Albuminuria in children

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Current Opinion in Nephrology and Hypertension 2009, 18:246–251

Purpose of review

Albuminuria is a marker of present and future cardiovascular and renal morbidity, and mortality, in adults. Because the roots of these diseases extend back into childhood, assessment of albuminuria has become relevant to child and adolescent clinical care.

Recent findings

Normal levels of albumin excretion in children are well below the cut-off for microalbuminuria. In healthy children, albuminuria relates to fasting insulin, but not blood pressure, BMI, lipid levels, fasting glucose, or insulin resistance. In obese children, albuminuria relates to multiple measures of insulin resistance. In children with type 1 diabetes, hemoglobin A1c seems to be the most consistent clinical predictor of microalbuminuria although multiple mechanisms seem to be involved, including genetic polymorphisms. Children with type 2 diabetes and hypertension already exhibit microalbuminuria.

Summary

When considering the population as a whole, children make ideal subjects in which to study the natural history of albuminuria given their relative lack of multiple morbidities commonly seen in adults. The unfortunate rise in 'adult' diseases in the pediatric age group makes this especially relevant. There is a need for longitudinal studies examining predictors of elevated urinary albumin levels as well as potential treatment strategies.

Keywords

albuminuria, children, epidemiology

Curr Opin Nephrol Hypertens 18:246–251

1062-4821

Introduction

Measurement of urinary albumin has become of increasing clinical interest in childhood because of recognition that the roots of adult cardiovascular and related diseases extend back into the first two decades of life. Historically, the focus has been on microalbuminuria (usually defined as albumin excretion 20–200 μg/min or 30–300 mg/g creatinine) as a predictor of future morbidity in diabetic populations [1–4]. However it is now widely accepted that microalbuminuria predicts not only renal disease but also cardiovascular disease in apparently healthy people [5], in the general population [6], and in those with hypertension [7]. Furthermore, the degree of albuminuria is a continuous variable (like blood pressure) with levels, even within the 'normal' range, predictive of future adverse events [8,9]. Albuminuria is believed to represent the integrated status of endothelial disease and function [10,11] in vascular beds, such as coronary or cerebral, as reflected by the renal glomerular endothelium. Evidence of abnormal endothelial structure and function has been found in hypertensive [12] and obese children [13]. Thus, it makes sense to suggest that the earliest stages of microalbuminuria may be found in children.

The study of albuminuria in children prior to the onset of overt adult clinical disease also is attractive for other reasons. Firstly, it can be difficult to determine etiologic or independent relations between albuminuria and other risk factors in adults who have longstanding, chronic multiple morbidities. Children provide a population largely free of significant disease burden, allowing assessment of predictors of albuminuria or factors associated with the prognostic significance of albuminuria. Secondly, the childhood obesity epidemic has been accompanied by increases in hypertension, type 2 diabetes, obstructive sleep apnea, and the metabolic syndrome. Because albuminuria has prognostic significance in these diseases, its study in children is increasingly relevant.

Albuminuria in healthy children

Although there have been large population-based studies defining normal levels and correlates of albumin excretion in adults, there have been fewer studies in children (see Table 1), and they have tended to measure overnight albumin excretion rate (AER) as opposed to albumin/creatinine ratios (ACRs) [14–20]. In general, mean values for AER range between 2 and 6 μg/min,

Table 1 Summary of studies measuring AER in normal children[†]

Site (reference)	*N*	Age (years)	AER mean (95th percentile)	Correlates
England [16]	374	4–16	24 h: Male: 6.64 mg/24 h/1.73 m^2 (26.0) Female: 8.30 mg/24 h/1.73 m^2 (40.5) Overnight: Male: 2.77 μg/min/1.73 m^2 (9.89) Female: 2.98 μg/min/1.73 m^2 (10.1)	Age, sex (24 h collection)
USA [17]	41	18–21	Not reported (7.6 μg/min)	ND
Norway [14]	150	10–18.5	Overall: 4.7 μg/min (15.1) Age < 13 years: 3.7 μg/min (13.3) Age > 13 years: 5.8 μg/min (20.4)	Tanner stage, age (males only)
Australia [15]	690	8–15	2.3 μg/min* (7.2 μg/min)	ND
Spain [19]	2224	2–18	<6 years: 2.3 μg/min (4.5) 6–9 years: 2.6 μg/min (4.5) 10–12 years: 3.1 μg/min (6.0) 13–15 years: 3.4 μg/min (6.4) 16–18 years: 3.3 μg/min (6.3)	Age, height, weight, BSA
England [20]	528	4–16	Male: 0.98–4.17 μg/min (4.57–19.95) Female: 0.79–5.13 μg/min (3.72–28.18)	Age, Tanner stage, height, weight
Italy [18]	281	7.5–18	Male: 2.3 μg/min* (6.1 μg.min) Female: 2.4 μg/min* (8.2 μg/min)	None
USA [23]	534	9–17	W: 0.16 mg/h B: 0.25 mg/h H: 0.40 mg/h O: 0.18 mg/h Male: 0.19 mg/h Female: 0.21 mg/h	ND
USA [21••]	354	11–17	4.0 μg/min (20.8)	Fasting insulin

AER, albumin excretion rate; B, Black race; BSA, body surface area; H, Hispanic; ND, not done; O, other race; W, White race.
[†] All results are from overnight timed collections, except as noted.
* Median.

and there is a slight increase with age until adolescence. The 95th percentile of AER distribution is more variable, ranging from 4.5 to 28 μg/min. AER increases from Tanner stage 1 to Tanner stage 3 and then remains stable [21••]. Much less work has been done to define the normal range of ACR in children (see Table 2), although the mean seems to fall between 8 and 10 mg/g in children older than 6 years.

Racial differences in albuminuria have been found in the pediatric population. In a cross-sectional study of 317 adolescents aged 15–18, the AER in daytime timed collections was higher in African–Americans than in Whites. African–American women had the highest AER, and a significant relation between systolic blood pressure (SBP) and AER was present in African–American men [22••]. Unpublished data from our Minneapolis cohort of 69 African–Americans and 285 Whites also support a racial difference in AER with African–Americans excreting higher levels than Whites (4.70 μg/min vs. 3.33 μg/min, $P = 0.004$), even after adjustment for BMI. In contrast, a 5 year longitudinal study of 534 children (62% Whites,

Table 2 Summary of studies measuring ACR (mg/g) in normal children

Reference	Age (years)	ACR mean (95th percentile)		Correlates
[19]	<6	Male: 12.3* (19.1)	Female: 11.9 (18.0)	None
	6–9	8.6 (17.1)	9.7 (16.5)	
	10–12	9.9 (14.3)	8.9 (14.7)	
	13–15	8.3 (15.8)	8.6 (13.8)	
	16–18	6.4 (13.45)	6.5 (12.9)	
[23]	9–17	Male: 7.4	Female: 9.6	ND
		W: 8.51		
		B: 8.87		
		H: 8.55		
		O: 7.87		
[14]	<13	8.8 (26.3)		Tanner (females), age (females)
	>13	9.6 (32.5)		

ACR, albumin/creatinine ratio; B, Black race; H, Hispanic; ND, not done; O, other race; W, White race.
* Median.

19% African–American, age 7.9 ± 1.4 years at baseline) using mostly spot urine collections found no statistically significant difference between races in AER or ACR; however both were higher in African–Americans and Hispanics than in Whites [23].

Relation of albuminuria to cardiovascular risk factors in childhood

Relations between cardiovascular risk factors and albumin excretion have not been well studied in children. In our cohort of 354 adolescents aged 11–17 [21••] AER was not significantly correlated with SBP, BMI, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) or cholesterol. A unique aspect of this study was the opportunity to assess the relation of albuminuria to insulin resistance and glucose. The correlation between AER and both fasting glucose and insulin resistance was not significant, but AER was significantly correlated with fasting insulin ($r = 0.09$, $P = 0.03$). Although the latter correlation is relatively weak, the significance may be an indicator of an early association between insulin metabolism and vascular integrity. By multiple linear regression, AER was not related to age, sex, BMI, or systolic blood pressure.

Albuminuria in obese children

The well known relation between obesity and albuminuria in adults also is found in the pediatric population. A study comparing 86 obese children (mean age 13, BMI 30.4) with 79 normal weight children (mean age 13.5, BMI 18.2) found ACR to be higher in the obese group (11.7 mg/g versus 9.0 mg/g, $P = 0.003$) [24]. Within the obese group, ACR was higher in those with fasting hyperinsulinemia, impaired glucose tolerance, or hypercholesterolemia. By correlation analysis, ACR was positively related to fasting glucose ($r = 0.225$, $P < 0.05$) and 2 h glucose during the glucose tolerance test ($r = 0.368$, $P < 0.001$) but not insulin, cholesterol, triglycerides, HDL-C, or blood pressure. A study of 277 obese children (mean age 13, BMI 36) found the prevalence of microalbuminuria to be 10.1% using spot ACR. The individuals with microalbuminuria had significantly higher glucose and insulin levels during an oral glucose tolerance test than the individuals without microalbuminuria [25]. There was no difference in microalbuminuria prevalence between obese individuals with and without the metabolic syndrome in this study; however, another study of obese children did find a higher prevalence in obese children with the metabolic syndrome (37 vs. 20%, $P < 0.05$) [26].

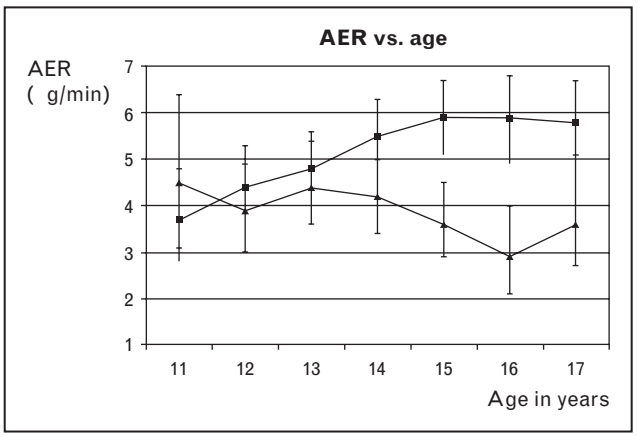
The previous studies all were derived from populations recruited from obesity clinics. More recently, an analysis of the general population using NHANES 1999–2004 data found that the overall prevalence of microalbuminuria was 8.9% in adolescents aged 12–19 years, with a prevalence of obesity (BMI ≥ 95th percentile) of 10.3%. Of interest, the prevalence of microalbuminuria was higher in nonobese than in obese teenagers (8.7 vs. 0.3%, $P = 0.005$). Although the lower percentage of obese teenagers with microalbuminuria is difficult to explain, the substantially higher percentage in obesity specific clinic populations may be related to the greater degree (severity) of obesity. Although the prevalence of microalbuminuria in obese teenagers in the NHANES study was low, there was a significant relation to impaired fasting glucose, HOMA-IR, hypertension, diabetes, and smoking status. In contrast, the presence of microalbuminuria in nonobese teenagers was related only to diabetes status [27••]. These studies may suggest that glucose or insulin metabolism mediate the relation between obesity and albuminuria.

Albuminuria in children with diabetes

As in the adult population, albuminuria in diabetic children has been shown to predict the development of diabetic nephropathy. The Oxford Regional Prospective Study of Childhood Diabetes (ORPS) recently examined levels of albuminuria within the normoalbuminuric range in relation to prediction of future kidney disease in type 1 diabetes mellitus. The relative risk of developing microalbuminuria increased from 1 in individuals in the lowest tertile of normal AER, to 2 and 4 in the middle and high tertiles of normal AER, respectively [28]. It has been previously shown in a cohort study of adolescents with type 1 diabetes mellitus that levels of microalbuminuria may vary within patients and may totally regress to normal [29]. In a second study from ORPS, patients were classified into three microalbuminuria phenotypes: persistent microalbuminuria (microalbuminuria at each clinic assessment); intermittent microalbuminuria (microalbuminuria at a clinic visit followed by a period of normal albumin excretion and then a return to microalbuminuria); or transient microalbuminuria (microalbuminuria followed by sustained normal albumin excretion). In this cohort female sex and hemoglobin A1c (A1c), but not blood pressure, smoking, or age at diagnosis, were positive predictors of microalbuminuria. After 10 years of follow-up, 135 (26%) individuals had microalbuminuria (65 persistent microalbuminuria, 17 intermittent microalbuminuria, 53 transient microalbuminuria). Diabetes duration and mean A1c were highest in the persistent microalbuminuria group. The development of overt proteinuria was predicted by persistent or intermittent microalbuminuria and by A1c but not by sex, blood pressure, smoking or age at diagnosis [30•].

Studies by our group have found that mean AER in a cohort of adolescents with type 1 diabetes mellitus,

Figure 1 Mean AER adjusted for sex, visit, age, SBP and BMI



Slope for healthy cohort (triangles) = −0.04, P = NS different from zero. Slope for T1DM (squares) = 0.04, P = 0.03. The slopes are significantly different from each other: P = 0.007. AER, albumin excretion rate; BMI, body mass index; SBP, systolic blood pressure.

although in the normal range, exceeds that of healthy adolescents (5.0 μg/min vs. 4.0 μg/min, $P = 0.01$) (Fig. 1) [21••], despite the young age of the patients with diabetes (mean age 13.5 years) and short diabetes duration (6.9 years). Predictors of AER in these teenagers with diabetes were BMI, SBP, Tanner stage, and A1c. A significant increase in AER over time was observed in the adolescents with diabetes of duration greater than the cohort's median duration (5.8 years), whereas there was no significant increase in those with diabetes of duration less than 5.8 years.

Among the multiple mechanisms in the pathogenesis of diabetic nephropathy is an association with advanced glycosylation end products (AGE) [31], which accumulate in patients with diabetes and have been linked to target organ damage [32]. Plantar fascia thickness has been used as an estimate of AGE in adults because direct measurement of AGE is clinically difficult. A recent report using plantar fascia thickness in over 300 teenagers with type 1 diabetes mellitus found that abnormally thickened plantar fascia at baseline predicted the development of elevated AER (defined as greater than 5 μg/min), retinopathy, and nerve abnormalities 3 years later [33].

It has been suggested that there are genetic predispositions to the development of diabetic nephropathy [34,35]. Folate metabolism has been related to endothelial dysfunction [36], which, in turn, precedes the development of microalbuminuria in type 1 diabetes mellitus [37,38]. Methylenetetrahydrofolate reductase (MTRR) and methionine synthase reductase gene polymorphisms in type 1 diabetes mellitus were examined recently to determine their relation to diabetic nephropathy. In 476 adolescents with type 1 diabetes mellitus the MTRR GG genotype was less frequent in those who developed elevated AER (AER > 7.5 ug/min). In multiple regression analysis this genotype was associated with a decreased risk of developing either AER more than 7.5 ug/min or AER more than 20 ug/min [39]. Polymorphisms in the renin–angiotensin system genes have also been implicated as predictors of diabetic nephropathy. A recent study of over 450 Australian children with type 1 diabetes mellitus found an association between a polymorphism of the angiotensinogen gene (AGT M235T) and the development of persistent microalbuminuria [40]. This polymorphism also is associated with higher serum levels of angiotensinogen [41] and with essential hypertension [42], a potentially relevant finding, as inhibition of renin–angiotensin system activity is associated with reduced urinary albumin excretion.

Microalbuminuria is often present at diagnosis in adults with type 2 diabetes mellitus, reflecting the association between insulin resistance and albuminuria [43]; however, it is difficult to define the relation between duration of type 2 diabetes mellitus and onset of microalbuminuria, because type 2 diabetes mellitus may exist for years before it is detected. With the rise of the obesity epidemic in children, the prevalence of type 2 diabetes mellitus prior to adulthood has increased, in association with an early development of microalbuminuria. The SEARCH for Diabetes in Youth Study, a multicenter, population-based study in children with type 1 and type 2 diabetes mellitus, recently reported a higher prevalence of ACR of at least 30 μg/mg in type 2 (mean age 16 years, diabetes duration 2 years, prevalence of elevated ACR 22%) than in type 1 diabetes mellitus (mean age 12 years, diabetes duration 3.7 years, prevalence of elevated ACR 9%) [44••]. The prevalence was higher in females and with longer diabetes duration in both groups. Racial minorities had an increased prevalence of elevated ACR, but only in type 2 individuals. A previous study of 26 teenagers with type 2 diabetes mellitus for less than 3 years' duration confirmed the early onset of microalbuminuria by finding an overall prevalence of microalbuminuria of 40%. Individuals with microalbuminuria had higher waist–hip ratios, total cholesterol, LDL-C, estimated glomerular filtration rate, and daytime ambulatory blood pressure parameters [45].

The SEARCH study also investigated the relation of birth weight to the prevalence of microalbuminuria in children with diabetes. Small for gestational age status has been linked to increased microalbuminuria in a cohort of Dutch young adults [46]. However, SEARCH was unable to find a relation between birth weight and ACR [47]. It is not clear whether a relation could not be detected because the presence of diabetes obscured any independent adverse association with birth weight or

because of the relatively young age and duration of diabetes (mean age 12, duration 3.4 years) in these individuals.

Albuminuria in children with other renal conditions

In addition to diabetes, albuminuria has been investigated as a marker of kidney status in other forms of kidney disease. A study of 66 patients with either unilateral renal agenesis or multicystic dysplastic kidney found a prevalence of microalbuminuria (AER $>20\,\mu g/min$) of 23%. Although the presence of microalbuminuria in these patients correlated with BMI ($r=0.47$, $P<0.001$) [48] microalbuminuria was not more prevalent in patients who were small for gestational age than patients who were appropriate for gestation age.

Microalbuminuria has been used as a prognostic marker for the development of chronic renal disease after hemolytic uremic syndrome (HUS). A study of 35 children seen 6–18 months after an episode of diarrhea-positive HUS and again after another 12 months found that the sensitivity of overt proteinuria at baseline in detecting children with kidney problems at follow-up was only 22%. However, this increased to 67% if microalbuminuria was also considered [49]. In another study of 19 children followed for 5 years after an epidemic of HUS resulting from community water contamination, the first morning void ACR was higher in the HUS-positive children than in community controls (20 ± 24 mg/g vs. 8 ± 7 mg/g, $P=0.01$), and the presence of microalbuminuria was more common in the HUS patients (20 vs. 3%, $P<0.05$) [50].

The significant association between albuminuria and essential hypertension in adults is widely recognized [51]. Because of the increasing prevalence of essential hypertension in pediatric practices, this association is relevant to children as well. At the present time few studies have been published. A study of 64 adolescents with essential hypertension (mean age 15.3 years, mean blood pressure 145/87, mean BMI 27.3) found a prevalence of microalbuminuria of 58%. The albumin/creatinine ratio predicted left ventricular mass index (LVMI) independently of BMI, systolic blood pressure, or CRP [52,53]. After 1 year of treatment with hydrochlorothiazide and an angiotensin-converting enzyme inhibitor there was a 45% decrease in the albumin/creatinine ratio, and the change in ACR was predictive of the change in LVMI [52]. In contrast, an earlier study comparing adolescents with normotension, essential hypertension without left ventricular hypertrophy, and essential hypertension with left ventricular hypertrophy found no difference in prevalence of microalbuminuria between groups (0.1, 0.1 and 0%, respectively) [54].

Conclusion

Recent work in pediatrics has defined normal ranges of albumin excretion and its predictors. Abnormal levels of albumin excretion have been found in pediatric subpopulations at cardiovascular risk (i.e. those who are obese or those with diabetes renal disease or hypertension). Much work remains to be done to define the prognostic significance of albuminuria in children, to evaluate treatment strategies that reduce levels of albuminuria and to determine whether such reductions result in clinical benefit.

References and recommended reading

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