CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Wofsy D, Hillson JL, Diamond B. Comparison of alternative primary outcome measures for use in lupus nephritis clinical trials. *Arthritis Rheum* 2013; 65: 1586–1591
2. Rovin BH, Parikh SV, Alvarado A. The kidney biopsy in lupus nephritis: is it still relevant? In: EM Ginzler, MA Dooley (eds). *Systemic Lupus Erythematosus*. Philadelphia: Elsevier, 2014, pp. 537–552
3. Hill GS, Delahouse M, Nochy D *et al.* A new morphologic index for the evaluation of renal biopsies in lupus nephritis. *Kidney Int* 2000; 58: 1160–1173
4. Hill GS, Delahousse M, Nochy D *et al.* Predictive power of the second renal biopsy in lupus nephritis: significance of macrophages. *Kidney Int* 2001; 59: 304–316
5. Hill GS, Delahousse M, Nochy D *et al.* Proteinuria and tubulointerstitial lesions in lupus nephritis. *Kidney Int* 2001; 60: 1893–1903
6. Hill GS, Delahousse M, Nochy D *et al.* Outcome of relapse in lupus nephritis: roles of reversal of renal fibrosis and response of inflammation to therapy. *Kidney Int* 2002; 61: 2176–2186
7. Zickert A, Sundelin B, Svenungsson E *et al.* Role of early repeated renal biopsies in lupus nephritis. *Lupus Sci Med* 2014; doi:10.1135/lupus-2014-000018
8. Alvarado A, Malvar A, Lococo B *et al.* The value of repeat kidney biopsy in quiescent Argentinian lupus nephritis patients. *Lupus* 2014; 23: 840–847
9. Singh A, Ghosh R, Kaur P *et al.* Protocol renal biopsy in patients with lupus nephritis: a single center experience. *Saudi J Kidney Dis Transpl* 2014; 25: 801–807
10. Gunnarsson I, Sundelin B, Heimburger M *et al.* Repeated renal biopsy in proliferative lupus nephritis—predictive role of serum C1q and albuminuria. *J Rheumatol* 2002; 29: 693–699
11. Askenazi D, Myones B, Kamdar A *et al.* Outcomes of children with proliferative lupus nephritis: the role of protocol renal biopsy. *Pediatr Nephrol* 2007; 22: 981–986
12. Ong LM, Hooi LS, Lim TO *et al.* Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology (Carlton)* 2005; 10: 504–510
13. Traitanon O, Avihingsanon Y, Kittikovit V *et al.* Efficacy of enteric-coated mycophenolate sodium in patients with resistant-type lupus nephritis: a prospective study. *Lupus* 2008; 17: 744–751
14. Austin HA, III, Muenz LR, Joyce KM *et al.* Prognostic factors in lupus nephritis. Contribution of renal histologic data. *Am J Med* 1983; 75: 382–391
15. Tamirou F, D'Cruz D, Sangle S *et al.* Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis* 2015; doi:10.1136/annrheumdis-2014-206897
16. Lent V, Harth J. Nephropathy in remnant kidneys: pathological proteinuria after unilateral nephrectomy. *J Urol* 1994; 152: 312–316
17. Karlen J, Linne T, Wikstad I *et al.* Incidence of microalbuminuria in children with pyelonephritic scarring. *Pediatr Nephrol* 1996; 10: 705–708
18. Parikh SV, Nagaraja HN, Hebert L *et al.* Renal flare as a predictor of incident and progressive CKD in patients with lupus nephritis. *Clin J Am Soc Nephrol* 2014; 9: 279–284

Received: 26.4.2015; Editorial decision: 11.7.2015

ORIGINAL ARTICLE

Nephrol Dial Transplant (2017) 32: 1344–1350
doi: 10.1093/ndt/gfw237
Advance Access publication 18 June 2016

Clinical associations of total kidney volume: the Framingham Heart Study

Daniel A. Roseman[1], Shih-Jen Hwang[1,2], Noriko Oyama-Manabe[3], Michael L. Chuang[1,4], Christopher J. O'Donnell[1,2,5], Warren J. Manning[4,6] and Caroline S. Fox[1,2,7]

[1]National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, MA, USA, [2]Division of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, MD, USA, [3]Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital, Sapporo, Japan, [4]Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA, [5]Cardiology Section, Veterans Affairs Boston Healthcare System, Boston, MA, USA, [6]Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA and [7]Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Correspondence and offprint requests to: Caroline S. Fox; E-mail: foxca@nhlbi.nih.gov

ABSTRACT

Background. Total kidney volume (TKV) is an imaging biomarker that may have diagnostic and prognostic utility. The relationships between kidney volume, renal function and cardiovascular disease (CVD) have not been characterized in a large community-dwelling population. This information is needed to advance the clinical application of TKV.

Methods. We measured TKV in 1852 Framingham Heart Study participants (mean age 64.1 ± 9.2 years, 53% women) using magnetic resonance imaging. A healthy sample was used to define reference values. The associations between TKV, renal function and CVD risk factors were determined using multivariable logistic regression analysis.

Results. Overall, mean TKV was 278 ± 54 cm^3 for women and 365 ± 66 cm^3 for men. Risk factors for high TKV (>90% healthy referent size) were body surface area (BSA), diabetes, smoking and albuminuria, while age, female and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 were protective. Participants with high TKV had higher odds of diabetes [odds ratio (OR) 2.15, $P < 0.001$] and lower odds of eGFR <60 mL/min/1.73 m^2 (OR 0.32, $P = 0.007$). Risk factors for low TKV (<10% healthy referent size) were age, female and eGFR <60 mL/min/1.73 m^2, while BSA and diabetes were protective. Participants with low TKV had higher odds of eGFR <60 mL/min/1.73 m^2 (OR 6.12, $P < 0.001$) and albuminuria (OR 1.56, $P = 0.03$).

Conclusions. Low TKV is associated with markers of kidney damage including albuminuria and eGFR <60 mL/min/1.73 m^2, while high TKV is associated with diabetes and decreased odds of eGFR <60 mL/min/1.73 m^2. Prospective studies are needed to characterize the natural progression and clinical consequences of TKV.

Keywords: albuminuria, cardiovascular disease risk factors, chronic kidney disease, magnetic resonance imaging, total kidney volume

INTRODUCTION

Kidney size is often assessed clinically using a single linear length measurement. However, total kidney volume (TKV) is an emerging biomarker for investigating the structural and functional basis of disease. Kidney volume is thought to provide prognostic information regarding chronic kidney disease (CKD) risk, while renal volumetric analysis has been applied to the study of kidney transplantation outcomes and renal artery stenosis [1–3]. Support for TKV to be used as an end-point in clinical trials of polycystic kidney disease has been proposed and automatic image processing techniques are being developed to advance this goal [4, 5]. However, the true clinical utility of TKV has yet to be realized because the current understanding of normal kidney volume is incomplete.

Normative values of TKV have not been established in an unselected general population and it remains unclear what defines high and low TKV. Prior studies in adults that explored the associations between kidney volume, renal function and cardiovascular disease (CVD) risk factors were limited by imaging modality, selection bias or sample size [6, 7]. This information is necessary to further advance TKV as a research and diagnostic parameter.

Measurement of kidney volume using ultrasound is operator dependent and has poor reproducibility [8, 9]. Computed tomography (CT) exposes the patient to ionizing radiation. Using magnetic resonance imaging (MRI) to obtain accurate kidney volume measurements has been validated in animals, used selectively in humans and was proposed as the method of choice for volumetric analysis [10, 11]. The aims of the present study were to define sex-specific reference values of TKV using MRI in a longitudinally followed community-based cohort with robust risk factor analysis and to identify the clinical covariates associated with high and low TKV.

MATERIALS AND METHODS

Study population

The Framingham Heart Study began in 1948 and the design has been described previously [12]. Offspring of the original cohort were enrolled starting in 1971 and examined every 4–5 years at clinic visits [13]. Starting in 1994, the Omni cohort was recruited from residents of Framingham, Massachusetts, who identified themselves as members of minority groups. The current study includes 1763 participants from Offspring exam 7 and 160 participants from Omni exam 1 who were without contraindications to MRI. Fifty-four participants were excluded due to uninterpretable imaging data, 3 were excluded for missing covariates and 14 were excluded for having at least one kidney with fewer than seven MRI slices because a kidney of that length is generally considered atrophic. A final sample size of 1852 participants was available for analysis. The study protocol was approved by the institutional review boards at Boston University Medical Center and Beth Israel Deaconess Medical Center. All participants provided written informed consent and the authors adhered to the ethical principles set forth in the Declaration of Helsinki.

TKV measurements

Kidney volume data were derived from noncontrast MRI abdominal images acquired from 2002 to 2005 using a 1.5-Tesla whole-body MRI system (Gyroscan ACS-NT, Philips Healthcare, Best, The Netherlands). Thirty-six transverse images ranging from the aortic arch to the aorto-iliac bifurcation were acquired using an ECG-gated, fat-suppressed, T2-weighted black blood turbo spin-echo sequence [14]. Abdominal images had a slice thickness of 5 mm with a 5-mm interslice gap; in-plane spatial resolution was 1.03 × 0.64 mm. Each image was analyzed by a single expert reviewer (N.O.-M.) for the presence of kidney. Renal parenchymal contours were manually traced in each slice using commercial software (QMass 6.1, Medis, Leiden, The Netherlands). Renal sinus fat, cysts and large vessels were excluded. Left and right kidney volumes were calculated using slice summation whereby the parenchymal area of each kidney slice was multiplied by a section interval of 1 cm (5-mm slice thickness + 5-mm intersection gap) and then summing all values. This process is sometimes referred to as the voxel-count or disk summation method and is considered the reference standard [9, 15, 16]. The left and right kidney volumes were then summed to derive the TKV since clinical parameters reflect combined renal function.

Clinical measurements

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Body surface area (BSA) was

calculated using the Mosteller formula [17]. Blood pressure was measured twice by a physician using a standardized protocol and the readings were averaged. Hypertension was defined as the use of antihypertensive medication, diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg. Diabetes was defined as the use of anti-diabetes medication or a fasting glucose of ≥126 mg/dL. Smoking status was defined as never, current or former at the time of the clinic visit.

Serum creatinine was measured using the Jaffe assay on a Roche Hitachi 911 (Roche Diagnostics, Indianapolis, IN, USA) with an intra-assay coefficient of variation of 3.1%. Statistical calibration of serum creatinine was performed due to the variation in laboratory assays. Briefly, creatinine values from the National Health and Nutrition Examination Survey (NHANES) III were first calibrated in the Cleveland Clinic laboratory using a correction factor of 0.23 mg/dL. Mean creatinine values from the Framingham Heart Study were then matched with the corresponding age- and sex-specific NHANES III means [18]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [19]. Albuminuria was defined as a urinary albumin-to-creatinine ratio (UACR) of ≥17 mg/g for men and ≥25 mg/g for women to account for the sex-specific differences in urinary creatinine excretion [20].

Statistical analyses

Dichotomous values are presented as proportions, normally distributed continuous values are presented as sample means with standard deviations and non-normally distributed variables are shown as medians with interquartiles. A healthy referent group was identified from the overall study group. Referent-group participants were those with total cholesterol ≤240 mg/dL, high-density lipoprotein (HDL) cholesterol ≥45 mg/dL for men and ≥55 mg/dL for women, 18.5 kg/m^2 < BMI < 30 kg/m^2, eGFR ≥60 mL/min/1.73 m^2 and free of hypertension, diabetes, albuminuria and CVD. From this group of 196 women and 112 men, the sex-specific lower 10th percentile and upper 90th percentile cut-off points of TKV were calculated to define low and high TKV, respectively. These thresholds were then applied to the overall group.

To study the relationships between volume and clinical characteristics, we applied linear regression models. Unadjusted univariate analyses used TKV as the dependent variable. The sex-specific standardized continuous or dichotomous independent variables were age, sex, BSA, hypertension, systolic and diastolic blood pressure, diabetes, glucose, eGFR, UACR, smoking status, total cholesterol, HDL cholesterol and triglycerides. Significant TKV predictors observed in the univariate models were subsequently used as independent variables for the multivariable-adjusted regression model.

Separately, we used stepwise logistic regression models to identify independent correlates for sex-specific low or high TKV compared with normal TKV. Candidate covariates included age, sex, height, weight, BSA, systolic blood pressure, use of antihypertensive medications, diabetes, fasting glucose, current smoking, eGFR <60 mL/min/1.73 m^2, albuminuria, use of lipid lowering therapy, total cholesterol, HDL cholesterol and triglycerides. We did not identify any significant sex interaction.

Finally, multivariable logistic regression models were used to determine the associations between either low or high TKV and characteristics including hypertension, diabetes, eGFR <60 mL/min/1.73 m^2 and albuminuria. For the dependent variables of hypertension and diabetes, we adjusted for age, sex, BMI and smoking. For the dependent variables of eGFR <60 mL/min/1.73 m^2 and albuminuria, we adjusted for age, sex, BMI, hypertension, diabetes and smoking. A two-tailed P-value of <0.05 was considered statistically significant. Statistical analyses were performed with SAS (version 9.2, SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

Sex-specific characteristics for all 1852 participants are detailed in Table 1. Overall, the mean age of our sample was 64.1 ± 9.2 years and 53% were women. The age range of participants was 37–89 years for women and 42–88 years for men. There were two participants <40 years old. Mean left kidney volumes for women and men were 141.0 ± 30.1 and 184.5 ± 34.9 cm^3, respectively. Mean right kidney volumes for women and men were 137.1 ± 28.1 and 181.4 ± 34.8 cm^3, respectively. Left and right kidney volumes and TKV for women were significantly less than volumes for men (all P< 0.001). The ratio of left to right kidney volume was 1.0 ± 0.2 in women and 1.0 ± 0.1 in men (P= 0.08). There was a positive correlation between TKV and the total number of renal slices (surrogate for length) of $r = 0.57$ for women and $r = 0.54$ for men (both P< 0.001). Mean TKV for women was 278.1 ± 54.4 and 365.8 ± 65.6 cm^3 for men. Distribution of TKV by 10-year age groups for all participants is provided in Table 2 and shows a progressive decline in women starting after the <50 years age group. The reduction in TKV occurred later in men, starting after the 50–59-year age group.

Predictors of TKV

Univariate- and multivariable-adjusted linear regression models assessing predictors of TKV are illustrated in Table 3. Significant independent predictors of increased TKV included male, increased BSA, hypertension, diabetes, increased glucose, increased eGFR, current smoker and increased triglycerides. Younger age, increased diastolic blood pressure and increased HDL cholesterol were significant in the univariate models but nonsignificant in the multivariable-adjusted analysis.

Thresholds for low and high TKV

The healthy referent group of 196 women and 112 men was used to determine reference TKV values. In this group, mean TKV was 267.1 ± 43.7 cm^3 for women and 354.8 ± 50.1 cm^3 for men. Sex-specific TKV lower than the 10th percentile of this healthy group defined low TKV. Low TKV cut-off points were 219.9 cm^3 for women and 301.0 cm^3 for men. Similarly, TKV higher than the upper 90th percentile in the referent group defined high TKV. The thresholds for high TKV were 322.2 cm^3 for women and 415.2 cm^3 for men.

Table 1. Demographic and clinical characteristics for study population stratified by sex

Characteristic	Women	Men
Number of participants	981 (53%)	871 (47%)
Age (years)	63.9 ± 9.2	64.3 ± 9.2
Height (cm)	161.4 ± 6.2	174.9 ± 6.6
Weight (kg)	71.2 ± 15.1	86.9 ± 13.4
Body mass index (kg/m^2)	27.4 ± 5.5	28.4 ± 4.1
Body surface area (m^2)	1.78 ± 0.20	2.05 ± 0.18
Non-Hispanic White	891 (90.8%)	805 (92.4%)
Hypertension	290 (29.7%)	326 (37.6%)
Diabetes	65 (6.7%)	97 (11.2%)
eGFR <60 mL/min/1.73 m^2	58 (6.0%)	62 (7.1%)
eGFR (mL/min/1.73 m^2)	86.0 ± 16.0	84.4 ± 15.7
Albuminuria	82 (8.6%)	146 (17.1%)
Cardiovascular disease	138 (14.1%)	213 (24.5%)
Smoking status		
Never	525 (53.5%)	411 (47.2%)
Current	172 (17.5%)	171 (19.6%)
Former	284 (29.0%)	289 (33.2%)
Total cholesterol (mg/dL)	205.9 ± 36.3	193.0 ± 33.7
HDL cholesterol (mg/dL)	60.7 ± 16.3	45.3 ± 12.3
Triglycerides (mg/dL)	108 (77, 157)	117 (80, 175)
Right kidney volume (cm^3)	137.1 ± 28.1	181.4 ± 34.8
Left kidney volume (cm^3)	141.0 ± 30.1	184.5 ± 34.9
TKV (cm^3)	278.1 ± 54.4	365.8 ± 65.6

Data are presented as mean ± standard deviation, number (%), or median and interquartiles (25%, 75%).
eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; TKV, total kidney volume.

Table 2. Median (10%, 90%) TKV of women and men by 10-year age groups

Age group	Women		Men	
	n	TKV (cm^3)	*n*	TKV (cm^3)
Overall	981	271 (217, 352)	871	360 (289, 447)
<50 years	53	288 (239, 373)	59	363 (301, 450)
50–59 years	308	284 (230, 368)	241	375 (307, 461)
60–69 years	343	270 (216, 348)	321	366 (297, 454)
≥70 years	277	256 (201, 322)	250	339 (265, 424)

TKV, total kidney volume.

Participant characteristics and TKV

Sex-specific clinical characteristics of all participants with low and high TKV are presented in Table 4. Low TKV was more commonly observed with increased age, eGFR <60 mL/min/1.73 m^2, albuminuria and CVD compared with both the middle and high TKV groups. Participants with high TKV had increased prevalence of hypertension, diabetes, lower HDL cholesterol, higher triglycerides and higher BSA compared with both the middle and low TKV groups.

Risk factors for TKV

Stepwise logistic regression models were used to identify significant cross-sectional correlates of high and low TKV and are presented in Table 5. Risk factors for low TKV compared with those in the middle group included age per 10-years [odds ratio (OR) 1.67, P< 0.001], female (OR 1.67, P< 0.001) and eGFR <60 mL/min/1.73 m^2 (OR 8.09, P< 0.001), while BSA (OR 0.24, P< 0.001) and diabetes (OR 0.47, P= 0.04) were protective. Risk factors of high TKV were BSA (OR 5.01, P< 0.001), diabetes (OR 2.01, P= 0.001), smoking (OR 1.94, P< 0.001) and albuminuria (OR 1.84, P= 0.005), while age per 10-years (OR 0.67, P< 0.001), female (OR 0.17, P< 0.001) and eGFR <60 mL/min/1.73 m^2 (OR 0.19, P< 0.001) were protective.

TKV and chronic diseases

We examined the associations between low and high TKV and characteristics including hypertension, diabetes, eGFR <60 mL/min/1.73 m^2 and albuminuria (Table 6). Compared with TKV in the middle group, low TKV had 6-fold higher odds of eGFR <60 mL/min/1.73 m^2 (OR 6.12, P< 0.001) and 1.6-fold higher odds of albuminuria (OR 1.56, P= 0.03). There was no association between low TKV and either diabetes or hypertension. High TKV was associated with higher odds of diabetes (OR 2.15, P< 0.001) and lower odds of eGFR <60 mL/min/1.73 m^2 (OR 0.32, P= 0.007). High TKV was not associated with either albuminuria or hypertension.

DISCUSSION

In this cross-sectional study of community-dwelling adults, we first determined normative values for TKV from a healthy reference cohort and then identified thresholds for low and high TKV. We found that low TKV was associated with worse indices of renal function including albuminuria and eGFR <60 mL/min/1.73 m^2 compared with normal TKV. There was also a progressive decline of TKV in women starting before the age of 50 and in men starting from the 50–59-year age group, suggesting a common pathway of volume loss. Risk factors for low TKV in both sexes included age and eGFR <60 mL/min/1.73 m^2, consistent with the idea of reduced renal reserve. For high TKV, identified risk factors included diabetes, BSA and smoking but not eGFR <60 mL/min/1.73 m^2. These findings coincided with the linear regression model showing that increased eGFR was a predictor of increased TKV as well as the logistic regression analysis demonstrating greater odds of diabetes and lower odds of eGFR <60 mL/min/1.73 m^2 with high TKV. Neither low nor high TKV was associated with hypertension. Taken together, these findings establish a novel approach to renal structural analysis based on volume thresholds and demonstrate unique associations between TKV and CKD risk factors.

Volumetric study of kidney macroanatomy and associated CVD and CKD risk factors has been carried out previously [21]. A study of 539 selected patients (age 52 ± 18 years) who underwent contrast-enhanced CT showed that TKV was correlated with age, BSA and eGFR but not hypertension or diabetes [22]. The current study refines the relationship between TKV and diabetes to show an association with high TKV but not low TKV and confirms the lack of an association with hypertension.

Another study of 1344 potential kidney donors (age 44 ± 12 years) used contrast-enhanced CT to identify significant predictors of kidney parenchymal volume [7]. These included current smoking, BMI, GFR, serum glucose, albuminuria and HDL cholesterol. We found similar predictors of increased TKV with the notable exception of albuminuria. This could have been due to our use of UACR instead of 24-h urine collections used earlier.

Table 3. Predictors of total kidney volume among all participants using linear regression where β indicates the increment in volume (cm^3) per standard deviation for continuous variables or presence of dichotomous variables

Characteristic	Univariate[a]		Multivariable[b]	
	β	P-value	β	P-value
Age (10-year)	−16.34	<0.001	−0.47	0.72
Male	87.71	<0.001	86.48	<0.001
Body surface area (m^2)	33.70	<0.001	31.12	<0.001
Hypertension	18.29	<0.001	7.26	0.002
Systolic blood pressure (mmHg)	−1.20	0.49	–	–
Diastolic blood pressure (mmHg)	1.76	<0.001	−0.28	0.79
Diabetes	40.37	<0.001	9.90	0.04
Glucose (mg/dL)	10.17	<0.001	3.23	0.02
eGFR (mL/min/1.73 m^2)	23.34	<0.001	24.80	<0.001
UACR (mg/g)	2.00	0.25	–	–
Current smoker	22.45	<0.0001	11.61	<0.001
Former smoker	−0.84	0.82	–	–
Total cholesterol (mg/dL)	−2.08	0.23	–	–
HDL cholesterol (mg/dL)	−9.21	<0.001	0.21	0.85
Triglycerides (mg/dL)	8.02	<0.001	5.02	<0.001

eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; HDL, high-density lipoprotein.
[a]Unadjusted single covariate analysis.
[b]Multivariable-adjusted using all significant predictors from the univarate analyses and where '–' indicates that characteristic was not included in model.

We also broadened the list of predictors to include hypertension, diabetes and increased triglycerides. Data from 493 elderly participants (age 79 ± 4 years) of the second AGES-Reykjavik Study showed an association between contrast-enhanced MRI-derived TKV and BMI, current smoking and diabetes [1]. Systolic and diastolic blood pressure did not enter the model and those observations are consistent with the present study. Overall, our findings extend the literature to show how clinically relevant covariates associate with well-defined high and low TKV in an unselected population.

Albuminuria, a marker of kidney damage, was previously reported to have a positive association with TKV. Those findings suggested that kidney enlargement was reflective of early injury as opposed to kidney volume reduction [1, 7]. In contrast to prior studies, we found an association between albuminuria and low TKV. There was no association between albuminuria and high TKV nor was UACR a significant predictor of increased TKV using linear regression analysis. However, albuminuria was observed in participants with high TKV (Table 4) and our results might be due to different populations, sex-specific definitions for albuminuria and collection methods.

eGFR is another marker used to evaluate kidney function that maintains a similar direction of association with TKV across most studies [1, 7, 22]. The current results showing an

Table 4. Characteristics of women and men stratified by total kidney volume using the lower 10th percentile and upper 90th percentile thresholds derived from the healthy referent sample

Characteristic	Women			Men		
	Low TKV[a]	Middle TKV group	High TKV[b]	Low TKV[c]	Middle TKV group	High TKV[d]
Number of participants	115	676	190	123	568	180
Age (years)	69.6 ± 8.1	63.9 ± 9.2	60.8 ± 8.1	69.4 ± 9.6	64.1 ± 9.0	61.3 ± 8.4
Height (cm)	156.6 ± 5.6	161.3 ± 5.8	164.6 ± 5.9	171.5 ± 6.6	174.7 ± 6.2	177.9 ± 6.7
Weight (kg)	62.0 ± 11.9	68.7 ± 11.7	85.6 ± 18.2	77.1 ± 11.7	85.3 ± 11.3	98.8 ± 12.4
Body mass index (kg/m^2)	25.3 ± 4.4	26.5 ± 4.5	31.6 ± 6.9	26.2 ± 3.6	28.0 ± 3.6	31.3 ± 4.2
Body surface area (m^2)	1.64 ± 0.17	1.75 ± 0.16	1.97 ± 0.22	1.91 ± 0.16	2.03 ± 0.15	2.21 ± 0.15
Non-Hispanic White	110 (95.7%)	610 (90.2%)	171 (90.0%)	113 (91.9%)	531 (93.5%)	161 (89.4%)
Hypertension	34 (29.6%)	187 (27.7%)	69 (36.5%)	45 (36.6%)	197 (34.9%)	84 (46.7%)
Diabetes mellitus	5 (4.4%)	39 (5.8%)	21 (11.1%)	11 (8.9%)	48 (8.5%)	38 (21.1%)
eGFR <60 mL/min/1.73 m^2	26 (22.8%)	32 (4.8%)	1 (0.53%)	30 (24.4%)	27 (4.8%)	7 (3.9%)
eGFR (mL/min/1.73 m^2)	73.7 ± 17.5	85.2 ± 14.9	94.8 ± 17.7	73.4 ± 18.1	84.8 ± 14.0	91.5 ± 14.8
Albuminuria	16 (14.6%)	46 (7.0%)	20 (10.9%)	29 (25.0%)	81 (14.7%)	36 (20.6%)
Cardiovascular disease	20 (17.4%)	95 (14.1%)	23 (12.1%)	34 (27.6%)	136 (23.9%)	43 (23.9%)
Smoking status						
Never	65 (56.6%)	365 (54.0%)	95 (50.0%)	61 (49.6%)	272 (47.9%)	78 (43.3%)
Current	18 (15.7%)	104 (15.4%)	50 (26.3%)	19 (15.5%)	102 (18.0%)	50 (27.8%)
Former	32 (27.8%)	207 (30.6%)	45 (23.7%)	43 (35.0%)	194 (34.2%)	52 (28.9%)
Total cholesterol (mg/dL)	208.4 ± 36.0	205.6 ± 34.6	205.2 ± 41.9	194.1 ± 35.4	193.8 ± 33.1	189.9 ± 24.3
HDL cholesterol (mg/dL)	62.6 ± 16.4	61.6 ± 16.5	56.3 ± 14.8	45.8 ± 10.9	46.2 ± 12.8	42.0 ± 11.0
Triglycerides (mg/dL)	107.0 (77, 156)	105.0 (74, 152)	124.0 (89, 165)	110 (78, 143)	115 (76, 174)	137 (96, 205)
Right kidney volume (cm^3)	100.5 ± 13.5	131.8 ± 16.3	178.2 ± 20.6	135.0 ± 14.8	176.2 ± 19.9	229.4 ± 24.3
Left kidney volume (cm^3)	99.0 ± 16.6	136.0 ± 17.3	184.3 ± 20.3	136.5 ± 19.0	180.0 ± 19.7	231.3 ± 24.2
TKV (cm^3)	199.5 ± 19.2	267.8 ± 27.3	362.5 ± 34.4	271.5 ± 26.3	356.2 ± 31.5	460.8 ± 42.5
Number of slices, right	9.0 ± 1.0	9.9 ± 1.0	10.8 ± 1.1	10.1 ± 0.9	10.8 ± 1.1	11.9 ± 1.1
Number of slices, left	9.4 ± 1.2	10.4 ± 1.0	11.4 ± 1.0	10.5 ± 1.4	11.2 ± 1.0	12.1 ± 1.0

Data are presented as mean ± standard deviation, number (%), or median and interquartiles (25%, 75%).
eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; TKV, total kidney volume.
[a]TKV <219.9 cm^3.
[b]TKV ≥322.2 cm^3.
[c]TKV <301.0 cm^3.
[d]TKV ≥415.2 cm^3.

Table 5. Results of multivariable-adjusted stepwise logistic regression models for significant risk factors associated with high and low TKV in women and men

Characteristic	High TKV			Low TKV		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Age (10-year)	0.67	(0.56–0.79)	<0.001	1.67	(1.39–2.01)	<0.001
Female	0.17	(0.12–0.24)	<0.001	6.96	(4.39–11.05)	<0.001
Body surface area (m^2)	5.01	(4.07–6.17)	<0.001	0.24	(0.19–0.32)	<0.001
eGFR <60 mL/min/1.73 m^2	0.19	(0.07–0.48)	<0.001	8.09	(4.85–13.50)	<0.001
Diabetes	2.01	(1.33–3.32)	0.001	0.47	(0.23–0.95)	0.04
Smoking, current	1.94	(1.40–2.71)	<0.001	Did not enter model		
Albuminuria	1.84	(1.20–2.83)	0.005	Did not enter model		

TKV, total kidney volume; OR, odds ratio; 95% CI, 95% confidence interval, eGFR, estimated glomerular filtration rate.

Table 6. Results of multivariable-adjusted logistic regression models tested for significant associations between high and low TKV and hypertension, diabetes, chronic kidney disease and albuminuria

Characteristic	High TKV			Low TKV		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Hypertension[a]	1.29	(0.98–1.70)	0.07	0.93	(0.68–1.28)	0.66
Diabetes[a]	2.15	(1.43–3.24)	<0.001	0.75	(0.42–1.34)	0.33
eGFR <60 mL/min/1.73 m^{2b}	0.32	(0.14–0.74)	0.007	6.12	(3.86–9.69)	<0.001
Albuminuria[b]	1.45	(0.97–2.17)	0.07	1.56	(1.03–2.37)	0.03

TKV, total kidney volume; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Adjusted for age, sex, body mass index and smoking.
[b]Adjusted for age, sex, body mass index, hypertension, diabetes and smoking.

association between low TKV and eGFR <60 mL/min/1.73 m^2 further explore this relationship at a more granular level not previously defined. Thus, an association between low TKV with albuminuria and eGFR <60 mL/min/1.73 m^2 supports the concept that small kidneys are reflective of established kidney disease.

TKV is a function of the number and size of nephrons [23]. However, an increase in kidney size is not thought to be due to hyperplasia or glomerular neogenesis but rather due to hypertrophy [24]. Within the nephron, recent evidence showed that glomerular as well as tubular hypertrophy is associated with clinical characteristics including BMI and albuminuria [25]. At the same time, nephrosclerosis is a volume-losing lesion associated with age [26]. These microstructural changes of volume expansion and volume loss are reflected at the macrostructural level and are important to consider when interpreting TKV. For example, our observation that older age is protective for high TKV could be a consequence of increased nephrosclerosis rather than decreased nephron hypertrophy. The net effect of these microscopic changes on kidney volume is an area of ongoing investigation [27].

Increased kidney volume is also associated with glomerular hyperfiltration [7]. Various clinical conditions are characterized by both hyperfiltration and enlarged kidneys including diabetes, pregnancy, smoking and obesity. In the current study, diabetes, smoking and BSA were all risk factors for high TKV and there were increased odds of diabetes with high TKV. These findings are in accord with earlier observations and suggest that high TKV may be a macroscopic reflection of altered nephron function with attendant structural changes in glomerular and tubular volume. Identifying the unique drivers of nephron hypertrophy and variation among the different nephron segments may support our understanding of TKV.

Low TKV appears to be consistent with reduced renal functional reserve based on the associations with eGFR <60 mL/min/1.73 m^2 and albuminuria. The idea of a smaller kidney and increased cortical echogenicity correlating with kidney disease is a well-accepted ultrasound finding [28]. CKD is generally considered to be injury through a common pathway of interstitial fibrosis, sclerotic glomeruli and tubular atrophy. The expansive nature of fibrosis and accumulation of scar tissue may progress to chronic and destructive pathological changes coupled with microvasculature rarefaction resulting in volume loss and renal dysfunction [29].

Our study posits that understanding kidney morphology may help identify individuals at risk for developing CVD and CKD. However, a central question when discussing TKV is the uncertainty of normal versus abnormal. Two earlier studies reported age- and sex-specific distributions of TKV across 10-year age groups from selected populations using CT [7, 22]. The current findings are consistent in showing that TKV in women starts to decrease at an earlier age compared with men, but our values are larger and this may be due to the differences in participant characteristics, image acquisition and analysis protocols.

It remains unclear whether high TKV represents an early adaptive and functional response with delayed maladaptive consequences [30]. A single longitudinal study measured kidney volume changes in the setting of weight loss therapy and this demonstrated the dynamic nature of TKV [6]. The study of 18 obese subjects had TKV measured by CT at baseline and then at 1 and 6 months after undergoing gastric bypass, gastric banding or diet initiation. All subjects lost weight and kidney volume was reduced in all but two patients. Measuring TKV and using set thresholds offers guidance to help interpret volumetric studies.

Strengths of our study include the large sample size from a community-dwelling population with a clinically relevant age range, robust risk factor ascertainment and use of noncontrast MRI coupled with manual segmentation. Limitations of the study include the cross-sectional study design and consequent lack of causal inference. Also, the study group was primarily non-Hispanic White Americans; our results may not be generalizable to other groups. Sex-specific thresholds for high and low TKV were not age-specific and this may be important in future studies given the observed reduction of TKV with age. A final limitation was our inability to distinguish cortical volume from medullary volume. This is particularly notable given findings that reduced TKV with age is attenuated by initial medullary volume increases.

In conclusion, this study demonstrates that low TKV is a structural marker of renal dysfunction and high TKV is associated with diabetes. Prospective studies are needed to characterize the natural progression of TKV with respect to CKD and CVD risk factors so as to confirm whether this structural biomarker portends future adverse outcomes.

CONFLICT OF INTEREST STATEMENT

None declared.

ACKNOWLEDGEMENTS

The Framingham Heart Study is conducted and supported in collaboration with Boston University by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH) project number N01HC25195; additional funding was provided by the NIH through the National Institute of Diabetes and Digestive and Kidney Diseases project number T32DK007053 to D.A.R. and NHLBI project number R01HL70279 to W.J.M., N.O.-M. and M.L.C.

REFERENCES

1. Woodard T, Sigurdsson S, Gotal JD *et al.* Segmental kidney volumes measured by dynamic contrast-enhanced magnetic resonance imaging and their association with CKD in older people. *Am J Kidney Dis* 2015; 65: 41–48
2. Cheung CM, Shurrab AE, Buckley DL *et al.* MR-derived renal morphology and renal function in patients with atherosclerotic renovascular disease. *Kidney Int* 2006; 69: 715–722
3. Poggio ED, Hila S, Stephany B *et al.* Donor kidney volume and outcomes following live donor kidney transplantation. *Am J Transplant* 2006; 6: 616–624
4. Alam A, Dahl NK, Lipschutz JH *et al.* Total kidney volume in autosomal dominant polycystic kidney disease: a biomarker of disease progression and therapeutic efficacy. *Am J Kidney Dis* 2015; 66: 564–576
5. Kline TL, Korfiatis P, Edwards ME *et al.* Automatic total kidney volume measurement on follow-up magnetic resonance images to facilitate monitoring of autosomal dominant polycystic kidney disease progression. *Nephrol Dial Transplant* 2016; 31: 241–248
6. Johnson S, Rishi R, Andone A *et al.* Determinants and functional significance of renal parenchymal volume in adults. *Clin J Am Soc Nephrol* 2011; 6: 70–76
7. Wang X, Vrtiska TJ, Avula RT *et al.* Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. *Kidney Int* 2014; 85: 677–685
8. Emamian SA, Nielsen MB, Pedersen JF. Intraobserver and interobserver variations in sonographic measurements of kidney size in adult volunteers. A comparison of linear measurements and volumetric estimates. *Acta Radiol* 1995; 36: 399–401
9. Bakker J, Olree M, Kaatee R *et al.* Renal volume measurements: accuracy and repeatability of US compared with that of MR imaging. *Radiology* 1999; 211: 623–628
10. Coulam CH, Bouley DM, Sommer FG. Measurement of renal volumes with contrast-enhanced MRI. *J Magn Reson Imaging* 2002; 15: 174–179
11. Pedersen M, Karstoft K, Lodrup A *et al.* Advantages and controversies in the era of intrarenal volumetry. *Am J Nephrol* 2011; 33 (Suppl 1): 40–45
12. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci* 1963; 107: 539–556
13. Feinleib M, Kannel WB, Garrison RJ *et al.* The Framingham Offspring Study. Design and preliminary data. *Prev Med* 1975; 4: 518–525
14. Oyama N, Gona P, Salton CJ *et al.* Differential impact of age, sex, and hypertension on aortic atherosclerosis: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 2008; 28: 155–159
15. Cohen EI, Kelly SA, Edye M *et al.* MRI estimation of total renal volume demonstrates significant association with healthy donor weight. *Eur J Radiol* 2009; 71: 283–287
16. Zollner FG, Svarstad E, Munthe-Kaas AZ *et al.* Assessment of kidney volumes from MRI: acquisition and segmentation techniques. *AJR Am J Roentgenol* 2012; 199: 1060–1069
17. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; 317: 1098
18. Fox CS, Larson MG, Leip EP *et al.* Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004; 291: 844–850
19. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
20. Mattix HJ, Hsu CY, Shaykevich S *et al.* Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. *J Am Soc Nephrol* 2002; 13: 1034–1039
21. Emamian SA, Nielsen MB, Pedersen JF *et al.* Kidney dimensions at sonography: correlation with age, sex, and habitus in 665 adult volunteers. *AJR Am J Roentgenol* 1993; 160: 83–86
22. Gong IH, Hwang J, Choi DK *et al.* Relationship among total kidney volume, renal function and age. *J Urol* 2012; 187: 344–349
23. Nyengaard JR, Bendtsen TF. Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec* 1992; 232: 194–201
24. Larsson L, Aperia A, Wilton P. Effect of normal development on compensatory renal growth. *Kidney Int* 1980; 18: 29–35
25. 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: 1892–1902
26. 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: 561–567
27. 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; (doi:10.1053/j.ajkd.2015.12.029, Epub ahead of print)
28. Hricak H, Cruz C, Romanski R *et al.* Renal parenchymal disease: sonographic-histologic correlation. *Radiology* 1982; 144: 141–147
29. Ohashi R, Kitamura H, Yamanaka N. Peritubular capillary injury during the progression of experimental glomerulonephritis in rats. *J Am Soc Nephrol* 2000; 11: 47–56
30. Hostetter TH, Olson JL, Rennke HG *et al.* Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981; 241: F85–F93

Received: 2.10.2015; Editorial decision: 18.5.2016