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Prevalence and progression of cardiovascular calcifications in peritoneal dialysis patients: A prospective study☆

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ABSTRACT

Background: Patients on dialysis may have abnormal serum levels of Ca, P and parathyroid hormone, with related bone diseases. This population has an increased risk of death, with cardiovascular calcification (CC) a contributing factor. Patients on peritoneal dialysis appear to be at increased risk of hyperlipidemia, a contributing factor to atherosclerotic plaque formation. Although several studies have described the presence and progression of CC in hemodialysis populations, there are fewer data in patients on peritoneal dialysis.

Study design: The Renal Osteodystrophy and Calcifications: Key factors in Peritoneal Dialysis (ROCK-PD) study was a 36-month, prospective observational study conducted in Italy. The study examined the presence and progression of CC in two cardiac valves and five arterial sites. The potential associations of serum Ca and P with mortality and cardiovascular morbidity, demographic, clinical and blood chemistry variables was investigated.

Results: CC was present in 77% of patients at baseline ($N = 369$) and in 90% of patients by study end ($N = 145$), progressing in 73% of patients. There were 42 deaths (11%). Analyses showed a marked correlation between baseline P levels and the presence of left ventricular hypertrophy. However, there were no consistent correlations between serum Ca or P with mortality or morbidity.

Conclusions: CC was common in peritoneal dialysis patients and progressed in a majority of patients.

Introduction

The signs and symptoms of chronic kidney disease mineral and bone disorder (CKD-MBD) worsen as renal function decreases [1]. Uncontrolled, this can lead to high levels of serum Ca, P and parathyroid hormone (PTH), increasing the risks of renal osteodystrophy, cardiovascular calcification (CC) and morbidity [2–5]. A dynamic bone disease can result from over-suppression of PTH in this population; the resulting Ca release and hypercalcemia are also linked with CC, increased risk of fractures and mortality [6]. International guidelines for CKD-MBD recommend targets for serum PTH, Ca and P [6]. However, these are difficult to achieve and dialysis patients remain at risk [4,7].

Patients on dialysis have increased risk of hyperlipidemia and cardiovascular disease (CVD) [4,8–13]. Patients on peritoneal dialysis (PD) with CVD or diabetes potentially have a higher overall mortality risk, which may depend in part on CC [14–16].

Data on CC in patients with CKD-MBD are mostly limited to hemodialysis (HD) or mixed dialysis populations [17,18]. Studies on progression of CC solely in patients on PD are few, and limited to 1-year follow up [8,19]. We therefore conducted the 3-year prospective observational Renal Osteodystrophy and Calcifications: Key factors (ROCK)-PD study to characterize the presence and progression of CC in a PD population and investigated the potential associations of CC and serum Ca and P with morbidity.

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Methods

Study population

This was a multicenter, observational, prospective study conducted in 38 dialysis centers across Italy between 2002 and 2007. The study did not guide treatment nor influence clinical management of patients.

Patients were enrolled if they were ≥18 years, receiving PD. Patients were excluded if their life expectancy was <6 months or they had evident malignancies. Patients were withdrawn in case of renal transplant, switching to HD, if the clinician deemed it appropriate for clinical or organizational reasons, or if the patient chose to withdraw. Withdrawn patients were not replaced.

Assessments

The study included 19 visits at 2-month intervals, a total of 36 months. Total plasma concentrations of Ca and inorganic P were measured each visit. Ca levels were adjusted if albumin was <4.0 g/dL. Patients were stratified at baseline into classes for Ca (<8.4, 8.4–9.5 and >9.5 mg/dL) and P (<3.5, 3.5–5.5 and >5.5 mg/dL). Hypercalcemia was defined as Ca >9.5 mg/dL. Hyperphosphatemia was defined as P >5.5 mg/dL. PTH levels were measured every 6 months. Each dialysis center used its own laboratory and PTH assays varied, though the same assay was used repeatedly for each patient.

Morpho-functional investigations of CV damage were conducted at months 0, 12, 24 and 36. Prevalence of CC was evaluated in the aortic and mitral valves, in the two common carotid arteries, in the abdominal aorta and in the two femoral arteries. The presence and severity of CC were measured using echocardiogram (valves) and Color Doppler ultrasound (arteries). Scans were performed and interpreted at each study center and, where possible, recorded on video or digitally. Calcification at a site was scored 0 (absent) or 1 (present), derived from a method from Blacher et al. [20] Severity ranges of calcification were thus: cardiac (0–2), vascular (0–5) and global (0–7). Progression of CC was defined as an increase of ≥1 on the calcification scale during the study.

The intima-media thickness (IMT) was measured in the right and left common carotid arteries at 0, 12, 24 and 36 months. Presence of atherosclerosis was confirmed when IMT was >0.77 mm.

Left ventricular mass index (LVMI) was calculated with ultrasound and normalized for body surface area. Left ventricular hypertrophy (LVH) was diagnosed when LVMI was >131 g/m^2 in males or >100 g/m^2 in females, based on values calculated in the Framingham study [21].

CV morbidity was measured using seven variables: 1) average duration of hospitalization days per year (total days in hospital × [360 ÷ total days in study]); 2) average number of hospitalizations per year (number of hospitalizations × [360 ÷ total days in study]); 3) total CC score; 4) valve calcification score; 5) artery calcification score; 6) presence of atherosclerosis; 7) presence of LVH. The composite morbidity score was calculated at study months 12, 24 and 36.

Mortality was measured by the number of deaths over the observation period.

Statistical analyses

Patients were excluded from the analysis if clinical, laboratory and ultrasound data at 0- or 6-month visits were missing.

Data were analyzed using SSPSS12.0. All statistical significance tests were two-tailed with a significance threshold of 5%. No procedures for missing data or adjustments for multiplicity were adopted.

Statistical analyses were conducted on the entire available population. Descriptive analyses were used for demographic variables.

Inferential analyses were conducted to determine statistical correlations between parameters. The correlation between baseline Ca and P with mortality was investigated through a logrank test comparison between Kaplan–Meier survival curves calculated for each of the classes of serum Ca and P respectively (see above).

For the study of associations between demographic, clinical and blood chemistry variables with progression of CC, appropriate tests based on the nature of each variable were conducted: chi-square test for pairs of qualitative variables, Spearman's correlation for pairs of quantitative variables, Kruskal–Wallis test for a quantitative and a qualitative variable. Mean values across study period of each parameter of interest were used for each correlation.

Multivariate logistic regression analyses for measures of CV morbidity (presence of LVH) were conducted at baseline. The model was built by entering the variables that the univaried analysis identified as significant, plus control variables, if any. A subsequent background elimination procedure led to the selection of the final model. Independent variables in the model included: classes of serum Ca, P, gender, age, and the global calcification score (assessed at each visit).

Results

Patient disposition

ROCK-PD ran from 2002 to 2007. Disposition of patients is shown in Fig. 1. There were 224 withdrawals, most frequently switching to HD (42%) and renal transplant (28%).

Demographics, dialysis vintage and concomitant therapies for analysis population

Baseline patient demographics are presented in Table 1.

Median lipid levels were at or slightly above the upper limit of normal.

Usage of active vitamin D (calcitriol) rose from 57% to 61% and usage of statins rose from 30% to 39% by study end. Total phosphate binder usage dropped slightly from 89% to 83%, owing mostly to a

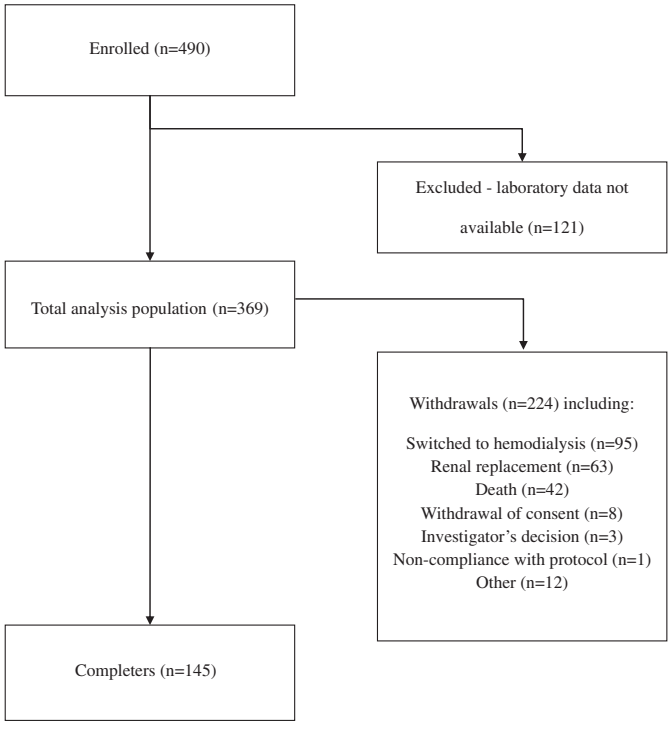

Fig. 1. Patient disposition.