Global glomerulosclerosis with nephrotic syndrome; the clinical importance of age adjustment

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Globally sclerotic glomeruli (GSG) occur with both normal aging and kidney disease. However, it is unknown whether any GSG or only GSG exceeding that expected for age is clinically important. To evaluate this, we identified patients with a glomerulopathy that often presents with nephrotic syndrome (focal segmental glomerulosclerosis, membranous nephropathy, or minimal change disease) in the setting of the Nephrotic Syndrome Study Network (NEPTUNE), China-Digital Kidney Pathology (DiKiP), and the Southeast Minnesota cohorts. Age-based thresholds (95th percentile) for GSG based on normotensive living kidney donors were used to classify each patient into one of three groups; no GSG, GSG normal for age, or GSG abnormal for age. The risk of end-stage renal disease or a 40% decline in glomerular filtration rate during follow-up was then compared between groups. Among the 425 patients studied, 170 had no GSG, 107 had GSG normal for age, and 148 had GSG abnormal for age. Compared to those with no GSG, the risk of kidney disease progression with GSG normal for age was similar but was significantly higher with GSG abnormal for age. This increased risk with GSG abnormal for age remained significant after adjustment for interstitial fibrosis, arteriosclerosis, age, hypertension, diabetes, body mass index, glomerulopathy type, glomerular filtration rate, and proteinuria. Thus, in patients with glomerulopathy that often presents with nephrotic syndrome, global glomerulosclerosis is clinically important only if it exceeds that expected for age.

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Nephrosclerosis is a term often used to describe chronic irreversible changes observed on a kidney biopsy specimen. These changes include global glomerulosclerosis, arteriosclerosis, arteriolosclerosis, and interstitial fibrosis and tubular atrophy (IFTA).[1] These histologic findings also predict a worse renal prognosis in patients with chronic kidney disease (CKD).[2–7] Accordingly, nephrologists often use these "chronic changes" to inform patients about their prognosis and to guide their management.[8] However, some degree of nephrosclerosis can also be observed with normal healthy aging in the absence of kidney disease.[9–12] Recent grading systems for chronic changes are not age-calibrated, but acknowledge uncertainty as to whether age-related changes are of prognostic importance.[8]

A recent study used carefully screened living kidney donors data to calculate the upper reference limit (95th percentile) for the number of globally sclerotic glomeruli (GSG) at a given age and number of glomeruli on a biopsy specimen (https://qxmd.com/calculate/glomerulosclerosis-on-biopsy-2015).[13] The clinical relevance of determining whether the amount of GSG on a patient's biopsy specimen is abnormal is unclear. In particular, is any global glomerulosclerosis of prognostic significance or just glomerulosclerosis that is abnormal for age? For example, 3 of 20 glomeruli being globally sclerosed would be a biopsy finding commonly expected for a healthy 60-year-old individual (95th percentile would be 4 globally sclerosed glomeruli) but abnormal for a 20-year-old individual (the 95th percentile would be 1 globally sclerotic glomerulus) (Table 1). The older patient may only have a gradual process of age-related nephrosclerosis of limited clinical relevance, whereas the younger patient may have a more rapid glomerular loss from an underlying disease with an increased risk of kidney failure. However, validation of these age-based reference limits has not yet been performed in a diseased population. Whether glomerulosclerosis is prognostically important independent of other clinical characteristics and biopsy findings is also unclear.

To validate the prognostic utility of age-based reference limits for glomerulosclerosis, we assessed the risk of kidney

Table 1 | Upper reference limit (95th percentile) for the number of globally sclerotic glomeruli based on age and number of glomeruli

	No. of glomeruli							
Age (yr)	1	2	3–4	5–8	9–16	17–32	33–48	49–64
18–29	0.5	0.5	0.5	0.5	1	1	1	1
30–34	0.5	0.5	0.5	0.5	1	1	1	1.5
35–39	0.5	0.5	0.5	0.5	1	1.5	2	2
40–44	0.5	0.5	0.5	1	1	2	2.5	3
45–49	0.5	0.5	1	1	1.5	2	3	4
50–54	1	1	1	1.5	2	3	4	5
55–59	1	1	1.5	1.5	2	3.5	4.5	6
60–64	1	1.5	1.5	2	2.5	4	5.5	7
65–69	1	2	2	2.5	3	4.5	6.5	8
70–74	1	2	2.5	3	4	5.5	7.5	9
75–77	1	2	2.5	3	4	6	8	9.5

These 95th percentile thresholds were determined with quantile regression using 1847 healthy normotensive living kidney donors in the Aging Kidney Anatomy study.[13] The percentage globally sclerotic glomeruli for these thresholds decreases with more glomeruli undergoing biopsy. For example, a 70-year-old patient with 5 glomeruli would have a 95th percentile of 60% (3/5) but with 49 glomeruli would have a 95th percentile of 18% (9/49). This occurs because the precision for distinguishing abnormal from normal improves when more glomeruli undergo biopsy.

disease progression as predicted by glomerulosclerosis in 3 different cohorts of patients defined by glomerulopathy on biopsy that often presents with nephrotic syndrome. Our primary objective was to compare the risk of kidney disease progression between patients with no GSG, GSG normal for age, and GSG abnormal for age. Our secondary objective was to determine whether GSG abnormal for age is predictive of kidney disease progression independent of other clinical and biopsy characteristics and across different populations.

RESULTS

There were a total of 425 patients studied; 183 patients from the Nephrotic Syndrome Study Network (NEPTUNE) cohort, 129 from the China-Digital Kidney Pathology (China DiKiP) cohort, and 113 patients from the Southeast (SE) Minnesota cohort (Figure 1). Baseline characteristics for each cohort and the overall cohort are summarized in Table 2. The prospective NEPTUNE cohort had up to 5 years of follow-up, with 28% leaving the study (2% died); the prospective China DiKiP cohort had up to 4.6 years of follow-up, with 18% leaving the study (0.5% died); and the historical SE Minnesota cohort had up to 22 years of follow-up, with 29% lost to follow-up in the medical record (12% died). Compared with the NEPTUNE and SE Minnesota cohorts, the China DiKiP cohort was younger; had a lower body mass index, less hypertension, and less diabetes; had higher estimated glomerular filtration rate (eGFR); had more minimal change disease (MCD) and less focal segmental glomerulosclerosis (FSGS); and had a lower incidence of CKD progression. The NEPTUNE and SE Minnesota cohorts were more similar.

The mean ± SD of the total number of glomeruli present on biopsy specimen was 24 ± 17 glomeruli (16% had <10 glomeruli with the fewest being 3 glomeruli, 31% had 10–19, 26% had 20–29, and 27% had >29 glomeruli). By global glomerulosclerosis category, 170 patients (40%) had no GSG, 107 patients (25%) had GSG normal for age, and 148 patients (35%) had GSG abnormal for age. Because GSG abnormal for age was defined using the 95th percentile threshold in healthy kidney donors, this exceeds what would be expected in a healthy population (35% vs. expected 5%, $P < 0.0001$). By primary diagnosis, FSGS (56% vs. expected 5.0%, $P < 0.0001$) and membranous nephropathy (MN) (19% vs. expected 5.0%, $P < 0.0001$) had more GSG than expected in a healthy population, but MCD (6.5% vs. expected 5.0%, $P = 0.53$) did not. The percentage of GSG showed substantial overlap between patients with GSG normal for age and patients with GSG abnormal for age for each of the 3 diagnoses (Figure 2).

Table 3 compares the characteristics of those with no GSG, GSG normal for age, and GSG abnormal for age. The presence of GSG normal for age compared with no GSG was associated with older age, hypertension, diabetes, and a lower eGFR. On multivariable analysis adjusting for each other clinical characteristic, only older age (odds ratio = 1.07 per year, $P < 0.001$) was independently associated with GSG normal for age compared with no GSG. The presence of GSG abnormal for age compared with no GSG was associated with older age, higher body mass index, hypertension, diabetes, lower proteinuria, and lower eGFR. On multivariable analysis including each of these clinical characteristics (age, body mass index, hypertension, diabetes, proteinuria, and eGFR), only lower eGFR ($P < 0.0001$) and lower proteinuria ($P = 0.01$) were independently associated with GSG abnormal for age compared with no GSG. Other biopsy findings (IFTA, arteriolar hyalinosis, and arteriosclerosis) were higher in those with GSG (normal or abnormal for age) compared with no GSG. The amount of IFTA was markedly more severe with GSG abnormal for age compared with GSG normal for age, whereas arteriosclerosis and arteriolar hyalinosis were only slightly more severe with GSG abnormal for age compared with GSG normal for age.

The risk of CKD progression was not different in those with GSG normal for age compared with no GSG (hazard ratio = 1.0, $P = 0.98$) but was higher in those with GSG abnormal for age compared with no GSG (HR = 3.7, $P < 0.0001$) (Figure 3). In a sensitivity analysis limited to NEPTUNE, classifying GSG as abnormal for age using digitally scanned and annotated images versus using clinical biopsy reports showed good agreement ($\kappa = 0.66$, $P < 0.0001$). Although the annotated images (rigorous method) detected more glomeruli (mean, 27 vs. 18, $P < 0.0001$) and more GSG (mean, 5 vs. 3, $P < 0.0001$) than the biopsy report (convenient method), the percentage of glomeruli that were GSG between the 2 methods showed a minimal difference (21% by annotated images vs. 20% by biopsy report, $P = 0.03$) and was highly correlated ($r = 0.90$). Furthermore, the risk of CKD progression with GSG abnormal for age compared with no GSG or GSG normal for age was similar by annotated images (HR = 2.4, $P = 0.0008$) or by pathology report (HR = 2.5, $P = 0.0006$) (Supplementary Figure S1).