CORONARY-ARTERY CALCIFICATION IN YOUNG ADULTS WITH END-STAGE RENAL DISEASE WHO ARE UNDERGOING DIALYSIS

WILLIAM G. GOODMAN, M.D., JONATHAN GOLDIN, M.D., PH.D., BEATRIZ D. KUIZON, M.D., CHUN YOON, M.D., PH.D., BARBARA GALES, R.N., DONNA SIDER, R.N., YAN WANG, PH.D., JOANIE CHUNG, M.S., ALETHA EMERICK, LLOYD GREASER, M.P.H., ROBERT M. ELASHOFF, PH.D., AND ISIDRO B. SALUSKY, M.D.

ABSTRACT

Background Cardiovascular disease is common in older adults with end-stage renal disease who are undergoing regular dialysis, but little is known about the prevalence and extent of cardiovascular disease in children and young adults with end-stage renal disease.

Methods We used electron-beam computed tomography (CT) to screen for coronary-artery calcification in 39 young patients with end-stage renal disease who were undergoing dialysis (mean [±SD] age, 19±7 years; range, 7 to 30) and 60 normal subjects 20 to 30 years of age. In those with evidence of calcification on CT scanning, we determined its extent. The results were correlated with the patients' clinical characteristics, serum calcium and phosphorus concentrations, and other biochemical variables.

Results None of the 23 patients who were younger than 20 years of age had evidence of coronary-artery calcification, but it was present in 14 of the 16 patients who were 20 to 30 years old. Among those with calcification, the mean calcification score was 1157±1996, and the median score was 297. By contrast, only 3 of the 60 normal subjects had calcification. As compared with the patients without coronary-artery calcification, those with calcification were older (26±3 vs. 15±5 years, $P<0.001$) and had been undergoing dialysis for a longer period (14±5 vs. 4±4 years, $P<0.001$). The mean serum phosphorus concentration, the mean calcium–phosphorus ion product in serum, and the daily intake of calcium were higher among the patients with coronary-artery calcification. Among 10 patients with calcification who underwent follow-up CT scanning, the calcification score nearly doubled (from 125±104 to 249±216, $P=0.02$) over a mean period of 20±3 months.

Conclusions Coronary-artery calcification is common and progressive in young adults with end-stage renal disease who are undergoing dialysis. (N Engl J Med 2000;342:1478-83.)

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THE life span of adults with end-stage renal disease is reduced, and cardiovascular disease accounts for approximately half the deaths among adults undergoing regular dialysis.[1,2] Contributing factors include hypertension, glucose intolerance, dyslipidemia, high serum homocysteine concentrations, and abnormalities in calcium and phosphorus metabolism.[3-9] Many of the same disturbances are present in children and young adults with end-stage renal disease, but little is known about the prevalence or extent of cardiovascular disease in these patients.

The presence and progression of calcified coronary-artery lesions can be determined by electron-beam computed tomography (CT).[10-13] The prevalence of coronary-artery calcification increases with age in both men and women, and the extent of calcification, as measured by electron-beam CT, is correlated with the extent and severity of angiographically documented atherosclerotic lesions.[13-15] Therefore, electron-beam CT may be a useful noninvasive method of screening among patients at risk for coronary artery disease.

Braun et al. noted that coronary-artery calcification was much more common among adult patients with end-stage renal disease who were undergoing hemodialysis than among normal subjects of the same age and sex.[16] Whether similar changes occur in younger patients on dialysis is not known. Few assessments of coronary-artery calcification have been performed in patients of either sex who are younger than 30 years of age, and there is no information about the prevalence of coronary-artery calcification in children or young adults with end-stage renal disease. We undertook this study to determine the prevalence and extent of coronary-artery calcification in children, adolescents, and adults who were 30 years of age or younger, who had end-stage renal disease, and who were undergoing regular dialysis.

METHODS

Study Subjects

All 66 patients who were 30 years of age or younger and who were undergoing regular dialysis in the UCLA Adult and Pediatric Dialysis Program were invited to participate in the study. Thirty-nine patients agreed to enroll; 23 were younger than 20 years old, and 16 were 20 to 30 years old. Twenty-one patients were treated with continuous cycling peritoneal dialysis, and 18 patients with thrice-weekly hemodialysis.

The causes of renal failure in the 39 patients included glomerulonephritis in 9, Alport's syndrome in 6, renal dysplasia in 7, obstructive uropathy in 3, vasculitis in 3, reflux nephropathy in 2, and polycystic kidney disease, diabetes mellitus, and tuberous sclerosis in 1 each. The cause of renal failure was unknown in six patients.

From the Departments of Medicine (W.G.G., D.S.), Radiological Sciences (J.G., C.Y., A.E., L.G.), Pediatrics (B.D.K., B.G., I.B.S.), and Biomathematics (Y.W., J.C., R.M.E.), UCLA School of Medicine, Los Angeles. Address reprint requests to Dr. Goodman at the Division of Nephrology, 7-155 Factor Bldg., UCLA Medical Center, 10833 Le Conte Ave., Los Angeles, CA 90095, or at wgoodman@ucla.edu.

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The clinical characteristics and causes of renal failure did not differ significantly between the patients treated with hemodialysis and those treated by peritoneal dialysis.

Screening for coronary-artery calcification was performed with electron-beam CT. The measurements were repeated in 22 patients after 18 to 24 months. The results of monthly serum biochemical determinations were collected for the six months immediately preceding each scan in each patient, and these results were averaged to obtain a mean value for each measurement. They included measurements of serum calcium, phosphorus, alkaline phosphatase, cholesterol, and albumin and calculations of the serum calcium–phosphorus ion product.[17,18] Serum parathyroid hormone was measured either monthly in patients treated with calcitriol or quarterly in those not receiving calcitriol.[17,18] We also obtained electron-beam CT scans of 32 women and 28 men between the ages of 20 and 30 years who had no known history of cardiovascular or renal disease.

Height, weight, and body-mass index (the weight in kilograms divided by the square of the height in meters) were measured when the scans were done. Information about primary causes of renal failure, systolic and diastolic blood pressure, the duration of chronic renal disease, the duration of treatment with dialysis (excluding, in the case of 27 patients, the intervals of adequate renal function as a result of renal transplantation), previous parathyroidectomy, and the use of calcitriol therapy was also gathered. The cumulative doses of calcium-containing medications and calcitriol during the six months immediately preceding the scans were calculated for each patient.

The study protocol was approved by the UCLA Human-Subjects Protection Committee. All study subjects, or a parent or guardian in the case of those who were younger than 18 years of age, gave written informed consent.

Protocol for Electron-Beam CT

All imaging procedures were performed with the same scanner (Evolution XP-150, Imatron, South San Francisco, Calif.).[19] Contiguous transverse imaging sections were obtained with the use of 3-mm collimation, starting approximately 2 cm below the carina and extending to the inferior margin of the heart. Images for each section were acquired with the use of a single slice during a 100-msec exposure while the subject held his or her breath. The timing of image acquisition was coordinated with the diastolic phase of the cardiac cycle at 80 percent of the RR interval with the use of electrocardiographic monitoring. Images were reconstructed with the use of a 260-mm or 300-mm field of view, a matrix of 512 by 512, and a sharp reconstruction filter.

All scans were scored with the use of Imatron software (version 12.25) by one of two technicians who had no knowledge of the clinical condition of the subjects being evaluated or the results of previous scans. Regions of interest were identified around foci of calcification within epicardial arteries, as defined by the presence of two contiguous pixels with density values of at least 130 Hounsfield units. As originally described by Agatston et al.,[19] the degree of coronary-artery calcification was then calculated by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion to yield a lesion-specific calcification score. The sum of the scores for all arterial lesions provides an overall score for each subject.[19] All images were reviewed by one of the radiologists most familiar with the method of determining these scores at our institution.

Statistical Analysis

The results are presented as means ±SD. The distribution of categorical variables among the groups was assessed by chi-square analysis or by Fisher's exact test.[20,21] Comparisons between groups were made with use of unpaired t-tests, and the rank-sum test was used for data that were normally distributed.[20,21] Paired t-tests were used to assess changes in coronary-artery calcification scores over time.[20]

RESULTS

The mean age of the 39 patients with end-stage renal disease who underwent screening for coronary-artery calcification was 19±7 years (range, 7 to 30). There were 20 female patients and 19 male patients. Four patients were black, 6 were white, 5 were Asian, and 24 were Hispanic. The mean duration of dialysis was 7±6 years (range, 0.3 to 21). Among the 23 patients who were younger than 20 years of age, none had evidence of coronary-artery calcification. In contrast, 14 of the 16 patients (7 women and 7 men) who were 20 to 30 years of age had evidence of coronary-artery calcification on CT scanning (Fig. 1). Their calcification scores averaged 1157±1996 (range,

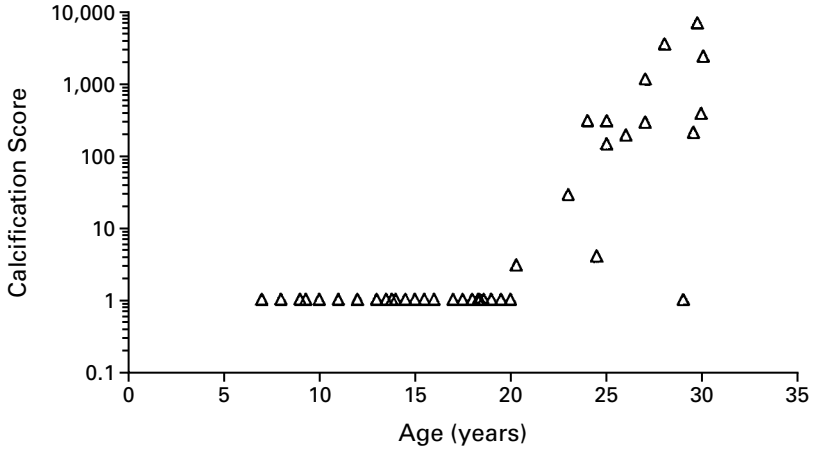

Figure 1. Coronary-Artery Calcification Scores in 39 Children and Young Adults with End-Stage Renal Disease Who Were Treated by Dialysis, According to Age.

Coronary-artery calcification was assessed by electron-beam computed tomography. The scale on the y axis is logarithmic.

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2 to 7047; median, 297). By comparison, coronary-artery calcification was found in only 3 of the 60 normal subjects, who were 20 to 30 years old. Two women (age, 24 and 28 years) had calcification scores of 2 and 1, and one 29-year-old man had a score of 77.

The patients with end-stage renal disease did not differ significantly from the normal subjects with respect to sex or racial or ethnic group, but the normal subjects were older (mean age, 26±4 vs. 19±7 years; $P<0.001$). Matching of patients and normal subjects according to sex, age (within two years), and body-mass index (within 10 percent) yielded 11 patients and 27 normal subjects, of whom 9 (82 percent) and 2 (7 percent), respectively, had coronary-artery calcification ($P<0.001$).

The patients with coronary-artery calcification did not differ significantly from those without calcification with respect to systolic and diastolic blood pressure, and the proportion of males in each group was similar (Table 1). Only one patient had diabetes mellitus, and his calcification score was zero. On average, the patients with calcification were older, however, and they had been undergoing dialysis longer. The median duration of dialysis was 13 years in the patients with coronary-artery calcification and 2 years in those without calcification. Therefore, the probability of calcification increased as a function of the duration of dialysis (Fig. 2).

Serum phosphorus concentrations tended to be higher and the calcium–phosphorus ion product in serum was significantly higher in the patients with coronary-artery calcification than in those without calcification (Table 1). Serum alkaline phosphatase concentrations were lower in those with coronary-artery calcification, whereas the serum calcium and parathyroid hormone concentrations did not differ significantly between the two groups. The amount of calcium ingested daily as a phosphate-binding agent was nearly twice as great in the patients with coronary-artery calcification as in those without calcification (6456±4278 vs. 3325±1490 mg per day, $P=0.02$).

The proportion of patients who were undergoing peritoneal dialysis or who were receiving calcitriol did not differ significantly between those with coronary-artery calcification and those without calcification. Thirteen of the 27 patients who had undergone a kidney transplantation had coronary-artery calcification, whereas only 1 of 12 patients who had not undergone transplantation had calcification ($P=0.03$). This difference was attributable, however, to the longer duration of dialysis in patients who had undergone transplantation, as compared with those who had not (9±7 vs. 3±3 years, $P<0.001$).

The proportion of patients who had undergone parathyroidectomy also did not differ significantly between those with coronary-artery calcification and those without calcification, but 6 of the 9 patients who had undergone parathyroidectomy (67 percent) had calcification, as compared with 8 of 30 patients who had not (27 percent; $P=0.05$). Again, these patients were older, on average, and they had been undergoing dialysis longer. The serum concentrations of calcium and phosphorus and the serum calcium–phosphorus ion product were higher in the patients who had undergone parathyroidectomy (data not shown).

None of the patients with coronary-artery calcification had symptoms of angina or a history of myocardial infarction, but six had electrocardiographic abnormalities, even after the exclusion of changes that were likely to be due to hypertension or an excess of extracellular fluid. The abnormalities were ischemic changes in five and first-degree atrioventricular block in one. Mitral-valve calcification was detected in two of the seven patients who were examined by echocardiography. One of these patients subsequently underwent mitral-valve and aortic-valve replacement,

TABLE 1. CHARACTERISTICS OF THE 39 PATIENTS, ACCORDING TO THE PRESENCE OR ABSENCE OF CORONARY-ARTERY CALCIFICATION.*

CHARACTERISTIC	CALCIFICATION (N=14)	NO CALCIFICATION (N=25)	P VALUE†
Age (yr)	26±3	15±5	<0.001
Sex (M/F)	7/7	12/13	0.91
Systolic blood pressure (mm Hg)	130±16	125±15	0.30
Diastolic blood pressure (mm Hg)	75±12	76±12	0.91
Duration of dialysis (yr)			
Mean	14±5	4±4	<0.001
Median	13	2	
Age at initiation of dialysis (yr)	13±4	12±5	0.44
Body-mass index	24.8±4.2	20.5±4.1	0.004
Serum calcium (mg/dl)	9.5±1.0	9.1±0.9	0.25
Serum phosphorus (mg/dl)	6.9±0.9	6.3±1.2	0.06
Serum calcium–phosphorus ion product (mg^2/dl^2)	65.0±10.6	56.4±12.7	0.04
Serum alkaline phosphatase (U/liter)	129±58	260±171	0.01
Serum parathyroid hormone (pg/ml)	361±182	445±490	0.46
Serum albumin (g/dl)	4.1±0.4	3.6±0.6	0.02
Serum cholesterol (mg/dl)	161±42	204±69	0.02
Dose of oral calcium (mg/day)	6456±4278	3325±1490	0.02

*Plus–minus values are means ±SD. Coronary-artery calcification was assessed by electron-beam computed tomography. To convert values for calcium to millimoles per liter, multiply by 0.25; to convert values for phosphorus to millimoles per liter, multiply by 0.32; to convert values for the calcium–phosphorus ion product to millimoles squared per liter squared, multiply by 0.083; to convert serum parathyroid hormone to picomoles per liter, multiply by 0.1; and to convert values for cholesterol to millimoles per liter, multiply by 0.256.

†All P values were determined with the use of unpaired t-tests.

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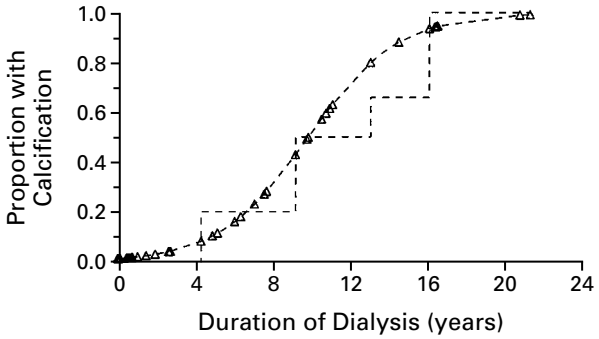

Figure 2. Prevalence of Coronary-Artery Calcification among 39 Patients with End-Stage Renal Disease, According to the Duration of Treatment with Dialysis.

Coronary-artery calcification was assessed by electron-beam computed tomography. The stepped dashed line indicates the proportion of patients with evidence of coronary-artery calcification within each interval of approximately four years. The curved line reflects estimates derived by logistic-regression analysis. All patients were 30 years of age or younger when they were first evaluated by electron-beam computed tomography. The duration of dialysis excludes intervals of adequate renal function as a result of renal transplantation in 27 patients.

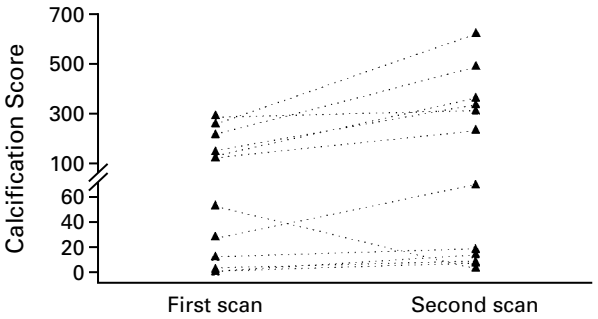

Figure 3. Coronary-Artery Calcification Scores in 10 Patients with Evidence of Coronary-Artery Calcification on the Initial Scan and in 2 Patients in Whom Calcification Was Detected during Follow-up.

Coronary-artery calcification was assessed by electron-beam computed tomography. The mean interval between the scans was 20 months (range, 12 to 41). All patients underwent regular dialysis, and all were 20 to 30 years of age at the time of the first scan.

and a calcified atheroma near the ostium of the right coronary artery was detected by echocardiography in the other.

CT scanning was repeated in 22 patients a mean of 22±7 months later. Among 12 patients who had no evidence of coronary-artery calcification on the initial scan, 2 had evidence of calcification on follow-up scanning. Among the 10 of these 22 patients who had evidence of coronary-artery calcification on the initial scan, 9 had a higher calcification score on follow-up scanning; the values nearly doubled (from 125±104 to 249±216) over a mean period of 20±3 months ($P=0.02$) (Fig. 3). Serum concentrations of phosphorus and the calcium–phosphorus ion product were positively correlated with the change in calcification scores at follow-up.

DISCUSSION

Our results indicate that coronary-artery calcification, as measured by electron-beam CT, is common in women and men who are 30 years old or younger and who have end-stage renal disease for which they are undergoing regular dialysis. It is quite uncommon, however, in normal subjects who are 20 to 30 years of age. Indeed, only 10 percent of women and 25 percent of men between the ages of 40 and 49 years who have normal renal function have coronary-artery calcification,[19] whereas in our study, seven of eight women (88 percent) and seven of eight men (88 percent) who were 20 to 30 years of age had calcification. Thus, coronary-artery calcification occurs more frequently in young adults with end-stage renal disease than in either normal subjects of the same age and sex or older adults with normal renal function.

Several established risk factors for coronary artery disease, such as elevated levels of systolic and diastolic blood pressure, male sex, and the presence of diabetes mellitus, were not associated with coronary-artery calcification in this relatively small study of young patients who were undergoing dialysis. Only one patient had diabetes, reflecting the low prevalence of diabetes among young adults who are undergoing dialysis.[22] Among those with coronary-artery calcification, serum cholesterol concentrations were lower and serum albumin concentrations and body-mass index were higher than in the patients without calcification. These findings do not support the view that malnutrition has a role in the development of coronary artery disease in young persons treated with dialysis, as has been suggested in the case of older adults.[23]

The duration of treatment with dialysis was substantially longer, however, in the patients with coronary-artery calcification than in those without calcification. All had undergone regular dialysis for at least five years, and most started dialysis as children or adolescents. Indeed, the age at which dialysis was started averaged 13±4 years among those with coronary-artery calcification.

The relation between coronary-artery calcification scores and clinically important coronary-artery lesions is controversial.[24] In persons older than 50 years of age, calcification scores of more than 10 but less than 100 are considered to reflect the presence of minimal or mild luminal stenosis.[19] Values of 100 to 400 suggest the presence of nonobstructive coro-

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nary artery disease, but stenotic lesions are found in some patients who have scores within this range.[19] The calcification scores ranged from 2 to 7047 in our patients, and values exceeded 100 in 11 of them. These findings indicate that many young adults with end-stage renal disease have radiographic evidence of clinically silent yet potentially serious coronary-artery lesions, and some have electrocardiographic and echocardiographic abnormalities. Further work will be required to determine whether the previously described relation between the presence of coronary-artery calcification and angiographically documented coronary-artery lesions in the general population applies to patients with end-stage renal disease.

When coronary-artery calcification was initially present, the degree of calcification increased during follow-up, and the mean calcification score nearly doubled in less than two years. The magnitude of change was greater than that reported previously in middle-aged adults, in whom the scores rose 24 percent per year.[25] Thus, the rate of progression of coronary-artery calcification in young adults treated with dialysis exceeds the rate of progression in older persons with normal renal function.

The mechanisms responsible for vascular calcification in patients with chronic renal failure remain uncertain, and the relation between arterial-wall calcification and the atherosclerotic process is not fully understood.[26] Calcium deposits are found, however, in a large proportion of atherosclerotic lesions, providing the basis for the use of electron-beam CT to screen for coronary artery disease.[24,27] The presence of coronary-artery calcification in young adult patients who are undergoing dialysis may therefore simply reflect the high prevalence of atherosclerosis documented previously among those with end-stage renal disease.[28,29]

It is possible, however, that alterations in mineral metabolism and the treatment of these abnormalities contribute to the development of vascular calcification in patients with end-stage renal disease.[30] Treatment with vitamin D has been associated with postmortem evidence of vascular and soft-tissue calcification in children with chronic renal failure.[31] On the basis of data from the U.S. Renal Data System, high serum phosphorus concentrations and high values for the calcium–phosphorus ion product in serum were independent risk factors for death in patients with end-stage renal disease.[9] Whether these factors, acting alone or in combination, directly influence the process of calcium deposition in the arterial wall remains to be determined, but an inverse relation between the serum calcitriol concentrations and the degree of coronary-artery calcification has been reported in subjects with normal renal function.[32]

Our results provide support for the concept that disturbances in mineral metabolism contribute to coronary-artery calcification in patients with end-stage renal disease. Patients with calcification had higher serum phosphorus concentrations and a higher calcium–phosphorus ion product in serum, and their daily intake of calcium-containing phosphate-binding agents was nearly twice as great as in those without calcification. Thus, long-term exposure to the abnormalities in mineral metabolism that characterize chronic renal failure and the treatment of these abnormalities appear to contribute to the development of coronary-artery calcification in young adults with end-stage renal disease.

Additional studies are needed to determine whether the use of large oral doses of calcium-containing phosphate-binding agents or the treatment of secondary hyperparathyroidism with vitamin D sterols promotes arterial-wall calcification in patients with end-stage renal disease. The adverse cardiovascular implications of coronary-artery calcification in patients with end-stage renal disease who are treated by long-term dialysis underscore the need to expedite renal transplantation in those in whom end-stage renal disease develops in childhood or adolescence.[33] Clinicians should be aware, however, that young adults undergoing regular dialysis may harbor clinically silent yet potentially serious coronary artery disease that is disproportionate to their age.

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