Screening for microalbuminuria in the general population: a tool to detect subjects at risk for progressive renal failure in an early phase?

Paul E. de Jong, Hans L. Hillege, Sara Joan Pinto-Sietsma and Dick de Zeeuw

Department of Medicine, Division of Nephrology and Department of Clinical Pharmacology, University Hospital Groningen, The Netherlands

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Introduction

The number of patients taken into renal replacement therapy programmes has gradually increased over the last decades. This may partly be due to improvements in dialysis techniques and a better availability of these programmes. However, the pattern of the cause of end-stage renal failure also has been changing over time. In the 1970s glomerulonephritis and pyelonephritis were the most prevalent causes for enrolment into renal replacement programmes. In the last decade the prevalence of these diseases diminished and increasingly end-stage renal failure was due to diabetes, predominantly type II, and renal vascular diseases such as hypertension and generalized atherosclerosis. Several reasons have been put forward to explain this change. First, and possibly most important, the incidence of diseases has been changing. In addition, the age of patients entering end-stage renal failure programmes increased progressively, and patients with atherosclerotic cardiovascular disease survive cardiac events and reach the stage of atherosclerotic end-stage renal failure. Unfortunately, most of these patients are referred to the nephrologist only at a time when renal function is close to the level where dialysis is required, that is when not much can be expected of conservative renoprotective treatments.

The purpose of this commentary is to hypothesize, on the basis of the existing evidence, what future options we have to predict, and thus possibly to prevent, the patient entering end-stage renal disease programmes. We will discuss first what factors are associated with progressive renal function loss in subjects with known renal diseases and secondly evaluate whether the data help us to detect subjects with progressive renal failure but without known renal disease in an early phase.

Factors associated with progressive renal failure in subjects with known pre-existing renal disease

The most well-known factors associated with progressive renal function loss in patients with established renal diseases are high blood pressure [1] and proteinuria [2]. First, it has been well documented that these two factors are associated with a more rapid decline in renal function. Secondly, it has been shown that treatment of high blood pressure [3] and the lowering of the proteinuria [4] are both associated with a less rapid decline in renal function over the years. Some studies also mention hyperlipidaemia to be associated with a more rapid loss of renal function [5]. Finally, genetic factors have also been shown to be involved, thus for example subjects with the ACE DD-genotype progress more rapidly to end-stage renal failure than those without that genotype [6].

Detection of subjects at risk for progressive renal function loss in the general population

The question then is whether subjects with a risk profile for losing renal function more rapidly after having had a renal insult (such as a glomerulonephritis), are also more susceptible to renal function loss without such a specific prior insult? In this respect we can learn much from the experience in diabetes [7]. It has been nicely demonstrated that in the first decade after the diabetes becomes manifest, the glomerular filtration rate (GFR) is increased, while at the same time urinary albumin excretion is still normal. Only after that episode of glomerular hyperfiltration does urinary albumin excretion reach the stage of microalbuminuria. In those years, GFR starts to decrease to ultimately reach the stage of chronic renal failure. In that time, urinary albumin excretion has reached the level of manifest proteinuria. Thus, even before microalbuminuria develops, GFR is elevated [7]. Indeed, both glomerular hyperfiltration [8] and microalbuminuria [9] have been documented to precede the development of progressive glomerulosclerosis.
If glomerular hyperfiltration and microalbuminuria are thus early signs of a later development of progressive renal failure in diabetes, is this sequence of events restricted to the diabetic condition, or does microalbuminuria also occur in the general population? And if so, is it also initially linked to glomerular hyperfiltration and later on to progressive renal failure in the general population?

The PREVEND study

To study the impact of microalbuminuria in the general population we initiated in Groningen the PREVEND (Prevention of Renal and Vascular End-stage Disease) study. In the first phase, the pre-screening phase, we invited all inhabitants of the city of Groningen, aged between 28 and 75 years to take part. Of the 85 000 subjects in that age group about 41 000 (48%) responded and sent in a morning urine sample and filled in a short questionnaire on demographic characteristics, and cardiovascular and renal diseases. We measured albumin concentration in the urine sample. A urinary albumin concentration of 20–200 mg/l was defined as microalbuminuria and a concentration of 10–20 mg/l was defined as high-normal albuminuria. In the overall population of 41 000 subjects, ~7%, had microalbuminuria. Of this group of 3000 subjects with microalbuminuria 75% were not known to have either diabetes or hypertension. Although the prevalence of microalbuminuria was higher in diabetic (16%) and hypertensive (11%) subjects, still 6.6% of subjects without known risk factors associated with microalbuminuria appeared to have microalbuminuria [10]. Interestingly, the percentage of subjects with microalbuminuria was different in men than in women: whereas the percentage was fairly stable over all ages in women, it greatly increased in men over 50 years of age (Figure 1).

To further study the mechanisms of microalbuminuria and to evaluate its impact in the long-term, we performed next a more accurate screening. To that purpose, we invited all subjects with a urinary albumin excretion >10 mg/l in the morning urine, together with a random sample of the remaining population with an albumin excretion <10 mg/l, for a more accurate screening. Altogether 8592 subjects participated in that screening programme. They delivered amongst others, two 24-h urine collections and blood was drawn for measurement of creatinine clearance. Microalbuminuria in these analyses was defined as 30–300 mg/24 h and high-normal albuminuria as 15–30 mg/24 h. As most of the subjects with microalbuminuria were not known to have diabetes and hypertension, what caused microalbuminuria in these subjects? Besides male gender and age, obesity [11] and smoking [12] were found to be important predictors for a higher risk of having microalbuminuria. It is noteworthy that all these factors are also associated with an increased risk for progressive renal function loss.

Microalbuminuria and renal function in the general population

With such a high prevalence of microalbuminuria in the general population, one wonders what the possible association between urinary albumin loss and renal function might be? Figure 2 shows creatinine clearance...
in the four subgroups of 24-h urinary albumin excretion of the PREVEND cohort. Notice that creatinine clearance is elevated in those with high-normal albuminuria (15-30 mg albumin/day), and becomes lower in those with microalbuminuria, to be clearly depressed in those with manifest proteinuria [13]. Although this is a cross-sectional observation, the identified pattern closely mimics that described in diabetes, with glomerular hyperfiltration at the time of only modest rises in albuminuria and a GFR that starts to decrease at the time that there is microalbuminuria. Indeed, in the general population, the relative risk of having glomerular hyperfiltration was found significantly increased in subjects with high-normal albuminuria and microalbuminuria, even after correction for confounders such as age, sex, body mass index, plasma glucose, blood pressure and smoking. Similarly the risk for having an impaired GFR was found increased in the subjects with manifest proteinuria [13].

A similar finding of glomerular hyperfiltration in relation to high-normal albuminuria and microalbuminuria has been described by Cerasola et al. [14] in subjects with essential hypertension. Creatinine clearance was increased in the subjects with an albumin excretion of 11–20 µg/min (comparable with what we called high-normal albuminuria) and in those with an albumin excretion of >20 µg/min (microalbuminuria) as compared with the group with an albumin loss <11 µg/min.

Microalbuminuria versus renal and cardiac prognosis

In diabetes it has been shown clearly that subjects with microalbuminuria have an enhanced risk of developing progressive renal failure compared with subjects with a normal albumin excretion [15]. The same can be concluded for essential hypertension. Bigazzi et al. [16] showed that the fall in GFR in patients with essential hypertension over a mean follow-up period of 7 years was greater in those with microalbuminuria at the start than in those with a normal albumin excretion at the start. In an analysis of those subjects who were followed for >5 years, creatinine clearance fell about twice as much in the subjects with microalbuminuria as in those without microalbuminuria [16]. Data on the change of creatinine clearance in the PREVEND population will be available in the coming 2 years. If indeed the subjects with high-normal albuminuria or with microalbuminuria will have a greater fall in GFR over the years than those with a normal albumin excretion, the impact of microalbuminuria seems to extend from that in patients with diabetes or essential hypertension to the general population.

Microalbuminuria enhances the risk for cardiovascular mortality in diabetic patients [15] and in patients with essential hypertension [16]. We recently showed that in the general population an increased albumin excretion is also associated with increased mortality. The odds ratio for mortality, after adjustment for confounders such as age, sex, blood pressure and glucose, was twice as high in the microalbuminuric group as compared with the normoalbuminuric group [17]. In that respect the data of Borch-Johnsen et al. [18] are also of interest. They showed in a 10-year follow-up of more than 2000 subjects that the presence of microalbuminuria more than doubled the predictive effect of the conventional atherosclerotic risk factors for the development of ischaemic heart disease, such as hypertension and hyperlipidaemia.

Conclusions

Microalbuminuria occurs frequently in the general population, even in subjects without diabetes and hypertension. Moreover, there is evidence that, as in diabetes, already modestly increased levels of albumin excretion are associated with an increased GFR in patients with essential hypertension and in non-diabetic non-hypertensive subjects. Finally, microalbuminuria is associated with an enhanced risk for cardiovascular mortality and probably also with an enhanced risk for progressive renal failure not only in diabetic patients but also in hypertensive and in non-diabetic, non-hypertensive subjects.

This leads us to conclude that screening for microalbuminuria may be an excellent tool, either alone or in combination with screening for hypertension and hypercholesterolaemia, to identify subjects at risk for progressive renal failure. Considering that the screening of the 41,000 subjects in our city was performed with a budget of ~300,000 Euro suggests the effort is worth the cost. A cost-effectiveness study to substantiate this hypothesis is about to start. Again in this respect, we should learn from the ongoing debate in diabetes, concerning the usefulness of screening for microalbuminuria to prevent nephropathy [19,20].

References