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 high-risk adolescents with Type 1 diabetes. In addition, there is growing interest in the development of new interventions targeting specific pathways implicated in DN.

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.

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MANAGEMENT PERSPECTIVE

Importance of reno-protection in adolescents with diabetes and microalbuminuria

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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 [10,16]. 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 [16].

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].

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

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Screening procedure</th>
<th>Population (n)</th>
<th>Years of T1D duration†</th>
<th>MA (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norgaard et al. (1989)</td>
<td>AER, 24 h urine</td>
<td>113</td>
<td>7.7 (4.0)</td>
<td>13</td>
<td>[36]</td>
</tr>
<tr>
<td>Rudberg et al. (1993)</td>
<td>AER, 24 h urine</td>
<td>156</td>
<td>6.9 (3.9)</td>
<td>10.9</td>
<td>[39]</td>
</tr>
<tr>
<td>Janner et al. (1994)</td>
<td>AER, overnight</td>
<td>164</td>
<td>1–12</td>
<td>20</td>
<td>[40]</td>
</tr>
<tr>
<td>Barkai et al. (1998)</td>
<td>AER, 24 h urine</td>
<td>74</td>
<td>3.1 (0.5)</td>
<td>10.8</td>
<td>[42]</td>
</tr>
<tr>
<td>Jones et al. (1998)</td>
<td>ACR, spot urine</td>
<td>233</td>
<td>3.9 (1.8–6.7)</td>
<td>14.5</td>
<td>[38]</td>
</tr>
<tr>
<td>Olsen et al. (2000)</td>
<td>AER, overnight</td>
<td>339</td>
<td>13.2 (8.9–24.5)</td>
<td>9.0</td>
<td>[37]</td>
</tr>
<tr>
<td>Svensson et al. (2004)</td>
<td>AER, overnight</td>
<td>94</td>
<td>11.8 (3.5)</td>
<td>18</td>
<td>[43]</td>
</tr>
<tr>
<td>Gallego et al. (2006)</td>
<td>AER, overnight</td>
<td>955</td>
<td>0.9–21.4</td>
<td>13.4</td>
<td>[45]</td>
</tr>
<tr>
<td>Amin et al. (2008)</td>
<td>ACR, spot urine</td>
<td>527</td>
<td>10.2 (3.2)</td>
<td>26</td>
<td>[11]</td>
</tr>
</tbody>
</table>

† 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

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**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.
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 as well as patients with first degree relatives with hypertension, dyslipidemia, Type 2 diabetes and clusters of these cardiovascular risk factors.

Candidate gene studies have identified several genes potentially associated with DN risk, although the results have not been consistent across different studies. 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. Other candidate genes which have been associated with DN are those encoding lipoproteins (in particular ApoE), aldose reductase and heparan sulfate. A recent genome-wide association study in adults with T1D from the Genetics of Kidneys in Diabetics (GoKinD) cohort has identified 11 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. 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. 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.

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

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. 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. 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.

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. 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.

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). Measurement of urinary albumin excretion is the basis for early detection of microalbuminuria and can be achieved with: 24-h urine collection; overnight

- 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 renoprotective 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
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-1 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 for 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.

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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.

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Papers of special note have been highlighted as:

- of interest
- of considerable interest


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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.


Importance of reno-protection in adolescents with diabetes & microalbuminuria

Management Perspective


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

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


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