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ORIGINAL ARTICLE

Relationship between serum osteoprotegerin and vascular calcifications in hemodialysis patients

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Abstract *Background:* Uremia is a vasculopathic process, and both cardiac calcification and vascular calcification seen from the early stages of chronic kidney disease. Osteoprotegerin could play a crucial role in atherosclerotic plaque formation, maturation and calcification. The goal of this study was to determine the relationship of serum osteoprotegerin with vascular calcification in patients with end stage kidney disease who were maintained on regular hemodialysis.

Methods: Sixty clinically stable chronic renal failure patients undergoing regular hemodialysis were enrolled in this cross sectional study. Thirty patients (mean age 56.7 ± 10.5 years) with abdominal aortic calcification were selected by basal abdominal X-ray who underwent multi-slice computerized tomography scan to measure coronary artery calcification score; and thirty patients (mean age 56.5 ± 8.4 years) without abdominal aortic calcification. All patients were evaluated by serum calcium, phosphorus, albumin, lipid profile, intact parathyroid hormone (iPTH), serum creatinine, serum urea, serum uric acid, serum C-reactive protein, and hemoglobin. Serum osteoprotegerin samples were collected before dialysis and estimated by the ELISA kit.

Results: Serum osteoprotegerin level was significantly higher in patients with vascular calcification than in those without calcifications. Serum osteoprotegerin correlated positively with serum phosphorus, calcium phosphorus product, alkaline phosphatase, iPTH, C-reactive protein, serum uric acid, low-density lipoprotein (LDL) and left ventricular mass index (LVMI) ($p < 0.005$), and negatively with hemoglobin, ejection fraction ($p < 0.005$) and HDL ($p < 0.05$).

Conclusions: These findings suggest that osteoprotegerin may be involved in the development of vascular calcification in hemodialysis patients.

1. Introduction

Vascular calcification (VC) is common in individuals with chronic kidney diseases.[1] Vascular calcification is highly

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prevalent in patients on dialysis as 94% of the patients had aortic calcification detected by lateral abdominal radiography.[2] Similarly, Jean et al.[3] reported a high prevalence 83% of vascular calcifications in hemodialysis (HD) patients in spite of a long and intensive dialysis strategy and adherence to guidelines. Emad et al. reported 78% of Egyptian HD patients showing abdominal aortic calcification.[4]

The pathogenesis of vascular calcifications is complex and not fully understood. It does not only consist of a simple precipitation of calcium and phosphorus, but also involves an active and modifiable process. Vascular calcification in chronic kidney diseases (CKD) may be interpreted as the result of the dysregulation of the equilibrium between calcification promoters and inhibitors in which several uremic factors, including abnormalities in the mineral metabolism, are implicated.[5]

Osteoprotegerin (OPG) is a cytokine of the tumor necrosis factor (TNF) receptor superfamily and is classed as an osteoclastogenesis inhibitory factor. OPG is expressed widely in many tissues besides osteoblasts, including spleen, bone marrow, heart, liver, and kidney.[6] The plasma level of OPG could serve as a surrogate marker of progression of atherosclerosis and calcification in patients with end-stage renal disease.[7]

It has also been demonstrated that serum Osteoprotegerin (OPG) levels are correlated with the severity of coronary artery disease and constitute an independent risk factor of the progression of atherosclerosis.[8] A study by Morena et al. suggests that there is a significant correlation between elevated serum OPG levels and cardiovascular mortality.[9]

We aimed to investigate the relation between osteoprotegerin level and cardiovascular calcification in hemodialysis patients.

2. Patients and methods

The study was carried out for a period of one year from January 2014 to January 2015 at El-Galaa Military Hospital. A total of 60 patients with clinically stable end stage kidney disease (ESKD) were enrolled in this cross-sectional study. According to lateral abdominal X-ray, we selected 30 patients with abdominal aortic calcification (group A) and they had been compared with another 30 patients selected without abdominal aortic calcification (group B). All patients were dialyzed via AVF three times a week for four hour session using polysulfone high flux dialyzer 1.6 m^2 surface area, with dialysate flow 500 ml/min and dialysate calcium concentration 1.25 mmol/l, using heparin as anticoagulant with tailored doses according to each case and bicarbonate based dialysate. The adequacy of dialysis was assessed using Kt/V formula (K is patient clearance, t dialysis time, V urea space).[10] Patients with the following criteria were included in the study: patients older than 25 years; parathyroid hormone (PTH) > 300 pg/ml; serum calcium > 8.4 mg/dl and calcium phosphorus product > 50 mg/dl. On the other hand, patients subjected to parathyroidectomy; severely anemic patients (Hb < 7 g/dl); patients with advanced cardiac dysfunction (EF% < 35%); patients on oral anticoagulants; and patients on regular hemodialysis less than 6 months and diabetics were excluded.

Each patient underwent full clinical evaluation, serum calcium, phosphorus, alkaline phosphatase albumin, lipid profile, PTH, serum creatinine, serum urea, Serum uric acid, C-reactive protein (CRP), and hemoglobin. Osteoprotegerin samples were collected before dialysis and stored at −80 °C until use. Serum OPG samples were estimated by the ELISA kit provided by Phoenix Pharmaceuticals, Prague-Czech. All patients were informed about the content of the study and gave their written approvals before enrollment. All procedures were performed in accordance with the ethical standards of Al-Azhar University's committee on human experiments.

Radiological evaluation: It was performed through Echocardiography to measure different cardiac parameters especially left ventricular diameters and ejection fraction. Lateral abdominal X-radiography of the aorta for grading of calcifications was as follows: 0, no aortic calcific deposits; 1, small scattered calcific deposits less than one-third of the corresponding length of the vertebral level; 2, medium quantity of calcific deposits about one-third or more, but less than two-thirds of the corresponding vertebral length; 3, severe quantity of calcifications of more than two-thirds or more of the corresponding vertebral lengths. To detect abdominal aortic calcification we used a validated 24-point abdominal aortic calcification score (AACS). For the 24-point score, calcified deposits along the anterior and posterior longitudinal walls of the abdominal aorta adjacent to each lumbar vertebra from L1 to L4 were assessed using the midpoint of the intervertebral space above and below the vertebrae as the boundaries. The scores, obtained separately for the anterior and posterior walls, resulted in a range from 0 to 6 for each vertebral level and 0 to 24 for the total score.[11] Multi-slice CT scan (MDCT) was used to measure coronary artery calcification score using Agatston score. The score was calculated using a weighted value assigned to the highest density of calcification in a given coronary artery. The density was measured in Hounsfield units, and score of 1 for 130–199 HU, 2 for 200–299 HU, 3 for 300–399 HU, and 4 for 400 HU and greater. This weighted score was then multiplied by the area (in square millimeters) of the coronary calcification. The tomographic slices of the heart were 3 mm thick and average about 64 slices from the coronary artery ostia to the inferior wall of the heart. The calcium score of every calcification in each coronary artery for all of the tomographic slices was then summed up to give the total coronary artery calcium score (CAC score).[12]

3. Statistical methods

All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. Data are presented as mean and SD. In addition, parametric tests for comparison of numerical variables between the study groups were done using Independent Samples T Test. For comparing categorical data Chi-squared test was performed. Correlation between numeric variables was done using Pearson's correlation equation. Stepwise multiple regression analysis was for detection of vascular calcifications predictors. P values less than 0.05 was considered statistically significant.

4. Results

Characteristics of study groups are summarized in Table 1. Both groups were matched regarding age, gender, body mass index (BMI), original kidney disease. The patients with vascular calcifications have higher duration of hemodialysis, serum