



### Jessica Phillips

BHSc, MBBS, is a basic paediatric trainee, Department of Paediatrics, Flinders Medical Centre, Adelaide, South Australia.

### Patrick J Phillips

MBBS, MA(Oxon), FRACP, MRACMA, GDipHlthEcon(UNE), is Senior Director, Department of Endocrinology, The Queen Elizabeth Hospital, South Australia. patrick.phillips@nwaahs.sa.gov.au

# Children get type 2 diabetes too

## Background

In recent years there has been a worldwide increase in the number of diagnoses of type 2 diabetes mellitus (T2DM) in children and adolescents. This has become a major focus for the work of the International Diabetes Federation. In Australia, most children and adolescents with diabetes have type 1 diabetes. However, more young Australians are developing T2DM.

## Objective

This article presents the case of a girl, Aroha, 13 years of age and of Polynesian descent, who presents with high random blood glucose levels. It outlines the diagnosis, treatment and prognosis of T2DM in children and adolescents.

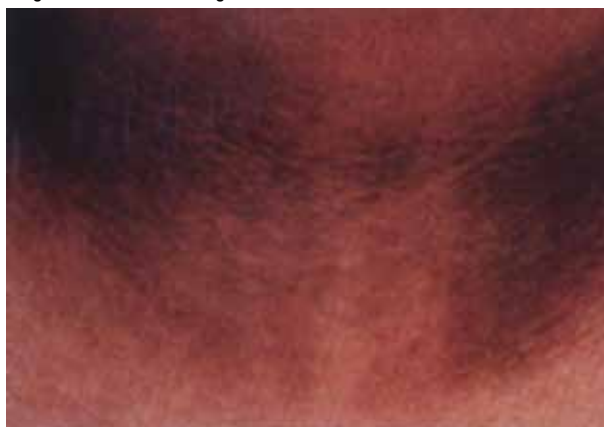
## Discussion

Type 2 diabetes is the consequence of a complex interaction between genes and the environment in a susceptible individual. Children with T2DM are generally overweight, often with central adiposity. Having one or more parents with T2DM gives offspring up to an 80% chance of developing T2DM. At risk children and adolescents should be screened for T2DM. It is important to check the glutamic acid decarboxylase (GAD) antibody to exclude type 1 diabetes. Symptoms and signs of the metabolic syndrome should be sought. Child and adolescent patients with T2DM face the psychological burden of living a lifetime with a chronic disease. Management is team based and team members include the general practitioner, diabetes educator, dietician and endocrinologist. Goals include achieving and maintaining normoglycaemia, weight reduction and increased physical activity. Lifestyle modification alone may control minor hyperglycaemia and metformin can be added to control moderate hyperglycaemia. In severe hypoglycaemia, insulin may be required initially to achieve normoglycaemia and can be phased out and metformin phased in later. Insulin is likely to be required again later in the natural history of disease. Little is known about factors affecting complication risk in children and adolescents with T2DM but they essentially have a 'double whammy' of diabetes and the metabolic syndrome and are likely to develop macrovascular complications much earlier than adults who develop T2DM.

## Case study – Aroha

Aroha, aged 13 years, presents with recurrent vaginal thrush. She is of Polynesian descent and has lived in Australia for 8 years. A finger prick random blood glucose level is performed with a result of 15 mmol/L. Urine dipstick testing reveals glucose but no ketones. Aroha has a body mass index (BMI) of 29 (>97<sup>th</sup> percentile) and had her first period at aged 10 years, but more recently her periods have become irregular and infrequent (3–4 monthly). Aroha's mother has noticed that she has had less energy over the last year or so, and a recent school report noted that Aroha's work is not up to her usual standard. Aroha removes her school shirt so you can measure her blood pressure (100/60 mmHg). You observe a velvety, light brown discolouration in her armpits (*Figure 1*). Aroha is embarrassed to admit she has similar colouring around her groin. On further questioning it is revealed that Aroha's father is very overweight and was diagnosed with 'sugar diabetes' 15 years ago. Both her parents and a younger sibling are overweight. Neither Aroha nor her mother had heard of obstructive sleep apnoea but both agree her father snores so loudly that he keeps the dogs awake! You order blood tests and arrange for an early review of Aroha.

Figure 1. Acanthosis nigricans



■ In recent years, there has been a worldwide increase in the number of diagnoses of type 2 diabetes mellitus (T2DM) in children and adolescents.<sup>1</sup> In the United States of America the incidence of T2DM in high risk groups (native American, African American, Latino, Asian American, Pacific Islander) approaches or exceeds that of type 1 diabetes mellitus (T1DM).<sup>2</sup>

**The American Diabetes Association (ADA) recommends the second yearly testing by fasting plasma glucose after the age of 10 years or puberty, whichever comes first.<sup>2</sup> In Australia, most children and adolescents with diabetes have T1DM.<sup>2</sup> Our case study, Aroha, is in a high risk group for T2DM (Table 1).**

Children with T2DM are generally overweight, often with central adiposity. This is in contrast to children with T1DM who are often underweight. Overweight is the main cause of the increasing incidence of T2DM.<sup>3,4</sup> Every year, more Australian children become overweight, therefore we can expect a rise in the incidence of T2DM to follow. The adverse health consequences associated with central obesity are depicted in *Figure 2*.

Girls are nearly twice as likely as boys to develop the insulin resistance which causes T2DM.<sup>4</sup> This is because girls have lower lean body mass and different fat distribution to boys. Polycystic ovary syndrome (PCOS) is also associated with insulin resistance; girls with PCOS are more likely to develop T2DM and vice versa. Puberty causes an increase in growth hormone and insulin-like growth factor which can increase insulin resistance and risk of T2DM.<sup>5</sup> The peak age of diagnosis T2DM coincides with the stage of greatest insulin resistance, which peaks at age 13–14 years.<sup>6,7</sup>

**Table 1. High risk groups for type 2 diabetes<sup>2</sup>**

- Overweight: (BMI 85<sup>th</sup> percentile for age and gender, weight 85<sup>th</sup> percentile for height, or weight 120% of ideal for height)

**Plus**

- Any two of the following:
  - family history of type 2 diabetes in a first or second degree relative
  - high risk ethnic group (indigenous, Asian, Pacific Islander)
  - signs or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, PCOS)
  - maternal history of diabetes or gestational diabetes

## Genes and environment

Type 2 diabetes is the consequence of a complex interaction between genes and the environment in a susceptible individual. In the paediatric population, neither is within the control of the patient. Having one or more parent with T2DM gives offspring up to an 80% chance of a child developing T2DM.<sup>4</sup> The rate in monozygotic twins is even higher. In utero genetic programming can also occur. Both prenatal undernutrition and gestational diabetes can cause permanent alterations in glucose metabolism in the embryo. This increases the risk of insulin resistance and T2DM.

While genes are important, the obesogenic environment is the phenotypic catalyst. The exception to this is maturity onset diabetes of the young (MODY), a monogenic gene defect (autosomal dominance) which accounts for the minority of cases of diabetes in children. As well, patients who develop MODY usually have a strong

family history (autosomal dominant) and present at age 15–30 years. They can be lean, normal or overweight.

## Diagnosis

Diabetes is diagnosed when:

- fasting blood sugar is >7.0 on two occasions
- fasting blood sugar is >7.0 or random blood sugar is ≥11.0 and the patient is symptomatic
- abnormal glucose tolerance test – 2 hour postglucose load blood sugar ≥11.0 mmol/L (usually performed when the fasting blood sugar is 5.5–6.9 mmol/L).<sup>8</sup>

Aroha has symptoms of hyperglycaemia (recurrent thrush and decreased energy). Usually, hyperglycaemia is caused by either T1DM or T2DM. Rare causes such as Cushing disease or cystic fibrosis, affecting the endocrine and exocrine systems respectively, or drug induced diabetes might need to be considered. In T2DM, signs of hyperglycaemia (fatigue, polyuria, nocturia and polydipsia) may coexist with signs of insulin resistance (overweight, acanthosis nigricans, hypertension, dyslipidaemia and PCOS). Aroha is overweight and has oligomenorrhoea (which raises the possibility of PCOS).

Although Aroha has features suggestive of T2DM, this doesn't mean she could not have T1DM. It is important to exclude this as uncontrolled T1DM can be associated with life threatening diabetic ketoacidosis.<sup>4</sup> A GAD antibody should be ordered; a negative result confirms Aroha has T2DM.

## Case study continued

Aroha's test results are as follows:

- haemoglobin A1c = 8.5%
- fasting glucose = 9 mmol/L
- C-peptide = high
- GAD antibody = negative

### Lipids

- LDL cholesterol = 2.6 mmol/L (normal <2.9)
- HDL cholesterol = 0.9 mmol/L (normal >1.0)
- triglycerides = 2.8 mmol/L (normal <1.7)
- total cholesterol = <4.5 mmol/L (normal <5.2)

## Further assessment

In addition to T2DM, Aroha has the metabolic syndrome. Metabolic syndrome has many names (syndrome X, the deadly quartet, the type 2 syndrome) and definitions. However, there are three major components:

- central obesity (*Figure 2*)
- abnormal glucose metabolism
- cardiovascular risk.

Aroha has components of all three. In this case, insulin resistance is also suggested by a high C peptide and the pigmentation affecting her axilla and groin (acanthosis nigricans) (*Figure 1*).

Like Aroha, a third of children and adolescents with T2DM will have dyslipidaemia, typically hypertriglyceridaemia and low HDL-C.<sup>9</sup> At this stage Aroha is normotensive. However, primary hypertension

is seen at presentation in up to a third of paediatric patients with T2DM.<sup>9</sup> Aroha's liver function tests are slightly abnormal. Obesity and T2DM predispose to a type of liver disease called 'nonalcoholic fatty liver disease'. At the mild end of the spectrum fat in the liver is the only abnormality seen on biopsy but with more severe disease inflammatory changes and fibrosis occur. Typically serum ALT is increased to more than twice the upper reference limit.

## Management

### Psychological

Child and adolescent patients with T2DM face the psychological burden of living a lifetime with chronic disease. A professional diabetes team including a diabetes educator, general practitioner, dietician and endocrinologist can be a source of support for social and psychological issues and arrange referral to more specialist services if required.

### Lifestyle

Aroha is part of a family; it is important to manage her in this context. Lifestyle recommendations for Aroha are essentially healthy recommendations for the entire family. Changes don't have to be immediate and drastic. The diabetes team will work with Aroha and her family in developing a structural plan to make achievable and

acceptable modifications over the medium and long term.

The first aim is to achieve and maintain normoglycaemia. Monitoring blood glucose levels (BGL) and glycosylated haemoglobin levels (HbA1C) provides short and long term feedback. The second aim is to prevent, or treat, the comorbidities associated with T2DM. Nonpharmacologic treatment includes weight reduction (particularly visceral fat) and increased physical activity. Control of body fat will influence other components of the metabolic syndrome (insulin resistance, dysglycaemia, hypertension, dyslipidaemia and prothrombosis) as well as other associated problems (*Figure 2*). The usual prescription of decreasing energy intake and increasing energy expenditure applies, but it will be important to ensure that nutritional requirements are met to ensure linear growth. The success of weight loss in decreasing insulin resistance has been shown by a study in overweight children with modest decreases in BMI (approximately 0.5 kg/m<sup>2</sup>).<sup>10</sup>

### Medication

There is little information about the long term outcomes of different medication management strategies for T2DM in children and adolescents. A long term trial 'treatment options for type 2 diabetes in adolescents and youth' (TODAY)<sup>11</sup> may define a preferred approach for this group of patients.

In the absence of paediatric data, adult guidelines are assumed to be relevant. Currently, metformin and insulin are the only hypoglycaemic agents approved by the US Federal Drug Administration for use in the paediatric population. When commencing insulin, traditional or analogue insulins can be used. However, the traditional insulins may be preferred because of limited experience with the analogues in children (especially basal analogues) and some concern about the long term adverse effects of analogue insulins.<sup>12</sup>

Management of girls and women of childbearing age should consider the potential obstetric implications of medications and minimise the risk of medications causing fetal damage. Many of the adult armamentarium for T2DM are contraindicated or not recommended during pregnancy (*Table 2*).<sup>13</sup> Assuming categories A, B1 and B2 are usually safe, this leaves insulin for hyperglycaemia, alpha methyl-dopa and alpha blockers

Figure 2. Adverse health consequences associated with central obesity

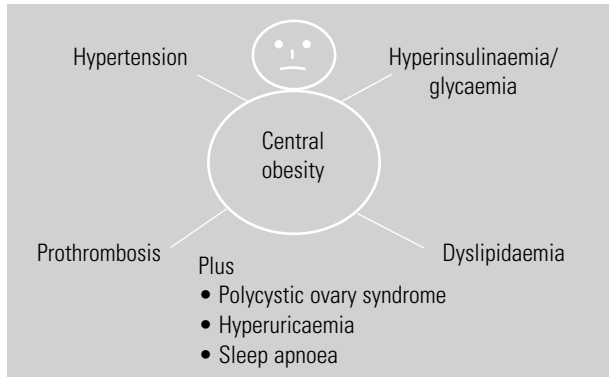


Table 2. Medications for type 2 diabetes and pregnancy category<sup>11</sup>

Commonly used	Glycaemia		Hypertension	Dyslipidaemia
	Oral metformin (C) Sulfonylurea (C)	Injected human insulin (A) Analogue insulin (B3)		
Other	<ul style="list-style-type: none"> <li>Glitazones (B3)</li> <li>Exenatide (C)</li> <li>Acarbose (B3)</li> <li>Glitinides (C)</li> <li>Gliptins (B3)</li> </ul>		<ul style="list-style-type: none"> <li>Alpha methyl dopa (A)</li> <li>Alpha blocker (B2)</li> <li>Clonidine (B3)</li> <li>Spirolactone (B3)</li> <li>K-sparing (C)</li> </ul>	<ul style="list-style-type: none"> <li>Resins (B1, B2)</li> <li>Nicotinic acid (B2)</li> </ul>

Note: A = okay; B1 = probably okay; B2 = possibly okay; B3 = possibly not okay; C = expected not okay; D = probably not okay

for hypertension, and resins and nicotinic acid for dyslipidaemia. Statins and metformin are also used in women of childbearing age and are generally considered safe despite the fact that they are in pregnancy Category C (while there is no evidence of teratogenesis or adverse fetal effects, insufficient data exist to state that harm does not occur) (Table 2).<sup>13</sup> The ADA recommends statins as first line therapy to control LDL cholesterol, but only in children over 10 years of age, resins as second line therapy and fibrates if hypertriglyceridaemia is present.

### Stepwise treatment to achieve normoglycaemia

The first step is guided by the severity of hyperglycaemia and symptoms. Lifestyle modification alone may control minor hyperglycaemia and metformin can be added to control moderate hyperglycaemia. In severe hypoglycaemia, insulin may be required initially to achieve normoglycaemia and can be phased out and metformin phased in. However, insulin is likely to be required later in

the natural history of disease. The KISS principle (Keep Insulin Safe and Simple) is the same for children as for adults.<sup>14</sup>

- First fix the fasting – add bed time basal insulin if needed
- Then tackle tea – add morning basal insulin if needed
- Find the hidden hyps – check BGL before lunch and before bed – and postprandial BGLs
- And check the A1c – to check overall glycaemic control.

The basal blood glucose values (before breakfast and before the evening meal) are controlled by basal insulin before bed and before breakfast respectively. Hyperglycaemia before lunch, late in the evening, and postprandially can be addressed by reviewing the amount and glycaemic index (glycaemic load) of the preceding meal, adding acarbose at that meal or adding pre-prandial bolus insulin before the meal. A suggested algorithm is outlined in Figure 3.<sup>14,15</sup>

Glycaemic targets A1c (<7%) and pre-prandial blood glucose (4–6 mmol/L) are generally recommended, but targets should be individualised and balance the costs of improving glycaemic control (risk of weight gain and hypoglycaemia, extra effort and expense) against the benefits of reducing the risk of future diabetes complications.

### Prognosis

Little is known about factors affecting complication risk in children and adolescents with T2DM and any beneficial or adverse effects associated with ethnic (eg. Polynesian) background. Extrapolating from adults, it is likely that prognosis will depend on stage of life of diagnosis and control of glycaemia and other risk factors including weight, dyslipidaemia and hypertension.

In T1DM, duration, hyperglycaemia and hypertension are major contributors to long term microvascular complications. Unless there is a ‘double whammy’ of T1DM plus the metabolic syndrome, there is no special predisposition to macrovascular complications until renal impairment sets up the ‘vicious cycle’ of progressive hypertension, dyslipidaemia, renal damage and cardiovascular disease (Figure 4).

Children with T2DM already have the ‘double whammy’ of diabetes and the metabolic syndrome. They will be exposed to cardiovascular risk factors from an early age and are likely to develop macrovascular complications much earlier than adults who develop T2DM.

Figure 3. Getting to target

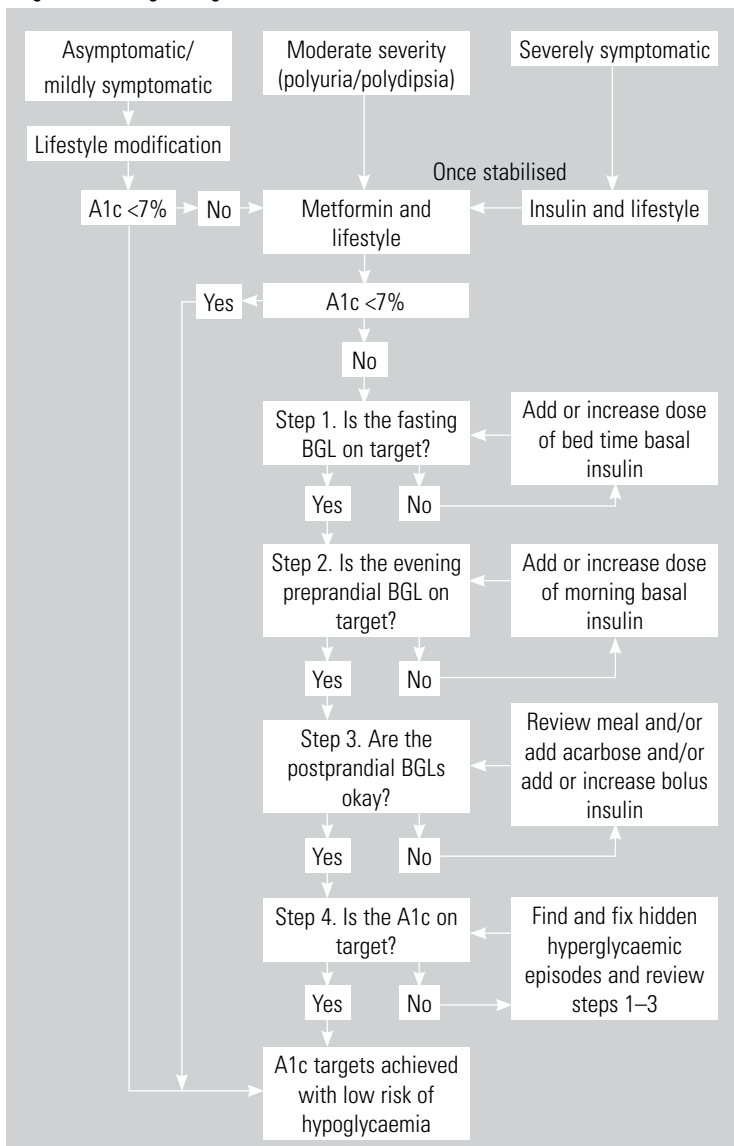
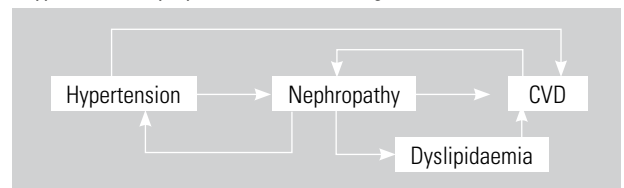


Figure 4. Nephropathy and the ‘vicious cycle’ of progressive hypertension, dyslipidaemia, renal damage and cardiovascular



### Case study continued

You refer Aroha to a dietician and diabetes educator for a lifestyle plan to ‘eat less (food), watch less (TV) and walk more’ and to learn about blood glucose monitoring. You advise her about when and who to contact if she has problems (eg. sick days, blood glucose

swings) or questions (eg. about parties or trips) and suggest she sees you in 3 months, or before as needed.

Three months later Aroha returns. She has lost 1.3 kg. You measure her height and see she has grown 2 cm (height 159 cm weight 70 kg, BMI = 27.8, percentile 90–95). She feels less tired; her periods are lighter and less irregular. Her mother bought her a Wii™ to encourage regular exercise and Aroha exercises most nights after school. You congratulate her on her success, suggest she continues the good work and arrange to see her in 3 months.

Conflict of interest: none declared.

### Acknowledgment

We are grateful to Dr David Everett, Senior Consultant Paediatrician at Flinders Medical Centre, South Australia, for helpful comments and suggestions.

### References

1. International Diabetes Federation. Available at [www.idf.org](http://www.idf.org).
2. American Diabetes Association. Management of dyslipidaemia in children and adolescents. *Diabetes Care* 2003;26:2194.
3. Craig M, Femia G, Brodya V, Lloyd M, Howard N. Diabetes. *Med J Aust* 2007;186:497–9.
4. Laffel L, Svoren B. Management of type 2 diabetes mellitus in children and adolescents. Available at [www.uptodate.com](http://www.uptodate.com) [Accessed 21 January 2008].
5. Goran M, Gower A. Longitudinal study on pubertal insulin resistance. *Diabetes* 2001;50:2444–50.
6. McMahon S, Haynes A, Ratnam N, et al. Increase in type 2 diabetes in children and adolescents in Western Australia. *Med J Aust* 2004;180:459–61.
7. Moran A, Jacobs Jr D, Steinberg J, Hong CP, Prineas R, Sinaiko A. Insulin resistance during puberty. Results from clamp studies in 357 children. *Diabetes* 1999;48:2039–44.
8. Diabetes management in general practice: Guidelines for type 2 diabetes, 2008/9. Melbourne: Diabetes Australia and The Royal Australian College of General Practitioners. Available at [www.racgp.org.au/guidelines/diabetes](http://www.racgp.org.au/guidelines/diabetes).
9. Laffel L, Svoren B. Epidemiology, presentation, and diagnosis of type 2 diabetes mellitus in children and adolescents. Available at [www.uptodate.com](http://www.uptodate.com) [Accessed 21 January 2008].
10. Reinehr T, Kiess W, Kapellen T, Andler W. Insulin sensitivity among obese children and adolescents, according to degree of weight loss. *Pediatrics* 2004;114:1569.
11. US National Institutes of Health. 2009. Available at <http://clinicaltrials.gov/ct2/show/NCT00081328>.
12. Garg SK, Hirsch HB, Skyler JS. Insulin glargine and cancer: An unsubstantiated allegation. *Diabetes Technol Ther* 2009;11:473–6.
13. Prescribing medicines in pregnancy, 4th edn. Publications approval number 2637. Canberra: Commonwealth of Australia, 1999.
14. Phillips PJ. KISS – keep insulin safe and simple. *Medicine Today* 2008; (Suppl May).
15. Phillips PJ, Twigg SM. Type 2 diabetes – which BGLs matter? The fasting, pre- and post-prandial glycaemia debate. *Aust Fam Physician* 2008;37:929–31.