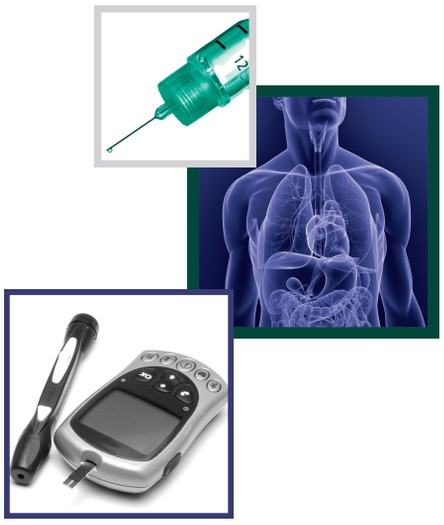
MANAGEMENT PERSPECTIVE

Importance of reno-protection in adolescents with diabetes and microalbuminuria



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Practice Points

- Early abnormalities in urinary albumin excretion and microalbuminuria are common findings during adolescence and they may be predictive of future risk of developing overt nephropathy and cardiovascular disease.
- The development of microalbuminuria during adolescence is associated with HbA1c, duration of diabetes, female gender, blood pressure, plasma lipids and puberty.
- Early identification of adolescents at risk for diabetic nephropathy is of paramount importance in order to implement prompt interventions.
- Annual screening for microalbuminuria is recommended in adolescents with Type 1 diabetes.
- Good glycemic control is the main primary prevention and treatment strategy in adolescents with Type 1 diabetes.
- The efficacy of additional interventions for cardio–renal protection, such as angiotensin-converting enzyme inhibitors and/or statins, is currently being investigated in high-risk adolescents with Type 1 diabetes.

SUMMARY Increases in urinary albumin excretion (microalbuminuria) can be detected in young people with Type 1 diabetes (T1D) during puberty, and they may indicate a risk for the development of overt diabetic nephropathy (DN) and cardiovascular disease. During adolescence, poor glycemic control, dyslipidemia, increases in blood pressure and inflammatory markers, female gender, and hormonal changes all contribute to the risk of microalbuminuria. Currently, interventions to reduce the long-term risk for DN in adolescents with T1D are mainly based on improving glycemic control, while there is no clear guidance on other potential cardio–renal protection strategies. The efficacy of angiotensin-converting enzyme inhibitors and statins is currently being investigated in adolescents with T1D at high risk of developing DN. In addition, there is growing interest in the development of new interventions targeting specific pathways implicated in DN.

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Prognosis of childhood-onset Type 1 diabetes

Over the last decades there has been a worldwide increase in the incidence of Type 1 diabetes (T1D), particularly in children younger than 5 years of age [1,2]. A recent UK study has reported an increased trend in the incidence of T1D between 1991 and 2008, from 9.7–13.2/100,000 to 15–23.3/100,000 person-years, in both children (0–14 years) and young adults (15–34 years), but with a larger annual increase in children: 4.1 versus 2.8% [3].

Childhood-onset T1D is associated with a significant risk of acute and chronic complications, which contribute to the overall burden of the disease [4]. Recent data have confirmed that, whereas during the first decade of diabetes acute complications, such as diabetic ketoacidosis, represent the main causes of death (73%), during the second and third decades renal and cardiovascular diseases (CVD) become the main determinants of mortality [5]. Over the last decades, improvements in diabetes management, mainly glycemic and blood pressure control, have been associated with better outcomes in people with T1D, with a declining trend in vascular complications [6,7], although overall mortality still remains higher compared with the general population [8–10].

An 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 risk of vascular complications [4]. Furthermore, diabetic vascular complications can show a different natural history and may be particularly aggressive in young people with T1D, mainly in those with poor glycemic control, who often show a faster clinical course than adults [11].

The burden of diabetic nephropathy

Diabetic nephropathy (DN) is one of the most common microvascular complications of T1D, reflecting structural changes occurring in the renal glomeruli, tubules and interstitium, and leading to the development of albuminuria, glomerulosclerosis, raised blood pressure and to a progressive decline in renal function [12].

The changes occurring in the kidney in patients with T1D are generally classified into five stages, reflecting specific and progressive alterations in the renal morphology and function [12]. The earliest stage (stage 1) is characterized by glomerular hypertrophy, hyperfiltration and hyperperfusion. This is followed by a stage of subclinical morphological changes and increases in albumin excretion rates (AERs) within the normal range (stage 2) [12]. Further increases in albumin excretion, with an AER between 30 and 300 mg/24h or 20–200 µg/min in a 24-h or timed urine collection, indicate the development of microalbuminuria (stage 3), which may further progress to overt proteinuria (macroalbuminuria); (AER >200 µg/min or >300 mg/24h) (stage 4) and, without any treatment, to end-stage renal disease (ESRD) (stage 5) [12].

Diabetic nephropathy affects about 15–40% subjects with T1D, with a peak incidence after 15–20 years diabetes duration, and represents the main cause of ESRD in developed countries as well as a significant determinant of CVD [13,14]. Patients with T1D and DN have a tenfold greater risk of CVD than patients without DN and the majority of patients with DN die of CVD-related causes even before the development of ESRD [15,16].

There is a large body of evidence indicating that people with T1D have an increased age-adjusted mortality risk compared with the general population [10]. Recent studies have shown that childhood-onset T1D is associated with a three- to fourfold increased mortality when compared with the general population [8,9]. Interestingly, longitudinal studies have shown that, in the absence of renal complications, mortality in patients with T1D is similar to that in the general population, whereas it significantly increases in subjects with abnormal urinary albumin excretion [16,17]. In the FinnDiane cohort of adults with T1D, the presence of microalbuminuria, macroalbuminuria and ESRD was associated with 2.8-, 9.2- and 18.3-times higher standardized mortality rates (SMRs), respectively, whereas in those with normoalbuminuria SMR was similar to that in the nondiabetic population [16]. Similarly, data from the Pittsburgh Epidemiology of Diabetes Complications Study of childhood-onset T1D showed a progressive increase of SMR from 2.0 for normoalbuminuria, 6.4 for microalbuminuria, 12.5 for macroalbuminuria and 29.8 for ESRD [17].

Renal involvement in adolescents with T1D

Although macroalbuminuria or ESRD are uncommon findings in children and adolescents with T1D [18], early structural and functional renal alterations develop soon after diagnosis of

diabetes, and often progress during puberty [19–22]. Biopsy studies have shown that renal lesions, such as basement membrane thickening and mesangial expansion, can be detected in young normoalbuminuric subjects and these changes are predictive of subsequent patterns in AER [19,23,24].

Hyperfiltration is often detected in young people with T1D and precedes the onset of microalbuminuria [22,25]. In some, although not all, studies increased glomerular filtration rate (GFR) has emerged as an independent predictor of microalbuminuria, and a recent meta-analysis has reported a 2.7-fold increased risk of developing microalbuminuria associated with hyperfiltration [26].

Microalbuminuria is a frequent finding among adolescents with T1D. Cross-sectional studies have reported a prevalence between 4 and 20% [27–35]. This variability is largely related to differences in diabetes duration across studies, together with variations in glycemic control and the criteria used to define microalbuminuria. Based on longitudinal studies, the cumulative prevalence of microalbuminuria is 10–26% during the first 10–15 years of T1D **(Table 1)** [11,20,36–43], and it becomes as high as 51% after 19 years of diabetes duration, as recently demonstrated by analysis of longitudinal data collected in the Oxford Regional Prospective Study (ORPS) [11]. This prevalence is significantly higher than that reported in adult cohorts (34%) after 18 years of diabetes duration and exposure to similar levels of glycemic control [44], thus suggesting that a diagnosis of T1D during childhood is associated with different risk factors for the development of microalbuminuria when compared with a later diagnosis during adult life [11,44].

The rate of progression of microalbuminuria to macroalbuminuria appears to be similar between adults and children with T1D, but in children macroalbuminuria occurs at an earlier age (18.5 vs 41 years) [11,44]. In the ORPS cohort, the cumulative prevalence of macroalbuminuria was 13.9% [11] and this was similar to the 14.6% prevalence reported in a similar inception cohort in adults [44], suggesting that progression is related to duration of diabetes regardless of the age at onset. Interestingly, both persistent (hazard ratio: 27.72 [7.99–96.12]) and intermittent microalbuminuria (hazard ratio: 8.76 [2.44–31.44]) during adolescence predicted progression to macroalbuminuria [11].

Recent studies have introduced the concept of 'regression to normoalbuminuria' and this phenomenon has been reported in approximately 40–50% adolescents with T1D [11,45], and occurs mainly after puberty. These rates of regression are similar to those reported in adults with T1D [6,46]. Recent updated results from the Diabetes Control and Complication Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) studies have reported a cumulative incidence of regression to normoalbuminuria of 40% after 10 years from the onset of microalbuminuria [6]. However, even though microalbuminuria regresses, the morphological changes occurring in the kidney can persist and increase the risk of its recurrence and progression to macroalbuminuria during follow-up [19]. This is supported by the ORPS data indicating an increasing number of 'intermittent' subjects originally described as transient, with continued follow-up [11].

Risk factors for the development of renal complications during adolescence

Adolescence represents a critical period for the lifetime risk of complications in childhood-onset T1D and it is during this period of life that the

Table 1. Microalbuminuria in children and adolescents with Type 1 diabetes: data from longitudinal studies.

Author (year)	Screening procedure	Population (n)	Years of T1D duration†	MA (%)	Ref.
Norgaard *et al.* (1989)	AER, 24 h urine	113	7.7 (4.0)	13	[36]
Rudberg *et al.* (1993)	AER, 24 h urine	156	6.9 (3.9)	10.9	[39]
Janner *et al.* (1994)	AER, overnight	164	1–12	20	[40]
Barkai *et al.* (1998)	AER, 24 h urine	74	3.1 (0.5)	10.8	[42]
Jones *et al.* (1998)	ACR, spot urine	233	3.9 (1.8–6.7)	14.5	[38]
Olsen *et al.* (2000)	AER, overnight	339	13.2 (8.9–24.5)	9.0	[37]
Svensson *et al.* (2004)	AER, overnight	94	11.8 (3.5)	18	[43]
Gallego *et al.* (2006)	AER, overnight	955	0.9–21.4	13.4	[41]
Amin *et al.* (2008)	ACR, spot urine	527	10.2 (3.2)	26	[11]

†Age and duration are expressed as mean (SD) or median (range or interquartile range), or ranges/means only.
ACR: Albumin:creatinine ratio; AER: Albumin excretion rate; MA: Microalbuminuria; T1D: Type 1 diabetes.

first signs of micro- and macrovascular complications appear [47]. During puberty hormonal and metabolic changes, as well as lifestyle, environmental exposures and genetic factors may interact with poor glycemic control and contribute to complications risk **(Figure 1)** [48].

High HbA1c values are a common finding among adolescents with T1D and they are closely linked to the risk of developing vascular complications [11,49–53]. In the ORPS cohort for each 1% increase in HbA1c there was a 39% increased risk of developing microalbuminuria **(Figure 1)** [11]. In addition, HbA1c was also an independent predictor of progression to macroalbuminuria, with a 42% increased risk for every 1% increase in HbA1c [11].

Puberty is generally associated with a physiological decrease in insulin sensitivity [54], which contributes to poor glycemic control. In addition, poor compliance is common among adolescents with T1D and this represents another determinant of high HbA1c levels [49].

However, the relationship between puberty and vascular complications is only partly mediated through poor glycemic control, as there is evidence that puberty itself is an independent risk factor [20,47]. The effect of puberty on complication risk may be mediated through growth hormone hypersecretion [55] and its effects on renal growth and glomerular hyperfiltration [22], and reduced free IGF-I levels [55]. In addition, during puberty, increased androgen levels have been associated with the presence of microalbuminuria [55], particularly in girls.

Elevated blood pressure, blood lipids and inflammatory markers are often increased in adolescents with T1D and all these factors have been linked to the development of microalbuminuria [56–58].

Environmental and dietary factors may also contribute to the risk of developing microalbuminuria during puberty. Smoking is a common finding among adolescents, and it has been reported in up to 48% of those with T1D [59]. In a large prospective study in young individuals with T1D, smoking was associated with a 2.8-fold increased risk of microalbuminuria, whereas smoking cessation caused a significant improvement in AER [60]. A high protein intake has been suggested as a potential risk factor for the development of DN, with a normalization of GFR associated with a reduction in protein intake [61,62]. Diet can be a source of advanced glycation end products (AGEs), which are key players in the pathogenesis of DN. In the context of diabetes, AGEs are mainly produced endogenously as a result of hyperglycemia [63]; however, specific foods and modes of cooking can contribute to the AGE load [64].

There is extensive evidence suggesting that the risk of developing microalbuminuria is partly genetic [65,66] and therefore, during puberty, genetic

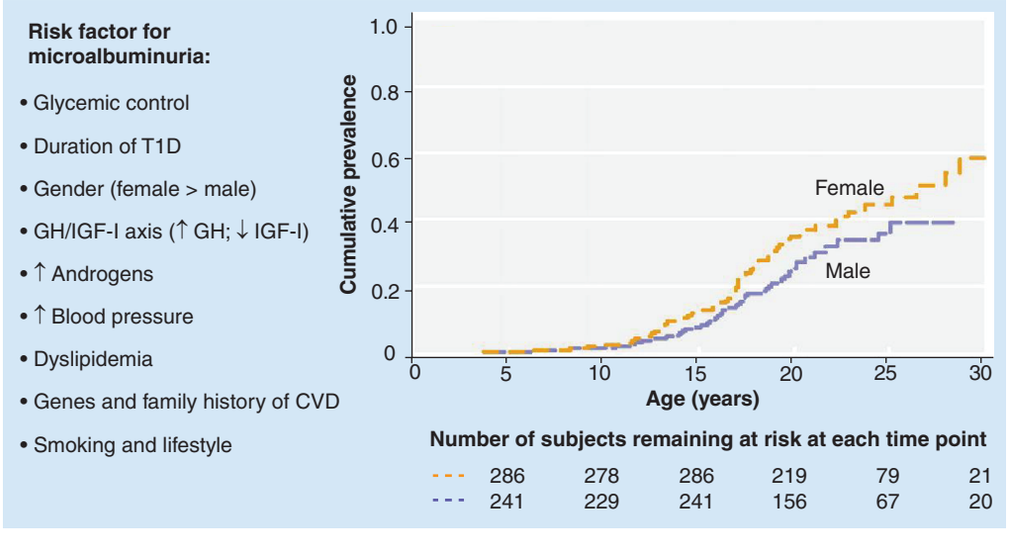

Figure 1. Cumulative prevalence of microalbuminuria in 527 children with Type 1 diabetes from the Oxford Regional Prospective Study and risk factors for microalbuminuria.
CVD: Cardiovascular disease; GH: Growth hormone; T1D: Type 1 diabetes.
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variants could interact with hormonal, metabolic and other environmental factors and contribute to the onset of microalbuminuria. Family studies have confirmed the role of a genetic predisposition to nephropathy risk, given that the prevalence of this complication is higher in patients with family members with nephropathy [66] as well in patients with first degree relatives with hypertension, dyslipidemia, Type 2 diabetes and clusters of these cardiovascular risk factors [67,68].

Candidate gene studies have identified several genes potentially associated with DN risk, although the results have not been consistent across different studies [69]. Among the most common genes studied in relation to DN are those encoding for components of the renin–angiotensin system (RAS). In particular, the insertion/deletion polymorphism in the angiotensin-converting enzyme gene has been the subject of several investigations. However, as emerged from a recent meta-analysis, it appears to have a small effect on the risk for developing DN in people with T1D [70]. Other candidate genes which have been associated with DN are those encoding lipoproteins (in particular ApoE), aldose reductase and heparan sulfate [69]. A recent genome-wide association study in adults with T1D from the Genetics of Kidneys in Diabetes (GoKinD) cohort has identified 11 single nucleotide polymorphisms in four chromosomal regions associated with advanced stages of DN [71]. Two of these single nucleotide polymorphisms, located near the *FRMD3* and *CARS* loci, and which were shown to be expressed in the human kidney, were replicated in the DCCT/EDIC cohort, therefore emerging as likely candidate variants influencing DN susceptibility [71]. However, further studies are required to replicate these findings in other populations, including young people with T1D and patients with earlier stages of DN, and to clarify the function of these genetic variants.

Consequences of renal involvement in young people with T1D

In adults with T1D there is convincing evidence showing that microalbuminuria is associated with a generalized endothelial dysfunction and is an independent predictor for CVD and mortality [72,73]. Over the last years, alterations in endothelial glycocalyx, a carbohydrate-rich layer lining the vascular endothelium, have been implicated as early key changes contributing to the development of endothelial dysfunction, microalbuminuria and CVD [74].

In children and adolescents with T1D microalbuminuria has been linked to the presence of cardiovascular risk factors, such as dyslipidemia [57], raised blood pressure [56] and inflammatory markers [58]. In addition, there are studies showing an association of impaired flow-mediated dilatation [75] and increased carotid intima-media thickness with microalbuminuria [76].

Studies performed in adults have shown that AER is a continuous renal and cardiovascular risk factor and, therefore, even mild increases within the normal range may predict cardiovascular events [77]. In adolescents with T1D, early abnormalities in albumin excretion, which can be detected already 1 year after diabetes onset, are strongly associated with future risk of microalbuminuria [21,78]. This suggests that consideration should be given to progression of albumin excretion, even within the normal range, and not just to specific cut-offs indicative of microalbuminuria/proteinuria. In the ORPS cohort, an albumin:creatinine ratio in the upper tertile at the age of 11–15 years, after adjustments, predicted 85% of subjects who developed microalbuminuria and all of the subjects who developed clinical proteinuria during follow-up [78].

The importance of early reno-protection in adolescents with T1D

The natural history of DN is characterized by many years of clinical silence, whilst relevant renal structural alterations develop [12]. Once clinical signs such as microalbuminuria develop, renal structural changes are often advanced and, although microalbuminuria can regress, the underlining renal morphological changes can persist and determine its reappearance and progression over time [19].

Therefore, screening at early stages during the course of diabetes is of utmost importance in order to implement prompt interventions, which are likely to be more effective than those started during later stages of the disease, when the structural changes are less likely to be reversible.

International guidelines for diabetes care for children and adolescents with T1D recommend yearly urine screening for microalbuminuria from 11 years of age with more than 2 years duration of T1D and from 9 years of age with more than 5 years duration of T1D **(Box 1)** [79]. Measurement of urinary albumin excretion is the basis for early detection of microalbuminuria and can be achieved with: 24-h urine collection; overnight

Box 1. Screening recommendations based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines 2006–2007.

- Screening recommendations:
  - Annual assessment of albumin excretion from the age of 11 years with 2 years diabetes duration and from age 9 years with 5 year diabetes duration
  - Method: urinary albumin:creatinine ratio or first morning albumin concentration
- Exclude other causes of increased albumin excretion:
  - Strenuous exercise
  - Orthostatic proteinuria
  - Hypertension
  - Acute febrile illnesses
  - Smoking
  - Urinary infection
  - Nephritis
  - Menstruation

timed urine collections; albumin:creatinine ratio or albumin concentration on a early morning spot urinary sample [79]. 24-h or timed urine collections are often difficult to obtain in children and adolescents. Assessing albumin:creatinine ratio in early morning urines is the easiest method to carry out in an office setting and it generally provides accurate information [79]. Persistent microalbuminuria is defined as two out of three abnormal samples collected over a period of 3–6 months [79].

Therapeutic strategies for reno-protection in adolescents with T1D

Glycemic control

The DCCT [80] and its observational follow-up study, the EDIC [81], have undoubtedly showed that complication risk significantly decreases with strict glycemic control both in adults and in adolescents. In the adolescent cohort of the DCCT, a positive effect of improved glycemic control on complication risk was obtained, with a 54% reduction in risk and progression of microalbuminuria in the intensive treated group when compared with the conventional treated group [52]. The benefit of intensive therapy during the DCCT persisted during years of follow-up, as highlighted by the EDIC results, although the difference in HbA1c levels between the two adolescent groups tended to wear off over time [81,82]. This led to the concept of a 'metabolic memory' which could explain the persistent benefit many years after the initial intervention.

However, the DCCT study also highlighted the difficulties encountered in managing diabetes during adolescence. In fact, in the adolescent intensive treated cohort mean HbA1c levels during the DCCT were significantly higher, by approximately 1%, when compared with the adult cohort [52]. This underlines the problems of achieving good glycemic control during puberty, when psychological issues, together with the effect of the physiological insulin resistance [54] and other changes in the hormonal milieu may provide challenges [49]. The suboptimal glycemic control in the DCCT was also associated with an increased risk of developing hypoglycemia and weight gain in adolescents when compared with the adult cohort [52,80].

Several other studies have confirmed the persisting difficulties in achieving a glycemic control within targets in adolescents [51,83], even though, over the last decades, there have been many advances in diabetes management with the implementation of new insulin formulations and regimens, pump therapy and easier ways of monitoring glucose levels. These observations underline the need of further treatment options in order to reduce the burden associated with vascular complications of diabetes **(Figure 2)**.

Angiotensin-converting enzyme inhibitors & angiotensin receptor blockers

In adults with T1D, the presence of microalbuminuria is a general indication for intervention with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) [84]. These recommendations are based on the evidence of a beneficial effect of these drugs on renal complications [85]. A meta-analysis including 12 trials with ACEIs in adult normotensive patients with T1D and microalbuminuria demonstrated a significant decrease in the progression to macroalbuminuria (odds ratio: 0.38 [95% CI: 0.25–0.57]) and a higher likelihood of regression to normoalbuminuria (odds ratio: 3.07 [95% CI: 2.15–4.44]) as well as a 50% decrease in AER in treated patients compared with placebo [84].

However, recent data have highlighted that blockers of the RAS do not necessarily change renal pathology [86]. The results of the Renin-Angiotensin System Study (RASS), which recruited 285 normoalbuminuric and normotensive subjects with T1D at a mean age of 29 years, indicated a lack of effect of 5-year RAS blockage, with either an ACEI (Enalapril) or an ARB (Losartan), on early structural glomerular changes, in normoalbuminuric patients with T1D [86]. These negative findings might be

related to the fact that intervention was started at an early stage of renal pathology, whereas in other investigations a beneficial effect was seen when applied at a more advanced stage of DN, therefore suggesting a different role of RAS at different stages of DN.

Up to now there is no definitive guidance for the use of ACEIs or ARBs in the pediatric population. The American Diabetes Association recommends to start treatment with ACEIs in presence of persistent microalbuminuria [87]. Similarly the recent guidelines of the International Society for Pediatric and Adolescence diabetes (ISPAD) suggest to use ACEIs or ARBs when persistent microalbuminuria is detected in order to prevent progression to proteinuria, even though the lack of evidence in this context is firmly acknowledged [79].

Four small studies with ACEIs have been performed in young people with T1D and persistent microalbuminuria [88–91]. Overall they have confirmed the results from studies in adults, showing that ACEIs decrease urinary albumin excretion. Only one study was designed as a small randomized double-blind, placebo-controlled trial, where Captopril (0.9 mg/kg/day) was administered for 3 months to 12 adolescents with T1D and microalbuminuria (mean age 14.4 ± 1.7 years) [88]. A mean decrease of 41 ± 44% in AER was reported in ten out of the 12 participants. However, even though these pediatric studies have showed the efficacy of ACEIs in reducing albumin excretion, it is difficult to draw definitive conclusions, given the small number of subjects included, the short follow-up and the lack of a placebo arm in the majority of studies. In addition, no data are available in subjects with high-normal AER, who are at high risk for later development of DN and potentially CVD [78]. Therefore, a large placebo-controlled trial is required to provide more robust evidence for the efficacy and to document adverse effects with the use of ACEIs during adolescence.

■ Statins

Dyslipidemia is a common finding among patients with diabetes, including adolescents [57,92,93] and it contributes to the increased risk of atherosclerotic disease as well as to microvascular complications [94]. Glycemic control is an important determinant of lipid levels in patients with diabetes [57,92,93], but despite attempts to improve HbA1c, lipid abnormalities often persist with long duration of diabetes.

Treatment with statins in adults with T1D has been associated with a significant decreased risk of cardiovascular events [95]. Given the reported association between abnormal cholesterol levels and renal damage, the effect of statins treatment on renal outcomes has also been investigated with positive results in reducing proteinuria and retarding the progression of chronic kidney disease [94,96,97]. The beneficial effect of statins on albumin excretion may be due to reduced cholesterol levels, together with other statin-related antioxidant, anti-inflammatory, antiproliferative and antithrombotic effects [96,98]. However, additional prospective randomized controlled trials are required to better explore the reno-protective effect of statins, particularly in the context of diabetes, where data are limited.

Up to now, there has been no general consensus on the role of statin treatment in children and adolescents with T1D and their use is very limited [92,93]. Management of dyslipidemia in pediatric patients relies on the results of trials conducted in adults [99] and on data from short-term trials conducted in children with familial hypercholesterolemia [100–102].

Statin treatment is an efficient lipid-lowering therapy in children and adolescents with familial hypercholesterolemia, where their use has also been associated with improved surrogate measures of early atherosclerosis, such as flow-mediated dilation and carotid intima-media thickness [100–102]. Recently, the results of a randomized crossover pilot study assessing the effect

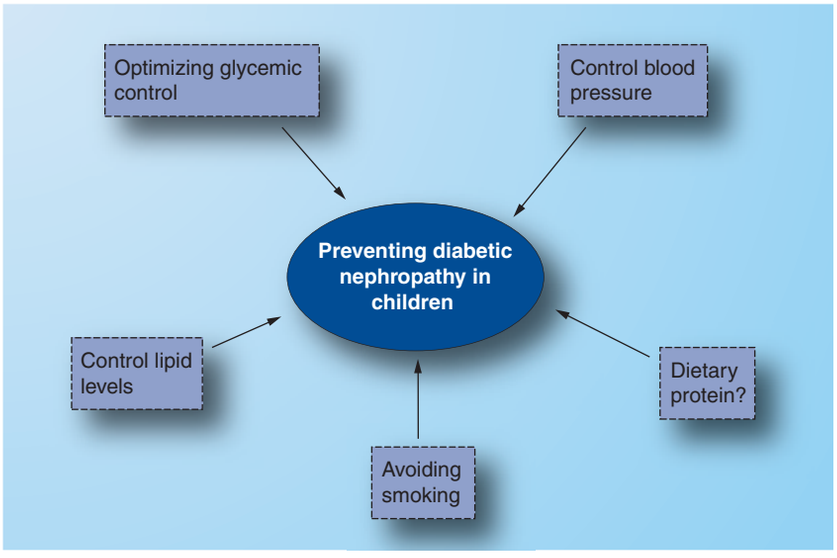

Figure 2. Strategies for preventing and treating diabetic nephropathy in adolescents with Type 1 diabetes.

of 12-week atorvastatin treatment in improving arterial stiffness in 51 children with T1D were reported [103]. Although the primary analysis failed to demonstrate an improvement in arterial stiffness or endothelial function associated with treatment with statins as compared with placebo, secondary analysis of change during the atorvastatin period alone provided proof of principle that atorvastatin therapy may be associated with reduced arterial stiffness in children with T1D. In addition, this study confirmed a good safety profile of atorvastatin in young people. However, large long-term randomized controlled trials are required to establish the long-term efficacy and safety of statins in young people with T1D.

■ Diet & smoking

A low protein diet seems to reduce the increase in AER and the decline in GFR in adults with T1D. A meta-analysis of studies investigating the effect of protein intake has shown that a dietary restriction to 0.5–0.8 g/kg/day reduces the risk of progression of DN in adults with diabetes [62]. However, there are few data on the effect of dietary proteins on the earlier stages of renal disease, and there are no specific data for children and adolescents.

Cigarette smoking has been associated with a 2.2-fold risk for progression of albuminuria [60], highlighting the importance of discouraging people with T1D from smoking as early as possible.

■ Current renal-protection trials in adolescents with T1D

The efficacy of ACEIs and statins in high-risk adolescents with T1D is currently being investigated by the Adolescent Diabetes Intervention Trial (AdDIT), a multicenter multinational trial, involving centers in the UK, Canada and Australia [104]. A total of 500 high-risk adolescents (aged 11–16 years), defined on the basis of their albumin excretion in the upper tertile of the normal range, are randomized to receive either ACEIs (quinapril) or statins (atorvastatin) or combination therapy or placebo for 3–4 years. The major end point of the study is the change in albumin excretion; secondary end points include markers of CVD, renal function, retinopathy, quality of life combined with assessment of compliance and potential health economic benefits. AdDIT will provide important data on the potential renal and cardiovascular protective effects of ACEIs and statins in high-risk adolescents. Long-term follow-up of the randomized subjects will provide direct evidence of disease outcomes, in addition to the data on early surrogate measures of DN and CVD.

The efficacy and safety of statins is also being investigated in a randomized placebo-controlled trial in young people with T1D (n: 80, aged 10–20 years) and hypercholesterolemia. Changes in LDL-cholesterol, inflammatory markers will be specifically assessed in this trial, although the potential effect on renal outcome is not assessed [201].

■ New experimental therapies for renal protection in T1D

New potential therapeutic strategies for the treatment of DN are emerging and they include drugs targeting specific pathways implicated in its pathogenesis. These include inhibitors of aldose reductase and protein kinase C, antagonists of AGEs, glycosaminoglycans, inhibitors of growth factors and antioxidants [105].

Based on the so-called 'unifying hypothesis', which suggests that an overproduction of superoxide by the mitochondrial electron transport chain represents the common mechanisms linking hyperglycemia to the activation of downstream pathways (i.e., protein kinase C, aldose reductase, AGEs, hexosamine and polyol pathways), drugs targeting superoxide production represent an appealing strategy for preventing and treating diabetic complications [106]. Recent studies have also highlighted the role of increased levels of serum uric acid in the pathogenesis of DN, and suggested treatment with allopurinol as a potential new strategy for preventing DN [107].

However, up to now, there are few experimental data on these new potential treatments and limited information derived from studies in humans, therefore underlining the need of future research in this area. Nevertheless, the overall objective of targeting specific metabolic and hemodynamic pathways implicated in the pathogenesis of DN could lead to the validation of these classes of drugs and discovery of novel pharmaceuticals.

Conclusion & future perspective

Early abnormalities in urinary albumin excretion and microalbuminuria are often detected during adolescence and they may be predictive of future risk of developing overt nephropathy and CVD. Poor glycemic control, duration of diabetes, blood pressure, plasma lipids, inflammatory

markers, female gender, abnormalities in the GH–IGF-I axis and increased androgens, have all been found to contribute to the risk of microalbuminuria during puberty. Although microalbuminuria can be transient or intermittent during adolescence, there is evidence that early structural changes associated with it persist and can influence recurrence and even progression to overt proteinuria during follow-up.

Therefore, early interventions could reduce the long-term risk for DN and CVD and improve the prognosis of young people with T1D. Currently, interventions are mainly based on improving glycemic control, whereas there are no clear guidance on the use of other drugs, such as ACEIs, ARBs and/or statins, which are increasingly being used in adults with T1D and persistent microalbuminuria. The AdDIT, which is currently evaluating the efficacy of ACEIs and statins in high-risk adolescents with T1D, will help to answer the question whether, in addition to encouraging young people to achieve a good glycemic control, additional interventions for cardio–renal protection should also be recommended.

Ongoing and future studies aiming at identifying new genetic and biochemical markers of early renal damage could enable earlier and more accurate ways of predicting patient risk in relation to the development of renal impairment. This could help in applying more intensive management strategies towards selected patients at high risk. In addition, the identification of DN susceptibility or protective genes and/or plasma/urine biomarkers could lead to novel biological insights and a better understanding of etiological pathways and also to the development of new preventive and therapeutic strategies.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Bibliography

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1 Soltesz G, Patterson CC, Dahlquist G. Worldwide childhood Type 1 diabetes incidence – what can we learn from epidemiology? *Pediatr. Diabetes* 8(Suppl. 6), 6–14 (2007).

2 Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood Type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. *Lancet* 373(9680), 2027–2033 (2009).

■ **Recent estimates of trends in the incidence of Type 1 diabetes indicate an overall annual increase of 3.9% and a doubling of new cases in children younger than 5 years by 2020.**

3 Imkampe AK, Gulliford MC. Trends in Type 1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991–2008. *Diabet. Med.* 28(7), 811–814 (2011).

4 Daneman D. Type 1 diabetes. *Lancet* 367(9513), 847–858 (2006).

5 Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset Type 1 diabetes. *Diabetes* 59(12), 3216–3222 (2010).

6 De Boer IH, Rue TC, Cleary PA *et al.* Long-term renal outcomes of patients with Type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Arch. Intern. Med.* 171(5), 412–420 (2011).

7 Mohsin F, Craig ME, Cusumano J *et al.* Discordant trends in microvascular complications in adolescents with Type 1 diabetes from 1990 to 2002. *Diabetes Care* 28(8), 1974–1980 (2005).

8 Asao K, Sarti C, Forsen T *et al.* Long-term mortality in nationwide cohorts of childhood-onset Type 1 diabetes in Japan and Finland. *Diabetes Care* 26(7), 2037–2042 (2003).

9 Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia* 49(2), 298–305 (2006).

10 Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. *JAMA* 290(14), 1884–1890 (2003).

11 Amin R, Widmer B, Prevost AT *et al.* Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset Type 1 diabetes: prospective observational study. *BMJ* 336(7646), 697–701 (2008).

■■ **Microalbuminuria occurs more frequently in subjects with childhood-onset Type 1 diabetes than in adults, is more common in females and the only modifiable predictor is high HbA1c. Microalbuminuria and high HbA1c predict progression to macroalbuminuria.**

12 Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 32(Suppl. 2), 64–78 (1983).

13 Jones CA, Krolewski AS, Rogus J, Xue JL, Collins A, Warram JH. Epidemic of end-stage renal disease in people with diabetes in the United States population: do we know the cause? *Kidney Int.* 67(5), 1684–1691 (2005).

14 Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. *BMJ* 313(7060), 779–784 (1996).

15 Tuomilehto J, Borch-Johnsen K, Molarius A *et al.* Incidence of cardiovascular disease in Type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. *Diabetologia* 41(7), 784–790 (1998).

16 Groop PH, Thomas MC, Moran JL *et al.* The presence and severity of chronic kidney disease predicts all-cause mortality in Type 1 diabetes. *Diabetes* 58(7), 1651–1658 (2009).

■■ **In the absence of renal disease, mortality rate in adults with Type 1 diabetes is similar to the general population, whereas it increases with progressive increases in albumin excretion.**

17 Orchard TJ, Secrest AM, Miller RG, Costacou T. In the absence of renal disease, 20 year mortality risk in Type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetologia* 53(11), 2312–2319 (2010).

18 Mollsten A, Svensson M, Waernbaum I *et al.* Cumulative risk, age at onset, and sex-specific differences for developing end-stage renal disease in young patients with Type 1 diabetes: a nationwide population-based cohort study. *Diabetes* 59(7), 1803–1808 (2010).

19 Steinke JM, Mauer M. Lessons learned from studies of the natural history of diabetic nephropathy in young Type 1 diabetic patients. *Pediatr. Endocrinol. Rev.* 5(Suppl. 4), 958–963 (2008).

20 Schultz CJ, Konopelska-Bahu T, Dalton RN *et al.* Microalbuminuria prevalence varies with age, sex, and puberty in children with Type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. *Diabetes Care* 22(3), 495–502 (1999).

21 Schultz CJ, Neil HA, Dalton RN, Dunger DB. Risk of nephropathy can be detected before the onset of microalbuminuria during the early years after diagnosis of Type 1 diabetes. *Diabetes Care* 23(12), 1811–1815 (2000).

■ **Early increases in albumin excretion within the normal range within 2 years of diagnosis can be detected in children who subsequently develop microalbuminuria.**

22 Amin R, Turner C, Van Aken S *et al.* The relationship between microalbuminuria and glomerular filtration rate in young Type 1 diabetic subjects: the Oxford Regional Prospective Study. *Kidney Int.* 68(4), 1740–1749 (2005).

23 Lawson ML, Sochett EB, Chait PG, Balfe JW, Daneman D. Effect of puberty on markers of glomerular hypertrophy and hypertension in IDDM. *Diabetes* 45(1), 51–55 (1996).

24 Kostraba JN, Dorman JS, Orchard TJ *et al.* Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. *Diabetes Care* 12(10), 686–693 (1989).

25 Rudberg S, Persson B, Dahlquist G. Increased glomerular filtration rate as a predictor of diabetic nephropathy – an 8-year prospective study. *Kidney Int.* 41(4), 822–828 (1992).

■ **In normoalbuminuric children with Type 1 diabetes, hyperfiltration predicted the development of microalbuminuria during an 8-year observational period.**

26 Magee GM, Bilous RW, Cardwell CR, Hunter SJ, Kee F, Fogarty DG. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. *Diabetologia* 52(4), 691–697 (2009).

27 Mathiesen ER, Saurbrey N, Hommel E, Parving HH. Prevalence of microalbuminuria in children with Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 29(9), 640–643 (1986).

28 Dahlquist G, Rudberg S. The prevalence of microalbuminuria in diabetic children and adolescents and its relation to puberty. *Acta Paediatr. Scand.* 76(5), 795–800 (1987).

29 Mortensen HB, Marinelli K, Norgaard K *et al.* A nation-wide cross-sectional study of urinary albumin excretion rate, arterial blood pressure and blood glucose control in Danish children with Type 1 diabetes mellitus. Danish Study Group of Diabetes in Childhood. *Diabet. Med.* 7(10), 887–897 (1990).

30 Joner G, Brinchmann-Hansen O, Torres CG, Hanssen KF. A nationwide cross-sectional study of retinopathy and microalbuminuria in young Norwegian Type 1 (insulin-dependent) diabetic patients. *Diabetologia* 35(11), 1049–1054 (1992).

31 Moore TH, Shield JP. Prevalence of abnormal urinary albumin excretion in adolescents and children with insulin dependent diabetes: the MIDAC study. Microalbinuria in Diabetic Adolescents and Children (MIDAC) research group. *Arch. Dis. Child.* 83(3), 239–243 (2000).

32 Mullis P, Kochli HP, Zuppinger K, Schwarz HP. Intermittent microalbuminuria in children with Type 1 diabetes mellitus without clinical evidence of nephropathy. *Eur. J. Pediatr.* 147(4), 385–388 (1988).

33 Cook JJ, Daneman D. Microalbuminuria in adolescents with insulin-dependent diabetes mellitus. *Am. J. Dis. Child.* 144(2), 234–237 (1990).

34 Bojestig M, Arnqvist HJ, Karlberg BE, Ludvigsson J. Glycemic control and prognosis in Type I diabetic patients with microalbuminuria. *Diabetes Care* 19(4), 313–317 (1996).

35 Donaghue KC, Fairchild JM, Chan A, Hing SJ, Howard NJ, Silink M. Diabetes complication screening in 937 children and adolescents. *J. Pediatr. Endocrinol. Metab.* 12(2), 185–192 (1999).

36 Norgaard K, Storm B, Graae M, Feldt-Rasmussen B. Elevated albumin excretion and retinal changes in children with Type 1 diabetes are related to long-term poor blood glucose control. *Diabet. Med.* 6(4), 325–328 (1989).

37 Olsen BS, Sjolie A, Hougaard P *et al.* A 6-year nationwide cohort study of glycaemic control in young people with Type 1 diabetes. Risk markers for the development of retinopathy, nephropathy and neuropathy. Danish Study Group of Diabetes in Childhood. *J. Diabetes Complicat.* 14(6), 295–300 (2000).

38 Jones CA, Leese GP, Kerr S *et al.* Development and progression of microalbuminuria in a clinic sample of patients with insulin dependent diabetes mellitus. *Arch. Dis. Child.* 78(6), 518–523 (1998).

39 Rudberg S, Ullman E, Dahlquist G. Relationship between early metabolic control and the development of microalbuminuria – a longitudinal study in children with Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 36(12), 1309–1314 (1993).

40 Janner M, Knill SE, Diem P, Zuppinger KA, Mullis PE. Persistent microalbuminuria in adolescents with Type I (insulin-dependent) diabetes mellitus is associated to early rather than late puberty. Results of a prospective longitudinal study. *Eur. J. Pediatr.* 153(6), 403–408 (1994).

41 Gallego PH, Bulsara MK, Frazer F, Lafferty AR, Davis EA, Jones TW. Prevalence and risk factors for microalbuminuria in a population-based sample of children and adolescents with T1DM in Western Australia. *Pediatr. Diabetes* 7(3), 165–172 (2006).

42 Barkai L, Vamosi I, Lukacs K. Enhanced progression of urinary albumin excretion in IDDM during puberty. *Diabetes Care* 21(6), 1019–1023 (1998).

43 Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset Type 1 diabetes: a population-based study in northern Sweden. *Diabetes Care* 27(4), 955–962 (2004).

44 Hovind P, Tarnow L, Rossing P *et al.* Predictors for the development of microalbuminuria and macroalbuminuria in patients with Type 1 diabetes: inception cohort study. *BMJ* 328(7448), 1105 (2004).

45 Gorman D, Sochett E, Daneman D. The natural history of microalbuminuria in adolescents with Type 1 diabetes. *J. Pediatr.* 134(3), 333–337 (1999).

46 Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in Type 1 diabetes. *N. Engl. J. Med.* 348(23), 2285–2293 (2003).

47 Schultz CJ, Amin R, Dunger DB. Markers of microvascular complications in insulin dependent diabetes. *Arch. Dis. Child.* 87(1), 10–12 (2002).

48 Lane PH. Diabetic kidney disease: impact of puberty. *Am. J. Physiol. Renal Physiol.* 283(4), F589–F600 (2002).

49 Dunger DB. Diabetes in puberty. *Arch. Dis. Child.* 67(5), 569–570 (1992).

50 Danne T, Mortensen HB, Hougaard P *et al.* Persistent differences among centers over 3 years in glycemic control and hypoglycemia in a study of 3,805 children and adolescents with Type 1 diabetes from the Hvidore Study Group. *Diabetes Care* 24(8), 1342–1347 (2001).

51 Petitti DB, Klingensmith GJ, Bell RA *et al.* Glycemic control in youth with diabetes: the SEARCH for diabetes in Youth Study. *J. Pediatr.* 155(5), 668–672 (2009).

52 Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J. Pediatr.* 125(2), 177–188 (1994).

■■ **Intensive diabetes management delays the onset and slows the progression of diabetic retinopathy and nephropathy when initiated in adolescents with Type 1 diabetes.**

53 Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J. Good glycemic control remains crucial in prevention of late diabetic complications – the Linkoping Diabetes Complications Study. *Pediatr. Diabetes* 10(3), 168–176 (2009).

54 Caprio S, Plewe G, Diamond MP *et al.* Increased insulin secretion in puberty: a compensatory response to reductions in insulin sensitivity. *J. Pediatr.* 114(6), 963–967 (1989).

55 Amin R, Schultz C, Ong K *et al.* Low IGF-I and elevated testosterone during puberty in subjects with Type 1 diabetes developing microalbuminuria in comparison to normoalbuminuric control subjects: the Oxford Regional Prospective Study. *Diabetes Care* 26(5), 1456–1461 (2003).

56 Marcovecchio ML, Dalton RN, Schwarze CP *et al.* Ambulatory blood pressure measurements are related to albumin excretion and are predictive for risk of microalbuminuria in young people with Type 1 diabetes. *Diabetologia* 52(6), 1173–1181 (2009).

57 Marcovecchio ML, Dalton RN, Prevost AT *et al.* Prevalence of abnormal lipid profiles and the relationship with the development of microalbuminuria in adolescents with Type 1 diabetes. *Diabetes Care* 32(4), 658–663 (2009).

58 Marcovecchio ML, Giannini C, Widmer B *et al.* C-reactive protein in relation to the development of microalbuminuria in Type 1 diabetes: the Oxford Regional Prospective Study. *Diabetes Care* 31(5), 974–976 (2008).

59 Masson EA, Macfarlane IA, Priestley CJ, Wallymahmed ME, Flavell HJ. Failure to prevent nicotine addition in young people with diabetes. *Arch. Dis. Child.* 67(1), 100–102 (1992).

60 Chase HP, Garg SK, Marshall G *et al.* Cigarette smoking increases the risk of albuminuria among subjects with Type I diabetes. *JAMA* 265(5), 614–617 (1991).

61 Toeller M, Buyken A, Heitkamp G *et al.* Protein intake and urinary albumin excretion rates in the EURODIAB IDDM Complications Study. *Diabetologia* 40(10), 1219–1226 (1997).

62 Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann. Intern. Med.* 124(7), 627–632 (1996).

63 Schmidt AM, Stern DM. RAGE: a new target for the prevention and treatment of the vascular and inflammatory complications of diabetes. *Trends Endocrinol. Metab.* 11(9), 368–375 (2000).

64 Koschinsky T, He CJ, Mitsuhashi T *et al.* Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc. Natl Acad. Sci. USA* 94(12), 6474–6479 (1997).

65 Borch-Johnsen K, Norgaard K, Hommel E *et al.* Is diabetic nephropathy an inherited complication? *Kidney Int.* 41(4), 719–722 (1992).

66 Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *N. Engl. J. Med.* 320(18), 1161–1165 (1989).

67 Rudberg S, Stattin EL, Dahlquist G. Familial and perinatal risk factors for micro- and macroalbuminuria in young IDDM patients. *Diabetes* 47(7), 1121–1126 (1998).

68 Marcovecchio ML, Tossavainen PH, Acerini CL *et al.* Maternal but not paternal association of ambulatory blood pressure with albumin excretion in young offspring with Type 1 diabetes. *Diabetes Care* 33(2), 366–371 (2010).

69 Susztak K, Sharma K, Schiffer M, McCue P, Ciccone E, Bottinger EP. Genomic strategies for diabetic nephropathy. *J. Am. Soc. Nephrol.* 14(8 Suppl. 3), S271–S278 (2003).

70 Ng DP, Tai BC, Koh D, Tan KW, Chia KS. Angiotensin-I converting enzyme insertion/deletion polymorphism and its association with diabetic nephropathy: a meta-analysis of studies reported between 1994 and 2004 and comprising 14,727 subjects. *Diabetologia* 48(5), 1008–1016 (2005).

71 Pezzolesi MG, Poznik GD, Mychaleckyj JC *et al.* Genome-wide association scan for diabetic nephropathy susceptibility genes in Type 1 diabetes. *Diabetes* 58(6), 1403–1410 (2009).

72 Stehouwer CD. Endothelial dysfunction in diabetic nephropathy: state of the art and potential significance for non-diabetic renal disease. *Nephrol. Dial. Transplant.* 19(4), 778–781 (2004).

73 Allen KV, Walker JD. Microalbuminuria and mortality in long-duration Type 1 diabetes. *Diabetes Care* 26(8), 2389–2391 (2003).

74 Satchell SC, Tooke JE. What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? *Diabetologia* 51(5), 714–725 (2008).

75 Jarvisalo MJ, Raitakari M, Toikka JO *et al.* Endothelial dysfunction and increased arterial intima-media thickness in children with Type 1 diabetes. *Circulation* 109(14), 1750–1755 (2004).

76 Peppa-Patrikiou M, Scordili M, Antoniou A, Giannaki M, Dracopoulou M, Dacou-Voutetakis C. Carotid atherosclerosis in adolescents and young adults with IDDM. Relation to urinary endothelin, albumin, free cortisol, and other factors. *Diabetes Care* 21(6), 1004–1007 (1998).

77 Klausen K, Borch-Johnsen K, Feldt-Rasmussen B *et al.* Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 110(1), 32–35 (2004).

78 Dunger DB, Schwarze CP, Cooper JD *et al.* Can we identify adolescents at high risk for nephropathy before the development of microalbuminuria? *Diabet. Med.* 24(2), 131–136 (2007).

79 Donaghue KC, Chiarelli F, Trotta D, Allgrove J, Dahl-Jorgensen K. ISPAD clinical practice consensus guidelines 2006–2007. Microvascular and macrovascular complications. *Pediatr. Diabetes* 8(3), 163–170 (2007).

■ **These are the most recent guidelines for screening and management of micro- and macrovascular complications in children with Type 1 diabetes.**

80 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N. Engl. J. Med.* 329(14), 977–986 (1993).

81 Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of Type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290(16), 2159–2167 (2003).

82 White NH, Sun W, Cleary PA *et al.* Effect of prior intensive therapy in Type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. *Diabetes* 59(5), 1244–1253 (2010).

83 Holl RW, Swift PG, Mortensen HB *et al.* Insulin injection regimens and metabolic control in an international survey of adolescents with Type 1 diabetes over 3 years: results from the Hvidore study group. *Eur.J. Pediatr.* 162(1), 22–29 (2003).

84 Should all patients with Type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann. Intern. Med.* 134(5), 370–379 (2001).

■■ **In this meta-analysis of 12 trials of angiotensin-converting enzyme inhibitors (ACEIs) in normotensive adults with microalbuminuria, treatment with ACEIs decreased the progression to macroalbuminuria and increased the likelihood of regression to normoalbuminuria.**

85 Lovell HG. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria. *Cochrane Database Syst. Rev.* 1, CD002183 (2001).

86 Mauer M, Zinman B, Gardiner R *et al.* Renal and retinal effects of enalapril and losartan in Type 1 diabetes. *N. Engl. J. Med.* 361(1), 40–51 (2009).

87 Silverstein J, Klingensmith G, Copeland K *et al.* Care of children and adolescents with Type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 28(1), 186–212 (2005).

88 Cook J, Daneman D, Spino M, Sochett E, Perlman K, Balfe JW. Angiotensin converting enzyme inhibitor therapy to decrease microalbuminuria in normotensive children with insulin-dependent diabetes mellitus. *J. Pediatr.* 117(1 Pt 1), 39–45 (1990).

89 Rudberg S, Aperia A, Freyschuss U, Persson B. Enalapril reduces microalbuminuria in young normotensive Type 1 (insulin-dependent) diabetic patients irrespective of its hypotensive effect. *Diabetologia* 33(8), 470–476 (1990).

90 Rudberg S, Osterby R, Bangstad HJ, Dahlquist G, Persson B. Effect of angiotensin converting enzyme inhibitor or β blocker on glomerular structural changes in young microalbuminuric patients with Type I (insulin-dependent) diabetes mellitus. *Diabetologia* 42(5), 589–595 (1999).

91 Yuksel H, Darcan S, Kabasakal C, Cura A, Mir S, Mavi E. Effect of enalapril on proteinuria, phosphaturia, and calciuria in insulin-dependent diabetes. *Pediatr. Nephrol.* 12(8), 648–650 (1998).

92 Edge JA, James T, Shine B. Longitudinal screening of serum lipids in children and adolescents with Type 1 diabetes in a UK clinic population. *Diabet. Med.* 25(8), 942–948 (2008).

93 Maahs DM, Wadwa RP, Mcfann K *et al.* Longitudinal lipid screening and use of lipid-lowering medications in pediatric Type 1 diabetes. *J. Pediatr.* 150(2), 146–150, 150 e1–e2 (2007).

94 Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. *Diabetes Metab.* 26(4), 254–264 (2000).

95 MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 360(9326), 7–22 (2002).

96 Campese VM, Park J. HMG-CoA reductase inhibitors and the kidney. *Kidney Int.* 71(12), 1215–1222 (2007).

97 Athyros VG, Papageorgiou AA, Symeonidis AN *et al.* Early benefit from structured care with atorvastatin in patients with coronary heart disease and diabetes mellitus. *Angiology* 54(6), 679–690 (2003).

98 Keane WF, Kasiske BL, O'Donnell MP, Kim Y. The role of altered lipid metabolism in the progression of renal disease: experimental evidence. *Am. J. Kidney Dis.* 17(5 Suppl. 1), 38–42 (1991).

99 Baigent C, Keech A, Kearney PM *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet* 366(9493), 1267–1278 (2005).

100 Avis HJ, Vissers MN, Stein EA *et al.* A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.* 27(8), 1803–1810 (2007).

101 Arambepola C, Farmer AJ, Perera R, Neil HA. Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Atherosclerosis* 195(2), 339–347 (2007).

102 Vuorio A, Kuoppala J, Kovanen PT *et al.* Statins for children with familial hypercholesterolemia. *Cochrane Database Syst. Rev.* 7, CD006401 (2010).

103 Haller MJ, Stein JM, Shuster JJ *et al.* Pediatric Atorvastatin in Diabetes Trial (PADIT): a pilot study to determine the effect of atorvastatin on arterial stiffness and endothelial function in children with Type 1 diabetes mellitus. *J. Pediatr. Endocrinol. Metab.* 22(1), 65–68 (2009).

104 Adolescent Type 1 Diabetes cardio–renal Intervention Trial Research Group. Adolescent Type 1 Diabetes Cardio–renal Intervention Trial (AdDIT). *BMC Pediatr.* 9, 79 (2009).

■■ **This represents the study protocol of the first trial of ACEIs and statins in adolescents with Type 1 diabetes at risk of developing nephropathy.**

105 Soro-Paavonen A, Forbes JM. Novel therapeutics for diabetic micro- and macrovascular complications. *Curr. Med. Chem.* 13(15), 1777–1788 (2006).

106 Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 54(6), 1615–1625 (2005).

107 Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in Type 1 diabetes: an inception cohort study. *Diabetes* 58(7), 1668–1671 (2009).

■ Website

201 Statins in children with Type 1 diabetes and hypercholesterolemia http://clinicaltrials.gov/ct2/show/NCT01236365 (Accessed 8 April 2011)