Microalbuminuria in pediatric patients with hypertension

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ABSTRACT

Microalbuminuria in adults has been found to be an early indicator of both renal and systemic vascular disease, as well as significant cardiovascular risk predictor and therapeutic marker. Its role in essential hypertension in adults has also been well established. As diseases like hypertension and obesity have their roots in childhood and are already present in children, influencing the morbidity in adulthood, the role of microalbuminuria has been extensively investigated in children as well. Most investigations have been performed in diabetic children, confirming its clinical significance. There is also enough evidence to suggest that microalbuminuria in obese children should be taken as seriously as in children with diabetes. In children with hypertension rare studies also indicate that its presence identifies hypertensive children with higher risk, although the exact role has to be confirmed in prospective and larger studies. The mechanisms of microalbuminuria onset could be the result of renal damage secondary to hypertension or underlying renal and systemic endothelial dysfunction. Evidence from small intervention studies in children with microalbuminuria also suggests that early intervention with antihypertensive drugs is likely to be beneficial, pointing out the role of microalbuminuria as a therapeutic marker in children too. In addition, we have to stress the importance of follow-up of children with microalbuminuria, confirmation of its persistence and identification of progression. However, longitudinal prospective studies in children, investigating its future cardiovascular risk, are still lacking.

Keywords: Microalbuminuria; Hypertension; Cardiovascular Diseases; Child

1. INTRODUCTION

Hypertension is one of the most important cardiovascular risk factors in both children and adults [1,2]. It is clearly identifiable in childhood, with increasing prevalence due to increased prevalence of childhood obesity [3-5], and associated with hypertension and cardiovascular diseases in adulthood [2,6]. Unfortunately, there is no prospective study, demonstrating direct association of hypertension in childhood with cardiovascular events later in adult life [7]. In recent years early markers of additional cardiovascular risk of these patients have been searched and investigated; among them also found microalbuminuria [8-11].

Microalbuminuria is defined as increased excretion of small quantities of albumin in urine, that is undetectable by standard protein dipstick testing, ranging from 30 to 300 mg per day [12], and is usually diagnosed on the basis of three positive tests over a 3 - 6-month period [13]. It can also be detected in a random spot urine as albumin creatinine ratio [14,15]. Microalbuminuria arises from increased leakage of albumin through the complex glomerular filtration barrier, requiring changes in physicochemical properties of its components that are the consequence of renal damage [16]. It may also reflect impaired vascular function in general [17]. There is also a possibility that level of albumin excretion in individuals represent the vascular state at birth, influenced with both genetic and environmental factors, that is associated with increased or reduced susceptibility to organ damage [17]. Complete understanding of mechanisms through which microalbuminuria occurs will enable development of potential therapies, influencing its onset and regression [16, 17].

It has been shown in adults that microalbuminuria is an early sign of both renal and systemic vascular disease [18,19]. In addition, it is a cardiovascular risk predictor, with effect independent from other risk factors [20]. It is also a sensitive marker for detecting new onset of other
cardiovascular risk factors, such as hypertension and diabetes [21,22]. Moreover, intervention studies have been performed, investigating the effect of microalbuminuria lowering in “healthy” individuals with microalbuminuria, showing therapeutic cardioprotection [23]. The role of microalbuminuria in adult patients with essential hypertension has also been confirmed, its routine measurement in hypertensive patients recommended and in the case of microalbuminuria intensified antihypertensive treatment introduced [24].

We are of the opinion that findings in adults cannot be simply extrapolated to children; therefore there is a need for relevant longitudinal studies to be performed in children and adolescents. Unfortunately, there are no studies yet, investigating the role of microalbuminuria in children as cardiovascular risk factor later in adult life, which is important future task. Anyway, the clinical significance of microalbuminuria in diabetic children has been confirmed [25,26] as well as in some other diseases in children [27-30]. Some small intervention studies have also been conducted, suggesting that early intervention with medications is likely to be beneficial in children too [31,32].

2. MICROALBUMINURIA IN HEALTHY CHILDREN

The prevalence of microalbuminuria in general population was found to be 7.8%, 6.1% in males, and 9.7% in females [33]. It was almost twofold prevalent among 6 - 19-year-old than in 20 - 39-year-old, increasing continuously starting at 40-year-old [33]. Possible explanation for high prevalence in adolescents might be the influence of orthostatic proteinuria [34]. A positive association was found between albumin excretion rate and pubertal developmental stage [35]. In addition, the problem of methodology [14,17], age, height dependency [36] and possible transient elevations [37] have to be mentioned. In a study investigating 3856 children the prevalence of microalbuminuria and macroalbuminuria was 6.5% and 0.6%, respectively, and regression established in 75.4% [37]. Recently, normative data on albumin excretion in healthy adolescents have been published [38]. It has been found that in healthy children, albuminuria relates to fasting insulin, but not to blood pressure, body mass index, lipid levels, fasting glucose, or insulin resistance [38,39].

It has been pointed out that children make ideal subjects to study the natural history of microalbuminuria given their relative lack of multiple morbidities commonly seen in adults [38]. It is very important in the context of results of studies in general population, showing that only slightly raised levels of albumin relates to increased cardiovascular risk [40]. It was also confirmed in recent meta-analysis [41]. Studies, investigating natural course of established microalbuminuria in healthy children are one of the important future task.

3. MICROALBUMINURIA IN DIFFERENT CHILDHOOD DISEASES

Microalbuminuria was most extensively investigated in children with both type 1 and type 2 diabetes [25,26] and its significant role established. In recent years its assessment has been utilized as a screening test for the presence of diabetes-related kidney disease [38]. In one of the studies it was present in 11.2% of type 1 diabetic children and proteinuria in another 6.8% of them [42]. In other studies even higher percentages of both have been found [43]. Significant association between the occurrence of microalbuminuria or proteinuria and poor glucose control has been confirmed [26,43]. In addition to poor glycemic control, clinical markers of insulin resistance were associated with its development [44]. There might be also the influence of some genetic polymorphisms [39]. It has also been found out that children and adolescents with type 1 diabetes with borderline microalbuminuria are more than twice as likely to develop persistent microalbuminuria compared to normoalbuminuria [44]. Natural course of microalbuminuria has also been studied [45]. The prevalence of microalbuminuria and macroalbuminuria in type 2 diabetic children was 18.5% and 2.9%, respectively [37]. This study also found out that microalbuminuria in these patients strongly predicts progression to macroalbuminuria, which supports its annual screening [37]. In another study significantly higher prevalence of microalbuminuria in diabetic children compared to adults was detected, corrected for glycemic control and duration of diabetes [46]. In diabetic patients role of hypertension in diabetes complications such as microalbuminuria were also investigated [47,48]. In one study, maternal blood pressure predicted microalbuminuria in children with diabetes [49]. Some small intervention studies have also been performed and found out that long-lasting treatment with angiotensin-converting enzyme inhibitors seems to be able to induce persistent remission, especially when associated with good metabolic control and high HDL-cholesterol levels [31,50,51]. Ongoing study investigating the role of angiotensin-converting enzyme inhibitors, statins, or combination therapy in type 1 diabetic children will provide important data on the potential renal and cardiovascular protective effects of these drugs [32].

In obese children, microalbuminuria relates to multiple measures of insulin resistance [39]. It predicts glucose intolerance and metabolic syndrome [52] and is associated with cardiovascular risk factors, including hypertension [27]. Its prevalence has been found to be 18% [28].
Obesity is associated with glomerular hyperperfusion and hyperfiltration, leading to obesity-related glomerulopathy [53]. In addition, authors suggested that recurrent states of postprandial glycaemia increase oxidative stress on the vasculature, leading to endothelial dysfunction and microalbuminuria [54]. Whether microalbuminuria predicts cardiovascular diseases in children as it does in adults, remains to be investigated [52]. However, it seems to be a strong predictor of insulin resistance and hypertension, both of which are strong risk factors for future cardiovascular disease and death [55]. Again, there are no long-term follow-up studies into late adulthood to provide direct cardiovascular morbidity and mortality.

Microalbuminuria has also been investigated in numerous nephrologic and other diseases, such as microhaematuria [56], sickle cell anemia [30,57], low-birth weight [58], congenital solitary kidneys [59], orthostatic proteinuria [34], metabolic syndrome [28].

At present, the data suggests that impairment of glucose metabolism, obesity-related proatherosclerotic pathways and the impact of haemodynamic load represent major factors for microalbuminuria development in children [35]. If persistent microalbuminuria is present, further investigation of cardiovascular factors, careful follow-up and intensive lifestyle interventions should be performed [35]. Some authors also proposed screening of children for proteinuria or microalbuminuria, mainly in high-risk groups, as reversibility of organ damage in early stages is possible [53]. However, other authors did not recommend it for general population, but only for high-risk patients, namely overweight and diabetic adolescents [27].

4. MICROALBUMINURIA IN CHILDREN WITH HYPERTENSION

The role of microalbuminuria in adults with hypertension is well established, representing a marker of cardiovascular complications and impaired renal function [24, 60,61]. In children, however, long-term studies are not available, but there are some studies, investigating microalbuminuria in the context of early sign of hypertensive organ damage [8,62]. Possible mechanisms of microalbuminuria onset could be the result of renal damage secondary to hypertension or underlying general, renal and systemic, endothelial dysfunction [24].

The prevalence of microalbuminuria in adult patients with hypertension in large population studies is quite different, varying from 8% to 23% [63,64]. In children, only few studies have been performed and demonstrated, that the prevalence is around 20% [9]. In some other studies even higher prevalence was found out [65]. In one of the studies investigating patients with white coat hypertension, microalbuminuria was not detected, suggesting its low hypertension-related renal risk [20]. The mean value of microalbuminuria in these patients was significantly lower than in patients with essential hypertension [20]. In another study investigating hypertensive target organ damage mean value of microalbuminuria was found to be 29.3 ± 11.4 mg per day [11]. Microalbuminuria was also strongly associated with left ventricular hypertrophy [8]. Some authors demonstrated positive association between family history of hypertension and microalbuminuria, indicating its increased predisposition to it [65]. It has also been shown that hypertension in childhood is associated with microalbuminuria in adulthood in African Americans but not in whites, suggesting that African Americans may be more susceptible to blood pressure-related renal damage than whites [10].

One intervention study with hydrochlorothiazide and angiotensin-converting enzyme inhibitor treatment specifically examined the effects of microalbuminuria lowering on regression of left ventricular hypertrophy in paediatric patients with hypertension and found out that microalbuminuria is its strong predictor, explaining 78% of the left ventricular hypertrophy [66].

Despite numerous studies in adults and studies in paediatric patients microalbuminuria has not been formally recommended as diagnostic marker in hypertensive children [67]. However, in recently published recommendations of the European Society of Hypertension about management of hypertensive children measurement of microalbuminuria has been mentioned as one of the routine tests performed in all hypertensive children, with the remark that its assessment has yet to be fully established [68]. At our department microalbuminuria screening has been performed in previous years and recommended as one of the basic tests of hypertensive organ damage [69]. We are of opinion, like most of the authors that ascertainment of the exact role of microalbuminuria in children with hypertension needs further studies, investigating also microalbuminuria predictors and possible resolution after treatment strategies [39]. Furthermore, long-term prospective studies with follow-up into adulthood are needed to find out its potential direct cardiovascular and renal risk.

5. CONCLUSION

In recent years the role of microalbuminuria in healthy children and in different childhood diseases, including essential hypertension, has been thoroughly investigated. Most investigations have been performed in diabetic children, confirming its clinical significance. The role of microalbuminuria in other high-risk paediatric populations such as hypertensive children has also been suggested, necessitating further confirmation. We also need studies...
investigating microalbuminuria predictors and possible effect of treatment strategies on its resolution. Moreover, prospective studies of healthy children with microalbuminuria are needed to investigate possible role of microalbuminuria in cardiovascular risk in general population. In addition, long-term prospective studies of children with hypertension and other high-risk paediatric populations with follow-up into adulthood are needed to find out its possible direct impact on cardiovascular morbidity and mortality. Finally, significance of microalbuminuria to be used as a target for early treatment and even prevention in children has to be established.

REFERENCES


Galler, A., Haberland, H., Näke, A., Hofer, S., Holder, M., Raile, K. and Holl, R.W. and German Federal Ministry


