Moving Points in Nephrology

Hypertension and the Kidney: Perspectives on the Relationship of Kidney Disease and Cardiovascular Disease

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Background and objectives: The kidney is important not only in the genesis of blood pressure elevation, but declining renal function is also important for predicting cardiovascular risk. The primacy of the kidney in causing essential hypertension was a topic of debate until the proof-of-principle experiment was performed, which demonstrated remission of essential hypertension in six African-American hypertensives with ESRD after they received successful kidney transplants from normotensive donors. The resolution of hypertension and hypokalemia in a patient with Liddle's syndrome and ESRD after subsequent successful renal transplantation also demonstrated the primacy of the kidney in a monogenic form of hypertension related to sodium epithelial channel dysfunction.

Design, setting, participants, & measurements: A review of the available evidence linking cardiovascular disease with chronic kidney disease.

Results: The cause for the inverse continuous relationship between kidney function and cardiovascular events in patients with native kidney disease and kidney transplant recipients is unknown but may be related to traditional and nontraditional cardiovascular risk factors. This is an important clinical concern and requires close attention to cardiovascular risk reduction measures.

Conclusions: Increased cardiovascular disease in patients with chronic kidney disease is an important clinical concern. Improved biomeasures of cardiovascular risk and response to therapy are needed.

Clin J Am Soc Nephrol 4: 2045–2050, 2009. doi: 10.2215/CJN.03050509

The kidney likely plays a primary role in the genesis and maintenance of essential hypertension. The work of Curtis *et al.* (1,2) demonstrated that the remission of essential hypertension and monogenic hypertension with hypokalemia (Liddle's syndrome) was possible after successful renal transplantation with kidneys from normotensive donors. These proof-of-principle experiments have built the foundation for continued study of the renal mechanisms for the handling of sodium, potassium, chloride, and other electrolytes in relation to extracellular volume expansion and hypertension. Likewise, the improvement of techniques for genome-wide association relationships provides interesting insight into the complexities of the genetic influences on renal sodium, water handling, and blood pressure (BP).

Also important are the epidemiologic observations that there is an inverse continuous relationship between renal function and cardiovascular events (3). Another interesting observation is the direct and continuous relationship between the level of albuminuria and cardiovascular events and kidney disease progression (4–9).

Published online ahead of print. Publication date available at www.cjasn.org.

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Why are cardiovascular disease (CVD) and chronic kidney disease (CKD) so intricately related? Classic Framingham Heart Study risk factors do not entirely explain this relationship, although they explain much of it (3,10). There are traditional and nontraditional risk factors in patients with CKD that could explain the increased propensity for cardiovascular events. Table 1 illustrates the many different traditional and nontraditional risk factors. Of the nontraditional factors, albuminuria maybe one of the most intriguing to assess in terms of predicting risk and indicating response to therapy.

Microalbuminuria and Cardiovascular Risk

Why is microalbuminuria such a powerful predictor of CVD outcomes? It may reflect nothing more than a higher prevalence of traditional risk factors. However, it remains an independent adverse prognostic risk factor even after adjustment for these risk factors (3,9). It also may reflect generalized endothelial dysfunction, increased vascular permeability, and abnormalities in coagulation or in the fibrinolytic system (11–15). Furthermore, it may denote greater severity of macrovascular disease and target organ damage in the body. It should be considered primarily a CVD risk factor as opposed to simply a renal disease progression risk factor because of the enormous cardiovascular event rate selection process that occurs in these patients over time.

ISSN: 1555-9041/412–2045

Table 1. Traditional and nontraditional risk factors[a]

Traditional Risk Factors	Nontraditional Factors
Older age	Albuminuria
Male gender	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher LDL cholesterol	Lipoprotein remnants
Lower HDL cholesterol	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of CVD	Inflammation (C-reactive protein)
Left ventricular hypertrophy	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance

[a]Reproduced and modified with permission from Sarnak *et al.* (3).

Reducing Albuminuria: A Biomeasure of Central Aortic Pulse Pressure?

Could a therapeutic intervention, (*e.g.*, that reduces albuminuria by 50% or renders a microalbuminuric patient normoalbuminuric) predict benefit with regard to kidney disease progression and even risk for subsequent cardiovascular events? Could the glomeruli within the kidneys serve as a barometer of an appropriate BP goal in an individual patient? This latter issue would be of substantial importance in patients with impaired renal autoregulation due to afferent arteriolar injury, which would result in an increase in glomerular capillary hydraulic pressure in direct proportion to systemic BP. Because the renal arteries directly come off of the central aorta, specific measures of central aortic pulse pressure by response to treatment may be of value in predicting the anti-proteinuric response and *vice versa*. A careful analysis of available clinical trial data suggests that this may indeed be the case. As will subsequently be discussed, a lower level of brachial artery BP sufficient to reduce glomerular capillary pressure (particularly in the setting of impaired glomerular autoregulation) is necessary. Current guidelines suggest that microalbuminuric patients have a goal BP below 130/80 mmHg (16).

However, could even lower BP be advantageous? Drugs that block renin angiotensin system also reduce glomerular capillary pressure as they reduce systemic BP (17), likely through their effects of dilating the efferent glomerular arteriole. They also reduce central aortic pulse pressure (18). Might there be a dose response relationship with renin angiotensin system blocking drugs and central aortic pulse pressure, and glomerular capillary pressure, which could be critical for reducing albuminuria.

Traditionally, we have used brachial artery cuff BP measurements to determine adequacy of therapy. However, some analyses suggest that changes in proteinuria may be more predictive of renal disease progression in nephropathic diabetics compared with brachial artery cuff BP measurements (6). Why? Is this simply a poor technique for measuring BP?

Because of the small wall-to-lumen ratio in distal arteries, changes in vessel stiffness are not as substantial with aging as compared with the elastic aorta, with a large-wall-to lumen ratio (19,20). Progressive aortic stiffening with aging is associated with a 2-fold or more increase in aortic pulse wave velocity. As a consequence, the reflected pressure wave from the peripheral arterioles summates with higher central aortic systolic BP to further increase systolic BP and myocardial workload (Figure 1). Thus, for the same cardiac ejection, central

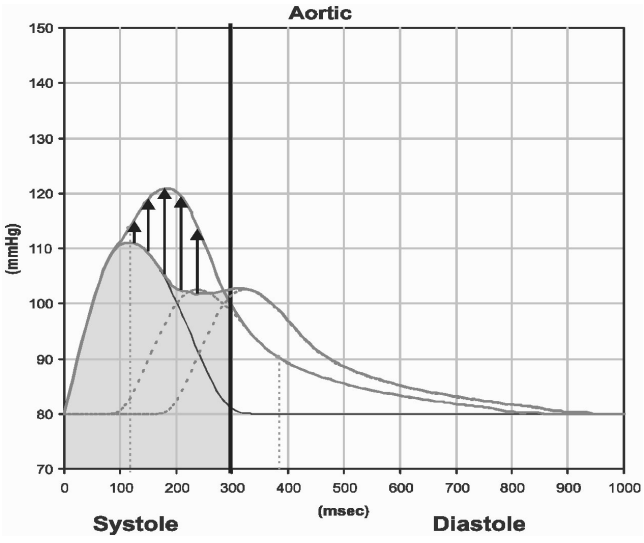

Figure 1. The effects of increasing aortic stiffness on central aortic pulse pressure. Shown here are the characteristic arterial pressure wave profiles. Forward and backward waves summate and increase left ventricular load (↑). This ultimately leads to left ventricular hypertrophy.

aortic pulse pressure dramatically rises and may not be evident in branchial vessels! Because the kidneys' circulation emanates from the aorta, they are much more vulnerable to the changes in central aortic pulse pressure. Thus, the glomerular filters could conceivably be at more risk from higher levels of central aortic pulse pressure with the vascular changes associated with aging and diabetes.

The kidneys possess an enormous microvascular surface, which receives approximately 20 to 25% of cardiac output. It may more objectively reflect the effects of central aortic pulse pressure because of the large "exposed" vascular surface area. Loss of glomerular filtration surface area over time could provide a graded perspective of coincident vascular disease throughout the body, because the renal circulation likely reflects injury from higher levels of central aortic pulse pressure shared by the coronary and cerebral vascular beds. Similarly, stabilization of kidney function with various therapeutic strategies may also correlate with lesser risk for progression of coronary and cerebral vascular disease.

Clinical Trials: Secondary Analyses and *Post Hoc* Analyses

Numerous studies demonstrate that in patients with microalbuminuria (whether diabetic or not) that microalbuminuria reduction may be predictive of slower progression to macroalbuminuria (21–23) (diabetics) or reduced likelihood of cardiovascular events (nondiabetics) (8).

Whereas microalbuminuria is a much better marker for risk of cardiovascular events (3,9), clinical albuminuria or proteinuria is a much better predictor of kidney disease progression and ESRD because it selects patients who are later in their course of renal disease that have survived past many of the earlier cardiovascular events that occur in patients with CKD. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL trial) (24), hypertensive type 2 diabetics, with clinical proteinuria and an estimated GFR of about 50 ml/min/1.73 m^2 were randomized to receive an angiotensin receptor blocker (ARB)-based multiple drug regimen (losartan) *versus* a traditional non-angiotensin converting enzyme (ACE) inhibitor/non-ARB regimen for a period of approximately 3 yr to evaluate the differential effect of the regimens on the risk of doubling of serum creatinine, ESRD, or death. Although the ARB-based regimen was associated with statistically significant reduction in risk for renal disease progression and ESRD, some of the most interesting observations were the predictive value of proteinuria (at baseline and during the course of the study) in predicting CVD and renal outcomes (4,5). Not only was the baseline spot urine protein to creatinine ratio predictive of risk for renal failure or cardiovascular events, but change in proteinuria (when measured at the 6-mo time point) was also predictive of progression of kidney disease and cardiovascular events. A reduction of proteinuria by at least 30% or more during the course of treatment correlated with reduction in the risk of ESRD (Figure 2), cardiovascular end points, or new onset of heart failure by the same 30% or more (Figure 3). Moreover, subsequent analysis of these studies illustrated that change of proteinuria was more predictive of outcome than change in office brachial artery BP during follow up (6). Likewise, a contemporaneous clinical trial done in hypertensive type 2 diabetics with kidney disease, the Irbesartan Diabetic Nephropathy Trial (IDNT), similarly showed that not only was baseline proteinuria predictive of the development of ESRD, but proteinuria during follow up (12 mo time point) also predicted renal disease progression and the development of ESRD (25). For each 50% reduction of proteinuria, there is a 50% reduced incidence of reaching ESRD (26).

An individual patient meta-analysis by Jafar and colleagues evaluated the effect of ACE inhibitor-based BP lowering regimens *versus* non-ACE inhibitor-based BP lowering regimens on the risk for developing ESRD in patients with nondiabetic kidney disease. Their meta-analysis demonstrated that residual

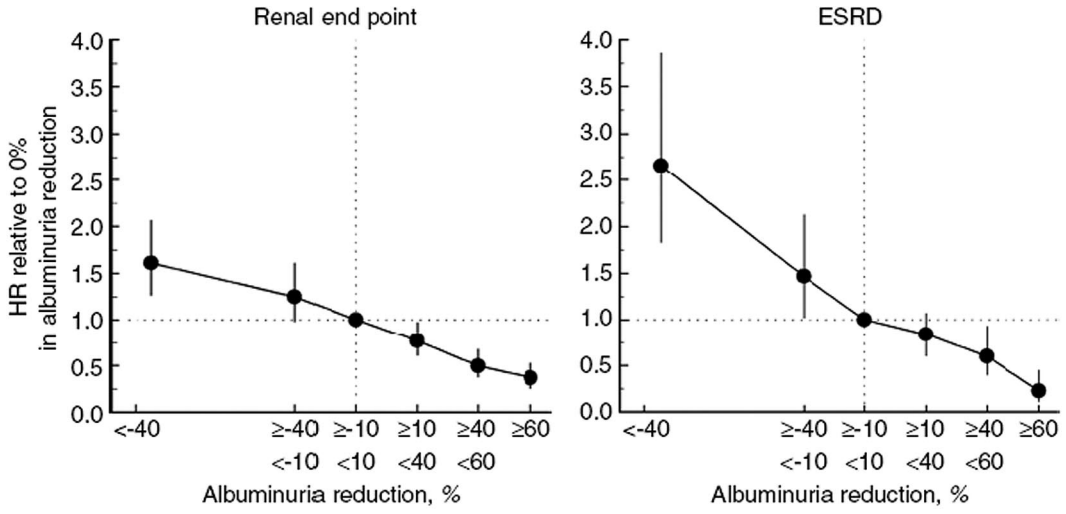

Figure 2. Relationship between percent reduction in albuminuria from baseline to month 6 and the hazard ratio for any renal end point (left) or ESRD (right) in the participants of the RENAAL study.

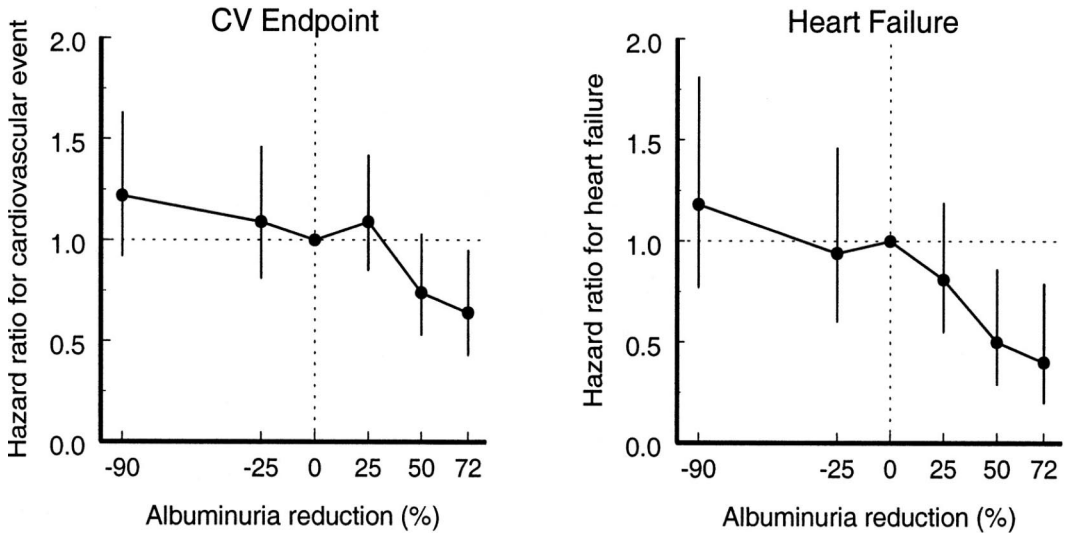

Figure 3. Relationship between percent reduction in albuminuria from baseline to month 6 and the hazard ratio for cardiovascular end points (left) or heart failure (right) in the participants of the RENAAL study.

proteinuria during follow up was continuously related to the risk for doubling serum creatinine or reaching ESRD (7). Thus, the literature in patients with kidney disease due to either diabetic or nondiabetic causes is quite consistent: residual proteinuria during the course of therapy is predictive of risk for developing ESRD. The secondary analysis from the RENAAL trial also demonstrated the importance of residual proteinuria in predicting CVD events.

Are all of these data coincidental? No prospective studies have been performed to test the hypothesis that planned reduction in microalbuminuria or clinical proteinuria can reduce the risk for or prevent ESRD or incident/recurrent cardiovascular events. However, the consistency of these data suggests that microalbuminuria or proteinuria may be a modifiable risk marker for progression of renal and CVD.

Is Central Aortic Pulse Pressure a Unifying Understanding?

Why are changes in albuminuria predictive of kidney and cardiovascular events? Is this just a better way to perhaps assess central aortic pulse pressure and diffuse arterial disease? The Conduit Artery Function Evaluation (CAFÉ) study (18) may provide some clues. The CAFÉ study was a subset of the participants of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial (27). ASCOT was a large study of nearly 20,000 patients who were randomized to receive a calcium channel blocker/ACE inhibitor regimen or a thiazide diuretic/beta blocker BP lowering regimen. In the overall trial, the calcium channel blocker/ACE inhibitor regimen-treated patients had fewer overall cardiovascular events. They also had lower BP the first few years of treatment. However, in the CAFÉ study participants, central aortic pressures were measured using noninvasive techniques. In the patients who received the calcium channel blocker/ACE inhibitor regimen, central aortic systolic pressures were substantially lower (4 mmHg) than in the beta blocker/thiazide-treated patients despite similar brachial artery BP measurements. Could this explain the difference between the therapeutic regimens on CVD outcomes? Might lower central aortic pressures be associated with less microalbuminuria or clinical proteinuria? Drugs that block the renin angiotensin system are effective in reducing albuminuria and central aortic systolic pressure. Unfortunately, urinary albumin excretion was not measured in this study. However, future studies will need to address whether reduction in central aortic pressures with arterial "destiffening" agents correlates with reduced albuminuria or proteinuria and may explain why certain therapeutic regimens (such as those that block the renin angiotensin system) may provide benefit with regard to kidney and cardiovascular outcomes despite similar BP reduction (using brachial artery cuff measurements).

Drug regimens that reduce brachial artery BP and microalbuminuria or proteinuria are associated with better renal and cardiovascular outcomes than regimens that lower BP without lowering proteinuria to the same degree. This may be related to lower central aortic pulse pressure or other unknown factors. Perhaps destiffening of the aorta? Perhaps the kidneys function as barometers in the body to provide an understanding about central aortic pulse pressure and provide a clue about arterial disease? Or, maybe they provide a 24-h measure of BP load as opposed to the casual brachial artery cuff readings that are obtained in the office? Further research is necessary to determine the optimal dosing of renin angiotensin system blockers and perhaps other vascular destiffening agents and whether they can be used in conjunction with each other to reduce proteinuria.

In summary, there is a high prevalence of CVD with CKD. Estimated GFR is useful in stratifying this risk. On the other hand, albuminuria should be considered a target for estimating risk and response to treatment. The presence of CKD and/or albuminuria/proteinuria should focus the clinician on global cardiovascular risk reduction strategies, including lower brachial artery BP, cholesterol and glucose goals, and perhaps

strategies to consider better means of reducing time-varying microalbuminuria and or albuminuria during follow up.

Acknowledgments

The author thanks Tia A. Paul from University of Maryland School of Medicine in Baltimore, Maryland, for expert secretarial assistance.

Disclosures

None.

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