Original research article

JVA The Journal of Vascular Access

Microcalcification in the arterial wall and its relationship to the ultrasound criteria of maturation of the arteriovenous fistula

The Journal of Vascular Access
1–6

DOI: 10.1177/1129729818775359
journals.sagepub.com/home/jva
SAGE

Weng Jun Tang[1], Azreen Syazril Adnan[2], Md Salzihan Md Salleh[3] and Arman Zaharil Mat Saad[1]

Abstract

Introduction: A functioning and reliable arteriovenous fistula is a lifeline for individuals suffering from chronic kidney disease. The success and failure to arteriovenous fistula maturation have been frequently related to patient and surgeon factors.

Method: In total, 138 participants with stage IV and V chronic kidney disease were included in this prospective observational study. Preoperative vascular mapping using ultrasound was performed to evaluate the condition and size of the vessels to fulfil the inclusion criteria. Intraoperatively, the vessel size was measured prior to anastomosis under magnified view. A specimen from the arterial wall of 5 mm in diameter was obtained from the arterotomy for histopathology assessment. Arteriovenous maturation was assessed at 6 weeks with the guidance of the ultrasound criteria of rule of sixes.

Results: From the total of 138 participants, 110 participants (79.7%) had matured arteriovenous fistula in 6 weeks. The mean size of the artery measured intraoperatively was 3.82 ± 1.33 mm and the vein was 4.05 ± 1.20 mm. Microcalcification in the arterial media which was hypothesised to be the cause of the arteriovenous fistula failure was insignificant, with a *p* value of 0.115. Despite having atherosclerosis in the artery, 83.3% of the arteriovenous fistula matured.

Conclusion: Microcalcification and atherosclerosis are frequently seen in the arteries of chronic kidney disease patients, but they do not explain arteriovenous fistula non-maturation.

Keywords

Arteriovenous fistula, chronic kidney disease, microcalcification

Date received: 11 November 2017; accepted: 11 April 2018

Introduction

A functioning and reliable arteriovenous fistula is a lifeline for every chronic kidney disease patient on regular haemodialysis treatment. The factors that determine the success or failure of the arteriovenous fistula maturation depend on the patient and surgeon.

Based on previous studies, it was discovered that 20%–50% of arteriovenous fistula had failed to mature.[1,2] This failure rate is alarming. To overcome the obstacle of non-maturation of arteriovenous fistula, research has shifted to the haemodynamic, anatomic, molecular and functional levels of the arteriovenous fistula creation.[3,4] The artery is important for providing sufficient blood flow through the fistula circuit, while the vein is the ultimate determinant used to assess the outcome of the arteriovenous fistula based on its size and rate of blood flow within it.

It has been shown that vascular calcifications mainly occur at the large elastic arteries and are commonly associated with ischaemic cardiac events and mortality.[5] Vascular calcification will either narrow the lumen of the artery

[1]Reconstructive Sciences Unit, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia
[2]Chronic Kidney Disease Resource Centre, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia
[3]Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia

Corresponding author:
Arman Zaharil Mat Saad, Reconstructive Sciences Unit, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan 16150, Malaysia.
Email: armanzaharil@gmail.com

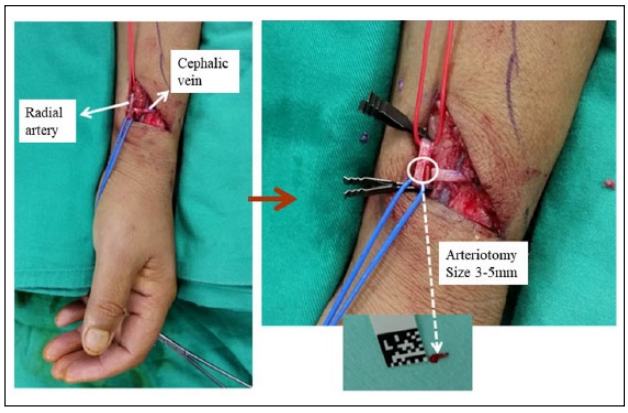

Figure 1. Arterial wall sampling during arteriovenous fistula creation.

leading to reduced blood flow which will cause ischaemia and infarction, or lead to an increase in stiffness of the artery causing poor dilatation and, thereby, inducing left ventricular hypertrophy, coronary hypoperfusion and failure of arteriovenous fistula to mature.[6,7]

We aim to evaluate the association between the presence of microcalcification in the intima–media of the arterial wall and arteriovenous fistula maturation. By assessing the vasculature histopathology, it has been postulated that microcalcification in the tunica intima and tunica media of the artery plays a role in arteriovenous fistula failure.

Method

An observational prospective cohort study was accomplished to evaluate the influence of histopathological findings of the arterial wall on the maturation of the arteriovenous fistula. This study was conducted under the Reconstruction Sciences Unit, Universiti Sains Malaysia, Kelantan from 1 March 2016 to 28 February 2017. In total, 138 participants with chronic kidney disease stages IV and V were scheduled for an elective autogenous arteriovenous fistula creation. Inclusion criteria for this study were vein and artery with a diameter of more than 2 mm and arteriosclerosis occlusion less than three quarter of the arterial lumen.

Preparation of participants

Preoperatively, participants who had consented to this study were clinically examined by the same single operating surgeon by checking the peripheral arterial pulsation noting strong or diminished character and the peripheral venous assessment of its patency, linear segments and engorged veins. Vascular mapping was performed using Doppler ultrasound to measure the vein and artery diameter which needs to be more than 2 mm to be included in this study. Vessels which were occluded or arteries with very dense arteriosclerotic plaque were omitted from this study. Participants who had consented were admitted to the surgical ward a day prior to the surgery. Arteriovenous fistula creations were done under local anaesthesia (by the surgeon) or regional block (by the anaesthetist) in the operation theatre.

Intraoperative

The chosen artery and vein were carefully dissected in a magnified view. A segment of arterial wall was excised under magnified view by cutting out 5 mm in diameter of the arterial wall in a circular shape and full thickness to facilitate an end-to-side anastomosis of the vein to artery (Figure 1). Sizes of the chosen vessels and arterotomy were measured intraoperatively in millimetres using a ruler before anastomosis. End-to-side anastomosis with interrupted 8/0 polypropylene was constructed under magnified view. Success of the anastomosis was determined by the presence of thrill on palpation of the vein at about 1–2 cm from the anastomosis site prior to the closure of the skin with nylon 4/0 suture.

Laboratory

The arterial wall specimen was put into formalin and sent to the histopathology laboratory to be processed and analysed. Histopathology of the arterial wall was analysed using a light microscope (Olympus BX51 UL 10×/0.30∞/-/FN26.5) where the clinical data of the patient were not revealed during the analysis to avoid bias.

The specimen was cut into 5-µm sections and stained with haematoxylin and eosin, Verhoeff–van Gieson and von Kossa staining. Verhoeff–van Gieson staining was performed to delineate the intima by enhancing the elastic lamina which outlines the border between the intima and media layers. Although microcalcification can be observed using haematoxylin and eosin staining, in this study, we added von Kossa staining to optimise visualisation of the microcalcifications as it is more specific for this mineral (Figure 2). Microcalcification may be present in both intima and media layers of the arterial wall.

Postoperative

Follow-ups of the patient at 2, 6 and 10 weeks were conducted to check for arteriovenous fistula complications and maturity of the fistula by feeling the intensity and presence of the thrill and confirming by Doppler ultrasound. Maturation assessment of the fistula is according to the National Kidney Foundation's KDOQI Clinical Practice Guidelines.[8] A matured arteriovenous fistula is when 6 cm of the straight segment of vein for cannulation is 6 mm in diameter, located less than 6 mm from the skin surface and with a 600 mL/min of blood flow. Outcomes of

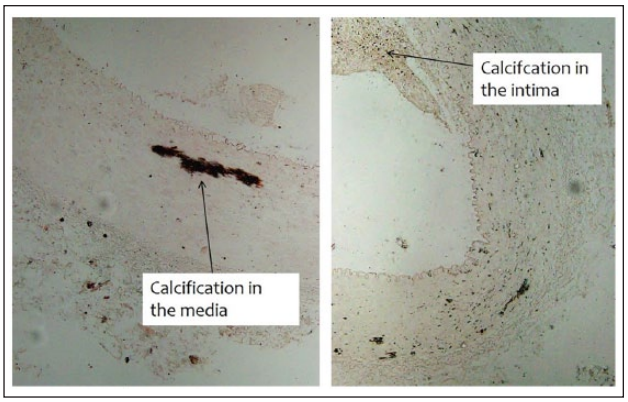

Figure 2. Calcification in the tunica media and tunica intima of the arterial wall.

the fistula were measured by the operating surgeon who is experienced in using a non-invasive ultrasound system (SonoSite TITAN® high-resolution ultrasound system) provided with an L38 transducer (10–5 MHz linear ultrasound transducer). If the fistula is matured at 6 weeks, it is classified as a matured fistula and the patient is allowed for trial of haemodialysis. If the fistula is not matured after 6 weeks, it is classified as a failed fistula.

Statistical analysis

Data were compiled and recorded on a spreadsheet using IBM SPSS version 22.0. To provide a statistical power of 80% to show a significant ($p < 0.05$) difference, we needed to enrol 132 participants. The collected demographic data were presented in numbers and percentages, with age in mean and standard deviation. Pearson's chi-square and multiple logistic regression were employed in this analysis. The p values < 0.05 were considered statistically significant in this study.

Results

This study consisted of 138 participants with chronic kidney disease stages IV and V undergoing placement of an arteriovenous fistula. Mean age of participants was 57.09 ± 11.71 (range 35–70 years) with an almost equal number of males ($n = 74$) and females ($n = 64$). In total, 69% of participants had arteriovenous fistula created after haemodialysis initiation, either through their previous functioning arteriovenous fistula or central venous catheter. And 78% of participants (with male dominating by 58%) have concomitant of two or three medical illnesses such as diabetes mellitus, hypertension and coronary heart disease (Table 1).

Of the 138 participants, 110 (79.7%) had arteriovenous fistula maturation within 6 weeks, while 28 (20.3%) had failed arteriovenous fistula. There was a higher success rate of maturation when arteriovenous fistula is created on the upper arm (93%) as compared to the forearm (70.4%).

Table 1. Demographic data.

Mean age	57.09 + 11.71
Gender	
Male	74 (53.6)
Female	64 (46.4)
Ethnics	
Malay	135 (97.8)
Chinese	3 (2.2)
Medical illness	
Diabetes mellitus	99 (71.7)
Hypertension	132 (95.7)
Coronary heart disease	29 (21)
Others	29 (21)
Chronic kidney disease	
Stage 4	26 (18.8)
Stage 5	112 (81.2)

Age is shown as mean ± standard deviation. Categorical variables are shown as number (percentage).

In this study, 60.9% of participants had no microcalcification in the tunica intima and media. On the contrary, 3.6% of participants had microcalcification detected in both tunica intima and media, while 8.7% had tunica media microcalcification only. Despite having tunica media microcalcification, 16 (94.5%) out of 17 arteriovenous fistula creations matured (Table 2). In addition to it, 35 (83.3%) out of 42 arteriovenous fistula creations matured despite having arteriosclerosis.

There was no significant difference in participants with diabetes mellitus and non-diabetes mellitus to have microcalcification in the arterial wall ($p = 0.147$). Diabetes mellitus participants were observed to have developed microcalcification in the arterial wall in only 14.1% and the remaining 85.9% did not develop microcalcification in the arterial wall ($p = 0.299$; Table 3). Microcalcification in the arterial wall was also insignificant in those with hypertension ($p = 0.740$; Table 3).

Table 4 presents the diameters of both artery and vein that were measured intraoperatively. Arteriovenous fistula is likely to mature ($p = 0.013$) when the mean value of the arterial internal diameter is 3.97 ± 1.34 mm (range 2.5–5.5 mm). Mean size of the brachial artery is larger than that of the radial artery (Table 5). The mean value of the vein's internal diameter was insignificant between the matured (3.47 ± 1.06 mm) and the failed arteriovenous fistulae (3.16 ± 1.06 mm; $p = 0.169$, range 2–5.5 mm). The created upper arm arteriovenous fistula had a higher tendency of up to 93% to mature compared to the forearm arteriovenous fistula (70.4%; $p = 0.001$).

Discussion

The success rate of arteriovenous fistula maturation of 79.9% in this study was in keeping with the reported success rate in the recent literature of 50%–80%.[7] Although

Table 2. Pathologic features and maturation outcomes.

	Arteriovenous fistula maturation		
	Matured AVF, *N* (%)	Failed AVF, *N* (%)	*p* value
Calcification			
Present	16 (94.5)	1 (5.9)	0.115
Absent	94 (77.7)	27 (22.3)	
Arteriosclerosis			
Present	35 (83.3)	7 (16.7)	0.484
Absent	75 (78.1)	21 (21.9)	
Diabetes mellitus			
Present	82 (82.8)	17 (17.2)	0.147
Absent	28 (71.8)	11 (28.2)	
Hypertension			
Present	26 (19.7)	106 (80.3)	0.417
Absent	2 (33.3)	4 (66.7)	
Placement of arteriovenous fistula			
Forearm	57 (70.4)	24 (29.6)	0.001
Upper arm	53 (93.0)	4 (7.0)	

AVF: arteriovenous fistula.
Results are shown as number (percentage).

Table 3. Pathologic features and microcalcification.

	Microcalcification		
	Present, *N* (%)	Absent, *N* (%)	*p* value
Arteriosclerosis			
Present	5 (11.9)	37 (88.1)	0.922
Absent	12 (12.5)	84 (87.5)	
Diabetes mellitus			
Present	14 (14.1)	85 (85.9)	0.299
Absent	3 (7.7)	36 (92.3)	
Hypertension			
Present	16 (12.1)	116 (87.9)	0.740
Absent	1 (16.7)	5 (83.3)	

Results are shown as number (percentage).

microcalcification in the tunica media or tunica intima was postulated to be a factor causing failure of arteriovenous fistula maturation, it was insignificant in this study. Despite the detection of microcalcification in the arterial wall, most of the arteriovenous fistula had matured according to the guidelines by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI). Arteriovenous fistula maturation was seen in 83.3% of artery with tunica intima microcalcification and 94.5% of artery with tunica media microcalcification.

In Allon et al.'s[3] series of 50 participants, it was demonstrated that there was a trend for microcalcification in non-maturing fistulas. Conversely, in this study with a larger sample size of 138 participants, microcalcification did not contribute to arteriovenous fistula non-maturation. Diabetes mellitus, in addition to chronic kidney disease, patients were frequently classified as poor candidates for placement of arteriovenous fistulae but in our study and in the study by Sedlacek et al.[9] evidence of successful arteriovenous maturation up to 82% and 70%, respectively, was reported. In total, 71% of arteriovenous fistula failure in this study was observed in patients with more than two comorbidities, in addition to chronic kidney disease, with or without microcalcification in the arterial wall.

Chronic kidney disease patients who had undergone long-term haemodialysis stand a higher chance of developing microcalcification in the arterial wall. Hyperuricaemia in a chronic kidney disease patient and the content of the dialysate during haemodialysis increase the precipitation of calcium into the arterial wall.[10] In addition, arterial wall microcalcification is commonly associated with long-standing diabetes mellitus and hypertension.[11] Despite all these, there was no significance seen in this study with only 14.1% of diabetes mellitus participants and 12.1% of hypertensive participants developing microcalcifications in the arterial wall of the small vessels of the upper limb. There may be an argument stating the presence of a selection bias in this study as all the participants will undergo a preoperative vascular mapping to decide on the best arteriovenous fistula creation site and the presence or absence of microcalcification is based on intraoperative and histopathology findings.

Studies have shown that microcalcifications in the artery were mainly in the large-calibre arteries which are up to four times as compared to the medium- and small-calibre arteries.[12] Tunica media of the large arteries such as the aorta and iliac arteries constitute predominantly of elastic fibres, while tunica media of the medium and small

Table 4. Vessel size and its influence on maturation of the fistula.

	Maturation		
	Matured AVF	Failed AVF	*p* value
Artery internal diameter (mm)	3.97 ± 1.34	3.25 ± 1.13	0.013
Arterotomy (mm)	4.17 ± 0.81	3.82 ± 0.84	0.040
Vein internal diameter (mm)	3.47 ± 1.06	3.16 ± 1.06	0.169

AVF: arteriovenous fistula.
Results are shown as mean ± standard deviation.

Table 5. Upper limb vessel sizes.

Location of vessel	Mean size (mm)
Forearm artery	3.08 ± 0.86
Forearm vein	3.10 ± 0.95
Upper arm artery	4.89 ± 1.15
Upper arm vein	3.84 ± 1.09

Results are shown as mean ± standard deviation.

arteries such as brachial, radial and digital arteries constitute mainly smooth muscles.[12] The differences of arterial wall structure of the large, medium and small arteries contribute to the functional changes in the vessel, thus predisposing the large-calibre arteries to be more prone to microcalcification. Microcalcification may be solely present in the tunica media or may be detected in both tunica intima and media.[13] Tunica intima microcalcification is mainly due to atherosclerotic plaques which may lead to ischaemia-related occlusion.[10] Tunica media microcalcification (also known as Monckeberg's sclerosis) is when the tunica media wall of the artery is calcified independently of atherosclerosis, and it was reported to be found in 14%–23% of haemodialysis patients.[14–16] Arteries with tunica media microcalcification will be stiffer, causing them to poorly dilate and, thereby, affecting the maturation of the fistula.[17] In this study, 6% of the participants presented with microcalcification in the tunica media wall of the artery independently of atherosclerosis which is lower than the number reported by Georgiadis et al.

Preoperative vessel mapping is important to measure the diameter of the vessels and to ensure their patency. The present guideline of the artery size of more than 2 mm is important and plays a main role in arteriovenous fistula maturation.[18] In one of the meta-analysis findings, it was documented that the artery diameter of less than 2 mm has a 40% chance of arteriovenous fistula maturation, while, when the size is more than 2 mm, 59% of the arteriovenous fistula will mature.[18] Internal diameter of the artery is usually smaller than that of the vein. Therefore, the main source of vascular resistance in a newly created fistula is usually the artery. The mean value of the artery's internal diameter is 3.83 ± 1.33 mm in this study, which was above the recommended value. This may be one of the factors contributing to arteriovenous fistula maturation despite having microcalcification in the arterial wall. As for the vein, the mean value of the vein's internal diameter in this study is 3.41 ± 1.07 mm which is also above the recommended value. Meta-analysis findings of the vein diameter to attain fistula maturation are less than 2 mm (29%) and more than 2 mm (71%).[18]

In addition, there is a higher chance of maturation in the upper arm arteriovenous fistula creation of up to 93% as compared to the distal forearm, that is, 70.4%. This could be explained based on Poiseuille's law $Q=\pi Pr^{4/8\eta l}$ where the flow is related to the pressure gradient across the vessel and its diameter.[19] In the upper arm, the pressure gradient is higher and the internal diameter of the artery is larger than that in the distal forearm. Due to larger artery internal diameter and higher pressure gradient in the upper arm, the vein could adequately dilate to allow the increase of blood flow required for maturation of the fistula. In order to not exhaust all possible locations for an arteriovenous fistula creation, distal forearm arteriovenous fistula creation proposed by Brescia[8] in 1966 still remains the gold standard.

In the presence of microcalcification, the flow could be affected as the artery will be either stiffer or partially occluded. However, if the internal diameter of the artery is more than 2.5 mm, the predicted blood flow would be adequate without the need for further expansion as reported by Kheda et al.[20] They addressed the issue by observing the relationship between vessel diameters, blood flow and circuit pressure. Artery diameter in the range of 2.5–5.0 mm is predicted to have a flow of 400–500 mL/min where the dilatation of artery is not required in attaining arteriovenous fistula maturation.[20] In keeping with the study by Kheda et al., the internal diameter of the artery in this study ranges from 2.5 to 5.5 mm (3.83 ± 1.33) which explained the reason for the maturation of the arteriovenous fistula despite the presence of microcalcification.

We had a few possible explanations contributing to the high success rate of arteriovenous fistula maturation despite microcalcifications in the arterial wall. First, careful selection of participants and preoperative evaluation of the vasculature quality and mapping played an important role. Second, vascular samples obtained may be too small to represent the entire artery. Third, population is heterogeneous with different anastomosis sites and comorbidities.

Fourth, the surgeon's skilful techniques may increase the success rate of arteriovenous fistula maturation.

Microcalcification, in this study, was difficult to be scored semi-quantitatively on a scale, as reported by Allon et al.,[3] and was therefore documented as present or absent. Microcalcification of the artery was seen as either scattered or concentrated in an area. Artery that is very calcified or stiff is excluded from arteriovenous fistula creation, as the failure rate is known to be high and it will compromise the chances of having a functional and matured arteriovenous fistula at the earliest possible time. In addition to it, arterotomy which was done may not have included the actual amount of microcalcification of the entire artery and placement will be at the arterial wall where there is no or very little arteriosclerotic plaque. Therefore, a whole circular artery should be taken to be analysed to give a more accurate finding which is not feasible in this study where the arteriovenous fistula creation was performed at end of the vein to the side of the artery. These are the bias and difficulties that were faced in this study.

In summary, microcalcification in the tunica intima and media of the artery does not affect the maturation of the arteriovenous fistula. Careful patient selection, excellent surgical skill and preoperative evaluation of vascular anatomy greatly contribute to the success rate of an arteriovenous fistula creation.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

JEPeM code: USM/JEPeM/15110481 (March 2016–February 2017)

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was made possible by the ethical approval (USM/JEPeM/15110481) and funding support from the Universiti Sains Malaysia short term grant (304/PPSP/61313172).

Informed consent

Informed consent and photo consent were obtained from the participants included in the study.

References

1. Asif A, Roy-Chaudhury P and Beathard GA. Early arteriovenous fistula failure: a logical proposal for when and how to intervene. *Clin J Am Soc Nephrol* 2006; 1(2): 332–339.
2. Sahasrabudhe P, Dighe T, Panse N, et al. Prospective long-term study of patency and outcomes of 505 arteriovenous fistulas in patients with chronic renal failure: authors experience and review of literature. *Indian J Plast Surg* 2014; 47(3): 362–369.
3. Allon M, Litovsky S, Young CJ, et al. Medial fibrosis, vascular calcification, intimal hyperplasia, and arteriovenous fistula maturation. *Am J Kidney Dis* 2011; 58(3): 437–443.
4. Masengu A, Maxwell AP and Hanko JB. Investigating clinical predictors of arteriovenous fistula functional patency in a European cohort. *Clin Kidney J* 2016; 9(1): 142–147.
5. Schlieper G, Schurgers L, Brandenburg V, et al. Vascular calcification in chronic kidney disease: an update. *Nephrol Dial Transplant* 2016; 31: 31–39.
6. London GM, Guérin AP, Marchais SJ, et al. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; 18(9): 1731–1740.
7. Dixon B. Why don't fistulas mature? *Kidney Int* 2006; 70(8): 1413–1422.
8. Brescia MJ, Cimino JE, Appel K, et al. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *New England Journal of Medicine* 1966; 275(20): 1089–1092.
9. Sedlacek M, Teodorescu V, Falk A, et al. Hemodialysis access placement with preoperative noninvasive vascular mapping: comparison between patients with and without diabetes. *Am J Kidney Dis* 2001; 38(3): 560–564.
10. Jono S, Shioi A, Ikari Y, et al. Vascular calcification in chronic kidney disease. *J Bone Miner Metab* 2006; 24(2): 176–181.
11. Boström KI. Where do we stand on vascular calcification? *Vascul Pharmacol* 2016; 84: 8–14.
12. Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, et al. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. *Nephrol Dial Transplant* 2009; 24(1): 239–246.
13. Drüeke TB. Arterial intima and media calcification: distinct entities with different pathogenesis or all the same? *Clin J Am Soc Nephrol* 2008; 3(6): 1583–1584.
14. Georgiadis GS, Georgakarakos EI, Antoniou GA, et al. Correlation of pre-existing radial artery macrocalcifications with late patency of primary radiocephalic fistulas in diabetic hemodialysis patients. *J Vasc Surg* 2014; 60(2): 462–470.
15. Floege J and Ketteler M. Vascular calcification in patients with end-stage renal disease. *Nephrol Dial Transplant* 2004; 19(Suppl. 5): V59–V66.
16. Schlieper G, Krüger T, Djuric Z, et al. Vascular access calcification predicts mortality in hemodialysis patients. *Kidney Int* 2008; 74(12): 1582–1587.
17. Guérin AP, London GM, Marchais SJ, et al. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 2000; 15(7): 1014–1021.
18. Smith GE, Gohil R and Chetter IC. Factors affecting the patency of arteriovenous fistulas for dialysis access. *J Vasc Surg* 2012; 55(3): 849–855.
19. Paulson WD and Jones SA. Hemodynamics of the hemodialysis access: implications for clinical management. *Contrib Nephrol* 2004; 142: 238–253.
20. Kheda MF, Brenner LE, Patel MJ, et al. Influence of arterial elasticity and vessel dilatation on arteriovenous fistula maturation: a prospective cohort study. *Nephrol Dial Transplant* 2010; 25: 525–531.