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NEPHROLOGY - ORIGINAL PAPER

Calcification in arteriovenous fistula blood vessels may predict arteriovenous fistula failure: a 5-year follow-up study

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Abstract
Purpose Arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. The impact of vascular calcification process on AVF survival remains unclear and results of several studies about this issue are controversial. In the light of the new knowledge about the different susceptibility for calcification process in different blood vessels, the aim of our study was to analyze whether the calcification of AVF-blood vessels may have an impact on AVF longevity.
Methods The study included 90 patients, 49 males and 41 females, all of them Caucasians, with a mean age 62 ± 11 years, on regular hemodialysis for more than 1 year with patent primary AVFs. Vascular calcification in AVF-blood vessels or in the anastomotic region was detected using X-ray examination.
Results Calcification in AVF-blood vessels was found in 62% of patients. Binary logistic regression analysis demonstrated that male gender, presence of diabetes mellitus and longer duration of AVF before calcification determination were associated with calcification of AVF-blood vessels. Using a Cox proportional hazard model adjusted for these standardized predicted values revealed that patients with present AVF-blood vessels calcification had increased risk to develop AVF failure with a hazard rate of 3.42 (95% confidence interval 1.00–11.67; $P = 0.049$).
Conclusions Calcifications of AVF-blood vessels are found frequently among dialysis patients and may jeopardize the survival of native AVF. We suggested the local X-ray as simple and valid method for detection of patients that are at risk for AVFs failure which should be monitored more closely.

Keywords Calcification · AVF-blood vessels · X-ray · AVF survival

Introduction

Arteriovenous fistula (AVF) is the preferred vascular access (VA) for hemodialysis because of less frequent thrombotic and infectious complications compared to arteriovenous grafts (AVG) and central venous catheters [1].

Thrombosis is the major cause of AVF failure [2, 3], and underlying stenosis promotes this event [4–6]. Stenosis is mediated by neointimal hyperplasia that occurs in the process of repair of the vessel after numerous AVF punctures. This process is not fully understood, but cytokines and pro-inflammatory factors may have an important role. It is recognized that in chronic hemodialysis (HD) patients many of these pro-inflammatory molecules are increased, all of which may contribute to neointimal hyperplasia and AVF failure [7–12].

Comprehensive review revealed the significance of surveillance of blood flow, static pressure, duplex ultrasonography, access recirculation and dynamic pressure with aim to prevent vascular access failure [13]. However,

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the impact of vascular calcification process on AVF duration remains unclear and results of several studies about this issue are controversial [14–17]. Vascular calcification frequently affects blood vessels in patients with kidney failure, and mechanism probably involves combination of passive processes related to cellular aging and an active process that involves differentiation of contractile vascular smooth muscle cells (VSMC) into 'osteoblast-like' cells [18]. This medial calcification (Monckeberg) leads to inadequate vasodilatation, and if affecting large blood vessels, it results in high pulse-wave velocity (PWV) and systolic blood pressure. The pathogenesis and relevance of the calcification process are less clear for arteriovenous fistulas since fistulas are made of arterial and venous blood vessels. Although the vein changes over the time and develops some arterial characteristics during AVF maturation, the question is whether calcification of the venous blood vessel shares the same mechanisms as arterial vessels.

Our previous findings confirmed the connection between overall vascular calcification score and fistula survival [14]. Paper recently published by Schlieper et al. [19] presented data about different susceptibility for calcification process in different blood vessels. Therefore, one may expect that distant vascular changes may not have an impact on AVF-blood vessels, so the aim of our study was to analyze whether the calcification of AVF-blood vessels may have an impact on AVF longevity.

Materials and methods

Patients

This single-center study included 90 patients with native AVF treated by chronic HD for more than 1 year at the Clinical Department for Nephrology, Zvezdara University Medical Center, Belgrade. In this study, we included all prevalent patients with functional primary AVF as vascular access. Patients with secondary/tertiary AVFs or with arteriovenous grafts (AVGs) or tunneled catheters were excluded from the study. All AVFs had latero-terminal anastomosis (radiocephalic fistula). 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 (18.9%), 250 ml/min in 24 (26.7%) and above 250 ml/min in 49 patients (54.4%). Patients with blood flow rates less than 250 ml/min were included in the study since flow rate was not restricted by fistula itself but by some other, mainly cardiovascular reasons (heart failure, unstable angina and rhythm disturbances). 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 cannulation technique excluded buttonhole needling.

Fig. 1 Calcification in AVF-blood vessels

Methods

Vascular calcification in AVF-blood vessels or in the anastomotic region was detected using plain posteroanterior X-ray examination of the forearm with the AVF (Fig. 1), as published previously [14, 20, 21]. X-ray data were analyzed by three independent investigators who did not have knowledge about patient characteristics. In addition to the general data, analysis included data from the medical records: time from AVF creation till 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. On the basis of X-ray findings, patients were categorized into II groups: Group I—without (w/o) calcification in AVF-blood vessels ($n = 34$) and Group II—with calcification presence in AVF-blood vessels, most probably in both arterial and venous branch ($n = 56$). 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. The Kolmogorov–Smirnov test was performed for making assumptions about the distribution of data which 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, Student's *t* test or Mann–Whitney test was used to analyze the differences in various baseline variables between the groups

of patients. Binary logistic regression analysis was used to analyze the relationship between vascular access calcification presence (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 and 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, 49 males and 41 females, all of them Caucasians, with a mean age 62 ± 11 years, on regular hemodialysis for more than 1 year with patent AVFs. Table 1 shows baseline data of patients in the group without and with vascular calcification in AVF-blood vessels. Patients were of similar age, and there were no differences between groups in time from AVF creation till calcification measurement, dialysis blood flow rate, smoking habits, PWV, iPTH, serum Ca, phosphorus, calcium times phosphorus product and presence of hypertension. The most frequent underlying disease was hypertensive nephrosclerosis (46.7%), followed by interstitial nephropathy (16.7%), glomerulonephritis (13.3%), autosomal dominant polycystic kidney disease (12.2%) and diabetes (7.7%). Almost 50% of the patients had an iPTH level in the KDIGO target range; 24% were below and 27% above the target range [22]. The groups were homogeneous in terms of primary renal disease except that the group of patients with calcification in AVF-blood vessels comprised significantly more males and patients with diabetes. Vitamin D metabolites (calcitriol) received 41% of the patients. Coumarins and acetyl salicylic acid were used in less than 10% of the study population and without significant differences between the groups.

Binary logistic regression analysis demonstrated that male gender, presence of diabetes mellitus and longer duration of AVF before calcification determination were associated with calcification of AVF-blood vessels (Table 2).

The impact of AVF-blood vessels calcification on AVF survival was determined using a Cox proportional hazard model adjusted for male sex, diabetes mellitus presence and duration of AVF before calcification determination and revealed that patients with present AVF-blood vessels calcification had increased risk to develop AVF failure with a hazard rate (HR) of 3.42 [95% confidence interval (CI) 1.00–11.67; $P = 0.049$] (Table 3; Fig. 2). It is shown that

Table 1 Baseline data of patients without and with calcifications in AVF-blood vessels

Variable	All	Calcification groups		
		Group I (w/o calcifications in AVF-blood vessels)	Group II (with calcifications in AVF-blood vessels)	P*
Patients no.	90	34	56	
Gender (men/women)	49/41	12/22	37/19	0.008
Age, years (mean ± SD)	62.7 ± 10.4	64.0 ± 11.0	61.9 ± 10.0	0.374
Diabetes mellitus, yes/no	10/80	0/34	10/46	0.012
Hypertension, yes/no	49/41	14/20	27/29	0.663
Smoking, yes/no	21/69	9/25	12/44	0.614
Time from AVF creation till calcification determination, months (mean ± SD) (median; IQR)	87 ± 56 77; 69	75 ± 46 66; 48	94 ± 61 81; 90	0.104
Dialysis blood flow rate, ml/min (mean ± SD) (Median; IQR)	261 ± 31 260; 30	259 ± 37 255; 65	263 ± 26 260; 30	0.530
iPTH, pg/mL (mean ± SD) (median; IQR)	509 ± 566 284; 538	385 ± 329 235; 455	584 ± 661 334; 666	0.062
Calcium, mmol/L[a]	2.33 ± 0.16	2.31 ± 0.15	2.34 ± 0.17	0.326
Phosphorus, mmol/L[a]	1.54 ± 0.39	1.49 ± 0.44	1.57 ± 0.36	0.367
CaxP[b]	3.60 ± 0.96	3.46 ± 1.07	3.69 ± 0.89	0.273
PWV, m/s (mean ± SD)	9.96 ± 2.80	9.88 ± 2.30	10.01 ± 3.07	0.815

iPTH intact serum parathormone, *PWV* pulse-wave velocity, *IQR* interquartile rang

* According to Chi-square test, Student's t test or Mann–Whitney test where appropriate

[a] Average of three measurements in the first study year

[b] Calcium times phosphorus product

Table 2 Binary logistic regression analysis of relationship between the presence of calcification in AVF-blood vessels and baseline variables

Variable	OR	95% CI for OR	*P*
Gender	0.134	0.04–0.45	0.001
Diabetes mellitus, yes[a]	39.498	1.22–139.50	0.034
Hypertension, yes	2.624	0.92–8.03	0.071
Smoking, yes	0.857	0.239–2.949	0.786
Time from AVF creation till calcification determination, months	1.014	1.004–1.029	0.009
Age	0.99	0.926–1.077	0.903
Dialysis flow rate	0.992	0.977–1.016	0.729
iPTH	1.001	1.000–1.002	0.103
Ca	2.505	0.076–121.129	0.556
Phosphorus	1.004	0.265–6.025	0.769
PWV	1.081	0.850–1.322	0.603

iPTH intact serum parathormone, *Ca* calcium, *PWV* pulse-wave velocity

[a] DM diagnosis was assigned for randomly selected patient according to Yates correction

Table 3 Impact of calcification in AVF-blood vessels on AVF failure (Cox proportional analysis)

Calcification groups	*P*	HR	95% CI
w/o calcifications in AVF-blood vessels		1.00	
With calcification in AVF-blood vessels	0.049	3.42	1.00–11.67

Adjusted on propensity score (i.e., standardized predicted value; see Table 2)

HR hazard rate, *CI* confidence interval

after five years 75.9% AVFs were still functioning in the group of patients with AVF-blood vessels calcification and 88.9% in the other group.

Discussion

Since native vascular access is the recommended access by local, national and international guidelines, different causes that may affect the longevity of AVFs were studied [1, 23–26].

We previously published that overall vascular calcifications may have an effect on AVF survival [14]. This finding was based on analysis of several blood vessels, which was an extensive and time-consuming methodology [14, 20, 27]. In the light of the new knowledge about the process of calcification in the region of different blood vessels, we suggest an easier method to predict AVF survival by analyzing only calcification of the AVF-blood vessels by X-ray. It was already published that this calcification score of AVF-blood vessels predicts mortality in HD patients [20]. By current paper, using Cox regression analysis we documented that patients with AVF-blood vessels calcification had 3.42 higher risk to develop AVF failure in five years adjusted for male, presence of diabetes mellitus and AVF duration before calcification determination which were found to be independent variables that influence calcification presence. After five years, 88.9% AVF were still functioning in the group of patients w/o AVF-blood vessels calcification and 75.9% in the other group.

Deleterious effects of vascular calcification on AVF patency may be related to mechanical forces (such as wall shear stress and mechanical stretch) [28]. The mechanical stretch, produced by intraluminal pressure, acts on endothelial cells and also on smooth muscle cells leading to medial hyperplasia [29]. Wall shear stress (SS) is tangential force with low magnitude on the endothelium, and it was shown that SS induces an anti-proliferative and anti-inflammatory phenotype in endothelial cells [30–32]. Also, disturbed blood flow, which is seen in AVFs and possibly enhanced in calcified AVFs, promotes dysfunctional endothelial phenotypes inducing secretion of pro-inflammatory mediators such as nuclear factor-kappa B (NF-kB) and increasing the expression of genes related to oxidation and proliferation [9, 33, 34].

There are few studies that have tried to identify the effect of calcification on vascular access survival. Choi et al. included 114 patients undergoing an AVF operation during which they obtained arterial specimens to identify arterial microcalcification. They followed these AVFs for one year and concluded that the group with microcalcifications had a significantly lower AVF patency rate than patients without [15]. However, Allon et al. performed a similar study in 127 patients and concluded that arterial microcalcifications had no impact on AVF maturation, stenosis and time to first intervention [16]. Although our study used a different methodology, our data are in agreement with the Korean study. It is difficult to compare our data with that of Allon et al. since they have focused on short-term AVF events. Similar to our study, Georgiadis et al. searched for calcification by X-ray in forearms where AVF creation was planned in 72

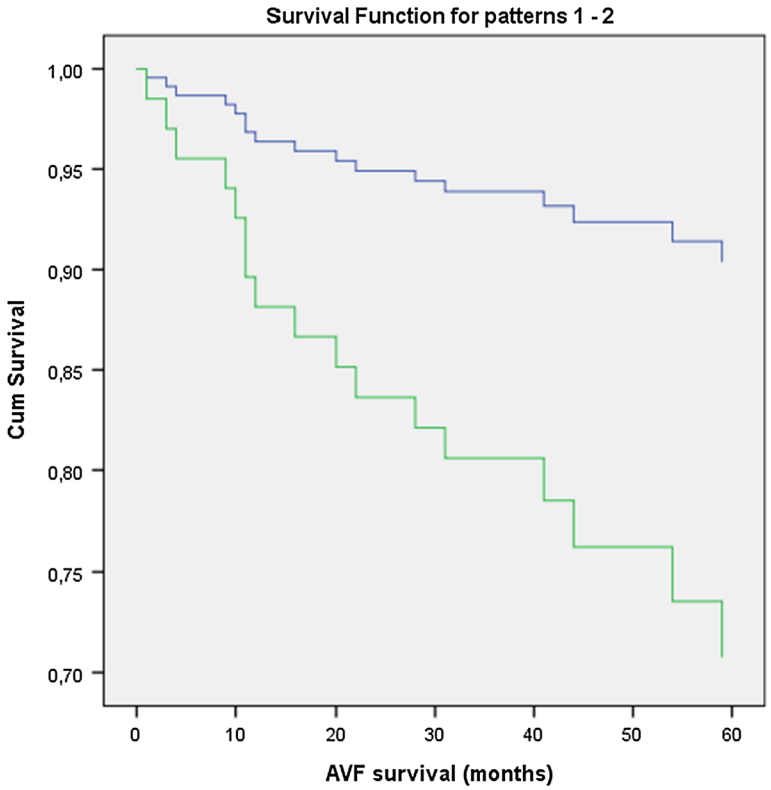

Fig. 2 Effect of calcification in AVF-blood vessels on AVF survival (Cox proportional analysis, censored for death and transplantation)

No of patients with functional AVF	Beginning of study	After 5 years follow-up
Group w/o VA calcification	36	32
Group with VA calcification	54	41

diabetic incident patients with ESRD. After four years of follow-up, they concluded that AVF survival was statistically lower in the group with preexistent calcification [17]. Our data extend these findings, given that we examined all patients regardless of the presence of diabetes.

We found that 62% of the patients had vascular access calcification, and this is more than in previous studies (Choi et al. 38%; Allon et al. 40%; Georgiadis et al. 54%). One explanation may be that our study included prevalent dialysis patients, whereas the previous three studies included incident patients. It is well known that calcification process progresses as dialysis vintage increases [35]. Also, it is worth mentioning that our patients use exclusively calcium-based phosphate binders, even above-recommended dose due to lack of non-calcium phosphate binders in our country.

Patients with calcification in the AVF-blood vessels did not have higher PWVs than patients without calcification. This suggests that the calcification of vascular accesses may precede and/or be independent of large artery calcification, probably due to very high and permanent shear stress and repeated puncturing.

All diabetic patients, and the majority of men, were in the group with a high prevalence of medial vascular calcification. Regardless of chronic kidney disease, vascular calcification is found more frequently in patients with diabetes and in males [36, 37]. Relatively small number of diabetic patients in our study group could be explained by the fact that we included prevalent patients with still-functioning primary AVF and diabetes mellitus has been already recognized as factor that shortens AVF patency [38].

The major limitation of the present study is the number of patients available for follow-up, but we selected only patients with primary AVFs. Our study would have been more reliable if we had followed incident instead of prevalent patients. However, the follow-up period of five years gives us a good insight into the role of vascular access calcification on AVF survival. Thus, patients with calcification of AVF-blood vessels should have more frequent follow-up of AVFs and closer adjustment of possible contributing factors.

The current study did not correlate AVF survival according to calcification grades because the overall number of patients was not sufficient for such detailed analysis. Finally, some additional risk factors that are not included in this study could be potentially important for AVF survival (comorbidity score, intradialytic hypotension, medications, biohumoral markers of endothelial damage, genetic milieu).

In conclusion, calcifications of AVF-blood vessels are found frequently among dialysis patients and may jeopardize the survival of native arteriovenous fistulas for hemodialysis. Our previous findings have shown that overall calcification score has impact on AVF failure [14]. Now, in this study, we suggested the local X-ray as simpler, less expensive, less harmful but valid method for detection of AVFs that are at risk of failure and that should be monitored more closely.

Compliance with ethical standards

Conflict of interest None.

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