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Impact of Vascular Calcifications on Arteriovenous Fistula Survival in Hemodialysis Patients: A Five-Year Follow-Up

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Key Words
Vascular access · Arteriovenous fistula · Vascular calcifications · Survival

Abstract
Background/Aims: Vascular calcifications are frequently found among dialysis patients, and the calcification process may influence the patient's outcome. The aim of the present study was to determine the role that vascular calcifications may have on autologous arteriovenous fistula (AVF) survival. ***Methods:*** This study included 90 patients (49 males, mean age 62 ± 11) with a native AVF treated by chronic hemodialysis (HD) for more than one year. The overall vascular calcification scores ranged from 0–11 (Adragao score + vascular access calcification score); patients were categorized into mild (score 0–3; n = 36), moderate (score 4–7; n = 24) and severe (score 8–11; n = 30) calcification groups. AVF survival was then followed for 5 years after calcification measurement or until the patient's death/transplantation. ***Results:*** Patients with more pronounced vascular calcifications were more frequently diabetic and male. Multiple linear regression analysis showed a significant relationship between calcification score and male gender, diabetes mellitus, previous duration of AVF, low dialysis flow rate and intact parathormone (iPTH) values. After multivariate adjustment for basal differences, Cox proportional analysis revealed a graded impact of calcification scores on AVF failure: moderate scores (were associated with a hazard rate (HR) of 3.82 (95% confidence interval (CI) 1.10–13.23) and severe scores with an HR of 4.65 (CI 0.97–22.38). ***Conclusion:*** Vascular calcifications are associated with worse survival of native arteriovenous hemodialysis fistulas.

Introduction

Adequate and functional long-term vascular access is pivotal to perform efficient hemodialysis (HD) [1]. Autologous arteriovenous fistulas (AVFs) provide the most reliable vascular access as compared to prosthetic arteriovenous grafts (AVG) and tunneled catheters. Patients with AVFs have less frequent vascular access-related infections, thrombosis and surgical interventions and have better survival [2]. The main causes of vascular ac-

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cess failure are stenosis at the anastomosis (intimal hyperplasia) and the non-maturation.

Vascular access thrombosis may be a consequence of neointimal hyperplasia that has been initiated by activated platelets, endothelial cell injury and vascular smooth muscle cell proliferation [3, 4].

Vascular calcifications are commonly seen in dialysis patients and are associated with passive processes connected with cellular aging, but there is also an active process that involves differentiation of contractile vascular smooth muscle cells (VSMC) into 'osteoblast-like' cells [5]. The prevalence of coronary artery calcifications ranges from 40 to nearly 100% in dialysis patients [6, 7]. Medial or circumferential calcifications (Monckeberg calcifications), which are frequently seen in end-stage renal disease (ESRD) patients, can lead to reduced compliance due to arterial stiffening, resulting in an impaired vasodilatation. These types of calcifications of the aorta would lead to increased pulse wave velocity, elevated pulse pressure and systolic hypertension. Lastly, calcification of the arterioles of the skin and other organs can lead to calciphylaxis and ischemic gut [8].

Literature data about the potential impact of vascular calcification on vascular access outcome are sparse. Therefore, the aim of the present study was to determine the role of vascular calcification on native AVF survival.

Materials and Methods

Patients

This single-center study included 90 patients with native AVF treated by chronic HD for more than one year at the Clinical Department for Renal Diseases, Zvezdara University Medical Center, Belgrade. The inclusion criterion was functional AVF as a primary vascular access. All AVF had latero-terminal anastomosis (radiocephalic fistula). We did not follow the blood flow rate in already mature arteriovenous fistulas. Patients were dialyzed for 4–5 h three times per week. The dialysis flow rate during HD was less than 250 ml/min in 17 patients (18.7%), 250 ml/min in 24 (26.4%) and above 250 ml/min in 50 patients (54.9%). Low-flux membranes were used in 18 patients (19.8%). High-flux membranes were used in 73 patients (80.2%): among them, 18 were treated by hemodiafiltration (HDF). The canulation technique excluded buttonhole needling.

Methods

Vascular calcifications were detected using X-ray examination, which was aimed at detecting linear medial calcifications of the iliac, femoral, radial and ulnar blood vessels and blood vessels of the hands and region of the vascular access. For calcification scoring, we used the method described by Adragao et al., which can yield scores from 0 to 8 [9]. In addition, the Adragao score was extended by adding calcification scores of the vascular access region (ulnar artery = 1, radial artery = 1 and fistula = 1; overall = 0–3), yielding an overall calcification score (Adragao score + vascular access score) between 0 and 11, as published previously [10, 11]. Vascular calcification was scored by three independent investigators who did not have knowledge about patient characteristics. In case of disagreement between investigators, the calcification score was presented as the mean of three measurements. According to the ROC curve analysis, it was confirmed that patients who had an overall vascular calcification score of over 3.5 had a greater risk for developing VA failure. This finding has helped us to define groups of patients according to the calcification score.

In addition to the general data, analysis included data from the medical records: AVF vintage before vascular calcification determination, characteristics of dialysis membrane, dialysis flow rate during HD, mineral metabolism indices and the use of vitamin D analogues. iPTH, serum calcium and phosphorus values were derived from the mean of three measurements from the previous three months.

Vascular access survival was followed for five years from the time of calcification measurements or until the patient's death/transplantation. The median follow-up time was 54 months (mean 46 months, SD = 17 months).

Pulse wave velocity was determined by the Complior SP system *(Artech Medical, Pantin, France)* with two sensors (carotid and femoral) for the simultaneous estimation of the pulse wave velocity between two points. Every patient had two measurements.

Statistical calculations were performed using the SPSS 20.0 software program. Data were expressed as percentages for categorical values, and mean values for continuous variables. Medians and interquartile ranges were used for continuous variables without normal distribution. Chi-square test or one way-ANOVA was used to analyze the differences in various baseline variables between three groups of patients defined by overall calcification score categories (0–3, 4–7, and 8–11). Multiple linear regression analysis was used to analyze the relationship between overall calcification score (dependent variable) and all baseline variables (age, gender, presence of diabetes mellitus, presence of hypertension, blood flow, AVF duration before and after calcification determination, iPTH, PWV – independent variables) in order to create a propensity score – standardized predicted values. The Cox proportional hazards model adjusted for standardized predicted values was used to determine hazard ratios for parameters that influenced AVF survival. A two-tailed p value <0.05 was considered statistically significant.

Results

The study included 90 patients on regular hemodialysis for more than one year with patent AVFs, 49 males and 41 females and mean age 62 ± 11. The most frequent underlying disease was hypertensive nephrosclerosis (46.7%), followed by interstitial nephropathy (16.7%), glomerulonephritis (13.3%), autosomal dominant polycystic disease (12.2%) and diabetes (7.7%). Almost 50% of the patients had an iPTH level in the KDIGO target range [12], 24% were below and 27% above the target

Table 1. Baseline data of patients from the three different overall calcification score groups

Variable	Total	Overall calcification score groups			p*
		0–3	4–7	8–11	
Patients, n	90	36	24	30	
Gender, men/women	49/41	14/22	12/12	23/7	0.008
Age, years, mean ± SD	62.7±10.4	63.0±10.7	64.2±9.2	61.2±10.9	0.582
DM, yes/no	10/80	0/36	1/23	9/21	<0.001
HTN, yes/no	49/41	20/16	13/11	16/14	0.983
Smoking, yes/no	21/69	8/28	6/18	7/23	0.969
AVF vintage before calcification determination, months					
Mean ± SD	87.4±56.3	87.5±53.5	77.7±47.4	95.0±65.9	0.536
Median; IQR	77; 69	77; 56	72.5; 61.5	85; 98.5	
Dialysis blood flow rate, ml/min					
Mean ± SD	261±31	261±34	265±29	258±29	0.657
Median; IQR	260; 30	257.5; 48	260; 30	260; 43	
iPTH, pg/ml					
Mean ± SD	509±566	414±302	557±737	583±649	0.429
Median; IQR	284; 538	312; 442.5	201.5; 745	347; 632	
Calcium, mmol/l**	2.33±0.16	2.34±0.14	2.32±0.20	2.33±0.17	0.939
Phosphorus, mmol/l**	1.54±0.39	1.48±0.35	1.51±0.44	1.64±0.39	0.229
PWV, m/s, mean ± SD	9.96±2.80	9.63±2.36	10.06±2.96	10.27±3.18	0.442

HTN = Hypertension; DM = diabetes mellitus; sPTH = serum parathormone; PWV = pulse wave velocity; IQR = interquartile range; * according to Chi-square test or one-way ANOVA where appropriate; ** average of three measurements in the first study year.

range. Forty-one percent of the patients received vitamin D metabolites (calcitriol). Acetyl salicylic acid and coumarin drugs were used in less than 10% of the study population and without significant differences between the groups.

Table 1 shows baseline data of patients in the three overall calcification score groups, that is, mild (0–3), moderate (4–7) and severe (8–11).

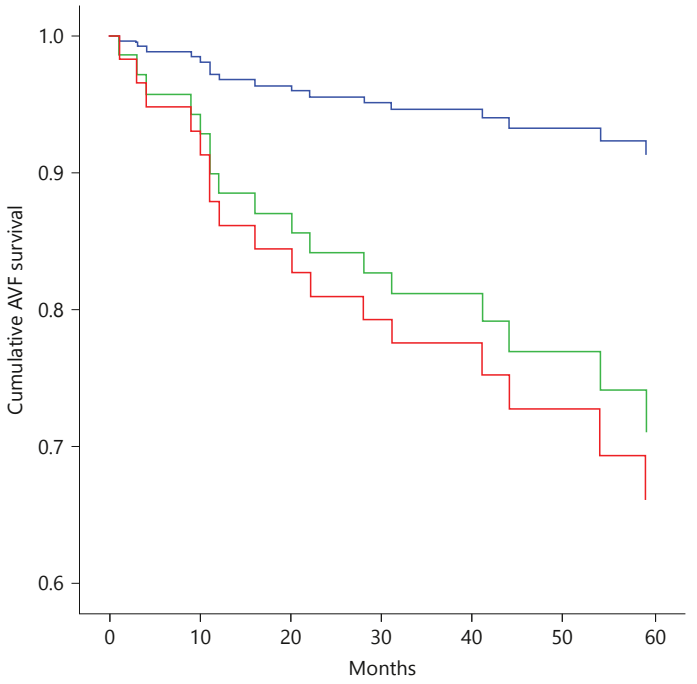
Patients in the three groups were of similar age and there were no differences between groups in AVF vintage before calcification measurement, dialysis blood flow rate, smoking habits, PWV, iPTH, serum Ca, phosphorus and presence of hypertension. There were significantly more males and diabetics in groups 2 and 3 (moderate and severe calcification groups) than in the mild calcification group. At the baseline, we did not observe significant difference in frequency of AVF intervention (angioplasty, surgical revision, or thrombectomy) between three groups (2 vs. 4 vs. 6, p = 0.195)

As shown in table 2, male gender, presence of diabetes mellitus, longer AVF vintage before calcification determination, higher iPTH and lower AVF blood flow rate were associated with higher calcification scores.

Table 2. Multiple linear regression analysis of relationship between calcification score and all baseline variables

Variable	b	beta	95% CI for b	p
Gender	–3.11	–0.432	–4.41 to –1.86	<0.001
Diabetes mellitus, yes	6.06	0.526	3.92 to 8.21	<0.001
Hypertension, yes	0.81	0.111	–0.46 to 2.08	0.210
Smoking, yes	0.87	0.010	–1.425 to 1.599	0.909
AVF vintage before calcification determination, months	0.017	0.262	0.005 to 0.029	0.005
Age	0.013	0.036	–0.06 to 0.08	0.733
Dialysis blood flow rate	–0.026	–0.217	–0.048 to –0.003	0.026
iPTH	0.001	0.191	0.000 to 0.002	0.032
Ca	–3.005	–0.136	–7.046 to 1.036	0.143
Phosphorus	1.025	0.110	–0.711 to 2.760	0.243
PWV	0.038	0.029	0.76 to 0.28	0.761

iPTH = Intact serum parathormone; Ca = calcium; PWV = pulse wave velocity.



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Calcification score groups	Start	12 months	36 months	End of study
Low calcification score (0–3)	36	35	32	32
Moderate calcification score (4–7)	24	21	18	17
Severe calcification score (8–11)	30	27	27	24

Fig. 1. Effect of different overall calcification scores on AVF survival (Cox proportional analysis).

Table 3. Impact of different overall calcification score groups on AVF failure (Cox proportional analysis)

Calcification score groups*	p	HR	95% CI
Low overall calcification score (0–3)	–	1.00	–
Moderate overall calcification score (4–7)	0.035	3.82	1.10–13.23
Severe overall calcification score (8–11)	0.055	4.65	0.97–22.38

HR = Hazard rate; CI = confidence interval; * adjusted on propensity score (i.e., standardized predicted value, see table 2).

The impact of different overall calcification scores on AVF survival was determined using a Cox proportional hazard model adjusted for differences presented in table 2. Patients with moderate overall calcification scores had a significantly higher risk of developing AVF failure (HR 3.82, CI 1.10–13.23) and patients with severe overall calcification scores had a 4.65-fold higher risk of developing vascular access failure (CI 0.97–22.38) (table 3; fig. 1).

Discussion

Although there were no randomized comparisons between different vascular forms of access and patient outcome, observational studies revealed a superiority of native fistulas. Therefore, fistulas are considered the preferred form of hemodialysis access and are endorsed by local, national and international guidelines [13, 14].

Numerous studies aimed to identify factors that influence long-term AVF patency [15, 16]. This study is of particular importance since data on the role of vascular calcification on long-term patency of vascular access are scarce. A study from Georgiadis et al. analyzed the same issue but only in patients with diabetes [17]. They confirmed that ESRD diabetics with radial artery Mönckeberg calcifications who had radiocephalic fistula had worse late clinical outcomes compared with ESRD diabetics with healthy distal arm vessels receiving the same access. Our data complement the findings given that it applies to all patients regardless of the presence of diabetes.

About one-third of uremic radial arteries collected at the time of AVF creation exhibit arterial calcifications, mostly in the media of the vessel [18]. In addition, one-third of the patients had calcification of the fistula vein at the time of AVF creation [19]. Several studies have tried to confirm that changes in the cephalic vein before creating the AVF affects primary AVF patency [20, 21], but the long-term effect of vascular calcifications on AVF survival has not yet been fully clarified.

In the present study, it was noted that there was graded increase in AVF failure with increasing vascular calcification scores. Although the real reasons for this finding are not entirely clear, the possible explanation is that vascular calcifications may potentiate vascular injury and neointimal hyperplasia by increasing a shear stress, mechanism already proposed by some authors [22]. The present study thereby extends our previous findings that higher vascular access calcification score is a predictor of mortality in hemodialysis patients [10]. Our data are not in agreement with data from Allon et al. who confirmed that preexisting arterial and venous abnormalities (intima thickness, medial fibrosis and arterial calcification) did not influence unassisted primary arterio-venous graft survival [22]. However, we presented data about native fistulas and patients with AVG were excluded from analysis. Also, while our dialysis population comprised Caucasians, they analyzed mainly the African American population. Therefore, their conclusions may not be applicable to our research.

In addition to the present finding, we also confirmed the presence of vascular access calcifications in a high percentage of patients. For instance, VA calcifications were scored from 0–3 (calcification of artery, vein and anastomosis). The extent of calcification of vascular access was closely related to the total calcification score: patients with a highest overall calcification score (8–11) had the highest vascular access calcification score (score 3) (unpubslished data).

One would expect more calcified arteries to be stiffer, and therefore have higher PWV; however, this was not the result of our study. But we noted that PWV was lower in patients with a lower calcification score (9.36 vs. 10.27) and we believe that the number of patients was the reason we did not get a significant difference.

Significantly more diabetic patients were in our severe calcification group. Diabetes mellitus is recognized as a powerful fibrogenic stimulus that induces, directly or through the formation of advanced glycation end products, a variety of types of micro- and macrovascular damage. It is also known that diabetic patients are prone to the formation of vascular calcification [23]. Although multiple linear regression analysis confirmed that male gender was significantly correlated with the calcification score, we are not aware that male gender is recognized to be of significance for the calcification process.

It is known that PTH as a uremia-related factor impacts on accelerated atherosclerosis, blood pressure and vascular calcification [24, 25]. Although in one Italian study, elevated PTH levels were associated with a significantly increased risk of AVF dysfunction [26], this has not been confirmed in a Taiwanese study [27]. In the present study, higher iPTH predicted a higher calcification score. PWV values were slightly increased in our higher calcification score groups, but the difference between the groups was not significant. A decreased AVF blood flow rate is another significant risk factor recognized by multiple regression analysis but similar literature data are lacking. This could be a secondary phenomenon since a decreased blood flow rate may be a consequence of a previously damaged vascular access.

The major limitation of the present study in addition to the number of patients available for follow-up is the different pre-measurement period of treatment and there were AVFs with a long vintage. Thus, we don't know the impact of vascular calcification on the initial AVF maturation or AVF survival in the first few years. Although a cohort analysis would be more reliable, the follow-up period of five years gives us a good insight into the role of vascular calcification on AVF survival. In addition, serial measurements of vascular calcification might significantly differ between patients after the initial determination. A higher number of patients would amplify the current finding about the influence of vascular calcifications on AVF longevity. Finally, some additional risk factors that are not included in this study could be potentially important for AVF survival.

Conclusion

Vascular calcifications are found frequently among dialysis patients. In addition to unfavorable effects on cardiovascular morbidity/mortality, vascular calcifications may jeopardize the survival of native arteriovenous fistulas for hemodialysis.

Disclosure Statement

None declared.

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