Relativity and the kidney: observations regarding glomerular density

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Progressive loss of kidney function consequent to relentless scarring of renal parenchyma is a dreaded consequence of many forms of renal disease, ultimately lead to death, dialysis or transplantation, unless progression can be forestalled. However, in many diseases, including IgA nephropathy and membranous nephropathy only a subset of patients will demonstrate such progressive kidney injury. Identification of patients with minimal or no risk of progression versus those with the highest risk, would allow stratification and targeting of aggressive treatments having potentially greater side effects, to those with highest risk who also would experience most potential benefit. Conversely, patients with minimal risk for progression could then be spared such risk.

Identification of patients at risk for development of chronic kidney disease has long been a goal in nephrology. Numerous markers have been sought to develop a ‘crystal ball’ to glean what the future likely holds for each patient. More than two decades ago, we identified glomerular hypertrophy as an early sign of events associated with ultimate progression to overt focal segmental glomerulosclerosis in patients who morphologically appeared to have minimal change disease [1]. Proteomic and genetic approaches have also been pursued to identify and stratify at-risk patients. The groundbreaking insights of Dr Barker, linking low birth weight to increased cardiovascular disease risk in adulthood, were applied to kidney disease by Brenner and his group [2–5]. These studies indicated that low nephron number, whether present at birth or acquired due to injury to some nephrons, was associated with increased renal and cardiovascular disease.

Now, the studies from Tsuboi et al. [6] indicate that a simple metric, namely low glomerular density, could be a risk factor for progression in idiopathic membranous nephropathy. The authors evaluated 65 Japanese patients, ranging from 15 to 84 years, excluding those with decreased estimated glomerular filtration rate (eGFR) at presentation. Glomerular density was calculated as number of glomeruli that were not globally sclerosed within a measured cortical area. Numerous other morphologic and clinical parameters were also assessed. Of note, proteinuria was similar at presentation in those with lower or higher glomerular density (3.2 versus 3.0 g/day), respectively. Glomerular density predicted the subsequent course, but only in those with persistent significant proteinuria, >1 g/24 h, on follow-up. Thus, the ultimate marker of long-term progression was the response of proteinuria to interventions, which included angiotensin-converting enzyme inhibitor, angiotensin receptor blocker and immunosuppression. Thus, among the 26 patients with proteinuria >1 g/day at follow-up, significant reduction in eGFR or end-stage renal disease occurred remarkably more frequently in those with lower glomerular density than those with higher glomerular density. Conversely, no influence of glomerular density was observed in those with lesser proteinuria on follow-up; in these 39 patients, no patients had significant reduction in eGFR or reached end-stage renal disease.

Areas of interest for future study include measures of glomerular volume and assessment of all glomeruli through serial-section analysis [7, 8]. Such detailed assessment of all glomeruli would include so-called ‘disappearing glomeruli’, i.e. globally sclerosed glomeruli becoming continuous with the surrounding fibrotic interstitium. Importantly, the technical variability of this methodology should also be determined. For example, the authors have not indicated whether different step levels of the biopsy yield different values for glomerular density or whether one core versus two or more cores offers more refinement of this metric.

Glomerular density is clearly a relative metric, reflecting both total number of glomeruli counted and cortical area assessed. Could patients with greater proteinuria have a larger cortical volume? Certainly, marked proteinuria and interstitial edema, or accompanying renal vein thrombosis with enlargement of kidney size due to congestion, could decrease glomerular density without affecting glomerular number directly, i.e. merely increasing the denominator. Other factors influencing glomerular density include the number of nephrons endowed at birth and the number that may have been lost. Of note, the glomerular density metric in this study was calculated without including globally sclerotic glomeruli. Indeed, 13 patients had global sclerosis of 10–20% of glomeruli, and 1 patient had global sclerosis of 30%, with an average of 6.1% global sclerosis in patients with low glomerular density versus only 2.5% in those with glomerular density above the authors’ threshold. Even in this relatively small sample, this difference had a P-value of 0.054, suggesting at least a trend for an association between global glomerulosclerosis (i.e. glomeruli that were not counted in
assessment of glomerular density) and lower glomerular density score. Interestingly, glomeruli with segmental sclerosis, included in the glomerular density metric, were also more common in the group with lower glomerular density (2 versus 0.2%). The infrequent and highly variable presence of segmental sclerosis likely underlies the lack of statistically significant difference in sclerosis between groups with higher versus lower glomerular density. Exclusion of patients with decreased renal function at time of biopsy likely explains why this lesion was so rare. Not surprisingly, interstitial fibrosis >10% was linked to lower glomerular density than interstitial fibrosis <10%, with similar distinction when the interstitial fibrosis threshold was set at 20%. Yet, these variables of interstitial fibrosis/tubular atrophy did not predict outcome in univariate or multivariate analysis nor did global sclerosis per se. The robust predictive value of the simple metric of glomerular density thus may have complex underlying pathophysiological mechanisms that may not be easy to unravel. Nonetheless, in this group of patients who were indistinguishable at the onset, this information, in conjunction with a response of proteinuria to therapeutic intervention, significantly contributed to identification of patients with poor prognosis.

Regardless of the causality of the decrease in number of glomeruli relative to cortical area, this simple technique may offer additional guidance to identify patients in whom we should target our most aggressive interventions.

Conflict of interest statement. None declared.

(See related article by Tsuboi et al. Low glomerular density is a risk factor for progression in idiopathic membranous nephropathy. Nephrol Dial Transplant 2011; 26: 3555–3560.)

References


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Rapid assessment of microbiological purity of dialysis water: the promise of solid-phase cytometry assessment and the epifluorescence microscopy method

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Over the last decade, microbiological contamination of water and dialysis fluid has become a major concern for haemodialysis (HD) patients being implicated in bioincompatibility and long-term side effects of HD. In the past, gross contamination of dialysis fluid was implicated in pyrogenic reactions particularly with the extensive use of bicarbonate buffered dialysate and high-flux dialysers [1]. Nowadays, even minor levels of microbial contamination of dialysis fluid are capable of triggering inflammation by activating monocyte–macrophage cells and releasing pro-inflammatory cytokines. Chronic microinflammation, a common feature of dialysis patients, represents the strongest amplifier of most common pathophysiologic pathways in kidney disease patients associated with malnutrition, accelerated atherosclerosis, B2M amyloidosis and erythropoiesis-stimulating agent (ESA) resistance [2–4]. This is the strongest argument for using ultrapure dialysis fluids (water and dialysate) in all dialysis modalities but particularly in high-flux HD and on-line haemodiafiltration (HDF) [5]. Based on these considerations, the status of dialysis fluid has changed over recent years in the view of nephrologists, being more and more perceived as a ‘pharmaceutical drug’ rather than a ‘medical device’ [6]. Tremendous efforts have been made by water and dialysis industry to improve the microbiological purity of

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