Prevention and treatment of microvascular disease in childhood type 1 diabetes

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Introduction: The incidence of type 1 diabetes (T1D) is increasing worldwide, particularly in children, and is associated with a significant burden, mainly related to the development of vascular complications. The prevention and treatment of microvascular complications, which include nephropathy, retinopathy and neuropathy, are of paramount importance to decrease the associated mortality and morbidity.

Sources of data: A literature search was performed on Medline and articles on microvascular complications, with particular emphasis on the increasing incidence of childhood T1D and its implications on prevention and treatment of complications, were selected.

Areas of agreement: The incidence of childhood T1D is increasing. Early identification of subjects at risk for long-term complications and early implementation of preventive and therapeutic strategies are fundamental in order to reduce the burden associated with microvascular complications of diabetes. Improving glycaemic control is the principle way of preventing and treating T1D complications.

Areas of controversy: In adults with T1D and microvascular complications, treatment with anti-hypertensive drugs and statins is increasingly common, whereas there are no definitive indications for treatment with these drugs in children and adolescents with early signs of complications.

Growing points: There is growing interest in the development of new preventive and therapeutic strategies targeting specific pathways implicated in the pathogenesis of microvascular complications.

Areas timely for developing research: Investigations to clarify genetic and environmental factors implicated in the pathogenesis of microvascular complications could lead to the identification of biochemical markers with high predictive values, to be used as a guide for screening and intervention programmes.

Keywords: microvascular complications/type 1 diabetes/prevention/treatment
The incidence of type 1 diabetes (T1D) is increasing worldwide at an annual rate of around 3–5%, particularly in children under the age of 5 years.\textsuperscript{1,2} Approximately 50–60% of patients with T1D are diagnosed before the age of 15 years, and in most Western countries T1D accounts for over 90% of cases of childhood and adolescent diabetes.\textsuperscript{3} In 2005, in Europe, the number of new cases of T1D in people younger than 15 years was estimated to be 15 000, and this number is predicted to rise to 24 400 in 2020.\textsuperscript{2}

The incidence of T1D increases with age, reaching a peak at puberty (10–14 years), and declines thereafter in women, whereas it remains relatively high in males until the age of 29–35 years.\textsuperscript{1} There are wide variations in the incidence rates of T1D across countries, with the lowest incidence reported in China and Venezuela (0.1 per 100 000 per year), and the highest incidence in Finland and Sardinia (37 per 100 000 per year).\textsuperscript{1} In the UK, T1D affects around 18–20 per 100 000 children per year.\textsuperscript{1}

Provision of health and social care for people with T1D is associated with significant costs, including those related to insulin replacement, hospitalization, general practitioner and hospital consultations, social support for carers and the treatment of complications.\textsuperscript{4} In addition, the burden of T1D is related to loss of life expectancy, which is reduced by 5–20 years.\textsuperscript{5} The early onset of T1D during childhood determines a longer exposure to the metabolic derangements of the disease when compared with adult-onset diabetes, therefore increasing the burden of the disease.\textsuperscript{5} Several lines of evidence have highlighted that the long-term prognosis of people diagnosed with T1D during childhood and adolescence remains poor.\textsuperscript{5,6} A study from the USA has shown that the number of life-years lost among children diagnosed with diabetes at the age of 10 years is 18.7 for boys and 19.0 for girls.\textsuperscript{5} Similar data have emerged from a European study, where childhood onset T1D has been associated with a 4-fold increased standardized mortality rate (SMR).\textsuperscript{6}

The morbidity and mortality associated with T1D is mainly related to the development of long-term microvascular and macrovascular complications.\textsuperscript{3} In developed countries diabetes is ranked among the leading causes of renal failure, blindness and lower limb amputation and as one of the main causes of deaths from cardiovascular disease (CVD).\textsuperscript{3} By the age of 20–39 years the SMR for coronary artery disease in 23 000 patients with T1D in the UK was increased 10-fold in men and 40-fold in women.\textsuperscript{7} The EURODIAB study, a large cross-sectional multicentre clinic-based study, revealed that, after a mean
T1D duration of 15 years, the prevalence of early renal disease was 30.6%, retinopathy 46% and impaired autonomic tests 19%. Similar data from the UK indicated that up to 37% of young adults aged 28–37 years, diagnosed with T1D during childhood, had serious microvascular complications.

Most of the devastating complications of diabetes could be prevented, delayed or reduced with the early implementation of preventive and therapeutic strategies, particularly in high-risk subjects.

**Microvascular complications of diabetes**

The microvascular complications of diabetes, resulting from a damage to the microvasculature of the kidney, retina and neurons, include nephropathy (DN), retinopathy (DR) and neuropathy. Although the pathogenesis of diabetic microangiopathy is incompletely understood, it is likely that it involves both metabolic and functional/haemodynamic factors, triggered by the effect of acute and chronic hyperglycaemia, and the interaction with environmental, hormonal and genetic factors (Fig. 1).

Significant associations have been reported between the different microvascular complications of diabetes, whereby patients with one complication often present a second one, suggesting common risk factors and/or pathogenetic mechanisms. Endothelial dysfunction, which is a common finding among people with T1D, could represent a major link between vascular complications.

![Fig. 1 Factors associated with the development of diabetic complications. CVD: cardiovascular disease; T2D: type 2 diabetes.](https://academic.oup.com/bmb/article-abstract/94/1/145/309334)
Diabetic microangiopathy is associated with an increased morbidity and mortality related to organ damage and to the development of CVD.\textsuperscript{12} Although clinically evident vascular complications are rarely diagnosed among children and adolescents with T1D, there is clear evidence that their pathogenesis develops during childhood and accelerates during puberty.\textsuperscript{13} Early subclinical manifestations, detected among young people with T1D, include progressive increases in albumin excretion rates (AER), glomerular hyperperfusion and hyperfiltration, subclinical changes in the retinal microvasculature and subtle impairments in the autonomic nervous system.\textsuperscript{14–16} These early alterations represent risk factors for progression towards more advanced stages of microvascular disease.\textsuperscript{13} There is evidence that vascular complications can be aggressive in adolescents with T1D, particularly in those with poor glycaemic control, and their progression is often faster than in adults.\textsuperscript{13}

**Diabetic nephropathy**

The most common microvascular complication of T1D is DN, which affects around 15–40% patients, with a peak incidence after 15–20 year diabetes duration.\textsuperscript{17} This complication represents the leading cause of end-stage renal disease (ESRD) in developed countries and is also a major determinant of cardiovascular morbidity and mortality.\textsuperscript{17} Early changes occurring in the kidney of patients with T1D include glomerular hyperfiltration and hyperperfusion, subclinical morphological changes and increases in AER within the normal range.\textsuperscript{17} Further increases in albumin excretion, with an AER between 30–300 mg/24 h and 20–200 $\mu$g/min in a 24-h or timed urine collection, signify the development of microalbuminuria (MA), which may further progress to overt proteinuria (AER $>200$ $\mu$g/min) and, without treatment, to ESRD.\textsuperscript{17}

Patients with T1D and DN have a 10-fold greater risk of CVD than patients without DN and this risk increases with the severity of renal involvement.\textsuperscript{18} In a 10-year follow-up study of 939 adults with T1D, mortality was 15% for patients with normoalbuminuria, 25% for those with MA and 44% for those with macroalbuminuria.\textsuperscript{12} DN is also an important risk marker for other microvascular complications, such as retinopathy, and is often associated with signs of dysfunction of the autonomic nervous system.\textsuperscript{17}

MA is the earliest clinical stage of clinical nephropathy, and its persistence is highly predictive of progression to overt proteinuria and of risk for CVD.\textsuperscript{17} In adult inception cohorts, the cumulative incidence of MA is around 30% after 20 years T1D duration,\textsuperscript{19} and the natural
history of nephropathy has been significantly influenced by interventions aiming at improving glycaemic control and blood pressure (BP).\textsuperscript{17}

In people with childhood-onset T1D, MA is often detected during puberty,\textsuperscript{13} with a cumulative prevalence of around 10–25\% after 5–10 year diabetes duration.\textsuperscript{20,21} The most recent data from the Oxford Regional Prospective Study (ORPS),\textsuperscript{22} a population-based inception cohort of children with T1D, has shown a cumulative prevalence of MA of 25.7\% after 10 years and of 50.7\% after 19 years of diabetes duration,\textsuperscript{22} which is significantly higher than that reported in adult cohorts (34\%) after a similar diabetes duration and exposure to similar levels of glycaemic control\textsuperscript{19} (Fig. 2). These data highlight that risk factors for the development of MA and rates of progression may be different for people diagnosed during childhood when compared with those diagnosed during adult life.\textsuperscript{19,22}

The rate of progression of MA to macroalbuminuria appears to be similar between adults and children with T1D, but in children macroalbuminuria occurs at an earlier age.\textsuperscript{19,22} In the ORPS cohort, the cumulative prevalence of macroalbuminuria was 13.9\% after 19 years diabetes duration\textsuperscript{22} and this is similar to the 14.6\% prevalence reported in a similar inception cohort in adults,\textsuperscript{19} suggesting that progression is related to duration of diabetes regardless of the age at onset.

Recent studies have introduced the concept of ‘regression to normoalbuminuria’ and this phenomenon has been reported in 31–58\% of

![Fig. 2 Cumulative prevalence of developing MA across age in 527 children with type 1 diabetes from the Oxford Regional Prospective Study, in relation to quarters of mean HbA1c.](https://academic.oup.com/bmb/article-abstract/94/1/145/309334/145/6308934)
adults with MA\textsuperscript{19,23} and in around 40–50\% adolescents with T1D\textsuperscript{21,22}.

Recent studies from Sweden\textsuperscript{24} and Australia\textsuperscript{25} have shown a decreasing trend in DN as well as in DR. However, these positive results are not worldwide. In fact, data from Iceland\textsuperscript{26} indicated an unchanged trend in the incidence of DN. Similarly, Amin \textit{et al.}\textsuperscript{27} have recently reported an unchanged prevalence of MA in a UK-based inception cohort of people with childhood onset T1D.

**Diabetic retinopathy**

DR represents the leading cause of vision loss in working age people in developed countries.\textsuperscript{28} DR is also associated with other microvascular complications, especially DN, and proliferative DR is strongly associated with cardiovascular events.\textsuperscript{29} DR begins with the appearance of non-proliferative retinal abnormalities, characterized by capillary microaneurysms, haemorrhages, exudates, the development of vascular obstruction and the infarction of the retinal nerve fibres causing cotton wool spots.\textsuperscript{30} Although this stage is not sight-threatening, it is highly predictive of progression to more advanced stages of retinopathy. Proliferative retinopathy is characterized by the development of new vessels, secondary to ischaemia, on the surface of the retina and/or the optic disc.\textsuperscript{30} These new vessels can bleed into the vitreous, and cause visual loss.\textsuperscript{30} This stage is associated with a high risk for visual impairment related to haemorrhages and retinal detachment.

Diabetic macular oedema, characterized by increased microvascular permeability and deposition of hard retinal exudates, can complicate both non-proliferative and proliferative retinopathy and is a serious cause of vision loss in patients with diabetes.\textsuperscript{30}

The prevalence of DR steadily increases with the duration of the disease, and almost all patients with T1D have some degree of retinopathy after 20 years.\textsuperscript{31} The prevalence of visual impairment in adults with T1D was 2–13\% in the most recent report of the Wisconsin Epidemiologic Study of DR, with cohorts with onset of diabetes studied during more recent years having a lower prevalence of visual impairment, independent of duration of diabetes.\textsuperscript{32} This is in agreement with some other recent studies reporting a declining incidence of retinopathy and other microvascular complications.\textsuperscript{24,33}

Children with T1D under the age of 10 years are at minimal risk of DR, but the prevalence rate increases after 5 years from diagnosis in post-pubertal patients.\textsuperscript{34} In an incident cohort, early retinopathy was detected in 12\% of prepubertal children compared with 29\% of adolescents, after 6-year T1D duration.\textsuperscript{35} Adolescents with T1D have a
higher risk of progression to sight-threatening DR when compared with adults and the progression may be particularly rapid when glycaemic control is poor. As for DN, some cases of regression have also been reported for DR.

**Diabetic neuropathy**

Diabetic neuropathy is defined by a clinical or subclinical disorder, without any additional causes of peripheral neuropathy other than diabetes, and can be either somatic or autonomic. Transient poor metabolic control may rarely be associated with acute sensory symptoms, whilst chronic distal symmetric polyneuropathy (DPN) is the most common form of diabetic neuropathy. DPN can occur with or without changes in the function of the autonomic nervous system. DPN implies symmetric damage of peripheral small sensory and large motor nerve fibres and it is symptomatic in up to 50% of patients. Dysfunction of peripheral small nerve fibres is characterized by parasthesiae, burning, deep-aching pain. If larger nerve fibres are affected, vibration, light touch and joint position senses are impaired, and tendon reflexes are absent. Focal or multifocal neuropathies include entrapment of a peripheral nerve, commonly the median, ulnar or peroneal nerve. Dysautonomic features may include different systems and manifest as postural hypotension and orthostatic lightheadedness, gastroparesis, gastric fullness, early satiety, sexual dysfunction, bladder dysfunction, gustatory sweating or anhidrosis and pupillomotor dysfunction.

In the most comprehensive epidemiological studies involving both adult and paediatric patients, the percentage of subjects affected by DPN ranged from 7 to 57%. More persistent and progressive neuropathy affects approximately 60–70% of adult patients with some degree of nerve damage. In a cohort of 278 subjects with T1D enrolled in the Diabetes Control and Complications Control (DCCT), subclinical DPN was detectable in 39% of the subjects on careful examination but they were asymptomatic.

These results, however, highlight the problem that prevalence rates of diabetic neuropathy will vary depending on different cohorts of patients studied, different testing modalities and different criteria and cut-off values.

**Risk factors for microvascular complications**

Several risk factors, both modifiable (glycaemic control, hypertension, dyslipidaemia, diet and smoking) and non-modifiable (diabetes
duration, puberty, genes, constitutional factors), have been related to the development of microvascular complications of T1D.

Glycaemic control
Poor glycaemic control is closely linked to the development of complications.39 Hyperglycaemia can promote many functional and structural changes in the microvasculature, through the activation of different mechanisms, including the polyol and hexosamine pathways, accumulation of non-enzymatic glycation end products, activation of diacylglycerol–protein kinase C pathway.40 However, glycaemic control does not entirely define risk of diabetic complications, particularly during puberty, when hormonal and metabolic changes, together with lifestyle, environmental exposures and genetic factors may also significantly contribute to complication risk.41 A complex interplay between environmental, biological and genetic factors might play a critical role in the pathogenesis of vascular complications of diabetes (Fig. 1).

BP and plasma lipids
Elevated BP and alterations in the circadian BP rhythm are common findings in people with T1D and have been associated with the risk of developing microvascular complications.42–44 Increases in BP have been found to precede or occur concomitant with the appearance of MA both in adults and adolescents with T1D.45 Similarly, higher than normal systolic and diastolic BP contribute to the development of DR, and this effect has been found to be independent of glycaemic control, duration of diabetes and albumin excretion.43 Lipid abnormalities have also been linked to the development and progression of DR as well as retinopathy and neuropathy, both in adolescents and adults with diabetes.44,46

Puberty
The development of microvascular complications rarely occurs before puberty, whereas there is an increasing trend in their rate of incidence during the pubertal years. Adolescence is often the most difficult period for young people with childhood onset T1D and their carers.47 It is a period of transition from physical immaturity to maturity and from psychological dependency to independence. Treatment may be complicated by poor compliance, difficulties in targeting insulin therapy and concerns about weight gain.47 Poor glycaemic control is a common finding among adolescents with T1D48,49 and it is closely linked to the development of microvascular complications.22 Puberty is associated with a decrease in insulin sensitivity, and adolescents with T1D are more insulin resistant when compared with healthy controls.47 However, risk of complications is only partially related to increases in
HbA1c during puberty and puberty may be an independent risk factor.22

**Gender**
A gender dimorphism has been found for vascular complications. In particular, during adolescence the risk for MA is higher in female than in male subjects with comparable glycaemic control,20,22 whereas among adults with T1D the risk is higher for males.19

**Environmental factors**
Environmental factors, including diet and lifestyle, can also contribute to the risk of developing microvascular complications. Smoking in people with T1D has been associated with an increased risk of developing MA, retinopathy and neuropathy.44,50,51 Short adult stature and poor pubertal growth have been associated with higher prevalence and incidence of microvascular complications in patients with T1D, and this could be related to childhood exposure to diabetes or to common pathogenetic factors between short stature and risk for vascular complications.52

**Genetic factors**
Genetic factors represent another important contributing factor for the development of microvascular complications, as suggested by the familial clustering of complications, and by the observation that only a subset of patients with poor glycaemic control develop severe long-term complications.53

**Screening for microvascular complications**
Diabetic microvascular complications are often asymptomatic during their early stages, and once symptoms develop, they may be harder to reverse. Therefore, systematic longitudinal repeated screening for microvascular complications initiated during early adolescence is currently recommended.54 Identification of subjects at risk and screening for subclinical signs of complications is essential for the early implementation of more intensive preventive and therapeutic strategies, which could change the course of vascular complications and improve the prognosis of people with diabetes (Table 1).

**Nephropathy**
It has been recommended that screening for MA should be performed annually from the age of 11 years in those with 2 years of diabetes duration and from the age of 9 years in subjects with 5 years diabetes...
Measurement of urinary albumin excretion is the basis for early detection of MA and can be achieved with: (1) 24-h urine collection; (2) overnight timed urine collections; (3) albumin-creatinine ratio (ACR) or albumin concentration on a early morning spot urinary sample.\textsuperscript{54,55} Twenty-four hours or timed urine collections are often difficult to collect in children and adolescents. Assessing ACR in early morning urines is the easiest method to carry out in an office setting and it generally provides accurate information.\textsuperscript{54,55}

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Screening recommendations are derived from the ISPAD and ADA guidelines.\textsuperscript{54,55}

Retinopathy

Early detection of retinopathy in patients with T1D is of paramount importance in order to prevent visual loss. The American Diabetes Association (ADA) recommends to start screening in patients with T1D aged 10 years or older after a disease duration of 3–5 years, with yearly follow-up.\textsuperscript{55} The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening from the age of 11 years in those with 2 year diabetes duration and from 9 years in those with a 5 year duration and after 2 years of diabetes duration in an adolescent.\textsuperscript{54} Screening before the age of 10 years is not generally recommended given the low prevalence of retinopathy in prepubertal children. Annual screening is generally recommended, even though clear evidence for a benefit of more frequent eye examinations is available only for cases of moderate to severe retinopathy.\textsuperscript{55}

Several techniques can be used to assess DR, including direct and indirect ophthalmoscopy, stereoscopic digital and colour film-based fundus photography, mydriatic or non-mydriatic digital colour or monochromatic single-field photography.\textsuperscript{28} The best technique to identify and grade retinopathy is represented by retinal photography, through dilated pupils, but dilated indirect ophthalmoscopy associated with biomicroscopy is an acceptable alternative.\textsuperscript{28}
Neuropathy

In contrast to well-established criteria for when starting screening for DN and DR, it is unclear when to commence screening for neuropathy. History and physical examination are generally the recommended methods of screening. Clinical examination, including history of pain, paresthesia, numbness and physical examination of ankle reflexes and vibration and light touch sensation, is a fundamental part of screening, although not being as sensitive or specific as nerve conduction studies.

Autonomic neuropathy can be assessed with specific autonomic nerve tests, such as heart rate response to deep breathing, standing from a lying position, Valsalva manoeuvre, heart rate variations at rest, QT interval, postural changes in BP and pupil responses to light and dark adaptation. These tests need to be carefully standardized and therefore they are not largely used as screening methods for complications at a population level.

Prevention and treatment

Glycaemic control

Observational and clinical studies have shown a clear relationship between the degree of glycaemic control and the risk of developing DN, DR and neuropathy. The DCCT and the Epidemiology of Diabetes Interventions and Complications (EDIC) have established the effectiveness of improved metabolic control in reducing the risk for the development and progression of all the three microvascular complications of T1D. The DCCT studied a cohort of 1441 subjects, aged 13–39 years, with T1D for 1–15 years. Intensive insulin therapy reduced the risk for the development of retinopathy by 76%, slowed the progression of retinopathy by 54% and reduced the development of proliferative or severe non-proliferative retinopathy by 47%. Intensive insulin therapy reduced the occurrence of MA by 39%, that of albuminuria by 54% and that of clinical neuropathy by 60% when compared with the conventional treated group. In the DCCT intensive treatment reduced also the risk of any CVD event by 42% and the risk of non-fatal myocardial infarction, stroke or death from CVD by 57%.

Remarkably, the DCCT follow-up study, EDIC, highlighted the important phenomenon of ‘metabolic memory’. Although, after 2 years from the end of the DCCT, HbA1c levels were similar between the previously intensively and conventionally treated groups, the rate of progression of complications in the previously intensive-treated group was
significantly lower.\textsuperscript{39,57} In other words, patients who benefited in the past from a better metabolic control continued to have an advantage in terms of development of complications several years later. Therefore, the EDIC data highlighted the need of implementing intensive management as soon as T1D is diagnosed.

The DCCT also showed that there is no clear threshold for HbA1c levels, below which complications are completely prevented.\textsuperscript{39} This finding underlines the need of reaching a glycaemic control as close to normal as possible, but always considering the risk for adverse events. The main adverse events associated with intensive treatment in the DCCT were weight gain and hypoglycaemia.\textsuperscript{39} In addition, during the first 18 months of treatment in the DCCT there was a worsening of retinopathy, which occurred in 13.1\% patients in the intensive-treated group compared with 7.6\% of those in the conventional group.\textsuperscript{39} This was more likely to happen in patients with high HbA1c levels who subsequently had a more rapid decline in levels (normoglycaemic re-entry).\textsuperscript{39} However, patients who experienced an initial worsening of their retinopathy with intensified therapy had the same or a better long-term outcome than those in the conventional-treated group.\textsuperscript{39}

The DCCT cohort included a group of 195 adolescents, aged 13–17 years.\textsuperscript{49} In this adolescent cohort a similar positive effect of improved glycaemic control on complication risk was obtained, even though mean HbA1c levels were significantly higher, by about 1\%, when compared with the adult cohort.\textsuperscript{49} In addition, the frequency of hypoglycaemia and weight gain was higher in the adolescent than in the adult cohort.\textsuperscript{49} These data highlight the importance of a good glycaemic control during puberty but confirm that psychological issues, physiological insulin resistance and other changes in the hormonal milieu, may provide challenges.\textsuperscript{47} Other studies have shown the difficulties in achieving good glycaemic control whilst avoiding hypoglycaemia and weight gain during adolescence,\textsuperscript{48} which may reduce compliance to intensification of insulin treatment. Although there have been considerable advances in diabetes therapy, with the development of insulin analogues, pump therapy and multiple insulin delivery algorithms and the implementation of better and easier way of monitoring daily glycaemia, achievement of acceptable HbA1c levels are still a problem in this age group.\textsuperscript{48,59} Many young people still do not achieve HbA1c levels low enough to prevent complications. Data from the UK National Diabetes Audit 2007/08 indicate that only around 17.7\% of children and adolescents with T1D have an HbA1c below 7.5\% and nearly 30\% had an HbA1c >9.5\%.\textsuperscript{59} Therefore, other strategies may need to be implemented to reduce complications risk, particularly during adolescence (Table 2).
There has been a growing interest in blocking the renin–angiotensin system as a means to prevent microvascular complications of diabetes, and in adults, reduction of BP has been shown to be an important option to prevent the progression of nephropathy and retinopathy. Treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are increasingly being recommended in adult patients with MA based on the evidence of a positive effect in reducing the rate of progression and in promoting regression of MA. A beneficial effect of ACEIs has been shown in microalbuminuric normotensive patients, in which the ACE inhibition can arrest the increase in or even reduce AER. This effect appears to be independent of baseline BP, renal function and type of diabetes. Both ACEIs and ARBs have been shown to be effective, but the use of ARBs has been associated with increased risk of all-cause mortality when compared with placebo. However, even though several clinical trials have shown that ACEIs can reduce progression of renal disease in diabetes, it appears that blockers of the renin–angiotensin system (RAS) do not necessarily change renal pathology. Recent data from the renin–angiotensin system study (RASS), a large long-term study, investigating the effect of early RAS blockade with either an ACEI (enalapril) or an ARB (losartan) on renal morphology, in initially normotensive normoalbuminuric subjects has confirmed previous finding of a lack of a significant effect of ACEIs on early renal structural alterations.

A beneficial effect of anti-hypertensive treatment, and in particular of treatment with ACEIs, has also been demonstrated for DR. The EURODIAB Controlled Trial of Lisinopril in T1D showed a significant effect of lisinopril in reducing by around 50% the progression of retinopathy in normotensive and normo- or microalbuminuric patients. In the RASS study, treatment with either enalapril or losartan reduced the progression of retinopathy by 65–70%. In the latter study, patients have no sign or minimal pre-proliferative retinopathy at baseline.
With regards to the paediatric population with T1D, there is no guidance for the use of ACEIs or ARBs in the context of MA or early retinopathy. Four small studies have been performed and confirmed the likely efficacy of ACEIs in adolescents with MA but there have been no formal randomized controlled trial. It is difficult to draw definitive conclusions from these studies and the issue of the potential long-term use of ACEIs in individual with MA raises also the problem related to potential side effects of these drugs, particularly in pregnancy. The ADA recommends to start treatment with ACEIs in adolescents in the presence of persistent MA. Similarly the recent ISPAD guidelines suggest to use ACEIs or ARB in the presence of persistent MA in order to prevent progression to proteinuria, even though they acknowledge the lack of evidence in this context.

Management of dyslipidaemia

Many large-scale interventional trials have demonstrated that treatment with statins, the most effective lipid lowering drug class, significantly reduces the risk of coronary heart disease events and total mortality. People with diabetes often present dyslipidaemia and statin therapy has been associated with a significant reduction in the risk of macrovascular complications. Statins have effects other than the reduction in cholesterol levels, including inhibition of arterial smooth muscle cell proliferation, prevention of oxidation of LDL cholesterol, plaque stabilization, effects on macrophages, improvement of endothelial dysfunction, anti-inflammatory and anti-thrombotic effects.

The National Institute of Clinical Excellence (NICE) guidelines recommend statin treatment for T1D adults with MA or two or more features of metabolic syndrome (http://www.nice.org.uk). The Joint British Societies’ Guidelines recommend statin treatment for people aged 18–39 years with T1D who have at least one of the following: (1) retinopathy, (2) nephropathy, (3) poor glycaemic control, (4) elevated BP requiring antihypertensive therapy, (5) raised total cholesterol, (6) features of metabolic syndrome or (7) a family history of premature CVD in a first-degree relative.

However, there is no consensus as to the role of statin treatment in children or adolescents with T1D largely because no RCTs have been conducted. Short-term trials of up to 2 years duration conducted in children with familial hypercholesterolaemia show treatment to be efficacious and safe, and management guidelines in adolescents with T1D, who often have hyperlipidaemia, are currently dependent on adult studies. Longer term trials in children and adolescents with T1D are therefore urgently needed to address clinical uncertainty.
Dyslipidaemia may also be a risk factor for retinopathy, and in particular for diabetic macular edema.\textsuperscript{27} There are limited studies on the use of statins in relation to retinopathy but small and short-term intervention studies have shown a positive effect with the reversal or stabilization of macular exudation but no impact on visual acuity.\textsuperscript{51} Data supporting the use of lipid lowering drugs for neuropathy are also limited and are based mainly on animal studies.\textsuperscript{72} Treatment of diabetic rats with statins has been associated with improvements in nerve conduction and pain perception.\textsuperscript{72} However, further research is required to clarify whether a similar beneficial effect could be detected in patients with diabetes.

Other treatment options

Nephropathy
A low protein diet seems to reduce the increase in AER and the decline in glomerular filtration rate in adults with T1D. A meta-analysis of studies investigating the effect of protein intake has shown that a diet restriction to 0.5–0.8 g/kg/day reduces the risk of progression of nephropathy.\textsuperscript{73} However, the effects of such stringent protein restriction on AER and pubertal growth has not been evaluated in children and adolescents with T1D.

Cigarette smoking has been associated with a 2.2-fold risk for progression of albuminuria\textsuperscript{50} as well as with an increased risk of retinopathy and neuropathy,\textsuperscript{44} highlighting the importance of discouraging people with T1D from smoking as early as possible.

Retinopathy
For severe forms of diabetic retinopathy or in presence of macular oedema, pan-retinal and focal retinal photocoagulation are required to reduce visual loss.\textsuperscript{51}

Neuropathy
Apart from improving glycaemic control, there are no other therapies for diabetic neuropathy, which provide unequivocal, safe and effective stabilization or reversal of the condition.\textsuperscript{37} There have been many trials, most providing only modest disease stability or no improvement, using aldose reductase inhibitors, alpha-lipoic acid, growth factors, antagonists of advanced glycation end products, C-peptide, intravenous immune globulin.\textsuperscript{37,74} Patients who have evidence of peripheral neuropathy need to be instructed in a careful foot examination\textsuperscript{74} and those with loss of sensation need to be placed in footwear to reduce the development of neurotrophic ulcers and callus formation.\textsuperscript{74}
Symptomatic and palliative drugs may be needed in subjects with painful neuropathy.74

**New potential therapeutic strategies**

New potential therapeutic possibilities for the treatment of microvascular complications are emerging and they include drugs targeting specific pathways implicated in their pathogenesis. These include inhibitors of aldose reductase, inhibitors of protein kinase C, antagonists of advanced glycation end-products, glycosaminoglycans, inhibitors of growth factors and anti-oxidants.75 Up to now, there are no definitive data to recommend the use of these new potential therapies but the overall objective of targeting specific metabolic and haemodynamic pathways implicated in the pathogenesis of diabetic microvascular complications could lead to validation of these classes of drugs and discovery of novel pharmaceuticals.

**Conclusions**

As the incidence of T1D continues to rise, particularly in children, the burden of microvascular complications will also increase and negatively influence the prognosis of young people with the disease. Therefore, early detection of risk factors and signs of complications is of paramount importance in order to facilitate the early implementation of intervention strategies, which could reduce their development and/or progression. The high prevalence of early markers of complications risk during adolescence should also prompt further debate as to the need for additional therapeutic interventions to provide protection from microvascular complications in this age group, where HbA1c levels inevitably deteriorate. Further investigations aiming at clarifying aetiological factors, both genetic and environmental, implicated in the pathogenesis of microvascular complications, and the identification of biological markers, which reflect their influence, could help in identifying subjects at particular risk for developing vascular complications, and allow the implementation of preventive and therapeutic strategies.

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References


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