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Detection and Clinical Patterns of Nephron Hypertrophy and Nephrosclerosis Among Apparently Healthy Adults

Aleksandar Denic, MD, PhD^{#1}, Mariam P. Alexander, MD^{#2}, Vidhu Kaushik, MBBS², Lilach O. Lerman, MD, PhD¹, John C. Lieske, MD¹, Mark D. Stegall, MD⁴, Joseph J. Larson³, Walter K. Kremers, PhD³, Terri J. Vrtiska, MD⁵, Harini A. Chakkera, MD⁶, Emilio D. Poggio, MD⁷, and Andrew D. Rule, MD, MSc¹

¹ Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

² Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

³ Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota

⁴ Division of Transplant Surgery, Mayo Clinic, Rochester, Minnesota

⁵ Department of Radiology, Mayo Clinic, Rochester, Minnesota

⁶ Division of Nephrology and Hypertension, Mayo Clinic, Arizona.

⁷ Department of Nephrology, Cleveland Clinic, Cleveland, Ohio.

[#] These authors contributed equally to this work.

Abstract

Background—Even among ostensibly healthy adults, there is often mild pathology in the kidney. The detection of kidney microstructural variation and pathology by imaging and the clinical pattern associated with these structural findings is unclear.

Study Design—Cross-sectional (clinical-pathological correlation).

Setting & Participants—Living kidney donors at Mayo Clinic (Minnesota and Arizona sites) and Cleveland Clinic 2000–2011.

Correspondence and offprint requests to: Andrew D. Rule, Mayo Clinic 200 1st St SW, Rochester, MN 55905, Phone: 507-266-1045, Fax: 507-266-7891, rule.andrew@mayo.edu.

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Contributions: Research idea and study design: ADR; data acquisition: AD, MPA, VK, MDS, HAC, EDP; data analysis/interpretation: AD, MPA, ADR, LOL, JCL, MDS, TJV, HAC, EDP; statistical analysis: AD, JLL, WKK, ADR; supervision or mentorship: ADR. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ADR takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Predictors—Pre-donation kidney function, risk factors, and contrast computed tomography scan of the kidneys. These scans were segmented for cortical volume and medullary volume, reviewed for parenchymal cysts, and scored for kidney surface roughness.

Outcomes—Nephrosclerosis (glomerulosclerosis, interstitial fibrosis/tubular atrophy, and arteriosclerosis) and nephron size (glomerular volume, profile tubular area, and cortical volume per glomerulus) determined from an implantation biopsy of the kidney cortex at donation.

Results—Among 1520 living kidney donors, nephrosclerosis associated with increased kidney surface roughness, cysts, and smaller cortical to medullary volume ratio. Larger nephron size (nephron hypertrophy) associated with larger cortical volume. Nephron hypertrophy and larger cortical volume associated with higher systolic blood pressure, higher glomerular filtration rate, higher urine albumin excretion, larger body mass index, higher serum uric acid, and family history of end-stage renal disease. Both nephron hypertrophy and nephrosclerosis associated with older age and mild hypertension. The net effect of both nephron hypertrophy and nephrosclerosis associating with cortical volume was that nephron hypertrophy diminished volume loss with age-related nephrosclerosis and fully negated volume loss with mild hypertension-related nephrosclerosis.

Limitations—Kidney donors are selected on health, restricting the spectrum of pathological findings. Kidney biopsies in living donors are a small tissue sample leading to imprecise estimates of structural findings.

Conclusions—Among apparently healthy adults, the microstructural findings of nephron hypertrophy and nephrosclerosis differ in their association with kidney function, macrostructure, and risk factors.

Keywords

Nephrosclerosis; arteriosclerosis; nephron hypertrophy; kidney volume; living kidney donor; subclinical renal pathology; biopsy; high-resolution imaging; contrast computed tomographic (CT) scan; kidney function; kidney macrostructure; kidney microstructure; hypertension; aging; chronic kidney disease (CKD) risk factor

The clinical assessment of kidney pathology relies almost exclusively on blood and urine markers to assess glomerular filtration rate (GFR) and detect proteinuria. Only select patients with severe kidney disease undergo a kidney biopsy to characterize underlying pathology. Blood and urine markers are convenient, safe, and relatively inexpensive, but are non-specific for the underlying pathology and are also confounded by non-kidney pathology and physiology.^{1, 2} Imaging studies could potentially detect macro-structural findings of the kidney that reflect underlying micro-structural pathology. A few studies have correlated imaging findings with kidney biopsy features, but have been limited to specific diseases or used ultrasound, which is relatively insensitive to the micro-structure of the kidney.³⁻¹⁰ It is unknown if high-resolution imaging can detect subclinical kidney pathology in apparently healthy adults without chronic kidney disease (CKD).

Studies have shown that contrast computed tomographic (CT) scans can detect kidney macro-structural variation that associates with age, kidney function, and CKD risk factors among ostensibly healthy adults without CKD.¹¹⁻¹⁵ Similarly, in this population, micro-

structural variations on kidney biopsy associate with age, kidney function and CKD risk factors.¹⁶⁻²¹ However, how macro-structure on CT relates to micro-structure on biopsy in apparently healthy adults is unknown. The patterns by which micro- and macro-structural kidney pathology associates with age, kidney function, and CKD risk factors are also unclear.

Therefore, we performed a multicenter study of living kidney donors who underwent an intensive kidney evaluation including a pre-donation contrast CT scan and an intra-operative kidney biopsy. Our goals were to describe how kidney macro-structure (CT) correlates with micro-structure (biopsy), identify structural findings that correlate with clinical characteristics, and to develop a conceptual model for how kidney structure, kidney function, and CKD risk factors inter-relate in apparently healthy adults.

METHODS

Study Population

The study population included living kidney donors who had undergone a core-needle biopsy of the donated kidney cortex during transplantation surgery at the three participating sites of the Aging Kidney Anatomy Study (Mayo Clinic, MN; Mayo Clinic, AZ; Cleveland Clinic, OH) during 2000-2011. These “time 0” biopsies provide baseline kidney histology for transplant programs that monitor the allograft with biopsies at regular intervals. The study was completed under Institutional Review Board approval; Minnesota donors without Minnesota Research Authorization were excluded.²²

All kidney donors underwent a thorough medical evaluation prior to donation with a prescheduled battery of tests. Acceptable criteria for donation varied by site and era, but in general included a 24-h urine albumin less than 30 mg and GFR normal for age; mild hypertension in older donors and moderate obesity (body mass index [BMI] <35 kg/m²) were allowed.²³ Patients with diabetes or cardiovascular disease were never accepted as donors. Hypertension was defined by an office blood pressure >140/90 mmHg or use of anti-hypertensive medication to lower blood pressure. The hypertension in donors can be qualified as “mild” as it was either borderline elevated blood pressure or controlled with one anti-hypertensive agent (with or without a thiazide diuretic). Potential donors with more severe hypertension were excluded from donation. Family history of end-stage renal disease (ESRD) was determined by the recipient being biologically related to the donor. The pre-donation evaluation included urinary iothalamate clearance to measure GFR, 24-h urine albumin excretion (except at Cleveland Clinic), BMI, and serum uric acid.

Macrostructure

There were multiple CT scanners and scanning protocols used across the 3 sites over the 12 years of study and slice thickness varied from 1 to 2 mm. The CT images from the angiogram/cortical phase were downloaded onto a workstation for processing. As described previously,¹¹ image analysts trained by a radiologist (T.J.V.) segmented kidney cortical and medullary volumes in a random order blinded to other donor characteristics using a semi-automated algorithm (ITK-SNAP software, version 2.2; University of Pennsylvania,

Philadelphia, PA).²⁴ The image analysts did not segment kidney volumes with CT images that had movement artifact or insufficient kidneys in the imaging window. Among donor CT scans with poor cortical-medullary differentiation due to timing issues with the intravenous contrast, the total kidney parenchymal volume (cortex and medulla) was instead segmented from non-contrast images, and cortical volume was estimated from this parenchymal volume. The cortical to medullary volume ratio was determined only in those who had directly measured cortex and medulla volumes.

One investigator (A.D.) scored all kidneys for surface roughness in a random order over a few days. The score was based on the involved proportion of the cortical surface: 0 if no roughness; 1, roughness up to 25%; 2, roughness of 26%-50%; and 3, roughness more than 50% (**Figure S1**, available as online supplementary material); congenital lobulation was not considered roughness. Presence of a parenchymal cysts ≥ 1 cm was identified (0-1 indicator variable) for each kidney. Presence of renal artery atherosclerosis defined by plaque or calcification not consistent with fibromuscular dysplasia was identified for each kidney (0-1 indicator variable).

Microstructure

Intra-operative needle core biopsy of the renal cortex was obtained at the time of donation. The tissue specimen was fixed in formalin and embedded in paraffin. Unstained sections from the tissue block were sent to the Mayo Clinic in Minnesota from the other sites for staining. Two sections (2- to 3- μ m thickness) from the biopsy core were stained, one with periodic acid-Schiff and one with Masson trichrome, and then scanned into high-resolution digital images (Aperio XT digital scanner, [Leica Biosystems](#)). **Item S1** describes the stereological measurements and equations used to characterize the microstructure from these images. *Nephron size* on biopsy was characterized by mean glomerular (non-sclerotic) volume, cortex volume per glomerulus (inverse of non-sclerotic glomerular density), and mean profile tubular area as previously described.¹⁸ *Nephrosclerosis* on biopsy was also characterized by glomerulosclerosis, ischemic (non-sclerotic) glomeruli, interstitial fibrosis and tubular atrophy, and arteriosclerosis (luminal stenosis or arteriolar hyalinosis). The number of non-sclerotic glomeruli, globally sclerotic glomeruli, and ischemic glomeruli (identified by periglomerular fibrosis, capsule thickening, and wrinkled tuft) were counted to determine percentage globally sclerotic glomeruli and percentage globally sclerotic and ischemic glomeruli. One renal pathologist (V.K.) characterized the proportion of cortical area occupied by fibrosis (0%, 1%-5%, 6%-10%, >10 %) (**Figure S2**) and number of distinct tubular atrophy/fibrosis foci. The percentage luminal stenosis was determined from the small-medium artery (if any) most orthogonal to its axis (**Figure S3**). Arteriolar hyalinosis evaluation was performed only at the Mayo Clinic, MN, site, as it required review of 10 biopsy sections for reasonable detection, and was defined as present or absent (0-1 indicator variable). Donors with a suboptimal biopsy section defined by compression artifact, less than 2 mm² of cortex, or less than 2 glomeruli were excluded.

Image processing analysis was centralized at one site (Mayo Clinic, MN) with training data, reproducibility studies, random order, and masking of donor characteristics to optimize accuracy and reliability of the image processing analysis.^{14, 18}

Statistical Analysis

Macro-structural measures were summed between the two kidneys (e.g., 0-1 indicator variables became three level ordinal variables 0, 1, and 2). Spearman's correlation between micro-structure on biopsy and the summed macro-structure of both kidneys on CT was performed. This correlation analysis was repeated between the micro-structure and macro-structure of the ipsilateral kidney and between the micro-structure and macro-structure of the contralateral kidney. Statistically significant differences between ipsilateral and contralateral correlations were determined from a common data set using bootstrap simulation. The Spearman's correlation of structural findings with age, mild hypertension (0-1 indicator variable), systolic blood pressure, measured GFR, 24-h urine albumin excretion, uric acid, and BMI was also assessed. Analysis with systolic blood pressure excluded donors with hypertension due to the blood pressure lowering effect of anti-hypertensive medication. These correlations were then age- and sex-adjusted using partial Spearman correlations.²⁵ Due to the nature of kidney donor-recipient relationships, donors with a family history of ESRD (often offspring donating to parent) were a mean 5 years younger than donors without a family history of ESRD (living unrelated donors). Thus, structural correlations with family history of ESRD were only reported with age-sex-adjustment. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, www.sas.com). Given the multiple correlations tested, $P < 0.01$ was used to define statistical significance.

RESULTS

Donor Characteristics

We identified, scanned, and reviewed the implantation kidney biopsies of 2085 donors. After excluding 244 with suboptimal biopsies and further excluding 321 who lacked usable CT scans, there were 1520 donors with both CT scans and biopsies available for study (1154 Mayo Clinic, MN; 275 Mayo Clinic, AZ; and 91 Cleveland Clinic site) (**Figure S4**). Measured GFR was available for analysis in 1401 (92%) and 24-h urine albumin in 1256 (83%) of these donors. The percentage luminal stenosis was evaluated in the 1324 (87%) donors who had a small-medium artery biopsied. Cortical volume was directly segmented in 1385 (91%) and estimated from total kidney volume in the remaining 135 (9%) donors. The clinical, biopsy, and CT characteristics of kidney donors are presented in **Table 1**. The mean age was 43 years, 41% were men, 53% had a family history of ESRD, 11% were hypertensive, 20% had some degree of interstitial fibrosis/tubular atrophy, 4% had a cyst > 1 cm, and 3% had any renal artery atherosclerosis. The mean blood pressure of hypertensive donors was 133/78 mm Hg compared to 119/72 mm Hg in normotensive donors. Among the hypertensive donors, 82% were treated with antihypertensive medications.

Correlation of Macrostructure on CT With Microstructure on Biopsy

The micro-structural findings on kidney biopsies were related to macro-structural findings on CT scan. Measures of larger nephron size correlated with larger cortical volume (**Table 2**). Nephron size measures correlated more strongly with larger cortical volume alone than with higher cortical to medullary volume ratio. Of the nephron size measures, larger non-sclerotic glomerular volume showed the strongest correlation with larger cortical volume. Measures of nephrosclerosis correlated more strongly with lower cortical to medullary

volume ratio than with smaller cortical volume alone (**Table 2**). Nephron size measures did not correlate with imaging pathology, except between cortex volume per glomerulus and renal artery atherosclerosis. Conversely, most biopsy measures of nephrosclerosis correlated with imaging pathology, except between percentage luminal stenosis and arteriolar hyalinosis. Arteriolar hyalinosis only correlated with renal artery atherosclerosis.

For most correlations of micro-structure with macro-structure, the degree of correlation was similar between the ipsilateral and contralateral kidney (**Table S1**). Some measures of nephrosclerosis were more correlated with cysts and renal artery atherosclerosis in the ipsilateral than contralateral kidney, but these differences were not statistically significant ($p>0.01$ for all).

Correlation of Clinical Characteristics With Macrostructure and Microstructure

Older age correlated with smaller cortical volume, imaging pathology, nephrosclerosis, and, to a lesser extent, larger nephron size on biopsy (**Table 3**). After age-sex-adjustment, mild hypertension correlated with imaging pathology, nephrosclerosis, and larger nephron size, but not cortical volume (**Table 4**). There was some evidence that lower GFR correlated with nephrosclerosis, but not after age-sex-adjustment. After age-sex-adjustment, larger cortical volume and nephron size correlated with higher systolic blood pressure, GFR, urine albumin, serum uric acid, and BMI (**Table 4**). Family history of ESRD correlated with larger nephron size but not cortical volume. Kidney surface roughness also correlated with higher BMI. Luminal stenosis correlated with lower 24-h urine albumin.

Sensitivity Analysis

Correlations with cortical volume were not substantively different excluding donors in whom cortical volume was estimated from total parenchymal volume instead of directly measured (**tables a-d of Item S2**).

DISCUSSION

Kidney cortical volume is primarily determined by the number and size of nephrons. The micro-anatomy correlations that we identified are consistent with two competing processes affecting cortical volume. The first is nephron hypertrophy leading to larger nephrons as detected by larger glomerular volume, cortex volume per glomerulus, and profile tubular area. The second is nephrosclerosis, a process that can be driven by ischemia from arteriosclerosis and leads to glomerulosclerosis and tubular atrophy.²⁶ Nephrosclerosis is initially observed in more superficial glomeruli where antecedent tubules contribute more to the cortex volume, and may be accompanied by compensatory hypertrophy of deeper (juxtamedullary) glomeruli whose antecedent tubules contribute more to medullary volume.¹⁹ These observations might explain why nephrosclerosis is more strongly correlated with a lower cortical to medullary volume ratio than lower cortical volume alone.

This study helps clarify the relationship between kidney risk factors, micro-structure, macro-structure, and function among apparently healthy adults (**Figure 1**). Age, mild hypertension, family history of ESRD, obesity, and hyperuricemia are all risk factors for underlying nephron hypertrophy, while age and mild hypertension are also risk factors for underlying

nephrosclerosis. Nephron hypertrophy associates with a larger cortical volume and associates with higher GFR and albuminuria. Nephrosclerosis associates with a smaller cortical volume, increases kidney surface roughness and parenchymal cysts, and associates with lower GFR and hypertension. Notably, nephrosclerosis and nephron hypertrophy have opposing associations with cortical volume. The net effect of these two associations with aging is smaller cortical volume, but with mild hypertension the net effect is no change in cortical volume. In donors without hypertension, systolic blood pressure was more correlated with nephron hypertrophy than nephrosclerosis, suggesting nephron hypertrophy may precede nephrosclerosis that occurs with hypertension.

Surface roughness may be attributable to the preferential loss of superficial nephrons in an irregular pattern due to variable arteriosclerosis of vessels supplying these nephrons.¹⁹ Surface roughness is also observed with gross pathological examination of kidneys from patients with hypertensive nephrosclerosis.²⁶ We found surface roughness to correlate with BMI, possibly due to asymmetrical nephron hypertrophy in cortical regions with less nephrosclerosis. Renal cysts originate from tubular diverticula and are known to become larger and more abundant with aging¹² and with CKD.^{27, 28} Rather than nephrosclerosis itself, hypertrophy and hyperplasia of remaining tubules^{29, 30} and the release of growth factors may contribute to the development of diverticula from these tubules³¹ and subsequent cyst formation. Arteriosclerosis includes both luminal stenosis and arteriolar hyalinosis. We found that luminal stenosis correlated more with decreased cortical to medullary volume and arteriolar hyalinosis correlated more with renal artery atherosclerosis. Prior investigations have found concurrent arteriolar hyalinosis on biopsy with large vessel atherosclerosis in patients with hypertension.³²⁻³⁴

Glomerular and nephron hypertrophy appears to be an adaptation to low nephron endowment³⁵⁻³⁷ hemodynamic³⁸ and metabolic stressors.^{39, 40} Tubular hypertrophy occurs with glomerular hypertrophy, possibly as a consequence of hyperfiltration requiring more sodium reabsorption in the proximal tubules.⁴¹ Other studies have demonstrated that obesity, hypertension and lower nephron number associate with larger glomerular and nephron size.^{36, 42-44} Inducing hyperuricemia in an animal model causes an increase in glomerular tuft size.⁴⁵ The pattern of glomerulosclerosis observed is consistent with an ischemic process due to the presence of pericapsular fibrosis, capillary wrinkling, atrophy and involution of the glomerular tuft, and finally obsolescence. Atherosclerosis and arteriosclerosis lead to rarefaction of the vascular supply and ischemia to nephrons resulting in the nephrosclerosis that associates with aging and hypertension.^{46, 47} Other age-related pathways besides ischemia may also contribute to nephrosclerosis.⁴⁸⁻⁵⁰

This study has potential limitations. Kidney donors are selected based on health, and this likely biased our correlations toward 0 by restricting the spectrum of pathology (only 3% of donors had more than 5% fibrosis on biopsy). Kidney biopsies in living donor kidneys provide a limited amount of tissue with resulting imprecision of structural findings, evidenced by coefficients of variation of 25%-29% between separate biopsies in the same donor.¹⁸ These two factors likely contributed to the relatively weak correlations with micro-structure observed. By using a large sample size, we were still able to characterize clinical

and imaging characteristics that associate with microstructure. The kidney donors studied were also predominantly white and few were older than 70 years.

There were also a few associations we could not explain that may be spurious. Renal artery atherosclerosis correlated with cortex volume per glomerulus, but not other measures of nephron size. Lower urine albumin correlated with more luminal stenosis on biopsy but not with other measures of nephrosclerosis.

In conclusion, we characterized the kidney structural findings on CT and biopsy among apparently healthy adults, revealing an intricate interplay between kidney micro-structure, macro-structure, risk factors, and function. Nephron hypertrophy and nephrosclerosis are the two dominant micro-structural patterns and both correlate with macro-structural findings on imaging. Longitudinal investigations are needed to determine the prognostic significance of these structural findings. New imaging modalities with less radiation and iodinated contrast risk are needed. Automated image processing tools that calculate kidney volumes and surface roughness from radiographic images would facilitate clinical utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Conceptual diagram of the kidney in apparently healthy adults. Risk factors, macro-structure, and kidney function are linked to two micro-structural characteristics: nephron hypertrophy and nephrosclerosis.

Table 1

Characteristics of 1520 kidney donors at three sites

Characteristics	Value
Demographic	
Mean age, y	43.4 (11.7)
Male sex	627 (41.3%)
Race	
White	1298 (85.4%)
Black	37 (2.4%)
American Indian/Alaska Native	25 (1.6%)
Asian	20 (1.3%)
Other	33 (2.2%)
Unknown	107 (7.0%)
Risk factors	
Family history of ESRD	810 (53.3%)
Mild HTN	161 (10.6%)
SBP, excluding those with mild HTN, mm Hg	119 (14)
BMI, kg/m ²	27.6 (4.9)
Uric acid, mg/dl	5.2 (1.4)
Kidney function	
Measured GFR, ml/min/1.73 m ²	115.0 (25.4)
24 hour urine albumin, mg	5.2 (8.5)
Biopsy measures	
Nonsclerotic glomerular volume, mm ³	0.0026 (0.0010)
Cortex per glomerulus, mm ³	0.079 (0.043)
Profile tubular area including lumen, μm ²	4488.9 (1509.5)
Globally sclerotic glomeruli	
0%	1003 (66.0%)
1%-5%	223 (14.7%)
6%-10%	156 (10.3%)
11%-15%	66 (4.3%)
>15%	72 (4.7%)
Globally sclerotic/ischemic glomeruli	
0%	937 (61.6%)
1%-5%	225 (14.8%)
6%-10%	175 (11.5%)
11%-15%	87 (5.7%)
>15%	96 (6.3%)
Luminal stenosis *	

Characteristics	Value
<50%	1006 (76.0%)
50%-75%	274 (20.7%)
>75%	44 (3.3%)
Cortical Fibrosis	
0%	1211 (79.7%)
1%-5%	262 (17.2%)
6%-10%	37 (2.4%)
>10%	10 (0.7%)
No. of fibrosis and atrophic tubules foci	
0	1212 (79.7%)
1	210 (13.8%)
2	98 (6.5%)
CT scan measures	
Measured cortex volume **, mm ³	207,280 (41,298)
Measured and estimated cortex volume **, mm ³	209,569 (43,483)
Medulla volume **, mm ³	81,086 (19,994)
Cortex / medulla volume	2.67 (0.69)
Total surface roughness **	
0	533 (35.0 %)
1-2	384 (25.3 %)
3-4	336 (22.1 %)
5-6	267 (17.6 %)
Any cyst >1cm:	
None	1453 (95.6%)
In one kidney	64 (4.2%)
In both kidneys	3 (0.2%)
Renal artery atherosclerosis:	
None	1471 (96.8%)
In one kidney	39 (2.6%)
In both kidneys	10 (0.7%)

Note: Values for categorical variables are given as number (percentage); for continuous variables, as mean $\pm$ standard deviation. Conversion factor for uric acid in mg/dL to μ mol/L, $\times 59.48$.

BMI, body mass index; CT, computed tomography; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HTN, hypertension; SBP, systolic blood pressure

* Total N does not add up to 1520 due to missing data

** Left + right.

Table 2

Spearman's correlation (r_s) of nephron size and nephrosclerosis with cortical volume and imaging pathology among 1520 kidney donors

	Cortical Volume				Imaging pathology						
	Cortical volume	P Value	Cortex / medulla	P Value	Surface Roughness	P Value	Cyst	1cm	P Value	Renal artery atherosclerosis	P Value
Nephron size											
Mean non-sclerotic glomerular volume	0.269	<0.001	0.184	<0.001	-0.017	0.5	0.034		0.2	0.011	0.7
Cortex volume per glomerulus	0.189	<0.001	0.132	<0.001	0.003	0.9	0.040		0.1	0.070	0.007
Mean profile tubular Area	0.164	<0.001	0.068	0.02	0.030	0.2	0.058		0.03	0.032	0.2
Nephrosclerosis											
% Globally sclerotic glomeruli	-0.084	0.001	-0.103	<0.001	0.080	0.002	0.067		0.009	0.101	<0.001
% Globally sclerotic and ischemic glomeruli	-0.081	0.002	-0.124	<0.001	0.073	0.004	0.079		0.002	0.102	<0.001
% Cortical fibrosis group	-0.053	0.04	-0.067	0.02	0.069	0.007	0.084		0.001	0.093	<0.001
No. of tubular atrophy / fibrosis foci	-0.053	0.04	-0.072	0.009	0.073	0.004	0.081		0.001	0.094	<0.001
% Luminal stenosis	-0.029	0.3	-0.100	0.001	0.044	0.1	0.036		0.2	0.050	0.07
Any arteriolar hyalinosis	0.020	0.5	-0.029	0.4	0.026	0.4	0.046		0.1	0.101	0.001

Note: Dark shading, + correlation $p < 0.01$; light shading, - correlation $p < 0.01$.

Table 3Spearman's correlations (r_s) of kidney structural findings with clinical characteristics

	Age	P Value	HTN	P Value	SBP*	P Value	GFR	P Value	24-h Urine Alb	P Value	Uric acid	P Value	BMI	P Value
Cortical volume														
Cortical volume	-0.207	<0.001	-0.016	0.5	0.124	<0.001	0.622	<0.001	0.215	<0.001	0.349	<0.001	0.404	<0.001
Cortex / medulla	-0.265	<0.001	-0.070	0.01	0.058	0.05	0.138	<0.001	0.040	0.2	0.200	<0.001	0.098	<0.001
Nephron size														
Mean nonsclerotic glomerular volume	-0.013	0.6	0.076	0.003	0.148	<0.001	0.176	<0.001	0.118	<0.001	0.238	<0.001	0.255	<0.001
Cortex volume per glomerulus	0.120	<0.001	0.102	<0.001	0.126	<0.001	0.060	0.03	0.099	<0.001	0.188	<0.001	0.228	<0.001
Mean profile tubular area	0.073	0.004	0.097	<0.001	0.130	<0.001	0.088	0.001	0.141	<0.001	0.077	0.003	0.186	<0.001
Imaging pathology														
Surface roughness	0.189	<0.001	0.098	<0.001	0.070	0.01	-0.042	0.1	-0.036	0.2	0.004	0.9	0.128	<0.001
Cyst 1 cm	0.178	<0.001	0.125	<0.001	0.012	0.7	-0.002	0.9	-0.007	0.8	0.065	0.01	0.047	0.07
Renal artery atherosclerosis	0.213	<0.001	0.132	<0.001	0.071	0.009	-0.088	0.001	0.041	0.1	0.013	0.6	0.022	0.4
Nephrosclerosis														
% globally sclerotic glomeruli	0.262	<0.001	0.152	<0.001	0.020	0.5	-0.155	<0.001	-0.055	0.05	-0.039	0.1	-0.013	0.6
% globally sclerotic and ischemic glomeruli	0.271	<0.001	0.132	<0.001	0.039	0.2	-0.141	<0.001	-0.043	0.1	-0.019	0.5	-0.003	0.9
% cortical fibrosis Group	0.217	<0.001	0.151	<0.001	0.077	0.005	-0.091	0.001	-0.022	0.4	0.017	0.5	0.008	0.8
No. of tubular atrophy / fibrosis foci	0.221	<0.001	0.154	<0.001	0.081	0.003	-0.093	0.001	-0.014	0.6	0.021	0.4	0.013	0.6
% Luminal stenosis	0.267	<0.001	0.019	0.5	0.023	0.4	-0.063	0.03	-0.107	<0.001	0.055	0.05	0.026	0.4
Arteriolar hyalinosis	0.143	<0.001	0.127	<0.001	0.107	0.001	-0.045	0.1	-0.010	0.8	0.041	0.2	0.033	0.3

Note: Dark shading, + correlation $p < 0.01$; light shading, - correlation $p < 0.01$.

Alb, albumin; BMI, body mass index; CT, computed tomography; GFR, glomerular filtration rate; HTN, hypertension; SBP, systolic blood pressure

* Excluded donors with hypertension.

Table 4
Age-sex-adjusted partial Spearman's correlations (r_s) of kidney structural findings with clinical characteristics

	HTN	P Value	SBP*	P Value	GFR	P Value	24h Urine alb	P Value	Uric Acid	P Value	BMI	P Value	Family history of ESRD	P Value
Cortical volume														
Cortical volume	0.020	0.4	0.118	<0.001	0.536	<0.001	0.192	<0.001	0.091	<0.001	0.416	<0.001	0.050	0.05
Cortex / medulla	0.006	0.8	0.091	0.002	-0.002	0.9	0.013	0.7	0.161	<0.001	0.106	<0.001	0.014	0.6
Nephron size														
Mean nonsclerotic glomerular volume	0.073	0.004	0.134	<0.001	0.131	<0.001	0.107	<0.001	0.164	<0.001	0.236	<0.001	0.089	0.001
Cortex volume per Glomerulus	0.063	0.02	0.097	<0.001	0.076	0.004	0.108	<0.001	0.138	<0.001	0.207	<0.001	0.128	<0.001
Mean profile tubular area	0.073	0.004	0.111	<0.001	0.089	0.001	0.142	<0.001	0.026	0.3	0.170	<0.001	0.065	0.01
Imaging pathology														
Surface roughness	0.049	0.06	0.051	0.06	0.058	0.03	-0.011	0.7	0.051	0.05	0.129	<0.001	0.002	0.9
Renal artery atherosclerosis	0.071	0.006	0.040	0.1	-0.020	0.4	0.065	0.02	-0.005	0.9	0.003	0.9	0.012	0.6
Cyst 1 cm	0.071	0.005	-0.018	0.5	0.045	0.09	0.010	0.7	0.026	0.3	0.024	0.3	0.003	0.9
Nephrosclerosis														
% Globally sclerotic Glomeruli	0.083	0.001	-0.019	0.5	-0.051	0.06	-0.023	0.4	-0.016	0.5	-0.026	0.3	0.013	0.6
% Globally sclerotic & ischemic glomeruli	0.056	0.03	-0.008	0.8	-0.046	0.09	-0.011	0.7	-0.022	0.4	-0.022	0.4	-0.004	0.9
% Cortical fibrosis group	0.091	<0.001	0.044	0.1	-0.023	0.4	0.004	0.9	0.004	0.9	-0.011	0.7	-0.024	0.3
No. of tubular atrophy / fibrosis foci	0.093	<0.001	0.047	0.09	-0.025	0.4	0.012	0.7	0.006	0.8	-0.007	0.8	-0.024	0.4
% Luminal stenosis	-0.066	0.02	-0.033	0.3	0.036	0.2	-0.081	0.007	0.055	0.05	-0.001	0.9	-0.002	0.9
Arteriolar hyalinosis	0.083	0.006	0.093	0.004	-0.009	0.8	0.001	0.9	0.007	0.8	0.016	0.6	0.049	0.1

Note: Dark shading, + correlation $p < 0.01$; light shading, - correlation $p < 0.01$.

Alb, albumin; BMI, body mass index; CT, computed tomography; ESRD< end-stage renal disease; GFR, glomerular filtration rate; HTN, hypertension; SBP, systolic blood pressure

* Excluded donors with hypertension; ESRD=End-stage renal disease;