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De novo Development of Heart Valve Calcification in Incident Peritoneal Dialysis Patients

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Background and Aims. Cardiac valve calcification (VC) is a frequent complication in chronic kidney disease and is considered a risk factor for all-cause and cardiovascular mortality. However, little is known about the pathophysiology mechanisms that originate it and the factors associated with its development. We undertook this study to analyze the frequency and factors related to de novo development of mitral valve calcification (MVC) and aortic valve calcifications (AVC) in incident peritoneal dialysis (PD) patients.

Methods. A prospective cohort of 124 incident PD patients was studied. Demographic and clinical data were recorded and blood assayed at baseline and after 1 year of follow-up for calcium, phosphorus, glucose, urea, creatinine, cholesterol, triglycerides by spectrophotometry assay; high-sensitivity C-reactive protein (CRP) by immunoturbidimetric ultrasensitive assay, intact parathormone (iPTH) and osteocalcin by electrochemiluminescence, fetuin-A and osteoprotegerin by EDI-ELISA. Valve calcification was evaluated by M-mode bidimensional echocardiogram.

Results. Sixty eight percent of patients were male, ages 43 ± 13 years; 51% were diabetic with 1.4 ± 1 months on PD. After 12.3 ± 1 months, 57 patients (46%) developed VC: AVC in 33 (57.8%), MVC in 15 (26.3%) and 9 (15.8%) patients in both valves. There was no correlation between AVC and MCV. In univariate logistic regression analysis, age, diabetes and elevated concentrations of OPG, iPTH and CRP were risk factors for development MVC. In multivariate analysis, only iPTH remained an independent risk factor as was also the case in AVC.

Conclusions. Age, diabetes, osteoprotegerin, parathormone and C-reactive protein are risk factors related to de novo development of MVC and iPTH for AVC in incident dialysis patients. © 2013 IMSS. Published by Elsevier Inc.

Key Words: Heart valve calcification, Peritoneal dialysis, Diabetes, Cardiovascular disease, Chronic kidney disease, Mineral metabolism.

Introduction

Presence of heart valve calcification is associated with chronic kidney disease (CKD); more advanced stages have higher rates of valve calcification (1,2). Valve calcification may be 5 to 10 times more frequent in patients with end-stage renal disease (ESRD) in comparison with a non-

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renal population (3). Prevalence of 35−44.5% has been reported for mitral valve calcification (MVC) and 25−52.0% for aortic valve calcification (AVC) in hemodialysis (HD) patients (4,5). Similar data were also reported in peritoneal dialysis (PD) patients (6).

Heart valve calcifications are associated with other vascular pathological conditions such as atherosclerosis and vascular calcifications (7) and have also been identified as risk factors for cardiovascular morbidity and mortality. MVC was associated with atrial fibrillation, stroke, and increased morbidity and mortality of cardiovascular origin in both the general and the CKD populations (8−10). On the other hand, AVC was reported as a risk factor for cardiovascular morbidity and mortality (11).

In spite of its high frequency and importance as a risk factor for cardiovascular mortality in CKD patients, little is known about the mechanisms and risk factors for their development. In cross-sectional studies, MVC was associated with inflammation (12) and hyperphosphatemia (4), and AVC seems to be associated with duration of HD treatment and some markers of mineral metabolism (13,14). However, studies about the development of new valve calcifications are not available. The aim of this study was to analyze the frequency and factors related to de novo development of MVC and AVC in incident PD patients.

Materials and Methods

Design

A prospective cohort study was performed in ESRD patients from six dialysis units in the metropolitan area of Mexico City affiliated with the national network of the Instituto Mexicano del Seguro Social. The protocol was approved by the Human Research and Ethics Committees of each of the participating hospitals. Patients gave their signed informed consent before enrollment in the study.

Patient Population

Two hundred forty-eight patients initiated PD in six hospitals participating in the study in the period between October 2009 and August 2010. Of these patients, 133 (54%) met the inclusion criteria. Of those accepted, three died, one was lost to follow-up and five had valve calcification at baseline and were excluded; 124 patients (50%) of the total population were included in the final analysis.

The patients were considered eligible for inclusion if they were incident (<3 months) on continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD). All were adults (18 years or older) without selection by gender, cause of renal disease or dialysis modality. Patients were excluded if they had pre-existing heart valve calcifications, heart failure, infections, malignancy, chronic liver disease, seropositivity for hepatitis or HIV or if they received immunosuppressive treatment. Patients with incomplete data were also excluded. All patients were dialyzed using conventional lactate-buffered glucose-based PD solutions. The patients received medications such as antihypertensives, calcium based-phosphate binders ($CaCO_3$ average 2.5 g/day) and $1\alpha25\ (OH)_2\ D_3$, (calcitriol, 0.25−0.75 μg/day) as indicated by their attending physicians.

Data Collection

After enrollment, basal clinical, biochemical and echocardiographic evaluations were performed. Second (final) similar evaluations took place at 12 months of follow-up. In the meantime, patients were followed by their health care team with bimonthly visits for their regular treatment and unscheduled visits and treatment as needed.

Demographic and Clinical Data

Demographic and clinical data were obtained from clinical files or directly from patient during scheduled visits. They included age, gender, smoking status, systolic and diastolic blood pressure (BP), body mass index, diabetes mellitus status, evolution time of kidney disease, and PD and pharmacology prescriptions.

Biochemical Parameters

Fasting venous blood samples were drawn for biochemical analyses. Glucose, urea, creatinine, albumin, cholesterol, triglycerides, total calcium (tCa), and phosphorous (PO_4) were performed by conventional spectrophotometry assay. High-sensitivity C-reactive protein (hs-CRP) was measured using the immunoturbidimetric ultrasensitive assay (Tina-quant CRP, Latex, Roche Diagnostics GmbH, Mannheim, Germany) (Hitachi 902 Automatic Analyser, Tokyo, Japan). The %CV of the CRP between run of assay was 5.8% at concentration for 5.5 mg/L and 1.5% in run with 4.0 mg/L. Intact parathormone (iPTH, 1−84) and MID-osteocalcin were analyzed by electrochemiluminescence immunoassay (Elecsys Modular Analytics 2010 Roche, Hitachi, Tokyo, Japan). Osteoprotegerin (OPG) and fetuin-A were determined by ELISA (MicroVue Eia Kit. Quidel Corp. Specialty Products, San Diego, CA and Epitope Diagnostic Inc., San Diego, CA, respectively). The intra-assay precision was 4.8−5.5% and inter-assay precision was 5.7−6.8%. Residual glomerular filtration rate (GFR) was measured as the average of 24 h urine urea and creatinine clearance.

Echocardiographic Measurements

Heart valve calcification was defined as bright echoes of >1 mm on one or more cusps of the aortic valve or mitral valve or mitral annulus or both and were measured using two-dimensional echocardiography using a digital commercial harmonic imaging ultrasound system with