Screening for chronic kidney disease can be of help to prevent atherosclerotic end-organ damage

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Abstract
Atherosclerotic damage to the kidney is one of the most prevalent causes of chronic kidney disease and ultimately kidney failure. It frequently coincides with atherosclerotic damage to the heart, the brain and the lower extremities. In fact, the severity of the damage in the various end organs runs in parallel. As damage to the kidney is easy to measure by monitoring albuminuria and eGFR, and as the early phases of kidney damage frequently precede the alarming symptomatology in the heart, brain and peripheral vasculature, we argue that the nephrologist should consider taking the lead in better organizing early detection and management of CKD. The nephrologist can guide the general practitioner and general health care workers to offer better preventive care to the subjects at risk of progressive atherosclerotic end-organ damage.

Keywords: albuminuria; chronic kidney disease; cardiovascular disease; eGFR; screening

Introduction
The end organs that suffer from generalized atherosclerosis are most often quoted to be the heart, the brain and the lower extremities. In the last decades it has become clear that chronic kidney disease (CKD), ultimately leading to kidney failure, is also often due to generalized atherosclerosis. This shows that the kidney is also an important organ susceptible for the detrimental effects of atherosclerosis. On the other hand, the risk for cardiovascular events is greatly increased not only in the late stage of kidney failure, but also in subjects with the earlier phases of CKD. Thus, a vicious circle arises that predisposes to cardiovascular disease and CKD progression, with atherosclerosis as driving force.

At present, most efforts to prevent atherosclerotic end organ damage focus on the risk factors that are argued to underlie progressive atherosclerosis, that is besides smoking and sedentary life style, hypertension, hyperlipidaemia and diabetes. As especially the latter three can be corrected relatively easily by drug treatment, many efforts are undertaken to detect and subsequently treat these underlying abnormalities. The general premise is that treatment of these risk factors will halt progressive vascular damage. It is, however, well known that many patients with hypertension or hyperlipidaemia need to be treated to prevent vascular events in a limited number of subjects. This leads to the question of whether we can better define which subject with a given risk factor will ultimately develop end-organ damage.

In this review we will discuss how generalized atherosclerosis results in parallel detrimental effects to the heart, the brain, the extremities and the kidneys. We will also discuss whether screening for the early phases of CKD, that is screening for elevated albuminuria, may be more efficient than screening for the traditional cardiovascular risk factors as diabetes, hypertension and hyperlipidaemia, if one aims to prevent future atherosclerotic end organ damage.

Early versus late signs of atherosclerotic damage in various end organs

The first overt signs of atherosclerotic end organ damage in the heart, brain and extremities are often acute symptoms with much distress: angina pectoris, transient ischaemic attack and intermittent claudication, respectively (Figure 1) [1]. These acute and alarming symptoms frequently lead to visits to emergency departments and to acute diagnostic and therapeutic interventions. When vascular end-organ damage progresses, it is again acute symptomatology that is observed in the heart, brain and extremities, e.g. myocardial infarction, cerebrovascular accident and arterial ulcers, respectively. Finally, these acute events result in failure of the involved organ, e.g. heart failure, vascular dementia and gangrene.

The acute onset of symptoms of vascular damage to the heart, the brain or the peripheral vessels differs from the absence of clinical symptoms of early atherosclerotic
damage to the kidney. Clinical symptoms associated with kidney damage are limited and develop only at the time that glomerular filtration rate (GFR) decreases to <30 (Stage 4 CKD), or even 15 mL/min/1.73 m² (Stage 5 CKD). However, atherosclerotic damage to the kidney can be detected already at the time that GFR is much better or even normal or supra-normal, that is by measuring albuminuria. It has been shown that with early onset diabetes, initially albuminuria rises into the range of micro-albuminuria, while in those years GFR is found to be supra-normal. Only after that initial rise in albuminuria, does the GFR start to decrease gradually. This sequence of events is well described in Type 1 and Type 2 diabetes mellitus [2, 3]. It has, however, also been described in subjects with hypertension and even in non-diabetic and non-hypertensive subjects: in the first years if there is micro-albuminuria, GFR is frequently supra-normal [4, 5].

While early atherosclerotic end-organ damage is relatively easy to quantify in the kidney, early damage is more difficult to quantify in the heart, brain and peripheral vasculature. Of course, a coronary calcium score may give an estimation of the degree of coronary atherosclerosis, left ventricular hypertrophy on echocardiography measures cardiac load, carotid intima-media thickness reflects the degree of generalized atherosclerosis and ankle brachial index monitors peripheral vascular insufficiency. However, these measures are difficult to use in epidemiological settings, more expensive to perform and therefore also less suitable for screening of vascular status in larger populations, such as subjects without cardiac or cerebral vascular symptoms.

Both the early (rise in albuminuria) and late (fall in GFR) parameter of chronic kidney damage are relatively easy to measure. Albuminuria can be quantified reliably from an albumin over creatinine ratio in a first morning void and estimated GFR (eGFR) from a serum creatinine value [6–10]. When assuming that the process of atherosclerosis occurs more or less in parallel in all end organs, it is tempting to assume that albuminuria and eGFR can be good and easy to achieve parameters to assess the degree of atherosclerotic end organ damage.

**Albuminuria: just a consequence of vascular damage?**

As mentioned above, it has always been reasoned that diabetes may cause an increase in albuminuria. In 30–40% of the subjects with Type 1 diabetes, after a period of 10 years of diabetic milieu, albuminuria will rise [2]. Similarly, in patients with Type 2 diabetes or hypertension, albuminuria may develop, although the prevalence of micro-albuminuria in hypertensives is lower than in diabetics [3, 11]. In the previous century, limited attention was given to the prevalence of increased albuminuria in non-diabetic and non-hypertensive subjects. The PREVEND study demonstrated that in a general population screening, in which subjects between 28 and 75 years delivered a first morning urine sample for measurement of albumin concentration, micro-albuminuria was present in 7.2% of the subjects. Of these subjects with micro-albuminuria 74.9% were not known to have a risk factor like diabetes and/or hypertension, whereas 18.9% were known to have diabetes and 6.2% hypertension [12]. In a second phase of this study, subjects were invited for detailed assessment
isolated micro-albuminuria was studied in the PREVEND study, a prospective, community-based, observational cohort study. Isolated micro-albuminuria was defined as micro-albuminuria (30–300 mg/24 h), in absence of a cardiovascular disease history, hypertension (blood pressure <140/90 mmHg, not using blood pressure-lowering drugs) and diabetes (fasting glucose <7.0 mmol/L, not using glucose-lowering drugs). Subjects with isolated micro-albuminuria had an increased risk for cardiovascular events and mortality (crude hazard ratio 2.23 (1.63–3.07); P < 0.001) compared with subjects without micro-albuminuria, CVD history, hypertension and/or diabetes. The absolute risks were, respectively, 14.3 and 6.6%, after a median follow-up of 10.5 years. This increased risk remained significant after adjustment for age and gender. The relative risk held by isolated micro-albuminuria was similar to the relative risk held by micro-albuminuria in subjects that did have a CVD history, hypertension and/or diabetes. Isolated micro-albuminuria thus indicates a poor prognosis, similar to diabetes or hypertension [19]. These findings are in line with recent data of the CKD Prognosis Consortium. This consortium has previously shown that the risk associated with increased albuminuria independently adds to the risk associated with impaired eGFR for all-cause and cardiovascular mortality [20]. More recently they showed that the relative risk for all cause and cardiovascular mortality and for end-stage renal disease associated with an increased albuminuria is at least as high in normotensive subjects compared with hypertensive subjects and in non-diabetic versus diabetic subjects [21, 22].

Micro-albuminuria preceding diabetes or hypertension

In recent years, also the opposite sequence of events has been described. Subjects with micro-albuminuria, but without the presence of diabetes are more prone to develop future diabetes than subjects without micro-albuminuria [23–25]. A similar finding has also been described for hypertension: subjects with micro-albuminuria in the context of a normal blood pressure are at increased risk to develop hypertension when compared with subjects without micro-albuminuria (Figure 3) [26–28]. These findings raise the question why subjects with micro-albuminuria maybe at risk developing these abnormalities. An explanation could be that the presence of micro-albuminuria reflects vascular endothelial damage [29]. A subject with vascular endothelial damage may be expected to be prone to develop hypertension.

Another explanation can be derived from the work of Brenner et al. [30] and Ritz et al. [31]. They suggested that a congenital reduction in the number of nephrons, either due to genetic factors or intrauterine events, leads to glomerular hypertrophy, intra-glomerular hypertension and tubular malfunction. These processes lead to systemic hypertension, glomerulosclerosis, progressive GFR loss and an increase in albuminuria (Figure 4). Along this line of reasoning, an increase in albuminuria is not the result of hypertension, but the occurrences of both abnormalities are processes that run in parallel. On top of this prenatal programming, there can be a second hit, such as increased sodium intake that accelerates development of progressive CKD and hypertension (Figure 4). In line with this
assumption is the recent finding by Forman et al. [32] who showed that the risk of an increased sodium intake to lead to hypertension is dependent on the presence of micro-albuminuria: a high salt intake was associated with a higher incidence of hypertension only in subjects with micro-albuminuria.

What predicts progressive chronic kidney disease?

Various reports evaluated which factors are associated with progressive CKD. Most of these reports studied the factors associated with loss of GFR in subjects known to have kidney diseases in general or more specifically in IgA nephropathy or diabetic nephropathy [33–36]. Other studies evaluated GFR loss in subjects with known cardiovascular disease or in the general population [37, 38]. In most of these studies it appeared that albuminuria is strongly associated with future GFR loss. Not only is amount of albuminuria associated with outcome, especially progression of albuminuria has been found to be associated with a worse cardiac and renal survival, both in diabetes, vascular disease, as well as in the general population [39–41]. It is therefore important to study which factors relate to a progressive increase in albuminuria.

We recently showed that baseline albuminuria is an important component of progressive albuminuria, outweighing factors such as blood pressure and glucose [42]. Intriguingly, it has been described that subjects even shortly after birth have a certain level of albuminuria, and that this level of albuminuria remains stable during a prolonged period, to increase at older age [43]. These data are in line with the aforementioned theory that prenatal renal programming, reflected by the individual level of
albuminuria, leads to progressive CKD and cardiovascular disease. These data also suggest that screening for albuminuria is more important than screening for cardiovascular risk factors to identify subjects at risk for progressive albuminuria, and perhaps even to identify subjects at risk for progressive renal and cardiovascular disease.

Measuring albuminuria to determine and monitor the effect of cardio-protective drugs

When we have defined albuminuria as a parameter to identify subjects at risk of progressive vascular and renal disease, we should next consider whether lowering of albuminuria is associated with beneficial effects of cardio-protective treatment on cardiac and renal outcome. Various studies in different types of patient groups showed that the beneficial effects of intervention in the renin–angiotensin–aldosterone system, be it with ACE inhibitors or with angiotensin II receptor blockers, to prevent either cardiovascular or renal end points, is dependent on baseline albuminuria. This holds true for patients with glomerular disease, advanced diabetic kidney disease, hypertensive kidney disease, and even in patients with isolated micro-albuminuria [44–49]. It has even been shown in an observational cohort study that the start of an ACEi or ARB as an antihypertensive agent in a general population setting is only effective to prevent CV events, when baseline albuminuria is elevated [50].

It has also been shown in diabetics that not only baseline albuminuria predicts outcome of renoprotective treatment, but also the change in albuminuria has impact. The more albuminuria is lowered, and as a consequence, the lower albuminuria on treatment is, the better the renal prognosis [51]. This effect has been shown again in various types of cohorts and has been shown to hold true for an individual patient in an individual trial, but also on trial level [52]. These findings lead to the hypothesis that these blood pressure-lowering agents should not be titrated only on blood pressure, but could also be titrated on albuminuria. In other words, if blood pressure allows, the dose might still be uptritrated when albuminuria is not yet lowered sufficiently. We hope that randomized controlled trials will definitively prove this concept. The implications of this hypothesis have already been implemented in the treatment of subjects with primary renal diseases and diabetic nephropathy in clinical practice in the hope to improve their renal prognosis.

What are the consequences of these findings for public health care?

Although we traditionally measure albuminuria and eGFR to identify a specific underlying kidney disease, at present many subjects with an elevated albuminuria and/or an impaired eGFR do not have any of the classical kidney diseases, but suffer from atherosclerotic damage to the kidney. As we have argued, damage in the kidney runs in parallel with damage in other end organs. As albuminuria and eGFR are relatively easy to monitor and thus also to follow over time, this places the kidney—and thus the nephrologist—more central in the approach of the patient with generalized atherosclerosis.

What does this mean for the CKD “screening approach”? Our plea for a more central role of the nephrologist does not of course imply that the nephrologist needs to see all patients with an abnormal albuminuria or eGFR who are estimated to form 10–12% of the general population. However, it implies that the nephrologist should be active or even take the lead in educating health care workers to measure albuminuria and eGFR in each individual with risk factors for, or signs of generalized atherosclerosis. One could even consider whether population-based screening for albuminuria and eGFR may not be more effective to detect subjects at risk for CV events, than just screening for CKD in subjects with known presence of CV risk factors. The PREVEND study indeed showed that a general population-based screening on albuminuria should be favoured over a targeted screening of only those with diabetes, hypertension, previous CV events and/or older age [53]. In other words, why should screening for CKD be limited to patients with known cardiovascular risk factors only? These patients are already treated for their cardiovascular risk factors, often with blood pressure-lowering agents, including RAAS inhibitors. Screening for CKD in such subjects will therefore not result in a change in treatment, and consequently, also not in a change in prognosis. We recently showed that indeed subjects detected to have CKD within this group of known increased CV risk were mostly already being treated with antihypertensive drugs, and moreover, do not have a worse renal and CV prognosis than those without CKD [53]. A screening approach that aims to identify subjects with CKD who have CV risk factors present, that are yet unknown at the time of screening, may be of more interest from a public health perspective to decrease the burden of disease.

What do our data mean for the “therapeutic approach” of a patient with CKD? Treatments to prevent progressive atherosclerosis overlap with measures to prevent progressive CKD. Population-wide campaigns to stop smoking, to stimulate a more active life style and to support the maintenance of a healthy diet are important steps to take. Next, on an individual basis, blood pressure lowering is one of the most important measures to prevent further progressive disease. It has become clear that, like in patients with diabetes, also in patients with proven CVD or proven CKD, blood pressure goals should preferably be below 130 systolic and 80 diastolic. Especially in the case of the presence of urinary protein loss, more stringent blood pressure goals and ACE inhibitors have been found superior to conventional treatment [16, 54, 55].

When accepting this kidney-centred view of monitoring and treating atherosclerosis, it is clear that nephrology can bring more health benefits than just preventing kidney failure. When renoprotective treatment is initiated in the patients with CKD, this is nearly always also the treatment of choice to prevent CV events. When aiming to promote screening for CKD, this implies that we should not limit the benefits of screening to the prevention of kidney failure, but that we should also consider the beneficial results with respect to cardiovascular outcome that
will be the result of such screening. These considerations also help explain why most studies to date argue that screening for CKD is not cost-effective. When cost-effectiveness is calculated only with the aim of prevention of kidney failure, the results will be disappointing [56]. However, if we also include the benefits to prevent cardiovascular events that will be achieved as a side effect of CKD screening, such screening programmes are more likely to be cost-effective [56, 57].

**Conclusion**

Atherosclerotic damage to the kidney is one of the most prevalent causes of CKD and ultimately kidney failure. It frequently coincides with atherosclerotic damage to the heart, the brain and the lower extremities. In fact, the severity of the damage in the various end organs runs in parallel. As damage to the kidney is easy to measure by monitoring albuminuria and eGFR, and as the early phases of kidney damage frequently precede the alarming symptomatology in the heart, brain and peripheral vasculature, we argue that the nephrologist should consider taking the lead in better organizing early detection and management of CKD. The nephrologist can guide the general practitioner and general health care workers to offer better preventive care to the subjects at risk for progressive atherosclerotic end organ damage.

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