Proteinuria
A Link to Understanding Changes in Vascular Compliance?
George Bakris

Hypertension is a well-known risk factor associated with high cardiovascular risk and kidney disease progression. Proteinuria commonly occurs in concert with hypertension in people with chronic kidney disease (CKD). The spectrum of albuminuria, from microalbuminuria (\(>30\) but \(<300\) mg per day) to macroalbuminuria (proteinuria) (\(>300\) mg per day) is associated with a linear increase in risk of cardiovascular events.\(^1\)\(^2\) Microalbuminuria correlates with the magnitude of C-reactive protein (CRP) elevations and has also been associated with a failure of nocturnal drops in arterial pressure, insulin resistance, as well as abnormal vascular responsiveness to a variety of stimuli.\(^3\)\(^-\)\(^7\) Thus, its presence indicates abnormal responses by vascular tissue, perhaps because of underlying inflammatory responses. Together, these data support the concept that microalbuminuria is associated with increased cardiovascular risk and that proteinuria represents even higher cardiovascular risk with high risk for progression to end-stage kidney disease.

Whereas most studies focus on the association between baseline proteinuria and kidney disease progression, others have concentrated on the impact of proteinuria and associated changes in vascular compliance. However, these later studies have focused on microalbuminuria rather than higher levels of proteinuria. In one study of 70 newly diagnosed patients with hypertension demonstrated higher values of carotid-femoral pulse wave velocity (PWV) in those with microalbuminuria. This difference remained statistically significant, even after correction for 24-hour systolic and diastolic blood pressure (BP), and body mass index. Moreover, a tight correlation was found between urinary albumin excretion and carotid-femoral PWV.\(^8\) Similar findings were noted in a comparable study cohort as well as in those with type 1 diabetes,\(^9\)\(^10\) whereas in the EURODIAB Prospective Complications Study, increasing age was associated with increasing pulse pressure, and this association was stronger in the presence of albuminuria.

In contrast to the many studies that examine vascular compliance changes in early hypertension without CKD, very few studies have examined this relationship at higher levels of albuminuria (proteinuria) in the presence of CKD. In one study of 21 patients with asymptomatic proteinuria of \(>1\) gram per day and 21 matched controls, Paisley et al noted that flow-associated dilation in the brachial artery was impaired in proteinuric subjects compared with controls. The group with proteinuria also had a higher CRP compared with controls.\(^1\)\(^1\) This association of elevated inflammatory markers accompanying albuminuria has been noted in other large studies.\(^7\)\(^12\)

The study by Agarwal and Anderson in this issue of the journal extends these previous finding in 2 ways: first, they studied people with advanced CKD; and second, they focused on the effect of proteinuria on the systolic component of BP assessed in 3 different ways.\(^1\) They checked BPs recorded in the clinic as well as by 24-hour monitoring and at home in a predominantly male cohort who had lost more than half their kidney function (estimated glomerular filtration rate [GFR] of 48 mL/min per 1.73 m\(^2\)) and did not have diabetes. They noted that the log of the urine protein/creatinine ratio was the strongest predictor of systolic BP elevation regardless of the BP measurement technique, with the strength of relationship between proteinuria and systolic BP highest for ambulatory BP and lowest for routine clinic BP. Other independent predictors of this relationship were age, race, and number of antihypertensive drugs being taken. It should be noted that estimated GFR was not an independent predictor of systolic BP by any technique. Thus, in their study, proteinuria was the most important correlate of systolic BP in older men.

Proteinuria signifies a membrane barrier defect not only in the podocytes and vascular endothelium of the kidney but in vascular tissues throughout the body. The contribution to this defect is through sustained long-term elevations in BP and resultant barrier disruption and cytokine activation through shear stress of the vessels. Although acute profound reductions in BP are associated with small reductions in proteinuria over a short period of time, these reductions become more pronounced over longer periods of follow-up (ie, \(>1\) year) and are associated with reductions in cytokine production.\(^1\)\(^4\)\(^,\)\(^1\)\(^5\) A whole host of cytokines from nephrin, angiotensin II, adiponectin, and many others have been implicated as factors that contribute to membrane barrier stability as it relates to development of proteinuria.\(^1\)\(^6\)\(^,\)\(^1\)\(^7\) Some recent data detail the effects of adiponectin on BP and other target organ injury in people with CKD. These effects may be of particular interest because they relate to the patients studied by Agarwal and Anderson who largely had metabolic syndrome. Adiponectin, the most abundant protein produced by adipocytes, appears to serve as a central regulatory protein in many of the physiological pathways controlling lipid and carbohydrate metabolism and to mediate various vascular processes. It displays...
anti-inflammatory and antiatherogenic properties, and, unlike other adipocytokines, its levels are paradoxically decreased in obesity and insulin-resistance states, including hypertension. Moreover, in people with proteinuric CKD, regardless of etiology, there is enhanced loss of adiponectin in the urine, further exacerbating the loss of this anti-inflammatory, anti-atherosclerotic cytokine. This reduction in adiponectin level is not a function of the magnitude of proteinuria, because in a separate study of >100 hypertensive people with normal kidney function, plasma adiponectin levels were lower when compared with normotensive controls and were associated with hypertensive retinopathy. Blocking the renin-angiotensin system has been shown to improve vascular compliance and increase adiponectin levels, factors that may contribute to the antiproteinuric effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Together, these findings would suggest that in the presence of CKD and the metabolic syndrome, factors that normally protect vascular integrity are lost, consequently accelerating the aging process of the vessels, rendering them stiffer more than time and, hence, decreasing vascular compliance. These data further strengthen the guideline recommendations that support measurement of spot urine albumin/creatinine not only in people with kidney disease or diabetes but in anyone with metabolic syndrome, a measurement that is cost-effective in such groups. It is becoming clear that albuminuria is a marker of vascular inflammation and associated with poor cardiovascular and renal outcomes. A recent analysis of the African American Study of Kidney Disease demonstrated that early reduction of proteinuria was a better predictor of renal outcome that was baseline GFR. This is consistent with the findings of Agarwal and Anderson, in which GFR was not an independent predictor of systolic BP. Thus, recent retrospective analyses of large outcome trials demonstrate that those with reduced levels of proteinuria from baseline and similar levels of BP reduction had fewer cardiovascular events and slower progression of kidney disease. Given this information, routine assessment of change in proteinuria or albuminuria should be strongly considered in future outcome trials to test its validity as an independent marker of outcome.

References
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