Medial Fibrosis, Vascular Calcification, Intimal Hyperplasia, and Arteriovenous Fistula Maturation

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Abstract

Background—Arteriovenous fistulas (AVF) for hemodialysis frequently fail to mature due to inadequate dilation or early stenosis. The pathogenesis of AVF non-maturation may be related to preexisting vascular pathology: medial fibrosis or micro-calcification may limit arterial dilation, and intimal hyperplasia may cause stenosis.

Study design—Observational study.

Setting & Participants—Chronic kidney disease patients (N=50) undergoing arteriovenous fistula (AVF) placement.

Predictors—Medial fibrosis, microcalcification, and intimal hyperplasia in arteries and veins obtained during AVF creation.

Outcome and Measurements—AVF non-maturation.

Results—AVF non-maturation occurred in 38% of patients despite attempted salvage procedures. Preoperative arterial diameter was associated with upper arm AVF maturation (p=0.007). Medial fibrosis was similar in patients with non-maturing and mature AVFs (60±14 vs 66±13%, p=0.2). AVF non-maturation was not associated with patient age or diabetes, even though both variables were significantly associated with severe medial fibrosis. Conversely, AVF non-maturation was higher in females than males, despite similar medial fibrosis in both sexes. Arterial micro-calcification (assessed semi-quantitatively) tended to be associated with AVF non-maturation (1.3±0.8 vs 0.9±0.8, p=0.08). None of the arteries or veins obtained at AVF creation had intimal hyperplasia. However, repeat venous samples obtained in 6 patients during surgical revision of an immature AVF exhibited venous neointimal hyperplasia.

Limitations—Single center study.

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Conclusion—Medial fibrosis and micro-calcification are frequent in the arteries used to create AVFs, but do not explain AVF non-maturation. Unlike previous studies, intimal hyperplasia was not present at baseline, but developed *de novo* in non-maturing AVFs.

A reliable vascular access is critical for delivery of adequate hemodialysis in patients with end-stage renal disease. The National Kidney Foundation KDOQI (Kidney Disease Outcomes Quality Initiative) vascular access guidelines, most recently updated in 2006, strongly recommend maximizing arteriovenous fistula (AVF) use in all patients with suitable vascular anatomy (1). Achieving this goal entails a number of intermediate steps, including pre-ESRD care by a nephrologist, pre-ESRD access surgery, adequate AVF maturation, and successful AVF cannulation by the dialysis staff (2). An unanticipated byproduct of aggressive AVF placement is the high proportion of AVFs that fail to mature, i.e., are not suitable for dialysis. Whereas 25–30 years ago, only about 10% of new AVFs failed to mature (3–5), in subsequent years, this proportion has risen to 20–50% (2). In a recent multi-center, randomized clinical trial of 877 subjects, AVF non-maturation occurred in 60% of patients (6). Thus, AVF non-maturation has emerged as the major obstacle to increasing AVF use in dialysis patients.

A better understanding of the pathogenesis of AVF non-maturation is imperative to achieve the KDOQI AVF goals (7). AVFs are created by a direct anastomosis between a native artery and vein. Sonographic preoperative vascular mapping is widely promoted to identify vessels suitable for AVF creation, by setting minimum vascular diameters and ensuring vessel patency (2). Although preoperative mapping increases AVF placement, it does not decrease AVF non-maturation (6, 8–11). This disappointing outcome suggests the existence of additional vascular properties affecting AVF immaturity that are not measured by standard preoperative ultrasound mapping.

Following creation of a successful AVF, the arterial blood flow increases 10–20 fold (7). This increase in blood flow is associated with arterial and venous dilation. Progress in elucidating AVF non-maturation has been hampered by our lack of understanding of intrinsic vascular abnormalities that impair vascular dilation. A plausible hypothesis is that pre-existing abnormalities in the artery or vein used to create an AVF may impede AVF maturation. Specifically, medial fibrosis or micro-calcification may limit arterial dilation (12), and intimal hyperplasia may cause stenosis (13). However, there is limited published evidence to address these hypotheses. A pilot study from Korea described the frequent occurrence of intimal hyperplasia in the arteries used to create AVFs, and the presence of intimal hyperplasia was associated with decreased AVF survival (14). Two small studies reported frequent intimal hyperplasia in the veins used for AVF creation, but did not correlate this pathologic finding with AVF maturation (15, 16).

The goal of the present study was to evaluate the potential impact of preexisting vascular abnormalities on AVF outcomes. Specifically, we postulated that preexisting medial fibrosis, micro-calcification and intimal hyperplasia are predictive of AVF non-maturation. To test these hypotheses, we obtained arterial and venous specimens from chronic kidney disease patients undergoing AVF surgery, and correlated the pathologic abnormalities with AVF outcomes. Additionally, in a subset of patients undergoing subsequent surgical revision of a non-maturing AVF, vein specimens were obtained and compared with those obtained at initial AVF creation.

Methods

Overview of study design

CKD patients scheduled for creation of a new AVF were invited to participate in this prospective observational study, which had been approved by our local Institutional Review Board. Preoperative duplex ultrasound was performed to measure arterial and venous diameters, and to exclude stenosis or thrombosis in the draining veins. At the time of AVF creation, the surgeon obtained specimens of the artery and vein. A pathologist who was unaware of the patients' clinical information assessed the specimens for arterial medial fibrosis and micro-calcification and for arterial or venous intimal hyperplasia. AVF suitability for dialysis within 6 months of AVF creation was determined clinically. Finally, we determined the predictive value of arterial medial fibrosis and micro-calcification for AVF non-maturation in our patient population. In a subset of patients who underwent surgical revision of the anastomosis because of AVF non-maturation, the surgeon obtained a specimen of the AVF draining vein from the site of the new anastomosis, slightly proximal to the initial anastomotic site.

Study population

The University of Alabama at Birmingham (UAB) provides medical care for approximately 500 hemodialysis patients. Ten clinical nephrologists, who are full-time members of the UAB Division of Nephrology, provide medical care to these patients. Almost all patient hospitalizations, surgical procedures, and radiologic procedures occurred at UAB Hospital. Four transplant and vascular access surgeons performed the initial access surgery, as well as subsequent surgical revisions. Members of the Department of Radiology performed radiologic diagnostic tests and interventions for dialysis access. All clinical information, including hospital discharge summaries, clinic notes, and surgical and radiologic reports, was available on an electronic medical record. Patients scheduled for a new AVF were invited to participate in this study. About 90% of the patients approached agreed to enroll in the study.

Preoperative vascular mapping

All patients underwent sonographic preoperative vascular mapping according to the standard UAB protocol (2, 8, 17). Vascular measurements were performed with the patient in a seated position, and the arm resting comfortably on an adjustable instrument stand. Arterial diameters were measured at the radial artery in the wrist and the brachial artery in the antecubital fossa. A tourniquet was moved sequentially up the arm to measure venous diameters at several locations in the forearm and the upper arm, and to evaluate for venous stenosis or thrombosis. Venography was obtained in selected patients with clinical suspicion of central vein stenosis. All measurements were recorded on a worksheet, which was provided to the surgeon prior to the patient's preoperative visit. Creation of an AVF required a minimum arterial diameter of 2 mm and a minimum venous diameter of 2.5 mm. If there were no suitable vessels for creation of a forearm AVF, the surgeon created an upper arm AVF, if possible.

Surgical procedure

The transplant surgeons placed three types of upper extremity AVFs, depending on the findings of the preoperative ultrasound: a radiocephalic (wrist) AVF, a brachiocephalic AVF, and a transposed brachiobasilic AVF. AVFs were created by performing a direct anastomosis between the side of the artery and the end of the vein. The surgeon obtained small specimens of the artery and vein used to create the AVF prior to performing the anastomosis. Specifically, these included a circumferential section of the vein, and a partial

(elliptical) section of the artery. Obtaining these samples was feasible in >90% of patients, and did not result in any postoperative complications. Rarely, the artery was too small for the surgeon to obtain a sample. Six patients with non-maturing AVFs and a peri-anastomotic stenosis underwent a subsequent surgical revision, at which time the surgeon obtained a specimen of the AVF draining vein at the site of new anastomosis, which was slightly proximal to the prior anastomosis for pathologic examination.

Pathologic studies on vascular specimens

Cross-sections of the arterial and venous samples were fixed in 10% neutral-buffered formalin and processed for light microscopy. A pathologist (S.L.) who was unaware of the clinical information and AVF outcomes performed all the histologic evaluations. All tissue samples were stained with H&E, and assessed for arterial medial fibrosis and arterial and venous intimal hyperplasia. Trichrome stains were performed to optimize visualization of medial fibrosis, with collagen staining blue and smooth muscle cells staining red. Medial fibrosis was quantified from the Trichrome stain of the entire arterial specimen, by using Bioquant Image Analysis® (Nashville, TN) to calculate the percent of the vascular specimen staining blue. The internal elastic lamina demarcates the border between intima and media, and is usually seen well on H&E staining. In selected cases, an elastic stain was also performed to better delineate the intima. The thickness of the vascular layer on the luminal side of the internal elastic lamina was used to assess intimal hyperplasia. Finally, a von Kossa stain was used to detect medial micro-calcification, which was graded by the pathologist on a semi-quantitative scale (0=none; 1 =mild; 2=moderate; 3=severe). The same pathologist also performed pathologic evaluation of the specimens of the AVF draining vein from the patients undergoing AVF surgical revision.

Determination of AVF suitability for dialysis

AVF suitability for hemodialysis was defined as the ability to cannulate the AVF with 2 needles with a dialysis blood flow ≥300 ml/min for at least 6 dialysis sessions in 1 month, and within 6 months of AVF creation (18). AVF's were deemed as unsuitable for dialysis if they failed to achieve these criteria despite attempted salvage procedures to promote maturation. For those patients who had not initiated dialysis within 6 months of AVF creation, AVF suitability was determined in the first month after dialysis was started. This definition has been validated repeatedly at UAB (2), and is similar to that used in a recent multi-center study (6).

Statistical analysis

We assumed an AVF non-maturation rate of 50% in patients with arterial medial fibrosis and 25% in those without arterial medial fibrosis. In order to provide a statistical power of 80% to demonstrate a significant (p<0.05) difference between the 2 groups, we needed to enroll a total of 45 subjects. Clinical, sonographic, and pathologic features were compared between patient subgroups using unpaired t-tests for continuous variables and Chi-square analysis for categorical variables. A p value < 0.05 was considered statistically significant.

Results

Our study consisted of 50 CKD patients undergoing placement of a new AVF. Among these 50 study patients, 19 (or 38%) had AVF non-maturation, whereas 31 (or 62%) had their AVF used successfully for dialysis at a median of 81 days following AVF creation. Those with non-maturing AVFs were more likely to be female, but were similar in age, race, diabetes, hypertension, vascular disease, congestive heart failure, and AVF location to patients whose AVF matured (Table 1). Almost 60% (29 of 50) AVFs were placed after initiation of dialysis, including 18 placed within the first year and 11 placed at later time

periods. The preoperative arterial and venous diameters did not differ significantly between non-maturing and mature AVFs among those patients receiving a forearm AVF (Table 2). The preoperative arterial diameters were significantly smaller for upper arm fistulas that failed to mature, as compared with those that matured (but still substantially greater than the minimal 2 mm diameter required by our protocol). However, the venous diameters were similar in both groups of patients receiving an upper arm fistula.

We did not observe intimal hyperplasia in any of the arterial specimens (Fig 1A,B). In contrast, medial fibrosis of varying degrees was observed in all the arterial specimens obtained at the time of AVF creation. Medial fibrosis was quantified from the trichrome stains of the arteries (Fig 1C,D). The mean medial fibrosis for the study population was $64 \pm 14\%$ (range, 32 to 90%), and did not differ significantly between non-maturing and mature AVFs (Table 3). Arteries with ≥70% medial fibrosis were classified as having severe medial fibrosis. The proportion of patients with severe medial fibrosis did not differ between those with mature AVFs and those with non-maturing AVFs. The frequency of severe medial fibrosis was greater in older patients and those with diabetes, but was not associated with sex, race, hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, or AVF location (Table 4).

About two-thirds of the patients had arterial micro-calcification, but the proportion did not differ significantly between those with mature and non-maturing AVFs (Table 3). The magnitude of micro-calcification was scored semi-quantitaively on a scale of 0 to 3 (Fig 2A,B). The mean micro-calcification score was similar for arteries with severe medial fibrosis and those with milder medial fibrosis (1.2 ± 0.9 vs 1.0 ± 0.7; p=0.6). There was no significant difference in the micro-calcification scores in patients with mature and non-maturing AVFs, although there was a trend (p=0.08) for greater micro-calcification in the non-maturing AVFs (Table 3).

None of the 50 venous samples obtained at AVF creation had evidence of significant intimal hyperplasia (Fig 2C). In six patients with non-maturing AVFs we obtained venous samples contiguous to the AVF anastomosis both at the time of AVF creation, and again 58 to 204 days later, when the AVF was surgically revised (without a prior angioplasty). These six patients had an anastomotic stenosis, and had not undergone AVF angioplasty or cannulation prior to the surgical revision. All 6 patients were female, 3 had diabetes, their ages ranged from 33 to 76, 2 had >70% arterial medial fibrosis, and 2 had arterial micro-calcification. Postoperative histology of the draining veins of non-maturing AVFs revealed severe neointimal hyperplasia in each case (Fig 2D), which had not been present in the venous sample obtained at the time of AVF creation.

Discussion

Our study documented a high frequency of medial fibrosis in arteries used to create AVFs in CKD patients. This observation is in keeping with a previous study documenting extensive medial fibrosis in CKD patients, which is present in multiple vascular beds (12). Successful maturation of AVFs requires arterial dilation (7). Severe medial fibrosis may limit arterial dilation by increasing arterial stiffness, since collagen is less distensible than smooth muscle (19). On the basis of these observations, we had postulated that severe arterial medial fibrosis would be associated with AVF non-maturation. Contrary to our hypothesis, severe medial fibrosis was not associated with AVF non-maturation. In fact, there was a total disconnect between medial fibrosis and AVF outcomes. AVF non-maturation was not associated with patient age or diabetes, even though both variables were associated with severe medial fibrosis. Conversely, AVF non-maturation was higher in females than males, despite very similar degrees of severe medial fibrosis in both sexes. Although the

preoperative arterial diameters were higher in patients with a mature upper arm AVF, this difference is unlikely to explain AVF maturation (11).

Why might medial fibrosis not be associated with AVF non-maturation? We propose three possible explanations. First, the vascular samples obtained might be too small to be representative of the entire artery used for AVF creation. Second, there could be alternative etiologies of increased arterial stiffness causing AVF non-maturation in our study population. Thus, for example, differences in vascular reactivity, genetic polymorphisms or medications may also affect AVF maturation, but were beyond the scope of the present study. Third, there may be a poor correlation between arterial anatomy and function. Thus, a recent study applied a mathematical model to predict AVF blood flow, and suggested that vascular dilatation may not be needed unless the vascular diameters are small (20).

Arterial calcification may decrease the distensibility of the arteries, thereby adversely affecting AVF maturation. We observed micro-calcification in a subset of the arterial specimens, but the degree of micro-calcification was not associated with medial fibrosis. There was a trend (p=0.08) for higher micro-calcification in non-maturing fistulas, which might have been significant with a larger patient sample.

The pathologic abnormalities observed in the current study differ from those described by other investigators. In their series of 59 patients, Kim et al described intimal hyperplasia in 76% of the arteries used to create AVFs, and this pathologic abnormality was associated with shortened AVF survival (14). In contrast, we did not observe arterial intimal hyperplasia in any of our 50 patients. The difference in baseline arterial histology between the two studies may be related to racial differences, as the patients reported by Kim et al were exclusively Asian, whereas ours were black or white. Two small studies described intimal hyperplasia in the veins used to create AVFs, but neither reported on the correlation between the venous histology and AVF outcome (15, 16). In contrast, we did not observe intimal hyperplasia in any of the 50 veins used to create an AVF.

Whereas arteriovenous graft failure is clearly related to aggressive venous intimal hyperplasia at the vein-graft anastomosis (21), the pathogenesis of AVF non-maturation remains poorly understood (22). Roy-Chaudhury et al (13) recently reported the presence of severe intimal hyperplasia in 4 patients with non-maturing AVFs, but could not verify whether the venous lesions were preexisting or developed after AVF creation. A preliminary report from the same group reported pre-existing intimal hyperplasia in 10 of 12 veins used for AVF creation (16), but did not report whether this abnormality predicted AVF non-maturation. In the current study we demonstrated the presence of severe venous neointimal hyperplasia in 6 patients with non-maturing AVFs, which was clearly not present in the venous samples obtained at the time of AVF creation. These paired observations strongly suggest that venous intimal hyperplasia develops *de novo* after AVF creation, although the cellular mechanism leading to it remains to be elucidated.

In summary, we have observed frequent arterial medial fibrosis in upper extremity arteries used to create AVFs in CKD patients. However, this vascular abnormality does not appear to be responsible for the pathogenesis of AVF non-maturation. Arterial micro-calcification may be predictive of AVF non-maturation, although a larger sample would be required to confirm this hypothesis. Contrary to prior reports, venous intimal hyperplasia was not found in any of our patients at the time of AVF creation. Severe intimal hyperplasia was observed at subsequent AVF revision for anastomotic stenosis, suggesting *de novo* neointimal hyperplasia development in these immature AVFs.

Acknowledgments

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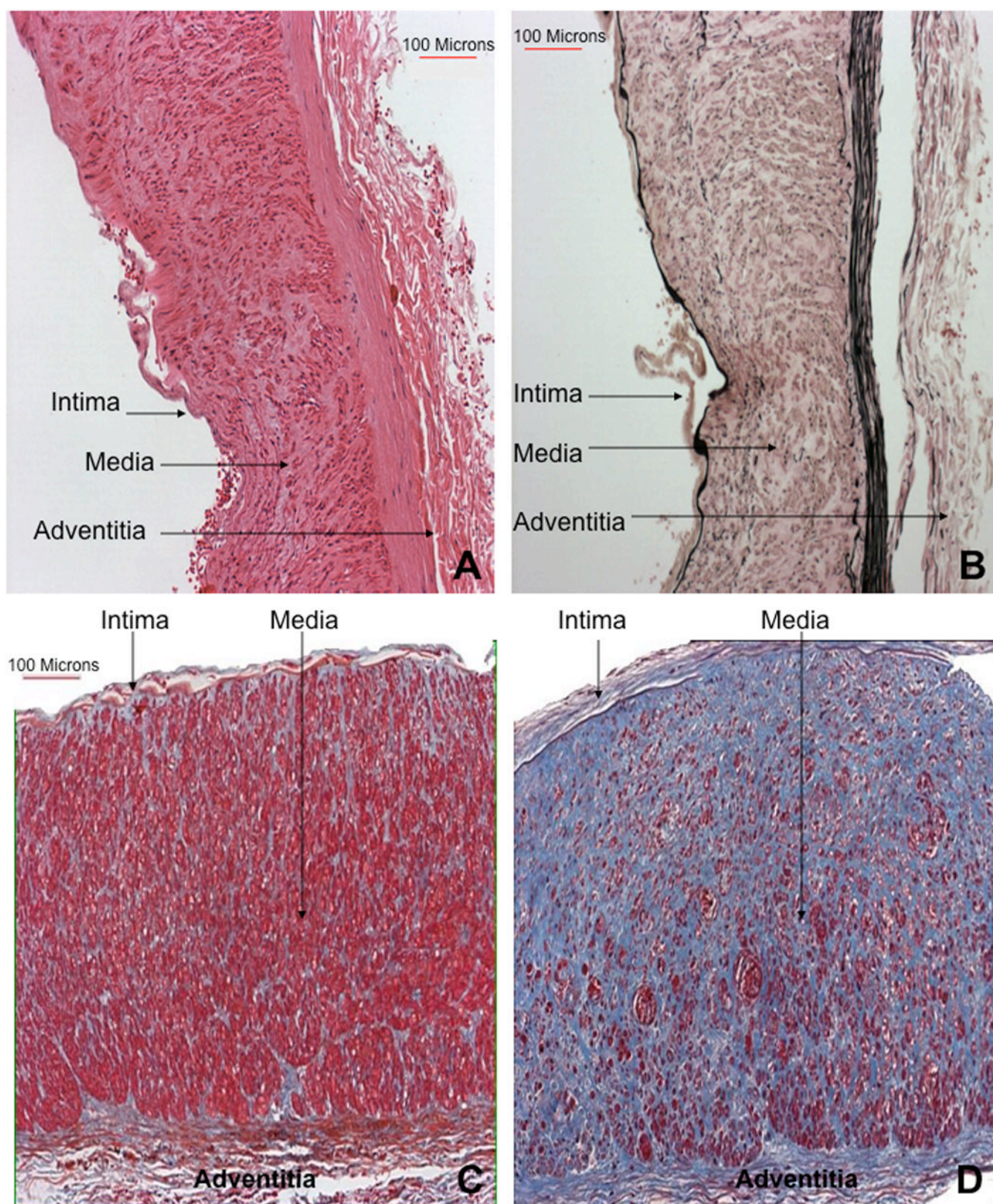
Figure 1.

Histologic section of artery at time of fistula placement stained with H&E (**A**) and elastic Van Gieson stain (**B**), showing the three vascular layers. The internal elastic lamina separates the thin intima from the thick media. Trichrome stain shows an artery with mild (32%) fibrosis (blue, **C**) and a second with significant (90%) fibrosis (**D**). The intimal layer is always thin.
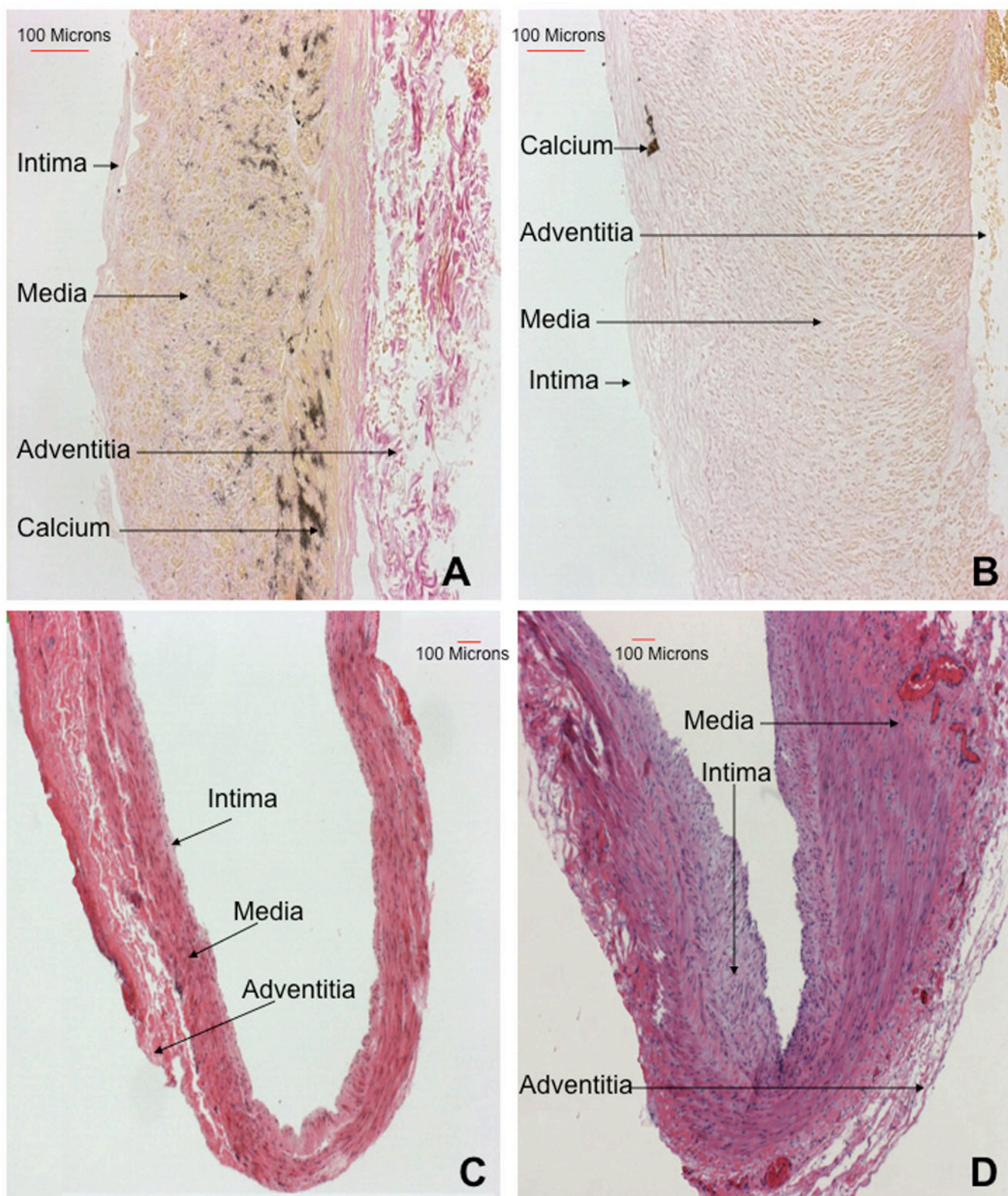
Figure 2.

Van Kossa stain (calcium salt stains black) of artery with heavy (**A**) and minimal (**B**) calcification. It is common for minimal calcification to be predominantly deposited in the internal elastic lamina. Vein H&E stained at original fistula placement (**C**) shows thin intimal layer; at reoperation 115 days following fistula creation (**D**), severe neointimal hyperplasia has developed.

Table 1

Clinical features of the study population by fistula outcome

	Non-maturing AVF	Mature AVF	P value
No. patients	19	31	
Age	54 ± 16	55 ± 13	0.8
Age ≥ 65 yr	5 (26%)	6 (19%)	0.6
Women	13 (68%)	12 (39%)	0.04
Black	12 (63%)	20 (64%)	0.9
Diabetes	10 (53%)	13 (42%)	0.5
HTN	18 (95%)	29 (94%)	0.9
CAD	2 (10%)	4 (13%)	0.8
PVD	1 (5%)	4 (13%)	0.8
CVD	2 (10%)	4 (13%)	0.8
CHF	5 (26%)	3 (10%)	0.1
AVF located on forearm	7 (37%)	9 (29%)	0.6
AVF created after dialysis initiation,	10 (53%)	19 (61%)	0.7

Age shown as mean +/− SD. Categorical variables shown as number (percentage).
AVF, arteriovenous fistula; HTN, hypertension; CAD, coronary artery disease; PVD, peripheral vascular disease;
CVD, cerebrovascular disease; CHF, congestive heart failure.

Table 2

Preoperative sonographic features of the vasculature

	Non-maturing AVF	Mature AVF	P value
No. forearm fistulas	7	9	
Forearm arterial diameter (mm)	3.0 ± 0.5	2.8 ±0.3	0.4
Forearm vein diameter (mm)	2.9 ± 0.4	3.0 ± 0.4	0.9
No. upper arm fistulas	12	22	
Upper arm arterial diam (mm)	4.0 ± 0.8	5.2 ± 1.1	0.007
Upper arm vein diam (mm)	3.9 ± 1.3	4.6 ± 1.5	0.2

The vascular diameters are those measured at the level of AVF anastomosis
AVF, arteriovenous fistula.

Table 3

Pathologic features of the vascular specimens

	Non-maturing AVF	Mature AVF	P value
No. patients	19	31	
Arterial medial fibrosis	60 ± 14	66 ± 13	0.2
Arterial medial fibrosis ≥ 70%	5 (26%)	11 (35%)	0.5
Arterial micro-calcification present	15 (79%)	19 (68%)[*]	0.6
Arterial micro-calcification score	1.3 ± 0.8	0.9 ± 0.8	0.08
Arterial intimal hyperplasia	0 (0%)	0 (0%)	0.9
Venous intimal hyperplasia	0 (0%)	0 (0%)	0.9

[*] Tissue specimen inadequate in 3 pts with a mature AVF.

Continuous variables shown as mean +/− standard deviation; categorical variables as number (percentage).

Table 4

Clinical features of patients with and without severe medial fibrosis.

	Medial fibrosis ≥ 70%	Medial fibrosis <70%	P value
No. patients	16	34	
Age ≥ 65 yr	7 (44%)	4 (12%)	0.01
Women	7 (44%)	18 (53%)	0.5
Black	8 (50%)	24 (70%)	0.2
Diabetes	10 (62%)	13 (38%)	0.01
HTN	16 (100%)	31 (91%)	0.2
CAD	2 (12%)	4 (12%)	0.9
PVD	2 (12%)	3 (9%)	0.7
CVD	3 (19%)	3 (9%)	0.3
CHF	1(6%)	7(20%)	0.2
AVF located on forearm	5 (31%)	11 (32%)	0.9

Continuous variables shown as mean +/− standard deviation; categorical variables as number (percentage).

AVF, arteriovenous fistula; HTN, hypertension; CAD, coronary artery disease; PVD, peripheral vascular disease; CVD, cerebrovascular disease; CHF, congestive heart failure.