Microalbuminuria: causes and implications

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Abstract Management strategies are increasingly focused on tackling the increasing burden of cardiovascular disease worldwide. Microalbuminuria is a powerful predictor of cardiovascular disease and mortality in adults. This holds true in the general adult population but is particularly recognized in those with diabetes, where it identifies those likely to develop progressive atherosclerotic vascular disease and renal impairment. The atherosclerotic process begins in childhood with likely consequences in later life. In-depth understanding of the mechanisms through which microalbuminuria occurs holds promise for designing therapies to arrest its development in the future. Microalbuminuria arises from increased leakage of albumin through the complex glomerular sieve known as the glomerular filtration barrier. This requires changes in the physio-chemical properties of components of this barrier. However, the increased glomerular permeability confirmed in disease does not necessarily correlate with recognized histological changes in the glomerulus, suggesting that perhaps more subtle ultrastructural changes may be relevant. The epidemiology of microalbuminuria reveals a close association between systemic endothelial dysfunction and vascular disease, also implicating glomerular endothelial dysfunction in microalbuminuria. This review discusses the mechanisms of microalbuminuria in disease, particularly the emerging role of the glomerular endothelium and its glycocalyx, and examines its implications for cardiovascular disease in the pediatric population.

Keywords Microalbuminuria · Glomerular filtration barrier · Endothelial dysfunction · Glomerular endothelial cell · Glycocalyx

Introduction

The term ‘microalbuminuria’ is a relative misnomer: it implies ‘small size’ but actually refers to the presence of a relatively ‘small quantity’ of protein in the urine. The term was first used nearly 30 years ago when referring to urinary protein excretion of 30–300 mg per day, which was below the detection threshold of a standard urine dipstick test [1]. Microalbuminuria is now defined as a urine albumin excretion (UAE) between 20 and 200 μg/min or 30 to 300 mg in an overnight or 24-h collection. This range of UAE, although used in the pediatric population, is derived from population studies in adults.

Relevance of microalbuminuria

The importance of microalbuminuria as an independent predictor of progressive renal disease and cardiovascular mortality was thereafter realized in a number of prospective and epidemiological studies particularly in patients with diabetes [2–4] and hypertension [5]. In adults, the link between microalbuminuria, cardiovascular disease, and progressive renal disease is now well established in patients with systemic diseases including diabetes mellitus [6]. Interestingly, microalbuminuria has also emerged to be an important risk factor for the development of cardiovascular disease, and all cause mortality in the general population [7]. Faced with the realization of increasing prevalence of obesity, type 2 diabetes [8], and metabolic syndrome [9] in
children, screening for microalbuminuria seems highly relevant in the pediatric population to detect and prevent cardiovascular disease. In this review, we discuss the current understanding of the pathophysiological mechanism underlying the appearance of increased albumin in the urine. We will review the epidemiological studies in microalbuminuria published regarding children and adolescents and discuss whether the implications for the pediatric population should be regarded as profound as in those for adults. During the discussions, we hold with the established view that increased trans-glomerular passage of albumin is the major source of microalbuminuria [10].

**Methodology used to estimate microalbuminuria**

Clinical studies in adults and children have used 24-h, overnight urine collections and spot urine testing to estimate UAE. Timed urine collections are generally more cumbersome in the pediatric population compared to spot urine testing for estimation for UAE. Simple alternatives include estimation of urine albumin concentration or albumin creatinine ratio estimated from spot urine samples. An albumin-to-creatinine ratio >10 mg/g is diagnostic of microalbuminuria and is shown to be superior to urine albumin concentration and comparable to 24-h urine collections [11, 12]. In adults, the use of the albumin-to-creatinine ratio particularly in the general population has been validated in a number of epidemiological studies [13–15] whereas in children there is relative paucity of such studies [16]. Due to a wider range of variation in UAE in children even within the normal range, it is recommended that the test should be repeated three times annually in diabetic subjects [17]. The mean albumin-to-creatinine ratio in normal children>6 years of age seems to fall between 8 and 10 mg/g (males: 7.5 mg/g; females 9.6 mg/g) [18]. Since, UAE is affected by exercise [19] and time of the day [20], early morning urine sample for the albumin creatinine ratio provides a more sensitive estimate of microalbuminuria. UAE is estimated to be the lowest in children<6 years old, followed by an increase through the adolescent years and a peak at age 15–16 years [16, 18]. Female gender [21], Tanner stage 4–5 of puberty, height, and weight [22] are all factors associated with a higher albumin excretion rate in healthy children. Cross-sectional studies of healthy adolescents have also reported higher albumin excretion in children of African American descent [23].

**Prevalence of microalbuminuria**

Data published from the third National Health and Nutritional Examination Survey (NHANES) [24] reported the prevalence of microalbuminuria in a sample of 22,244 subjects aged 6 to >80 years to be 7.8% (6.1% in males and 9.7% in females) with progressively increasing prevalence in adults >40 years of age. In contrast to the trend in adults, microalbuminuria among 6–19 year-olds (15%) was noted to be almost twofold more prevalent than in 20–39 year-olds adults (7.3%). Also, 6–19-year-old females even had higher prevalence rates than their male counterparts and were comparable to 60–79-year-old women. A further cross-sectional study analyzing the NHANES data for 12–19-year-old adolescents [25] showed that despite the presence of cardiovascular risk factors, overweight teenagers had a lower prevalence rate of microalbuminuria compared to healthy controls. Although low, within the group of obese children with microalbuminuria, there appeared to be significant association with the presence of hypertension, insulin resistance, and diabetes. The reason for the lower prevalence of microalbuminuria in obese teenagers is uncertain but perhaps lower exercise levels in obese teenagers leads to less confounding influence by orthostatic proteinuria [26]. This is opposite to the findings in adults where a number of studies have shown a positive relationship of obesity with microalbuminuria [27, 28]. As expected, microalbuminuria is five-fold more prevalent in children with diabetes [24].

One obvious explanation for the apparent increase in prevalence of microalbuminuria in healthy adolescents is possible confounding influence of orthostatic proteinuria. This has been reported in 20% of adolescents males [29] and increases with teenage years but tends to settle spontaneously after 20 years of age [30]. Orthostatic proteinuria in isolation is a benign condition and is not associated with long-term risk of renal disease [31, 32] but with a potential to mask underlying primary kidney disease [33]. Imaging studies show entrapment of the left renal vein in the fork between the aorta and proximal superior mesenteric artery in most cases of postural proteinuria [34, 35]. This is known as the ‘nutcracker phenomenon’. Partial obstruction of left renal vein in an upright position leads rise in glomerular trans-capillary hydraulic pressure difference and efferent arteriolar resistance leading increased UAE. These hemodynamic changes are partially mediated via the actions of angiotensin II [36]. It is therefore important that orthostatic proteinuria is considered during assessment of children and adolescents with microalbuminuria.

**Relationship between microalbuminuria and cardiovascular risk in children**

In the adult population, there is indeed mounting evidence indicating the relationship between microalbuminuria and
cardiovascular risk [37]. The threshold level, however, to define normality in epidemiological studies is inconsistent. Post-hoc analyses of major clinical trials indicate that an incremental increase in microalbuminuria, even within the normal range is associated with an increased rate of cardiovascular events in adults [3, 5, 38]. This was also confirmed in a recent, meta-analysis of 105,872 subjects, which showed that the hazard ratio for all-cause and cardiovascular mortality (adjusted for age, genetics, history of CV disease, systolic blood pressure, diabetes, smoking, and total cholesterol) rises progressively with increase in UAE well below the microalbuminuria range, increasing to 1.83 with microalbuminuria in subjects with normal renal function [39].

The relationship between microalbuminuria and cardiovascular disease in the pediatric population is not as well studied as in adults [18]. There is a clear association between childhood obesity, elevated blood pressure, and high fasting insulin levels that persists into adulthood [9]. Childhood obesity, high blood pressure, and hyperlipidemia are also risk factors for developing atherosclerosis in young individuals [40]. It is well known that the pre-clinical atherosclerotic process beginning in childhood has the potential to be reversed [41]. Microalbuminuria seems to predict glucose intolerance and metabolic syndrome among obese children [42, 43]. Data from the Oxford Regional Prospective Study (ORPS), a population-based study of children with type 1 diabetes, has shown a significantly higher (50% compared to 34%) prevalence of microalbuminuria in children compared to adults corrected for glycemic control and duration of diabetes [44]. In their longitudinal study, Rademacher and colleagues [45] reported that adolescents with type 1 diabetes have higher UAE compared to normal healthy controls even prior to developing microalbuminuria. Body mass index, systolic blood pressure, and glycemic control predicted the onset of microalbuminuria and its progression was related to the duration of diabetes. In their healthy cohort, UAE was not correlated with an adverse outcome of blood pressure or insulin resistance [45]. In children with type 1 diabetes, endothelial dysfunction is known to coincide with microalbuminuria [46]. Exposure to hyperglycemia in unrecognized type 2 diabetes is also known to cause vascular complications earlier, with significantly higher rates of microalbuminuria at presentation [47, 48]. Interestingly, maternal blood pressure has been shown to predict microalbuminuria in young offspring with diabetes [49]. Type 2 diabetes diagnosed in early youth is associated with worse outcomes leading to higher rates of diabetic nephropathy and death, compared to adult-onset type 2 diabetes or non-diabetics [50]. Microalbuminuria is also a risk factor for development of left ventricular hypertrophy in adolescents with essential hypertension [51].

Overall, the evidence linking microalbuminuria and cardiovascular disease in healthy children is less convincing than in the adult population. Further studies with long-term follow-up of healthy children with microalbuminuria are needed. In obese children, microalbuminuria seems to be a consistent predictor of insulin resistance and hypertension, both of which are strong risks for future cardiovascular disease and death [52]. Again, there are no long-term studies with follow-up into late adult life to provide direct estimates of cardiovascular mortality. In children with diabetes, progression of UAE, (even within the normal range) starts early and is associated with worse cardiovascular outcomes than adults.

Microalbuminuria as a marker of generalized endothelial damage

The vascular endothelium, owing to its strategic location at the interface between flowing blood and other components of vascular wall, is sensitive to mechanical stimuli like shear stress and hormonal stimuli, from vasoactive substances. In response to these varied stimuli, it releases agents that regulate vasomotor function and inflammatory processes, and affect homeostasis. Vasodilator substances produced by the endothelium include nitric oxide (NO), prostacyclin, and C-type natriuretic peptide, which balance the vasoconstricting effect of endothelin-1, angiotensin II, thromboxane A2, and reactive oxygen species (ROS) [53]. Endothelial dysfunction is a well-known contributor to the pathophysiology of cardiovascular disease, including hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, and chronic renal failure [54]. Specific damage of the glomerular endothelial has been implicated in diseases like hemolytic uremic syndrome, pre-eclampsia, and acute ischemic renal injury [55–57].

Alteration in endothelial function is known to precede the development of morphological atherosclerotic changes and has a primary role in the development of a lesion and later clinical complications [58]. This process starts early in childhood [59, 60]. Markers of endothelial dysfunction like increased capillary permeability are known to be present well before the onset of microalbuminuria in type 1 diabetes and also show evidence of progression in association with it [61, 62]. This is difficult to establish in type 2 diabetes as it is often complicated by the presence of other risk factors for vascular disease at presentation and discerning the relationship of hyperglycemia and its sequelae to endothelial dysfunction is difficult. Although microalbuminuria may occur without the evidence of endothelial dysfunction, von Willebrand Factor levels, a marker of endothelial dysfunction, can predict its develop-
The link between endothelial dysfunction and microalbuminuria in type 1 diabetes seems to be important in predicting the development of diabetic nephropathy and susceptibility to micro- and macrovascular disease.

Endothelial dysfunction, as an important antecedent of microalbuminuria in both types of diabetes, provides an attractive explanation for the association between microalbuminuria and vascular disease in diabetes, but is endothelial dysfunction enough to cause a breach in the sieving action of kidney leading to microalbuminuria? Glomerular endothelium is exposed to the same diabetic microenvironment as other endothelia, and it is highly likely that as a result of this exposure, it also becomes dysfunctional. Whether dysfunction of the glomerular endothelium can lead to microalbuminuria will be better understood once we consider the structure and function of the glomerular filtration barrier (GFB) in the next section.

**Glomerular filtration barrier as a complex sieve**

Glomerular capillaries are highly specialized and have high permeability to water (hydraulic conductivity) and small solutes yet, are highly resistant to the escape of macromolecules (like albumin) in urine [64]. These properties are as a result of a unique, three-layer structure (Fig. 1) known as the glomerular filtration barrier (GFB). The GFB on the luminal side of the capillary is comprised of fenestrated glomerular endothelium with its glycocalyx, podocytes (glomerular visceral epithelial cells) on urinary side and glomerular basement membrane (GBM), which is sandwiched between the two cell types [65]. The GFB is primarily responsible for the sieving action of the kidney and in the healthy filters approximately 80 l of plasma every day.

Podocytes, or more specifically their inter-digitating foot processes, form the outer layer of the GFB (Fig. 1). The gaps between adjacent foot processes, known as the ‘filtration slits’ (25–60 nm), are spanned by the slit diaphragm. This is like a molecular scaffold thought to form the most restrictive barrier to water and macromolecular passage [66]. The effect of mutations in podocyte-specific proteins, which form the complex slit diaphragm (e.g., nephrin, mutations result in congenital nephrotic syndrome), indicate the importance of podocytes in restricting the passage of protein [67]. Alterations in

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**Fig. 1** Schematic drawing of components of the glomerular filtration barrier (GFB). Fenestrated glomerular endothelial cells (GEnC) form the luminal side of the sieve and facilitate the high flux of water and small molecules (blue arrows); glomerular basement membrane (GBM) in the middle, and the podocyte foot processes and slit diaphragms on the urinary side. The GEnC (including the fenestrae) are covered by a mesh-like, anionic layer of glycocalyx composed of sialic acid-rich glycoproteins and proteoglycans consisting of core proteins and attached branching glycosaminoglycan chains (mainly heparan sulphate and chondroitin sulphate). The glycosaminoglycan hyaluronan is non-covalently bound to the cell surface and other glycocalyx components. Adsorbed plasma proteins including albumin (yellow dots) and orosomucoid (purple dots) contribute to the high negative charge of the glycocalyx layer. In the healthy, all the three components of the GFB work together to conserve 99.9% of proteins in the capillary lumen.
podocyte ultrastructure, particularly effacement of its foot process, are a common histological abnormality seen in kidney biopsy specimens and is associated with proteinuric kidney diseases including diabetes. Although discrete effacement of the podocyte foot process is an indicator of podocyte injury, it is an unreliable predictor of mild protein excretion [68–70].

The glomerular basement membrane (GBM) is a basal lamina specialized for the structural requirements of the GBM and its filtration function. It is a hydrated meshwork of collagens and laminins to which are attached negatively charged proteoglycans. Traditional concepts have therefore characterized the GBM as a charge-selective barrier. However, more recent analyses indicate that its contribution to the barrier to protein passage is small [65].

Glomerular endothelial cells are adapted to enable the high hydraulic conductivity of the GBM, necessary for filtration. These highly specialized cells have areas of numerous circular transcellular pores 60–80 nm in diameter [65, 71, 72] referred to as fenestrae. Initially these fenestrations were thought of as ‘empty’ and therefore providing little resistance to the passage of proteins. Advances in fixation techniques in electron microscopy have allowed the demonstration of glomerular endothelial glycocalyx which is 200–400 nm in thickness [73]. The glycocalyx covers both fenestral and inter-fenestral domains of the glomerular endothelial cell luminal surface at the interface of the endothelium and the blood flow [74].

The glycocalyx is a dynamic hydrated layer largely composed of glycoproteins and proteoglycans with adsorbed plasma proteins. Proteoglycans, particularly heparan sulphate proteoglycans (HSPG), are largely responsible for the anionic charge characteristics of the glycocalyx. Selective removal of endothelial glycocalyx from coronary vessels increases permeability providing evidence that it constitutes a barrier to macromolecular permeability [75].

Therefore, the presence of a significant glomerular endothelial glycocalyx implies that the glomerular endothelium contributes significantly to the barrier to macromolecules [76, 77]. Experimental data certainly supports this view. Mice treated with glycocalyx-degrading enzymes show reduction in thickness of glomerular endothelial glycocalyx coinciding with increased albumin excretion [78]. In rats, under physiological perfusion conditions, albumin is confined to the glomerular capillary lumen and endothelial fenestrae, implying resistance at the level of glomerular endothelial surface [79]. Endothelial glycocalyx has the correct anatomical distribution (on the surface of endothelial cells including in fenestral openings) to explain this distribution. Reactive oxygen species (ROS), which are known to damage the glycocalyx [80], cause heavy proteinuria without any identifiable structural changes in the GFB using standard electron microscopy techniques [81]. Interestingly, a recent study showed that disruption of glomerular endothelial glycocalyx by induction of ROS can cause proteinuria [82]. Furthermore the ability of human glomerular endothelial cell glycocalyx to form a permeability barrier to macromolecules can also be directly demonstrated in vitro [77].

Structural and functional alterations in GFB associated with microalbuminuria

Even though the glomerular structural changes typical of glomerular diseases like diabetic nephropathy are commonly established by the time microalbuminuria becomes apparent [83], these changes are heterogeneous and can be found in patients without microalbuminuria [70]. Early changes include an increase in glomerular size, thickening of the GBM, expansion of the mesangium, and effacement of podocyte foot processes [70, 83]. The increase in glomerular size is due both to mesangial expansion and to enlargement in glomerular capillaries due to hemodynamic changes. Glomerular structural changes are less marked in type 2 diabetes, with only a third conforming to the classical pattern observed in type 1 diabetes [84].

Effacement of podocyte foot processes is an indicator of podocyte injury, but an unreliable predictor of protein excretion. Surely, proteinuria can occur in complete absence of structural changes in podocytes [85]. This is particularly evident in diabetic microalbuminuria associated with type 2 diabetes where podocyte ultrastructure may be unchanged [86]. Perhaps a likely explanation to reconcile this issue is that the lower proportion of podocytes seen in early disease is due to an increase in mesangial and endothelial cells while podocyte loss occurs at a later stage.

As discussed in the previous section, the hypothesis brought forward is that glomerular endothelial glycocalyx is well placed to play an important role in the pathogenesis of microalbuminuria. There is emerging evidence showing that total systemic glyocalyx volume is reduced by acute hyperglycemia in human subjects [87]. Also, type 1 diabetics have reduced systemic glyocalyx volume, which coincides with the onset of microalbuminuria [88]. GBM thickening alone, without change in composition, does not significantly affect its protein permeability characteristics.

Increased passage of albumin across the GFB in diabetic microalbuminuria can be confirmed in experimental models. Detailed analysis of permeability characteristics of the GFB to molecules of varying size and charge has been used to estimate whether the increased flux of albumin is due to loss of size or charge selectivity of the GFB. In the animal models of diabetes the primary defect seems to be in charge selectivity [89], but in healthy non-diabetic individuals with microalbuminuria, loss of both charge and size selectivity
of the GFB is seen [90]. In both type 1 and type 2 diabetes, defects in charge-selectivity occur earlier than loss of size selectivity [86, 91].

Conclusions

In summary, microalbuminuria in the healthy pediatric population appears to be more prevalent than in young adults. Obesity is an established risk factor for diabetes and metabolic syndrome. However, obese children in the absence of diabetes do not have a higher prevalence of microalbuminuria. Microalbuminuria in non-diabetic and non-obese children is not associated with cardiovascular risk factors. In contrast, in obese children, cardiovascular risk factors such as impaired fasting glucose, insulin resistance, and hypertension are strongly associated with microalbuminuria. This shows that the association between cardiovascular risk factors and microalbuminuria is strongly modified by being overweight.

Unlike the literature in adults, there is a paucity of clinical evidence from longitudinal studies that analyzes the long-term cardiovascular risks in healthy children with microalbuminuria. In diabetic children, the onset and progression of microalbuminuria carries a similar prognostic profile to adults. Microalbuminuria is an indicator of generalized endothelial dysfunction and is regarded as a common pathway of injury to both renal and systemic vascular beds. Progression of microalbuminuria to overt nephropathy is accompanied by predictable structural changes in the glomerulus including loss and damage to the podocyte. The endothelial glycocalyx, apart from acting as a barrier to protein permeability, also protects the endothelium against atherosclerosis [92]. Disturbance of the endothelial glycocalyx as the common process underlying both microalbuminuria and generalized endothelial dysfunction is the most plausible explanation for the profound cardiovascular complications seen in these patients.

The evidence from studies in the pediatric population does not provide clear estimates of cardiovascular risks in relatively healthy children who develop microalbuminuria and clearly further epidemiological studies are necessary to determine its ramifications. Therefore, currently widespread screening in the pediatric population cannot be justified. However, studies so far provide enough evidence to suggest that microalbuminuria in obese children, even in the absence of diabetes, should be taken as seriously as in diabetic children. We recommend that overweight children and parents should be motivated early on and engaged for lifestyle advice (exercise, cessation of smoking, diet) with close monitoring. Evidence from small studies suggests that early intervention with ACE inhibitor therapy is likely to be beneficial [93, 94]. The Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT) is an ongoing multi-center, randomized, double-blind clinical trial that will hopefully report on the use of ACE inhibitor and statin therapy in adolescents with type 1 diabetes and hopefully provide long-term data on cardiovascular outcomes after this intervention [95]. Clinicians should also give careful consideration to progression of UAE rather than being rigid about the threshold for microalbuminuria.

Finally, we hope that with increasing understanding of the molecular mechanisms of microalbuminuria, novel therapies will be designed that prevent and reverse endothelial dysfunction association with microalbuminuria and the resultant cardiovascular disease.

Multiple-choice questions (answers appear following the reference list):

1. In estimating microalbuminuria, the following statement is true:
   a) early morning spot urine for albumin creatinine ratio is the best
   b) 24-h urine collection should always be done when possible
   c) urine protein creatinine ratio is as reliable as the urine albumin creatinine ratio
   d) the standard urine dip stick in the clinic is equally reliable

2. The estimates of prevalence of microalbuminuria in children are:
   a) higher compared to young adults
   b) higher in girls and children from an ethnic background
   c) are likely confounded by the effects of orthostatic proteinuria
   d) all of the above

3. Postural or orthostatic proteinuria
   a) is not a benign condition and indicates progressive kidney disease
   b) more common in obese girls
   c) mostly associated with ‘nutcracker syndrome’
   d) should be managed with ACE inhibitors

4. Generalized endothelial dysfunction is
   a) rarely seen in children
   b) usually precedes the onset of microalbuminuria
   c) is reversed in early adult life
   d) is exclusively seen in diabetic children

5. The glomerular endothelial glycocalyx layer
   a) is a dynamic layer that is produced by glomerular endothelial cells
   b) is vulnerable to damage in systemic diseases
   c) is an important contributor to resistance to protein permeability
   d) all of the above
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Answers:
1. a
2. d
3. c
4. b
5. d