Vascular Calcification in Hemodialysis Patients: A Cross-Sectional, One Center Observational Study

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Abstract. *Background and objective: Increasing evidence suggests that vascular calcification is one of the most important factors for outcomes of hemodialysis patients. The use of plain radiography has already been suggested as an adequate replacement for expensive and not easily available methods, such as computed tomography in Kidney Disease: Improving Global Outcomes guidelines for vascular calcification assessment, but it was not widely outspread in everyday clinical practice. Experts highlight the necessity of extended studies using these simple nonexpensive methods. The aim of the study was to evaluate the prevalence and the characteristics of vascular calcification in hemodialysis patients of our center and to identify the impact of vascular calcification on all-cause mortality.*

Methods: The observational prospective single-center study included 95 prevalent patients on maintenance hemodialysis in the dialysis unit of the Hospital of Lithuanian University of Health Sciences Kauno klinikos. The simple vascular calcification score (SVCS) was evaluated as it is described by Adragao et al. with SVCS ⩾ 3 considered as a cut-off value. For the more detailed analysis, the group of patients with SVCS ⩾ 3 was divided into 2 subgroups: SVCS 3–5 (mild vascular calcification) and SVCS 6–8 (severe vascular calcification). The patients were followed from the baseline examination until the death or until the end of May 2017. Demographical, clinical data, and anamnesis of pre-existing diseases were collected from medical records of each patient. Statistical analyses were performed using SPSS 24 software package.

Results: SVCS was evaluated in 95 patients: 54 men (56.8%) and 41 women (43.2%). On the day of SVCS evaluation, the mean age of patients was 61.01 ± 15.7 (22–86) and the mean HD vintage was 39.74 ± 46.2 months (1–182). Nineteen patients (20%) were diabetic, 38 (40%) had diagnosed pre-existing cardiovascular diseases, and most of them 88 (92.6%) were hypertensive. SVCS ⩾ 3 was found in 57 patients (60%), and SVCS < 3 in 38 patients (40%). The survival rate in the group of SVCS < 3 was 92.1%, and it was significantly different compared with the groups of SVCS 3–5 (71.4%) and SVCS 6–8 (44.4%), log-rank 0.001. There was a statistically significant difference in the survival rate comparing groups with SVCS 0–2 and SVCS 3–5 (92.1% vs. 71.4%, respectively, log-rank 0.026). The difference in the groups with SVCS 3–5 vs. SVCS 6–8 did not reach the level of significance (71.4% vs. 44.4 %, respectively, log-rank 0.057). The multivariate logistic regression analysis revealed that age and hemodialysis vintage were important risk factors for mortality, but SVCS ⩾ 3 had the highest impact increasing the risk of all-cause mortality by 7.34 times.

Conclusions: Clinical significant vascular calcification was diagnosed in more than a half of patients (60%). The severe injury was present in 22.1% of prevalent patients. Present vascular calcification was associated with the increase in mortality by 7.34 times.

Introduction

Dialysis patients are known to have higher total and cardiovascular mortality as compared with general population [1–3]. Increasing evidence suggests that vascular calcification is one of the most important factors for outcomes of hemodialysis (HD) patients. Recommendations concerning screening for vascular calcification differ. Although in Kidney Disease: Improving Global Outcomes (KDIGO) recommendations it was stressed, that patients with known vascular calcification should be considered at the highest cardiovascular risk, an indiscriminated screening was recommended neither by KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) guidelines nor by American National Kidney Foundation [4]. On the other hand, the European Renal Best Practice work group concluded that it is reasonable to screen every incident dialysis patient [5]. The golden standard for the diagnosis of vascular calcification is electron beam computed tomography or multislice computed tomography [6–8]. The methods were not used widely as they

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are not easily available and expensive. The use of plain radiography has already been suggested as an adequate replacement for these methods in KDOQI guidelines for vascular calcification assessment [4], but it was not widely outspread in everyday clinical practice. Experts highlight the necessity of extended studies using these simple nonexpensive methods.

For the first time in our HD unit, we introduced to practice the evaluation of possible vascular calcification by plain radiography for all prevalent HD patients and hypothesized that evaluation of vascular calcification may be important in predicting clinical outcomes.

The aim of the study was to evaluate the prevalence and the characteristics of vascular calcification in hemodialysis patients of our center and to identify the impact of vascular calcification on all-cause mortality.

Methods

The observational prospective single-center study included prevalent patients (n = 95) on maintenance HD in the dialysis unit of the Hospital of Lithuanian University of Health Sciences Kauno klinikos. The study was approved by Kaunas Regional Biomedical Research Ethics Committee (protocol No. BE-2-9).

Demographical, clinical data, and anamnesis of pre-existing diseases were collected from medical records of each patient. After measurement of vascular calcification, the follow-up was started. The HD patients were observed for death (primary endpoint of the study). The patients were followed from the baseline examination until death or until the end of May 2017. The mean follow-up was 1016 days (23–1560).

SVCS was evaluated in all the patients during a 7-month period starting February 2013 with SVCS $\geqslant$ 3 considered as a cut-off value as described by Adragao et al. [9]. For the more detailed analysis, the group of patients with SVCS $\geqslant$ 3 was divided into 2 subgroups: SVCS 3–5 (mild vascular calcification) and SVCS 6–8 (severe vascular calcification). The radiograms were evaluated by a single experienced radiologist blinded to clinical data. The score was evaluated in plain radiographic films of the pelvis and hands. The pelvis radiographic films were divided into 4 sections by 2 imaginary lines: a horizontal line over the upper limit of both femoral heads and a median vertical line over the vertebral column. The films of the hands were divided, for each hand, by a horizontal line over the upper limit of the metacarpal bones. The presence of linear calcifications in each section was counted as 1 and its absence as 0. The final score was the sum of all the sections, ranging from 0 to 8. Vascular calcifications were deliberately evaluated only in muscular arteries: iliac, femoral, radial, and digital. Only linear calcifications, with or without patchy calcifications, were considered for the final calcification score because they outline the vessel wall and have undoubtedly vascular localization.

Information about pre-existing diseases was collected. The patients were considered having cardiovascular disease if coronary, cerebrovascular, and peripheral vascular morbidity was present in anamnesis. Coronary artery disease was diagnosed if the patient had angina pectoris, myocardial infarction and/or underwent percutaneous coronary intervention or coronary bypass surgery. Diagnosis of cerebrovascular disease was based on the presence of stroke or transient ischemic attack. The peripheral vascular disease was diagnosed if there was claudication, ischemic ulcers, non-traumatic amputation, or revascularisation operation

The patients with self-reported or physician-reported diabetes mellitus or with current use of hypoglycemic medication were categorized as diabetic. The patient was determined as hypertensive if the physician-reported hypertension in the medical records was present and/or antihypertensive medicine was prescribed. HD duration as well as age were evaluated on the day of SVCS assessment.

Variables were expressed as frequencies for discrete factors. For continuous factors, mean values ± standard deviation and median were used where appropriate. Statistical comparison was performed using the 2-tailed chi-square test for categorical variables, the 2-tailed Student *t* test or the Mann-Whitney test for continuous variables. For all comparisons, P value < 0.05 was considered statistically significant. For survival analysis, the Kaplan-Meier survival curves were compared by the log-rank test. The univariate analysis was performed using age, gender, DM, HD vintage, hypertension, vascular calcification, and pre-existing cardiovascular diseases. Variables that affected all-cause mortality ($P < 0.05$) in the univariate analysis were included in the multivariate logistic regression analysis model to determine factors associated with all-cause mortality. Statistical analyses were performed using SPSS 24 software package.

Results

SVCS was evaluated in 95 patients: 54 men (56.8%) and 41 women (43.2%). On the day of SVCS evaluation, the mean age of the patients was 61.01 ± 15.7 (22–86) and the mean HD vintage was 39.74 ± 46.2 months (1–182). Nineteen patients (20%) were diabetic, 38 (40%) had diagnosed pre-existing cardiovascular diseases, and most of them – 88 (92.6%) – were hypertensive. The end-stage renal disease was caused by diabetic (19%) and hypertensive nephropathy (17%), chronic glomerulonephritis (19%), chronic interstitial diseases (26%), and other causes (19%).

Table 1. Simple vascular calcification score in hands and pelvis separately

SVCS	Hands	Pelvis
0	47 (49.5%)	24 (23%)
1	9 (9.5%)	11 (11.6%)
2	19 (20%)	6 (6.3%)
3	4 (4.2%)	4 (4.2%)
4	16 (16.8%)	50 (52.6%)

SVCS, simple vascular calcification score.

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%), and score 8 in 15 patients (15.8%).

SVCS $\geqslant$ 3 was detected in 57 patients (60%), and SVCS < 3 in 38 patients (40%). For detailed analysis, the patients were divided into 3 groups separating patients with mild vs. severe vascular cal-

Table 2. Univariate analysis of factors of all-cause mortality (n = 95)

Factor	OR	*P*	95% CI for OR
Male	1.1	0.828	0.458–2.6
Age (per 1 year increase)	**1.07**	**0.0001**	**1.032–1.1**
HD duration(per 1 month increase)	**1.01**	**0.005**	**1.004–1.024**
DM	2.52	0.08	0.895–7.096
Hypertension	0.539	0.1	0.253–1.14
Pre-existing CVD	0.714	0.46	0.288–1.77
SVCS ≥ 3	**9.7**	**0.001**	**2.69–35.51**

HD, hemodialysis; DM, diabetes mellitus; CVD, cardiovascular diseases; SVCS, simple vascular calcification score; OR, odds ratio; CI, confidence interval.

Table 3. Multivariate analysis of all cause mortality (n = 95)

Factor	OR	*P*	95% CI for OR
SVCS $\geqslant$ 3	7.34	0.04	1.86–28.9
Age (per 1 year increase)	1.05	0.015	1.01–1.09
HD duration (per 1 month increase)	1.012	0.055	1.0–1.024

SVCS, simple vascular calcification score; OR, odds ratio; CI, confidence interval.

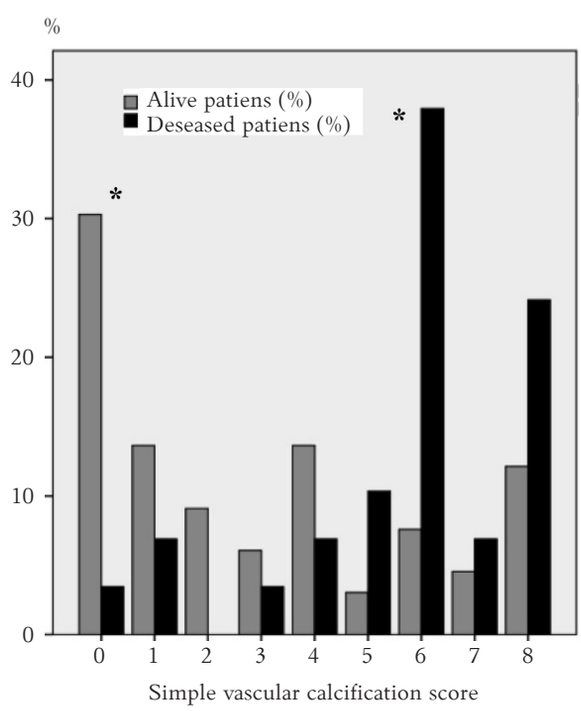

Fig. 1. Death frequency in groups with different simple vascular calcification scores

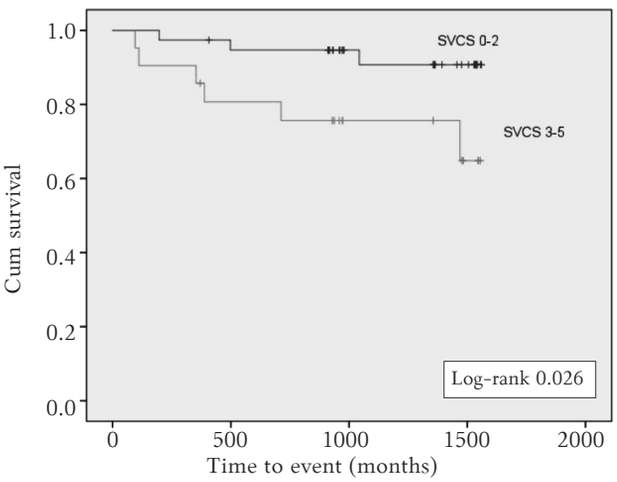

Fig. 2. Comparison of survival in patients with simple vascular calcification score < 3 and 3–5
SVCS, simple vascular calcification score.

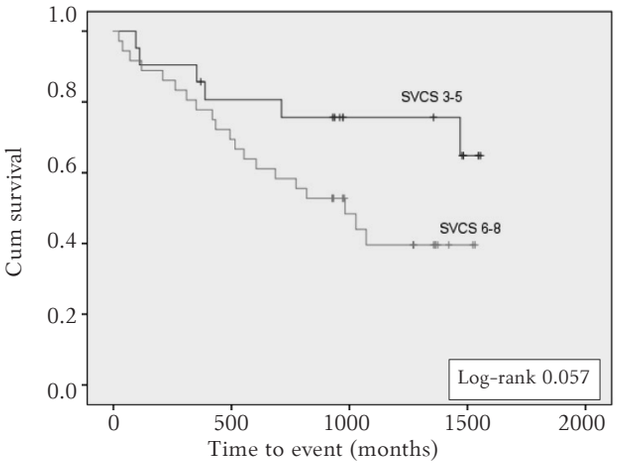

Fig. 3. Comparison of survival in patients with simple vascular calcification score 3–5 and 6–8
SVCS, simple vascular calcification score.

cification. 36 patients (37.9%) had severe vascular calcification with SVCS 6-8 and 21 patient (22.1%) had mild vascular calcification with SVCS 3–5. The rest 38 (40%) had no signs of calcification or SVCS was less then 3. The distribution of SVCS separately in hands and the pelvis were also evaluated and presented in Table 1.

During the observational period, 29 deaths occurred, of which 14 were cardiovascular. Detailed analysis of death frequency within the groups with different vascular calcification is presented in Figure 1. Statistical significant differences were observed in the groups SVCS 0 and SVCS 6 ($P < 0.05$). In the group without signs of vascular calcification (SVCS 0), only one patient died during the observational period; and in the group SVCS 6, of 16 patients 11 died.

The survival rate in the group of SVCS < 3 was 92.1%, significantly different compared with groups of SVCS 3–5 (71.4%) and SVCS 6–8 (44.4%), log-rank 0.001. Detailed analysis was performed and presented in Figures 2 and 3. It revealed that there was a statistically significant difference in survival comparing the groups with SVCS 0–2 and SVCS 3–5 (92.1% vs. 71.4% respectively, log-rank 0.026). The difference in the groups with SVCS 3–5 vs. SVCS 6–8 did not reach the level of significance (71.4% vs. 44.4%, respectively, log-rank 0.057).

As the survival analysis did not show the statistically significant differences in subgroups of the patients with mild vs. severe vascular calcification, the further analysis was performed comparing the patients with SVCS < 3 vs. SVCS ⩾ 3.

As presented in Table 2, the univariate analysis identified several factors associated with mortality, including age, HD duration, and vascular calcification. The multivariate logistic regression analysis results are shown in Table 3. Age and hemodialysis vintage remained important risk factors for mortality, but SVCS ⩾ 3 had the highest impact increasing the risk of all-cause mortality by 7.34 times.

Discussion

In the current study, for the first time in Lithuania, we reported the frequency and characteristics of vascular calcification of all prevalent HD patients in the biggest hemodialysis center. Moreover, our study confirmed the contribution of vascular calcification to mortality and usefulness of the SVCS assesed by a simple radiological method in predicting outcomes of HD patients.

We confirmed the high prevalence of vascular calcification in hemodialysis patients. Only 22.1% of our patients were free of calcification lesions. The findings are quite similar to the data of a study performed in Portugal by Adragao et al., who found SVCS 0 in 25.2% of hemodialysis patients. Contrary to the frequencies presented by the authors of the original method, we found higher rates of severe vascular calcification with SVCS 7 and 8: SVCS 7 – 0% vs. 5.3% and SVCS 8 – 3.3% vs. 15.8%, respectively [9]. Breznik et al. from Slovenia investigated several imaging methods for evaluation of vascular calcification. Chronic hemodialysis patients (n = 28) were enrolled in the study. The majority of investigated patients (85%) had vascular calcification lesions in hands and 75% in pelvis [10]. For comparison, in our study, vascular calcification in hands was less common, and was diagnosed in 50.5% of the patients. The frequency of vascular calcification lesions in the pelvis was nearly similar as we found calcification in the pelvis in 77% of our patients.

Recently published literature reveals that the frequency of vascular calcification differs significantly and ranges between 17% and 85% between centers and patients' groups. The higher frequency of vascular calcification was shown in studies having the

largest number of participants: a study from China performed by Chen HC with 438 patients involved and the multicenter observational study presented by Kraus MA and coauthors with 275 patients (80% and 77.5%, respectively) [11, 12]. The exceptionally low level of vascular calcification was observed in patients from Iraque (only 18.5%) despite the fact that there were no significant differences in patients' age or other demographic criteria [13]. The study from South Africa deserves special attention revealing a striking difference between races, showing that the black race was associated with the significantly lower rate of vascular calcification (17.5%.vs. 56.6%) [14]. However, most of the studies report that vascular calcification is found in 45–65% of patients [15–18].

As research articles represent heterogeneity estimating both primary aims of the studies and diagnostic methods of vascular calcification, it is difficult to compare prevalence and characteristics of vascular calcification of patients in our center and the data of other centres. Despite the fact that there is insufficient amount of studies to draw significant conclusions, we revealed that the frequency of vascular calcification of patients in our center was quite similar to the data presented from European countries (Portugal and Slovenia) although the results from Asian countries as well as Brazil and Mexica reported lower levels of prevalent vascular calcification in studied HD patients.

As mentioned above, computed tomography is the golden standard for evaluation of vascular calcification, but the use of plain radiography is considered as an adequate alternative and is recommended by guidelines for everyday use. Kauppila index and SVCS by Adragao are most commonly used radiographic methods for evaluation of vascular calcification in clinical studies of patients with chronic kidney disease. Kauppila et al. showed abdominal aortic calcification as a predictor of various cardiovascular events. They also introduced an abdominal aortic calcification score [19]. An SVCS for pelvic and hand arteries was introduced by Adragao et al. [9]. The authors of the method proved that SVCS $\geqslant$ 3 was associated with cardiovascular mortality and hospitalization rates and suggested that this simple scoring system could be a convenient tool for assessment of cardiovascular risk in HD patients. In our study published earlier, we confirmed that SVCS was also associated with novel nonfatal cardiovascular events in HD patients [20].

The small study of 28 patients performed by Breznik et al. compared different methods of vascular calcification evaluation. Vascular calcification was assessed with coronary computed tomography and lateral lumbar, pelvic and hand radiographs. Vascular stiffness was evaluated using aortic pulse wave velocity and ankle-brachial index measurements. A statistically significant correlation was demonstrated between all the following parameters: coronary artery calcification score, aortic pulse wave velocity, abdominal aortic calcification score, simple vascular calcification scores in the pelvis and hands and led authors to a conclusion that simple imaging methods could provide confident vascular damage assessment and, therefore, potentially guide therapy adjustments [10].

There are two main types of vascular calcification in HD patients contributing to a higher cardiovascular risk and acting through different mechanisms: atherosclerosis, which mainly affects intima, is driven by traditional risk factors and is responsible for occlusive conditions, and media calcification, which is present in muscle type conduit arteries and does not obstruct the arterial lumen, but affects hemodynamics significantly to contribute to a higher cardiovascular risk in HD patients [21–23]. The Kauppila's score evaluates changes in the abdominal aorta, a large elastic type artery where atherosclerotic intimal changes are typical. Several studies have confirmed the association between vascular calcification established by the Kauppila score and nonspecific risk factors such as age, diabetes, and hemodialysis vintage [11,13,15,24]. Vascular calcification present in elastic vessels is known to be associated with an elevated risk of cardiovascular events and mortality. However, to evaluate causes and outcomes of vascular calcification that are more specific for kidney patients, we deliberately chose a method that evaluates muscular arteries and only linear lesions were calculated anticipating that these factors were more typical for media calcification.

Adragao et al. have proved that SVCS $\geqslant$ 3 was associated with cardiovascular morbidity and mortality and this threshold is used widely. We hypothesized that this higher risk might be attributed to the subgroup of the patients with the highest SVCS and performed survival analysis distinguishing the groups of mild vascular calcification with SVCS 3–5 vs. patients with severe vascular calcification with SVCS 6–8. We did not find any statistically significant difference in survival between these 2 groups; however, the difference between the survival of patients with SVCS $<$ 3 vs. SVCS 3–5 was statistically significant. Based on this finding, we presume that the role of the degree of severity of vascular calcification maybe less important than it could have been expected.

We also confirmed that among factors related to mortality of hemodialysis patients, vascular calcification plays one of the pivotal roles with SVCS $\geqslant$ 3 increasing the risk of death by more than 7 times. Age and HD vintage had less impact on overall survival as compared with vascular calcification of patients in our centre.

Our results are consistent with studies published lately [9, 10, 12] and give a broad spectrum of possible future research analysing causes and risk factors influencing vascular calcification in our hemodialysis patients.

Debates whether screening for vascular calcification could be translated into better outcomes continue.With our data, we intend to support the view that despite the fact that we have no strong data on clinical outcomes, we should take into account new data suggesting that vascular calcification may be attenuated with appropriate treatment and is, therefore, important to be diagnosed.

In this context, we would advocate for using simple, easily available, but the prognostically good score in everyday practice as knowledge about vascular calcification may allow us to identify patients at risk and to modify their treatment regimes in the most optimal way.

The main limitations were a relatively small number of patients and the observational and cross-sectional nature of the study. Further studies are needed for evaluation of factors that may be important in the development and progresion of vascular calcification in hemodialysis patients.

In conclusion, for the first time, we reported the prevalence and characteristics of vascular calcification in one of the biggest hemodialysis centers in Lithuania. Clinical significant vascular calcification was diagnosed in more than a half of patients (60%). The severe injury was present in 22.1% of prevalent one-center hemodialysis patients. Present vascular calcification was associated with the increase in mortality by 7.34 times.

Conflict of Interests

The authors have declared that no conflict of interest exists.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (approval No. BE-2-9) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Authors' contributions

VP: study design, data collection and interpretation, writing the first draft, and preparation of the final manuscript; IAB: study design, data interpretation, and preparation of the final manuscript; EJ: radiological data analysis, and preparation of final manuscript; VK: study design, data interpretation, and preparation of final manuscript.

All authors read and approved the final manuscript.

This manuscript describes original work and is not under consideration by any other journal. The results presented in this paper have not been published previously in whole or part.

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