

# Kidney Volume Associations with Subclinical Renal and Cardiovascular Disease: The Diabetes Heart Study

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## Key Words

Kidney volume · Glomerular filtration rate · Diabetes mellitus · Coronary atherosclerosis · Aorta atherosclerosis · Multidetector computed tomography, calcified plaque measurements

## Abstract

**Background:** The prognostic significance of total kidney volume (TKV) in subjects with type 2 diabetes mellitus (T2DM) is unknown. **Methods:** One hundred and seventy unrelated Caucasians with T2DM underwent multidetector-row computed tomography of the neck, chest, and abdomen to measure calcified plaque in the coronary artery (CorCP), carotid artery (CarCP), and infrarenal aorta (AorCP). Spearman's rank correlation coefficients were used to assess associations between TKV and subclinical renal and cardiovascular disease. Partial correlation coefficients were computed to adjust for the potential confounding effects of age, sex, body mass index, glomerular filtration rate (GFR), diabetes duration, and hemoglobin A<sub>1c</sub>. Values are expressed as mean ± SD (median in parentheses). **Results:** The study group (51% female) had a mean age of 62.9 ± 8.5 (62.3) years, a T2DM duration of 11.5 ± 6.8 (10.0) years, a urinary albumin:creatinine ratio of 109.9 ± 396 (17.6) mg/g, a GFR of

63.8 ± 12.8 (63.2) ml/min, a TKV of 272.4 ± 69.7 (261.9) cm<sup>3</sup>, CorCP 2,170 ± 3,394 (653), CarCP 374 ± 673 (104), AorCP 14,569 ± 17,480 (8,370), and a carotid artery intima-media thickness of 0.70 ± 0.14 (0.68) mm. Adjusting for age, sex, body mass index, diabetes duration, GFR, and hemoglobin A<sub>1c</sub>, the TKV was significantly associated with AorCP (r = 0.20, p = 0.016), but not with CorCP, CarCP, or carotid artery intima-media thickness (all p ≥ 0.25). No significant associations were detected between TKV and blood pressure or albuminuria. **Conclusions:** In Caucasians with T2DM, TKV and calcified atherosclerotic plaque in the infrarenal abdominal aorta are positively associated. Common mechanisms linking renal matrix deposition with aortic atherosclerosis may underlie this association and require further study.

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## Introduction

Traditionally, sonography has been the primary modality for the estimation of renal size; however, it is highly operator dependent [1]. It had been difficult to accurately measure kidney mass or volume until the development of noninvasive multidetector computerized tomography (MDCT). The prognostic value of total

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kidney volume (TKV), measured using MDCT, and correlations between TKV and subclinical atherosclerosis in diabetes have not yet been evaluated.

Albuminuria and reduced glomerular filtration rate (GFR) are both potent and independent risk factors for cardiovascular disease (CVD). Diabetic subjects with albuminuria have been demonstrated to be far more likely to die from CVD than progress to elevated serum creatinine concentrations or renal replacement therapy [2]. Similarly, patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) are at high risk of suffering cardiac complications and stroke relative to subjects without nephropathy [3]. Calcified atherosclerotic plaque and carotid artery intima-media thickness (IMT) are widely accepted measures of subclinical atherosclerosis. Carotid artery IMT predicts incident coronary heart disease [4, 5], and the prevalence and incidence rates of coronary heart disease increase with increasing coronary artery calcified plaque (CorCP) [6, 7]. To determine the usefulness of measuring TKV with MDCT, we determined correlations between TKV and albuminuria, blood pressure, and measures of subclinical atherosclerosis in unrelated Caucasians with type 2 diabetes mellitus (T2DM).

## Patients and Methods

### Patient Population

The Diabetes Heart Study (DHS) is a family-based investigation designed to identify genes producing susceptibility to subclinical CVD [8, 9]. T2DM index cases (defined as diabetes onset  $\geq 35$  years of age, in the absence of historical evidence of diabetic ketoacidosis) were recruited from hospitals and community clinics. One hundred and seventy unrelated Caucasian subjects with T2DM enrolled in the DHS with serum creatinine concentrations  $\leq 1.6$  mg/dl were randomly selected for measurement of TKV.

In the DHS, participants receive B mode ultrasound for carotid artery IMT, CT for measurement of calcified plaque in the coronary arteries, aortic arch, carotid arteries, and abdominal aorta and bone densitometry. The participants also undergo electrocardiography, fasting serum and urine chemistries, and interviews for past medical history, medications, and lifestyle.

### Imaging Methods

CorCP, carotid artery calcified plaque (CarCP), and infrarenal aorta calcified plaque (AorCP) measurements were performed on a four-channel MDCT (MDCT4) with cardiac gating and capable of 500-ms temporal resolution using the segmented reconstruction algorithm (LightSpeed QXi; General Electric Medical Systems, Waukesha, Wisc., USA). The techniques for the coronary and carotid scans have previously been described in detail [8–10]. In brief, participants were placed in the supine position on the CT couch over a quality control calibration phantom (Image Analysis, Columbia, Ky., USA) for scans of the heart and abdomen. The participants were repositioned for the carotid artery bifurcation

scan of the neck and placed in a head holder to aid in positioning.

The abdomen scan series was used to measure TKV. The technical factors for this series were: 120 kV, 250 mA, 0.8-second gantry rotation in helical mode (7.5 mm/s), 2.5-mm slice thickness, and standard reconstruction kernel. The display field of view was 35 cm, resulting in a pixel dimension of 0.68 by 0.68 mm. The TKV was measured as the sum of the right and left kidneys determined separately, except in those with only one kidney and who denied prior surgical nephrectomy. The renal outlines were identified and measured by a single investigator (A.M.S.).

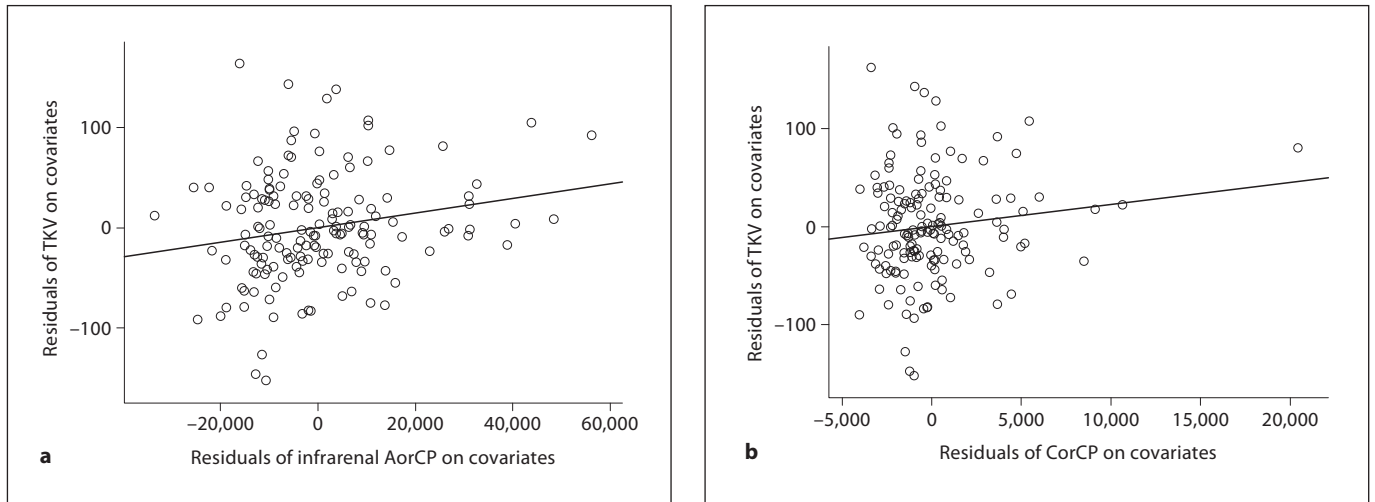
Computed tomography scans of all three vascular territories (coronary, carotid, and renal) were analyzed on an Advantage Windows Workstation with the SmartScores software package (General Electric Medical Systems) using a modified Agatston scoring method which adjusts for slice thickness and uses the conventional threshold of 130 HU.

Carotid artery IMT measurements were performed with the participants in the supine position using high-resolution B-mode carotid ultrasonography with a 7.5-MHz transducer and an AU5 ultrasound machine (Biosound Esaote, Indianapolis, Ind., USA), as previously described [9].

### Statistical Methods

To demonstrate the demographic characteristics of the study population, the sample mean values and standard deviations were computed for the continuous characteristics [e.g., age, diabetes duration, body mass index (BMI), blood pressure, GFR, and serum cholesterol] and the measures of TKV and subclinical CVD (CorCP, CarCP, AorCP, and IMT). For the discrete demographic characteristics, such as gender and smoking, proportions were calculated.

This post hoc analysis was performed in a subgroup of unrelated Caucasian subjects participating in the DHS to assess for associations between TKV and measures of subclinical renal disease and CVD. Associations are presented by the Spearman rank correlation coefficient, since our major interest was to detect potential correlations between TKV and albuminuria, blood pressure, and measures of subclinical atherosclerosis. Spearman's rank correlation coefficient is a nonparametric measure of correlation. The TKV was not normally distributed in this cohort, thus assumptions about the distributions of the variables need not be made. Partial correlation coefficients were computed to adjust for the potential confounding effects of age, sex, BMI, diabetes duration, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), and GFR determined by the MDRD (Modification of Diet in Renal Disease) equation using demographic and serum variables:  $GFR = 170 \cdot (\text{plasma creatinine})^{-0.999} \cdot (\text{age})^{-0.176} \cdot (\text{blood urea nitrogen})^{-0.170} \cdot (\text{albumin})^{+0.318} \cdot (0.762 \text{ if female}) \cdot (1.18 \text{ if black})$ . Partial correlation coefficients were obtained via computing the Spearman rank correlation coefficient between the residuals from models regressing TKV and measures of subclinical renal disease and CVD, respectively, onto age, sex, BMI, diabetes duration, HbA<sub>1c</sub>, and GFR. A simple scatter plot without covariate adjustment does not take into account the effect of the other covariates in the model. Thus, an untransformed added variable plot was used to demonstrate the association for the phenotype of interest (e.g., calcified plaque in a given vascular bed), after adjusting for other covariates. It is calculated as the residual from regressing TKV against all the covariates, omitting the single measure of subclinical renal disease or CVD.



**Fig. 1. a** Association between TKV and infrarenal abdominal AorCP after adjustment for age, sex, diabetes duration, HbA<sub>1c</sub>, BMI, and GFR. **b** Association between TKV and CorCP after adjustment for age, sex, diabetes duration, HbA<sub>1c</sub>, BMI, and GFR.

Next, the residual from regressing only the single measure of subclinical renal disease or CVD against the remaining covariates is determined. Finally, the residuals from the first step are plotted against the residuals from the second step. Regression lines are included in the figures to allow for improved visualization. Interpretation of these relationships is based on the Spearman rank correlation coefficient. SAS software version 9.1 (SAS Institute, Cary, N.C., USA) was used for all statistical analyses.

## Results

Characteristics of the Caucasian diabetic study group included 51.2% (87/170) females, 62.3% current or former smokers, 49.1% (82/170) were prescribed either angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, and 49.4% (84/170) received statins. Subjects had a mean age of  $62.9 \pm 8.5$  (SD) (median 62.3) years, a duration of T2DM of  $11.5 \pm 6.8$  (10.0) years, HbA<sub>1c</sub>  $7.5 \pm 1.4$  (7.3) %, BMI  $32.2 \pm 6.3$  (31.7) kg/m<sup>2</sup>, modified MDRD equation GFR  $63.8 \pm 12.8$  (63.2) ml/min, and urinary albumin:creatinine ratio (ACR)  $109.9 \pm 395.9$  (17.6) mg/g (table 1). Radiographic characteristics included: TKV  $272.4 \pm 69.7$  (SD) (median 261.9) cm<sup>3</sup>, CorCP  $2,170 \pm 3,394$  (653), CarCP  $374 \pm 673$  (104), AorCP  $14,569 \pm 17,480$  (8,370), and carotid artery IMT  $0.70 \pm 0.14$  (0.68) mm (table 1). Two study participants had congenital solitary kidneys: 1 with TKV 185.3 cm<sup>3</sup> and GFR 59.5 ml/min and 1 with TKV 156.2 cm<sup>3</sup> and GFR 66.3 ml/min.

Crude associations between TKV and subclinical renal disease and CVD were computed after adjustment for age and sex (table 2). In this model, TKV was positively and marginally associated with AorCP ( $r = 0.15$ ;  $p = 0.057$ ), and a trend toward a positive association was observed for urinary ACR ( $r = 0.14$ ;  $p = 0.066$ ) and CorCP ( $r = 0.12$ ;  $p = 0.117$ ). No evidence of an association was observed between TKV and either CarCP or IMT (both  $p > 0.6$ ).

Table 2 also contains the results of the fully adjusted model, accounting for the effects of age, sex, BMI, diabetes duration, HbA<sub>1c</sub>, and GFR. In the fully adjusted model, the association between TKV and AorCP increased ( $r = 0.20$ ,  $p = 0.016$ ); however, the previously identified trends toward association between TKV and urinary ACR and CorCP were no longer evident (both  $p > 0.2$ ), and no significant relationships were observed between TKV and CarCP, carotid artery IMT, and systolic or diastolic blood pressure.

Figure 1 reveals the distribution of residual effects from covariates plotted against residuals that remained from the effects of the amount of calcified plaque in the abdominal aorta (fig. 1a) and coronary artery (fig. 1b). The residuals of AorCP had a significant relationship with TKV after accounting for the effects of the other covariates ( $p = 0.016$ ), while residuals from CorCP did not ( $p > 0.2$ ).

**Table 1.** Demographic characteristics of the study population (n = 170, 87 female and 83 male)

Variable	Mean	SD
Age, years	62.9	8.5
Diabetes duration, years	11.5	6.8
BMI, kg/m <sup>2</sup>	32.28	6.3
Systolic blood pressure, mm Hg	139.6	18.2
Diastolic blood pressure, mm Hg	70.9	9.9
HbA <sub>1c</sub> , %	7.5	1.4
Urinary ACR, mg/mg	109.9	395.9
GFR, ml/min	63.8	12.8
HDL cholesterol, mg/dl	42.7	11.2
LDL cholesterol, mg/dl	103.3	34.3
AorCP	14,569.5	17,480.1
CorCP	2,169.6	3,394.4
CarCP	374.3	672.6
Carotid artery IMT, mm	0.7	0.14
TKV, cm <sup>3</sup>	272.4	69.7

## Discussion

Computerized tomography scans of the chest and abdomen are noninvasive tests that permit precise quantification of TKV, as well as measurement of subclinical atherosclerosis in the coronary, aorta, and carotid artery circulations. Declining renal function and increasing albuminuria independently predict the amount of calcified atherosclerotic plaque [10] and an increased frequency of clinical CVD events [3]. Disagreement exists over how to best quantify renal function in individuals with CKD. These novel analyses explored potential TKV associations with subclinical CVD, blood pressure, and albuminuria.

We found the mean TKV to be  $300.5 \pm 73.1$  cm<sup>3</sup> in males and  $245.6 \pm 54.5$  cm<sup>3</sup> in females. Limited data exist regarding normal renal volumes measured by CT. In a study to determine the normal distribution of abdominal organ volume on 149 CT scans, mean organ volumes were 156.5 ml for each kidney in females and 193.1 ml for each kidney in males [11]. Therefore, these total volumes were larger than observed in our study; however, they were adjusted for patient height and weight. Unlike in the current report, 'thresholding' was not used to isolate the renal parenchyma and most of the CT scans were contrast enhanced. These factors may have contributed to the larger kidney sizes reported in that study. A recent study [12] used magnetic resonance imaging to assess TKV in patients without a history of kidney disease and

**Table 2.** Spearman correlations (r) between TKV and covariates

Covariate	Model 1		Model 2	
	r	p	r	p
Urinary ACR	0.14	0.07	0.06	0.45
CorCP	0.12	0.12	0.10	0.25
CarCP	0.03	0.66	0.08	0.31
AorCP	0.15	0.06	0.20	0.02
Systolic blood pressure	0.02	0.80	-0.04	0.64
Diastolic blood pressure	-0.04	0.58	-0.09	0.24
IMT	0.035	0.66	0.07	0.42
Diabetes duration	0.05	0.55	0.001	0.99

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, diabetes duration, HbA<sub>1c</sub>, BMI, and GFR.

found larger kidney volumes: an average kidney volume of 202 and 204 ml for males and 154 and 156 ml for females for the right and left kidneys, respectively.

The consistent positive association that was observed between TKV and infrarenal calcified atherosclerotic plaque may have implications for the coincident development of CKD and CVD in subjects with T2DM. The TKV, reported as the sum of right and left kidney volumes, was not independently associated with urinary ACR, systolic or diastolic blood pressure, carotid artery IMT, or calcified plaque in the coronary or carotid circulations. Since all forms of CKD are associated with CVD, it would seem reasonable to expect negative associations to be present between TKV and calcified atherosclerotic plaque. Kidney size typically declines in most forms of chronic nephropathy, likely in concert with reduced renal mass and declining nephron number. Diabetic renal disease is unusual in that renal size typically increases early in the course of renal disease.

Increased kidney size has been noted to precede the development of proteinuria in type 1 diabetes. Nephromegaly is also a feature of T2DM with nephropathy. In a prospective cohort study of T2DM, kidney size was larger among diabetic versus matched nondiabetic participants and increased during the 6-year follow-up period [13]. In our study population, 111 of the 170 subjects had an ACR between 0 and 30 mg/g, and only 7 had overt proteinuria (ACR >300 mg/g). Therefore, the DHS population with minimal proteinuria and relatively preserved renal function should allow for detection of relationships between TKV (as a marker of early diabetic nephropathy) and subclinical CVD.

Aortic calcification is an important risk factor for coronary heart disease. In an autopsy study, Takasu et al. [14] demonstrated that aorta calcification on a nonenhanced CT was correlated with aortic intimal thickness and atheromatous degeneration. In 133 newly diagnosed individuals with T2DM, Siitonen et al. [15] found that diabetic males had more abdominal aortic calcification than nondiabetic males, and positive associations were observed between aorta calcium and ischemic changes on electrocardiogram. Aortic calcium is an independent predictor of incident coronary heart disease [16], and a 9-year prospective study [17] found that the prevalence of aorta calcium increased with age and was associated with a sixfold increase in risk of CVD events among men aged 45 years. Reaven et al. [18] detected an increase in the prevalence of peripheral arterial disease, coronary artery disease, and cerebrovascular disease in subjects with T2DM who had detectable abdominal aorta calcium. In hemodialysis patients, abdominal aortic calcification, as determined by lateral X-ray, was associated with increased cardiovascular and all-cause mortality [19]. Correlations between abdominal aorta calcification on standard flat-plate X-ray and electron beam CT coronary artery calcium have also been described [20].

Despite the association of TKV with AorCP, there was a lack of a relationship between TKV and CorCP, CarCP, or carotid artery IMT. Other reports revealed that abdominal aortic atherosclerosis is more strongly correlated with peripheral vascular disease ( $p < 0.0001$ ) than with coronary disease ( $p < 0.05$ ), and correlations between aortic atherosclerosis and cerebrovascular disease were absent [14]. Autopsy studies also revealed that aortic atherosclerotic lesions likely precede development of cor-

onary lesions [21] and that age is the strongest predictor for abdominal aortic calcification. Although the factors that are responsible for atherosclerosis in the abdominal aorta are clearly similar to those in the coronary and carotid circulations, the correlations between amounts of calcified plaque in these three vascular beds ranged from only 0.59 to 0.72 among all 1,125 diabetic participants in the DHS [22]. Several conventional CVD risk factors appear to have differential impacts on the development of calcified plaque in these three beds, particularly smoking, male gender, and history of prior myocardial infarction.

This study demonstrated strong positive associations between TKV and calcified atherosclerotic plaque in the infrarenal aorta, an association that was independent of kidney function. Additional studies will be necessary to determine whether common factors (e.g., oxidized lipid species) provide a common mechanism for development of abdominal AorCP and increased renal volume. Prospective studies are also needed to determine whether increased renal volumes as measured by abdominal CT are clinically predictive of future cardiovascular events in subjects with T2DM.

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