Renal biomarkers: novel surrogates of small and large vessel disease?
Rhian M. Touyz and Guido Grassi

Journal of Hypertension 2011, 29:1700–1702

Kidney Research Centre, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada and Clinica Medica, Ospedale San Gerardo, Monza (Milan), Department of Prevention and Clinical Medicine, University of Milano-Bicocca, Milan, Italy

See original paper on page 1796

Chronic kidney disease (CKD) is reaching epidemic proportions in the Western world with a growing number of patients requiring dialysis for end-stage renal disease [1]. Patients with CKD, and especially those with diabetes, do not die from renal pathology, but rather from cardiovascular disease, including heart failure, peripheral vascular disease and myocardial infarction [2,3]. In addition, recent evidence indicates that patients with CKD are at greater risk of cerebrovascular disease, including stroke, vascular dementia and cognitive impairment leading to the concept of renocerebrovascular disease [4,5]. With the increasing incidence of hypertension and diabetes and an aging population, it is predicted that CKD and its associated cerebrovascular comorbidities will become a major worldwide public health problem [1,6,7]. Accordingly, there has been much interest in identifying biomarkers that accurately reflect kidney disease early in its development so that preventive measures can be instituted. In current clinical practice, estimated glomerular filtration rate (eGFR), based on urea and creatinine, and microalbuminuria are the biomarkers most commonly used to track progression/regression of kidney disease [8]. Many novel biomarkers have recently been identified using genomic and proteomic approaches, including, urine neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 and podocin, although their utility in predicting risk of kidney injury still awaits further clarification [8].

The recent epidemiological and clinical trends in CKD provoke a number of important questions. First, is CKD a vascular disease that is a continuum of small and large vessel disease of the cardiovascular and cerebrovascular systems? Second, do biomarkers of kidney injury reflect vascular disease in other systems and vice-versa? Finally, do renal biomarkers predict vascular risk beyond the kidney? In the current issue of the journal, Turner et al. [9] address, in part, these complex issues. In particular, they questioned whether biomarkers of kidney disease, specifically increased serum creatinine (SCr) and urine albumin-to-creatinine ratio (UACR), are associated with cerebral small vessel arteriosclerosis, reflected by increased subcortical white matter hyperintensity (WMH) volume on brain MRI, and with peripheral large vessel arteriosclerosis, determined by decreased ankle-brachial index (ABI). The study was performed in a large cohort, comprising both black and white, male and female participants. Using sophisticated statistical analysis, results demonstrate that after age adjustment, increased SCr and UACR correlated with increased WMH volume and with decreased ABI. Age, race, sex, hypertension, diabetes, total cholesterol, and smoking made similar overall contributions to the prediction of kidney and small and large vessel disease. However, contributions that the modifiable risk factors (hypertension, diabetes, total cholesterol, smoking) made to prediction of increased SCr and UACR were disproportionate to their relative contributions to prediction of decreased ABI. Taken together, the authors conclude that CKD detected by increased renal biomarkers (SCr and UACR) primarily reflects small vessel arteriosclerosis, which involves the kidneys. Although the study is not particularly novel, there are a number of strengths that should be highlighted. First, the study group is relatively large comprising multiple racial groups. Second, this is one of few studies that correlate renal biomarkers with cerebral WMH and ABI in the same individual. Third, this study demonstrates important associations between kidney disease and vascular injury in other organs. However, as is the case for most clinical investigations, this study is essentially associative and as such it is not possible to draw conclusions regarding mechanisms.

What is becoming increasingly evident is that the same risk factors that cause stroke and cardiovascular disease also cause CKD [10]. Evidence of small vessel disease in one organ increases the likelihood of finding it in another. For example, small vessel disease in the retina increases the probability of finding it in the brain [11] and individuals with macular degeneration develop cognitive deficits more frequently and have a higher incidence of strokes than patients with other causes of low vision [12–15]. This concept is further supported by the study...
of Turner et al. [9], which demonstrates an association between increased renal biomarkers and evidence of cerebral small vessel disease and peripheral large vessel disease. These data are important because a simple measure of renal function, as is routinely performed in clinical medicine, may shed light not only on kidney well being, but also on vascular status in other target organs of cardiovascular disease, including the brain, heart and peripheral vessels. As such biomarkers of kidney disease could be a window to vascular disease in distant organs. In fact, recent proteomic analysis has revealed distinct markers of vascular disease in patients with CKD [16]. Indeed, it would be very useful to be able to assess the risk of concomitant or predicted stroke, vascular dementia, myocardial infarction, cardiac failure, peripheral vascular disease and other cardiovascular morbidities based on an index of renal function.

The findings of Turner et al. [9], although supporting the above concept in general, do have limitations that warrant further discussion. First, although SCr and UACR are traditionally used as surrogates to monitor CKD progression, increased levels are suggestive of well established kidney disease [8,17]. Few biomarkers reliably reflect early renal damage. Moreover, changes in SCr and UACR may be influenced by factors that alter renal perfusion independently of kidney disease [8]. For example, prerenal factors (dehydration, blood loss, altered vasomotor tone, age-related decreases in renal blood flow) and postrenal factors (obstruction or extravasation of urine to the peritoneal cavity) may cause increases in the renal biomarkers that do not necessarily reflect primary kidney damage. In this context, changes in SCr or eGFR cannot distinguish between prerenal, intrinsic renal or postrenal causes of renal dysfunction. When these biomarkers are increased as a consequence of primary renal injury, they cannot be used to determine the location of that injury (glomerular versus tubular, or the specific tubular segment affected). In glomerular disease, albuminuria may occur as a result of structural injury leading to an increased number of larger nonsize-selective pores, and to partial loss of charge selectivity [18].

Turner et al. suggest that increased SCr and UACR observed in their study are reflective of arteriosclerosis in the kidney, as levels of these biomarkers correlated significantly with indices of arteriosclerosis and vascular damage in small cerebral and large peripheral arteries [9]. However, based on the limitations relating to SCr and UACR and the fact that there are no direct measures by renal vessel structure or function by imaging or functional testing in the study under discussion, it is premature to conclude that CKD detected by increased SCr or UACR primarily reflects small vessel arteriosclerosis involving the kidneys.

Another concern that needs to be addressed relates to the strategies employed to measure small and large vessel arteriosclerosis in the brain (WMH volume) and periphery (ABI). Evidence of increased subcortical WMH volume on brain MRI does not specifically reflect arteriosclerosis of small vessels. MRI is now routinely used to evaluate white matter lesions, which reflects ischemic damage, due to many conditions, besides arteriosclerosis, including aging, angiopathies, leukoencephalopathies andBinswanger’s disease amongst others [18]. The ABI is a simple, inexpensive diagnostic test used to assess peripheral artery disease and not specifically atherosclerosis [19,20]. Many factors can influence ABI, such as aneurysms, nonatherosclerotic stenosis and connective tissue disease. Moreover, the sensitivity and specificity of measurement are influenced by age, comorbidities and race. For example, sensitivity is low in elderly individuals, in patients with diabetes and in blacks [19,20]. Hence, in the study of Turner et al. [9], the presumption that increased WMH volume and decreased ABI definitively reflect arteriosclerosis in small cerebral arteries and in large peripheral vessels, which may reflect arteriosclerosis in small arteries of the kidneys because of the correlations with renal biomarkers, requires reconsideration. Perhaps it would be more appropriate to conclude that generalized vascular disease associates with renal dysfunction that may reflect renal vascular damage. However, the data do not allow us to exclude the putative role of intrinsic kidney damage as a cause of increased SCr and UACR.

In spite of the limitations, the study by Turner et al. [9] highlights the idea that vascular disease in one region may be reflective of processes in another and that the same risk factors that cause stroke and peripheral vascular disease also cause CKD [21,22]. The suggestion that renal biomarkers may be fingerprints of arteriosclerosis in target organs beyond the kidney is provocative and the concept that noninvasive measures of CKD (SCr and UACR) may provide physicians the ability to predict the severity of arteriosclerosis in target organs is attractive. However, before these extrapolations are made much research is still needed before such approaches can be routinely employed in the clinic.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

References


