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Coronary artery, aortic wall, and valvular calcification in nondialyzed individuals with type 2 diabetes and renal disease

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Coronary artery, aortic wall, and valvular calcification in nondialyzed individuals with type 2 diabetes and renal disease.

Background. Individuals with end-stage renal disease (ESRD) have highly prevalent and severe vascular and valvular calcification. We undertook this study to test the hypothesis that vascular and valvular calcification begins and is often severe long before diabetic renal disease progresses to ESRD.

Methods. A total of 32 nondialyzed individuals with type 2 diabetes mellitus and diabetic renal disease (albumin excretion rate >30 μg/min) [mean glomerular filtration rate (GFR), 49.8 ± 6.1 mL/min/1.73 m^2] were identified and compared with a group of 18 normoalbuminuric diabetics. We used 3:1 matching to identify 95 nondiabetic controls without renal disease, matched for age, gender, ethnicity, and the presence/absence of dyslipidemia, hypertension, and known coronary artery disease (CAD).

Results. Using electron beam computed tomography (CT), the prevalence of coronary artery calcification was significantly greater among diabetic renal disease individuals (prevalence, 94% vs. 59%, $P < 0.001$; median score, 238 vs. 10, $P < 0.001$) than the nondiabetic controls. The coronary artery calcification scores were significantly more severe among diabetic renal disease individuals than either the diabetic or nondiabetic controls. Among individuals with diabetic renal disease, the coronary artery calcification and aortic wall calcification scores were several-fold greater among those with known CAD than among those without. There was also a significantly greater prevalence of aortic and mitral valve calcification among diabetic renal disease individuals than nondiabetic controls (aortic, 23% vs. 6%, $P = 0.03$; mitral, 25% vs. 2%, $P < 0.001$). Multivariate analysis using all three groups reproduced these findings and also consistently identified age and diabetic renal disease as additional predictors for the presence or severity of coronary artery and aortic wall calcification.

Conclusion. In this first, systematic analysis among nondialyzed individuals with diabetic renal disease, these data demonstrate that vascular and valvular calcification is present and often severe long before the disease progresses to ESRD. The data also suggest that the coronary artery and aortic wall calcification may represent atherosclerosis.

Key words: diabetes mellitus, renal disease, calcification, coronary artery, aortic valve, mitral valve.

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Calcification of the blood vessels and cardiac valves has been recognized for over 100 years. The introduction of electron beam computed tomography (CT) has refocused attention on this complication of renal failure. Electron beam CT is noninvasive and highly sensitive in detecting calcification and hence is a valuable tool for population-based studies to measure vascular (coronary artery and aortic wall) and valvular (aortic and mitral) calcification [1–3].

Recent studies using electron beam CT have found a high prevalence and severity of coronary artery calcification in patients with end-stage renal disease (ESRD) [4–10]. This is concerning, since in the general population coronary artery calcification detected by electron beam CT correlates strongly with atherosclerotic plaque burden and the coronary artery calcification score predicts future fatal/nonfatal cardiovascular events [11]. It is possible that the increased coronary artery calcification contributes to the high cardiovascular morbidity and mortality in patients with ESRD, since a history of myocardial infarction or angina is associated with higher coronary artery calcification scores in these patients [8, 9]. While there has been some correlation between the traditional risk factors for cardiovascular disease and coronary artery calcification in these studies, several investigators have also demonstrated a correlation between coronary artery calcification and serum phosphorus, calcium-phosphorus product, serum intact parathyroid hormone, use of calcium-based phosphate binders, and markers of inflammation [5, 8–10]. Thus, in individuals with ESRD, there are questions regarding the pathophysiology of the increased coronary artery calcification, the relationship of the coronary artery calcification score with plaque burden, and the prognostic value of a given coronary artery calcification score. It is also unclear at what stage of renal disease coronary artery calcification first begins or accelerates. Although several studies have demonstrated a correlation between the prevalence and severity of coronary artery calcification and the presence of

microalbuminuria or proteinuria in diabetics, no systematic study of this issue has been performed [12–16].

These recent studies in ESRD patients have also found a high prevalence of valvular calcification [4, 8, 9]. This is also concerning since valvular calcification, even in the absence of significant stenosis, is associated with increased morbidity and mortality [17, 18]. Several echocardiographic studies in individuals with ESRD have demonstrated strong correlations of valvular calcification with altered calcium and phosphorous metabolism [19–22]. Little is known about the magnitude of the problem and its correlates in nondialyzed patients with renal disease.

This study was undertaken to evaluate coronary artery, aortic wall, and valvular calcification in nondialyzed individuals with diabetic renal disease. This is an appealing group to study, because their calcification scores are less likely to be influenced by the alterations in calcium and phosphorous metabolism and medication regimens characteristic of ESRD patients. The prevalence and severity of calcification in subjects with diabetic renal disease were compared to normoalbuminuric diabetics and a matched group of nondiabetic controls without renal disease.

METHODS

Patient selection and data collection

This is a cross-sectional, case-control study of vascular and valvular calcification in individuals with type 2 diabetes mellitus and diabetic renal disease. Diabetic renal disease was defined by the presence of proteinuria or albuminuria, without the need for dialysis, and individuals were included if they met at least one of the following criteria: urine protein >150 mg/day, urine albumin >30 μg/min or >30 mg/day, spot protein/creatinine ratio >0.15 or spot albumin/creatinine ratio >0.03. Normoalbuminuria was defined as urine albumin <30 μg/min or <30 mg/day, or spot albumin/creatinine ratio <0.03. The protocol was reviewed and approved by the Institutional Review Board of the Research and Education Institute at Harbor-UCLA Medical Center (HUMC).

The data for all individuals who are referred for electron beam CT scanning at St. John's Cardiovascular Research Center at HUMC have been entered into a computerized database. Data on risk factors for cardiovascular disease, including a history of diabetes mellitus, are available for all individuals who have undergone scanning since January 1998. This database was reviewed to identify diabetic individuals who had undergone scanning between January 1998 and June 2001, had received medical care at HUMC, and had a urine protein measurement proximate to the time of the electron beam CT scan. Of the 51 individuals thus identified, 11 individuals were excluded for the following reasons: seven were undergoing dialysis therapy, one had focal segmental glomerulosclerosis (FSGS) on renal biopsy, and three had discordant results from two sets of urine protein data collected close together in time. Of the remaining 40 patients, 32 were classified as having diabetic renal disease and eight as having normoalbuminuria (diabetic controls, see below).

The data on the following four groups of patients are presented as follows: (*1*) diabetic renal disease, obtained from a review of the electron beam CT database (N = 32) [estimated glomerular filtration rate (GFR), 49.8 ± 6.1 mL/min/1.73 m^2]; (*2*) diabetic controls, obtained from a review of electron beam CT database (N = 8) (mean GFR, 86.4 ± 9.9 mL/min/1.73 m^2) up until June 2001; (*3*) diabetic controls, studied as a part of an ongoing prospective study (N = 10) (mean GFR, 111.2 ± 13.8 mL/min/1.73 m^2) and whose data were entered into the electron beam CT database during the period June 2001 to June 2002; and (*4*) nondiabetic controls, without renal disease (N = 95). The nondiabetic controls were identified from the electron beam CT database, using 3:1 matching with individuals with diabetic renal disease. The following parameters were matched to identify controls: age, gender, ethnicity, and the presence/absence of dyslipidemia, hypertension, and known coronary artery disease (CAD).

Medical records were reviewed to determine ethnicity, traditional risk factors for cardiovascular disease (age, gender, dyslipidemia, hypertension, current tobacco use, obesity, family history of premature CAD, and menopause status), history of known CAD (myocardial infarction, angina, positive stress test, angiographic evidence of CAD, and history of myocardial revascularization), diabetes-related factors [duration of diabetes mellitus and glycosylated hemoglobin (HbA_{1C})], and renal-specific factors [serum creatinine, blood urea nitrogen (BUN), serum albumin, 24-hour urine protein excretion and GFR]. The GFR was calculated using the regression equation derived from the Modification of Diet in Renal Disease study [23].

Electron beam CT

Electron beam CT studies were performed with a C-150 XL Ultrafast computed tomographic scanner (Imatron, South San Francisco, CA, USA). The protocol used for data acquisition has been described previously [24]. The scans of all individuals were retrieved, and the vascular and valvular calcification was scored by a single, highly experienced technician, using both the Agatston as well as volumetric method [25, 26].

Statistical analysis

To test for statistically significant differences in the prevalence of vascular and valvular calcification between various groups or subgroups, chi-square or Fisher's exact test were used, as appropriate. As the number of diabetic controls were small, subgroup analyses was restricted to

individuals with diabetic renal disease and nondiabetic controls. For us to include any risk factor for analyses, we required that information for that risk factor be available on at least 75% of the subjects. Data on the following risk factors were obtained on <75% of diabetic renal disease individuals: current tobacco use, obesity, family history of premature CAD, and menopausal status. Thus, no analyses were performed using these risk factors. Continuous variables are expressed either as the mean ± standard error of the mean (SEM) or as median and interquartile range, as appropriate. To test whether there were significant differences between two groups, *t* tests were used for normally distributed variables and the Mann-Whitney rank sum test was used for nonnormally distributed variables. As the calcification scores were right-skewed, they were log transformed for further analyses. To determine the significance of differences in calcification scores in more than two groups, analysis of variance (ANOVA) was used. Pearson correlation coefficients were computed to test the association between continuous variables and calcification scores. Multivariate analyses were performed by combining all three groups: diabetic renal disease patients, diabetic controls, and nondiabetic controls. Multivariate linear models were used to test the combined effects of the presence of diabetic renal disease, age, gender, dyslipidemia, hypertension, and known CAD on the calcification scores at each of the four sites (coronary artery, aortic wall, aortic valve, and mitral valve). Analysis of covariance (ANCOVA) was used when the outcome was the log-transformed raw score. When the outcome was expressed as prevalence, a logistic regression model was used. In these models, dummy variables were used to represent diabetic and nondiabetic controls, so that each was compared to diabetic renal disease. Colinearities in the independent variables prevented us from obtaining reliable results in the logistic models for the prevalence of aortic and mitral valve calcification. A P value ≤ 0.05 was considered significant.

RESULTS

Patient demographics

There were no differences in the age, gender distribution, prevalence of hypertension or dyslipidemia or known CAD or either the severity or prevalence of calcification at any of the vascular or valvular sites between the two groups of diabetic controls. They did differ on duration of diabetes (4.6 ± 1.7 vs. 14.5 ± 1.6 years, $P = 0.008$). Therefore, the two groups were combined for all analyses and duration of diabetes was used as a covariate in comparisons between this group and the group with diabetic renal disease. The diabetic control population did not differ from the diabetic renal disease subjects on age, gender, prevalence of dyslipidemia, or known CAD (Table 1). However, the individuals with diabetic renal disease had significantly higher prevalence of hypertension (90% vs. 56%, $P = 0.01$; Table 1). The mean duration of diabetes mellitus for the 32 diabetic renal disease individuals at the time of electron beam CT was 12.7 ± 1.1 years, the last measured HbA_{1C} was 7.9% ± 0.3%, the serum creatinine proximate to the time of electron beam CT was 2.0 ± 0.3 mg/dL, and the GFR was 49.8 ± 6.1 mL/min/1.73 m^2. The average serum albumin was 3.3 ± 0.1 g/dL and the mean 24-hour urine protein excretion was 4.7 ± 0.8 g/day. The diabetic controls had a mean duration of diabetes mellitus of 10.1 ± 1.6 years, the last measured HbA_{1C} was 8.7% ± 0.5% ($N = 13$), an average serum creatinine of 0.9 ± 0.3 mg/dL, and a GFR of 101.9 ± 9.6 mL/min/1.73 m^2.

Table 1. Characteristics of individuals in the three study cohorts

	Diabetic renal disease	Diabetic controls	Nondiabetic controls
Number	32	18	95
Age *years*	57 ± 1.5	58.2 ± 1.9	57 ± 0.9
Gender *male/female*	13/19	11/7	39/56
Ethnicity			
Hispanic	20 (62%)	12 (67%)	59 (62%)
African American	8 (25%)	2 (11%)	24 (25%)
Caucasian	2 (6%)	4 (22%)	6 (6%)
Asian	2 (6%)	0	6 (6%)
Dyslipidemia	24 (75%)	15[a] (88%)	73 (77%)
Hypertension	28[b] (90%)	10 (56%)	70 (74%)
Known coronary artery disease	15 (47%)	6 (33%)	57 (60%)

[a]$N = 17$; [b]$N = 31$

The 32 diabetic renal disease individuals and 95 controls were well matched for age, gender, ethnicity, and presence/absence of dyslipidemia (Table 1). There was a statistically nonsignificant trend toward a higher prevalence of hypertension (90% vs. 74%, $P = 0.09$) and a lower prevalence of known CAD (47% vs. 60%, $P = 0.22$) in diabetic renal disease individuals compared to controls.

Correlation between Agatston and volumetric method

The coronary artery, aortic wall, and aortic and mitral valve calcification scores were calculated for each individual using both the Agatston and the volumetric method. The two values for each of the four sites were highly correlated ($r = 0.99$, $P < 0.001$ for each), and since past literature has primarily used the Agatston method, all statistical analyses were performed using the Agatston scores.

Coronary artery calcification

Coronary artery calcification was present in 94% of diabetic renal disease individuals, compared to all the diabetic controls and 59% of nondiabetic controls ($P <$ 0.001, compared to diabetic renal disease) (Table 2, Fig.

Table 2. Subgroup analyses of the prevalence and severity of coronary artery calcification in individuals with diabetic renal disease and nondiabetic controls

	Prevalence, % patients		Severity, median score	
	Diabetic renal disease	Nondiabetic controls	Diabetic renal disease	Nondiabetic controls
Overall	94%[a] ($N = 32$)	59% ($N = 95$)	238[a] (55–789)	10 (0–90)
Gender				
Male	92% ($N = 13$)	67% ($N = 39$)	619[b] (82–972)	18 (0–168)
Female	95%[b] ($N = 19$)	54% ($N = 56$)	232[a] (52–470)	6 (0–61)
Dyslipidemia				
Present	92%[b] ($N = 24$)	55% ($N = 73$)	224[a] (49–789)	6 (0–89)
Absent	100% ($N = 8$)	73% ($N = 22$)	506[b] (171–679)	27 (0–111)
Hypertension				
Present	96%[b] ($N = 28$)	67%[d] ($N = 70$)	238[a] (64–789)	17[d] (0–155)
Absent	67% ($N = 3$)	36% ($N = 25$)	4 (2–470)	0 (0–18)
Known coronary artery disease				
Present	100%[b] ($N = 15$)	60% ($N = 57$)	543[a,c] (232–894)	16 (0–93)
Absent	88% ($N = 17$)	58% ($N = 38$)	74[b] (14–257)	7 (0–97)

The numbers in parentheses associated with the coronary artery calcification scores are the interquartile ranges in each designated subgroup.
[a]$P < 0.001$ for difference between diabetic renal disease individuals and controls; [b]$P < 0.05$ for difference between diabetic renal disease individuals and controls
[c]$P = 0.004$ for difference between diabetic renal disease individuals with and without known coronary artery disease
[d]$P = 0.01$ for difference between controls with and without hypertension

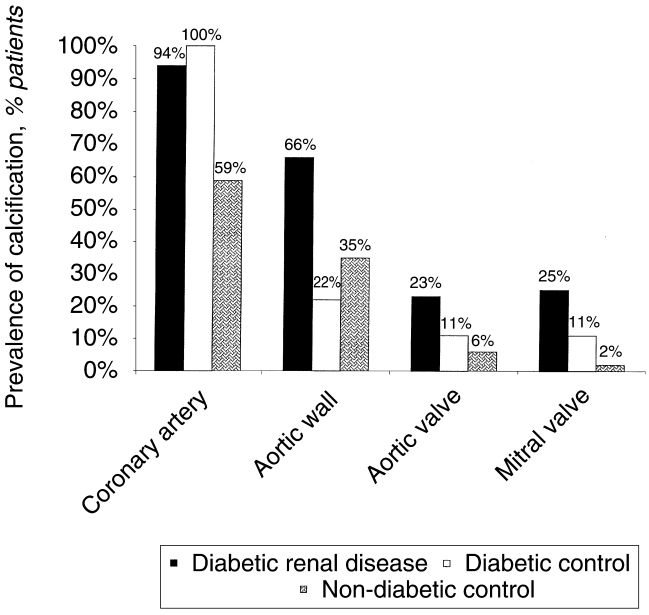

Fig. 1. The prevalence of coronary artery, aortic wall, aortic valve and mitral valve calcification in individuals with diabetic renal disease ($N = 32$), diabetic controls ($N = 18$) and in nondiabetic controls ($N = 95$). Compared to diabetic controls, individuals with diabetic renal disease had a significantly greater prevalence of aortic wall calcification (66% vs. 22%, $P = 0.008$). Compared to nondiabetic controls, individuals with diabetic renal disease had a significantly greater prevalence of coronary artery calcification (94% vs. 59%, $P < 0.001$), aortic wall calcification (66% vs. 35%, $P = 0.004$), aortic valve calcification (23% vs. 6%, $P = 0.02$), and mitral valve calcification (25% vs. 2%, $P < 0.001$).

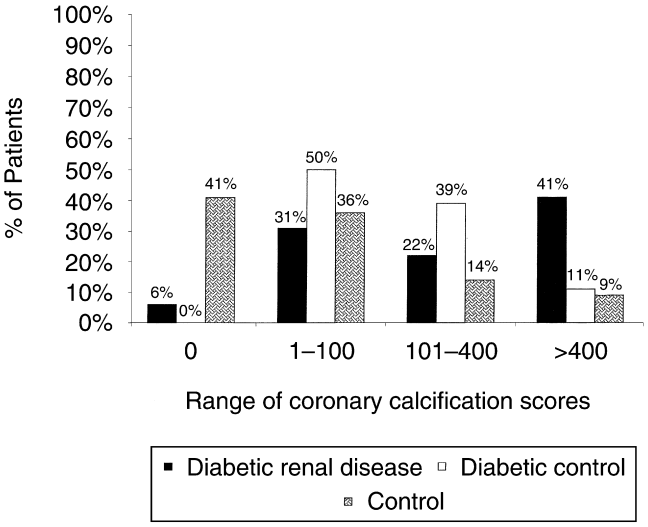

Fig. 2. The range of coronary artery calcification scores in diabetic renal disease individuals, diabetic controls, and nondiabetic controls. There was a significant difference in the range of distribution of coronary artery calcification scores between individuals with diabetic renal disease and nondiabetic controls ($P < 0.001$). Severe calcification (score >400) was present in 41% of individuals with diabetic renal disease compared to 11% of diabetic controls ($P = 0.06$) and 9% of nondiabetic controls ($P < 0.001$).

1). The results of the subgroup comparisons of prevalence of coronary artery calcification between diabetic renal disease individuals and nondiabetic controls are summarized in Table 2. The range of ccoronary artery calcification scores in individuals with diabetic renal disease, diabetics, and nondiabetic controls are presented in Figure 2. Severe calcification (coronary artery calcification score > 400) was present in 41% of diabetic renal disease individuals, compared to 11% of diabetic controls ($P = 0.06$, compared to diabetic renal disease) and 9% of nondiabetic controls ($P < 0.001$, compared to diabetic renal disease). The median coronary artery calcification score in diabetic renal disease individuals was 2.5-fold greater than in diabetic controls [238 (55 to 789) vs. 96 (12 to 202), $P = 0.0001$] and 24-fold greater than in nondiabetic controls [238 (55 to 789) vs. 10 (0 to 90), $P < 0.001$) (Table 2, Fig. 3).

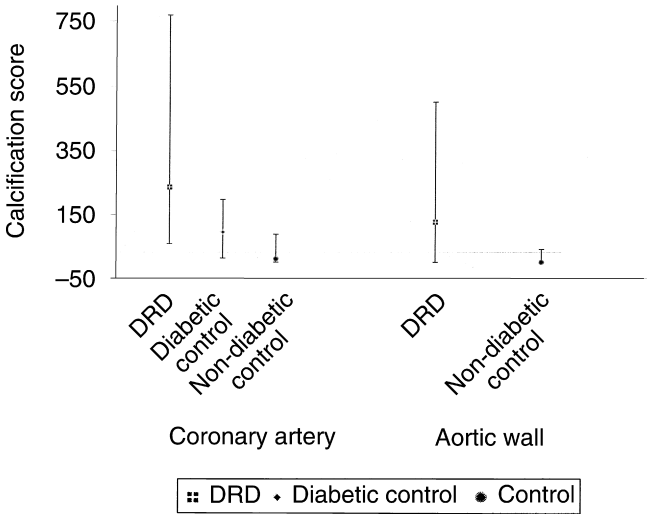

Fig. 3. The median coronary artery and aortic wall calcification scores in diabetic renal disease individuals (DRD) ($N = 32$), diabetic controls ($N = 18$) and in nondiabetic controls ($N = 95$). The horizontal lines (from top to bottom) represent the 75th and 25th percentile for the scores in individuals with diabetic renal disease and among controls. The median coronary artery calcification scores were significantly greater in individuals with diabetic renal disease than among diabetic controls [238 (55 to 789) vs. 96 (12 to 202), $P = 0.0001$] or nondiabetic controls [238 (55 to 789) vs. 10 (0 to 90), $P < 0.001$]. Similarly, the aortic wall calcification scores were significantly greater in individuals with diabetic renal disease than among nondiabetic controls [127 (0 to 520) vs. 0 (0 to 42), $P = 0.001$]. The median aortic wall calcification score, as well as the interquartile range among diabetic controls was 0 and was significantly lower than among individuals with diabetic renal disease ($P = 0.004$). Thus, these data are not presented in the figure.

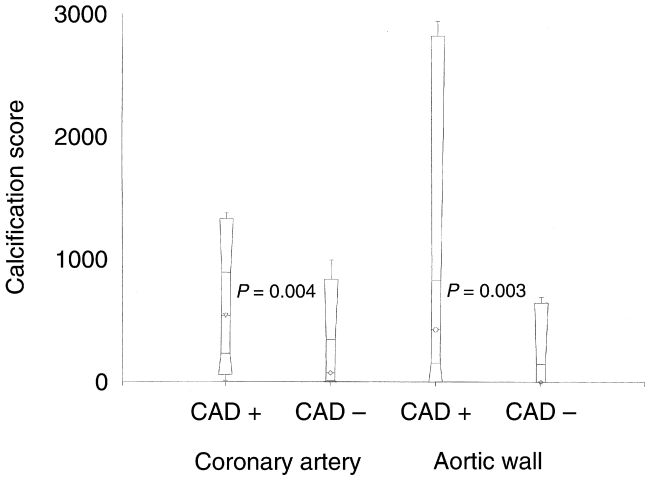

Fig. 4. Box and whisker plots for the coronary artery and aortic wall calcification scores in diabetic renal disease individuals with ($N = 15$) and without known coronary artery disease (CAD) ($N = 17$). The horizontal lines (from top to bottom) represent the maximum, 90th, 75th, 50th, 25th, and 10th percentiles. The median coronary artery calcification scores were significantly greater in individuals with known CAD compared to those without [543 (232 to 894) vs. 74 (14 to 257), $P = 0.004$]. The aortic wall calcification scores were significantly greater in individuals with known CAD compared to those without [427 (155 to 829) vs. 0 (0 to 88), $P = 0.003$].

There was no significant difference in prevalence of coronary artery calcification in various subgroups of diabetic renal disease individuals (Table 2). In addition, there was no significant difference or correlation between the coronary artery calcification scores in diabetic renal disease individuals based on ethnicity, traditional risk factors for cardiovascular disease (Table 2), diabetes-related factors (duration of diabetes mellitus and HbA_{1C}), and renal-specific factors (serum creatinine, BUN, serum albumin, 24-hour urine protein excretion, or GFR). There was a trend toward a longer duration of diabetes mellitus among individuals with GFR ≤ 30, when compared to those with GFR > 30 (15.2 ± 1.9 years vs. 11.4 ± 1.4 years); however, this difference did not reach statistical significance ($P = 0.10$). No significant differences were noted in the coronary artery calcification scores among diabetic renal disease individuals with GFR ≤ 30 [median, 216 (14 to 758), $N = 11$] and > 30 [median, 250 (72 to 845), $N = 20$] ($P = 0.45$). However, the median coronary artery calcification score among diabetic renal disease individuals with known CAD was significantly greater than among diabetic renal disease individuals without known CAD [543 (232 to 894) vs. 74 (14 to 257), $P = 0.004$] (Table 2, Fig. 4).

Among the nondiabetic controls, there was a significantly higher prevalence of coronary artery calcification (67% vs. 36%, $P = 0.01$) and median coronary artery calcification score (17 (0 to155) vs. 0 (0 to18), $P = 0.005$) in individuals with hypertension compared to those without hypertension (Table 2). There was also a significant correlation between age and coronary artery calcification score ($r = 0.39$, $P < 0.001$). However, there was no significant difference in coronary artery calcification prevalence based upon gender, dyslipidemia or known CAD, and no significant difference in coronary artery calcification score based upon ethnicity, gender, dyslipidemia or known CAD (Table 2).

Using multivariate linear models to study all the subjects together (diabetic renal disease and diabetic as well as nondiabetic controls), increasing age, and the presence of diabetic renal disease were significant, independent predictors for the presence of coronary artery calcification. In the ANCOVA model, in addition to age and the presence of diabetic renal disease, male gender and the presence of hypertension were all independent predictors of a greater severity of coronary artery calcification.

Aortic wall calcification

Aortic wall calcification was present in 66% of diabetic renal disease individuals, compared to 22% of diabetic controls ($P = 0.008$) and 35% of nondiabetic controls ($P = 0.004$) (Fig. 1). Subgroup comparisons between diabetic renal disease individuals and nondiabetic controls revealed a significantly higher prevalence of calcifi-

cation in diabetic renal disease individuals that were female, with or without dyslipidemia, hypertensive, or with known CAD, compared to the corresponding subgroup of nondiabetic controls. The median aortic wall calcification score in diabetic renal disease individuals was greater than that in diabetic [median scores, 127 (0 to 520) vs. 0 (0 to 0), $P = 0.004$] as well as nondiabetic controls [127 (0 to 520) vs. 0 (0 to 42), $P = 0.001$] (Fig. 3). Subgroup comparisons between diabetic renal disease individuals and nondiabetic controls revealed a significantly higher median calcification score in diabetic renal disease individuals that were Hispanic, male or female, with or without dyslipidemia, or with hypertension or known CAD compared to the corresponding subgroup of nondiabetic controls.

Among individuals with diabetic renal disease, there was a significantly greater prevalence (87% vs. 47%, $P = 0.05$) and median aortic wall calcification score [427 (155 to 829) vs. 0 (0 to 88), $P = 0.003$] (Fig. 4) among those with known CAD compared to those without known CAD. In addition, there was a significant correlation between age and the calcification score ($r = 0.45$, $P = 0.01$). Among nondiabetic controls, there was no significant difference in the prevalence of aortic wall calcification in the various subgroups, but there was a significant correlation between age and the calcification score ($r = 0.40$, $P < 0.001$).

Using multivariate linear models, increasing age and the presence of diabetic renal disease were the only significant predictors of the prevalence and severity of aortic wall calcification.

Valvular calcification

A total of 44% of individuals with diabetic renal disease had calcification of at least one of the two valves. Aortic and mitral valve calcification were, respectively, present in 23% and 25% of diabetic renal disease individuals, compared to 11% and 11% of diabetic controls ($P =$ NS for both) and 6% and 2% of nondiabetic controls ($P = 0.02$ and $P < 0.001$, respectively) (Fig. 1). Subgroup comparisons between diabetic renal disease and nondiabetic control individuals revealed a significantly higher prevalence of aortic valve calcification in diabetic renal disease individuals who were female, hypertensive, or with known CAD compared to the corresponding subgroup of nondiabetic controls. There was a significantly higher prevalence of mitral valve calcification in individuals with diabetic renal disease who were male or female, with or without dyslipidemia or known CAD, or hypertensive compared to the corresponding subgroup of nondiabetic controls.

There was no significant difference in the prevalence of aortic valve calcification in the various subgroups of diabetic renal disease individuals, but there was a significantly greater prevalence in male nondiabetic controls compared to female nondiabetic controls. There was no significant difference in prevalence of mitral valve calcification in the various subgroups of diabetic renal disease individuals or nondiabetic controls.

Diabetic renal disease individuals with aortic valve calcification had a significantly greater BUN (52 ± 9 mg/dL vs. 32 ± 4 mg/dL, $P = 0.02$) and duration of diabetes mellitus (18 ± 3 years vs. 11 ± 1 years, $P = 0.02$) compared to diabetic renal disease individuals without calcification. However, there were no other significant relationships between the presence or absence of aortic valve calcification and traditional, diabetes-related or renal-specific factors, or coronary artery calcification, aortic wall calcification, or mitral valve calcification. There were no significant relationships between the presence or absence of mitral valve calcification and any of the above factors in the diabetic renal disease individuals.

As indicated above, the presence of colinearities in the independent variables prevented us from obtaining reliable results in the logistic models for the prevalence of aortic and mitral valve calcification. Using ANCOVA, increasing age and the presence of diabetic renal disease were significant predictors for the presence of aortic valve calcification. The presence of diabetic renal disease was the only significant, independent predictor for the presence of mitral valve calcification.

DISCUSSION

In this first systematic analysis, we report a near-universal prevalence of coronary artery calcification among both nondialyzed individuals with diabetic renal disease as well as normoalbuminuric diabetics. Coronary artery calcification and aortic wall calcification were significantly more severe in the diabetic renal disease individuals compared to both the diabetic and the nondiabetic controls without renal disease. Finally, aortic and mitral valve calcification was highly prevalent among nondialyzed individuals with diabetic renal disease.

Several recent studies have addressed the issue of coronary artery calcification in individuals with ESRD [4–9]. The 94% prevalence of coronary artery calcification in our diabetic renal disease individuals is similar to the prevalence of 83% to 92% recently reported in adults with ESRD [5, 8, 9]. This high prevalence of coronary artery calcification in our diabetic renal disease individuals indicates that coronary artery calcification in diabetics with renal disease begins long before they reach ESRD. Our data do suggest that in most individuals with diabetic renal disease, the coronary artery calcification scores are not as high as those reported in individuals with ESRD [4, 7–9]. Nevertheless, 41% of the diabetic renal disease individuals had severe coronary artery calcification (score >400), a score that is associated with a significantly

higher risk for adverse cardiovascular events in the general population.

Two concerns have been raised with respect to the significance of coronary artery calcification in individuals with ESRD. First, in the general population, coronary artery calcification scores represent a quantitative estimate of the total atherosclerotic plaque burden, and predict adverse cardiovascular outcomes [11]. While the calcification that occurs with atherosclerosis is localized to the intima of the blood vessels, individuals with diabetes mellitus or those with advanced renal failure also develop medial calcification, unrelated to atherosclerosis. Although most studies of medial calcification in individuals with renal failure have examined arteries other than the coronary arteries [27–30], early autopsy studies suggested that medial calcification in the coronary arteries was infrequent [31–34]. Subsequent publications, limited to a few case reports, suggested that even when medial calcification occurred in the coronaries, it represented only a small fraction of the overall coronary calcification burden [35, 36]. However, a systematic analysis of the relative contribution of intimal and medial calcification to the overall coronary calcification has not been performed. Indeed, a recent analysis of coronary morphology from individuals with ESRD reported greater atherosclerotic plaque calcification (intimal) and an increased thickness of the media, when compared to individuals with normal renal function; however, no data on the presence or severity of medial calcification were presented [37]. In this study of diabetic renal disease individuals, the only important predictor of the severity of coronary artery calcification was the presence of known CAD. These data are consistent with those reported by two recent studies in individuals with ESRD [8, 9] and suggests that a significant proportion of coronary artery calcification may represent intimal calcification, associated with atherosclerotic plaque. Despite these considerations, in the absence of histologic data, the precise contribution of medial calcification to the overall coronary artery calcification score cannot be defined.

Second, disturbances in divalent ion metabolism, elevated serum parathyroid hormone, the use of calcium-based phosphate binders and chronic inflammation are associated with the prevalence, severity and progression of coronary artery calcification in ESRD individuals [5, 8–10]. Although the vast majority of diabetic renal disease individuals had only mild to moderate renal insufficiency (GFR 49.8 $\pm$ 6.1 mL/min/1.73 m^2), it is possible that these disturbances may contribute to the severity of coronary artery calcification in nondialyzed diabetic individuals with renal disease. When the GFR declines below 70 mL/min/1.73 m^2, serum parathyroid hormone and phosphorus increase and serum calcium decreases [38]. Specifically, changes in serum levels of parathyroid hormone and phosphorus are closely correlated to changes in GFR [38]. In this present analysis there was no significant correlation between any measure of renal function and either the prevalence or severity of coronary artery calcification, but the relatively small sample size may have limited our ability to demonstrate a significant relationship. None of the individuals with diabetic renal disease in our study were treated with phosphate binders or vitamin D or its analogs. Finally, recent studies have highlighted the relationship between vascular calcification in individuals with ESRD and markers of inflammation [9, 39]. Data on markers of inflammation was not available in this study and future studies need to evaluate the importance of this issue in nondialyzed individuals with diabetic renal disease. Thus, it is likely that the relative importance of various pathogenetic factors in vascular calcification may differ at various stages of renal failure.

This study also demonstrates a significantly higher prevalence of valvular calcification in diabetic renal disease individuals compared to controls. The data on mitral valve calcification are consistent with the early echocardiographic studies [20, 40]. Among individuals without renal disease, vascular calcification is rare before the age of 60. Only 4% have aortic valve calcification and only 0.2% to1.1% have mitral valve calcification [41, 42]. In the general population, the prevalence of both aortic and mitral valve calcification increases progressively with increasing age [42–45]. Indeed, the prevalence of aortic valve calcification of 23% in our study population with a mean age of 57 years is similar to the 23% to 28% prevalence reported among the elderly [42, 45]. The prevalence of 25% for mitral valve calcification in our diabetic renal disease individuals is substantially greater than reported among the elderly in the general population. Only 7% to 15% of individuals >60 years of age have been reported to have mitral valve calcification [42, 43]. However, the prevalence of aortic and mitral valve calcification does not approach the levels reported in ESRD populations using electron beam CT (aortic valve calcification, 34% to 55%; and mitral valve calcification, 45% to 59%) [4, 8]. Hence, like coronary artery calcification, valvular calcification appears to begin early in the course of progressive renal insufficiency in a significant proportion of individuals with diabetic renal disease, long before ESRD.

Multiple studies in individuals without renal disease have demonstrated correlations between valvular calcification and the traditional risk factors for cardiovascular disease and the presence of atherosclerotic disease at other sites, causing some authors to conclude that valvular calcification represents atherosclerosis [43, 45–50]. However, several echocardiographic studies in ESRD patients have consistently demonstrated correlations between valvular calcification and age, duration of dialysis, serum phosphorous, calcium-phosphorous product, and parathyroid hormone levels [19–22], as opposed to the

traditional risk factors for cardiovascular disease. Finally, among individuals with ESRD, aortic valve calcification ascertained by electron beam CT correlated with coronary artery calcification in both the studies that have looked at this issue; mitral valve calcification correlated with coronary artery calcification in only one of the two studies [4, 8]. In this study, other than a higher BUN and longer duration of diabetes mellitus among individuals with aortic valve calcification, there were no other relationships between the presence or absence of aortic or mitral valve calcification and the traditional risk factors for cardiovascular disease, diabetes-related factors, renal-specific factors, or coronary artery calcification or aortic wall calcification. Hence, future studies need to focus on the pathophysiologic basis and significance of the high prevalence of valvular calcification among nondialyzed individuals with diabetic renal disease.

We believe that the presence of renal disease plays an important role in explaining the high prevalence and severity of calcification in the diabetic renal disease individuals. First, our data suggest that among diabetics, the calcification burden is greater in individuals who have renal disease. Second, these findings are consistent with a progressive increase in cardiovascular morbidity and mortality with increasing degrees of urine protein excretion [51, 52]. Third, five previous studies have reported on the prevalence and severity of coronary artery calcification in subsets of diabetics with and without renal disease [12–16]. Yoshida et al [12] reported that coronary artery calcification was present in only 61% of diabetic Japanese subjects (with and without renal disease), compared to 94% of our diabetic renal disease individuals. Moreover, the mean coronary artery calcification score in individuals with normoalbuminuria, microalbuminuria and overt proteinuria progressively increased from 69 to 323 to 570, respectively [12]. Wagenknecht et al [13] reported that coronary artery calcification was present in 80% of their diabetic subjects, with a median score of only 84, substantially less than our diabetic renal disease individuals, and at least partially explained by the fact that only 24% had renal disease. Moreover, coronary artery calcification was associated with the albumin-creatinine ratio. Similar results have been reported in three studies in individuals with type 1 diabetes [14–16]. Hence, it is likely that the presence of renal disease contributed significantly to the high prevalence and severity of coronary artery calcification in diabetic renal disease individuals. However, it is important for future studies to include a control group of nondiabetic patients with chronic renal failure to clarify the relative contribution of diabetes mellitus and factors associated with chronic kidney disease to vascular calcification.

CONCLUSION

Nondialyzed individuals with diabetic renal disease have a significantly greater prevalence and severity of vascular and valvular calcification compared to matched nondiabetic controls with normal renal function. Coronary and aortic wall calcification is significantly greater among individuals with diabetic renal disease, when compared to normoalbuminuric diabetics. This demonstrates that the severe calcification seen in subjects with ESRD actually begins long before renal insufficiency is severe enough to require dialysis. The increased coronary artery calcification and aortic wall calcification may represent atherosclerosis; the significance of valvular calcification needs to be defined in future studies.

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