

Proteinuria, a marker of cardiovascular risks

Introduction

The association between chronic kidney disease (CKD) and cardiovascular disease has long been recognized and current guidelines recommend that patients with CKD be considered to be at particularly high cardiovascular risk.¹ Although often transient and benign, the persistent presence of protein or albumin in the urine has marked clinical significance as an early indicator of underlying renal pathology, preceding tangible decline in renal filtration function. In addition to its role as a marker for CKD risk, it is now widely accepted that proteinuria is an independent predictor of cardiovascular morbidity and mortality across divergent populations.

The presence of CKD is a powerful predictor of adverse clinical outcomes.^{2,3} cardiovascular disease is by far the most common cause of death in dialysis-dependent and renal transplant patients. Only a small minority of the CKD population progress to endstage renal disease requiring renal replacement therapy (RRT), with death prior to RRT being far more common. A 2010 meta-analysis with data for over 1 million subjects reported that stage 3 CKD (eGFR<60mL/minute/1.73m²) was associated with both cardiovascular and all-cause mortality.⁴ In a systematic review of associations between non-dialysis-dependent CKD and mortality, Tonelli et al reported that the absolute risk of death increased exponentially with declining renal function.⁵ Even the earliest, clinically silent stages of CKD have been associated with major cardiovascular disease. In addition to reduced eGFR, ACR and dipstick positive proteinuria have also been associated with graded cardiovascular and all-cause mortality, acting as risk multipliers across all levels of renal function.^{6,7} In a large Canadian study, Hemmelgarn et al found that heavy proteinuria independently increased risk of death, myocardial infarction (MI) and progression of CKD in particular patient groups.⁸

Evidence now suggests that proteinuria has implications for all-cause mortality and cardiovascular outcomes at a general population level, not only in individuals with CKD. Population based cohort studies have shown that multivariable relative risks of cardiovascular disease mortality for proteinuria range from 1.2–2.9.⁹ The Prevention of Renal and Vascular Endstage Disease (PREVEND) study included over 40,000 individuals and found that a 2-fold increase in ACR equated to close to a 30% increase in risk for cardiovascular mortality.¹⁰ Moreover, this relationship is constant across distinct ethnic groups,^{11–13} and in elderly populations.¹⁴ In terms of cardiovascular morbidity, dipstick positive proteinuria and ACR have emerged as predictors of cardiovascular diseases including ischemic heart disease, stroke, and hypertension in the general population, with some sources suggesting that proteinuria is a stronger predictor of outcome than traditional risk factors such as blood pressure and cholesterol.^{15,16} Indeed, the Heart Outcomes Prevention Evaluation (HOPE) study found that proteinuria was associated with adverse outcome independently of traditional cardiovascular risk factors.¹⁷ Furthermore, cardiovascular risk appears to be increased even at levels of urinary protein excretion that are not considered to be pathological,¹⁷ and in fact there is no distinct threshold level that confers increased cardiovascular risk; rather, increasing albuminuria is associated with a graded increase in risk.¹⁸ Proteinuria has also been associated with increased risk of atherosclerotic events affecting the peripheral vasculature. Patients with proteinuria have been shown to have increased risk of incident stroke. A 2010 meta-

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Anuj Maheshwari

Babu Banarasi Das University, India

Correspondence: Anuj Maheshwari, Babu Banarasi Das University, India, Tel +91 9918116016 Email dranuym@gmail.com

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analysis of studies totalling 48,000 participants reported that the presence of Microalbuminuria was associated with a future stroke risk 90% greater than that of normoalbuminuric individuals.¹⁹ The impact of Microalbuminuria was greatest on ischemic stroke incidence in those with a prior history of cerebrovascular disease and found to be relatively modest within the diabetic population.²⁰ a further meta-analysis of the relationship between proteinuria and stroke has suggested that risk rises with degree of urinary protein excretion.^{21,22}

In the hypertensive population, studies suggest that Microalbuminuria confers a 4 times greater risk of subsequent ischemic heart disease than in normoalbuminuric individuals.^{23,24} this effect appears to be independent of conventional atherosclerotic risk factors. In addition, albuminuria has been associated with the presence of left ventricular hypertrophy in patients with hypertension and diabetes.^{25–27} It has also been demonstrated that in individuals with stable underlying coronary artery disease, proteinuria confers increased risks of all-cause and cardiovascular mortality, even at lower levels within the defined “normal range”.^{28–31} This has also been shown in individuals who have recently suffered a coronary event.^{32,33} The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) study showed that macro- rather than Microalbuminuria was a better predictor of mortality in this group.³⁴

Mechanisms underlying cardiovascular consequences of proteinuria

The Steno hypothesis suggested that urinary protein excretion not only reflects localized subclinical renal disease but also a more generalized vascular endothelial dysfunction.³⁵ High-sensitivity troponin T (hs-TnT) as a marker of vascular micro necrosis has been found to independently predict transitions in albuminuria grade.³⁶ Microalbuminuria is also accompanied by a fall in adiponectin levels and elevated C-reactive protein (CRP),³⁷ and there appears to be a significant correlation between degree of proteinuria and CRP level. Evidence has also linked proteinuria with asymmetric dimethylarginine (ADMA), an inflammatory biomarker which causes endothelial dysfunction through inhibition of nitric oxide production.³⁸ Circulating von Willebrand Factor (vWF) antigen is released in greater concentrations in response to endothelial cell damage. Levels of vWF have been shown to be higher in patients with Microalbuminuria compared to control subject.³⁹ Macro vascular endothelial dysfunction assessed by flow-mediated dilatation has been shown to be impaired in individuals with proteinuria. Vascular endothelial growth factor (VEGF) is another interesting potential mechanistic link between

proteinuria and endothelial dysfunction. Use of VEGF-antagonists as angiogenesis inhibitors for the treatment of patients with cancers have been associated with increased incidence of proteinuria and hypertension, an effect which was reversed on withdrawal of therapy.⁴⁰

As well as inflammation and endothelial dysfunction, thrombogenic factors have been implicated as potential mechanisms underlying the relationship between proteinuria and cardiovascular disease. In addition to vWF, soluble vascular cell adhesion molecule, fibrinogen, and tissue plasminogen activator have been found to correlate with urinary albumin excretion.⁴¹ A variety of hemostatic abnormalities have been described in patients with diabetes,⁴² and it has been suggested that high platelet adhesiveness and erythrocyte aggregation demonstrated in diabetic patients with proteinuria could indicate increased thrombosis risk.

Both insulin resistance and proteinuria have been associated with atherogenesis. The Insulin Resistance Atherosclerosis Study involving 982 non-diabetic participants found that Microalbuminuria subjects had lower insulin sensitivity and higher plasma insulin levels compared to normal albumin uric participants, leading the authors to propose that insulin resistance has a role to play in the increased cardiovascular risk conferred by proteinuria. Hyperinsulinemia has been shown to cause renal vasodilatation and increased glomerular filtration rate in rats, with some suggesting that this localized elevated pressure is involved in regulating urinary albumin excretion.²⁹ As well as demonstrating association between insulin resistance and Microalbuminuria, Bianchi et al noted that in patients with essential hypertension, Microalbuminuria was associated with altered lipid profile and an abnormal circadian blood pressure pattern, thus forming part of a cluster with potential to modify cardiovascular risk in these individuals.

Conclusion

The significant burden on health services posed by cardiovascular disease has prompted investigation of prognostic markers and therapeutic targets. There is a clear association between proteinuria and cardiovascular outcomes despite marked heterogeneity in the literature when considering the method of detection used and classification of degree of proteinuria. This association has been demonstrated both in disease population including hypertensives, diabetic patients, and those with CKD, as well as in otherwise healthy individuals. Proteinuria has evolved into a surrogate marker of cardiovascular risk and it seems intuitive that earlier detection and more aggressive intervention may serve to reduce risk in affected individuals. Several publications have considered the cost-effectiveness of population screening. In 2003 Boulware et al concluded that population screening for dipstick proteinuria was not cost-effective in terms of CKD morbidity and mortality unless specifically targeted towards higher risk groups such as hypertensive or elderly patients and done at less frequent intervals. When considering prevention of cardiovascular events, an analysis of the PREVEND-IT study was more favourable. RAAS inhibition, together with control of additional cardiovascular risk factors, remains the mainstay of treatment for individuals with proteinuria. Studies of earlier and more aggressive intervention with two or more RAAS blocking agents have demonstrated reduction in proteinuria but this has not yet translated into reduction in hard clinical cardiovascular endpoints and these studies have also reported a greater degree of side effects and adverse events.

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Conflict of interest

Author declares there is no conflict of interest.

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