REVIEW

Comorbidities and complications: when, how and who to screen and when to treat? Microalbuminuria in adolescents with Type 1 diabetes

M Loredana Marcovecchio[1,2] & David B Dunger*[1]

Practice Points

- ■ Screening
    - − Microalbuminuria, the earliest clinical manifestation of diabetic nephropathy, often develops during adolescence.
    - − Adolescents with Type 1 diabetes should undergo annual screening for microalbuminuria from the age of 9–11 years.
    - − Screening for microalbuminuria should be based on urinary albumin excretion rates in timed urine collections or albumin:creatinine ratios in first morning urine samples.
- ■ Prevention & treatment
    - − Prevention and treatment of microalbuminuria is mainly based on achieving good glycemic control, whereas the efficacy and safety of other interventions (angiotensin-converting enzyme inhibitors and statins) are currently being investigated.

SUMMARY Progressive increases in albumin excretion and microalbuminuria can be detected in young people with childhood-onset Type 1 diabetes during puberty. Risk factors for microalbuminuria during puberty include hyperglycemia, diabetes duration, female gender, high blood pressure and lipid levels, changes in sex hormones, reduced IGF-I levels, together with other, as yet unidentified, genetic and environmental factors. Annual screening for microalbuminuria during puberty is recommended for the early detection of this marker of later diabetes complications. When microalbuminuria is detected, the first treatment strategy is to improve glycemic control, a known modifiable risk factor, whereas the efficacy and safety of additional interventions, such as angiotensin-converting enzyme inhibitors or statins, is not yet established, and are currently being evaluated.

Microalbuminuria in adolescents with Type 1 diabetes

Abnormal urinary albumin excretion is a key clinical manifestation of renal involvement in patients with Type 1 diabetes [1]. In the context of diabetes, increased leakage of albumin occurs because of changes in renal glomeruli, characterized by thickening of the glomerular membrane, increased glomerular size, mesangium expansion and effacement of podocyte foot

[1]University Department of Paediatrics & University of Cambridge Metabolic Research Laboratories, Level 8, Box 116 Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, UK
[2]Department of Paediatrics, University of Chieti, Chieti, Italy
*Author for correspondence: Tel.: +44 1223 336886; Fax: +44 1223 336996; dbd25@cam.ac.uk

processes [2]. Loss of albumin and other proteins in the urine appears to also be related to renal tubulo-interstitial alterations, which can occur early during the clinical course of diabetes [3]. Albumin excretion is strongly influenced by glycemic control, with significant increases even occurring during short periods of hyperglycemia [4].

Albumin excretion rates progressively increase during the natural history of diabetic nephropathy. Small increases in albumin excretion within the normal range can be detected at the time of diabetes onset and during the following years. Values of albumin excretion of 20–200 µg/min or 30–300 mg/day, characterize the stage of microalbuminuria. Further increases in albumin excretion lead to proteinuria or macroalbuminuria **(Figure 1)** [1].

Microalbuminuria, a term that is currently being replaced with 'high albuminuria', is an early marker of renal injury and a recognized risk factor for the progression towards more advanced stages of diabetic nephropathy. In addition, studies in adults suggest that microalbuminuria is an independent risk factor for the development of cardiovascular disease [5,6].

Microalbuminuria often develops during puberty, whilst its prevalence during the prepubertal period is generally low [7–10]. The increasing prevalence of microalbuminuria during puberty is due to the influence of hormonal and metabolic changes, as well as poor compliance with treatment [11].

In children and adolescents with Type 1 diabetes, the prevalence of microalbuminuria is approximately 4–20%, based on cross-sectional studies [10,12–20]. Longitudinal studies have reported a prevalence of 14.5 and 24% after a duration of diabetes of 8.5 and 15 years, respectively [7,19]. In the population-based inception cohort of children with Type 1 diabetes of the Oxford Regional Prospective Study (ORPS), the cumulative prevalence of microalbuminuria was 25.7% after 10 years and 50.7% after 19 years from the onset of diabetes [21]. Scant data are available on the progression of microalbuminuria to macroalbuminuria in adolescents with Type 1 diabetes. In the ORPS cohort the progression rate was approximately 13% after 3.2 years from the onset of microalbuminuria [21].

The natural history of microalbuminuria is not always characterized by a progression to more advanced stages of nephropathy, such as proteinuria and renal failure. Recent studies have reported that many cases of microalbuminuria can regress to normoalbuminuria during follow-up. In particular, among adults with Type 1 diabetes, the percentage of regression to normoalbuminuria may be 40–50% [21]. Studies in young people with Type 1 diabetes have shown that regression to normoalbuminuria can also occur in this population. In particular, microalbuminuria is persistent in only 50% of adolescents whereas in the other 40–50%, urinary albumin excretion returns to the normal range 3–10 years following the onset of microalbuminuria [21,22]. Although these data are encouraging, it should be borne in mind that cases of transient or intermittent microalbuminuria can become persistent with longer follow-up. Data from the ORPS cohort suggest that intermittent microalbuminuria is an independent risk factor for progression to macroalbuminuria, similarly to persistent microalbuminuria [21]. In addition, regression to normoalbuminuria does not necessarily mean that there is a parallel regression of renal morphological changes associated with increased albumin excretion [23]. Therefore, renal function should be monitored over time in any patient developing microalbuminuria.

Another important observation has been that, during adolescence, early increases in albumin excretion, within the normal range, already occurs during the first years after diagnosis. This may predict future risk of developing microalbuminuria [24]. In the ORPS cohort, an
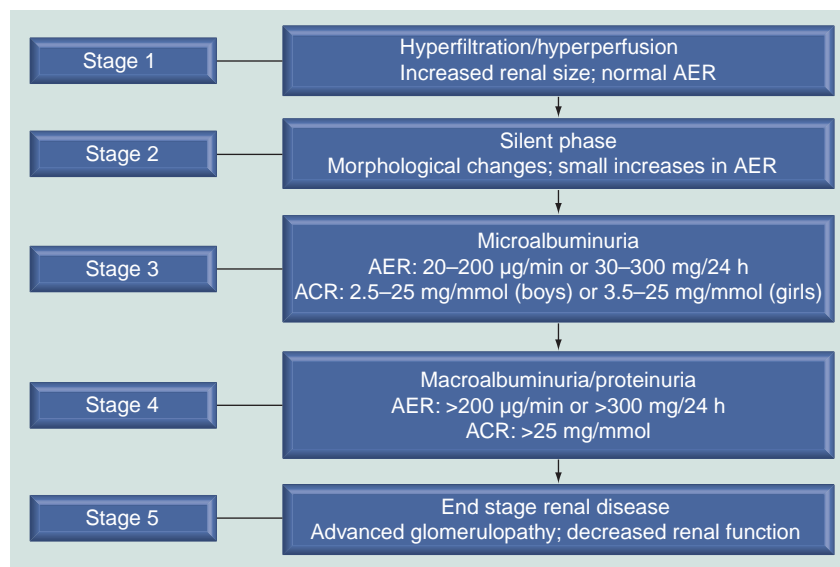

Figure 1. Stages of diabetic nephropathy.
ACR: Albumin:creatinine ratio; AER: Albumin excretion rate.

Stage 1 — Hyperfiltration/hyperperfusion. Increased renal size; normal AER

Stage 2 — Silent phase. Morphological changes; small increases in AER

Stage 3 — Microalbuminuria. AER: 20–200 µg/min or 30–300 mg/24 h. ACR: 2.5–25 mg/mmol (boys) or 3.5–25 mg/mmol (girls)

Stage 4 — Macroalbuminuria/proteinuria. AER: >200 µg/min or >300 mg/24 h. ACR: >25 mg/mmol

Stage 5 — End stage renal disease. Advanced glomerulopathy; decreased renal function

albumin:creatinine ratio (ACR) in the upper tertile of the normal range at the age of 11–15 years, emerged to be a strong and independent predictor for the development of microalbuminuria and macroalbuminuria during follow-up [25]. In line with these findings, adult studies have shown that small increases in albumin excretion, both in the normal and microalbuminuric range, predict not only nephropathy, but also cardiovascular risk [26,27]. Altogether, these data suggest that albumin excretion is a continuous risk factor for renal and cardiovascular complications of Type 1 diabetes, and attention should be paid even to small increases in albumin excretion below the specific range of microalbuminuria.

During puberty, changes in albumin excretion are also paralleled by changes in glomerular filtration rate (GFR). Hyperfiltration is common among adolescents with Type 1 diabetes, where it is associated with renal hypertrophy and can predict the development of microalbuminuria [28]. With the onset of microalbuminuria, or even before this event, GFR tends to decline and without any treatment this could indicate progression to renal failure [28].

Risk factors for microalbuminuria in adolescents with Type 1 diabetes

During adolescence, several factors, both genetic and environmental, can influence the development of microalbuminuria and other vascular complications of diabetes. The characteristic hormonal and metabolic milieu of puberty makes this population particularly vulnerable to the effect of the metabolic derangement of diabetes.

Poor glycemic control is a common finding among adolescents with Type 1 diabetes [29–31] and it is closely linked to the development of microalbuminuria and progression to macroalbuminuria [21]. The physiological decrease in insulin sensitivity that occurs during puberty [32], and is more marked in adolescents with Type 1 diabetes compared with their healthy peers [33], contributes to hyperglycemia. Insulin omission to control weight gain can be a common finding among adolescent girls, and can be another contributing factor to poor glycemic control. High HbA1c levels are also independently associated with the risk of progressing to macroalbuminuria, whereas better glycemic control appears to characterize subjects who regress to normoalbuminuria [21].

During pubertal years, several factors other than glycemic control can promote the development of microalbuminuria. Of note is the sexual

dimorphism for complications risk, with a higher percentage of females developing microalbuminuria during puberty, in contrast to the higher risk of males developing microalbuminuria during their adult life [21]. The higher female risk for microalbuminuria [20,21,34] could be due to the increased testosterone levels reported in girls developing this complication [34]. This hypothesis is also supported by animal studies, where sex steroids have been found to be directly implicated in the pathogenesis of diabetic kidney disease [35].

Puberty is characterized by rapid renal growth and glomerular hyperfiltration [36], and these two factors can affect microalbuminuria risk, independently of glycemic control [36,37]. These may be linked to abnormalities in the growth hormone–IGF-I axis, characterized by increased circulating growth hormone levels and decreased IGF-I concentrations, which have been associated with a higher risk for microalbuminuria, mainly in females [34,38]. Short adult stature has also emerged as a risk factor for microalbuminuria, probably reflecting childhood exposure to diabetes, or common pathogenic factors between short stature and risk for vascular complications [39].

In addition, microalbuminuria during adolescence is associated with markers of subclinical inflammation and atherosclerosis, supporting the concept that microalbuminuria is a marker of more generalized endotheliopathy [40]. Abnormalities in blood pressure are associated with risk of microalbuminuria in adolescents with Type 1 diabetes [41,42]. An abnormal decline in night time blood pressure has been found to precede the development of microalbuminuria [41]. Similarly, increased diastolic blood pressure has been shown to predict adolescents who later develop microalbuminuria [42]. Lipid abnormalities are also associated with rates of urinary albumin excretion [43].

Although environmental factors, such as diet, lifestyle and smoking, can also contribute to the risk of developing microalbuminuria [44–46], these are still largely undefined.

Genetic influences represent other important contributing risk factors of microalbuminuria, a highly heritable trait, even in populations without diabetes. The role of genetic factors is supported by the familial clustering of nephropathy, as well as by the observation that some patients develop microalbuminuria independently of glycemic control [47]. In addition, a family history of insulin resistance, hypertension, dyslipidemia and cardiovascular disease appears to be more

common among adolescents developing microalbuminuria, compared with those who remain free of this complication [40]. Although being subject to extensive research, to date no specific genes implicated in diabetic nephropathy have been identified.

When, who & how to screen

Microalbuminuria should be carefully evaluated during adolescence as it is the first manifestation of incipient nephropathy and a key predictor for progression towards more advanced renal damage. Annual screening for microalbuminuria during puberty should allow an early identification of this complication and implementation of intervention to slow its progression and promote regression.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends that screening for microalbuminuria should be performed annually from the age of 11 years in patients with 2 years of diabetes duration, and from the age of 9 years after 5 years of diabetes duration [48]. The American Diabetes Association (ADA) recommends starting annual screening once the child is 10 years old with a diabetes duration of 5 years, and to test more frequently if values are increasing [49]. The decision to start screening for microalbuminuria at approximately the age of 10 years reflects the influence of puberty on the development and progression of this complication. However, although early screening is strongly recommended, there are no data on its long-term effect in reducing complications or prolonging life expectancy.

Screening can be performed with:

- 24-h urine collection

- Timed urine collection (e.g., 4-h or overnight)

- ACR or albumin concentration in a spot early morning urine sample [48,50]

The definition of microalbuminuria differs depending on the method used for screening **(Table 1)**. If a 24-h or a timed urine collection is performed, the standard definition is based on values between 20–200 µg/min or 30–300 mg/l. Values above the upper limit for microalbuminuria are diagnostic of macroalbuminuria/proteinuria. However, 24-h or timed urines are not easy to collect and there may be a lack of accuracy. Assessing ACR in a spot urinary sample is a valid alternative and generally provides accurate information. First voided urine in the morning is preferable owing to diurnal variations in albumin excretion and

postural effects, but if this collection cannot be used, uniformity of timing for different collections in the same individual should be employed [50]. When using ACR, microalbuminuria is defined as values between 2.5–25 mg/mmol in males and 3.5–25 mg/mmol in females, based on the ISPAD guidelines. Different cutoffs for boys and girls are used owing to the well-known sex-related differences in creatinine excretion.

Factors such as exercise, infections, fever and marked hyperglycemia, can influence albumin excretion, as well as kidney diseases or systemic inflammatory diseases. Therefore, all these factors need to be excluded when interpreting elevated albumin excretion. Storage of urines at -20°C can also influence albumin concentrations; therefore, it is preferable to keep them at -70°C or carry out early measurement of fresh samples [51].

Definition of persistent microalbuminuria is based on several consecutive samples, since there is substantial within-subject variation in urinary albumin excretion. Persistent microalbuminuria is usually defined as two out of three abnormal samples collected over a period of 3–6 months [48]. Regular follow-up is important to identify rapid or slow progression to microalbuminuria, as well as cases of regression to normoalbuminuria. Regular longitudinal follow-up of albumin excretion is also important to identify patients with progressive, small increases of urinary albumin excretion within the normal range, which might be a prelude to the development of microalbuminuria [25].

Although urinary albumin excretion is generally the cornerstone for the diagnosis of microalbuminuria and more advanced stages of nephropathy, the evaluation of GFR may also have an important role in identifying alterations in renal function during the early and late stages of diabetic nephropathy [5].

Recently, there has been growing interest in the identification of new biomarkers, which could help define patient risk in terms of renal outcomes. In this context, recent progress in the fields of genomics, proteomics and metabolomics represent a valuable means to characterize new markers that are more sensitive and specific than urinary albumin excretion. In addition, the identification of biomarkers predicting the natural history of microalbuminuria appears to be of paramount importance, as they could allow discerning 'progressors' from 'nonprogressors' and, therefore, the identification of subjects at higher risk who need more intensive treatment strategies. Recently, decreased excretion of renal tubular markers has

been found to be associated with a higher likelihood of regression of microalbuminuria [3]. Future studies are required in this area to improve early detection and predict progression of diabetic kidney disease.

When & how to treat

Achieving a tight glycemic control is the primary goal of any intervention aimed at preventing the development and progression of microalbuminuria and other micro- and macro-vascular complications of diabetes. There is extensive evidence, based on both observational and experimental studies, showing a direct association between HbA1c and complications risk.

The DCCT and the EDIC have been landmark studies in this field, clearly showing a significant reduction in the risk for the development and progression of vascular complications of Type 1 diabetes with improved glycemic control [52,53]. In the DCCT, intensive insulin therapy reduced the occurrence of microalbuminuria by 39% and overt albuminuria by 54%. Remarkably, the DCCT follow-up study, EDIC, highlighted the important phenomenon of 'metabolic memory'; whereby patients who benefited in the past from a better metabolic control continued to be protected from the development of vascular complications many years later. Recently, the 10-year EDIC follow-up data have also shown that in the DCCT adolescent cohort, this metabolic memory wore off in the long term, mainly due to a worse glycemic control during the earlier DCCT [54]. These findings underline the importance of achieving a good glycemic control during adolescence. However, it also recognizes the difficulties encountered in managing Type 1 diabetes during adolescence, when psychological issues, together with the effect of the physiological insulin resistance [32] and other changes in the hormonal milieu, can represent important obstacles to successful treatment [11]. In addition, intensive insulin therapy is not exempt from negative consequences, being associated with an increased risk of hypoglycemia and weight gain. Taken together, these data suggest that other strategies may need to be implemented to reduce complications risk during adolescence.

In adults with Type 1 diabetes, the presence of microalbuminuria is a general indication for intervention with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers and/or statins [55,56]. These recommendations are based on evidence of a beneficial effect of ACEIs in decreasing the progression

Table 1. Screening methods for the diagnosis of microalbuminuria.

Screening method	Definition of microalbuminuria
24-h or timed collection	Albumin excretion rate of 20–200 µg/min or 30–30 mg/day
Albumin:creatinine ratio in a spot urine sample	2.5–25 mg/mmol in males 3.5–25 mg/mmol in females
Albumin concentration in early morning urine samples	30–300 mg/l

from microalbuminuria to macroalbuminuria, as well as increasing the likelihood of regression to normoalbuminuria [55,57]. Similarly, statin treatment may reduce not only the risk of cardiovascular events [56] but also rates of proteinuria and progression of chronic kidney disease [58–60].

In adolescents with Type 1 diabetes, there is no definitive consensus on the use of ACEIs and/or statins when microalbuminuria is detected. The ADA recommends starting treatment with ACEIs in the presence of persistent microalbuminuria [49]. Similarly, ISPAD suggests using ACEIs or angiotensin receptor blockers when persistent microalbuminuria is detected, in order to prevent progression to proteinuria, even though the lack of evidence in this context is firmly acknowledged [48].

■ Adolescent interventions with ACEIs

A few small studies have assessed the effect of ACEIs on albumin excretion in young people with Type 1 diabetes and persistent microalbuminuria [61–64]. Overall, these studies have confirmed adult findings of a positive effect on urinary albumin excretion. However, these results are based on a small number of subjects, a short follow-up and a lack of a placebo arm in the majority of studies, therefore limiting the possibility of drawing clear conclusions. In addition, there are no data on the potential effect of ACEIs in subjects with high-normal albumin excretion rates, who are at high risk for later development of nephropathy and, potentially, cardiovascular disease [25]. Furthermore, at present there is no clear evidence regarding whether early treatment of microalbuminuria with antihypertensive drugs, such as ACEI, might prevent end-stage renal disease or death due to cardiovascular disease. Therefore, there is a strong need for further long-term studies in this field.

■ Adolescent interventions with statins

Abnormal lipid profiles are often detected in adolescents with Type 1 diabetes [65–67] and they appear to contribute to the increased risk

of endothelial dysfunction, as well as of micro-albuminuria [58]. However, there is no clear guidance on the role of statin treatment in children and adolescents with Type 1 diabetes and increased albumin excretion and, thus, their use has been limited [65,66]. Management of dyslipidemia in pediatric patients relies on the results of trials conducted in adults [68] and in children with familial hypercholesterolemia [69–71]. However, it is of utmost importance to assess the long-term efficacy and safety of statins in young people with Type 1 diabetes.

■ AdDIT

The efficacy of ACEIs and statins in high-risk adolescents with Type 1 diabetes is currently being investigated by the AdDIT, a multicenter, multinational study involving centers in the UK, Canada and Australia [72]. Five hundred high-risk adolescents (aged 10–16 years), defined on the basis of their albumin excretion in the upper tertile of the normal range, are randomized to receive either ACEIs (quinapril), statins (atorvastatin), combination therapy or placebo for 3–4 years. The primary study end point is to assess variations in albumin excretion associated with treatments. Secondary study end points include changes in cardiovascular and renal function markers, retinopathy, quality of life, together with an assessment of compliance with treatment and potential health economic benefits. AdDIT will provide key data on the potential renal and cardiovascular protective effects of ACEI 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 nephropathy and cardiovascular disease.

Conclusion

Early longitudinal changes in albumin excretion and the development of microalbuminuria are often detected in adolescents with Type 1 diabetes. Early identification of adolescents at risk of this complication can allow the implementation of early interventions. Therefore, annual screening for microalbuminuria is strongly recommended during adolescence. At present, achieving a good glycemic control is the main primary prevention and treatment strategy in adolescents with Type 1 diabetes and microalbuminuria.

Future perspective

Over the coming years, ongoing and future studies will allow a better understanding of the potential beneficial effects of other interventions (e.g., angiotensin-converting enzyme and statins) in adolescents with Type 1 diabetes and increased albumin excretion. In addition, future research will hopefully lead to the development of new reliable markers of renal function, which could be useful in clinical practice for early identification of renal damage. This could guide screening programs and the early implementation of preventive and treatment strategies.

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