Albuminuria in non-primary renal disease: risk marker rather than risk factor

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The impact of an increased urinary albumin excretion in predicting future renal function loss in subjects with diabetes was emphasized already in the 1980s–1990s [1,2]. During these years, the terminology of ‘early diabetic nephropathy’ was introduced to indicate diabetic subjects with microalbuminuria. In this early phase of diabetic nephropathy, the glomerular filtration rate (GFR) is still generally well preserved. Early nephropathy contrasts with the later phase of overt nephropathy in which albuminuria increases into the macroalbuminuria range and the GFR falls below 60 ml/min to finally progress to the level of end-stage renal disease (ESRD). The documentation of the early phase of kidney damage with microalbuminuria but still normal GFR helped to better understand the impact of albuminuria in the loss of renal function in diabetes. Moreover, it led to the demonstration that early intervention by interfering in the renin–angiotensin–aldosterone system (RAAS) [3,4] slows the progression of nephropathy in diabetic patients.

Data on the impact of albuminuria on the progressive decline of renal function in non-diabetic renal disease received attention in the 1990s. The findings from large clinical trials, showing the beneficial effect of lowering albuminuria by using agents that interfere with the RAAS to (partially) prevent progression to ESRD [5,6], gave a boost to the concept of focussing the treatment in renal pa-
patients on albuminuria and not only on blood pressure [7]. These studies often focused on subjects with macroalbuminuria and a GFR in the range of Stage 3 or 4 chronic kidney disease (CKD) which was mostly due to glomerular disorders. Thus far, no trials have shown that the lowering of albuminuria in the early phase (which is the case in microalbuminuria with a GFR >60 ml/min, thus in Stage 1 or 2 CKD) slows the progressive decline of renal function. There is, however, some evidence that ACE inhibition in subjects with non-diabetic microalbuminuria may prevent future cardiovascular events [8].

In this issue of the journal, Lorenzo et al. nicely show the parallel impact of albuminuria on progressive loss of renal function in patients with diabetic and non-diabetic CKD [9]. In an observational cohort study, they followed the loss of GFR in diabetic and non-diabetic patients. Progression was faster in the diabetic compared to the non-diabetic group. The more rapid progression was, however, fully related to the higher albuminuria in the diabetic group: after adjustment for albuminuria, the progression of GFR was comparable to that in the non-diabetic group. This led the authors to conclude that it is not the diabetes itself, but the albuminuria related to the underlying disease that best predicts progressive decline of renal function. Of particular interest is the underlying diagnosis of the CKD in non-diabetic subjects. These were mostly patients with ischaemic or vascular nephropathy. Interestingly, these causes of ESRD currently form the great majority of new ESRD cases and outweigh the number of subjects with ESRD due to the classical glomerular or interstitial renal diseases [10].

How should we understand the conclusion that it is more the level of albuminuria that determines the disease progression rather than the underlying causes of increased urinary albumin loss? At first glimpse, it seems surprising, when one considers that elevated albuminuria, just as diabetes itself, is a risk factor for progressive renal function loss. An elevation of albuminuria should not, however, be seen as a risk factor but rather as evidence of early organ damage that is related to specific risk factors. Besides diabetes, also hypertension, obesity and smoking, as well as other factors, should be mentioned. In other words, microalbuminuria is proof of early damage, i.e. it is a marker of damage. This is illustrated in Figure 1 in which we separate the early from the late consequences of the vascular risk factors for various end organs. These risk factors first result in early signs of vascular damage and lead only after a longer episode to the classical manifestations of end organ damage. The organs suffering from vascular risk factors not only include the heart, peripheral vasculature and brain, but also the kidneys. For the first three organs, clinical manifestations are generally acute with a severe symptomatology. In contrast, the renal end organ damage, in relation to vascular risk factors, is in general relatively asymptomatic. On the other hand, the loss of kidney function is easily and accurately measurable and quantifiable and gradually progressive. The earlier signs of end organ damage may also be evaluated. Much literature focuses on the reliability of coronary calcium scores and left ventricular hypertrophy to diagnose early coronary and cardiac pathology. Similarly, an impaired intima–media thickness or early cognition disorders may indicate early carotid and intra-cerebral damage. With regard to the kidney, evidence is accumulating that microalbuminuria, even in the presence of (near) normal renal function, is an early sign of damage in the (vasculature of the) kidney and is, therefore, the criterion to define Stage 1 and 2 CKD. Moreover, when considering these early markers of damage of the various end organs, microalbuminuria is the cheapest and easiest factor to measure repeatedly during the follow-up of a patient. Of course, aspects of variability in the measurement should be taken into account [11].

When looking into the findings of Lorenzo et al. from this perspective, it is not unexpected that the documentation of early damage will better predict the progressive nature of end organ damage than the risk factor that caused the early damage. When following the same line of reasoning, it is likely that left ventricular hypertrophy better predicts who will develop heart failure than the presence of hypertension and early cognition deficits will better be related to full-blown dementia than the presence of hyperlipidaemia. This illustration may also make it easier to understand why an elevated albuminuria adequately predicts not only future ESRD [12,13], but also future cardiovascular and cerebrovascular events [13,14]. Considering CKD in such a way places nephrology at the heart of vascular medicine; it once more emphasizes that the kidney is actually a mirror of the systemic vasculature.

This nephrology-centred view on vascular medicine cannot, of course, be extrapolated to the classical causes of progressive CKD, such as glomerulonephritic and interstitial disorders. In those cases, it is not the longstanding influence of vascular risk factors but a (mostly acute) specific pathology of the kidney. The knowledge that we can screen for early damage and then follow up and treat the patient while monitoring changes in these markers of end organ damage to optimize treatment may, in the future, help to prevent the progression to ESRD or overt cardiovascular disease in these patients.
Daily online haemodiafiltration: the perfect ‘stimulus package’ to induce growth?

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References


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Failure of statural growth is a hallmark of chronic kidney disease (CKD) in children. Despite major advances in the understanding and therapy of uraemic growth failure, 35% to 50% of children with end-stage renal disease still grow up to become small adults with a final height below the third percentile of the general population [1–4]. In this issue of Nephrology Dialysis Transplantation, Fischbach et al. report impressive catch-up growth in children undergoing an intense daily haemodiafiltration regimen [5]. Apart from defining a potential novel therapeutic strategy for uraemic growth failure, their findings provide food for thought regarding the mechanisms of uraemic growth failure.

Growth failure is the common endpoint of a variety of abnormalities associated with CKD [6]. Protein-energy malnutrition due to anorexia and chronic inflammation is an important cause of impaired growth, particularly in infants and young children who have low nutritional stores and high energy and protein demands to cope with their rapid physiological growth rates [7,8]. Uraemic anorexia may be related to elevated circulating satiety factors such as tryptophan, cholecystokinin, leptin and others [9,10].

Alterations of acid–base, fluid and electrolyte balance are additional factors compromising infant growth, as evidenced by the severe growth failure observed in patients with inherited isolated tubular dysfunctions. Metabolic acidosis has a particularly strong adverse effect on growth, probably via activation of the proteasome–ubiquitin pathway and suppression of endogenous growth hormone (GH) secretion [11,12]. Paediatric nephrologists have learned to provide adequate nutrition, fluids and electrolyte balance and bicarbonate supplements by routine use of nasogastric or gastrostomy tube feeding, resulting in largely normal growth rates even in anuric infants [8].