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The density of calcified plaques and the volume of calcium predict mortality in hemodialysis patients

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ABSTRACT

Background and aim: In the general population lipid-rich plaques are prone to rupture and healing of the plaque involves calcification. Patients undergoing hemodialysis have a severe derangement of mineral metabolism and calcification of the arterial tree may have different implications.
Methods: Between 2004 and 2005, 125 hemodialysis patients (60 men) underwent computed tomography imaging for quantification of coronary artery calcium via the Agatston and the Volume methods. Since the Agatston score is derived by multiplying the density by the volume of a calcified lesion, the Agatston/Volume ratio (AVR) is an indication of the density (i.e. calcium accumulation) within the plaque.
Results: Patients were classified as high AVR (>1) or low (≤1) AVR. Survival analyses tested the association between AVR and all-cause mortality during a median follow-up of 5 years. The mean age was 57.2±13.5 years; 75% of the patients had AVR >1. The mortality rate of patients with AVR >1 was significantly higher than in patients with AVR ≤1 (Hazard Ratio(HR): 2.46; 95% Confidence Intervals(CI): 1.16–5.21, $p \leq 0.018$). After adjustment for confounders, AVR >1 remained independently associated with all-cause mortality (HR: 2.24; 95% CI: 1.02–4.88, $p \leq 0.042$). There was a significant interaction of plaque density and calcium volume on mortality.
Conclusions: Increased plaque density is an independent predictor of all-cause mortality in hemodialysis patients. These data suggest that increased calcium content in the coronary arteries of patients in dialysis is an index of high-risk rather than a marker of plaque stabilization.

1. Introduction

The prognostic value of coronary artery calcium (CAC) has been documented in the general population and in patients with chronic kidney disease (CKD) [1,2]. Both presence and extent of CAC are associated with an increased rate of cardiovascular (CV) events and all-cause mortality [3–6]. Furthermore, the addition of CAC to demographic, clinical and laboratory parameters significantly improves risk stratification [7].

A recent report of the Multi-Ethnic Study of Atherosclerosis (MESA) study, showed that CAC predicts CV risk beyond traditional risk factors and significantly ameliorates risk stratification as suggested by the improvement in C-statistics and net reclassification index (NRI) [6]. However, in a reanalysis of the MESA study the investigators also showed that plaque density is inversely associated with the occurrence of incident cardiovascular events at any level of plaque volume in subjects with normal renal function [7]. This is in line with the purported mechanism of plaque rupture in the general population, where a large lipid core (low density area) covered by a thin fibrous cap is believed to be prone to sudden rupture and intra-luminal clot formation.

However, the situation may be quite different in patients suffering from advanced CKD where a severely altered mineral

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metabolism leads to dense calcification of the atherosclerotic plaque and media layer of the vessel wall [1]. Accordingly, we investigated whether the density of calcified coronary artery plaques predicted all-cause mortality in a prospective observational cohort of maintenance dialysis patients.

2. Materials and methods

Between 2004 and 2005, 154 adult CKD patients receiving maintenance dialysis were recruited to participate in a prospective, observational research study. Patients were recruited from 2 centers in the US (Denver, CO and New Orleans, LA, USA) and underwent electron beam computed tomography (EBCT) imaging for quantification of coronary artery calcium via the Agatston score (CAC) and the volume score (CVS = calcium volume score). Inclusion criteria were adult age (>18 years) and ability to sign an informed consent and follow instructions for a clinical study. Pregnant women or women planning a pregnancy within the following 6 months, patients with active symptoms of coronary artery disease, prior coronary artery bypass surgery or coronary artery stent placement, ongoing atrial fibrillation or a weight over 300 pounds were excluded. The latter 2 exclusion criteria were adopted to avoid motion artefacts due to atrial fibrillation and due to the weight limit of the CT scanner radiological bed. Study procedures have been described previously [8]. The study protocol was approved by the local internal review boards. All ethical principles as listed in the declaration of Helsinki [9] on human subjects research were closely followed.

Twenty-nine of the original 154 patients were excluded from the current analyses due to missing data or poor image quality, leaving a sample size of 125 patients. With the exception of age and prevalence of atherosclerotic vascular disease (ASCVD), no statistically significant difference in demographic and case mix was noted between subject included and excluded from the current analyses (Supplemental Table 1). Demographic and clinical variables of all patients were collected at study entry. Self-reported variables included age, sex and race. Body mass index was calculated as the ratio of body weight (Kg) and height (m^2). Medical charts were reviewed to assess the presence of the following comorbid conditions: diabetes mellitus, history of atherosclerotic cardiovascular disease (ASCVD: history of myocardial infarction, angina, peripheral and cerebrovascular disease), hypertension (defined as blood pressure greater than 140/90 mmHg or the use of antihypertensive medications), congestive heart failure (CHF) and dialysis *duration*. Blood pressure was measured with participants in the supine position using the arm contralateral to that of an arteriovenous fistula or shunt. The measurement was performed with a manual aneroid sphygmomanometer after a 15- to 20-min rest. The average of three measurements obtained 30-s apart was then recorded in the patient's case report form. Current medications were recorded at the same time blood pressure and PWV assessments. Pulse Wave Velocity (PWV) and augmentation index were assessed via applanation tonometry as previously reported [10]. Blood pressure and PWV were measured at the same time, and current medications were recorded. Electron beam CT (EBCT) of the chest was performed according to a standard protocol as described previously [8]. Briefly, 40–50 consecutive 3 mm thick slices were acquired for each study participant. The field of view extended from the top of the aortic arch to the diaphragm. Tomographic imaging was performed at end inspiration and timed to 80% of the R (wave)-to-R interval on the surface electrocardiogram. A calcium score for each calcific plaque along the course of the coronary arteries was calculated according to the Agatston (CAC = coronary artery calcium) score [11] as well as the volume (CVS = calcium volume score) [12] method. The inter- and intra-reader reproducibility of these methods are approximately 8–10% [13]. The total radiation dose administered with electron beam CT was about 1.0 mSv (total recommended dose is 5 mSv yearly for nonmedical personnel). All scans were reviewed by two experienced investigators (PR and AB) and a consensus was reached on interpretation of all results.

2.1. Study endpoint

The endpoint of interest for the current analyses was all-cause mortality. Mortality was assessed searching the Social Security Death Index (http://ssdi.rootsweb.com/ssdi.rootsweb.com) master file using patients' name and social security number. Searches were conducted for mortality occurring until study completion on June 21, 2011.

2.2. Statistical analysis

To test the association between coronary artery calcium plaque density and risk of death, we calculated the ratio of Agatston (CAC) and volume scores (CVS) for each patient. Since the Agatston score is essentially derived by multiplying density (expressed as a cofactor) by the volume of a calcified plaque, the ratio of the Agatston and Volume score [(Agatston (density*volume)/volume = AVR)] is an expression of the calcium content (i.e density) per plaque volume unit. Patients were arbitrary classified as high AVR (>1) or low AVR (<1). Due to its skewed distribution, the CVS was log transformed. Demographic, clinical, and laboratory characteristics were analyzed in the overall sample and according to AVR (i.e. low vs high). Continuous and categorical variables are expressed as mean and standard deviation (SD) or median [interquartile range] and proportions, respectively. Analysis of variance and Chi-square test were utilized to test the statistical significance across study participant categories (Table 1). The Spearman correlation test was used to test the linear association of plaque density and coronary artery calcification evaluated via Agatston and volume score. Logistic regression was used to identify factors independently associated with AVR (Table 2). All-factors associated with high AVR on univariable analysis with a p-value <0.10 were forced into the multivariable-adjusted model. Follow-up time was calculated as the number of months between study inception for each participant and date of death or study completion on June 21, 2011. Survival analyses tested the association between AVR and all-cause mortality during a median follow-up of 5 years. Cumulative mortality curves were calculated by AVR category using the Kaplan–Meier method (Fig. 1). Poisson regression was used to calculate the overall mortality rate and the mortality rate in each AVR category (Table 3). The hazard of all-cause death associated with a high AVR was estimated using Cox survival analyses. Hazard ratios were calculated initially without adjustments. Subsequent models included adjustment for demographic variables (age, sex) and for case mix (diabetes mellitus, ASCVD, hypertension, congestive heart failure) (Table 3). Due to the association of AVR with CVS (Table 2), we adopted a similar multi-step approach to test whether AVR predicts all-cause mortality independently of CVS and whether AVR modifies the CVS-mortality relationship. To test for a potential effect modulation of plaque density and volume on mortality, an interaction term was forced into the Cox survival model and results were tested against demographic variables and case-mix (Table 4). Statistical significance was set at 0.05. All analyses were completed using R version 3.1.3 (2015-03-09; The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 125 middle-age (mean age: 57.2 ± 13.5 years) men and