Original Article

Assessment of Coronary Artery Calcification in Hemodialysis Patients Using Multi-Detector Spiral CT Scan

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Cardiovascular disease in association with coronary artery calcification (CAC) is the leading cause of death in patients with end-stage renal disease (ESRD). The evaluation of CAC has been performed by electron beam CT scan. The purpose of the present study was to assess CAC using multi-detector spiral CT (MDCT) and to evaluate contributors to CAC in these patients. Fifty-three patients on chronic hemodialysis participated in this study. Their mean age was 61.0 ± 9.6 years, and the mean duration of dialysis therapy was 6.7 ± 5.4 years. We used an automatic device to measure arterial pulse wave velocity (PWV) as an index of arterial wall stiffness. The aortic calcification index (ACI) was quantified morphometrically by CT scan. The CAC score correlated positively with ACI score ($r = 0.863$, $p < 0.0001$). Linear regression analysis indicated that the CAC scores correlated positively with age ($r = 0.406$, $p = 0.0023$), C-reactive protein ($r = 0.38$, $p = 0.0047$) and PWV ($r = 0.303$, $p = 0.0271$). Stepwise regression analysis indicated that ACI (β -coefficient = 0.862 , $p < 0.0001$) and arterial PWV (β -coefficient = 0.303 , $p < 0.0001$) were independently associated with CAC score. The mean CAC score of patients with cardiac events ($2,568.5 \pm 2,575.1 \text{ mm}^3$) was significantly higher than that ($258.0 \pm 409.2 \text{ mm}^3$) of patients without cardiac events. In conclusion, our results showed clearly that assessment of CAC score using MDCT may be predictive for detecting the presence of coronary artery disease. CAC is indirectly associated with increased arterial stiffness and the extent of aortic calcification in hemodialysis patients. We did not find a significant correlation between CAC score and parameters of mineral metabolism, including serum levels of calcium, phosphorus and parathyroid hormone. A longitudinal prospective study is required to assess the predictive value of this technique in determining cardiac events in large numbers of hemodialysis patients. (*Hypertens Res* 2004; 27: 527–533)

Key Words: renal dialysis, coronary artery disease, vascular calcification, arterial stiffness, multi-detector spiral CT scans

Introduction

Cardiovascular disease accounts for more than 50% of deaths among patients with end-stage renal disease (ESRD), and the annual cardiovascular mortality rate is more than an order of magnitude greater than in the non-ESRD population

(1). Numerous factors have been proposed to contribute to this increased risk, including dyslipidemia (2), oxidative stress (3), hyperhomocysteinemia (4), increased serum levels of phosphorus (5), and hyperparathyroidism (6). Recently, coronary artery calcification (CAC) has been recognized as an important risk factor for cardiovascular disease in patients undergoing hemodialysis (7).

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Received March 9, 2004; Accepted in revised form April 8, 2004.

Noninvasive imaging techniques have recently been introduced into the routine diagnosis of coronary artery disease (CAD). Studies of CAC measurements by electron beam computed tomography (EBCT) scan in patients with ESRD have demonstrated 2- to 5-fold more CAC than in age- and sex-matched individuals with angiographically proven coronary artery disease (7). In a follow-up of these hemodialysis patients, every patient had an increase in CAC score when followed up just 1–2 years later. Recently, Goodman *et al.* (8) demonstrated a high prevalence of CAC among young adults receiving dialysis for more than 10 years using EBCT scan.

Unfortunately, EBCT machines are not readily available due to relatively high initial and maintenance costs and limited uses other than the quantification of CAC. A more widely available technology is that of multi-detector spiral CT (MDCT). Recent new software adaptations and increased speed of gantry rotation have allowed the use of spiral CT scans to quantify CAC. However, there has been only one evaluation of CAC in dialysis patients using spiral CT (9).

The aim of the present study was to assess CAC in hemodialysis patients using MDCT scan and to evaluate contributors to CAC in these patients.

Methods

Patients and Study Design

The study subjects were 53 (32 men and 21 women) maintenance hemodialysis patients enrolled in the Dialysis Unit of Takeda General Hospital. The underlying diseases were type 2 diabetes mellitus (DM) in 21 patients and chronic glomerulonephritis without DM in 32. We excluded patients with severe illnesses such as liver cirrhosis and congestive heart failure or apparent acute inflammatory symptoms.

We retrospectively reviewed the subject's medical records to verify the diagnosis of cardiac events. Cardiac events were defined as a subsequent occurrence of angina pectoris or myocardial infarction. Angina pectoris was diagnosed by the presence of myocardial ischemia according to typical angina symptoms or reversible ischemic changes on ECG. Myocardial infarction was diagnosed by QRS change in ECG (abnormal Q or poor R progression), hypokinesia of wall motion on echocardiogram, or elevation of serum myocardial enzyme (creatinine kinase-MB).

Hemodialysis was performed three times weekly (4 h/day) using hollow-fiber dialyzers such as cellulose triacetate (FB, Nipro, Osaka, Japan) and polysulfone (PS, Fresenius, Germany). All patients had undergone dialysis for at least 6 months prior to the study, using the same membrane and the same dialysis procedure for at least 3 months. The dialysate potassium concentration was 2.0 mEq/l, and the calcium concentration was 3.0 mEq/l. The mean blood flow rate was 200 ml/min, and the mean dialysate flow rate was 500 ml/min. Residual urine volumes of the hemodialysis patients were

less than 100 ml/day. At the time of pulse wave velocity (PWV) measurement, blood pressure was measured with a standard mercury sphygmomanometer and cuffs adapted to arm circumference. Blood pressure was recorded after the subjects had been recumbent for at least 10 min.

Blood was drawn in the morning after an overnight fast of at least 12 h before starting a dialysis session. EDTA-plasma was used for measuring lipids and serum was used for the other biochemical assays, including the assay of albumin, which was measured using a commercially available kit (IATRONE Co., Tokyo, Japan). C-reactive protein (CRP) levels were determined by a latex-aggregation method (IATRONE). Intact parathyroid hormone (iPTH) levels were measured by radioimmunoassay (normal range: 10–65 pg/ml) as previously described (10). Other measurements were made by routine methods.

Investigations were performed in the morning before the first weekly dialysis session. Each subject gave informed consent to participate in the study. This study was approved by the ethics committee of our hospital.

Assessment of CAC by MDCT Scan

CT scans were performed with the 8-slice technique on the model Light Speed Ultra (Yokokawa Medical Co., Tokyo, Japan). Slices of 1.25 mm-thickness were acquired in groups eight at a time under the following conditions: 120–140 kVp, 85–150 mA, 500-ms exposure, and 0.5 s gantry rotation time. The entire heart was covered in a single breath-hold (20–30 s). All images from multi-slice CT were transferred to a dedicated workstation (Yokokawa Medical Co.). With this workstation, the score according to the algorithm suggested by Agatston *et al.* (11) (area $\times$ cofactor; 1: 130–199H; 2: 200–299H; 3: 300–399H; 4: >400 H), along with the volume (area $\times$ slice increment), mass (area $\times$ slice increment $\times$ mean CT density/250), and density (mass/volume) were determined by one radiologist. On the basis of the ECG tracing, the software program automatically selected a reduced set of diastolic images from each cardiac cycle. All pixels with density >130 H were automatically highlighted in color on the images. The radiologist assigned one of four locations to each calcified plaque: left main, left anterior descending, circumflex or right coronary artery. The score for each plaque equals the plaque area $\times$ weighting factor $\times$ increment/slice width. The score for the entire specimen equals the sum of the scores for each plaque. The intra-reader variability for CAC was 1.8% mean using volume calculations.

Determination of Aortic Calcification Index (ACI) by Abdominal CT Scan

We performed a prospective longitudinal study using CT scans to detect aortic calcification. As previously described (12, 13), the abdominal aorta was studied by non-contrast CT scan in consecutive sequential 8-mm slices, and the ACI

Table 1. Characteristics of the Hemodialysis Patients

Characteristics	Total
Number of patients	53
Age (years)	61.0 ± 9.6
Male (%)	60.4
Duration of dialysis (years)	6.7 ± 5.4
Systolic blood pressure (mmHg)	148.7 ± 20.5
Diastolic blood pressure (mmHg)	84.8 ± 9.6
Serum albumin (g/dl)	3.6 ± 0.3
Total cholesterol (mg/dl)	139.1 ± 29.9
HDL cholesterol (mg/dl)	41.6 ± 15.2
Triglycerides (mg/dl)	101.3 ± 68.1
C-reactive protein (mg/dl)	0.2 ± 0.1
Pulse wave velocity (cm/s)	2,306.6 ± 690.3
Aortic calcification index (%)	18.6 ± 17.8
Coronary artery calcification score	1,356.3 ± 2,039.3

HDL, high-density lipoprotein.

was estimated as the proportion of aortic circumference covered by calcification. By this method, arteriosclerosis was quantified morphometrically in the cross-section with the most extensive atherosclerosis. The arithmetic mean values of three measurements were calculated and used for analysis. Two observers independently checked the ACI. Reproducibility was absolute for the patients studied. The sequence and orientation of CT scans were standardized, and the qualities of scans were primarily dependent on the hardware used. To optimize reproducibility, all scans from the cross-sectional study were done by the same investigator using the same CT equipment as previously described (14).

Assessment of PWV

Within 1 week after CAC measurement, assessment of PWV was performed. Occlusion and monitoring cuffs were placed snugly around both sides of the upper and lower extremities, with patients in the supine position. Then, pressure waveforms of the brachial and tibial arteries were recorded after 15 min of bed rest using an automatic waveform analyzer (BP-203RPE; Colin, Komaki, Japan). Electrocardiographic monitoring was performed with electrodes placed on both wrists. Heart sounds, S1 and S2, were detected by a microphone set on the left edge of the sternum at the fourth intercostal space. The pressure waveforms obtained at two different sites were simultaneously recorded to determine the time interval between the initial rise in the brachial and tibial pressure waveforms, as previously described (15). The best 10 consecutive pulses were analyzed, and the average PWV from the heart to the posterior tibial artery was calculated by dividing the distance by the time interval. Two measurements were performed in each leg and the average value was used for the analysis. PWV was expressed in centimeters per second. The coefficient of variation of the PWV was less

than 5%. This method has been validated in patients free of ESRD (16), type 2 diabetic patients (17), patients with coronary artery disease (18), and patients on chronic dialysis (19).

Statistical Analysis

All values are expressed as the means ± SD. Differences between mean values of the two groups were assessed by ANOVA. Pearson's correlation coefficient was used to test the association between two kinds of parameters. To assess the combined influence of variables on PWV, ACI, and CAC, we used a stepwise linear regression analysis with forward and backward elimination procedures. Statistical analyses were performed using the Stat View statistical software package (Stat View 5; SAS Institute, Cary, USA). Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Baseline Characteristics in Hemodialysis Patients

Clinical parameters of the hemodialysis patients in the present study are summarized in Table 1. Their mean age was 61.0 ± 9.6 years, and the mean duration of dialysis therapy was 6.7 ± 5.4 years. Thirty-two patients (60.4%) were men, 21 patients (39.6%) had diabetes. Figure 1 shows an example of calcium deposition in the coronary arteries of a patient undergoing hemodialysis. The mean value of CAC score was $1,356.3 \pm 2,039.3 \text{ mm}^3$ in the present study, ranging from 0 to $9,924 \text{ mm}^3$. Four patients had no calcium deposition in their coronary arteries. Only five patients had previously undergone coronary angiography and all of the patients had stenosis of two or three coronary arteries.

Relationship between ACI and CAC Score

Sclerosis of the aorta reflects early atherosclerosis and is correlated with coronary arteriosclerosis (20). To examine the relationship between aortic calcification and CAC, a univariate analysis was performed. The CAC score correlated positively with ACI ($r = 0.863$, $p < 0.0001$).

Assessment of the Factors Related to CAC

To examine whether DM is related to CAC score, the CAC scores were compared in hemodialysis patients with or without DM. There was no significant difference in the CAC scores in patients with DM ($1,588.0 \pm 1,644.7 \text{ mm}^3$) or without DM ($1,204.2 \pm 2,273.8 \text{ mm}^3$). To assess the relationship of clinical parameters to CAC, univariate linear regression analyses were performed. The CAC scores correlated positively with age ($r = 0.406$, $p = 0.0023$), CRP ($r = 0.38$, $p = 0.0047$) and PWV ($r = 0.303$, $p = 0.0271$). A stepwise linear regression analysis was performed to adjust for the influ-

Fig. 1. Axial cross-sections (1.25 mm slice thickness) obtained by multi-detector spiral CT in a 62-year-old patient at baseline. A, left coronary artery; B, right coronary artery.

Table 2. Correlation between CAC Score Related Parameters

Variables	<i>r</i>	<i>p</i> value
Age (years)	0.406	0.0023
Duration of dialysis (years)	0.148	0.2911
Systolic blood pressure (mmHg)	0.251	0.0692
Diastolic blood pressure (mmHg)	0.227	0.1019
Calcium (mg/dl)	0.144	0.3063
Phosphorus (mg/dl)	0.025	0.8588
Intact PTH (pg/ml)	0.210	0.1326
Total cholesterol (mg/dl)	0.105	0.4555
HDL cholesterol (mg/dl)	0.187	0.1808
Triglycerides (mg/dl)	0.011	0.9385
C-reactive protein (mg/dl)	0.380	0.0047

CAC, coronary artery calcification; PTH, parathyroid hormone; HDL, high-density lipoprotein.

Table 3. Stepwise Regression Analysis for CAC and Related Parameters

Independent variables	β -Coefficient	<i>p</i> value
ACI	0.862	<0.0001
Arterial PWV	0.303	<0.0001
Adjusted $r^2 = 0.797$		
<i>F</i> value = 102.9		

CAC, coronary artery calcification; ACI, aortic calcification index, PWV, pulse wave velocity.

ences of different pathogenic factors on CAC score in all patients. The clinical parameters of age, duration of dialysis, body mass index (BMI), blood pressure, serum levels of albumin, cholesterol, triglyceride, CRP, calcium $\times$ phosphorus product, and iPTH were not independently associated with CAC score (Table 2). Stepwise regression analysis indicated

Fig. 2. Comparison of coronary artery calcification (CAC) score in hemodialysis patients with (+) or without (-) cardiac events (CAD). * $p < 0.001$ vs. CAD (+).

that ACI (β -coefficient = 0.862, $p < 0.0001$) and arterial PWV (β -coefficient = 0.303, $p < 0.0001$) were independently associated with CAC score (Table 3).

Correlation between Cardiac Events and CAC

To examine the relationship between cardiac events and CAC, the patients were divided into two groups according to the presence or absence of cardiac events such as angina pectoris or myocardial infarction. Twenty-five of 52 dialysis patients studied had previously had cardiac events. The mean CAC score of patients with cardiac events ($2,568.5 \pm 2,575.1$ mm³) was significantly higher than that (258.0 ± 409.2 mm³) of patients without cardiac events (Fig. 2).

Discussion

Recent studies have introduced the use of EBCT to assess CAC in patients with ESRD, and demonstrated markedly increased CAC scores (7, 8). The use of EBCT has allowed more precise quantification of vascular calcification than plain X-rays or non-contrast CT because of its excellent temporal resolution, which enables imaging only during diastole. However, EBCT has limited application except in the assessment of coronary calcification and is not readily available in many hospitals. In contrast, most general hospitals have a multipurpose spiral CT, and the newer spiral CTs have been introduced with software adjustments to allow gated imaging. The progress in spiral CT equipment has improved the variability in spiral CT (21).

In the present study, the CAC score ranged from 0 to 9,924 with a mean score of $1,356.3 \pm 2,039.2$ (median 754). While the median scores in the present study were similar to CAC scores in several recent studies employing EBCT (9, 22), the median was larger. The differences may reflect the higher mean age of our patient population (61 vs. 49 or 57 years), or longer duration of dialysis (80 vs. 25 or 37 months). In non-dialysis patients, the magnitude of CAC has been shown to correlate with angiographically proved obstructive coronary artery disease by spiral CT (23, 24). At this time, there are no published reports comparing EBCT and spiral CT with angiographic findings or prospective cardiac events in ESRD patients. However, it is possible that the progression of vascular calcification may be an additional cardiovascular risk factor in hemodialysis patients.

Arterial stiffness increases with age and hypertension (25, 26). In patients with ESRD, arterial stiffness has been shown to be increased in comparison to age- and blood pressure-matched non-uremic subjects (26, 27). In hemodialysis patients, aortic PWV has been associated with mediocalcosis of the aorta and an elevation in $\text{Ca} \times \text{P}$ product (27). After the arteries become stiffer, the PWV increases and is responsible for an early return of wave reflections from the periphery to the ascending aorta, leading to left ventricular hypertrophy and altered coronary perfusion (26, 28). In the present study, a stepwise linear regression analysis revealed that the CAC score was independently associated with PWV in hemodialysis patients. Recent studies have shown that arterial stiffness is a major predictor of all-cause and cardiovascular mortality in hemodialysis patients (29, 30). The presence of CAC could possibly be associated with increased stiffness of the coronary arteries. The increase of arterial stiffness is certainly multifactorial. Therefore, it remains unclear whether or not increased stiffness of the coronary arteries is directly related to the progression of CAC in hemodialysis patients.

Vascular calcification is also strongly associated with an increased risk of cardiovascular events and mortality in uremic patients (30, 31). As in non-uremic patients, calcification in those with ESRD occurs in the arterial intima in associa-

tion with atherosclerotic plaques (32). However, medial calcification can also occur and probably increases arterial stiffness and ventricular afterload (33). Braun *et al.* (7) previously evaluated 49 ESRD patients with EBCT. Their results showed that the extent of CAC in patients with ESRD was significantly greater than that in non-ESRD patients with coronary artery diseases. In 39 children and young adults with ESRD, Goodman *et al.* (8) found CAC in 36%. Calcification was related to age, dialysis vintage, serum albumin, the calcium $\times$ phosphorus product, and the prescribed dose of oral calcium. In the present study, ACI and arterial PWV were independent variables contributing to the magnitude of CAC according to stepwise linear regression analysis. Calcium deposition in the arterial walls of the large arteries and coronary arteries may progress simultaneously in hemodialysis patients. However, we have no evidence to prove a direct correlation. Therefore, it is difficult to interpret the relationship between CAC score and ACI.

A higher CAC score characterized hemodialysis patients with a history of CAD. This is not unexpected. The agreement between CAC and clinical symptoms of CAD, as well as findings on coronary angiography, was shown previously for the general population (34–36). Raggi *et al.* found a significant relationship of CAC by EBCT to a history of various cardiovascular events (22). Given the difference in the magnitude of calcification in the coronary arteries of dialysis patients compared with non-ESRD patients, and the substantial risk for cardiovascular disease in ESRD patients compared with the general population, it is possible that the excess calcification may be an additional cardiovascular risk factor unique to the ESRD patients.

The potential for misclassification bias was the main limitation of this study. We may have missed significant associations among certain laboratory variables and CAC, 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 CAC, especially those that vary widely day-to-day (*e.g.*, serum phosphorus levels). The exclusion of subjects with uncontrolled diabetes and/or hypertension probably resulted in a study sample with less severe CAC than an unselected hemodialysis population.

In conclusion, we have shown clearly that a higher CAC score characterized hemodialysis patients with a history of CAD. CAC is associated with an increase in arterial stiffness and in the extent of aortic calcification in hemodialysis patients with aortic calcification 1) making the most important contribution to and 2) having the most important relation to the magnitude of CAC. We did not find a significant correlation between CAC score and mineral parameters, including serum levels of Ca, P and iPTH. Assessment of CAC score using MDCT may be predictive for detecting the presence of CAD. However, conclusions from this study should be interpreted with great caution because of the serious methodological limitations (*i.e.*, the cross-sectional study design, hetero-

geneity of the study population, and relatively small number of patients). A longitudinal prospective study is required to assess the progression of CAC using MDCT in large numbers of hemodialysis patients.

Acknowledgements

We thank Mr. Masahiro Haga for blood sampling and Mr. Hiroyuki Ashikaga for assessment of ACI and CAC. We also gratefully acknowledge Dr. Bierta Barford for her critical reading of our manuscript.

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