagnosis in the UK, which probably reflects increasing obesity rates in this age group. This increase in young-onset type 2 diabetes appears to be disproportionately affecting those from minority ethnic backgrounds.

**Young-onset type 2 diabetes is associated with high lifetime risk of complications and mortality**

Type 2 diabetes presenting at a young age signifies an extreme phenotype characterised by the presence of obesity and other adverse cardiovascular risk factors.7 Benhalima and colleagues described the clinical characteristics of 185 patients with type 2 diabetes diagnosed before 35 years of age who were attending a specialist hospital clinic.8 Forty-nine percent of patients had a minority ethnic background, 70% had a family history of diabetes, 63% had suboptimal glycaemic control (HbA1c >7% [53mmol/mol]) and 65% had at least three cardiovascular risk factors. Of particular concern, 46% of patients had not been reviewed in the preceding year at the clinic. This typical phenotype of obesity, poor glycaemic control and other features of the metabolic syndrome has also been noted in several other UK cohorts of young-onset type 2 diabetes.9–11

These phenotypic characteristics appear to confer high risk of diabetes-related complications. Steele and
colleagues\textsuperscript{11} reported the microvascular and macrovascular complications affecting 83 patients with young-onset type 2 diabetes (diagnosed <45 years) after approximately 17 years disease duration: 36% of patients had clinically-significant microvascular disease (i.e. more than background retinopathy or persistent microalbuminuria/proteinuria) and 30% had clinically-significant macrovascular disease.

There are now increasing data which suggest a worse overall prognosis of young-onset type 2 diabetes compared with type 2 diabetes diagnosed in older age. Hillier and colleagues compared outcomes over a four-year period in a large cohort of American patients with early-onset (diagnosed aged 18–45 years) versus usual-onset (>45 years) newly-diagnosed type 2 diabetes.\textsuperscript{12} The rate of development of retinal and renal microvascular complications was similar between the two groups in this study. Compared with age-matched, non-diabetic control subjects, patients with early-onset type 2 diabetes had an eight-fold overall hazard of developing any macrovascular complication versus a four-fold overall hazard for patients with usual-onset type 2 diabetes. Studies in UK and Chinese cohorts have reported similar findings, namely that young-onset type 2 diabetes patients have excess risk of macrovascular complications which unfortunately present in middle age, in part determined by prolonged disease duration.\textsuperscript{9,13}

Several studies have convincingly shown that the overall prognosis of young-onset type 2 diabetes is also worse compared with individuals with type 1 diabetes diagnosed at a similar age. Constantino and colleagues examined an Australian hospital diabetes clinical database (with >20 years of follow-up data) and reported excess complications and mortality associated with young-onset type 2 diabetes (diagnosed aged 15–30 years) compared with type 1 diabetes patients matched for age at diabetes onset.\textsuperscript{14} Unsurprisingly, the patients with young-onset type 2 diabetes had higher BMI and other adverse cardiovascular risk factors such as high triglycerides, low HDL-cholesterol, hypertension, and higher prescription of statins and antihypertensive medications. Despite shorter duration of diabetes and comparable levels of glycaemia, mortality rates were higher in young-onset type 2 diabetes (11% vs 6.8%, $p=0.03$), and deaths in both groups occurred in middle age. Furthermore, there was marked excess of macrovascular disease in young-onset type 2 diabetes compared with type 1 diabetes including ischaemic heart disease (12.6% vs 2.5%, $p<0.0001$) and stroke (4.3% vs 0.7%, $p=0.002$). Similar findings were seen in American and Chinese cohort studies.\textsuperscript{15,16} These studies suggest the increased cardiovascular risk is driven by features of metabolic syndrome rather than dysglycaemia alone.

Thus, there is accumulating evidence that young-onset type 2 diabetes is associated with an extremely adverse metabolic profile and poor long-term outcomes. Of further concern, this age group have traditionally not engaged well with medical services.\textsuperscript{17} For example, data from the 2011–2012 NDA showed that only 40.2% of those with type 2 diabetes aged 20–29 years received all eight care processes, compared to ~60% of the over 50s. This is comparable with similar aged individuals with type 1 diabetes.

The evidence-base to guide optimal management of patients with young-onset type 2 is limited

The International Society for Paediatric and Adolescent Diabetes published guidelines on the management of type 2 diabetes in children and adolescents, which were largely based on consensus expert opinion in the absence of high-quality comparative-effectiveness research studies.\textsuperscript{18} These guidelines promote sensible management goals including weight loss, normalisation of glycaemia and control of associated comorbidities such as hypertension and dyslipidaemia. More recently, a joint EASD/ADA position statement emphasised the need for a patient-centred approach in the management of type 2 diabetes and specified that HbA\textsubscript{1c} targets should be more stringent in younger patients who accrue risk of diabetes-related complications over their lifetimes.\textsuperscript{19} Unfortunately, there is no clear or specific guidance how clinicians should achieve these goals, and, therefore, management decisions are (perhaps inappropriately) extrapolated from the evidenced-based protocols that guide current treatment of type 2 diabetes presenting in older adults.

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study was the first multi-ethnic, multi-centre, randomised controlled trial to compare three treatment arms in 699 obese youths (aged 10–17 years) with newly-diagnosed type 2 diabetes: metformin monotherapy, metformin plus rosiglitazone, and metformin and intensive lifestyle intervention.\textsuperscript{20} Only 50% of patients experienced a durable response to metformin alone (HbA\textsubscript{1c} <8% [64 mmol/mol] for at least six months) which was not significantly different to the metformin and lifestyle intervention arm. This response to metformin was less effective than previously reported in older-onset type 2 diabetes patients.\textsuperscript{21} In this study, most patients required rapid escalation to multiple oral hypoglycaemic agents and/or insulin to achieve good glycaemic control. Furthermore, the high incidence of microalbuminuria, hypertension and dyslipidaemia over the course of the TODAY study is consistent with previous data suggesting that the development of serious diabetes complications occurs prematurely in young-onset type 2 diabetes, and further highlights the need for a multi-faceted approach to manage these patients.\textsuperscript{22}

Research is needed to guide optimal management and resolve many unanswered questions

It is clear that there is urgent need for high-quality research studies to determine the optimal therapeutic strategy in patients with young-onset type 2 diabetes with hard clinical outcomes, i.e. reduction in morbidity and mortality. Data from the UKPDS have emphasised the positive long-term benefits (the so-called legacy effect) of early glycaemic control in older patients with type 2 diabetes,\textsuperscript{23} and it is probable that good glycaemic control in young-onset type 2 diabetes will also confer long-term protection. Sadly, a sound evidence base to guide clinicians looking after patients with young-onset type 2 diabetes is likely to be several years away. Other outstanding areas of uncertainty include the role of bariatric surgery, whether these patients should be managed in primary or secondary care, the use of newer
glucose-lowering agents in children and adolescents, and the use of teratogenic medications in women of child-bearing age.

Conclusions

In conclusion, young-onset type 2 diabetes is not a benign condition. Worryingly, the numbers of young adults with type 2 diabetes in the UK are rapidly increasing. Of further concern, current data suggest that these patients are suboptimally managed, which may reflect an incorrect but widespread perception that these patients are low risk, absence of evidence-based clinical guidelines and disinclination to expose these patients to potentially lifelong therapies. Accumulating evidence has emphasised the high lifetime risk of diabetes-related complications and death in these patients. Furthermore, young-onset type 2 diabetes is frequently accompanied by features of the metabolic syndrome, and, therefore, aggressive management strategies are necessary to optimise glycaemic control, improve the overall cardiovascular risk profile and reduce associated complications and mortality. The TODAY study highlighted the difficulties of effective lifestyle and therapeutic management, which are further compounded by challenges in engaging these patients with the currently available medical resources.

Gaya Thanabalasingham,1 BM BCh, MRCP, Specialty Registrar Diabetes & Endocrinology
Katharine R Owen,1,2 BSc, MD, FRCP, Specialty Registrar Diabetes & Endocrinology, Academic Researcher and Honorary Consultant
1Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK
2Oxford NIHR Biomedical Centre, University of Oxford, Oxford, UK

Declarations of interests

There are no conflicts of interest declared.

References


Drug notes

Find out how non-diabetes drugs impact diabetes patients. Visit the Practical Diabetes website and click on drug notes.

Aliskiren
Amlodipine
Bisoprolol
Bromocriptine
Bumetanide
Carbamazepine
Cilostazol
Clopidogrel
Coleselvam
Dabigatran
Darbepoetin alfa
Diazoxide
Digoxin
Dipyridamole
Dopemiderone
Doxazosin
Dronedaron
Duloxetine
Eplerenone
Erythromycin
Ezetimibe
Gabapentin
Indapamide
Ibivradine
Labetalol
Lidocaine
Lorcaserin
Losartan
Methylodopa
Metoclopramide
Nicorandil
Nifedipine
Omocor
Orlistat
Prasugrel
Prolonged-release nicotinic acid
Quinoline
Ramipril
Ranolazine
Rimonabant
Rivaroxaban
Rosuvastatin
Sibutramine
Spironolactone
Tadalafil
Torcetrapib

www.practicaldiabetes.com

PRACTICAL DIABETES VOL. 31 NO. 6

COPYRIGHT © 2014 JOHN WILEY & SONS