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End-Stage Renal Disease

Cardiac Calcification in Adult Hemodialysis Patients

A Link Between End-Stage Renal Disease and Cardiovascular Disease?

Paolo Raggi, MD,* Amy Boulay, MPH,† Scott Chasan-Taber, PHD,‡ Naseem Amin, MD,§ Maureen Dillon, MA,† Steven K. Burke, MD,† Glenn M. Chertow, MD, MPH‖

New Orleans, Louisiana; Waltham and Cambridge, Massachusetts; and San Francisco, California

OBJECTIVES We sought to determine clinical and laboratory correlates of calcification of the coronary arteries, aorta and mitral and aortic valves in adult subjects with end-stage renal disease (ESRD) receiving hemodialysis.

BACKGROUND Vascular calcification is known to be a risk factor for ischemic heart disease in non-uremic individuals. Patients with ESRD experience accelerated vascular calcification, due at least in part to dysregulation of mineral metabolism. Clinical correlates of the extent of calcification in ESRD have not been identified. Moreover, the clinical relevance of calcification as measured by electron-beam tomography (EBT) has not been determined in the ESRD population.

METHODS We conducted a cross-sectional analysis of 205 maintenance hemodialysis patients who received baseline EBT for evaluation of vascular and valvular calcification. We compared subjects with and without clinical evidence of atherosclerotic vascular disease and determined correlates of the extent of vascular and valvular calcification using multivariable linear regression and proportional odds logistic regression analyses.

RESULTS The median coronary artery calcium score was 595 (interquartile range, 76 to 1,600), values consistent with a high risk of obstructive coronary artery disease in the general population. The coronary artery calcium scores were directly related to the prevalence of myocardial infarction ($p < 0.0001$) and angina ($p < 0.0001$), and the aortic calcium scores were directly related to the prevalence of claudication ($p = 0.001$) and aortic aneurysm ($p = 0.02$). The extent of coronary calcification was more pronounced with older age, male gender, white race, diabetes, longer dialysis vintage and higher serum concentrations of calcium and phosphorus. Total cholesterol (and high-density lipoprotein and low-density lipoprotein subfractions), triglycerides, hemoglobin and albumin were not significantly related to the extent of coronary artery calcification. Only dialysis vintage was significantly associated with the prevalence of valvular calcification.

CONCLUSIONS Coronary artery calcification is common, severe and significantly associated with ischemic cardiovascular disease in adult ESRD patients. The dysregulation of mineral metabolism in ESRD may influence vascular calcification risk. (J Am Coll Cardiol 2002;39:695–701)

More than 350,000 persons in the U.S. have end-stage renal disease (ESRD), and at least 10-fold more have a significant degree of renal insufficiency (1,2). Cardiovascular disease accounts for more than 50% of deaths among persons with ESRD, and the annual cardiovascular mortality rate is more than an order of magnitude greater than in the non-ESRD population, especially among younger (<70 years) individuals (3). Certain factors have been proposed to contribute to this exceptionally increased risk, including dyslipidemia, hyperhomocysteinemia, oxidative stress of uremia and hemodialysis, and the relatively infrequent use of aspirin, beta-adrenergic antagonists, lipid-lowering agents, and estrogen replacement therapy in this population (4–10). Recently, interest has focused on the roles of hyperphosphatemia, elevated levels of the calcium x phosphorus product and hyperparathyroidism in the development of cardiovascular disease in ESRD. Goodman et al. (11) recently demonstrated a high prevalence of coronary artery calcification among young adults receiving dialysis, especially those who had been receiving dialysis for more than 10 years.

In the context of a randomized clinical trial comparing two classes of phosphate binders, we obtained baseline electron-beam tomography (EBT) scans on 205 patients receiving maintenance hemodialysis. The main goals of this analysis were to determine whether cardiovascular disease was related to the vascular calcification scores derived by EBT and to determine clinical correlates of the extent of

From the *Section of Cardiology, Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana; †GelTex Pharmaceuticals, Inc., Waltham, Massachusetts; ‡Boston Biostatistics, Inc., §Genzyme, Inc, Cambridge, Massachusetts; and the ‖Division of Nephrology, Department of Medicine, University of California, San Francisco, San Francisco, California. Dr. Burke, Ms. Dillon, and Ms. Boulay are employees of GelTex Pharmaceuticals, Inc., a subsidiary of Genzyme, Inc. Dr. Amin is an employee of Genzyme, Inc. All have equity interest in Genzyme, Inc. Drs. Raggi, Chasan-Taber, and Chertow have no equity interest in Genzyme, Inc. Dr. Raggi and Dr. Chertow serve on the Physician Advisory Board of Genzyme, Inc. Dr. Chasan-Taber works for a firm retained by Genzyme, Inc., for statistical analysis of clinical trials. Funding provided by Genzyme, Inc.

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Abbreviations and Acronyms

ASVD = atherosclerotic vascular disease
CAD = coronary artery disease
EBT = electron-beam tomography
ESRD = end-stage renal disease
HDL = high-density lipoprotein
LDL = low-density lipoprotein
MI = myocardial infarction
PTH = parathyroid hormone

coronary artery, aortic and valvular calcification in this population.

METHODS

Subjects. Subjects were adult (age >18 years) patients receiving maintenance hemodialysis enrolled in a randomized clinical trial comparing calcium-based phosphate binders (calcium carbonate or calcium acetate) with sevelamer hydrochloride, a non-calcium, non-aluminum-containing polymer. There were 15 participating dialysis centers: seven in the U.S. and eight in western Europe. Subjects with the following history were excluded from participation: serious gastrointestinal disease (including dysphagia, active untreated gastroparesis, severe motility disorder, major intestinal surgery, markedly irregular bowel function), ethanol or drug dependence or abuse, active malignancy, HIV infection, vasculitis, severe hyperphosphatemia (defined as consistently having a serum phosphorus concentration >8.0 mg/dL, due to poor adherence with phosphate binders), or those whose diabetes mellitus or hypertension was so poorly controlled as to interfere with the conduct of the study as deemed by the investigator. Baseline data on demographic, dialysis-specific and clinical characteristics were obtained, as were a variety of biochemical parameters (including serum phosphorus, calcium, intact parathyroid hormone [PTH], and total, high-density and low-density lipoprotein cholesterol [HDL and LDL], and triglycerides). The LDL level was calculated using Friedewald's formula (12). Atherosclerotic vascular disease (ASVD) was documented by the clinical diagnoses of coronary artery disease (CAD) (a history of myocardial infarction [MI] or angina pectoris, or evidence of obstructive disease by angiography), cerebrovascular disease (a history of thrombotic stroke or transient ischemic attack) and peripheral vascular disease (a history of claudication, lower extremity revascularization or aortic aneurysm). Written informed consent was obtained from all subjects. The study was conducted in compliance with the recommendations of the Committees on Human Research at each of the participating medical centers (see Appendix).

Imaging procedure. All subjects underwent an EBT imaging procedure on a C-100 or C-150 scanner (Imatron; South San Francisco, California). Imaging was performed with a 100-ms scanning time and a single-slice thickness of 3 mm. Thirty-six to 40 tomographic slices were obtained for each subject during two breath-holding periods for the C-100 scanner and a single breath-holding period for the C-150 scanner. Tomographic imaging was electrocardiographically triggered at 60% or 80% of the R-R interval (according to each individual imaging center's protocol) and proceeded from the level of the carina to the diaphragm. Thus, this imaging protocol prevented the visualization of a portion of the aortic arch. All areas of calcification with a minimal density of 130 Hounsfield units within the borders of the coronary arteries, aorta, mitral and aortic valves were computed. A calcified plaque was considered present if at least three contiguous pixels with a density of ≥130 Hounsfield units were measured (an area equivalent to 1.03 mm^2). The radiation exposure from one EBT scan is approximately 1 rem.

The acquired images were reviewed on a NetraMD workstation (ScImage; Los Altos, California). The total volume and density of calcification were derived in the following areas: 1) coronary arteries (left main, left anterior descending, left circumflex and right coronary artery); 2) aorta (with the exclusion of the top portion of the aortic arch that was not included because of the imaging protocol used); and the 3) mitral and 4) aortic valves. The calcium score originally described by Agatston et al. (13) was calculated. The "Agatston score" incorporates the density of calcification, multiplying the calcification volume by a weighted density coefficient (13).

Scans were considered of acceptable research quality only if the images were free from artifacts due to motion, respiration or asynchronous electrocardiographic triggering. Repeat scanning was required in only one case. To ensure the continuity and consistency of the calcium score interpretation, a single expert investigator unaware of the subjects' clinical status reviewed all EBT scans.

Statistical analysis. For descriptive purposes, subjects were classified into four coronary calcification groups: none (calcium score = 0), mild to moderate (calcium score = 1 to 400), severe (calcium score = 401 to 1,000) and very severe (calcium score >1,000). This classification is a modification of the categorization proposed by Rumberger et al. (14), who recommended dividing coronary artery calcification scores into four categories. Calcium scores <10 indicate the presence of minimal atherosclerotic plaque. Calcification scores between 11 and 100 indicate mild plaque burden. These two groups experience a low likelihood of obstructive CAD. Calcium scores between 101 and 400 indicate moderate plaque burden and a relatively high likelihood of CAD. Finally, calcium scores >400 indicate severe and extensive atherosclerotic disease. Patients with calcification scores in this range are very likely to have obstructive CAD, with a high risk of developing symptomatic myocardial ischemia (14). For this study, the classification was modified to accommodate the more extensive degree of calcification observed in the hemodialysis population. Therefore, the mild and moderate categories were combined into a single category. Additionally, a fourth category, "very severe," was

created to categorize those subjects with markedly elevated calcium scores.

Baseline characteristics were described using conventional descriptive statistics such as mean ± standard deviation, median ± interquartile range and proportions. Correlation between sites of calcification was described with the Spearman correlation coefficient. To evaluate whether EBT had prognostic value in the hemodialysis population, we used the Wilcoxon rank sum test to examine the associations among coronary artery and aortic calcium scores with cardiovascular (i.e., MI, angina pectoris) and peripheral vascular disease (i.e., claudication or lower extremity revascularization, aortic aneurysm) outcomes. Linear regression analysis was conducted in the 170 subjects with evidence of coronary artery calcification (and the 164 subjects with evidence of aortic calcification), to investigate whether the extent of calcification was related to any demographic, clinical or laboratory variables. The calcium scores were highly right-skewed, and therefore, log-transformed prior to inference testing. Age, gender, race, diabetes and dialysis vintage (time since the initiation of dialysis) were included in all models. Smoking status, vitamin D usage, prior parathyroidectomy, and screening serum albumin, hemoglobin, phosphorus, calcium, PTH, and lipids (total, HDL, LDL cholesterol and triglycerides) were candidate variables in multivariable analyses. Variables denoting the presence or absence of vascular disease were not included in the model building process, as they may have resulted from, rather than caused, calcification. As a confirmatory approach, we used proportional odds logistic regression to estimate the associations among categories of calcium score and candidate explanatory variables. This approach allowed the inclusion of all subjects. The proportional odds assumption was tested and deemed non-significant using the Score test (15).

All reported p values are based on two-tailed tests of statistical significance. Analyses were conducted using SAS 6.12 (SAS Institute; Cary, North Carolina).

RESULTS

Baseline subject characteristics are outlined in Table 1. Demographic characteristics of the study sample were similar to the general ESRD population in the U.S. and Europe. Calcification of the coronary arteries, aorta and mitral and aortic valves was frequent and severe (see below). Figure 1 shows an example of calcium deposition in the coronary arteries of an asymptomatic individual extracted from the general population (Fig. 1A) and a subject with ESRD (Fig. 1B).

Correlation between EBT-measured calcification and coronary heart disease/peripheral vascular disease. The coronary artery calcium scores were directly related to the prevalence of coronary, cerebral and peripheral vascular disease in the study subjects. Figure 2 shows the prevalence of ASVD by calcium score category. Tables 2 and 3 show the proportion of subjects in each calcium score category with prevalent vascular disease.

Table 1. Baseline Characteristics of Study Subjects (n = 205)

Characteristics	Data
Age (yr)	56.8 ± 14.9
Gender (% female)	35.6%
Race (% black)	17.6%
Diabetes (%)	29.8%
Dialysis vintage* (mo, median, interquartile range)	36.8 (17.1 to 62.5)
Presumed cause of ESRD (%)	
Diabetes	23.5%
Hypertension	17.2%
Glomerulonephritis	22.1%
Polycystic kidney disease	10.3%
Interstitial nephritis	4.9%
Other	22.1%
Current smoking (%)	8.3%
History of kidney transplantation (%)	15.3%
History of parathyroidectomy (%)	7.4%
Vitamin D usage (%)	52.5%
Albumin (g/dl)	3.9 ± 0.2
Hemoglobin (g/dl)	11.6 ± 1.3
Albumin-adjusted calcium (mg/dl)	9.6 ± 0.7
Phosphorus (mg/dl)	5.7 ± 1.4
Calcium × phosphorus (mg^2/dl^2)	55.1 ± 13.5
Intact PTH (pg/ml, median, interquartile range)	145 (67 to 268)
Total cholesterol (mg/dl)†	185.4 ± 40.9
HDL cholesterol (mg/dl)	45.4 ± 14.5
LDL cholesterol (mg/dl)	103.3 ± 33.3
Triglycerides (mg/dl)	195.7 ± 169.2

*Full range of dialysis vintage 1.9 to 310.7 months, or 0.2 to 25.9 years. †HMG-CoA reductase inhibitors prescribed in 28.5%, fibrates prescribed in 0.5% of subjects.

ESRD = end-stage renal disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTH = parathyroid hormone.

Coronary artery calcification. The median coronary artery calcium score was 595 (interquartile range, 76 to 1,600). Fewer than one in five subjects (17%) had no evidence of coronary calcification. More than 70% of subjects had scores above the 75th percentile for age- and gender-matched persons without ESRD. A score greater than the 75th percentile has been shown to be associated with a high risk of future MI and coronary death in the general population (16).

Table 4 shows the linear regression results. Calcification was more pronounced with older age, male gender, non-black race, diabetes, longer dialysis vintage and higher serum concentrations of calcium and phosphorus. This model explained 36% of the variance in coronary artery calcification. Notably, tobacco use, lipids, PTH, and serum albumin and hemoglobin (markers of overall health in the hemodialysis population) were not significantly related to the extent of coronary artery calcification. Since age, gender, race, diabetes and vintage are immutable, it is worth considering the associations of serum calcium and phosphorus on calcification relative to these other factors. For example, a 1-mg/dl higher serum calcium value corresponds to the same increase in calcification as more than five years (63.5 months) of receiving dialysis; a 1-mg/dl higher serum

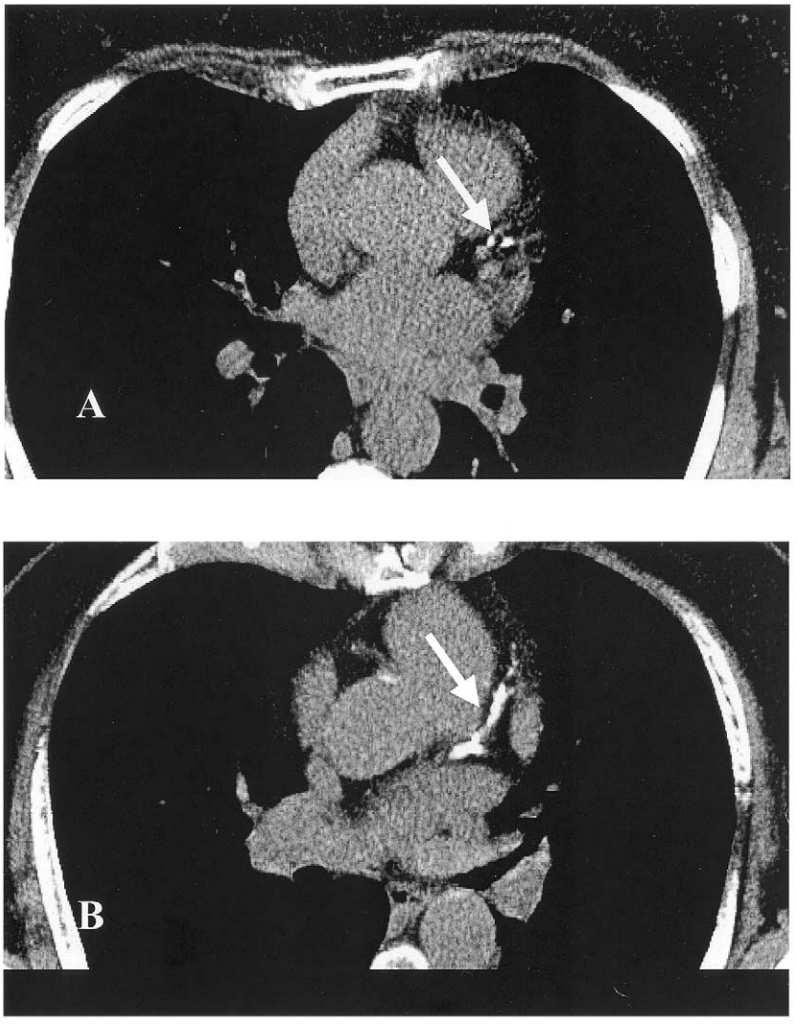

Figure 1. The subject in **A** is a 68-year-old healthy female volunteer with calcification in the middle left anterior coronary artery (**white arrow**) and a total coronary artery calcium score of 45 (approximately 50th percentile for age and gender). The patient with end-stage renal disease in **B** is a 70-year-old woman with extensive calcification in the middle and distal left anterior coronary artery (**black arrow**). The coronary artery calcium score was 374, corresponding to >90th percentile for age and gender.

phosphorus corresponds to the same increase in calcification as nearly 2½ years (28.8 months).

Proportional odds logistic regression confirmed these findings, as the odds of being in higher categories of calcification increased significantly with older age ($p = 0.02$), male gender ($p = 0.02$), diabetes ($p = 0.01$), longer

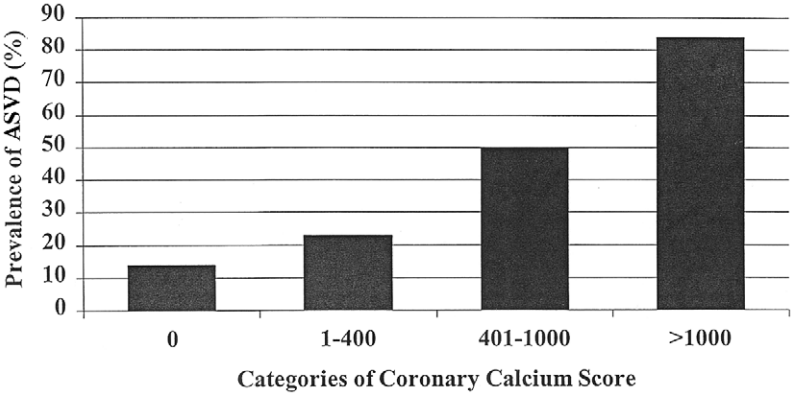

Figure 2. The prevalence of atherosclerotic vascular disease by coronary artery calcium score category. ASVD = atherosclerotic vascular disease.

Table 2. Clinical Correlates of Coronary Artery Calcification Score

	0	1–400	401–1,000	>1,000	p Value
Previous MI (%)	6%	2%	10%	30%	<0.0001
Angina (%)	9%	10%	19%	41%	<0.0001
Known CAD (%)	3%	17%	26%	60%	<0.0001
Any ASVD	14%	23%	50%	84%	<0.0001

ASVD = atherosclerotic vascular disease; CAD = coronary artery disease; MI = myocardial infarction.

dialysis vintage ($p < 0.0001$) and higher concentrations of calcium ($p = 0.009$) and phosphorus ($p = 0.01$). Non-black race was of borderline significance ($p = 0.07$).

Aortic calcification. The median aortic calcium score was 629 (interquartile range, 25 to 3,662). Subjects with claudication ($p = 0.001$) and a known aneurysm ($p = 0.02$) had significantly higher aortic calcium scores than subjects without these conditions.

Multivariable linear regression analysis was conducted using the log-transformed aortic calcium score as the dependent variable. When added individually to the core model (age, age squared, gender, race, diabetes and dialysis vintage), serum phosphorus ($p = 0.007$) and PTH ($p = 0.006$) were significantly associated with aortic calcification, although serum calcium ($p = 0.92$) was not. Table 5 shows the multivariable linear regression results, adjusting simultaneously for these factors. The model R^2 was 0.50. In contrast to the coronary artery model, gender and diabetes were not significantly associated with the extent of aortic calcification.

There are no conventional methods of categorizing patients by aortic calcium score. Using tertiles of aortic calcification, the proportional odds regression analysis confirmed the linear regression findings. Older age ($p = 0.002$), non-black race ($p = 0.0008$), longer dialysis vintage ($p = 0.0007$) and higher concentrations of serum phosphorus ($p = 0.03$) and PTH ($p = 0.03$) were significantly associated with higher tertiles of aortic calcification.

Mitral and aortic valve calcification. Valvular calcification was less frequent than vascular calcification in general. Nevertheless, the prevalence and extent of valvular calcification were remarkable. Forty-five percent of subjects had calcification of the mitral valve, and 34% of subjects had calcification of the aortic valve, compared with an expected prevalence of 3% to 5% in the general population (17). Twenty-one percent of subjects had calcification of both valves. Aortic and mitral valve calcification scores were directly but relatively weakly correlated with each other (Spearman $r = 0.30$, $p < 0.0001$) and with coronary calcification (mitral valve $r = 0.35$, aortic valve $r = 0.28$, $p < 0.0001$). Coronary artery and aorta calcification were more strongly correlated ($r = 0.60$, $p < 0.0001$).

Unlike calcification of the coronary arteries or aorta, there were few clinical predictors of the presence or extent of valvular calcification. Whether by standard logistic regression with the presence or absence of calcification as the dependent variable, or proportional odds logistic regression (comparing the odds of having two vs. one vs. no calcified valves), only dialysis vintage was significantly associated with valvular calcification risk. Linear regression analysis in the smaller subset of patients with valvular calcification (aortic and/or mitral) demonstrated no significant correlates (demographic, clinical or laboratory) of the valvular calcification scores.

Table 3. Clinical Correlates of Aortic Calcification Score

	0	Tertile 1	Tertile 2	Tertile 3	p Value
Claudication (%)	7%	7%	25%	25%	0.001
Aneurysm (%)	0%	0%	6%	5%	0.02

Table 4. Multivariable Linear Regression With Extent of Coronary Calcification as Dependent Variable

Variable	Parameter Estimate	p Value
Intercept	−6.717388	
Age	0.211344	0.0003
Age squared	−0.001359	0.0077
Female	−0.587547	0.0167
Black race	−0.586606	0.0539
Diabetes	0.616307	0.0153
Dialysis vintage	0.008350	<0.0001
Calcium	0.529816	0.0013
Phosphorus	0.240085	0.0047

Overall model p value <0.0001, n = 170 for subjects with non-zero coronary calcification, parameter estimates per year age, per month vintage, per 1 mg/dl calcium and phosphorus.

DISCUSSION

Herein we describe EBT findings in 205 adult patients receiving maintenance hemodialysis. There was a high prevalence of calcification of the coronary arteries, aorta and cardiac valves, and though the range was wide, the majority of patients showed coronary calcification to a degree far greater than expected for age- and gender-matched individuals in the normal population. Furthermore, the prevalence of preexisting cardiovascular disease was proportional to the severity of vascular calcification.

Table 5. Multivariable Linear Regression With Extent of Aortic Calcification as Dependent Variable

Variable	Parameter Estimate	p Value
Intercept	−5.575276	
Age	0.252359	0.0040
Age squared	−0.000950	0.2121
Female	−0.044508	0.9036
Black race	−1.462062	0.0015
Diabetes	−0.323171	0.3896
Dialysis vintage	0.006576	0.0331
Phosphorus	0.244545	0.0621
PTH	0.001809	0.0647

Overall model p value <0.0001, N = 164 for subjects with non-zero aortic calcification, parameter estimates per year age, per month vintage, per 1 mg/dl phosphorus, and per 1 pg/ml parathyroid hormone (PTH).

Coronary artery calcium and cardiovascular disease. Coronary calcium is a highly sensitive marker of underlying atherosclerotic disease (18–20), and coronary calcification has been shown to be associated with cardiovascular events in individuals unaffected by renal disease (16,21,22). Margolis et al. (23) reported that patients with coronary calcification visualized by fluoroscopy during coronary angiography had a five-year survival rate of 58% compared with 87% for patients without calcification. The negative prognostic significance of coronary artery calcification appeared to be independent of the severity of coronary luminal obstruction seen on angiography. Detrano et al. (24) showed that among 1,461 patients undergoing coronary angiography, those with coronary calcium in more than one vessel by EBT were 2.2 times more likely to suffer a cardiovascular event than subjects with no calcified vessels. Several additional reports of asymptomatic patients have also indicated that the relative risk of coronary events is significantly increased in the presence of coronary calcification. Raggi et al. (16) demonstrated that an elevated age- and gender-specific calcium score percentile was the most powerful predictor of MI and death. Indeed, the EBT calcium score adds incremental prognostic value above and beyond other "traditional" risk factors for CAD (25).

Previous use of EBT in ESRD. Braun et al. (26) previously evaluated 49 ESRD patients with EBT imaging. These investigators observed that the extent of coronary calcification in ESRD was significantly greater than in non-ESRD patients with established CAD. In 39 children and young adults with ESRD, Goodman et al. (11) found coronary artery calcification in 36%. Calcification was clearly related to age (calcification in 0 of 23 patients <20 years, and 14 of 16 patients 20 to 30 years of age). Dialysis vintage (time since initiation of dialysis), body mass index, serum albumin, the calcium-phosphorus product and the prescribed dose of oral calcium were also associated with calcification. No multivariable analyses were conducted.

Our findings extend those of Braun et al. (26) and Goodman et al. (11). With a larger cohort of adult hemodialysis patients, we found that advanced age, male gender, diabetes, vintage and the serum concentrations of calcium and phosphorus were all significantly and independently associated with the extent of coronary artery calcification. There was also a trend toward increased calcification among non-black compared with black subjects. There were no significant associations among lipid levels, PTH, albumin, or hemoglobin and the extent of coronary artery calcification.

Study limitations. Misclassification bias is the major limitation of this study. We may have missed significant associations among certain laboratory variables and vascular calcification, as a single baseline laboratory value may not reflect the time-averaged exposure. Misclassification may have lessened the strength of some of the significant predictors of calcification, especially those that vary widely day-to-day (e.g., serum phosphorus). The exclusion of subjects with uncontrolled diabetes and/or hypertension probably resulted in a study sample with less severe overall calcification than an unselected hemodialysis population. The study sample was also biased by the exclusion of subjects with severe hyperphosphatemia. Their inclusion might have strengthened the association between serum phosphorus and the extent of calcification.

Obviously, the cross-sectional design does not allow causal inference. However, since serum phosphorus and calcium have been directly correlated with mortality in patients with ESRD (8), these findings support the hypothesis that cardiovascular calcification might be modifiable based on the degree to which one could control or prevent dysregulation of mineral metabolism associated with ESRD and dialysis therapy. The absence of an association between lipids and cardiovascular calcification does not necessarily indicate that dyslipidemia is of less importance in this population than in others, because confounding by nutritional status, as well as inflammatory and liver diseases may mask such an association.

Summary. Vascular and valvular calcifications are common and severe in the adult hemodialysis population. Prospective observational studies, and clinical trials aimed at modifying the course of calcification, will be required to better understand the link between calcification and cardiovascular outcomes in ESRD and to determine whether renal disease, dialysis, or both, are responsible for the excessive degree of calcification in this population.

Reprint requests and correspondence: Glenn M. Chertow, MD, MPH, Department of Medicine Research, UCSF Laurel Heights, 3333 California Street, Suite 430, San Francisco, California 94118-1211. E-mail: chertowg@medicine.ucsf.edu.

REFERENCES

1. U.S. Renal Data System. USRDS 2000 Annual Report. Bethesda, Maryland: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
2. Jones coronary artery, McQuillan GM, Kusek JW, et al. Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis 1998;32:992–9.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32 Suppl:S112–S119.
4. Becker BN, Himmelfarb J, Henrich WL, Hakim RM. Reassessing the cardiac risk profile in chronic hemodialysis patients: a hypothesis on the role of oxidant stress and other non-traditional risk factors. J Am Soc Nephrol 1997;8:475–86.
5. Oda H, Keane WF. Lipid abnormalities in end-stage renal disease. Nephrol Dial Transplant 1998;13:45–9.
6. Bostom AG, Lathrop L. Hyperhomocysteinemia in end-stage renal disease: prevalence, etiology, and potential relationship to arteriosclerotic outcomes. Kidney Int 1997;52:10–20.
7. Nishizawa Y, Shoji T, Kawagishi T, Morii H. Atherosclerosis in uremia: possible roles of hyperparathyroidism and intermediate density lipoprotein accumulation. Kidney Int 1997;62 Suppl:S90–2.
8. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998;31:601–17.
9. U.S. Renal Data System. USRDS 1998 Annual Report. Chapter IV. Medication use among dialysis patients in the DMMS. Bethesda,

Maryland: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
10. Ginsburg ES, Walsh B, Greenberg L, Price D, Chertow GM, Owen WF, Jr. Effects of estrogen replacement therapy on the lipoprotein profile in postmenopausal women with ESRD. Kidney Int 1998;54: 1344–50.
11. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478–83.
12. Nauck M, Kramer-Guth A, Bartens W, Marz W, Wieland H, Wanner C. Is the determination of LDL cholesterol according to Friedewald accurate in CAPD and HD patients? Clin Nephrol 1996;46:319–25.
13. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
14. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review of guidelines on use in asymptomatic persons. Mayo Clin Proc 1999;74:243–52.
15. McCullagh P, Nelder JA. Generalized Linear Models. 2nd ed. Chapman & Hall, 1989:151–5.
16. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron beam computed tomography. Circulation 2000;101:850–5.
17. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–7.
18. Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA. Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study. J Am Coll Cardiol 1992;20:1118–26.
19. Sangiorgi G, Rumberger JA, Severson A, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using non-decalcifying methodology: electron beam computed tomography and coronary artery disease: scanning for coronary artery calcification. J Am Coll Cardiol 1998;31:126–33.
20. Mautner SL, Mautner GC, Froehlich J, et al. Coronary artery disease: prediction with in vitro electron beam CT. Radiology 1994;192:625–30.
21. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. J Am Coll Cardiol 2000;36:1253–60.
22. Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. Am J Cardiol 2000;86:495–8.
23. Margolis JR, Chen JT, Kong Y, Peter RH, Behar VS, Kisslo JA. The diagnostic and prognostic significance of coronary artery calcification: a report of 800 cases. Radiology 1980;137:609–16.
24. Detrano RC, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 1996;27:285–90.
25. Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. Am Heart J 2001;141:375–82.
26. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. Am J Kidney Dis 1996;27: 394–401.

APPENDIX

STUDY SITES AND INVESTIGATORS

United States

University of California San Francisco: G. M. Chertow, G. Caputo; *Beth Israel Deaconess Medical Center:* A. Kuhlik, M. Derman, M. Clouse; *Mayo Clinic:* J. T. McCarthy, J. Breen; *Rogosin Institute:* J. Silberzweig, J. Markisz; *University of California Los Angeles:* W. Goodman, J. Goldin; *Dallas Nephrology Associates:* R. Toto, M. Boyce.

Germany

Heidelberg: J. Bommer, M. Georgi; *Berlin:* R. Krause, G. Asmus, B. Hamm; *Hanover:* R. Brunkhorst; *Bochum:* D. H. W. Grönemeyer; *Bamberg:* W. Schulz; *Nurnberg:* J. Braun; *Erlangen:* W. Moshage.

Austria

Graz: H. Holzer, R. Rienmüller.