Editorial

Nephron Hypertrophy and Glomerulosclerosis in Normal Donor Kidneys

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In this issue of *CJASN*, Elsherbiny *et al.* of the Mayo and Cleveland Clinics, describe a study of intraoperative biopsies of 1395 living donor kidneys (1), which shows two distinct patterns of structural change that might be related to kidney function and risk factors for CKD (1). The first phenomenon is nephron hypertrophy and the second is nephrosclerosis. The authors propose that the first phenomenon is a consequence of a net hypertrophic driving force probably associated with the metabolic syndrome, or due to lower nephron endowment (or in some cases, nephron loss). The second phenomenon lacks signs of nephron hypertrophy, and is associated with global glomerulosclerosis.

Glomerular volume was measured by the Weibel–Gomez method, and a tubular profile area and the densities of nonsclerotic and sclerotic glomerular areas were measured by morphometry. Nephron hypertrophy was determined by larger glomerular area, increased tubular profile area, and decreased density of nonsclerotic glomeruli, which was the result of glomeruli being spread apart by an increased volume of the tubular compartment. Nephrosclerosis was characterized by higher glomerular density, a lower total glomerular area, and increased "global-sclerotic glomerulus density."

Nephron hypertrophy was significantly correlated with male sex, age, high body mass index (BMI), higher uric acid, hypertriglyceridemia, lower HDL cholesterol, higher blood glucose, higher levels of urinary albumin (although still within the normal range), higher GFR, and a family history of ESRD. With multivariate adjustment, hypertrophy retained its significant association with male sex, BMI, uric acid, and family history of ESRD. Hypertension was significantly correlated with the density of globally sclerotic glomeruli and age.

The average patient age was 44 years, 43% were male, 52% had a family history of ESRD, 11% were hypertensive, and 12.4% had the metabolic syndrome. Most of these 1395 people were presumably included in a recent study by that same group, in which participants were identified as 89% white, 34% as obese (BMI $\geq$30 kg/m^2), and 10% were over 60 years old (2). In that prior study the authors reported that contrast-enhanced CT measurements of cortical volume per body surface area were related to age, GFR, and the same aspects of the metabolic syndrome analysed in the current article. Although the contrast studies showed a general decline in cortical volume and GFR with age, subjects with features of the metabolic syndrome had higher cortical volume and higher GFRs than the other group. At that time the authors proposed that hypertrophy versus atrophy of glomeruli might explain these differences. The current article provides microanatomical evidence to support that notion.

The sample size in this study is very large, and the state of tissue on harvesting (18-gauge punch-needle biopsy) and its handling, were presumably excellent. From most perspectives, the series represents "supernormal" kidneys, given the exclusion of potential donors with significant kidney functional abnormality, with hyperglycemia or diabetes, or with severe hypertension. However, a high proportion of people had relatives with ESRD, as anticipated, at least for living related donors of people who already have ESRD.

Our data on autopsies from >400 people without known kidney disease support the notion that glomerular hypertrophy and glomerulosclerosis are separate processes (3–8). African Americans and remote living Australian Aborigines, when compared with American Whites, Australian Whites and Senegalese Africans, had larger mean glomerular volume and greater variability of glomerular volumes within individual kidneys, but they had no excessive glomerular sclerosis either of the segmental or global types. In Aborigines, these changes are clearly associated with low nephron number (7), which is probably explained by reduced nephron endowment associated, at least in part, with low birthweight. There was not a conspicuously lower nephron number among African Americans, although adequacy of nephron number in the context of current body size needs further exploration. It was only among whites that elevated BP could be related to low nephron number, whereas high BP in African Americans was not conspicuously related to lower nephron numbers. Perhaps the advance exclusion of severely hypertensive people in this donor series weighs against full discernment of links of either the hypertrophic or globally sclerotic types of glomerular lesions to hypertension. It would, however, be interesting to know how African-American status segregated with family history of ESRD, hypertension, glomerulomegaly, and later single-kidney GFR in these donors. Kidney weights would also have been of interest, given that they are largely determined by the volume of the tubular compartment.

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We also previously described glomerulomegaly in diseased kidney renal biopsies in remote-living Australian Aborigines, which is compatible with the "nephron underendowment" scenario (9,10). Furthermore, the later development of CKD in many living related Aboriginal kidney donors suggests that those donors had marginal renal functional reserve prior to donation (11).

An additional point made briefly in this report more fully discussed by Glassock and Rule (12) and also evident from our autopsy series (8), is that the risk for progression, whether or not there is nephron hypertrophy, is by global glomerulosclerosis or glomerular obsolescence with preglomerular arteriolar sclerosis. This brings into question the putative important role for glomerular hypertension and FSGS in the pathogenesis of arteriolar nephrosclerosis. Although FSGS-like pathology can be found in the late stages of CKD of any type, as a decompensated glomerulosclerosis, it seems to play little role in the early to intermediate phase of hypertensive nephrosclerosis, even when glomerular hypertrophy is present.

The authors infer that both nephron hypertrophy and nephrosclerosis could be flagging potential mechanisms for progressive CKD; the first with albuminuria and segmental sclerosis and the second with extensive ischemic glomerulosclerosis and with less albuminuria. These are indeed distinctions we see among our patients with CKD. Furthermore, those with significant proteinuria/albuminuria have a more progressive course (13). However, some overlap is likely, as the authors acknowledge: compensatory hypertrophy could develop in remaining glomeruli when nephron numbers become limiting after extensive loss from glomerulosclerosis, unless other factors, such as vascular disease, constrain the hypertrophic process.

The work of Tsuboi and colleagues on kidney biopsies supports some of the structural inferences. They propose that glomerular number, inversely, can be inferred from glomerular density in histologic sections, and they documented lower glomerular density and larger tubular areas in participants with obesity-related glomerulopathy (14,15). They also noted that lower glomerular density with individual glomerular enlargement weighed against remission in minimal change disease, and carried a worse prognosis in IGA nephropathy and membranous nephropathy (16–19). In fact, work of Tsuboi's group infers that at least part of the heightened sensitivity to renal disease in Japanese people (20) is marked by glomerular and tubular hypertrophy, the drivers of which are now under investigation.

The desirability of techniques for noninvasive assessment of glomerular number and volume distribution is again highlighted by these findings. The recent report from Beeman *et al.* (21), showing that glomeruli can be imaged, counted, and sized in *ex vivo* human kidneys using magnetic resonance imaging, inspires efforts to develop noninvasive techniques for use in patients, not only to assess CKD risk and its pathways, and for diagnostic and prognostic purposes, but perhaps also for assessment of potential donor suitability.

A key finding in those reports and in the study by Elsherbiny *et al.* (1) concerns tubular hypertrophy, as determined by increases in "tubular area." It is not clear to what extent tubular cell hyperplasia and/or hypertrophy contribute, and whether this varies by disease state. It also raises questions as to whether such lengthening and hypertrophy of the tubule is uniform across tubular segments. This issue of symmetric versus asymmetric tubular hypertrophy has been largely ignored in nephrology; however, it is worthy of attention, given the marked functional differences between the different nephron segments. A combination of immunolabeling to distinguish the nephron segments and stereologic techniques for estimating the length of specific nephron segments would allow us to estimate the length ratios of different nephron segments and explore associations with clinical parameters.

The study by Elsherbiny *et al.* reminds us of the additional information that can be gleaned from thorough morphometric analysis of renal biopsies. The consistency of the inferences from this source, from our autopsy series, and from the observations of Tsuboi *et al.* might reasonably prompt other centers to apply such techniques in their own evaluations of kidney biopsies, aiming to increase knowledge of pathways and ultimately improve diagnoses and treatments.

Disclosures

None.

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