Acute and chronic complications of type 2 diabetes mellitus in children and adolescents

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With the increase in prevalence of type 2 diabetes mellitus in adolescents, a rise in incidence of secondary comorbidities—including hypertension, hyperlipidaemia, nephropathy, and retinopathy—is anticipated. Furthermore, findings of studies in young adults have suggested that the development and progression of clinical complications might be especially rapid when the onset of type 2 diabetes is early, raising the possibility of a serious public-health challenge in the next few decades. To date, reports of the epidemiology and natural history of secondary complications specifically in adolescents with type 2 diabetes have been scarce. Yet, we must begin to understand the extent of the coming challenge. To this end, we have reviewed reports on acute and long-term comorbidities associated with type 2 diabetes in young people and have looked at mounting evidence that this group could be at increased risk for development of early complications.

15 years ago, type 2 diabetes mellitus accounted for less than 3% of all cases of new-onset diabetes in adolescents, but now 45% of cases are attributed to it.1 Young people with this disorder are obese and, therefore, prone to secondary comorbidities including hypertension, hyperlipidaemia, non-alcoholic fatty liver disease, and metabolic syndrome, all of which are associated with increased cardiovascular risk. To date, only limited data are available for the secondary morbidity of type 2 diabetes in children and adolescents. Hillier and Pedula have shown more aggressive development of clinical complications—particularly microalbuminuria and risk of myocardial infarction—in adults diagnosed with type 2 diabetes between the ages of 18 and 44 years than in those identified after 45 years of age. Furthermore, adolescents with type 2 diabetes show poor adherence to medical care and treatment and, therefore, could be at especially high-risk for development of early complications.2 Here, we review the most up-to-date reports of acute and long-term comorbidities associated with type 2 diabetes in children and adolescents and examine mounting evidence that this group is at risk of developing early complications.

Acute complications
Adolescents with type 2 diabetes can present with various acute crises that impart a substantial short-term risk of morbidity and mortality. These include diabetic ketoacidosis, hyperglycaemic hyperosmolar state, and malignant hyperthermia-like syndrome with rhabdomyolysis.

Diabetic ketoacidosis
In several studies of young people with type 2 diabetes, diabetic ketoacidosis has been recorded.3,4 In Cincinnati, 42% of African-American adolescents presented with ketonuria and 25% met criteria for diabetic ketoacidosis at presentation.5 In Arkansas, 25% of young people with type 2 diabetes presented with diabetic ketoacidosis and 11% of Canadian First Nations children had episodes of this acute complication.6,7 Diabetic ketoacidosis in patients with type 1 diabetes is associated with substantial morbidity, and reported mortality rates in national population-based studies range from 0.15% (USA) to 0.31% (UK).8,9 Currently, no reports have been published on morbidity or mortality associated specifically with this acute complication in adolescents with type 2 diabetes.

Hyperglycaemic hyperosmolar state
Hyperglycaemic hyperosmolar state is a life-threatening emergency. Standard diagnostic criteria are blood glucose concentrations greater than 33 mmol/L (600 mg/dL) and serum osmolality of more than 330 mOsm/L, with mild acidosis (serum bicarbonate >15 mmol/L) and mild ketonuria (≤15 mg/dL).10 Precipitating causes can usually be identified and include underlying infections, medications, non-adherence to diabetes treatment, undiagnosed diabetes, substance abuse, and coexisting chronic disease.

In the first report of a child with hyperglycaemic hyperosmolar state secondary to type 2 diabetes, workers described an 11-year-old boy with autism, morbid obesity, acanthosis nigricans, and asthma (ethnic origin was not...
specified). Subsequently, seven obese African-American young people (six male) aged 13–21 years with previously unrecognised diabetes were reported. All were initially diagnosed with diabetic ketoacidosis, but review of their records indicated that they met criteria for hyperglycaemic hyperosmolar state. All seven died, and in post-mortem examinations of three, an absence of insulitis—a pathological inflammatory reaction in the pancreatic islets, characteristic of type 1 diabetes—was recorded, supporting the clinical diagnosis of type 2 diabetes. In another case series of four African-American children aged 9–14 years (two boys) who developed hyperglycaemic hyperosmolar state, two died (one from hypovolemic shock and one from rhabdomyolysis and multisystem organ failure) and two were discharged from the hospital in good health. Researchers have described eight African-American young people aged 11–17 years (seven males) with type 2 diabetes who were treated for hyperglycaemic hyperosmolar state. All had alteration of mental status ranging from confusion to coma; one died on the sixth day of admission, possibly due to massive pulmonary embolism, but the remainder made a complete recovery.

Rare complications as a result of the hyperglycaemic hyperosmolar state have also been recorded in young people. We reported a case of a Hispanic adolescent with type 2 diabetes who had hyperglycaemic hyperosmolar state and acute necrotising pancreatitis leading to death. An Asian patient with type 2 diabetes who had hyperglycaemic hyperosmolar state developed widespread necrosis of the small bowel, secondary to thrombosis of the superior mesenteric artery.

In a systematic review of the records of 190 children with type 2 diabetes diagnosed over a 5-year period at the Children’s Hospital of Philadelphia, Fournier and colleagues recorded seven (3.7%) patients aged 10–17 years (five males, mean age at presentation 13.3 years) who had hyperglycaemic hyperosmolar state at presentation. All affected youngsters were African-American and three had been diagnosed previously with developmental delay. One child developed multisystem organ failure and died, giving a case-fatality rate of 14.3%. Survivors had no appreciable neurodevelopmental sequelae.

In summary, 29 cases have been reported of adolescents with hyperglycaemic hyperosmolar state, of whom 26 were African-American and 22 were male. Developmental delay was recorded in at least four patients. As in adults, this complication in young people is associated with substantial mortality (12 of 29 [41.4%]).

Malignant hyperthermia-like syndrome with rhabdomyolysis

Malignant hyperthermia-like syndrome is an acute complication of type 2 diabetes. Hollander and coworkers reported this syndrome in six adolescent males (aged 14–18 years, five obese, four African-American) at initial presentation of their diabetes. The features of this syndrome include hyperglycaemic hyperosmolar state complicated by a malignant hyperthermia-like event with fever, rhabdomyolysis, and severe cardiovascular instability after administration of insulin. Four of the six patients died.

Chronic complications

Adherence to medical treatment might have a role in reduction of the risk of developing chronic complications of type 2 diabetes in young people. Findings of a Japanese study of treatment attrition in young people aged 10–19 years with type 2 diabetes showed that 57% failed to attend regular clinical follow-up visits for more than 20 months. Those who dropped out of care had a substantially higher body mass index, higher mean arterial blood pressure, and a more abnormal lipid profile than those who continued to receive regular treatment. Furthermore, fewer patients who dropped out had a proper diet or took regular exercise compared with those who continued with follow-up visits. Evidence for poor diabetes control in adolescents was also noted in Canada where, during active follow-up, mean total glycated haemoglobin (HbA1c) concentration in adolescent patients with type 2 diabetes was 12% irrespective of age—none maintained a level of HbA1c within the target range. Goland and colleagues recorded poor adherence to medical regimens by 65 young people with type 2 diabetes, with 65% missing several appointments and most reporting discontinuation of drugs periodically.

In the following sections, we describe presence of complications (hypertension, microalbuminuria, background retinopathy, dyslipidaemia, etc) at diagnosis of type 2 diabetes, their prevalence after several years of follow-up, and their progression (to macroalbuminuria and proliferative diabetic retinopathy). We present data comparing the rate of progression between adolescents with type 2 and type 1 diabetes mellitus. When available, we also compared complications in young people with type 2 diabetes with those in adults with this disorder.

Hypertension

The association between type 2 diabetes and hypertension is well documented in adults and findings suggest a similar relation in adolescents, with prevalence of hypertension at presentation varying between 10% and 32%. In a study from Texas, 49% and 11% of young people with type 2 diabetes had systolic and diastolic blood pressures, respectively, greater than the 95% percentile for age, sex, and height at presentation, whereas 55% and 19% had systolic and diastolic blood pressures greater than the 90% percentile. Indeed, hypertension at diagnosis is eight times as frequent in adolescents with type 2 diabetes compared with those with type 1 disease.

Nephropathy

Microalbuminuria is also typical at presentation. In Pima Indians with type 2 diabetes identified during childhood,
microalbuminuria was noted in 22% at diagnosis, with no cases of macroalbuminuria seen. In young Maori individuals, microalbuminuria was reported at diagnosis in 14% (average age 19-1 years).

The rate of progression of microalbuminuria and nephropathy seems to be rapid in adolescents with type 2 diabetes (table 1). Findings of a study showed that 40% of 26 predominantly Latino and African-American individuals aged 10-18 years who had been diagnosed with type 2 diabetes for less than 3 years had microalbuminuria. No substantial differences were recorded between patients who developed microalbuminuria and those who did not in terms of demographics, random blood-pressure readings, echocardiographic findings, or HbA1c concentrations. However, in people with type 2 diabetes, average daytime systolic blood pressure was higher in those with microalbuminuria than in individuals without this disorder.

Yokoyama and coworkers described a Japanese cohort of 1065 patients diagnosed with type 2 diabetes before 30 years of age. Those with current confirmed nephropathy or neuropathy were excluded, leaving 426 study participants whose mean age at diagnosis of diabetes was 22.6 (SD 5.6) years. During mean follow-up of 6-8 years, 41 developed microalbuminuria (incidence 14.1 per 1000 person-years [95% CI 10.4-19.1]) at a mean age of 35.2 (9.4) years. Factors shown to affect development of nephropathy in this study were duration of diabetes, high HbA1c during follow-up, and diastolic blood pressure.

In Pima Indians diagnosed with type 2 diabetes during childhood, frequency of microalbuminuria rose from 22% at presentation to 58% after 10 years, whereas macroalbuminuria was detected in 16%. Similarly, microalbuminuria increased from 14% to 62% in young Maori patients over 10 years, whereas the rate of progression of microalbuminuria in adolescents who had type 1 diabetes mellitus for the same duration was only 18%.

In other studies comparing prevalence of microalbuminuria in patients with childhood-onset type 2 and type 1 diabetes mellitus, adolescents with type 2 diabetes have rapid progression of nephropathy (table 2). Yoo and coworkers studied 141 Korean patients with type 1 and 22 with type 2 diabetes (age 8-28 years). Glycaemic control—as indicated by amount of HbA1c—in this cohort was inadequate overall, but no difference was noted between individuals with type 1 and type 2 diabetes (mean 9.4% [SD 2.4] and 10.3% [2.3], respectively). Although mean disease duration was shorter in people with type 2 versus type 1 diabetes (5.5 [3.9] vs 8.1 [3.4] years, respectively), persistent microalbuminuria and macroalbuminuria were recorded in 18.2% and 4.5% of patients with type 2 diabetes.
diabetes, respectively, compared with only 11·3% and 2·8% of those with type 1 diabetes (table 2). Similarly, Scott and colleagues did a multicentre study across New Zealand of 105 people with type 2 and 662 with type 1 diabetes. Microalbuminuria was recorded in 72% of those with type 2 diabetes compared with 17% with type 1 disease, despite shorter disease duration (3 vs 6 years, respectively).29

Prevalence of diabetes complications and their risk factors was compared in 1433 young people with type 1 and 68 with type 2 diabetes (age <18 years) from New South Wales, Australia.30 Despite shorter disease duration (1·3 vs 6·8 years), microalbuminuria and hypertension were significantly more prevalent (28% and 36%, respectively) in individuals with type 2 diabetes compared with type 1 diabetes (6% and 16%). In multivariate analyses, microalbuminuria was associated with high amounts of HbA1c.

In Japanese patients with early-onset diabetes mellitus,31 incidence of nephropathy was reported based on age of diagnosis and compared in individuals with type 1 and type 2 diabetes. For those diagnosed age 0–9 years, the incidence of nephropathy was 25·5 per 1000 person-years for children with type 2 diabetes and 4·87 for those with type 1 diabetes. Incidence for those diagnosed age 10–19 years was 12·44 and 6·63 per 1000 person-years, respectively. The higher incidence of nephropathy in patients with type 2 diabetes held true even when accounting for duration of disease. For example, after 5–9 years, incidence density in individuals with type 1 disorder was 0·75 per 1000 person-years compared with 8·26 per 1000 person-years in those with type 2 diabetes (figure). Altogether, the cumulative incidence of nephropathy after 30 years of postpubertal diabetes was significantly higher for type 2 (44·4% [95% CI 37–58]) than for type 1 diabetes (20·2% [14·9–25·8]; p<0·0001). Furthermore, although incidence of nephropathy in type 1 patients has declined during past decades, in those with type 2 diabetes it has remained persistently high.31

Rapid progression of nephropathy can lead to end-stage renal disease. Of 1065 Japanese individuals diagnosed with type 2 diabetes before the age of 30 years, 31 (3%) developed renal failure needing dialysis at a mean age of 35 years.27 In a long-term follow-up study (15 years’ duration), data for 51 young people diagnosed with diabetes before age 17 years were available.21 Three women age 26, 28, and 29 years had end-stage renal disease and had been on dialysis for 2 months, 1 year, and 6 years, respectively. Furthermore, two sudden deaths on dialysis were reported.21

Table 2: Prevalence of hypertension and nephropathy in adolescents with type 2 versus type 1 diabetes

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Hypertension at diagnosis</th>
<th>Microalbuminuria at diagnosis</th>
<th>Follow-up (years)</th>
<th>Hypertension at follow-up</th>
<th>Microalbuminuria at follow-up</th>
<th>Macroalbuminuria at follow-up</th>
<th>Age at diagnosis of diabetes (years)</th>
<th>Age at diagnosis of complications (years)</th>
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<td>Scott et al (1997); Arkansas</td>
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<tr>
<td>Type 1 49</td>
<td>4%</td>
<td>..</td>
<td>8</td>
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<td>8–19</td>
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<td>Type 2 50</td>
<td>32%</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>13·9 (5·0–4·1)</td>
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<td>McGrath et al (1999); Maori</td>
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<tr>
<td>Type 1 18</td>
<td>..</td>
<td>0</td>
<td>8·4</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
<td>12·4 (1·2–22)</td>
<td>20·9 (9–38)</td>
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<tr>
<td>Type 2 28</td>
<td>..</td>
<td>14%</td>
<td>10·1</td>
<td>39%</td>
<td>35%</td>
<td>27%</td>
<td>19·5 (5·2–29·5)</td>
<td>29·5 (11–49)</td>
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<td>Yoo et al (2004); Korea</td>
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<tr>
<td>Type 1 141</td>
<td>..</td>
<td>..</td>
<td>8·1 (5·0–3·4)</td>
<td>..</td>
<td>11·3%</td>
<td>2·8%</td>
<td>8–28</td>
<td>..</td>
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<td>Type 2 22</td>
<td>..</td>
<td>..</td>
<td>5·5 (5·0–3·9)</td>
<td>..</td>
<td>18·2%</td>
<td>4·5%</td>
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<td>Eppens et al (2006); Australia</td>
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<td>Type 1 1433</td>
<td>..</td>
<td>..</td>
<td>6·8 (4·7–9·6)*</td>
<td>16%</td>
<td>6%</td>
<td>..</td>
<td>8·1 (4·8–10·8)*</td>
<td>15·7 (13·9–17)*</td>
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<tr>
<td>Type 2 68</td>
<td>..</td>
<td>7%</td>
<td>1·3 (0·6–3·1)*</td>
<td>36%</td>
<td>28%</td>
<td>..</td>
<td>13·2 (11·6–15)*</td>
<td>15·3 (13·6–16·4)*</td>
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<tr>
<td>Scott et al (2006); New Zealand</td>
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<tr>
<td>Type 1 662</td>
<td>..</td>
<td>..</td>
<td>6</td>
<td>..</td>
<td>17%</td>
<td>..</td>
<td>16–25</td>
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<tr>
<td>Type 2 105</td>
<td>..</td>
<td>..</td>
<td>3·5 (0·3)</td>
<td>20%</td>
<td>72%</td>
<td>..</td>
<td>20 (5·0–4·1)</td>
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</tbody>
</table>

Data are mean (range) unless otherwise indicated. *Median (IQR).

Figure: Incidence of nephropathy in Pima Indians with type 2 diabetes and Japanese patients with type 1 and type 2 diabetes, based on disease duration
We identified only one study that directly compared incidence of nephropathy in patients with type 2 diabetes based on age of disease onset. Krakoff and colleagues noted that in Pima Indians, nephropathy did not differ in those diagnosed before 20 years of age, age 20–39 years, or aged 40–59 years (figure).

Retinopathy
Similar to nephropathy, retinopathy can be present at diagnosis of diabetes (table 1). In a large Japanese study of 1065 patients diagnosed with type 2 diabetes before the age of 30 years, no specific information was provided about age distribution. However, 99 (9.3% of the initial cohort) had retinopathy before their first visit and 135 (12.7%) developed proliferative retinopathy before age 35 years. Of these 135 individuals, 32 (24%) were blind by a mean age of 32 years. Many had no symptoms of diabetes and did not receive regular treatment until after they developed severe diabetic complications. Female gender and slightly raised blood pressure were additional risk factors for background and proliferative diabetic retinopathy. In a second Japanese study, workers examined progression of retinopathy. Of 322 patients with type 2 diabetes who were free of diabetic retinopathy at entry, 88 developed background retinopathy after 5.7 years, yielding an incidence of 48.1 per 1000 person-years (95% CI 39–59). Similarly, 50 of 160 individuals who presented with background diabetic retinopathy developed proliferative retinopathy after 7.1 years, with an incidence of 57.7 per 1000 person-years (55–60). Poor metabolic control and disease duration were risk factors for progression, along with high-normal diastolic blood pressure.

We identified two studies comparing incidence and progression of retinopathy in adolescents with type 2 and type 1 diabetes. In a comparative clinic-based study, 1433 patients with type 1 and 68 with type 2 diabetes were assessed by seven-field stereoscopic retinal photography. Retinopathy was significantly more frequent in individuals with type 1 diabetes than in those with type 2 diabetes (20% vs 4%, p=0.04). However, median duration of diabetes was strikingly shorter in patients with type 2 diabetes—1.3 years (IQR 0.6–3.1) compared with 6.8 years (4.7–9.6), respectively (p<0.0001)—making conclusions difficult to draw. Similarly, Scott and colleagues reported that 4% of 105 people with type 2 diabetes had background retinopathy versus 10% with type 1 diabetes. Disease duration was 3 years for adolescents with type 2 diabetes compared with 10 years in those with type 1 diabetes.

In a comparison of incidence of retinopathy in Pima Indian adolescents, young adults, and adults with type 2 diabetes, Krakoff and coworkers noted that retinopathy rates were lower in individuals in whom diabetes was diagnosed in youth, and the complication did not arise in any person before 20 years of age.

Dyslipidaemia
Review of studies of dyslipidaemia is complicated by the fact that many different definitions for the disorder are used. In some cases, researchers report only total cholesterol concentrations, whereas others provide full lipid profiles but use different cutoffs. However, a general

<table>
<thead>
<tr>
<th>Site or population</th>
<th>Patients</th>
<th>Age of onset of diabetes (years)</th>
<th>At diagnosis</th>
<th>Duration &lt;5 years</th>
<th>Duration 5-10 years</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagot-Campagna et al (1998)²⁴ Pima Indians 41 18% 30% Cholesterol†</td>
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<tr>
<td>Hotu et al (2004)³⁷ New Zealand 18 15 (11–19) 85% (1.8 years) HDL cholesterol &gt;4.5 molar units</td>
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<tr>
<td>McGrath et al (1999)²⁵ Maori 28 19 (2-29) 62.5% (10 years) Cholesterol &gt;5.04 mmol/L</td>
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<tr>
<td>Yung et al (2003)³⁸ Winnipeg, MB; Aboriginal origin 153 7-20 60% Cholesterol† 40% LDL† 51% Triglycerides† 15% Low HDL†</td>
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<tr>
<td>Newfield et al (2003)³⁹ Mexican American; black people from San Diego, CA 28 13 (8.8-17.6) 54% Cholesterol &gt;5.17 mmol/L 46% LDL &gt;3.36 mmol/L 61% Triglycerides &gt;1.69 mmol/L 44% HDL &lt;0.9 mmol/L</td>
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<tr>
<td>Wei et al (2003)⁴⁰ Taiwan 137 13 (13.7 years) Cholesterol &gt;5.17 mmol/L 27% LDL &gt;3.66 mmol/L 27% Triglycerides &gt;1.69 mmol/L 12% HDL &lt;0.9 mmol/L</td>
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<tr>
<td>Eppens et al (2006)⁴¹ Australia 68 13 (11–15) 32% Cholesterol &gt;5.17 mmol/L 32% LDL &gt;3.66 mmol/L 53% Triglycerides &gt;1.69 mmol/L</td>
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<tr>
<td>Kershner et al (2006)⁴² Multicentre USA 283 &gt;10 33% Cholesterol &gt;5.17 mmol/L 24% LDL &gt;3.36 mmol/L 29% Triglycerides &gt;1.69 mmol/L 44% HDL &lt;1 mmol/L</td>
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*Duration of diabetes since diagnosis. †Cutoff amounts not provided.

Table 3: Presence of dyslipidaemia in adolescents with type 2 diabetes
overview indicates that many adolescents have substantial hyperlipidaemia at diagnosis of type 2 diabetes (table 3). In Pima Indians, hypercholesterolaemia was recorded in 18% at diagnosis of type 2 diabetes, whereas in a national surveillance study of type 2 diabetes in Taiwanese children, hypercholesterolaemia—defined as a concentration of total cholesterol of 5·17 mmol/L—was present in 27%. In a study from San Diego, California, first available lipids after diagnosis were analysed in 28 adolescents with type 2 diabetes (mean age 13-7 years): 61% had triglyceride concentrations greater than 1·69 mmol/L, 46% had LDL cholesterol amounts of more than 3·36 mmol/L, and 44% had HDL cholesterol levels of less than 0·9 mmol/L. In 68 Australian young people (age 15 years) with a duration of type 2 diabetes of less than 3 years, hypercholesterolaemia (>5·17 mmol/L) was noted in 32% and hypertriglyceridaemia (>1·69 mmol/L) in 53%.

In Auckland, New Zealand, 85% of adolescents with type 2 diabetes had dyslipidaemia, defined by an HDL cholesterol/total cholesterol ratio of more than 4·5 molar units during 6 years of follow-up. In 153 young people from Winnipeg, Canada, age 7–20 years with type 2 diabetes, amounts of total cholesterol, LDL cholesterol, and triglycerides were raised in 60%, 41%, and 51%, respectively. HDL cholesterol concentrations were low in 15%, and 20% had both raised LDL cholesterol and triglycerides. None of the individuals was being treated with drugs for lipid abnormalities. Prevalence of lipid abnormalities in young people from the USA older than 10 years of age with type 1 (n=1963) or type 2 (283) diabetes was assessed in a cross-sectional population-based study undertaken at six centres. In those with type 2 diabetes, 33% had a concentration of total cholesterol of more than 5·17 mmol/L, 24% had LDL cholesterol amounts more than 3·36 mmol/L, 29% had triglyceride concentrations of more than 1·69 mmol/L, and 44% had HDL cholesterol levels lower than 1·00 mmol/L. Proportions for type 1 diabetes were 19%, 15%, 10%, and 12%, respectively. Of note, only 1% of patients were receiving drugs to treat dyslipidaemia.

Non-alcoholic fatty liver disease
Non-alcoholic fatty liver disease is now the most frequent cause of chronic liver disorder in obese individuals, and might progress to cirrhosis, portal hypertension, and need for liver transplantation. In particular, diabetes is a strong independent predictor of progression to fibrosis in non-alcoholic fatty liver disease. Prevalence of raised liver enzymes in 49 young people (age 8–18 years) with type 2 diabetes was studied by Dean and Sellers in Winnipeg, Canada. 22% had alanine aminotransferase concentrations higher than twice the upper limit of normal and 16% had amounts higher than three times normal. 6% of individuals had three times the normal levels of both alanine and aspartate aminotransferases.

In 39 patients from the Children’s Hospital in San Diego who were age 9–18 years and diagnosed with type 2 diabetes, liver enzymes were twice the normal amount in about 23% and were three times normal in 8%. One child had cholelithiasis and needed cholecystectomy. Prevalence of raised alanine aminotransferase was 48% in 115 adolescents with type 2 diabetes studied in Denver, Colorado.

Cardiovascular and atherosclerotic complications
Information on overt cardiovascular complications in young people with type 2 diabetes is scarce. Early signs of cardiovascular involvement were investigated by electrocardiography, ambulatory blood pressure measurements, and echocardiography in 22 Hungarian children and adolescents with type 2 disease who were followed up for 1–12 years. Mean night-time systolic and diastolic blood pressure levels were substantially higher in the group with diabetes compared with age-specific reference values. As many as 71% had diminished nocturnal decline in blood pressure (non-dippers), which is a known predictor of cardiovascular risk. Ultrasonographic variables indicating posterior and septal wall thickness were above the reference range in 47% of children. Ettinger and colleagues reported left-ventricular hypertrophy in five of 24 (22%) adolescents with type 2 diabetes who underwent an echocardiogram up to 3 years after diagnosis. 14 of 1065 Japanese patients diagnosed with type 2 diabetes before age 30 years developed atherosclerotic vascular disease at a mean age of 36 years. Of 20 young people aged 15-5 years with type 2 diabetes (mean duration 1·7 [SD 0·4] years), substantially higher aortic pulse-wave velocity values were recorded compared with obese and healthy-weight controls, indicating increased arterial stiffness. These findings were interpreted as being consistent with premature ageing of the cardiovascular system.

Neuropathy
As far as we know, no systematic reports on incidence of neuropathy in children and adolescents with type 2 diabetes have been published, and available information is restricted to a few case reports. In 28 young Maori people with type 2 diabetes (mean duration 10 years), one had erectile dysfunction, one had peripheral vascular disease with arterial foot ulcers, and two had peripheral neuropathy. In an Australian study from New South Wales, rates of peripheral and autonomic neuropathy did not differ in adolescents younger than 18 years with type 1 and type 2 diabetes (27% and 61% vs 21% and 57%, respectively). However, as noted above, duration of type 2 diabetes was 1·3 years (range 0·6–3·1) compared with 6·8 years (4·7–9·6) in people with type 1 diabetes. The equal prevalence of neuropathy despite shorter disease duration raises the possibility that incidence is higher in
adolescents with type 2 diabetes than in those with type 1 disease. However, current data are inadequate to draw reliable conclusions.

Psychiatric disorders

In a retrospective chart review of 237 paediatric patients with type 2 diabetes at the Children’s Hospital of Philadelphia, 46 (19-4%) had neuropsychiatric disease at presentation of diabetes, including depression, schizophrenia, bipolar disorder, autism, mental retardation, attention-deficit hyperactivity disorder, obsessive-compulsive disorders, and behaviour disorder. Sex or ethnic origin did not differ in affected individuals. 63% were prescribed at least one psychotropic drug.

Information about prevalence of eating disorders in adolescents with type 2 diabetes is scarce. In an early study of young people with the disease in Cincinnati, three of 11 met criteria for binge-eating disorder and six showed relevant characteristics. 61% of health-care providers believed that their young patients with type 2 diabetes had a higher prevalence of eating disorders than other children, in the absence of supporting data.

Health-related quality of life

A comparison of health-related quality of life was done in 91 young people with type 2 diabetes and both healthy children (n=400) and those with type 1 disease (237). Two scales were used: 1) the paediatric quality of life instrument 4-0 generic core scale, which looks at physical, emotional, social, and school functioning; and 2) the paediatric quality of life inventory diabetes module, which encompasses five scales (diabetes symptoms, treatment barriers, treatment adherence, worry, and communication). Youngsters with type 2 diabetes reported lower health-related quality of life than did healthy people for all scales, except physical functioning. They also had lower generic scores for total scale score, psychosocial health, and school functioning compared with those with type 1 disease.

Pregnancy

Diabetes during pregnancy is associated with enhanced maternal risk, increased fetal and neonatal pathological findings, and long-term effects on the offspring. These adverse outcomes are exacerbated by poor adherence to pre-pregnancy care, late scheduling for the first visit to the prenatal clinic, and poor glycaemic control at the first appointment. Offspring are likely to be delivered before 37 weeks’ gestation and to be large for gestational age. In a series of 51 Canadian patients diagnosed with type 2 diabetes when younger than 17 years, 56 pregnancies and 35 livebirths were recorded, giving a pregnancy loss rate of 38%. In a study from Japan, researchers reported no difference in maternal complications between women with type 1 diabetes (mean age at onset 17-8 years) and type 2 diabetes (26-0 years). However, although the group with type 1 diabetes had no children with congenital malformations, 5-8% of those with type 2 diabetes had such events, despite shorter disease duration (5-6 years vs 11-5 years).

Perinatal mortality and congenital anomaly rates for babies born to women with type 1 or type 2 diabetes were assessed in a population-based pregnancy cohort in England, Wales, and Northern Ireland. 652 women had type 2 diabetes and 1707 had type 1 diabetes. Age of onset was median 15 years (IQR 9-23) in those with type 1 disease and 29 years (25-34) for women with type 2 diabetes. Age of delivery was median 30 years (IQR 26-34) and 34 years (30-37), respectively. Perinatal mortality was nearly four times higher than that in the general maternity population but comparable in babies of women with type 1 (31.7 per 1000 births) and type 2 (32.3 per 1000 births) diabetes. Prevalence of major congenital anomaly was more than double that expected for both diabetic groups (48 per 1000 births for type 1 and 43 per 1000 for type 2 diabetes).

Offspring of Pima Indian women who had diabetes during pregnancy were obese and had a high prevalence of type 2 diabetes in later childhood or adolescence, with exposure to the diabetic intrauterine environment estimated to account for 40% of cases in children age 5-19 years and in about 70% of individuals age 25-34 years. An association between the diabetic intrauterine environment and renal disease has also been reported. The odds of increased urinary excretion of albumin in babies born to mothers who had diabetes during pregnancy was 3-8 times (95% CI 1-7-8-4) that of offspring of prediabetic women; the odds of raised urinary albumin in offspring of non-diabetic and prediabetic mothers were similar (0-94, 0-59-1-5).

In summary, a pregnancy complicated by diabetes is an important risk factor for early onset of insulin resistance, type 2 diabetes, and, possibly, accelerated diabetes complications in offspring. Therefore, a vicious cycle of increasing prevalence of diabetes from generation to generation could be created.

Other disorders

Isolated reports have been published of various other disorders in adolescents with type 2 diabetes, including polycystic ovary syndrome, necrobiosis lipoidica, and amputations of fingers and toes, and deaths from other complications have also been recorded. To date, none of these has been reported in a systematic manner.

Discussion

Currently, published studies addressing risk for development of diabetes-related complications in patients diagnosed with type 2 diabetes during childhood and adolescence vary from population-based to case series, with substantial variability in age-range and duration of follow-up. Furthermore, criteria for definition of comorbidities, such as hyperlipidaemia and non-alcoholic
fatty liver disease, and tests used to identify and assess complications vary widely. Moreover, many reports are of very small study groups and pertain to specific populations, such as the Pima Indians and the Maori of New Zealand. Therefore, their generalisability is uncertain. Finally, we should recognise that obesity, even in a young person with normal glycaemic control, is associated with increased risk for comorbidities including non-alcoholic fatty liver disease, microalbuminuria, dyslipidaemia, and accelerated atherosclerosis. Despite these limitations, important observations can be made about the burden of comorbidities in patients diagnosed with type 2 diabetes at an early age and areas that warrant further study can be identified.

Occurrence of type 2 diabetes during adolescence seems to place the individual at increased risk of morbidity and mortality during the most productive years of life. Findings of the reports reviewed here suggest that the microvascular complications of the disorder, such as nephropathy and retinopathy, are being identified at an early age and usually at the time of diagnosis. Unfortunately, early onset of type 2 diabetes is associated with risk for complications qualitatively similar to that seen in adult patients with the disease and with a rate of progression that can be more rapid than in adolescents with type 1 diabetes.

Guidelines for initiation of antihypertensive and antilipid treatments for adults with type 2 diabetes are well-established. Paediatricians, however, do not have such support and are hesitant to treat adolescents with such drugs because of the young age of the patient and reluctance to expose them to side-effects. Therefore, risk for later cardiovascular morbidity and mortality might be further increased by delayed treatment. The American Academy of Pediatrics (AAP) committee on Native American child health, in collaboration with the Indian Health Service diabetes programme, the US Centers for Disease Control and Prevention, and the AAP section on endocrinology, has developed guidelines to enhance medical care for American Indian and Alaskan Native children with type 2 diabetes. These guidelines recommend that adolescents with this disorder should be screened for either proteinuria or microalbuminuria if proteinurica is absent at the time of diagnosis. A fasting lipid profile, including total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations, should be done when initial metabolic stabilisation is obtained, about 1–3 months after diagnosis. Liver function tests, including aspartate and alanine aminotransferase concentrations, should be obtained as well. Funduscopic examination with dilation to detect signs of diabetic retinopathy is recommended shortly after diagnosis by a skilled eye-care professional. These tests should be repeated annually. We suggest that these guidelines might be appropriate for all adolescents with type 2 diabetes.

Long-term data are seriously scarce for the potential benefits of early initiation of adjunctive treatments in young people with type 2 diabetes in terms of improved morbidity and mortality. Nevertheless, in view of the power of antihypertensive drugs and statins in all populations so far studied, a strong argument can be made that such treatment should not be postponed and should be initiated with appropriate monitoring.

In summary, substantial morbidity and mortality have been reported in children and adolescents with type 2 diabetes. Microvascular complications can be present at time of diagnosis and their rate of progression might be higher than in young people with type 1 diabetes. These findings, although still limited, suggest that we urgently need to develop approaches to awareness and early management of type 2 diabetes and associated abnormalities while designing long-term studies to establish the value of early initiation of adjunctive treatments.

Conflict of interest statement
We declare that we have no conflict of interest.

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References


