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## Albuminuria and Prognosis in CKD: Truth Be Told

In this issue of *Advances in Chronic Kidney Disease*, Guest Editors de Zeeuw, Parekh, and Soman have composed a synthesis of the known knowns and known unknowns regarding proteinuria. Correspondingly, the authors reveal the truth, as they know it, regarding a host of proteinuric entities, which will be considered problems of albuminuria for the purposes of this discussion.

In 1750, Cotugno first coined the term albuminuria from a patient with nephrosis and “dropsy.” Despite that he erred in his conception of why the urine of his patient contained albumin, nonetheless, he associated albuminuria with a disease state.<sup>1</sup> He and others, including Richard Bright, were clearly cognizant of the prognostic importance of heavy albuminuria in nephrotic syndromes, even then. Their observations were subsequently documented and have been repeatedly confirmed at patient- and trial-levels. In recognition of the clinical importance of proteinuria, the National Kidney Foundation proposed an albuminuria screening strategy that would limit false-positive results and amplify the sensitivity of testing. The albuminuria algorithm called for 2 additional, separate examinations over 3 to 6 months, to unequivocally establish albuminuria.<sup>2</sup> However, the additional testing for higher grade albuminuria may be unnecessary because higher levels of albuminuria persisted in all instances, at a median follow-up interval of 17 days.<sup>3</sup>

Albuminuria is important and is accepted in some circles as a CKD biomarker. However, it is not a surrogate endpoint for CKD because it fails to adequately fulfill the Prentice criteria: (i) A valid surrogate endpoint must be statistically correlated with the true clinical endpoint and should predict the clinical outcome of interest. (ii) A valid surrogate endpoint must fully capture the treatment’s aggregate effect on the true clinical endpoint and should account for every major effect of the treatment.<sup>4</sup> In accordance with these tenets, a Pro and Con debate, “Microalbuminuria heralds a poor prognosis,” was staged at the National Kidney Foundation’s Spring Clinical Meetings in 2011. Before either speaker presented his case, the participants demonstrated their

enthusiasm for the hypothesis, and nearly three-fourths of those present voted affirmatively. At the end of the session, there was a 10% dropoff. The majority had prevailed, but was it correct?

Following glomerular ultrafiltration, the concentration of albumin in Bowman’s space is approximated at just 4 mg/L. Consequently, the importance of albumin’s appearance in the final urine might seem disproportionately large. Indeed, albumin represents a minority of urinary protein in the normal individuals. It had long been held that normal individuals would not excrete albumin in an amount >0.5 to 1 g/d, in the total absence of proximal tubular albumin reabsorption. This concept has been recently challenged, and some contend that nephrotic range proteinuria from physiologic glomerular sieving of albumin may be the norm.<sup>5</sup> Albumin’s complex traversal through the tripartite barriers of endothelium, glomerular basement membrane, and podocytes is considered a failure of glomerular permselectivity, and success is represented by retardation of albumin’s passage into the ultrafiltrate. Glomerular impediment to passage of protein is influenced not only by structural pathobiology but also by extraglomerular factors. Inflammation accompanied by elevated cytokine levels may lead to proteinuria as may heightened intraglomerular capillary pressure, hyperglycemia, severe acute kidney injury, sepsis, exercise, fever, heart failure, and other states of sympathetic nervous system hyperactivation that are frequently accompanied by elevated angiotensin II levels. In the end, it is albumin that escapes proximal tubular reclamation with transcytosis to the basolateral membrane that ultimately determines albuminuria. Thus, persistent albuminuria (fixed proteinuria) represents its collective escape from damaged glomeruli and tubuli.

The process of measurement and quantitation usually occurs first by albumin’s association with a cationic

dye-impregnated urine dipstick, and later by either a urine protein-to-creatinine ratio (PCR) or albumin-to-creatinine ratio (ACR). However, there is a significant correlation between the semiquantitative dipstick and more quantitative protein concentration testing,<sup>6</sup> which is not widely appreciated. Historically, the PCR preceded the standardization and automation of ACR by many years, and was the parameter upon which many trial-level data are based. The ACR is conducted with standardized technology and antibodies specifically directed against albumin, whereas the PCR may be carried out with various pH indicator dyes.<sup>7</sup> Consequently, the ACR is considered the method of choice by standards- and guidelines-producing bodies and organizations. Remarkably, fragmented albumin, a byproduct of tubular processing, may not be detected by “gold standard” albumin-specific antibodies because these were generated against intact molecules. In addition, the variability of urine albumin excretion may exceed the coefficient of variation of the test itself, thereby making trend analysis less precise. To reduce the variability, there is an advantage to performing morning ACRs.<sup>8</sup>

Ironically, the indicator dye-based protein concentration measurements will quantitate these “missed” fragments, the residua of tubular albumin metabolism. For this reason some have advocated that PCR evaluations are superior to ACRs for detection of albuminuria. Moreover, PCRs detect other, nonalbumin proteins, including those of lower (eg,  $\beta_2$  microglobulin, light chains) and higher (eg, intact immunoglobulins) molecular weight. However, PCRs cannot discriminate among the various urinary proteins. Therefore, the ACR is clearly superior to the PCR, even in some tubular disorders.<sup>9</sup> Exceptions occur in circumstances in which a nonalbumin protein constitutes the principal urinary protein rather than albumin. The clinical scenarios in which this issue becomes paramount are few (eg, myeloma, Dent’s disease), and the associated systemic disorders are typified by paraproteins that incite substantial glomerular and/or tubular pathology.

Microalbuminuria, at any given time, only indicates that there is deviation from normality in glomerulotubular processing. Neither the mechanism(s) nor the site(s) of disrupted physiology and their respective magnitudes may be elucidated clinically. Furthermore, the durations of past or future protein excretion cannot be prognosticated either. Trend analysis extending over months to years may be required to determine progression of CKD and the accrual of risk, particularly cardiovascular risk. To this end, a Kidney Disease: Improving Global Outcomes (KDIGO) CKD Prognosis Consortium qualified risk by melding the estimated glomerular filtration rate with the degree of albuminuria.<sup>10</sup> To determine the joint contribution to ESRD and other renal outcomes, the Consortium conducted a meta-analysis of 9 general population cohorts (N = 845, 125 participants) plus 8 additional cohorts (N = 173, 892 patients) with high risk for CKD. Their meta-analysis

confirmed that lower estimated glomerular filtration rate plus albuminuria, quantitated as a single ACR measurement, imposed greater risk for cardiovascular and kidney disease outcomes than either alone.

More recent data from a retrospective analysis of 10,290 diabetic, hypertensive patients from a Kaiser Permanente population-based sample characterized the course of these hypertensive and diabetic individuals.<sup>11</sup> Of 3187 patients with microalbuminuria, 668 regressed to normoalbuminuria, 630 progressed to macroalbuminuria, and of these, just 10 developed ESRD. Of the 5908 persons who were originally normoalbuminuric, 2839 developed microalbuminuria, of which 370 developed macroalbuminuria. Five of the last group developed ESRD. Of the 1195 originally macroalbuminuric subjects, 52 progressed to ESRD, with likely tubulointerstitial fibrosis invoked by a proteinuria-induced, cytokine-mediated inflammation. These data underscore both sides of the original tenet. Essentially, microalbuminuric risk for progression to ESRD varied as a function of the degree of extant diabetic kidney disease at the time of entry into the study and was subsequently altered by physician-driven therapy. Clearly, within each stratum, some patients may have responded less well than the group as a whole and progressed to ESRD. Again, this must be taken within the context of trend analysis. The latter allows for treatment effects that mitigate microalbuminuria, which may also include therapies extrinsic to the kidneys, such as those for heart failure. Essentially, if albuminuria is worsening, risk factor management should commensurately increase, not only for albuminuria but also for other parameters, such as glycemic control, elevated blood pressure, and dyslipidemia.<sup>2</sup>

The overall literature reflects the same verisimilitudes: treatment responders have better prognoses than nonresponders. Unlike the Pisse Prophets who simply divined the urine, nephrologists must conduct trend analysis; they must define, measure, and measure again urinary albumin from those with CKD so as to extrapolate its prognostic import.<sup>12</sup> This truth has been known for a long time and reminds of us the following words of physician-philosopher, William James, in his work, *Pragmatism*: “When a thing is new, people say ‘It is not true.’ Later, when its truth becomes obvious, they say ‘It is not important.’ Finally, when its importance cannot be denied, they say ‘Anyway, it is not new.’” And equally important, “Beliefs are considered to be true if and only if they are useful and can be practically applied.”<sup>13</sup>

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Editor

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