Increased Single-Nephron GFR in Normal Adults: Too Much of a Good Thing . . . or Maybe Not?

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An individual’s GFR is the sum of all of his or her single nephron glomerular filtration rates (snGFRs). A recent biopsy study in kidney donors by Denic et al.1 in the New England Journal of Medicine provides insights into the relationships between increased single-nephron glomerular filtration rate (snGFR), biopsy abnormalities, and certain risk factors for kidney disease.

What Does This Important Study Show?
The study analyzed intraoperative biopsies in adult kidney transplant donors, for whom predonation iohexol-mass-measured GFR and kidney size on computed tomography had been determined. Biopsy specimens were graded for nephron (ie, glomerulus plus tubule) number and size and glomerular sclerosis (>10% of glomeruli), arteriosclerosis (>50% intimal thickening), and interstitial fibrosis. An average snGFR was calculated for each individual from measured GFR divided by total nephron number, which was defined as the product of the density of functioning nephrons on biopsy and total renal cortical volume on computed tomography, that is, snGFR = GFR/[nephron density] × (total cortical volume)]. Cortical volume increases as GFR increases in normal kidney donors.2 Therefore, for any given GFR, reduced density of functioning nephrons was the major determinant of a higher average snGFR. Within any age bracket, individual average snGFRs varied widely, but across age groups, group averages were similar, at 80 ± 40 nl/min. In the cohort as a whole, increasing average snGFR was associated with glomerulosclerosis and arteriosclerosis, but not interstitial fibrosis. Higher average snGFRs were also associated with increasing body mass index and measures of low nephron endowment at birth.

To many nephrologists, this study would suggest that glomerular hyperfiltration contributed to biopsy specimen abnormalities. Subtle hyperfiltration damage seemed to occur in ostensibly healthy individuals. However, the authors cautioned that higher average snGFRs could well have been a secondary beneficial adaptation to nephron loss. Interpretation of their findings is also complicated by variations in kidney microanatomy. In various human study populations, average nephron number varies up to 13-fold, and mean glomerular volume varies up to 7-fold. Within an individual kidney, glomerular volumes can vary as much as 8-fold.3 This may give most individuals a population of larger, high-snGFR “hyperfiltering” nephrons. In this way, hyperfiltration could be ubiquitous, and the point at which it becomes pathologic would be especially unclear.

Glomerulosclerosis or arteriosclerosis was seen in 15% of kidney donors aged 18 to 29 years, 43% aged 50 to 59 years, and 57% aged 65 to 69 years. However, the kidneys in these individuals were aging particularly well. GFR selection criteria for kidney donors become more stringent with age. In the general population, median GFR decreases by an average of about 5 to 10 mL/min per decade, and the normal range is wide.4 The usual threshold of 80 mL/min for acceptable donation allows almost all young candidates, but will exclude the lowest third of normal GFRs in middle-aged individuals, who are also excluded from donation if they are even minimally macroalbuminuric or have other early manifestations of kidney disease.5 The low-risk nature of the donor cohort may diminish the clinical significance of the abnormal biopsy results in this study. Exclusion of low-normal GFRs in middle-aged candidates may also have favored the constancy of snGFRs across age groups.

How Does This Study Compare With Prior Studies?
Some of the associations in the current study have been previously reported in the same donor cohort, in which more than half had a family history of end-stage renal disease (ESRD).6–8 An association between fewer but larger nephrons and both short stature and family history of ESRD suggested an effect of lower nephron endowment at birth, with higher snGFRs and increased renal risks in later life.3 Fewer but larger nephrons with higher snGFRs also were associated to variable degrees with increased body mass index, GFR, blood pressure, and microalbuminuria.6,7 Nephron hypertrophy compensated entirely for renal cortical volume loss from hypertensive nephrosclerosis and was associated with less volume loss from age-related nephrosclerosis.7 A declining total number of functioning plus sclerotic glomeruli suggested an ongoing substantial reabsorption of nonfunctional nephrons with advancing age in healthy individuals.8 The current study found an association between increasing average snGFR and arteriosclerosis; in previous studies, arteriolar hyalinosis was associated with older age, hypertension, and lower GFR.7

In previous literature, the term hyperfiltration is inconsistently and somewhat arbitrarily defined.9,10 It always means a high GFR or snGFR, but it can also connote that this is abnormal and likely pathologic. The most frequent operational threshold is simply a high-normal GFR, usually higher than 130 to 140 mL/min/1.73 m².
Measurement of GFR is not standardized among studies, and most thresholds do not consider variable nephron endowment or normal age-related losses of GFR. Increased sngfr that is maintained by increased glomerular capillary pressures may well be more damaging than increased sngfr that result from increased glomerular plasma flow with expansion of filtering area with no change in filtration fraction. As the authors state, the increased glomerular size described in the present study is more consistent with the latter more benign process.

In the clinical literature, hyperfiltration is commonly associated with diabetic nephropathy and obesity-related kidney disease, but its contribution to disease progression is uncertain for several reasons. The estimated increase in kidney disease, but its contribution to disease progression is largely absent in animals that were fed a low-protein diet, is uncertain for several reasons. The estimated increase in sngfr with obesity or diabetes is typically less than the apparently benign increase after kidney donation. Hyperfiltration does not always occur in progressive diabetic chronic kidney disease and may result from changes in proximal tubule function. It may not be an important contributor to progressive diabetic nephropathy. The increased ESRD risks of obesity may principally be due to eventual diabetes or cytokine-mediated vascular damage. Most importantly, with kidney damage from a variety of causes, surviving glomeruli adapt by hyperfiltering, which minimizes the contribution of pre-existing hyperfiltration to disease progression.

Sngfr is increased by ~50% in normal pregnancy, but the long-term effects of an increased sngfr are arguably best isolated in kidney donors, for whom it appears to be low risk. About 30% of predonation GFR is lost at donation. In the first few months, glomerular surface area and kidney size gradually increase, and sngfr increases by ~40%. Low-grade proteinuria and mild hypertension gradually appear in a significant fraction of donors and appear relatively benign. During the next several years, GFR stabilizes or increases, and sngfr increases even more. This appears to be low-pressure hyperfiltration, save perhaps in some older or obese donors. In contrast to this overall benign scenario, drastically reducing kidney mass by >90% in rats produces high-pressure hyperfiltration and glomerular damage with immediate progressive loss of GFR. Surprisingly, in the same seminal study, this dramatic result was largely absent in animals that were fed a low-protein diet, which has a minimal effect on CKD progression in humans.

What Are the Implications for Nephrologists?

Although the study raises important basic science questions, the authors were cautious about its clinical implications. Increased sngfr may have been an adaptation to other biopsy abnormalities rather than their cause. For example, increased sngfr is not a known cause of arteriosclerosis, although they were associated in the study. Other associations in the study may not have major clinical effects. For example, hypertension appeared to cause nephrosclerosis on biopsy. However, in well-screened populations, isolated hypertension is a minor risk factor for loss of GFR. ESRD rates in the general population can be successfully modeled by assuming that it causes an incremental loss of GFR per decade of only 1 mL/min/1.73 m². Aside from the controversy about when high sngfrs become pathologic, the clinician will likely not be able to identify most patients who have them. Simply measuring GFR will not suffice. The current study used a complex methodology that extrapolated biopsy samples to whole-kidney average sngfr estimates. Its ability to estimate precisely an average sngfr in a given individual has been questioned, because whole-kidney studies show that nephron size, number, and distribution vary considerably. The authors advised that their techniques are best used in large cohorts to identify potentially important relationships for further study.

Because Denic et al did not evaluate the postdonation outcomes of their participants, their study does not help inform donor candidates about future CKD or ESRD risks after donation, a topic of great importance and active investigation within the transplantation community. Recent retrospective studies have suggested an increased risk for ESRD after kidney donation. In these studies, ESRD is delayed and infrequent and has not been attributed to kidney damage from high postdonation sngfrs. Rather, some authors have suggested that loss of GFR at donation simply reduces “renal reserve” and thus permits new-onset kidney diseases in donors to reach ESRD more often over any defined period, as compared with controls with 2 kidneys and higher GFRs. Ongoing longitudinal follow-up of large postdonation cohorts should provide valuable information on long-term renal outcomes in kidney donors. For now, Denic et al have contributed important basic and clinical insights that invite further studies as we consider whether high GFRs can be too much of a good thing.

Article Information

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