Type 2 diabetes in adolescents

A growing issue

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The prevalence of type 2 diabetes in adolescents is increasing but the rate is still low and this type is much less common than type 1 diabetes. Confirming the presence and type of diabetes is important to ensure appropriate therapy is commenced to control glycaemia and prevent complications or the progression of any that are already present. Lifestyle modifications are the mainstay of treatment, and metformin and/or insulin are the main medication options.

The prevalence of type 2 diabetes in adolescents is increasing,[1] following an increase in both the prevalence and degree of obesity in this age group. Type 1 diabetes, however, remains the most common form of diabetes in adolescents and is approximately ten times more common than type 2 diabetes in this age group.[2,3] All adolescents suspected of having diabetes should be assessed urgently to prevent possible progression to diabetic ketoacidosis. Distinguishing type 2 diabetes from type 1 diabetes can

Key points

- **Type 2 diabetes is becoming more common in adolescents, but the overall prevalence is still low, and much below that of type 1 diabetes.**
- **Type 2 diabetes onset generally coincides with mid to late puberty, during the peak of physiological pubertal insulin resistance.**
- **Patients with type 2 diabetes are usually asymptomatic at presentation, being diagnosed incidentally or on screening after consideration of risk factors (family history of type 2 diabetes, obesity, signs of insulin resistance and high-risk race/ethnicity).**
- **Diagnosis of type 2 diabetes is by glucose-based tests or glycated haemoglobin (HbA_{1c}): fasting plasma glucose ≥7.0 mmol/L; 2 h plasma glucose after an oral glucose tolerance test ≥11.1 mmol/L; or HbA_{1c} ≥48 mmol/mol (6.5%). Each test has its limitations.**
- **Treatment of type 2 diabetes is multidisciplinary. Lifestyle modification is the focus, with use of oral hypoglycaemics and insulin therapy depending on the degree of clinical decompensation.**
- **Vigilance in follow-up health care is especially required in adolescents with diabetes as lifestyle and antihyperglycaemic medication interventions are often not very effective or durable in this patient population.**

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Table. Clinical characteristics of type 1 and type 2 diabetes in adolescents[2,9,10]

Clinical characteristic	Type 1 diabetes	Type 2 diabetes
Pathophysiology	Absolute insulin deficiency secondary to beta cell destruction	Insulin resistance with relative insulin deficiency
Prevalence	10 to 13 per 100,000	18 per 100,000
Relatives	5% have type 1 diabetes	75 to 100% have type 2 diabetes
Clinical signs and symptoms	Weight loss, polyuria, polydipsia, ketosis at presentation	Overweight/obese, absent or mild polyuria and polydipsia, glycosuria, ketonuria at diagnosis (33%), ketoacidosis at presentation (5 to 25%) Strong family history of type 2 diabetes
Associated disorders	Autoimmune disorders (thyroid, adrenal, vitiligo), coeliac disease	Acanthosis nigricans, polycystic ovary syndrome, metabolic syndrome

be difficult given that obesity prevalence is rising and that up to 30% of those with type 1 diabetes are obese at presentation.[4]

Type 2 diabetes in youth is most common in the second decade of life, with a median age of 13.5 years at diagnosis, coinciding generally with the peak of physiological pubertal insulin resistance, which may unmask overt type 2 diabetes in some previously compensated peripubertal adolescents.[4] The median age of onset is one year earlier in girls than boys.[4]

The prevalence of type 2 diabetes in children and adolescents varies depending on country and ethnic group. Data from the USA suggest that the prevalence of type 2 diabetes in people aged younger than 20 years is expected to quadruple in the next 40 years based on an annual increase of 2.3% per year.[5] In Australia, the prevalence of type 2 diabetes increases with age, and 0.01% of 10 to 14-year-olds and 0.04% of 15 to 19-year-olds were found to have type 2 diabetes.[2] In terms of new cases of type 2 diabetes in Australian children, the rate has not risen in the 2011–2012 national survey conducted by the Australian Bureau of Statistics compared with a previous survey in 2001–2002.[2] The mean annual incidence rate of type 2 diabetes was reported to be approximately 2.0 to 2.6 per 100,000 in the nonindigenous population[2,3,6] and much higher in the indigenous population at 12.7 per 100,000.[3] Australian indigenous people are at greater risk of type 2 diabetes as they have multiple risk factors including obesity, physical inactivity, genetic predisposition, gestational diabetes and challenging socioeconomic situations.[3,7] As a result, the significant morbidity and mortality associated with type 2 diabetes will further contribute to a worse health outcome.

This article reviews the screening, diagnosis and treatment of type 2 diabetes in adolescents.

Pathophysiology of type 2 diabetes in adolescents

The development of type 2 diabetes is a complex process involving genetic predisposition, behavioural factors and environmental factors. Despite the strong evidence of the genetic component in type 2 diabetes, the increasing prevalence now occurring supports a major role of environmental elements.[8]

Glucose homeostasis is achieved through balancing insulin secretion by pancreatic beta cells and insulin action in the peripheral tissues. Impaired glucose tolerance occurs due to insulin resistance to insulin-stimulated glucose uptake in the periphery.[4] In children and adolescents, impaired glucose metabolism tends to occur in mid to late puberty, with peak growth hormone secretion contributing to insulin resistance. At the end of puberty, spontaneous return to normal glucose metabolism can occur in most adolescents with previously impaired glucose intolerance.[9] The subsequent development of overt type 2 diabetes is due to the combination of insulin resistance and failure of insulin secretion by the pancreatic beta cells.[9]

The compounding impact of obesity further impairs glucose metabolism. Hyperinsulinism is common in obese children, in whom insulin-stimulated glucose metabolism is lowered compared with nonobese peers. In addition, the presence of excess adipose tissue results in the production of other factors that can worsen insulin resistance, such as leptin, adiponectin and tumour necrosis factor-α.[9] Despite the link between insulin resistance in obese adolescents and the development of type 2 diabetes, most of these individuals will not progress to type 2 diabetes in their adolescent years.

Diagnosis

Confirming the presence and type of diabetes is important to ensure appropriate therapy is commenced. The diagnosis of type 2 diabetes is based on the detection of hyperglycaemia and presence of symptoms.[4]

Although most adolescents with type 2 diabetes have no symptoms at presentation and are diagnosed incidentally or as part of a complication screen or obesity work-up, ketoacidosis, polyuria and polydipsia may occur. Presentations reported at the time of diagnosis with type 2 diabetes in a Western Australian study ranged from diabetic ketoacidosis in 5% to polyuria and polydipsia in 38% to as an incidental finding or part of an investigative work-up for obesity

in 53% of the 43 patients.[6] The clinical symptoms of types 1 and 2 diabetic in adolescents are compared in the Table.[2,9,10]

Hyperglycaemia can be measured by glucose-based tests or by glycated haemoglobin (HbA_{1c}). Glucose-based tests and HbA_{1c} do not necessarily detect diabetes in the same individuals, as glucose-based tests are measuring glycaemia at one point in time and there is considerable day-to-day variation in glycaemia whereas HbA_{1c} is a marker for chronic glycaemia. If the glucose-based and HbA_{1c} results are discordant, the test with a result above the diagnostic cut-off value should be repeated.

Current guidelines for the diagnosis of type 2 diabetes in children and adolescents are based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) and American Diabetes Association (ADA)[4,8,11] recommendations. These guidelines are extrapolated from the adult cohort and should be used cautiously, with awareness of the limitations of the various tests used. The glycaemia diagnostic criteria for type 2 diabetes and prediabetes used in Australia are listed in Box 1. The glucose-based tests used diagnostically in Australia are fasting plasma glucose (FPG) and two-hour plasma glucose (2 h PG) after a 75 g oral glucose tolerance test (OGTT). Criteria based on random blood glucose are not used in this country but are used in the USA when symptoms of diabetes (including polyuria, polydipsia, nocturia, unexplained weight loss and excessive tiredness) are present.[11] For diagnosis of prediabetes in Australia, the criteria include impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). In the USA, the criteria for prediabetes also include an HbA_{1c} in the range of 39 to 47 mmol/mol (5.7 to 6.4%);[11] however, neither the WHO nor the Australian Diabetes Society (ADS) endorse a particular HbA_{1c} range for prediabetes. The range defined for impaired fasting glucose is also different between Australia and the USA.

1. Diagnostic criteria for type 2 diabetes and prediabetes in Australia

Criteria for diagnosis of type 2 diabetes* [4,8,11]

- Fasting (no caloric intake for ≥8 hours) plasma glucose (FPG) ≥7.0 mmol/L

OR

- Two-hour plasma glucose post a 75 g oral glucose tolerance test (2 h PG post OGTT) ≥11.1 mmol/L

OR

- Glycated haemoglobin (HbA_{1c}) ≥48 mmol/mol (6.5%)

In an asymptomatic patient with any positive result, the test should be repeated to confirm the diagnosis.

For greater likelihood of concurrence between tests, it is recommended that a test with a result above the diagnostic cut-off is repeated using a newly collected sample for confirmation.

Criteria for diagnosis of prediabetes† [12]

- Impaired fasting glucose/glycaemia (IFG):
  - FPG 6.1 to 6.9 mmol/L and
  - 2 h PG post OGTT <7.8 mmol/L (if measured)
- Impaired glucose tolerance (IGT):
  - FPG <7.0 mmol/L and
  - 2 h PG post OGTT 7.8 to 11.0 mmol/L

* Random blood glucose level (≥11.1 mmol/L) is not used in Australia for diagnosis of diabetes. It is, however, included as one of the criteria in the USA when symptoms of diabetes (including polyuria, polydipsia, nocturia, unexplained weight loss and excessive tiredness) are present.[11]

† HbA_{1c} between 39 and 47 mmol/mol (5.7 and 6.4%) has been defined by the American Diabetes Association as prediabetes.[11] However, neither the WHO nor the Australian Diabetes Society endorse a particular HbA_{1c} range for diagnosing prediabetes.

The role of HbA_{1c} in the diagnosis of type 2 diabetes in Australia

The glucose-based protocol for diagnosis of type 2 diabetes has been used for several decades, and is still widely used. It is, however, inconvenient because it requires the patient to fast overnight prior to the test, and it is also time-consuming and has poor reproducibility. A systematic review found that the reproducibility of an OGTT result in adults was 73% for diagnosis of diabetes and 49% for diagnosis of prediabetes.[13] The concordance rate of OGTT for diagnosis of diabetes in obese adolescents was reported to be even lower, at around 30%.[14] According to the Australian NHMRC guidelines, people with equivocal glucose results (FPG of 5.5 to 6.9 mmol/L, or random plasma glucose of 5.5 to 11.0 mmol/L) should undergo an OGTT.[15] The compliance, however, is poor, and only 27 to 42% of the people who should have a follow-up OGTT test do so.[16,17]

The addition of the new criterion of HbA_{1c} equal to or greater than 48 mmol/mol (6.5%) to the existing glucose-based criteria for diagnosis of type 2 diabetes was first recommended by the ADA in 2009 and then endorsed by the WHO in 2011 and by the ADS in 2012.[18-20] Subsequently, HbA_{1c} testing was endorsed in 2014 by the ISPAD Clinical Practice Consensus Guidelines for screening, diagnosis and treatment of type 2 diabetes in children and adolescents.[4] It is important to acknowledge the previously mentioned point that glucose-based and HbA_{1c} tests do not necessarily detect diabetes in the same individuals as glucose-based tests are measuring glycaemia at one point in time whereas HbA_{1c} is a marker for chronic glycaemia. The concordance between FPG and 2 h PG post-OGTT results is also imperfect.[11]

HbA_{1c} is a good tool for opportunistic detection of type 2 diabetes in adults and perhaps more so in adolescents as is does not require fasting.[21] In a study using HbA_{1c} to screen all adult patients admitted to a South Australian tertiary hospital, 11% (262/2360 patients) were found to have undiagnosed diabetes.[16] This facilitates early detection and intervention, which minimises diabetes-associated complications.

Haemoglobinopathy is one of the main limitations of using HbA_{1c} for diagnosis and monitoring of diabetes. However, the analytical interference of haemoglobinopathy has been minimised by modern technology, and the prevalence of haemoglobin variants in the clinical samples in the community setting is generally low. Of 849 children of unknown ethnicity screened for diabetes in 2015, only 1.1% were found to have haemoglobin variants identified through high performance liquid chromatography (Lu ZX, unpublished data).

HbA_{1c} is not appropriate for either diagnosis or monitoring of diabetes in patients who have any conditions in which red blood cell survival half-life is altered. Certain types of haemoglobin variants can alter red cell turnover, impacting on the HbA_{1c} results. Conditions such as pregnancy (in second and third trimesters), haemolysis and recent blood loss or transfusion can also shorten red cell lifespan and affect the accuracy of the HbA_{1c} results.[20-21] Measuring haemoglobin concurrently may identify the problematic cases.

It may be time to move to an HbA_{1c}-based algorithm for screening and diagnosis of diabetes.[22] In patients in whom using HbA_{1c} is problematic, glucose-based tests can be used to confirm the diagnosis.

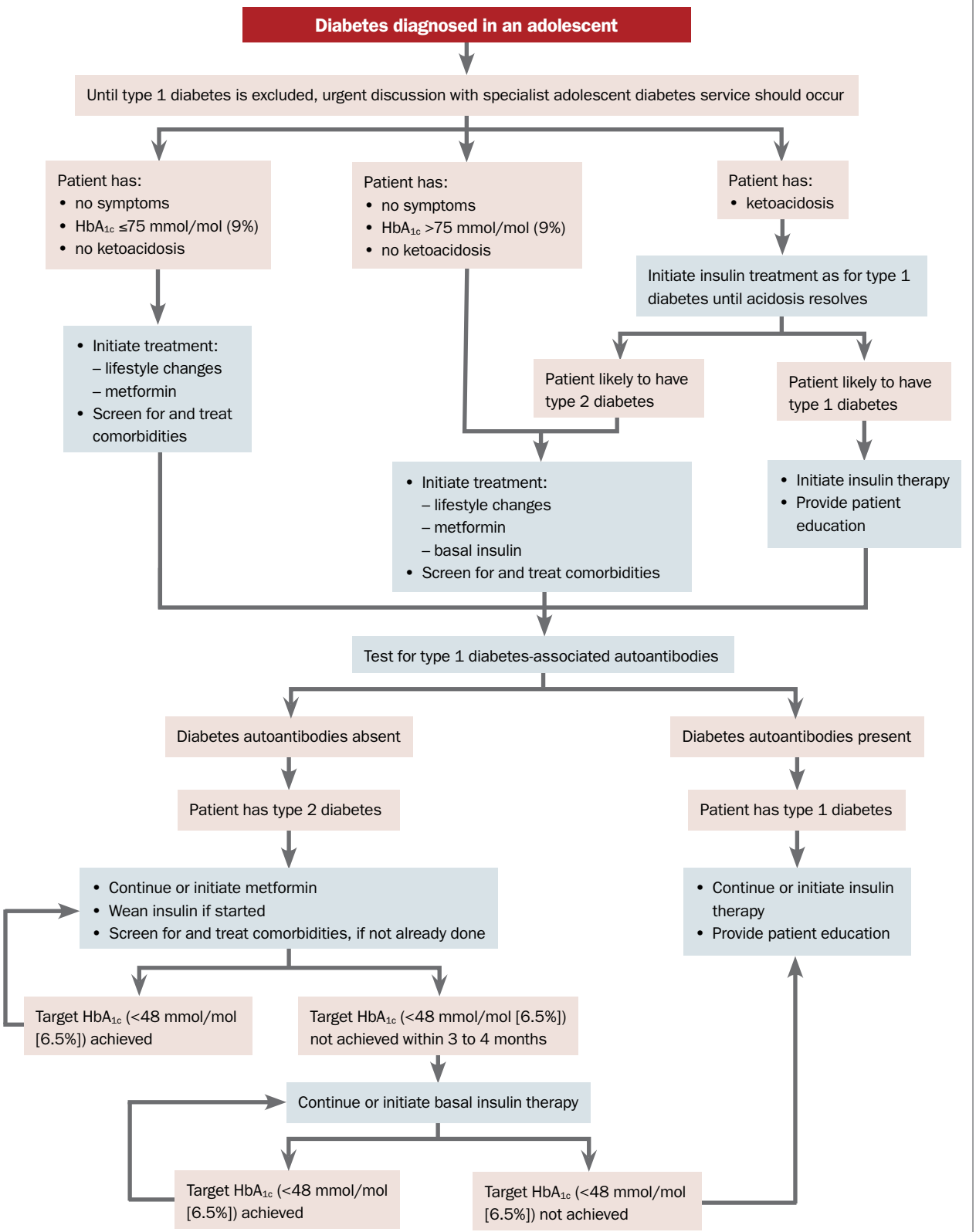
Is there a need to test for diabetes autoantibodies?

The current ISPAD guidelines suggest testing all adolescent patients presenting with diabetes for type 1 diabetes-associated autoantibodies once the diagnosis is established. The presence of autoantibodies can be helpful where the diagnosis is unclear, such as in an overweight/obese pubertal patient presenting with symptoms suggestive of type 1 diabetes (i.e. weight loss and ketoacidosis). Depending on race and ethnicity, 15 to 40% of patients clinically diagnosed with type 2 diabetes have type 1 diabetes-associated autoantibodies.[4] The presence of autoantibodies in type 2 diabetes has been reported to predict rapid development of insulin requirement and other autoimmune disorders.[4] In people with type 1 diabetes, 2 to 4% may be autoantibody-negative at diagnosis.[23]

Should all obese adolescents be screened for type 2 diabetes?

Despite the increased prevalence of type 2 diabetes in adolescents, the overall prevalence of type 2 diabetes is still low. Therefore, to focus on diagnosing adolescents at high-risk of having diabetes, current recommendations from the ADA and the International Diabetes Federation suggest screening only those who are significantly overweight and have multiple risk factors (Box 2).[1,11] The ISPAD guidelines emphasise

An approach to treatment of adolescents with type 2 diabetes, based on ISPAD guidelines*



* Adapted from: International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines. Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2014; 15 (Suppl 20): 26-46.[1]

2. Testing of at-risk children and adolescents for type 2 diabetes: American Diabetes Association recommendations[11]

When
- Age 10 years or onset of puberty, whichever occurs first

Frequency
- Every 3 years

Criteria
- Presence of any one of the following:
  - BMI >85th percentile for age and gender
  - weight for height >85th percentile
  - weight >120% of ideal weight for height

  PLUS
- Presence of any two of the following risk factors:
  - family history of type 2 diabetes in first- or second-degree relative
  - descendant of native American, African American, Hispanic American, Asian or South Pacific Islander ethnic groups (including indigenous population)
  - signs of insulin resistance or conditions associated with insulin resistance, including acanthosis nigricans, hypertension, dyslipidaemia, polycystic ovarian syndrome or small-for-gestational age birth weight
  - maternal history of diabetes or gestational diabetes during the child's gestation

that 'generalized screening of obese youth is unlikely to be cost-effective in most populations'.[4]

Treatment

Treatment of type 2 diabetes is multifaceted and is aimed at achieving normal blood glucose values and HbA_{1c} below 48 mmol/mol (6.5%).[4] The importance of a multidisciplinary team involving paediatricians, diabetes educators, dietitians, social workers and clinical psychologists is invaluable (Figure).[4,5,24] With type 2 diabetes, there is a strong focus on family-based therapy to modify lifestyle factors to achieve and maintain a healthier diet, an appropriate weight range and adequate exercise.

Medications for the treatment of type 2 diabetes are currently generally limited to metformin and insulin therapy in the paediatric population, initiated as either monotherapy or in combination depending on presentation at diagnosis (flow chart).[4,25] The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study reported monotherapy with metformin achieved a durable, but suboptimal, glycaemic control of HbA_{1c} below 64 mmol/mol (8%) for six months in only half of the study population over a two-year period.[26] This suggests that additional therapy will often be required, in addition to improving adherence to therapy, to achieve the optimal treatment target of HbA_{1c} below 48 mmol/mol (6.5%) . Other oral hypoglycaemic agents are available but their use in paediatrics requires further validation.[4,8]

Figure. Dietary advice is part of the lifestyle management of diabetes in adolescents.

An approach to the initial and subsequent treatment of adolescents with type 2 diabetes is given in the flow chart.[4]

Complications and comorbidities

As patients with type 2 diabetes are often asymptomatic at presentation, they may have had diabetes for an extended time before diagnosis and possibly already developed complications. It is important therefore to also screen for complications and comorbidities at the initial diagnostic work-up.

Few studies have investigated complications and comorbidities of type 2 diabetes in adolescents, but renal complications, hypertension, ocular complications, cardiovascular risk factors (including abnormal lipid profiles) and psychosocial dysfunction have all been described. Some microvascular and macrovascular complications (such as albuminuria) appear to be more prevalent in adolescent patients with type 2 diabetes than in those with type 1 diabetes.[9,27,28] In addition, insulin resistance has been described as a syndrome including lipid abnormalities, hypertension, ovarian hyperandrogenism, hepatosteatosis and sleep-disordered syndrome.[4]

Conclusion

Type 2 diabetes in adolescents is increasing in incidence. Lifestyle modifications are the current mainstay of treatment, and metformin and/or insulin are the main medication options. The significant complications and comorbidities that develop at an early stage reinforces the crucial need for ongoing effort to prevent this condition. **ET**

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A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

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