

# Management of diabetes complications in youth

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**Abstract:** Type 1 and type 2 diabetes are increasing in prevalence and diabetes complications are common. Diabetes complications are rarely studied in youth, despite the potential onset in childhood. Microvascular complications of diabetes include retinopathy, diabetic kidney disease or nephropathy, and neuropathy that may be somatic or autonomic. Macrovascular disease is the leading cause of death in patients with type 1 diabetes. Strict glycaemic control will reduce microvascular and macrovascular complications; however, they may still manifest in youth. This article discusses the diagnosis and treatment of complications that arise from type 1 and type 2 diabetes mellitus in youth. Screening for complications is paramount as early intervention improves outcome. Screening should commence from 11 years of age depending on the duration of type 1 diabetes or at diagnosis for patients with type 2 diabetes. Diabetic retinopathy may require invasive treatment such as laser therapy or intravitreal antivascular endothelial growth factor therapy to prevent future blindness. Hypertension and albuminuria may herald diabetic nephropathy and require management with angiotensin converting enzyme (ACE) inhibition. In addition to hypertension, dyslipidaemia must be treated to reduce macrovascular complications. Interventional trials aimed at examining the treatment of diabetes complications in youth are few. Statins, ACE inhibitors and metformin have been successfully trialled in adolescents with type 1 diabetes with positive effects on lipid profile, microalbuminuria and measures of vascular health. Although relatively rare, complications do occur in youth and further research into effective treatment for diabetes complications, particularly therapeutics in children in addition to prevention strategies is required.

**Keywords:** adolescents, albuminuria, children, diabetes complications, diabetes mellitus, hypertension, metformin, nephropathy, retinopathy

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## Introduction

The prevalence of both type 1 and type 2 diabetes mellitus is increasing<sup>1</sup> and complications of diabetes are common.<sup>2,3</sup> While new advancements such as islet cell transplantation have been shown to improve glycaemic control and hypoglycaemia unawareness,<sup>4</sup> long-term complications are still an ongoing burden for patients with diabetes. As diabetes duration is a major contributor to diabetes complications, it is concerning that more young children are being diagnosed with diabetes, and hence, more individuals will potentially be at risk for microvascular complications as they enter adulthood. In a recent publication, one in three youths with type 1 diabetes and almost three in

four youths with type 2 diabetes had evidence of at least one diabetic complication.<sup>3</sup> Types of diabetes complications do not differ between patients with type 1 and type 2 diabetes; however, the prevalence does. Retinopathy may be more common in youth with type 1 diabetes than type 2 diabetes, and microalbuminuria and hypertension may be more common in youth with type 2 diabetes, despite a shorter duration.<sup>5</sup> Complications develop at a younger age in patients with type 2 diabetes compared with those with type 1.<sup>6</sup>

Diabetes also contributes to earlier mortality from cardiac disease. Age of disease onset is important in determining survival in type 1

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diabetes: loss of life years is increased in those diagnosed under the age of 10 years compared with those diagnosed aged 26–30 years.<sup>7</sup> The risk of coronary heart disease and acute myocardial infarction is 30-times increased in patients diagnosed with type 1 diabetes under the age of 10 years.<sup>7</sup> Diabetes affects the retina, peripheral nerves and renal glomeruli leading to microvascular complications of diabetes. The cells in these structures are unable to downregulate glucose uptake leading to an overproduction of superoxide by the mitochondrial electron transport chain and resultant oxidative stress.<sup>8</sup> Microvascular complications are specific to diabetes, while macrovascular complications are not; however, people with diabetes are at a higher risk than the general population.<sup>8</sup>

In diabetes, there is accelerated atherosclerosis which confers an increased risk of cardiovascular disease above the general population.<sup>8</sup> Heart failure may also be a complication of diabetes, due to persistent hyperglycaemia leading to abnormal fluid loads and haemodynamic and renovascular derangement.<sup>8</sup> The biggest risk for albuminuria and retinopathy is duration of disease.<sup>9</sup> Puberty is a critical time in the lifetime risk of diabetes complications as this is the time when first signs of complications appear.<sup>9</sup>

Strict glycaemic control reduces both microvascular and macrovascular complications and the target for glycated haemoglobin (HbA1c) in pre-pubertal children and adolescents has now been lowered to <7.0%.<sup>10,11</sup> While there is evidence that sustained hyperglycaemia is deleterious,<sup>12,13</sup> the contribution of glucose variability and hypoglycaemic episodes is unclear<sup>14</sup> and therefore HbA1c may not provide the only means for measuring glycaemic control. Continuous glucose monitoring can help capture glucose variability which allows for more specific insulin adjustment<sup>15</sup> and provides the tool for us to use ‘time in range’ as a goal of therapy.<sup>16</sup> Continuous infusion of insulin subcutaneously *via* pump therapy can improve HbA1c<sup>17–19</sup> and may reduce the risk of retinopathy and peripheral neuropathy.<sup>20</sup> Improving glycaemic control in children requires a multidisciplinary team approach and it is essential that developmentally appropriate self-management education and support, nutritional education and psychosocial support is provided to both the patient and family.<sup>21</sup> This requires a balance between adult supervision and

independent self-management, which will evolve as the young person matures.<sup>21–23</sup> Glycaemic targets are more likely to be met when both the child and parent jointly manage diabetes tasks.<sup>21</sup> Improvement in longevity and quality of life are vital goals in the future of management of youth with diabetes.

Youth with diabetes are usually not studied in interventional trials for the treatment of diabetes complications, thus there is a paucity of evidence<sup>24</sup> for age-specific intervention. To date the major interventional study in type 1 diabetes that specifically included and reported on adolescent outcomes was the Diabetes Control and Complications Trial (DCCT) which was completed in 1993.<sup>12</sup> The DCCT showed that intensive treatment of type 1 diabetes reduced the development of diabetes complications and the effect continued during the observational phase in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.<sup>25</sup> The Adolescent Type 1 Diabetes Cardiorenal Intervention Trial (AddIT) was recently completed and specifically looked at the use of statins and ACE inhibition in the treatment of complications in adolescents with type 1 diabetes.<sup>26</sup> There is even less evidence for the treatment of youth with type 2 diabetes. While the incidence of type 2 diabetes in youth is increasing, the absolute number of patients remains small and therefore finding patients for clinical trials is challenging.<sup>27</sup>

In this article we review the burden of microvascular and macrovascular complications that arise from type 1 and type 2 diabetes, the specific screening and management recommendations for these complications in children and adolescents, which is summarised in Table 1, and the paucity of evidence due to the lack of interventional trials in this population.

## Microvascular complications

### Retinopathy

Diabetic retinopathy is classified as mild-to-moderate nonproliferative, severe nonproliferative or proliferative. In addition, there may be macular oedema, characterized by decreased vascular competence and microaneurysms which produce exudation and swelling in central retina.<sup>28</sup> Mild-to-moderate nonproliferative retinopathy is not vision-threatening and may or may not progress.

**Table 1.** Summary of treatment recommendations.

Test	Commence <sup>a</sup>	Repeat	Abnormal	Treatment
Dilated eye examination with specialist using fundal photography or mydriatic ophthalmoscopy	From 11 years of age once has had diabetes for 2–5 years	Every 2 years if low risk	Vision-threatening retinopathy  Diabetic macular oedema with vision loss	Laser or anti-VEGF  Anti-VEGF
Urine albumin/creatinine ratio (× three samples)	From 11 years of age once has had diabetes for 2–5 years	Annually	Two out of three samples show proteinuria	ACE-I or ARB
Foot examination	From 11 years of age once has had diabetes for 2–5 years	Annually		
Blood pressure	Every visit		>95th centile for age, sex and height	Lifestyle for 3–6 months and then antihypertensives
Random lipid profile	From 11 years regardless of duration, unless strong family history in which case from 2 years	Every 5 years	Confirm with fasting sample. Abnormal if fasting LDL >2.6 mmol/l	Lifestyle for 3–6 months and then consider statins from 11 years of age

<sup>a</sup>Screening should commence at diagnosis of type 2 diabetes as duration is presumed to be longer. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; LDL, low-density lipoprotein; VEGF, vascular endothelial growth factor.

It is characterized by microaneurysms, retinal haemorrhages, cotton wool spots (from ischaemia and microinfarction), hard exudates (from protein and lipid leakage), intraretinal microvascular abnormalities and venular dilation and tortuosity.<sup>28</sup> In addition to the above, severe nonproliferative retinopathy is characterized by vascular obstruction, increased number of retinal haemorrhages and microaneurysms, and marked venous abnormalities and is vision-threatening.<sup>28</sup> Neovascularisation in the retina or vitreous posterior space is described as proliferative diabetic retinopathy.<sup>28</sup> This is vision-threatening, as the new tortuous vessels are fragile and permeable vessels may rupture or bleed into the vitreoretinal space.<sup>8,28</sup>

Retinopathy is associated with diabetes duration, age, HbA1c, higher blood pressure and socioeconomic disadvantage.<sup>29,30</sup> Adolescents are at higher risk than adults of progression to vision-threatening stages of retinopathy than adults.<sup>31</sup> This may be due in part to the difficulty achieving glycaemic targets.<sup>32</sup> Retinopathy was present in 9% of 11–17 year olds with 2 to 5 years' duration of type 1 diabetes.<sup>33</sup> In an older cohort of those diagnosed with diabetes aged 15–30 years, there was a

similar prevalence of retinopathy in patients with type 1 and type 2 diabetes (41% and 37% respectively).<sup>34</sup>

Because progression to vision-threatening retinopathy is asymptomatic, regular screening for retinopathy has been recommended since the early 1990s.<sup>12,35–37</sup> Screening with a dilated and comprehensive eye examination performed by an ophthalmologist or optometrist should commence following 2–5 years' duration of diabetes, once a child reaches 11 years of age.<sup>28</sup> If diabetes has been present for less than 10 years and the patient has good glycaemic control, screening can then occur every 2 years, but more frequently if they are at high risk.<sup>21,28</sup> The burden of testing and personnel requirements have led to newer methods of automation (deep learning algorithms) and a desire for prediction scores.<sup>38</sup>

Regression can occur with improved glycaemic control; however, rapid improvement in glycaemic control can also lead to the progression of retinopathy, so more intensive monitoring should occur.<sup>28</sup> Early blockade of the renin-angiotensin system in patients with type 1 diabetes may slow the progression of retinopathy, even in the

absence of hypertension,<sup>39</sup> although this has not been demonstrated in adolescents with type 1 diabetes.<sup>40</sup>

Vision-threatening retinopathy should be treated with laser photocoagulation or antivascular endothelial growth factor (VEGF) intravitreal injections.<sup>28</sup> It should be noted that laser treatment is frequently associated with visual field reduction and night blindness among other complications,<sup>41</sup> and thus, alternate treatment options are often sought. Anti-VEGF treatment is also used for diabetic macular oedema with visual loss.<sup>28</sup> The RISE and RIDE study secondary outcomes perhaps show better results with anti-VEGF treatment for those with severe nonproliferative retinopathy than proliferative retinopathy.<sup>42</sup> Hence, diagnosis of these earlier nonsymptomatic stages may become even more important.

In persistent cases of vitreal haemorrhages, surgery may be indicated.<sup>28</sup> A medication used for the treatment of hypertriglyceridaemia, fenofibrate, has been shown to reduce the need for laser treatment of diabetic retinopathy in adults with type 2 diabetes irrespective of the lipid concentration effect.<sup>43</sup> Further investigation is required but perhaps offers a mechanism to reduce the burden of more invasive treatment options.<sup>44</sup>

There is also an increased risk of cataract and glaucoma.<sup>8</sup> In severe cases, lens extraction may be required during adolescence.

#### *Diabetic kidney disease*

*Hypertension.* Hypertension is a risk factor for microvascular complications including diabetic nephropathy and retinopathy and should be screened for at least annually,<sup>28</sup> and preferably at every visit.<sup>21</sup> Hypertension in children is defined as a blood pressure  $\geq$ 95th centile for age, sex and height under the age of 13 years, and systolic blood pressure  $\geq$ 130 or diastolic blood pressure  $\geq$ 80 mmHg in adolescents  $\geq$ 13 years old.<sup>28,45</sup> Elevated blood pressure (formerly prehypertension) in children is defined as a blood pressure at the 90–95th centile and in adolescents as  $\geq$ 120–129/80 mmHg.<sup>28</sup> It is confirmed by showing an elevated measurement on three separate days and confirmation may require 24 h ambulatory monitoring.<sup>21,28,46</sup> Initial management is with lifestyle interventions for 3 to 6 months; however, if no improvement is seen, then medical management

should be considered.<sup>21,28,45</sup> Treatment may be initiated with an ACE inhibitor, angiotensin receptor blocker (ARB), calcium channel blocker or thiazide diuretic, although if there is comorbid albuminuria then ACE inhibition (or angiotensin receptor blockade) is recommended.<sup>21,28,45</sup> The goal of treatment is to reduce blood pressure to consistently lower than the 90th centile for the child's age, sex and height.<sup>21,45</sup> ACE inhibition has been shown to offer renal protection even in the absence of hypertension<sup>47</sup> and should be considered as a primary prevention for microvascular complications.<sup>48</sup>

*Albuminuria.* The presence of albuminuria is a risk factor for diabetic nephropathy, cardiovascular disease and mortality.<sup>8,49</sup> Albuminuria (formerly known as microalbuminuria) is defined as an albumin/creatinine ratio of:

#### Males

- 2.5–25 mg/mmol
- 30–300 mg/g

#### Females

- 3.5–25 mg/mmol
- 42–300 mg/g<sup>28</sup>

Levels above this range denote proteinuria (previously known as macroalbuminuria).

Albuminuria was present in 3% of 11–17 year olds with 2 to 5 years' duration of type 1 diabetes.<sup>33</sup> In an older cohort of those diagnosed with diabetes aged 15–30 years, there was a higher prevalence of albuminuria in patients with type 2 diabetes (47%) compared with those with type 1 diabetes (5.7%).<sup>34</sup> In a subset of these patients with 2 to 5 years' duration of diabetes, 42% of patients with type 2 diabetes and 5.3% of patients with type 1 diabetes had albuminuria.<sup>34</sup> Screening should commence for albuminuria following 2–5 years' duration of type 1 diabetes once a child reaches 11 years of age.<sup>21,23,28</sup> Once commenced, screening should occur annually with three separate first morning urinary albumin/creatinine ratio samples collected over a 3–6 month period, and considered positive if two of three are affected.<sup>28</sup> If albuminuria is persistent, management with ACE inhibitors or ARBs is recommended to help prevent progression to proteinuria.<sup>21</sup> In adolescents aged 10–16 years with type 1 diabetes and urine albumin-to-creatinine ratio values in the upper tertile, ACE inhibition was associated with a lower incidence of

microalbuminuria, although this association did not reach statistical significance.<sup>40</sup> In a small group of normotensive adolescents with type 1 diabetes who had microalbuminuria or nephropathy, the ACE inhibitor captopril was associated with a significantly decreased albumin excretion rate.<sup>47</sup> The dose of pharmacological management should be titrated to ensure blood pressure is within the normal range.<sup>21</sup> With tight glycaemic control, and antihypertensive agents, albuminuria can regress.<sup>50</sup>

An albumin/creatinine ratio at the high end of the normal range characterizes adolescents that have a greater risk for progression of carotid intimal media thickness and albuminuria and retinopathy.<sup>26,51</sup>

### Neuropathy

Diabetic neuropathy can involve the somatic and autonomic nervous systems. The most common type is diabetic sensorimotor polyneuropathy, also referred to as peripheral neuropathy. Initially sensory loss occurs, followed by a loss of motor function. Numbness may progress to persistent pain. Risk factors for peripheral neuropathy in type 1 diabetes include older age, duration of diabetes, smoking, increased diastolic blood pressure, obesity, elevated low-density lipoprotein (LDL) cholesterol and triglycerides, and lower HDL cholesterol.<sup>52</sup> In type 2 diabetes, the risk factors are: older age, male sex, diabetes duration, smoking and a low high-density lipoprotein (HDL) cholesterol level.<sup>52</sup> Peripheral nerve abnormality was present in 16% of 11–17 year olds with 2 to 5 years' duration of type 1 diabetes when measured by thermal and vibration thresholds.<sup>33</sup> Screening with a comprehensive foot examination should commence following 2–5 years' duration of diabetes once a child reaches 11 years and then annually thereafter.<sup>21,28</sup> The foot should be inspected, pulses palpated and proprioceptive, vibratory and monofilament sensation should be assessed.<sup>21</sup> Peripheral neuropathy may also be assessed using the self-administered questionnaire Michigan Neuropathy Screening Instrument.<sup>52,53</sup>

Autonomic neuropathy may involve the cardiovascular, urogenital or gastrointestinal systems. Cardiovascular autonomic neuropathy may present as postural hypotension, exercise intolerance, resting tachycardia or bradycardia or reduced heart rate variability.<sup>50</sup> Cardiac autonomic dysfunction was found to be associated with an elevated urine albumin/creatinine ratio, indicating those at high

risk for nephropathy are also at a high risk for autonomic dysfunction.<sup>52</sup> Gastrointestinal autonomic neuropathy may lead to gastroparesis, diarrhoea and faecal incontinence. Urogenital autonomic neuropathy may manifest as bladder paresis and erectile dysfunction. There is currently no recommended screening technique for autonomic neuropathy.<sup>28</sup>

### Macrovascular complications

Macrovascular disease is the leading cause of morbidity and mortality in adults with type 1 diabetes, and atherosclerosis starts in childhood.<sup>23,24,34,54</sup> A retrospective cohort examining patients diagnosed with type 1 diabetes between ages 15 and 30 years found that 30.3% deaths were caused by cardiovascular events and the first cardiovascular events occurred in the third decade of life.<sup>34</sup> Even with excellent glycaemic control, patients with type 1 diabetes still have an increased risk for cardiovascular disease-related death.<sup>55</sup> Risk factors for macrovascular disease include hyperglycaemia, hypertension, dyslipidaemia, diabetic kidney disease, obesity, insulin resistance, and lifestyle factors such as smoking, exercise, diet, sleep, and stress, and depression.<sup>24</sup> Hypoglycaemia may be an additional risk factor.<sup>56</sup> An early age at diagnosis also increases the risk of cardiovascular disease.<sup>7</sup> Severe diabetic retinopathy may also be an independent risk factor for cardiovascular disease.<sup>57</sup>

Other markers for predicting cardiovascular health are used in research settings such as measures of carotid intima media thickness, and arterial stiffness, cardiac magnetic resonance imaging (MRI) and cardiopulmonary fitness.<sup>24</sup> As technology advances these methods may be utilized in routine screening programs.

Although cardiovascular events are not expected in youth, subclinical cardiovascular disease may be present within the first decade from diagnosis of type 1 diabetes.<sup>21</sup> In a retrospective cohort of patients diagnosed with diabetes aged 15–30 years, 5.7% of patients with type 1 diabetes and 14.4% of patients with type 2 diabetes had evidence of macrovascular disease.<sup>34</sup> Blood pressure should be screened at least annually,<sup>28</sup> and preferably every visit.<sup>21</sup> Management of hypertension was discussed in the section titled 'Diabetic kidney disease'. Screening for dyslipidaemia should occur from the age of 11 years regardless of the

**Table 2.** Prevalence of complications in patients with type 1 versus type 2 diabetes in two age groups.

Complication	Type 1		Type 2	
Mean age at time of assessment	38.9 years*	17.9 years <sup>+</sup>	40.4 years*	22.1 years <sup>+</sup>
Retinopathy	41%	5.6%	37%	9.1%
Albuminuria	15.3%	5.8%	47.4%	19.9%
Peripheral neuropathy		8.5%		17.7%
Macrovascular disease	5.7%		14.4%	
Hypertension	24.6%	10.1%	49.3%	21.6%

\*Data from retrospective cohort of patients diagnosed with diabetes between ages 15 and 30 years who attended the Royal Prince Alfred Diabetes Service in Sydney, Australia. Mean age.<sup>34</sup>

<sup>+</sup>Data from observational study of patients diagnosed with diabetes before the age of 20 years who attended five locations in the United States.<sup>3</sup>

duration of diabetes (once stabilized).<sup>28</sup> If there is a family history of hypercholesterolaemia or early cardiovascular disease, screening should commence at the age of 2 years.<sup>21,28</sup> Nonfasting lipid screening is appropriate, and if abnormal the patient should have a fasting sample.<sup>21,28</sup> If the fasting LDL cholesterol is  $>2.6$  mmol/l, lifestyle measures and improvement in glycaemic control should be instituted.<sup>28,58</sup> In type 2 diabetes, a reduction in insulin resistance (through physical activity, weight reduction and metformin use) can also reduce hyperlipidaemia.<sup>58</sup> If the LDL cholesterol is not  $<3.4$  mmol/l, statins should be considered from 11 years of age.<sup>21,28,40</sup> Statins are not approved in those under 10 years.<sup>21</sup> Statins have been shown to improve the lipid profile in adolescents with type 1 diabetes.<sup>40</sup> Monitoring treated dyslipidaemia should occur with fasted cholesterol profiles. A fasting LDL cholesterol of  $<2.6$  mmol/l is the target with treatment.<sup>21</sup>

While metformin may improve HbA1c in adolescents,<sup>59</sup> other studies have shown no improvement in glycaemic control.<sup>60</sup> Nevertheless, metformin has been shown to improve vascular smooth muscle function in children with type 1 diabetes with weight in the normal range independently of improvement in HbA1c, although, there was no benefit on other markers of cardiovascular health in this cohort.<sup>61</sup> Metformin demonstrated a good safety profile up to 12 months of study duration.<sup>61</sup> More recently, metformin has been shown to improve carotid intima media thickness, and aortic wall shear stress and stiffness which are markers for cardiovascular disease.<sup>62</sup>

The prevalence of smoking in youth with type 1 and type 2 diabetes increases with age, and patients with type 1 diabetes who were current or previous smokers had a higher prevalence of dyslipidaemia.<sup>63</sup> The association was similar in type 2 diabetes but due to the smaller cohort did not reach statistical significance.<sup>63</sup> Smoking avoidance helps prevent both microvascular and macrovascular complications.<sup>21</sup> Youth should be discouraged from smoking or counselled to cease.<sup>21</sup>

### Type 2 diabetes

Data on outcomes for people diagnosed with type 2 diabetes in childhood are limited compared with type 1 diabetes;<sup>58</sup> however, they appear to be of a more lethal phenotype.<sup>34</sup> When matched for duration of diabetes, a higher prevalence of diabetes complications have been reported in youth with type 2 diabetes compared with type 1, except in the case of cardiac autonomic neuropathy, where it is equally distributed<sup>1,3,34</sup> (see Table 2). Complications may already be present at the time of diagnosis of type 2 diabetes, thus screening should commence at diagnosis. The risk for diabetes complications may be driven by different pathophysiology in type 1 and type 2 diabetes therefore disease-specific preventive strategies and therapies may be warranted, however at this stage more information is required.<sup>24</sup>

In addition to first line management of type 2 diabetes, metformin may decrease albuminuria in patients with type 2 diabetes.<sup>64</sup> This may be due to reducing oxidative stress on renal tubules,

although the exact mechanism is unknown.<sup>64</sup> Newer glucose-lowering agents sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have also shown some promising effects in adults with type 2 diabetes. They have been shown to reduce cardiovascular events in adult patients with type 2 diabetes and with or at high risk of atherosclerotic cardiovascular disease.<sup>65</sup> However, SGLT2 inhibitors are not indicated for use in type 1 diabetes and the safety in children has not been established.<sup>66</sup> Sotagliflozin, a dual sodium glucose cotransporter 1 and 2 inhibitor, was recently shown to have some promising effects on glycaemic targets and had nonglycaemic cardiovascular benefits in adults with type 1 diabetes, although its use was associated with increased risk of diabetic ketoacidosis in some patients.<sup>67</sup> GLP1 receptor agonists have been used in the treatment of obesity in children;<sup>68</sup> however, they are not currently listed in the guidelines for the treatment of diabetes in children.<sup>21</sup> The benefit of SGLT2 inhibitors and GLP1 receptor agonists is less evident in those at a low risk for cardiovascular disease,<sup>65</sup> which is more likely to be a younger population.

### Special circumstance: pregnancy

Female youth with complications of diabetes may be commenced on potentially teratogenic medications. Exposure of a developing foetus to ACE inhibitors or ARBs by maternal ingestion of these medications will result in damage to the infant renin-angiotensin system. Neonatal complications of maternal treatment include renal failure, oligohydramnios, death, arterial hypotension, intrauterine growth restriction, respiratory distress syndrome, pulmonary hypoplasia, hypocalvaria, limb defects, persistent patent ductus arteriosus or cerebral complications.<sup>69</sup> In those children exposed, the long-term outcome is poor.

Statins are not recommended in pregnancy due to a potential teratogenic effect; however, more recent studies have found no clear link between congenital anomalies and statins.<sup>70</sup> Indeed there may be a role for pravastatin in preventing pre-eclampsia in women.<sup>70</sup> Nevertheless, statins should still be avoided in pregnancy until more information is available.

Thus, counselling post-pubertal females who are managed with ACE inhibitors, ARBs or statins, is

imperative and alternate treatment should be sought if pregnancy occurs.<sup>21</sup>

### Interventional trials for diabetes complications in youth

Interventional trials designed to examine complications in youth with type 1 diabetes are few. See Table 3 for a list of trials registered at <http://clinicaltrials.gov> accessed on 17 January 2019. A summary of the two most significant interventional trials for diabetes complications in youth are discussed.

#### *Adolescent type 1 diabetes cardiorenal intervention trial*

The AddIT study examined patients with type 1 diabetes between the age of 10 and 16 years with urine albumin-to-creatinine ratio values in the upper tertile. The study demonstrated that statin use resulted in a statistically significant improvement in lipid profile.<sup>40</sup> ACE inhibition was associated with a lower incidence of microalbuminuria and lower systolic blood pressure, although neither of these associations was statistically significant.<sup>40</sup> Neither drug was able to significantly reduce retinopathy progression or carotid intima media thickness over the median of 2.5 years of intervention.<sup>40</sup> Although otherwise well tolerated, 25% of participants required a dose reduction of their ACE inhibitor largely due to postural hypotension. Serious adverse reactions due to the ACE inhibitor included a clinically significant decrease in the estimated glomerular filtration rate in two patients, a hypotensive episode in one patient and an elevated alanine aminotransferase level in one patient.<sup>40</sup> There were no serious adverse events related to the statin treatment.

#### *Metformin*

Metformin may have a role in cardiovascular health in patients with diabetes, irrespective of improvements in glycaemic control and insulin sensitivity. In adults aged 40 years and older with type 1 diabetes, despite no improvement in glycaemic control, it is suggested that metformin could play a wider role in cardiovascular risk management with reduction in body weight, LDL cholesterol and reduction in atherosclerosis progression measured by averaged maximal carotid intima media thickness.<sup>73</sup>

**Table 3.** Interventional trials for drugs to reduce diabetes complications in type 1 diabetes in youth taken from <http://clinicaltrials.gov> on 17 January 2019.

Study title	Age	Intervention	Location	Status
Adolescent type 1 diabetes cardiorenal intervention trial	10–16 years	Statin ACE inhibitor	Perth, Australia Toronto, Canada	Completed, published <sup>40</sup>
Vitamin B complex and diabetic nephropathy in type 1 diabetes	12–18 years	Vitamin B complex	Cairo, Egypt	Completed
Role of carnosine as an adjuvant therapy for diabetic nephropathy in paediatrics with type 1 diabetes	5–18 years	Carnosine	Cairo, Egypt	Completed, published <sup>71</sup>
Efficacy of telmisartan and the combination of telmisartan and ramipril in type 1 diabetes patients with nephropathy	14 years +	Telmisartan and ramipril	Chandigarh, India	Completed, published <sup>72</sup>
Flavonoids in the treatment of endothelial dysfunction in children with diabetes	12–21 years	Flavonoids	Texas, USA	Withdrawn
EMERALD: effects of metformin on cardiovascular function in adolescents with type 1 diabetes	12–21 years	Metformin	Colorado, USA	Completed, published <sup>62</sup>

ACE, angiotensin converting enzyme.

In patients with type 1 diabetes between the ages of 8–18 years, metformin improved vascular smooth muscle function independently of the improvement in HbA1c and lowering insulin dose over the 12 month study period of the Adolescent type 1 diabetes cardiorenal intervention trial.<sup>61</sup>

In patients between 12 and 21 years with type 1 diabetes, improvements in MRI-derived measures of aortic and carotid vascular health with the use of metformin have been demonstrated over a 3 month study period.<sup>62</sup> Furthermore, there was improvement in weight, body mass index and fat mass in that time, in addition to insulin sensitivity measured by a hyperinsulinaemic euglycaemic clamp.<sup>62</sup>

### Future

As the prevalence of both type 1 and type 2 diabetes in young people increases, the duration of illness increases and puts more young people at risk of the development of diabetes complications during youth. While some treatments have been examined in youth, many are extrapolated from adult studies. While extrapolation of data from adult studies may be appropriate in some cases, the intensity of the autoimmunity and the more rapid loss of beta cells in children with type 1 diabetes when compared with adults with new-onset

type 1 diabetes suggests that the populations are not always comparable.<sup>74</sup> It is imperative that future interventional trials are undertaken to examine the most appropriate treatment options for diabetes complications in this age group. Furthermore, many studies examining new treatments for type 2 diabetes require the participants to be treatment-naïve, which is essentially impossible as all youth with newly diagnosed type 2 diabetes should be treated immediately with metformin or insulin.<sup>75</sup> Moreover, diabetes complications develop over a period of time and the prevalence in youth may not be high enough to provide power in a study. As a result, surrogate outcomes need to be examined that may not be reliable markers of the true outcome, and more studies are required to examine how interventions may improve the long-term outcome.<sup>24</sup>

### Conclusion

Complications of diabetes infer a high mortality risk and are common in youth with diabetes.<sup>2,3</sup> There is a paucity of interventional trials examining the treatment of diabetes complications in youth.<sup>24</sup> Prevention is key and this may be achieved by improved glycaemic control.<sup>12–14</sup> Nevertheless, screening for complications is imperative, as at risk youths must be identified and treated. The future must include more research to better treat complications in youth as well as improvements in



prevention. Increasingly sensitive tools will be used in screening; however, their correlation with future risk must be examined.

### Authors' note

L.E.G. and K.C.D. researched the scientific literature and wrote the Review. L.E.G. and K.C.D. made substantial contributions to the content and reviewed and edited the Review before submission. L.E.G. prepared the tables.

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