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Original article

Association between vascular calcification assessed by simple radiography and non-fatal cardiovascular events in hemodialysis patients

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ABSTRACT

Background. – Vascular calcification (VC) is one of the factors associated with cardiovascular mortality in hemodialysis (HD) patients. Recommendations concerning screening for VC differ. Possible ability to prevent and reversibility of VC are major subjects on debate whether screening for VC could improve outcomes of renal patients. The objective of the study was to evaluate the significance of simple vascular calcification score (SVCS) based on plane radiographic films and to test its association with non-fatal cardiovascular events in patients on chronic HD.

Methods. – A study population consisted of 95 prevalent HD patients in the HD unit of Hospital of Lithuanian University of Health sciences Kaunas Clinics. Clinical data and laboratory tests information were collected from medical records. SVCS was evaluated as it is described by Adragao et al. After measurement of VC, HD patients were observed for novel non-fatal cardiovascular events.

Results. – Patients were divided into two groups: SVCS ≥ 3 (57 patients [60%]) and < 3 (38 patients [40%]). The Kaplan–Meier survival curves show a significant difference in non-fatal cardiovascular events in the group with SVCS ≥ 3 vs. < 3 group (26.3% vs. 7.8%; log rank 5,49; $P = 0.018$). Multivariate Cox regression analysis confirmed a negative impact of VC, hyperphosphatemia, and lower ejection fraction on cardiovascular events. No statistically significant differences were observed comparing parameters of Ca-P metabolism disorders between groups with different SVCS. On separate analysis, the presence of VC in hands was also associated with higher rate of novel cardiovascular events (score 0 goup–5 events [10.6%] vs. score ≥ 1 group–13 events [27%], log rank $P = 0.035$).

Conclusion. – VC assessed by simple and inexpensive radiological method was an independent predictor of novel non-fatal cardiovascular events in HD patients.

1. Abbreviations

VC	vascular calcification
HD	hemodialysis
Ca	calcium
P	phosphorus
SVCS	simple vascular calcification score
PTH	parathyroid hormone
Hb	hemoglobin
ALP	alkaline phosphatase
CRP	C-reactive protein
BMI	body mass index

2. Introduction

Dialysis patients show an increased total and cardiovascular mortality [1]. Among end-stage renal disease patients, the risk of cardiovascular mortality is significantly higher than in healthy individuals [2,3] and cardiovascular mortality is the main cause of

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death in hemodialysis (HD) patients [1,2]. This high cardiovascular risk is not completely explained only by conventional risk factors, such as hypertension, hyperlipidemia, and diabetes [2,4]. As interventions that have been successful in the general population have failed to decrease mortality in HD patients [5], more attention is focused on non-traditional cardiovascular risk factors, particularly those related to abnormal mineral metabolism. Vascular calcification (VC) is a central contributor to cardiovascular disease and mortality [6–8]. There are two main types of VC in HD patients contributing to higher cardiovascular risk and acting through different mechanisms. Atherosclerosis, which mainly affects the intima, is driven by traditional risk factors and is responsible for occlusive conditions [9]. Media calcification is present in muscle type conduit arteries and does not obstruct the arterial lumen but affects hemodynamics [8,10]. Recommendations concerning screening for VC differ. An indiscriminated screening was not recommended neither by KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention and Treatment of CKD-MBD published in 2009 nor by American National Kidney Foundation [11]. On the other hand, the European Renal Best Practice work group concluded that it is reasonable to screen every incident dialysis patient [12]. However, possible ability to prevent and reversibility of VC are major subjects of debate whether screening for VC could improve outcomes of renal patients [13,14]. Still in KDIGO recommendations, it was stressed that patients with known VC should be considered at highest cardiovascular risk. Despite the lack of proof that early detection of VC leads to improved clinical outcomes, we hypothesized that evaluation of VC using simple radiological method can be useful in identifying particular patients at highest risk for cardiovascular events. These high-risk patients may benefit most from less calcifying mineral metabolism treatment regimes, such as non-calcium based phosphate binders, additional attention controlling traditional and non-traditional risk factors for cardiovascular diseases and more intense preventive cardiovascular screening and monitoring. The objective of the study was to evaluate the significance of simple vascular calcification score based on plane radiographic films and to test its association with non-fatal cardiovascular events in patients on chronic HD.

3. Methods

An observational, prospective, 3 years single-centre cohort study included 95 prevalent patients treated with HD in Hospital of Lithuanian University of Health sciences Kaunas Clinics. The study was approved by Kaunas Regional Biomedical Research Ethics Committee (protocol number BE-2-9).

After measurement of VC, laboratory tests and heart ultrasound, HD patients were observed for novel non-fatal cardiovascular events (primary end-point of the study). Cardiovascular events consisted of coronary, cerebrovascular and peripheral vascular morbidity. Coronary artery disease was diagnosed if the patient had angina pectoris, myocardial infarction and/or vascular lesions in a percutaneous coronary intervention or coronary bypass surgery. Diagnosis of cerebrovascular disease was based on the anamnesis of stroke, transient ischaemic attack, detection of cerebral infarction on computed tomography scan. The peripheral vascular disease was diagnosed if there was claudication, ischemic ulcers, amputation or revascularisation operation. If any of these conditions (coronary/cerebrovascular/peripheral vascular disease) has been found for the first time during the observational period, the patient was considered as having a novel cardiovascular event. Clinical data and laboratory test information were collected from medical records of each patient. HD duration, as well as age, were evaluated on the day of simple vascular calcification score (SVCS) assessment.

SVCS was evaluated in all patients during a 7-month period as described by Adragao et al. [15]. The analysis of plain radiographic films of pelvis and hands was performed by a single radiologist blinded to clinical data. The pelvis radiographic films, as well as films of the hands, were each divided into four sections. VC was qualitatively determined as absent (score 0) or present (score 1) and the final score was a sum of all the sections ranging from 0 to 8 with SVCS ≥ 3 considered as cut-off value as it is suggested by Adragao et al. Only linear calcifications, with or without patchy calcification were considered for the final calcification score as they outline the vessel wall and have vascular location. To evaluate separately muscular arteries with a greater tendency to media calcification, the distinct analysis of hands score was performed, considering score ≥ 1 as present VC.

Demographic, clinical, laboratory data, as well as heart ultrasound parameters, were collected from ambulatory records of the patients. Kt/V, levels of calcium (Ca), ionized Ca, phosphorus (P), parathyroid hormone (PTH), hemoglobin (Hb), albumin, alkaline phosphatase (ALP), cholesterol, C-reactive protein (CRP) were assessed at the moment of SVCS evaluation and at the start of dialysis for each patient. To evaluate possible influence of dialysis vintage, age, body mass index (BMI), as well as biochemical parameters on SVCS, we compared means of those tests in SVCS ≥ 3 and < 3 groups.

Ca, ionized Ca, P, albumin, ALP, CRP, cholesterol were measured with automated clinical system UniCel DxC 800 Synchron (Becman Coulret, Brea, USA). PTH was measured with automated enzyme immunoassay analyzer AIA 2000 (Tosoh Corporation, Tokyo, Japan). Hb was obtained with the automated hematology analyzer Sysmex XE-5000 (Sysmex Corporation, Kobe, Japan).

Variables were expressed as frequencies, percentages for discrete factors and mean values $\pm$ standard deviation (SD) for continuous factors. Statistical comparison was performed using the two-tailed Chi^2 test for categorical variables and two-tailed Student's *t*-test or Mann–Whitney test for continuous variables. Association between two continuous variables was evaluated by calculating Spearman correlation coefficient. Kaplan–Meier and Cox regression were used to evaluate time to cardiovascular event. For all comparison P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software package.

4. Results

Our study included 95 chronic HD patients: 54 (57%) men and 41 (43%) women. On the day of SVCS evaluation, the mean age of patients was 61.01 ± 15.7 (22–86) years. The mean HD vintage was 39.74 ± 46.21 months (1–182). Nineteen patients (20%) were diabetic. Eleven (11.6%) patients died during the follow-up period.

The distribution of SVCS was the following: score 0 in 21 patients (22.1%), score 1 in 11 patients (11.6%), score 2 in 6 patients (6.3%), score 3 in 5 patients (5.3%), score 4 in 11 patients (11.6%), score 5 in 5 patients (5.3%), score 6 in 16 patients (16.8%), score 7 in 5 patients (5.3%), score 8 in 15 patients (15.8%). Analysing separately calcification of muscular arteries in hands: score 0 was found in 47 patients (49.5%) and score $\geq$ 1–48 patients (50.5%).

To compare results, patients were divided into two groups: SVCS ≥ 3 (57 patients [60%]) and < 3 (38 patients [40%]). We found that patients with SVCS ≥ 3 were older as compared to patients with SVCS < 3 and had diabetes more often. There were no significant differences in HD duration, BMI as well as the frequency of hypertension and anamnestic cardiovascular diseases between the groups (Table 1). Laboratory findings of the study population are summarized in Table 2.

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