ORIGINAL ARTICLE

Single-Nephron Glomerular Filtration Rate in Healthy Adults

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ABSTRACT

BACKGROUND

The glomerular filtration rate (GFR) assesses the function of all nephrons, and the single-nephron GFR assesses the function of individual nephrons. How the single-nephron GFR relates to demographic and clinical characteristics and kidney-biopsy findings in humans is unknown.

METHODS

We identified 1388 living kidney donors at the Mayo Clinic and the Cleveland Clinic who underwent a computed tomographic (CT) scan of the kidney with the use of contrast material and an iothalamate-based measurement of the GFR during donor evaluation and who underwent a kidney biopsy at donation. The mean single-nephron GFR was calculated as the GFR divided by the number of nephrons (calculated as the cortical volume of both kidneys as assessed on CT times the biopsy-determined glomerular density). Demographic and clinical characteristics and biopsy findings were correlated with the single-nephron GFR.

RESULTS

A total of 58% of the donors were women, and the mean (±SD) age of the donors was 44±12 years. The mean GFR was 115±24 ml per minute, the mean number of nephrons was 860,000±370,000 per kidney, and the mean single-nephron GFR was 80±40 nl per minute. The single-nephron GFR did not vary significantly according to age (among donors <70 years of age), sex, or height (among donors ≤190 cm tall). A higher single-nephron GFR was independently associated with larger nephrons on biopsy and more glomerulosclerosis and arteriosclerosis than would be expected for age. A higher single-nephron GFR was associated with a height of more than 190 cm, obesity, and a family history of end-stage renal disease.

CONCLUSIONS

Among healthy adult kidney donors, the single-nephron GFR was fairly constant with regard to age, sex, and height (if ≤190 cm). A higher single-nephron GFR was associated with certain risk factors for chronic kidney disease and certain kidney-biopsy findings. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases.)

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The glomerular filtration rate (GFR) is considered to be the most important assessment of kidney function. In clinical practice, the total GFR, which is the sum of all the single-nephron GFRs, is determined. Previous studies that have counted glomeruli at autopsy have shown considerable variation in the number of nephrons (210,000 to 2,700,000 nephrons per kidney),[1,2] owing to congenital factors (nephron endowment at birth) and acquired factors (loss of nephrons). Variation in the number of nephrons hinders the assessment of function at the nephron level. In particular, nephron loss may result in a compensatory increase in the single-nephron GFR, which allows the total GFR to remain unchanged.

Pioneering work in animals, in which glomeruli underwent direct in vivo measurement of the single-nephron GFR, showed that the single-nephron GFR increases to adapt to either a reduced number of nephrons or increased metabolic demand.[3,4] The single-nephron GFR varies according to genetic strains, decreases with volume depletion, and increases with age, body weight, acute volume expansion, and surgical removal of one kidney.[4-7] The extent to which data from animals apply to humans has proved elusive. Enlarged glomeruli in humans suggest maladaptive increases in the single-nephron GFR or hyperfiltration.[8-11] An increase in the single-nephron GFR is often inferred from an increase in the total GFR (since new nephrons are not generated).[12] However, to our knowledge, the determination of the actual single-nephron GFR in humans has not been possible.

We developed a method to determine the single-nephron GFR in living kidney donors. Kidney donors are selected on the basis of good health and thus do not have clinically evident chronic kidney disease or major risk factors for chronic kidney disease, such as diabetes or cardiovascular disease. Nonetheless, substantial variation exists among donors across categories of age, sex, height, kidney function, kidney-biopsy findings, and some risk factors for chronic kidney disease. Studying the association of the single-nephron GFR with these characteristics may provide insights into the function of the human nephron.

METHODS

STUDY POPULATION

We analyzed data from the Aging Kidney Anatomy study as described previously.[13-15] Data sources were all from the usual care of kidney donors, and the study was approved by an institutional review board with a waiver of informed consent.

The study population included living kidney donors from 2000 through 2011 at the Mayo Clinic, in Minnesota, and the Cleveland Clinic, in Ohio. Before donation, the donors underwent a computed tomographic (CT) scan of the kidneys with the use of contrast material and measurement of iothalamate clearance for the assessment of the total GFR, and at the time of donation, they underwent a needle-core biopsy of the donated kidney. Additional donors 65 years of age or older who had been patients at the Mayo Clinic in the period from 2012 through 2015 were included in the study to increase the sample of older donors. All the donors underwent a thorough medical evaluation before donation, with a prescheduled battery of tests.

Hypertension was defined as a blood pressure greater than 140/90 mm Hg or the use of antihypertensive medication to lower blood pressure. Only donors with mild hypertension (defined as a blood pressure that was either slightly elevated or controlled with one antihypertensive agent, with or without the use of a thiazide diuretic) were accepted. A family history of end-stage renal disease was determined according to biologic relationship to the kidney recipient. The predonation evaluation also included the determination of the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), the 24-hour urinary albumin excretion, and the serum uric acid level. Acceptable criteria for donation varied according to study site and calendar year, but mild hypertension in older donors and moderate obesity (BMI, 30 to 35) were generally allowed; the 24-hour urinary albumin excretion had to be less than 30 mg, and the total GFR had to be normal for the donor's age.[16]

KIDNEY-BIOPSY MORPHOMETRIC AND STEREOLOGIC ASSESSMENTS

A needle-core biopsy sample of the kidney cortex was obtained during the transplantation surgery. The tissue specimen was fixed in formalin and embedded in paraffin. Two consecutive 3-μm sections were stained (one with periodic acid–Schiff and one with Masson's trichrome) and scanned into high-resolution digital images (Aperio XT System scanner). The inclusion criteria for all the biopsy sections were that they could not contain an artifact that severely distorted microstructures,

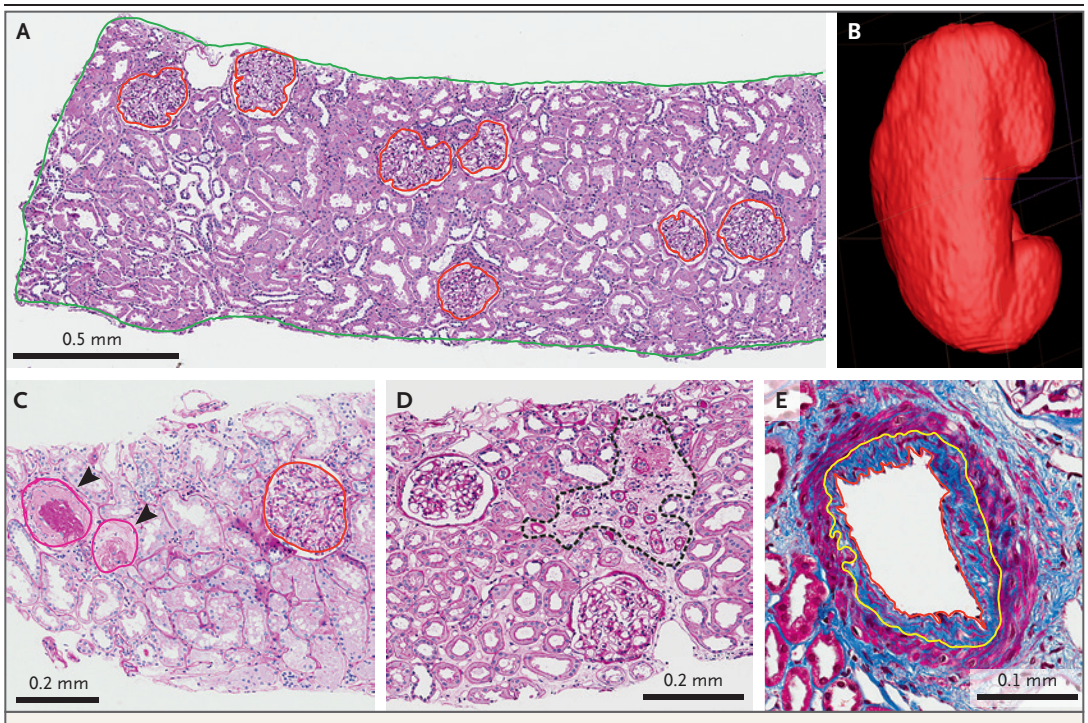

Figure 1. Kidney-Biopsy Sample with Structural Measurements.

The volume and density of nonsclerotic glomeruli were calculated with the use of stereologic assessments from the area of their cross sections (red outline) and the area of the cortex (green outline) (Panel A). The number of tubules in an area of cortex measuring 1 mm^2 (excluding glomeruli, fibrosis, and arteries) was used to calculate the mean cross-sectional tubular area. The volume of the kidney cortex was determined by means of CT scans with the use of contrast material (Panel B) and was multiplied by the nonsclerotic glomerular density to calculate the number of nephrons. Panel C shows a specimen with glomerulosclerosis (in >10% of glomeruli); the number of globally sclerotic glomeruli (pink outlined areas with arrowheads) was divided by the number of both nonsclerotic glomeruli (red outline) and globally sclerotic glomeruli. Panel D shows a specimen with interstitial fibrosis (in >5% of the cortex); the percentage of the cortex that had fibrosis with tubular atrophy (black dashed outline) was estimated by means of visual inspection. Panel E shows a specimen with arteriosclerosis (intimal thickening of >50% of an artery lumen within the biopsy sample; a threshold just met by the specimen shown); the percent of artery luminal stenosis was calculated from the area of intima (shown between the yellow and red outlines) divided by the area of intima plus lumen (inside the red outline).

they had to have an area with at least 2 mm^2 of cortex, and they had to have at least four glomeruli.

Specific measurements of nephron size were the mean nonsclerotic glomerular volume and the mean cross-sectional tubular area (Fig. 1). Specific measurements of nephrosclerosis were glomerulosclerosis (globally sclerosed glomeruli in ≥10% of all glomeruli), interstitial fibrosis (fibrosis and tubular atrophy of >5% of the cortex), and arteriosclerosis (intimal thickening of >50% of an artery lumen within the biopsy sample) (Fig. 1). The total number of nephrons was calculated as the density of nonsclerotic glomeruli in the biopsy sample times the cortical volume of both kidneys and rounded to the nearest 10,000 nephrons. The single-nephron GFR was then calculated as the total GFR divided by the calculated total number of nephrons (see the Detailed Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

STATISTICAL ANALYSIS

Age was categorized as 18 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 64 years, 65 to 69 years, and 70 to 75 years. The mean total GFR, the mean number of nephrons, and the mean single-nephron GFR were calculated for each age group. Multivariable linear regression was used to evaluate the relation between the single-nephron GFR and age (as a continuous variable), sex, BMI (continuous variable), height (continuous variable), the serum uric acid level (continuous variable),

Table 1. Characteristics of the Living Kidney Donors at Donation.*

Characteristic	Donors (N=1388)
Age — yr	44.2±11.9
Female sex — no. (%)	809 (58.3)
Height — cm	171.0±9.5
Race — no. (%)†	
White or unknown	1301 (93.7)
Black	30 (2.2)
American Indian or Alaska Native	10 (0.7)
Asian	20 (1.4)
Other	27 (2.0)
Risk factors	
Family history of end-stage renal disease — no. (%)	728 (52.5)
Mild hypertension — no. (%)	167 (12.0)
Body-mass index‡	27.9±4.9
Uric acid — mg/dl§	5.2±1.4
Kidney function	
Measured total GFR — ml/min	115±24
24-hr urinary albumin excretion — mg¶	5.2±8.7
Biopsy results‖	
Nonsclerotic glomerular volume — mm^3	0.0027±0.0010
Tubular area — μm^2	4669±1490
Glomerulosclerosis — no. (%)	149 (10.7)
Arteriosclerosis — no./total no. (%)	285/1210 (23.6)
Interstitial fibrosis — no. (%)	57 (4.1)
Calculated nephron-related values	
No. of nephrons per kidney	860,000±370,000
Single-nephron GFR — nl/min	80±40

* Plus–minus values are means ±SD. GFR denotes glomerular filtration rate.
† Race was determined from medical records.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ To convert values for uric acid to micromoles per liter, multiple by 59.48.
¶ The 24-hour urinary albumin excretion was assessed in 1221 donors at the Minnesota site only.
‖ Glomerulosclerosis was defined as global sclerosis in more than 10% of the glomeruli, arteriosclerosis as intimal thickening of more than 50% of an artery lumen within the biopsy sample, and interstitial fibrosis as fibrosis and tubular atrophy in more than 5% of the cortex.

family history of end-stage renal disease (yes vs. no), and hypertension (yes vs. no). An additional model included the 24-hour urinary albumin excretion as a predictor with the use of only the donors at the Minnesota site (data not available at the Ohio site). Separate multivariable regression models examined the relation between the single-nephron GFR and the findings of nephrosclerosis and the measurement of nephron size on biopsy. The associations of the number of nephrons and the total GFR with these same demographic, clinical, and biopsy-sample characteristics were also assessed in multivariable models. To assess the robustness of the associations, sensitivity analyses were performed that limited the sample to donors with at least 4 mm^2 of cortex in the tissue obtained during biopsy or to donors younger than 70 years of age, and site-specific analysis was performed. All the statistical analyses were performed with the use of JMP software, version 10.0 (SAS Institute).

RESULTS

DONOR CHARACTERISTICS

We identified 1388 living kidney donors (1282 donors at the Mayo Clinic [25 of whom were added to increase the sample of donors ≥65 years of age] and 106 at the Cleveland Clinic) who had undergone a CT scan and kidney biopsy to determine the number of nephrons and an iothalamate clearance to determine the total GFR. Arteriosclerosis was assessed in the 1210 donors who had an artery present in the kidney-biopsy sample, and 24-hour urinary albumin excretion values were available in 1221 donors. The demographic, clinical, biopsy-sample, and CT characteristics of the donors are presented in Table 1.

ASSOCIATIONS WITH DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The number of nephrons per kidney and the total GFR both declined with age, whereas the single-nephron GFR remained stable at approximately 79 nl per minute until 70 years of age (Table 2, and Fig. S1A in the Supplementary Appendix). The single-nephron GFR was higher among the 13 donors who were 70 to 75 years of age at donation than among donors younger than 70 years of age (110 vs. 79 nl per minute, P<0.001), which reflects nephron loss that exceeds the age-related decline in the total GFR. The total GFR did not show the expected decline from the subgroup of donors 65 to 69 years of age to the subgroup of donors 70 to 75 years of age, but there were few donors in the oldest group. The number of nephrons was higher in men than in women (910,000 vs. 830,000, P<0.001), as was the total GFR (124 vs. 108 ml per minute, P<0.001). However, the single-

Table 2. Age-Group Differences in the Number of Nephrons per Kidney, the Single-Nephron GFR, and Total GFR among 1388 Living Kidney Donors.

Age Group	No. of Donors	No. of Nephrons	Single-Nephron GFR	Total GFR
			nl/min	*ml/min*
18–29 yr	190	970,000±430,000	79±42	127±25
30–39 yr	339	930,000±350,000	77±36	124±24
40–49 yr	417	850,000±360,000	81±42	114±23
50–59 yr	300	810,000±360,000	80±40	106±20
60–64 yr	73	750,000±310,000	79±36	101±18
65–69 yr	56	720,000±260,000	76±33	95±17
70–75 yr	13	480,000±170,000	110±44	96±25

Table 3. Demographic and Clinical Characteristics as Predictors of the Number of Nephrons per Kidney, Single-Nephron GFR, and Total GFR.*

Characteristic	No. of Nephrons		Single-Nephron GFR		Total GFR	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
			nl/min		*ml/min*	
Age, per 10 yr	–60,000	<0.001	1	0.28	–7.1	<0.001
Female sex	–60,000	0.03	6	0.08	–3.8	0.01
Body-mass index, per SD	0	0.85	6	<0.001	9.6	<0.001
Height, per SD†	30,000	0.03	4	0.006	9.2	<0.001
Uric acid, per SD	–40,000	0.002	1	0.42	–3.7	<0.001
Family history of end-stage renal disease	–70,000	<0.001	8	<0.001	0.8	0.43
Mild hypertension	–20,000	0.59	3	0.39	1.5	0.36

* The estimate is the difference with the presence of the characteristic versus its absence (female sex vs. male sex; presence vs. absence of family history of end-stage renal disease; and mild hypertension vs. no hypertension) or with the level increase of the characteristic (for age, body-mass index, height, and uric acid level). The standard deviation (SD) was 4.9 for body-mass index, 9.5 cm for height, and 1.4 mg per deciliter (80 μmol per liter) for uric acid. The analysis was adjusted for each of the other demographic or clinical characteristics in the 1388 donors.
† Statistical significance for the single-nephron GFR was influenced by donors with a height of more than 190 cm.

nephron GFR did not differ significantly between men and women (81 nl per minute and 79 nl per minute, respectively; P=0.28) (Fig. S1B, S1C, and S1D in the Supplementary Appendix).

In an analysis that was adjusted for each of the other clinical characteristics, higher BMI, taller height, and family history of end-stage renal disease were associated with a higher single-nephron GFR (Table 3). Of these variables, higher BMI and taller height were also associated with higher total GFR. Older age, female sex, shorter height, and higher uric acid levels were associated with a lower total GFR because these characteristics were associated with a lower number of nephrons. The association of a family history of end-stage renal disease with both a lower number of nephrons and a higher single-nephron GFR resulted in no association with the total GFR. Mild hypertension was not associated with the number of nephrons, the single-nephron GFR, or the total GFR. In models that included 24-hour urinary albumin excretion values, a higher urinary albumin excretion was associated with a higher total GFR but was not associated with either the number of nephrons or the single-nephron GFR (Table S1 in the Supplementary Appendix).

In an unadjusted analysis, we also observed an increase in the single-nephron GFR with higher

BMI (P<0.001 for trend). The single-nephron GFR was not associated with height (as a continuous variable) up to 190 cm in men or women (P>0.05 for the comparisons in each sex subgroup), but the 31 participants who were taller than 190 cm (all men) had a higher single-nephron GFR than did other donors (98 vs. 79 nl per minute, P=0.008). These tall donors also had a higher total GFR than other donors (147 vs. 114 ml per minute, P<0.001), although the number of nephrons was similar (900,000 and 860,000, respectively; P=0.55). Donors with a family history of end-stage renal disease had a higher single-nephron GFR than did those without such a family history (83 vs. 75 nl per minute, P=0.002). Details are provided in Figure S2 in the Supplementary Appendix.

ASSOCIATIONS WITH BIOPSY FINDINGS

The kidney-biopsy findings of glomerulosclerosis, arteriosclerosis, larger glomerular volume, and larger tubular area were independently associated with a higher single-nephron GFR (Table 4, and Figs. S3 and S4 in the Supplementary Appendix). Nephrosclerosis (specifically, glomerulosclerosis or arteriosclerosis) was associated with both a lower number of nephrons and a higher single-nephron GFR, and the net effect was no association with total GFR. The status of having larger nephrons (larger glomerular volume or tubular cross-sectional area) was also associated with both a lower number of nephrons and a higher single-nephron GFR, but the net effect was an association with a higher total GFR.

To estimate whether the clinical characteristics that were associated with the single-nephron GFR were mediated by larger nephron size or nephrosclerosis, we performed multivariable analyses with demographic and clinical characteristics and with biopsy-sample characteristics (Table S2 in the Supplementary Appendix). The associations of a higher single-nephron GFR with higher BMI, taller height, and family history of end-stage renal disease were attenuated in the analysis that was adjusted for nephron size, which suggests that larger nephrons are the main reason that a higher single-nephron GFR is associated with these clinical characteristics.

SENSITIVITY ANALYSES

The associations of demographic, clinical, and biopsy-sample characteristics with the single-nephron GFR did not differ significantly according to age (P>0.05 for all age-by-characteristic interactions), nor did they substantially change in analyses that were limited either to donors who had a biopsy sample with at least 4 mm^2 of cortex or to donors younger than 70 years of age. Associations were consistent between the two study sites except that we found that higher BMI was not associated with a higher single-nephron GFR at the Ohio site. Details are provided in Tables S3 through S6 in the Supplementary Appendix.

Table 4. Biopsy-Sample Characteristics as Predictors of the Number of Nephrons per Kidney, Single-Nephron GFR, and Total GFR.*

Characteristic	No. of Nephrons		Single-Nephron GFR		Total GFR	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
			nl/min		*ml/min*	
Nephrosclerosis						
Interstitial fibrosis	20,000	0.58	−8	0.11	−2.4	0.44
Glomerulosclerosis	−200,000	<0.001	22	<0.001	−1.1	0.58
Arteriosclerosis	−50,000	0.03	8	0.001	1.8	0.21
Nephron size						
Glomerular volume, per SD	−160,000	<0.001	18	<0.001	2.8	<0.001
Tubular area, per SD	−30,000	<0.001	4	<0.001	1.7	0.01

* The estimate is the difference with the presence of the characteristic versus its absence (for each nephrosclerosis category) or with the level increase of the characteristic (for nephron size). The standard deviation (SD) was 0.0010 mm^3 for glomerular volume and 1490 μm^2 for tubular area. The analysis was adjusted for age, sex, and each of the other biopsy-sample characteristics in the 1210 donors who had an artery present within the kidney-biopsy sample.

DISCUSSION

A key finding in the present study is that the single-nephron GFR varied little according to age, sex, and height (if ≤190 cm), despite substantial variation in the number of nephrons in this population of normal, healthy kidney donors. This absence of significant variation in the single-nephron GFR suggests that nephron function is similar across common physiological differences among healthy humans. Certain acquired risk factors for chronic kidney disease (e.g., obesity) or inherent risk factors for chronic kidney disease (e.g., family history of end-stage renal disease) were associated with a higher single-nephron GFR, which appears to be driven by larger individual nephron size. Nephrosclerosis that was observed in a biopsy sample and that exceeded a level that would be expected for age was correlated with a higher single-nephron GFR, independent of nephron size.

We observed a higher single-nephron GFR among the very few donors who were 70 years of age or older than among younger donors, which we speculate is attributable to the selection bias that probably occurs with the oldest donors. Although age-based criteria were used to select donors, persons with a total GFR below a threshold of approximately 70 to 80 ml per minute are not accepted as donors, regardless of age.

The number of nephrons declines with age, owing to nephrosclerosis[15]; but the single-nephron GFR in the remaining nonsclerotic glomeruli does not increase with age (at least among persons <70 years of age). The mechanisms underlying the failure to compensate for this loss of nephrons are unclear but might be due to a concurrent decrease in metabolic demand that could influence the GFR. The absence of an increase in glomerular volume[14] or glomerular filtering capacity[17] with healthy aging is consistent with that observation. There was no evidence of effect modification according to age on the higher single-nephron GFR that was associated with other characteristics.

Several plausible mechanisms may account for the associations of clinical characteristics and biopsy-sample findings with a higher single-nephron GFR. Obesity is a risk factor for chronic kidney disease[18] and is known to increase the total GFR.[19] Obesity increases renal metabolic demand, leading to an increase in the single-nephron GFR that can become maladaptive, resulting in obesity-related glomerulopathy.[10] Patients with a family history of end-stage renal disease may have a familial predisposition toward fewer nephrons because of genetic and epigenetic factors.[1] However, an increased single-nephron GFR compensates for fewer nephrons, resulting in a sustained total GFR.

Height was associated with a higher total GFR, which was related primarily to a higher number of nephrons but also possibly related to a higher single-nephron GFR in the relatively few participants who were taller than 190 cm. Adult height correlates directly with birth weight,[20] and birth weight may be considered to be a surrogate for nephron endowment.[21] To our knowledge, there is no evidence that tall stature (>190 cm) is a risk factor for chronic kidney disease. However, tall stature in a person who had a low birth weight (and for whom there may be low nephron endowment) has been linked to hypertension,[22,23] which is a risk factor for chronic kidney disease.

Nephrosclerosis is an ischemic process that leads to nephron loss. The presence of nephrosclerosis probably explains the age-related decline in the total GFR over time.[14,15,24] Seemingly healthy persons can also have more nephrosclerosis than expected for their age, yet may not have a further reduction in the total GFR.[14,24] This study showed that nephrosclerosis exceeding that expected for age decreased the number of nephrons but was generally accompanied by a compensatory higher single-nephron GFR, which maintained the total GFR. The apparent failure of the single-nephron GFR to increase with the expected age-related nephron loss, whereas it increased with nephrosclerosis beyond the level expected for age, may support an age-based approach to the identification of chronic kidney disease.[25]

Previous studies have linked larger nephrons to a higher single-nephron GFR in an animal model,[26] and the present study extends this finding to humans. In studies in animals, surgical renal ablation leads to a higher glomerular pressure and blood flow, which drives increases in both glomerular size and single-nephron GFR.[11] Indeed, glomerular enlargement with a higher single-nephron GFR may prevent nephron destruction caused by glomerular hypertension.[27] In the present study, we observed an association of some clinical characteristics with a higher single-nephron GFR (obesity, family history of end-stage renal

disease, and height >190 cm), and these findings are also associated with larger nephrons.[14] Nephrosclerosis was associated with a higher single-nephron GFR, independent of nephron size. Thus, a larger nephron size on biopsy is an imperfect surrogate for a higher single-nephron GFR. The identification of the point at which a high single-nephron GFR becomes maladaptive and leads to chronic kidney disease would entail additional studies in populations that are less healthy than the donors we studied.

Our study has certain limitations. The Weibel–Gomez stereologic models do not account for variation in the glomerular volume distribution within biopsy samples, which may have introduced a small level of bias in the nephron-number estimates. Nonetheless, our estimates of the number of nephrons in living humans are similar to those calculated by the disector–fractionator method that is applied to kidneys obtained from an autopsy.[15,28] There is also good agreement between the Weibel–Gomez method and a method based on assessment of multiple consecutive kidney-biopsy sections.[29] We could determine only the mean single-nephron GFR, which might be higher in deep glomeruli than in superficial glomeruli.[30] The coefficient of variation for repeat-test single-nephron GFR is estimated at 41% on the basis of a coefficient of variation of 33% for the number of nephrons[15] and a coefficient of variation of 8% for the total GFR.[31] Therefore, for population-level inferences, the mean number of nephrons could be reasonably estimated only to the nearest 10,000 nephrons, and the mean single-nephron GFR to the nearest 1 nl per minute; neither may have sufficient reliability for individual-level inferences. The study population was limited in that most of the living kidney donors were white. Selection on the basis of health probably biased the associations toward the null hypothesis. A higher single-nephron GFR might be associated with more severe hypertension and albuminuria than was seen in our study.

In conclusion, the single-nephron GFR can be calculated in living humans when a measured total GFR, kidney-biopsy sample, and cortical volume of the kidneys determined by means of radiographic imaging are available.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Hoy WE, Ingelfinger JR, Hallan S, Hughson MD, Mott SA, Bertram JF. The early development of the kidney and implications for future health. J Dev Orig Health Dis 2010;1:216-33.
2. Bertram JF, Douglas-Denton RN, Diouf B, Hughson MD, Hoy WE. Human nephron number: implications for health and disease. Pediatr Nephrol 2011;26:1529-33.
3. Brenner BM, Troy JL, Daugharty TM, Deen WM, Robertson CR. Dynamics of glomerular ultrafiltration in the rat. II. Plasma-flow dependence of GFR. Am J Physiol 1972;223:1184-90.
4. Hayslett JP, Kashgarian M, Epstein FH. Functional correlates of compensatory renal hypertrophy. J Clin Invest 1968;47:774-99.
5. Brenner BM, Bennett CM, Berliner RW. The relationship between glomerular filtration rate and sodium reabsorption by the proximal tubule of the rat nephron. J Clin Invest 1968;47:1358-74.
6. Horster M, Valtin H. Postnatal development of renal function: micropuncture and clearance studies in the dog. J Clin Invest 1971;50:779-95.
7. Brenner BM, Daugharty TM. The measurement of glomerular filtration rate in single nephrons of the rat kidney. Yale J Biol Med 1972;45:200-10.
8. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol 2012;8:293-300.
9. Hodgin JB, Bitzer M, Wickman L, et al. Glomerular aging and focal global glomerulosclerosis: a podometric perspective. J Am Soc Nephrol 2015;26:3162-78.
10. D'Agati VD, Chagnac A, de Vries AP, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. Nat Rev Nephrol 2016;12:453-71.
11. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 1981;241:F85-F93.
12. Melsom T, Stefansson V, Schei J, et al. Association of increasing GFR with change in albuminuria in the general population. Clin J Am Soc Nephrol 2016;11:2186-94.
13. Elsherbiny HE, Alexander MP, Kremers WK, et al. Nephron hypertrophy and glomerulosclerosis and their association with kidney function and risk factors among living kidney donors. Clin J Am Soc Nephrol 2014;9:1892-902.
14. Denic A, Alexander MP, Kaushik V, et al. Detection and clinical patterns of nephron hypertrophy and nephrosclerosis among apparently healthy adults. Am J Kidney Dis 2016;68:58-67.
15. Denic A, Lieske JC, Chakkera HA, et al. The substantial loss of nephrons in healthy human kidneys with aging. J Am Soc Nephrol 2017;28:313-20.
16. Poggio ED, Rule AD, Tanchanco R, et al. Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. Kidney Int 2009;75:1079-87.
17. Tan JC, Busque S, Workeneh B, et al. Effects of aging on glomerular function and number in living kidney donors. Kidney Int 2010;78:686-92.
18. Kramer H, Luke A, Bidani A, Cao G, Cooper R, McGee D. Obesity and prevalent and incident CKD: the Hypertension Detection and Follow-Up Program. Am J Kidney Dis 2005;46:587-94.
19. Hall JE, Brands MW, Dixon WN, Smith MJ Jr. Obesity-induced hypertension: renal function and systemic hemodynamics. Hypertension 1993;22:292-9.
20. Eide MG, Øyen N, Skjaerven R, Nilsen ST, Bjerkedal T, Tell GS. Size at birth and gestational age as predictors of adult height and weight. Epidemiology 2005;16:175-81.

21. Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. Am J Kidney Dis 1994;23:171-5.
22. Eriksson J, Forsén T, Tuomilehto J, Osmond C, Barker D. Fetal and childhood growth and hypertension in adult life. Hypertension 2000;36:790-4.
23. Leon DA, Koupilova I, Lithell HO, et al. Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. BMJ 1996;312:401-6.
24. Rule AD, Amer H, Cornell LD, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med 2010;152:561-7.
25. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. Adv Chronic Kidney Dis 2016;23:19-28.
26. Wang X, Johnson AC, Williams JM, et al. Nephron deficiency and predisposition to renal injury in a novel one-kidney genetic model. J Am Soc Nephrol 2015;26:1634-46.
27. Lenihan CR, Busque S, Derby G, Blouch K, Myers BD, Tan JC. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. J Clin Invest 2015;125:1311-8.
28. Bertram JF. Counting in the kidney. Kidney Int 2001;59:792-6.
29. Fulladosa X, Moreso F, Narváez JA, Grinyó JM, Serón D. Estimation of total glomerular number in stable renal transplants. J Am Soc Nephrol 2003;14:2662-8.
30. Horster M, Thurau K. Micropuncture studies on the filtration rate of single superficial and juxtamedullary glomeruli in the rat kidney. Pflugers Arch Gesamte Physiol Menschen Tiere 1968;301:162-81.
31. Rule AD, Bailey KR, Lieske JC, Peyser PA, Turner ST. Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. Kidney Int 2013;83:1169-76.