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Intimal Hyperplasia and Arteriovenous Fistula Failure: Looking Beyond Size Differences

Roberto I. Vazquez-Padron,[1] *Juan C. Duque*,[2] *Marwan Tabbara*,[1] *Loay H. Salman*,[3] *and Laisel Martinez*,[1]

Abstract

The development of venous intimal hyperplasia (IH) has been historically associated with failure of arteriovenous fistulas (AVFs) used for hemodialysis. This long-standing assumption, made on the basis of histologic observations, has been recently challenged by clinical studies indicating that the size of the intima by itself is not enough to explain stenosis or AVF maturation failure. Irrespective of this lack of association, IH is present in most native veins and fistulas, is prominent in many patients, and suggests a role in the vein that may not be reflected by its dimensions. Therefore, the contribution of IH to AVF dysfunction remains controversial. Using only clinical data and avoiding extrapolations from animal models, we critically discuss the biologic significance of IH in vein remodeling, vascular access function, and the response of the venous wall to repeated trauma in patients receiving hemodialysis. We address questions and pose new ones such as the following: What are the factors that contribute to IH in preaccess veins and AVFs? Do cellular phenotypes and composition of the intima influence AVF function? Are there protective roles of the venous intima? This review explores these possibilities, with hopes of rekindling a critical discussion about venous IH that goes beyond thickness and AVF outcomes.

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Introduction

Intimal hyperplasia (IH) is a buildup of myofibroblast-like cells (neointimal cells) and extracellular matrix (ECM) within the tunica intima, the innermost layer of the vein (1). In preaccess veins of patients with CKD, IH manifests as an idiopathic and benign histologic feature that does not compromise blood flow (2–6). After arteriovenous fistula (AVF) creation, expansion of the intima may remain innocuous or aggravate inward remodeling, leading to stenosis and access failure (3). The actual contribution of IH in relation to other transformation processes in the wall after AVF creation remains uncertain (7). Importantly, once stenosis becomes a pathology, it is not easily treatable, with frequent recurrences after endovascular procedures (8–14). The lack of more effective therapies against stenosis reflects our simplistic view of the processes of intimal expansion and wall remodeling, and our unawareness of the characteristics that distinguish between benign and occlusive IH.

This review critically discusses what we know about IH in human veins and AVFs, what we are missing, and how this knowledge may influence IH-targeted therapies to improve AVF outcomes. We discuss the historical assumption that IH alone causes stenosis and AVF failure and extend our debate beyond IH size, the focus of published research in this area. Finally, we highlight the necessity for innovation, state-of-the-art omics, and single-cell technology to clarify the actual role of IH in venous remodeling.

Preexisting IH

IH in the Preaccess Vein: More Common than Previously Thought

The cephalic and basilic veins are the preferred choices for AVF creation (15). These are medium-sized veins with the three vascular layers well defined (tunica intima, tunica media, and tunica externa or adventitia) and diameters between 1 and 5 mm (Figures 1 and 2) (16,17). The intima is the innermost layer of the vessel and is demarcated by a thin or discontinuous internal elastic lamina on the medial side, and a continuous endothelial line that separates it from the lumen. Thin folds of collagen-rich connective tissue, covered by endothelium, extend from the intima and form the valves at regular intervals along the vein.

The size of the intima layer in preaccess veins ranges from almost inexistent to thick and rich in intimal cells and ECM, with this latter scenario being the norm rather than the exception (2–6,18–24). Almost 20 years ago, Wali *et al.* (25,26) observed generalized IH in cephalic veins from 20 patients with renal failure. In more recent and larger patient cohorts (N=57–129), maximal intimal thickness (the longest distance between the media and the lumen) ranged from 1 to 660 μm in forearm and upper-arm preaccess veins

[1]DeWitt Daughtry Family Department of Surgery, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida
[2]Katz Family Division of Nephrology, Department of Medicine, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida
[3]Division of Nephrology, Albany Medical College, Albany, New York

Correspondence: Dr. Laisel Martinez, Division of Vascular Surgery, University of Miami Miller School of Medicine, 1600 NW Tenth Avenue, RMSB 1011B, Miami, FL 33136. Email: lmartinez6@med.miami.edu

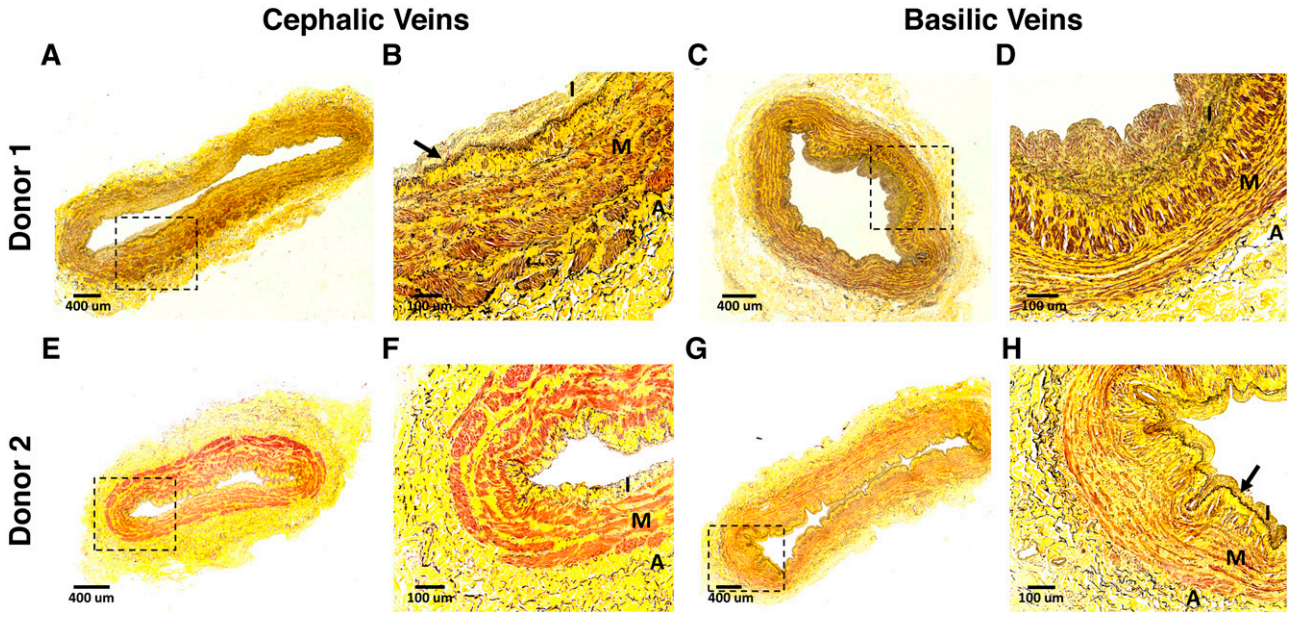

Figure 1. | **Minimal to moderate intimal hyperplasia in trauma donors with normal renal function.** (A–D) Cross-sections of the (A and B) cephalic and (C and D) basilic veins from a Hispanic 56-year-old male without history of hypertension, diabetes, or coronary artery disease. (E and F) Cephalic and (G and H) basilic veins from a Hispanic 55-year-old male with history of controlled hypertension (<5 years). Sections were stained with Movat pentachrome stain, with cells showing in brown/red, collagen in yellow, and elastin in black. Boxed areas in (A), (C), (E), and (G) are magnified in (B), (D), (F), and (H), respectively. Arrows in (B) and (H) identify the internal elastic lamina. A, adventitia; I, intima; M, media.

(Table 1), with higher values in the latter (2,4,6). The Hemodialysis Fistula Maturation (HFM) Study confirmed the high prevalence of IH in 365 preaccess veins and quantified it as the percentage of luminal occlusion (Table 1) (5). Of the patients, 22% presented moderate IH (21%–40% luminal occlusion), whereas 35% portrayed severe IH (>41% occlusion). In agreement with Allon *et al.* (4), the percentage of luminal occlusion was lower in cephalic veins (mean 31%) than in upper-arm vessels (mean 40%). Martinez *et al.* (3) expressed IH as intima/media area ratio (I/M ratio) in 110 upper-arm veins to account for morphometric changes in the media, such as atrophy or hypertrophy (18,20,25,26). The median I/M ratio in this cohort was 0.32, in line with previous reports of cephalic and other preaccess veins (Table 1) (18,19,24).

Despite its common occurrence in preaccess veins, whether IH development is influenced by CKD remains unknown because experimental animal models do not develop spontaneous IH. Various studies support an increase in IH in the setting of CKD (6,21,25–27), but the number of non-CKD upper-extremity veins is low (three to 15 individuals), which makes it difficult to draw a definite conclusion on this issue. The I/M ratio of the great saphenous vein was also found to be significantly higher in patients with CKD compared with controls, and in those with ESKD versus CKD stages 1 and 2 (27), but it is not clear whether these groups were matched with respect to age and baseline characteristics. It is tempting to speculate that IH increases during the course of renal dysfunction secondary to volume/flow overload (anemia, sodium, and water retention) and other poorly defined clinical factors. However, frequent IH was observed in cephalic and saphenous veins from elderly patients with normal renal function (28), suggesting uremia is not the only vascular insult causing intimal thickening. Synergistic insults may include endothelial dysfunction in CKD and vascular injury related to venipuncture or catheterization. On the other hand, the presence of a thick intima in basilic veins (2,3), as in the superficial cephalic vein (4–6,19), suggests that mechanisms other than venipuncture-related trauma promote IH. Single-cell sequencing and spatial proteomics may help identify differences in cell and ECM composition (if any) between the CKD and non-CKD preaccess intima. This may, in turn, uncover common and disease-relevant origins of IH.

Composition of the Preaccess Intima: Identifying Knowledge Gaps

Three types of cells predominate in the intima of preaccess veins: endothelial cells (ECs), smooth muscle cells (SMCs), and myofibroblasts/fibroblasts (1,2,5,18–20,29). ECs line the luminal side of the intima, whereas SMCs and myofibroblasts, embedded in ECM, populate the core of the layer. ECs play an essential role in preventing thrombosis, but their contribution to controlling IH has not been fully elucidated. Although there is wide support for the inhibitory effect of EC-derived nitric oxide in intimal cell proliferation and migration (30), there is also evidence for other endothelial paracrine factor(s) that stimulate venous IH (31). The overall effect of the endothelium on IH is likely dependent on flow and pathophysiologic conditions. Along these lines, profound changes in EC and SMC morphology (25,26,32) and function (33–39) have been detected in patients with CKD.

Using a combination of contractile (smooth muscle myosin heavy chain [SM-MHC], desmin, h-caldesmon, calponin), synthetic (vimentin), and pan SMC markers (α-smooth muscle actin [αSMA]), various groups have observed a mixture

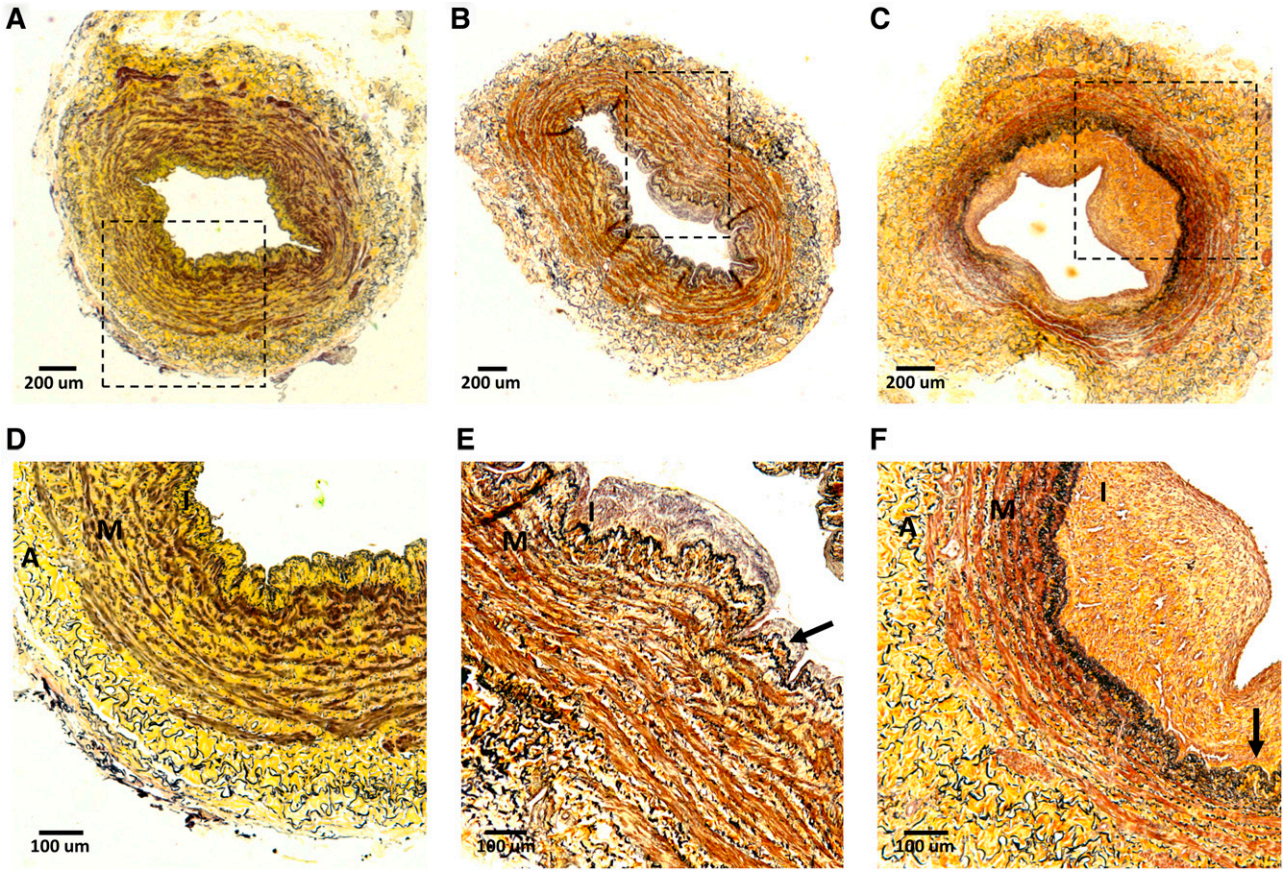

Figure 2. | **Variability in intimal hyperplasia in preaccess basilic veins from patients with ESKD.** (A–C) Cross-sections of basilic veins collected during first-stage surgery of a two-stage brachiobasilic arteriovenous fistula (AVF). Patient in (A) is a 42-year-old Black female with history of hypertension; patient in (B) is a 68-year-old Black female with hypertension and diabetes; and patient in (C) is a 65-year-old Hispanic female positive for hypertension, diabetes, and coronary artery disease. All three veins matured successfully after AVF creation. Sections were stained with Movat pentachrome stain, with cells showing in brown/red, collagen in yellow, and elastin in black. Boxed areas in (A) to (C) are magnified in (D) to (F), respectively. Arrows in (E) and (F) identify the internal elastic lamina. A, adventitia; I, intima; M, media.

of SMC and/or myofibroblast phenotypes in the intima of preaccess veins (2,18–20,29,40,41), whose functions remain uncertain. Contractile SMCs are typically associated with low proliferation and migration rates, and low secretion of ECM (42). The opposite behavior is characteristic of "synthetic" or "myofibroblastic" SMCs that have lost expression of contractile markers. Serum from patients with dialysis favors the synthetic transformation of cultured human SMCs by promoting epigenetic downregulation of contractile gene expression (27). Interestingly, despite the high number of synthetic SMCs in preaccess veins, they show minimal staining of the proliferation and metabolic markers Ki-67 and phosphoglucomutase 1, respectively, suggesting that intimal cells are relatively quiescent before access creation (5,18). The HFM Study also reported rare apoptotic cells by cleaved caspase 3 expression in <10% of analyzed intimas (four of 48) (5). How expression of contractile markers in CKD veins relates to venoconstriction or dilation is unclear. A thick intima likely serves as a barrier for the diffusion of both circulatory vasoactive factors and EC-derived molecules that regulate medial SMC contraction or dilation. This may be an advantageous adaptation to reduce vasoconstrictive responses. On the other hand, studies in saphenous veins proposed that intimal thickness >120 μm is associated with impaired endothelium-dependent vasodilation (43). If there is a signaling cascade of soluble factors from ECs or the lumen that is amplified by intimal myofibroblasts or SMCs remains to be discovered.

In contrast with the abundance of inflammatory cells in the arterial intima with disease, the number of immune cells in preaccess veins is minimal. Approximately 50% of analyzed veins in the HFM Study (25 of 48) showed only one CD68-expressing macrophage in the intima, with approximately 7.7 cells in the whole section (5). Martinez *et al.* (44) also reported low numbers of $CD68^+$ macrophages (about 40 cells per cross-section) in 45 basilic veins, mostly located at the edge between the media and the adventitia. In terms of T cells, Lee *et al.* (18) observed minimal $CD3^+$ staining in the intima. Despite the low levels of immune infiltration in preaccess veins, a transcriptomic analysis uncovered expression of myeloid-related inflammatory genes in intimal and medial SMCs and myofibroblasts, suggesting a key role of resident cells in vascular inflammation (44). Five genes (*CSF3R*, *FPR1*, *S100A8*, *S100A9*, and *VNN2*)

Table 1. Intimal morphometry and associations with arteriovenous fistula outcomes in the hemodialysis population

Study	N[a]	Vein	Parameter(s)	Measurements[b]	Association(s)
Preexisting intimal hyperplasia					
Feinfeld *et al.* (23)	15	Brachial (n=15)	Ave. I thickness	6.0±0.9 μm	N/A
Lee *et al.* (18)	12	Cephalic (n=6), axillary (n=3), antecubital (n=1), basilic (n=1), brachial (n=1)	Ave. IM thickness	0.34±0.12 mm	Significant association with maturation failure (P=0.03, n=7)
			Max. IM thickness	1.16±0.30 mm	N/A
			I/M area ratio	0.24±0.07	N/A
			% Luminal occlusion	47%±9%	Lack of association with maturation failure (P=0.09, n=7)
Wasse *et al.* (24)	10	Cephalic, basilic	Ave. I thickness	0.066±0.019 mm	N/A
			Max. I thickness	0.166±0.042 mm	N/A
			Mean I/M thickness ratio	0.26±0.07	N/A
			Max. I/M thickness ratio	0.69±0.19	N/A
			Intimal area	0.27±0.08 mm^2	N/A
			I/M area ratio	0.24±0.06	N/A
Allon *et al.* (4)	113	Upper arm (65%), forearm (35%)	Max. I thickness	0.022 (0.013–0.045) mm	Lack of association with postoperative stenosis (P=0.49)
Lee *et al.* (21)	29	N/A	Mean I/M thickness ratio	0.43±0.07	N/A
			Max. I/M thickness ratio	0.86±0.07	N/A
Lazich *et al.* (19)	18	Cephalic (n=18)	Max. I thickness	0.052–0.81 mm	N/A
			Intimal area	0.16–7.70 mm^2	N/A
			I/M area ratio	0.07–1.80	N/A
			Mean I/M thickness ratio	0.07–1.99	N/A
			Max. I/M thickness ratio	0.14–2.44	N/A
			% Luminal stenosis	45%–96%	N/A
Tabbara *et al.* (2)	57	Basilic (n=54), brachial (n=3)	Max. I thickness	0.18 (0.10–0.20) mm	Lack of association with primary unassisted patency (P=0.2, n=52)
			I/M area ratio	N/A	Lack of association with primary unassisted patency (P=0.2, n=52)
HFM Study (5,52)[c]	365	Cephalic (69%), basilic (29%), brachial (2%)	% Luminal occlusion	28%±27% (cephalic), 40%±30% (basilic), 21%±23% (brachial)	Lack of association with postoperative stenosis at 1 day (P=0.49), 2 weeks (P=0.91), or 6 weeks (P=0.07); lack of association with unassisted (P=0.07) or overall maturation failure (P=0.11)
Martinez *et al.* (3)	110	Basilic (n=104), brachial (n=4), cephalic (n=2)	I/M area ratio	0.32 (0.22–0.52)	Lack of association with maturation failure (P=0.7)
Allon *et al.* (6)	129	Upper arm (65%), forearm (35%)	Max. I thickness	0.037±0.040 mm	N/A

Table 1. (Continued)

Study	N[a]	Vein	Parameter(s)	Measurements[b]	Association(s)
Postoperative intimal hyperplasia					
Roy-Chaudhury *et al.* (41)	4	Cephalic (n=4), all early failures	Mean I/M thickness ratio	3.12±0.43	N/A
			Max. I/M thickness ratio	7.77±1.49	N/A
			I/M area ratio	1.67±0.10	N/A
			% Luminal stenosis	86%±3%	N/A
Lee *et al.* (21)	20	Cephalic (n=15), basilic (n=5); all stenotic segments	Mean I/M thickness ratio	3.84±0.55	N/A
			Max. I/M thickness ratio	7.78±0.88	N/A
Tabbara *et al.* (2)	79	Basilic (n=74), brachial (n=5)	Max. I thickness	0.62 (0.38–0.86) mm	Lack of association with maturation failure (P=0.3); lack of association with primary unassisted patency (P=0.6)
			I/M area ratio	N/A	Lack of association with maturation failure (P=0.4); lack of association with primary unassisted patency (P=0.8)
Duque *et al.* (71)[d]	14	Basilic (n=12), brachial (n=2); all AVFs had stenotic and nonstenotic segments	I area	3.33 (1.94–4.86) mm^2 in nonstenotic, 3.33 (2.29–5.16) mm^2 in stenotic	Lack of association with focal stenosis (P=0.26)
			Min. I thickness	0.09 (0.05–0.31) mm in nonstenotic, 0.11 (0.05–0.43) mm in stenotic	Lack of association with focal stenosis (P=0.18)
			Max. I thickness	0.75 (0.54–1.08) mm in nonstenotic, 0.98 (0.78–1.20) mm in stenotic	Lack of association with focal stenosis (P=0.22)
			Min. IM thickness	0.37 (0.17–0.70) mm in nonstenotic, 0.30 (0.23–0.88) mm in stenotic	Lack of association with focal stenosis (P=0.22)
			Max. IM thickness	1.14 (0.84–1.38) mm in nonstenotic, 1.38 (1.30–1.57) mm in stenotic	Lack of association with focal stenosis (P=0.13)
			I/M area ratio	0.97 (0.63–1.18) in nonstenotic, 1.00 (0.70–1.20) in stenotic	Lack of association with focal stenosis (P=0.73)
Martinez *et al.* (3)	115	Basilic (n=97), brachial (n=14), cephalic (n=4)	I/M area ratio	0.77 (0.48–1.30)	Lack of association with maturation failure by itself (P=0.09, n=115), but significant association in AVFs with high medial fibrosis (P=0.04, n=58)

Ave., average; I, intima; N/A, not reported or studied; IM, intima plus media; max., maximum; I/M, intima/media; HFM, Hemodialysis Fistula Maturation; AVF, arteriovenous fistula; min., minimum.

[a]Number of veins analyzed after study exclusions.

[b]Values presented as mean±SEM (SD in the HFM Study [5,52] and Allon *et al.* [6]), median (interquartile range), or range in Lazich *et al.* (19).

[c]Data obtained from Alpers *et al.* (5) and Cheung *et al.* (52).

[d]Pairwise comparison of stenotic and adjacent nonstenotic segments in upper-arm AVFs.

were associated with AVF maturation failure, and expression of *S100A8* and *S100A9* had a weak correlation with postoperative IH (44). Wasse *et al.* (24) also found expression of TNF-α, TGF-β, and IL-6 in the intima of preaccess veins. Immunohistochemistry analyses demonstrate that not all cells in the intima and media are positive for these proteins (24,44), demonstrating again a heterogeneity of SMC and myofibroblast phenotypes with potential implications for the inflammatory status of the vessel.

The ECM composition of the intima is an important aspect of remodeling, and perhaps the most neglected characteristic of this layer. The HFM Study observed significant interpatient variability by histology in the amount and distribution of collagen and proteoglycans in the intima (5). Intimal expansion in earlier reports of 20 cephalic veins was also characterized by marked deposition of fragmented collagen fibers and dispersed elastin (25,26). Intimal calcification was observed in 2% of the patients in the HFM Study and 15% in Wali *et al.* (5,25). It is important to note that the proportion and configuration of the ECM and the types of ECM proteins in the intima may play a role in cell proliferation and migration (45–48), vein stiffness (49,50), and/or compressibility of this layer under high flow conditions (51). Accumulation of collagen is associated with fibrosis, whereas high proteoglycan content may confer resistance to compression and act as a reservoir of cytokines and growth factors that influence cell survival and proliferation (49,51). Future proteomic studies are needed for a more accurate characterization of the intimal ECM.

Does Preexisting IH Increase the Risk of AVF Failure?

The initial idea that preexisting IH potentially led to stenosis and poor AVF outcomes has been recently challenged in several independent studies (2–4,52). Allon *et al.* (4) studied the association between maximal intimal thickness in the preaccess vein and postoperative AVF stenosis. Of the 113 patients included in the analysis, 50% developed a hemodynamically significant stenosis. However, there was no association between IH and the presence of postoperative stenosis (Table 1). This lack of association remained true when analyzed by type of AVF and location of the stenosis (4). The results of this study were confirmed by the HFM Study in 365 individuals (52). The development of stenosis was evaluated by ultrasound at 1 day, 2 weeks, and 6 weeks after AVF creation. Preexisting IH (percentage of luminal occlusion) was not associated with AVF stenosis at any of these time points, nor with the internal diameter of the vessel (52).

The relationship between preexisting IH and maturation failure was analyzed by the HFM Study and Martinez *et al.* (3,52). The HFM Study found a significant association between the preexisting percentage of luminal occlusion and venous blood flow rate at 6 weeks after access creation (Table 1). However, the association with unassisted or overall maturation failure did not reach statistical significance (52). Preexisting I/M ratio also failed to predict nonmaturation in 110 patients in the study by Martinez *et al.* (3). Lastly, Tabbara *et al.* (2) analyzed the association between preexisting IH and primary unassisted patency in 52 upper-arm fistulas. Neither maximal intimal thickness nor I/M area ratio predicted loss of primary patency. Although there seems to be no association between preexisting intimal morphometry and AVF failure, additional studies are needed to assess the effects of intimal cell and ECM composition on postoperative outcomes.

Postoperative IH

IH after AVF Creation: Selective Activation of Preexisting Cells?

The transformation of the vein after AVF creation remains one of the least understood processes in vascular biology. Current knowledge emphasizes the role of ECs in sensing arterial shear stress to release vasodilators that potentially lead to maturation (53,54). However, the endothelium is almost certainly severely damaged by surgical trauma, secondary to the common use of dilators and saline flushing to expand venous size before anastomosis. This suggests that intimal and medial cells likely play a protagonist's role as mechanosensors of hemodynamic changes and vascular trauma. The best evidence we have about postoperative remodeling of the intima is from two-stage AVFs, which allow us to collect a biopsy of the remodeled vein (now a fistula) during transposition surgery.

In upper-arm fistulas, maximal intimal thickness increased approximately four-fold with respect to the preaccess vein, with values ranging from 0.1 to 2.0 mm in 79 patients who underwent two-stage AVF creation (Table 1) (2). This increase was not associated with the waiting time between AVF creation and transposition surgeries, or with the thickness of the intima in the preaccess vessel. The lack of relationship between preexisting and postoperative IH agrees with a selective activation of cells in the wall and different responses to surgical or hemodynamic injury between patients. Moreover, the absence of correlation between IH and the time between AVF creation and transposition surgeries suggests that most intimal expansion occurs early during maturation. Medial atrophy is frequently seen in AVFs (Figure 3), possibly as a result of cell death or migration of SMCs into the intima. This SMC loss is either replaced by ECM (fibrosis) or results in thinning of the media. A median I/M area ratio of 0.77 was reported in 115 two-stage AVF cross-sections, significantly higher than in native veins (Table 1) (3). In agreement with maximal intimal thickness, I/M ratio also demonstrated a lack of correlation between preexisting and postoperative values in pairwise analyses.

In contrast to native veins (5), IH in most upper-arm AVFs is eccentric (Figure 3). Unequal hemodynamic forces along the length of the vein are thought to explain this morphometry. This has been recently imaged in mice (55), although confirmatory studies in large animal models and humans are needed. It has been proposed that low wall shear stress, pulsatile stretch, and flow turbulence causes injury and elicits proliferation of intimal cells (56–60). However, it is possible that such eccentric appearance may be explained by pockets of increased cell proliferation, migration, and/or ECM deposition; and that these pockets are determined, in turn, by the phenotypes of the preexisting intimal cells.

At the cellular level, the postoperative remodeling process seems to favor the intimal expansion and/or survival of myofibroblasts and synthetic SMCs in the AVF wall. Tabbara *et al.* (2) observed that the intima of upper-arm AVFs collected at the time of transposition was mostly made up of synthetic SMCs (positive for αSMA, negative for SM-

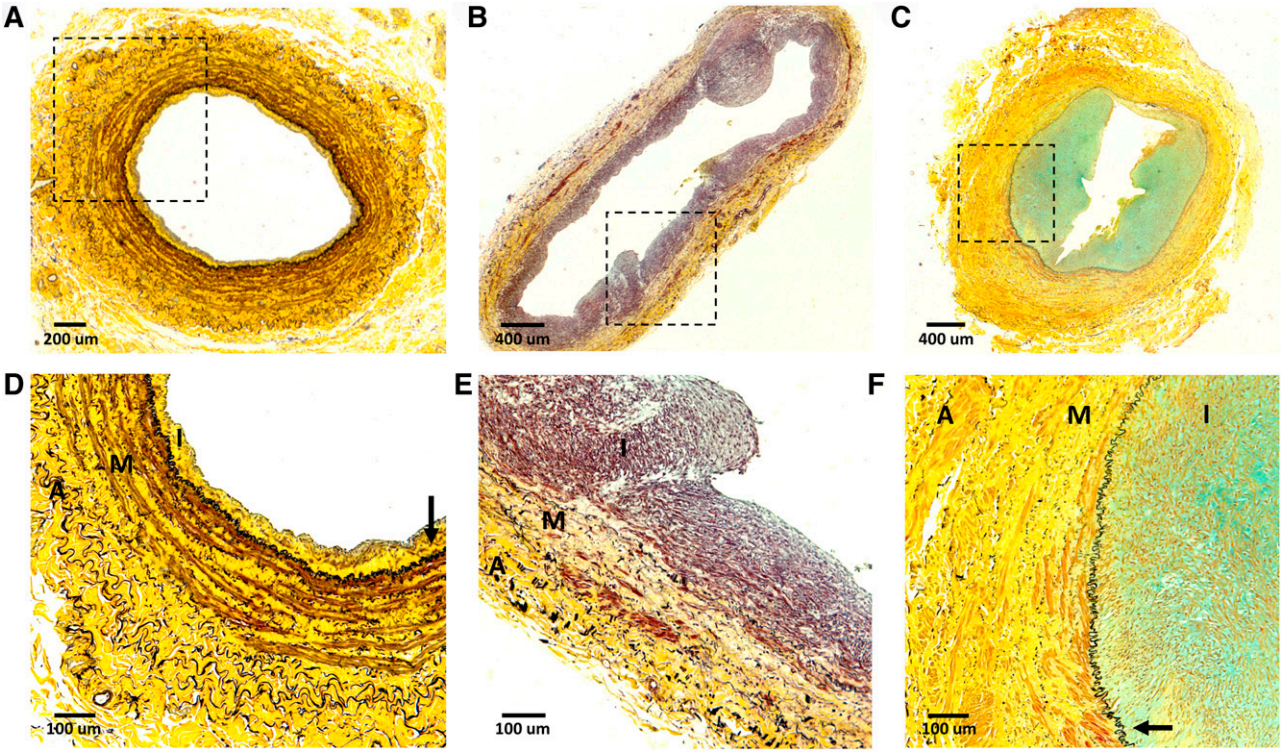

Figure 3. | **Heterogeneity of venous remodeling in AVFs from patients with ESKD.** (A–C) Cross-sections of juxta-anastomotic AVF segments from two-stage brachiobasilic fistulas collected during second-stage surgery (77–91 days after AVF creation). Patient in (A) is a 38-year-old Hispanic male with history of hypertension, patient in (B) is an 80-year-old Black female with hypertension and diabetes, and patient in (C) is a 40-year-old Black male positive for hypertension and coronary artery disease. All three AVFs failed to mature and underwent a salvage procedure or creation of a new fistula. Sections were stained with Movat pentachrome stain, with cells showing in brown/red, collagen in yellow, proteoglycans in blue, and elastin in black. Boxed areas in (A) to (C) are magnified in (D) to (F), respectively. Arrows in (D) and (F) identify the internal elastic lamina. A, adventitia; I, intima; M, media.

MHC). Other studies also reported a majority of myofibroblasts (αSMA^+, $vimentin^+$, $desmin^-$) (40,41,61) and reduced expression of SM-MHC and calponin (29) in the intima of stenotic samples collected at the time of AVF revision. In all studies, medial SMCs retained contractile protein expression (2,29,40,41). The proportions and phenotypes of AVF intimal cells that are actively proliferating remain unknown. High intimal levels of the proliferation marker proliferating cell nuclear antigen (PCNA) were observed in stenotic areas of resected AVFs (41,62), but were contradicted by the more accurate marker Ki-67 (63). High PCNA and cyclin dependent kinase 2 (CDK2) levels in the study by de Graaf *et al.* (62) were also accompanied by significantly lower expression of the cell cycle regulator $p21^{Waf1}$. Future single-cell tracing experiments will help define whether the increase in synthetic SMCs and myofibroblasts in the AVF intima is due to the postoperative dedifferentiation and expansion of contractile SMCs in the wall, or proliferation of a preexisting synthetic population. This information will be instrumental for the design of targeted therapies.

The role of immune cell infiltration in postoperative IH and AVF dysfunction is not clear at the moment. Increased macrophage and T-cell infiltration was seen in 15 stenotic AVF sections compared with preaccess veins (64). In contrast, a comparison of 13 nonthrombosed stenotic samples and 23 thrombosed specimens revealed that immune cell infiltration was in fact characteristic of the latter (65). Similar to the localization of proinflammatory proteins in intimal SMCs and myofibroblasts in preaccess veins (44), various studies have also demonstrated elevated inflammatory and oxidative markers in resident intimal cells of resected AVF specimens (64,66). It is important to note that most of the information about immune cell infiltration after AVF creation comes from extrapolation from animal models (67–70), where it is possible to obtain AVF samples early after surgery. Whether inflammation from infiltrated or resident cells plays a role in human AVF maturation or dysfunction will require the analysis of early human AVF samples (within 2 weeks of surgery), including nonstenotic segments. This may be possible through a multicenter collection of veins from steal syndrome and stenotic accesses that require early surgical revision.

As in preaccess veins, the ECM composition of the AVF intima has been barely studied. Martinez *et al.* (3) observed various levels and patterns of ECM deposition in the intima of two-stage transposition fistulas, although a comparative analysis of the samples was not presented. These patterns included intimas that were mostly cellular (low in ECM), with widespread ECM distribution, or with separate areas for cells and ECM deposition. Such interpatient variability in composition is likely relevant to the occlusive character of the intima, the response of the vein to cannulation injury, and the efficacy of endovascular treatments.

Postoperative IH and AVF Outcomes: Let Us Update the Theory

The most important question about IH is whether growth of this layer after AVF creation underlies access failure. Various case reports of AVFs that failed observed the presence of moderate to severe IH, but lacked a comparative group of functional fistulas (21,29,41,61). Despite this limitation, these observations reinforced the assumption that a thicker intima was responsible for AVF failure. The analysis of postoperative samples from two-stage upper-arm AVFs has challenged this idea (2,3,71).

Tabbara *et al.* (2) found a lack of association between postoperative IH (measured as maximal intimal thickness and I/M ratio) and maturation failure in a cohort of 79 individuals (Table 1). These analyses were not adjusted for any other clinical characteristics. Martinez *et al.* (3) also failed to find an association between I/M ratio and maturation failure in 115 individuals after adjusting for sex effects. Interestingly, the same study demonstrated that postoperative medial fibrosis was significantly associated with failure. Furthermore, IH was associated with failure only in those AVFs with medial fibrosis over the median value, and not in the other half of the accesses (Table 1) (3). Given that high medial fibrosis can adversely influence the biomechanical properties and distensibility of AVFs, this study proposed that, under highly fibrotic wall conditions, high IH is occlusive, but not when the vessel is able to compensate through other biomechanical mechanisms. This underscores the importance of understanding AVF remodeling as a whole and the mechanistic relationships between IH and other wall remodeling processes.

Pairwise comparisons of adjacent stenotic and nonstenotic segments from 14 two-stage upper-arm AVFs further confirmed that IH does not define the true luminal area of the access (71). In this report, there were no significant differences in intima size between both segments (Table 1). Lastly, no significant association has been found between maximal intimal thickness or I/M ratio and primary unassisted patency (2). The above postoperative data on maturation failure, focal stenosis, and primary patency are limited to upper-arm AVFs due to practical limitations. It is possible that postoperative IH has a larger effect on the outcomes of forearm fistulas.

Research Models, Current Challenges, and Pending Questions

Role of Animal Models in the Study of IH

Animals are essential to address basic science questions such as the origin and differentiation of intimal cells, temporal remodeling of the wall, and the effects of local and circulatory stimuli or treatments (29,67,68,72–79). Research mice and rats have the added advantage of allowing genetic manipulation (gene knockins and knockouts, cell labeling, *etc.*) and inclusion of high numbers of animals. Swine and sheep are often used as translational models to test pharmacologic and endovascular interventions, primarily in arteriovenous grafts (80–83). Arguably, the best animal model for AVF functional studies is the one in sheep, due to the superficial location of peripheral veins, which allows for not only AVF creation but also for potential cannulation (73).

Most animal models develop a certain form of venous IH within 2–6 weeks after AVF creation (29,67,68,72,74–79). However, they have important limitations for the study of the occlusive role of IH in AVF remodeling and failure. In the case of small animals, there are profound differences in preexisting vein morphology (very thin walls and subendothelial space) and hemodynamic characteristics (low blood flow) with respect to humans (29,67,68, 76,78,79). In addition, most models lack an underlying long-term CKD component and a human-equivalent definition of failure. These limitations underscore the necessity of expanding tissue biobanks of human AVFs to all possible forms to promote retro-translational studies, where human findings could be further dissected at the mechanistic level in animal models. Excellent reviews of AVF and CKD animal models have been included in the *References* (84–87).

Current Challenges in Treating AVF Stenosis: A Call for Mechanism-based Approaches

The idea that IH was the main cause of stenosis in AVFs motivated the use of therapies that treat restenosis in coronary circulation to salvage dysfunctional accesses. As a result, percutaneous transluminal angioplasty (PTA) became the first-line treatment for postoperative stenoses (15). Angioplasty mechanically stretches the vein and compresses the intima, but may cause significant injury to the vessel. Although efficacious in the short term, PTA frequently requires reintervention within 1 or 2 years after the first angioplasty procedure, either due to regrowing of occlusive IH and/or fibrotic scarring of the AVF wall (8–14). Stent placement is the last line of treatment for recurrent and high recoil stenoses due to concerns of vein depletion, stent migration or fracture, and intrastent thrombosis (88,89). Stent grafts are favored for in-stent restenosis (15,89), but are prone to "edge stenosis," which occurs close to both ends of the stent and migrates toward the center (90,91).

In an attempt to improve postprocedure patency, antiproliferative drugs (mainly paclitaxel) are delivered to the AVF wall by means of drug-eluting balloons (DEB) or stents. Multiple individual studies have shown patency and/or reintervention benefits of DEB versus conventional angioplasty (12–14,92–95). However, meta-analysis studies have yielded variable conclusions, and patency rates >6 months still have much room for improvement (96–99). The observed variability in efficacy with antiproliferative agents and failure to significantly extend long-term patency may indicate insufficient delivery or retention of the drug (100–102), low sensitivity of cells to treatment (103), or a mismatch between the therapeutic effects of the drug and mechanisms of restenosis in AVFs. *In vitro* data suggest that paclitaxel targets all three presumed processes of restenosis (proliferation, migration, and ECM production) (104,105). However, it is not clear which of these cellular mechanisms are actually targeted in AVFs *in vivo*. Of note, the effect of paclitaxel in SMCs is cytostatic and not cytotoxic (106,107). Therefore, any stenotic mechanisms that remain unaffected may continue happening or possibly worsen after DEB treatment.

Antistenotic treatment modalities to improve venous remodeling during maturation include perivascular delivery of sirolimus (108), allogeneic ECs (109,110), or pancreatic elastase (111,112), and devices (VasQ, Optiflow) that support the ideal angle of arteriovenous anastomosis (113–117). The latest results on the sirolimus implants are pending (108).

VasQ resulted in high maturation rates in single-arm and retrospective studies (117–119), but mixed results in short-term primary or secondary patency compared with the control arm (114,118,119). The rest are currently not recommended by the Kidney Disease Outcomes Quality Initiative guidelines due to lack of phase 3 studies (Optiflow) or significant benefits in AVF outcomes (ECs, elastase) (15). Far infrared radiation and external pneumatic compression (Fist Assist) have shown promising results in AVF maturation parameters (120–123) and secondary patency after PTA in specific patient demographics (124), but require further validation in a broader hemodialysis population. These clinical trials illustrate the desire to innovate in the search for preventive and postoperative AVF treatments. However, until we understand how human AVF cells respond to flow disturbances, repeated cannulations, and endovascular trauma at the molecular level, it is likely that any successes will come after significant trial and error.

What to Look at Beyond Intimal Thickness

Why have we failed to find an association between intima size measurements and AVF outcomes? The answer may be methodologic and/or biologic in nature. From the methodologic point of view, there are many limitations to the way we measure intima size. Two-dimensional and static histologic assessment of IH misses the actual size of the lumen under circulation. In addition, none of the measurements considers the potential compressibility of the intima or distensibility of the vessel. At least one clinical study has reported a lack of association between maximal intimal thickness by histology and internal diameter of the vein (4), illustrating the limitations of two-dimensional morphometry measurements in determining luminal area.

From the biologic point of view, intima size only represents a partial measurement of inward remodeling. Looking for associations between intima size and AVF outcomes ignores other macro processes of the wall, such as inward remodeling of the media, outward remodeling of the wall, and changes in the ECM. Importantly, we still do not understand what drives any of these processes. Is it cell death, changes on SMC phenotypes, or SMC- or immune cell-derived inflammation? Are IH and medial fibrosis mechanistically related? From the biomechanical point of view, how compressible is the intima? What characteristics make it more or less compressible? Does vein distensibility change after AVF creation? A better understanding of the role of SMCs and myofibroblasts in intimal expansion and wall remodeling, and where in the range of their phenotypic transformation they become problematic, will require detailed phenotypic analyses and single-cell omics techniques in clinically relevant human samples.

Lastly, the complexity of AVF remodeling lies in identifying an optimal level of IH and fibrosis that maintains vein integrity under extreme hemodynamic conditions and frequent cannulations, but without causing stenosis. Thus, can we envision protective roles for the intima? Does it prevent excessive immune cell infiltration? Does it protect medial SMCs from the oxidative stress of high oxygen pressures? Do synthetic cells confer regenerative capacity for wall healing after cannulation? We must consider all of these possibilities if we truly want to optimize maturation and prevent restenosis after endovascular treatments.

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Author Contributions

J. C. Duque was responsible for data curation; J. C. Duque, L. Martinez, M. Tabbara, and R. I. Vazquez-Padron were responsible for methodology; J. C. Duque, L. Martinez, and R. I. Vazquez-Padron were responsible for formal analysis; L. Martinez was responsible for visualization; L. Martinez, L. H. Salman, M. Tabbara, and R. I. Vazquez-Padron conceptualized the study; L. Martinez and R. I. Vazquez-Padron were responsible for funding acquisition, provided supervision, and wrote the original draft; and all authors were responsible for investigation and reviewed and edited the manuscript.

References

1. Dilley RJ, McGeachie JK, Prendergast FJ: A review of the histologic changes in vein-to-artery grafts, with particular reference to intimal hyperplasia. *Arch Surg* 123: 691–696, 1988 https://doi.org/10.1001/archsurg.1988.01400300033004
2. Tabbara M, Duque JC, Martinez L, Escobar LA, Wu W, Pan Y, Fernandez N, Velazquez OC, Jaimes EA, Salman LH, Vazquez-Padron RI: Pre-existing and postoperative intimal hyperplasia and arteriovenous fistula outcomes. *Am J Kidney Dis* 68: 455–464, 2016 https://doi.org/10.1053/j.ajkd.2016.02.044
3. Martinez L, Duque JC, Tabbara M, Paez A, Selman G, Hernandez DR, Sundberg CA, Tey JCS, Shiu YT, Cheung AK, Allon M, Velazquez OC, Salman LH, Vazquez-Padron RI: Fibrotic venous remodeling and nonmaturation of arteriovenous fistulas. *J Am Soc Nephrol* 29: 1030–1040, 2018 https://doi.org/10.1681/ASN.2017050559
4. Allon M, Robbin ML, Young CJ, Deierhoi MH, Goodman J, Hanaway M, Lockhart ME, Litovsky S: Preoperative venous intimal hyperplasia, postoperative arteriovenous fistula stenosis, and clinical fistula outcomes. *Clin J Am Soc Nephrol* 8: 1750–1755, 2013 https://doi.org/10.2215/CJN.02740313
5. Alpers CE, Imrey PB, Hudkins KL, Wietecha TA, Radeva M, Allon M, Cheung AK, Dember LM, Roy-Chaudhury P, Shiu YT, Terry CM, Farber A, Beck GJ, Feldman HI, Kusek JW, Himmelfarb J; Hemodialysis Fistula Maturation Study Group: Histopathology of veins obtained at hemodialysis arteriovenous fistula creation surgery. *J Am Soc Nephrol* 28: 3076–3088, 2017 https://doi.org/10.1681/ASN.2016050598
6. Allon M, Litovsky SH, Tey JCS, Sundberg CA, Zhang Y, Chen Z, Fang Y, Cheung AK, Shiu YT: Abnormalities of vascular histology and collagen fiber configuration in patients with advanced

chronic kidney disease. *J Vasc Access* 20: 31–40, 2019 https://doi.org/10.1177/1129729818773305
7. Rothuizen TC, Wong C, Quax PH, van Zonneveld AJ, Rabelink TJ, Rotmans JI: Arteriovenous access failure: More than just intimal hyperplasia? *Nephrol Dial Transplant* 28: 1085–1092, 2013 https://doi.org/10.1093/ndt/gft068
8. Wu CC, Wen SC, Yang CW, Pu SY, Tsai KC, Chen JW: Plasma ADMA predicts restenosis of arteriovenous fistula. *J Am Soc Nephrol* 20: 213–222, 2009 https://doi.org/10.1681/ASN.2008050476
9. Clark TW, Hirsch DA, Jindal KJ, Veugelers PJ, LeBlanc J: Outcome and prognostic factors of restenosis after percutaneous treatment of native hemodialysis fistulas. *J Vasc Interv Radiol* 13: 51–59, 2002 https://doi.org/10.1016/S1051-0443(07)60009-8
10. Romann A, Beaulieu MC, Rhéaume P, Clement J, Sidhu R, Kiaii M: Risk factors associated with arteriovenous fistula failure after first radiologic intervention. *J Vasc Access* 17: 167–174, 2016 https://doi.org/10.5301/jva.5000459
11. Malka KT, Flahive J, Csizinscky A, Aiello F, Simons JP, Schanzer A, Messina LM, Robinson WP: Results of repeated percutaneous interventions on failing arteriovenous fistulas and grafts and factors affecting outcomes. *J Vasc Surg* 63: 772–777, 2016 https://doi.org/10.1016/j.jvs.2015.09.031
12. Troisi N, Frosini P, Romano E, Guidotti A, Chisci E, Michelagnoli S: Freeway paclitaxel-releasing balloons to treat recurrent stenosis of arteriovenous fistula in hemodialysis patients. *Minerva Cardioangiol* 66: 233–237, 2018 https://doi.org/10.23736/S0026-4725.17.04534-0
13. Yin Y, Shi Y, Cui T, Li H, Chen J, Zhang L, Yu Z, Li H, Yan Y, Wu K, Jin Q: Efficacy and safety of paclitaxel-coated balloon angioplasty for dysfunctional arteriovenous fistulas: A multicenter randomized controlled trial [published online ahead of print January 5, 2021]. *Am J Kidney Dis* 10.1053/j.ajkd.2020.11.022
14. Trerotola SO, Saad TF, Roy-Chaudhury P; Lutonix AV Clinical Trial Investigators: The Lutonix AV Randomized Trial of paclitaxel-coated balloons in arteriovenous fistula stenosis: 2-Year results and subgroup analysis. *J Vasc Interv Radiol* 31: 1–14.e5, 2020 https://doi.org/10.1016/j.jvir.2019.08.035
15. Lok CE, Huber TS, Lee T, Shenoy S, Yevzlin AS, Abreo K, Allon M, Asif A, Astor BC, Glickman MH, Graham J, Moist LM, Rajan DK, Roberts C, Vachharajani TJ, Valentini RP; National Kidney Foundation: KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update [published correction appears in *Am J Kidney Dis* 77: 551, 2021]. *Am J Kidney Dis* 75[Suppl 2]: S1–S164, 2020 Available at: https://doi.org/10.1053/j.ajkd.2019.12.001. Accessed May 20, 2021
16. Spivack DE, Kelly P, Gaughan JP, van Bemmelen PS: Mapping of superficial extremity veins: Normal diameters and trends in a vascular patient-population. *Ultrasound Med Biol* 38: 190–194, 2012 https://doi.org/10.1016/j.ultrasmedbio.2011.11.008
17. van Bemmelen PS, Kelly P, Blebea J: Improvement in the visualization of superficial arm veins being evaluated for access and bypass. *J Vasc Surg* 42: 957–962, 2005 https://doi.org/10.1016/j.jvs.2005.06.021
18. Lee T, Chauhan V, Krishnamoorthy M, Wang Y, Arend L, Mistry MJ, El-Khatib M, Banerjee R, Munda R, Roy-Chaudhury P: Severe venous neointimal hyperplasia prior to dialysis access surgery. *Nephrol Dial Transplant* 26: 2264–2270, 2011 https://doi.org/10.1093/ndt/gfq733
19. Lazich I, Chang A, Watson S, Dhar P, Madhurapantula RS, Hammes M: Morphometric and histological parameters in veins of diabetic patients undergoing brachiocephalic fistula placement. *Hemodial Int* 19: 490–498, 2015 https://doi.org/10.1111/hdi.12289
20. Oprea A, Molnar A, Encică S, VlăduŢiu DŞ, Scridon GT, Săcui DM, Săsărman VA, Mircea PA: Effect of the veins histopathological characteristics and preexisting medical conditions on arteriovenous fistula maturation and primary patency in patients with end-stage renal disease: An observational, prospective study. *Rom J Morphol Embryol* 58: 871–880, 2017
21. Lee T, Somarathna M, Hura A, Wang Y, Campos B, Arend L, Munda R, Roy-Chaudhury P: Natural history of venous morphologic changes in dialysis access stenosis. *J Vasc Access* 15: 298–305, 2014 https://doi.org/10.5301/jva.5000212
22. Allon M, Litovsky S, Young CJ, Deierhoi MH, Goodman J, Hanaway M, Lockhart ME, Robbin ML: Medial fibrosis, vascular calcification, intimal hyperplasia, and arteriovenous fistula maturation. *Am J Kidney Dis* 58: 437–443, 2011 https://doi.org/10.1053/j.ajkd.2011.04.018
23. Feinfeld DA, Batista R, Mir R, Babich D: Changes in venous histology in chronic hemodialysis patients. *Am J Kidney Dis* 34: 702–705, 1999 https://doi.org/10.1016/S0272-6386(99)70396-3
24. Wasse H, Huang R, Naqvi N, Smith E, Wang D, Husain A: Inflammation, oxidation and venous neointimal hyperplasia precede vascular injury from AVF creation in CKD patients. *J Vasc Access* 13: 168–174, 2012 https://doi.org/10.5301/jva.5000024
25. Wali MA, Eid RA, Dewan M, Al-Homrany MA: Intimal changes in the cephalic vein of renal failure patients before arterio-venous fistula (AVF) construction. *J Smooth Muscle Res* 39: 95–105, 2003 https://doi.org/10.1540/jsmr.39.95
26. Wali MA, Eid RA, Dewan M, Al-Homrany MA: Pre-existing histopathological changes in the cephalic vein of renal failure patients before arterio-venous fistula (AVF) construction. *Ann Thorac Cardiovasc Surg* 12: 341–348, 2006
27. Monroy MA, Fang J, Li S, Ferrer L, Birkenbach MP, Lee IJ, Wang H, Yang XF, Choi ET: Chronic kidney disease alters vascular smooth muscle cell phenotype. *Front Biosci* 20: 784–795, 2015 https://doi.org/10.2741/4337
28. Davies AH, Magee TR, Baird RN, Sheffield E, Horrocks M: Pre-bypass morphological changes in vein grafts. *Eur J Vasc Surg* 7: 642–647, 1993 https://doi.org/10.1016/S0950-821X(05)80710-8
29. Zhao J, Jourd'heuil FL, Xue M, Conti D, Lopez-Soler RI, Ginnan R, Asif A, Singer HA, Jourd'heuil D, Long X: Dual function for mature vascular smooth muscle cells during arteriovenous fistula remodeling. *J Am Heart Assoc* 6: e004891, 2017 https://doi.org/10.1161/JAHA.116.004891
30. Ahanchi SS, Tsihlis ND, Kibbe MR: The role of nitric oxide in the pathophysiology of intimal hyperplasia. *J Vasc Surg* 45: A64–A73, 2007 https://doi.org/10.1016/j.jvs.2007.02.027
31. Allen KE, Varty K, Jones L, Sayers RD, Bell PR, London NJ: Human venous endothelium can promote intimal hyperplasia in a paracrine manner. *J Vasc Surg* 19: 577–584, 1994 https://doi.org/10.1016/S0741-5214(94)70029-X
32. Wali MA, Eid RA, Al-Homrany MA: Smooth muscle changes in the cephalic vein of renal failure patients before use as an arteriovenous fistula (AVF). *J Smooth Muscle Res* 38: 75–85, 2002 https://doi.org/10.1540/jsmr.38.75
33. Bolton CH, Downs LG, Victory JG, Dwight JF, Tomson CR, Mackness MI, Pinkney JH: Endothelial dysfunction in chronic renal failure: Roles of lipoprotein oxidation and pro-inflammatory cytokines. *Nephrol Dial Transplant* 16: 1189–1197, 2001 https://doi.org/10.1093/ndt/16.6.1189
34. Małyszko J, Małyszko JS, Myśliwiec M: Endothelial cell injury markers in chronic renal failure on conservative treatment and continuous ambulatory peritoneal dialysis. *Kidney Blood Press Res* 27: 71–77, 2004 https://doi.org/10.1159/000075810
35. Kuczmarski JM, Darocki MD, DuPont JJ, Sikes RA, Cooper CR, Farquhar WB, Edwards DG: Effect of moderate-to-severe chronic kidney disease on flow-mediated dilation and progenitor cells. *Exp Biol Med (Maywood)* 236: 1085–1092, 2011 https://doi.org/10.1258/ebm.2011.011008
36. Costa-Hong V, Bortolotto LA, Jorgetti V, Consolim-Colombo F, Krieger EM, Lima JJ: Oxidative stress and endothelial dysfunction in chronic kidney disease. *Arq Bras Cardiol* 92: 381–386, 398–403, 413–418, 2009 10.1590/s0066-782x2009000500013
37. Han L, Zhang Y, Zhang M, Guo L, Wang J, Zeng F, Xu D, Yin Z, Xu Y, Wang D, Zhou H: Interleukin-1β-induced senescence promotes osteoblastic transition of vascular smooth muscle cells. *Kidney Blood Press Res* 45: 314–330, 2020 https://doi.org/10.1159/000504298
38. Iwamoto Y, Maruhashi T, Kajikawa M, Oda N, Kishimoto S, Matsui S, Hashimoto H, Aibara Y, Yusoff FM, Hidaka T, Kihara Y, Chayama K, Noma K, Nakashima A, Goto C, Higashi Y: Chronic kidney disease is associated with vascular smooth muscle dysfunction but not with endothelial dysfunction. *Int J*

Cardiol 254: 284–290, 2018 https://doi.org/10.1016/j.ijcard.2017.10.122
39. Recio-Mayoral A, Banerjee D, Streather C, Kaski JC: Endothelial dysfunction, inflammation and atherosclerosis in chronic kidney disease–a cross-sectional study of predialysis, dialysis and kidney-transplantation patients. *Atherosclerosis* 216: 446–451, 2011 https://doi.org/10.1016/j.atherosclerosis.2011.02.017
40. Lee T, Wang Y, Arend L, Cornea V, Campos B, Munda R, Roy-Chaudhury P: Comparative analysis of cellular phenotypes within the neointima from vein segments collected prior to vascular access surgery and stenotic arteriovenous dialysis accesses. *Semin Dial* 27: 303–309, 2014 https://doi.org/10.1111/sdi.12172
41. Roy-Chaudhury P, Arend L, Zhang J, Krishnamoorthy M, Wang Y, Banerjee R, Samaha A, Munda R: Neointimal hyperplasia in early arteriovenous fistula failure. *Am J Kidney Dis* 50: 782–790, 2007 https://doi.org/10.1053/j.ajkd.2007.07.019
42. Rensen SS, Doevendans PA, van Eys GJ: Regulation and characteristics of vascular smooth muscle cell phenotypic diversity. *Neth Heart J* 15: 100–108, 2007 https://doi.org/10.1007/BF03085963
43. Li FD, Sexton KW, Hocking KM, Osgood MJ, Eagle S, Cheung-Flynn J, Brophy CM, Komalavilas P: Intimal thickness associated with endothelial dysfunction in human vein grafts. *J Surg Res* 180: e55–e62, 2013 https://doi.org/10.1016/j.jss.2012.06.017
44. Martinez L, Tabbara M, Duque JC, Selman G, Falcon NS, Paez A, Griswold AJ, Ramos-Echazabal G, Hernandez DR, Velazquez OC, Salman LH, Vazquez-Padron RI: Transcriptomics of human arteriovenous fistula failure: Genes associated with nonmaturation. *Am J Kidney Dis* 74: 73–81, 2019 https://doi.org/10.1053/j.ajkd.2018.12.035
45. Nelson PR, Yamamura S, Kent KC: Extracellular matrix proteins are potent agonists of human smooth muscle cell migration. *J Vasc Surg* 24: 25–33, 1996 https://doi.org/10.1016/S0741-5214(96)70141-6
46. Hollenbeck ST, Itoh H, Louie O, Faries PL, Liu B, Kent KC: Type I collagen synergistically enhances PDGF-induced smooth muscle cell proliferation through pp60src-dependent crosstalk between the alpha2beta1 integrin and PDGFbeta receptor. *Biochem Biophys Res Commun* 325: 328–337, 2004 https://doi.org/10.1016/j.bbrc.2004.10.031
47. Raines EW: The extracellular matrix can regulate vascular cell migration, proliferation, and survival: relationships to vascular disease. *Int J Exp Pathol* 81: 173–182, 2000 https://doi.org/10.1046/j.1365-2613.2000.00155.x
48. Raines EW, Koyama H, Carragher NO: The extracellular matrix dynamically regulates smooth muscle cell responsiveness to PDGF. *Ann N Y Acad Sci* 902: 39–51, discussion 51–52, 2000 https://doi.org/10.1111/j.1749-6632.2000.tb06299.x
49. Xu J, Shi GP: Vascular wall extracellular matrix proteins and vascular diseases. *Biochim Biophys Acta* 1842: 2106–2119, 2014 https://doi.org/10.1016/j.bbadis.2014.07.008
50. Wang R, Raykin J, Li H, Gleason RL Jr, Brewster LP: Differential mechanical response and microstructural organization between non-human primate femoral and carotid arteries. *Biomech Model Mechanobiol* 13: 1041–1051, 2014 https://doi.org/10.1007/s10237-014-0553-0
51. Gandhi NS, Mancera RL: The structure of glycosaminoglycans and their interactions with proteins. *Chem Biol Drug Des* 72: 455–482, 2008 https://doi.org/10.1111/j.1747-0285.2008.00741.x
52. Cheung AK, Imrey PB, Alpers CE, Robbin ML, Radeva M, Larive B, Shiu YT, Allon M, Dember LM, Greene T, Himmelfarb J, Roy-Chaudhury P, Terry CM, Vazquez MA, Kusek JW, Feldman HI; Hemodialysis Fistula Maturation Study Group: Intimal hyperplasia, stenosis, and arteriovenous fistula maturation failure in the Hemodialysis Fistula Maturation Study. *J Am Soc Nephrol* 28: 3005–3013, 2017 https://doi.org/10.1681/ASN.2016121355
53. Remuzzi A, Bozzetto M: Biological and physical factors involved in the maturation of arteriovenous fistula for hemodialysis. *Cardiovasc Eng Technol* 8: 273–279, 2017 https://doi.org/10.1007/s13239-017-0323-0
54. Asif A, Roy-Chaudhury P, Beathard GA: Early arteriovenous fistula failure: A logical proposal for when and how to intervene. *Clin J Am Soc Nephrol* 1: 332–339, 2006 https://doi.org/10.2215/CJN.00850805
55. Pike D, Shiu YT, Cho YF, Le H, Somarathna M, Isayeva T, Guo L, Symons JD, Kevil CG, Totenhagen J, Lee T: The effect of endothelial nitric oxide synthase on the hemodynamics and wall mechanics in murine arteriovenous fistulas [published correction appears in *Sci Rep* 9: 15555, 2019]. *Sci Rep* 9: 4299, 2019 https://doi.org/10.1038/s41598-019-40683-7
56. Predel HG, Yang Z, von Segesser L, Turina M, Bühler FR, Lüscher TF: Implications of pulsatile stretch on growth of saphenous vein and mammary artery smooth muscle. *Lancet* 340: 878–879, 1992 https://doi.org/10.1016/0140-6736(92)93287-W
57. Paszkowiak JJ, Dardik A: Arterial wall shear stress: Observations from the bench to the bedside. *Vasc Endovascular Surg* 37: 47–57, 2003 https://doi.org/10.1177/153857440303700107
58. Corpataux JM, Haesler E, Silacci P, Ris HB, Hayoz D: Low-pressure environment and remodelling of the forearm vein in Brescia-Cimino haemodialysis access. *Nephrol Dial Transplant* 17: 1057–1062, 2002 https://doi.org/10.1093/ndt/17.6.1057
59. Shiu YT, Rotmans JI, Geelhoed WJ, Pike DB, Lee T: Arteriovenous conduits for hemodialysis: How to better modulate the pathophysiological vascular response to optimize vascular access durability. *Am J Physiol Renal Physiol* 316: F794–F806, 2019 https://doi.org/10.1152/ajprenal.00440.2018
60. Bartlett M, Diaz-Zuccarini V, Tsui J: Computer assisted Doppler waveform analysis and ultrasound derived turbulence intensity ratios can predict early hyperplasia development in newly created vascular access fistula: Pilot study, methodology and analysis. *JRSM Cardiovasc Dis* 10: 20480040211000185, 2021 https://doi.org/10.1177/20480040211000185
61. Roy-Chaudhury P, Wang Y, Krishnamoorthy M, Zhang J, Banerjee R, Munda R, Heffelfinger S, Arend L: Cellular phenotypes in human stenotic lesions from haemodialysis vascular access. *Nephrol Dial Transplant* 24: 2786–2791, 2009 https://doi.org/10.1093/ndt/gfn708
62. de Graaf R, Dammers R, Vainas T, Hoeks AP, Tordoir JH: Detection of cell-cycle regulators in failed arteriovenous fistulas for haemodialysis. *Nephrol Dial Transplant* 18: 814–818, 2003 https://doi.org/10.1093/ndt/gfg033
63. Hofstra L, Tordoir JH, Kitslaar PJ, Hoeks AP, Daemen MJ: Enhanced cellular proliferation in intact stenotic lesions derived from human arteriovenous fistulas and peripheral bypass grafts. Does it correlate with flow parameters? *Circulation* 94: 1283–1290, 1996 https://doi.org/10.1161/01.CIR.94.6.1283
64. Stracke S, Konner K, Köstlin I, Friedl R, Jehle PM, Hombach V, Keller F, Waltenberger J: Increased expression of TGF-beta1 and IGF-I in inflammatory stenotic lesions of hemodialysis fistulas. *Kidney Int* 61: 1011–1019, 2002 https://doi.org/10.1046/j.1523-1755.2002.00191.x
65. Chang CJ, Ko YS, Ko PJ, Hsu LA, Chen CF, Yang CW, Hsu TS, Pang JH: Thrombosed arteriovenous fistula for hemodialysis access is characterized by a marked inflammatory activity. *Kidney Int* 68: 1312–1319, 2005 https://doi.org/10.1111/j.1523-1755.2005.00529.x
66. Weiss MF, Scivittaro V, Anderson JM: Oxidative stress and increased expression of growth factors in lesions of failed hemodialysis access. *Am J Kidney Dis* 37: 970–980, 2001 https://doi.org/10.1016/S0272-6386(05)80013-7
67. Wong CY, de Vries MR, Wang Y, van der Vorst JR, Vahrmeijer AL, van Zonneveld AJ, Roy-Chaudhury P, Rabelink TJ, Quax PH, Rotmans JI: Vascular remodeling and intimal hyperplasia in a novel murine model of arteriovenous fistula failure. *J Vasc Surg* 59: 192–201.e1, 2014 https://doi.org/10.1016/j.jvs.2013.02.242
68. Duque JC, Martinez L, Mesa A, Wei Y, Tabbara M, Salman LH, Vazquez-Padron RI: CD4(+) lymphocytes improve venous blood flow in experimental arteriovenous fistulae. *Surgery* 158: 529–536, 2015 https://doi.org/10.1016/j.surg.2015.02.018
69. Guo X, Fereydooni A, Isaji T, Gorecka J, Liu S, Hu H, Ono S, Alozie M, Lee SR, Taniguchi R, Yatsula B, Nassiri N, Zhang L, Dardik A: Inhibition of the Akt1-mTORC1 axis alters venous remodeling to improve arteriovenous fistula patency [published correction appears in *Sci Rep* 10: 8301, 2020]. *Sci Rep* 9: 11046, 2019 https://doi.org/10.1038/s41598-019-47542-5

70. Roy-Chaudhury P, Khan R, Campos B, Wang Y, Kurian M, Lee T, Arend L, Munda R: Pathogenetic role for early focal macrophage infiltration in a pig model of arteriovenous fistula (AVF) stenosis. *J Vasc Access* 15: 25–28, 2014 https://doi.org/10.5301/jva.5000151
71. Duque JC, Tabbara M, Martinez L, Paez A, Selman G, Salman LH, Velazquez OC, Vazquez-Padron RI: Similar degree of intimal hyperplasia in surgically detected stenotic and nonstenotic arteriovenous fistula segments: A preliminary report. *Surgery* 163: 866–869, 2018 https://doi.org/10.1016/j.surg.2017.10.038
72. Wang Y, Krishnamoorthy M, Banerjee R, Zhang J, Rudich S, Holland C, Arend L, Roy-Chaudhury P: Venous stenosis in a pig arteriovenous fistula model–anatomy, mechanisms and cellular phenotypes. *Nephrol Dial Transplant* 23: 525–533, 2008 https://doi.org/10.1093/ndt/gfm547
73. Florescu MC, Foster KW, Sacks AR, Lof J, Stolze EA, Fry GM, Bumgardner DP, Tysinger T, Kuchta MJ, Runge HJ, Hadley WB, Morris MC: Sheep model of hemodialysis arteriovenous fistula using superficial veins. *Semin Dial* 28: 687–691, 2015 https://doi.org/10.1111/sdi.12407
74. Krishnamoorthy MK, Banerjee RK, Wang Y, Zhang J, Sinha Roy A, Khoury SF, Arend LJ, Rudich S, Roy-Chaudhury P: Hemodynamic wall shear stress profiles influence the magnitude and pattern of stenosis in a pig AV fistula. *Kidney Int* 74: 1410–1419, 2008 https://doi.org/10.1038/ki.2008.379
75. Chan JS, Campos B, Wang Y, Mistry M, Lee T, Munda R, Arend L, Roy-Chaudhury P: Proliferation patterns in a pig model of AV fistula stenosis: Can we translate biology into novel therapies? *Semin Dial* 27: 626–632, 2014 https://doi.org/10.1111/sdi.12240
76. Manning E, Skartsis N, Orta AM, Velazquez OC, Liu ZJ, Asif A, Salman LH, Vazquez-Padron RI: A new arteriovenous fistula model to study the development of neointimal hyperplasia. *J Vasc Res* 49: 123–131, 2012 https://doi.org/10.1159/000332327
77. Skartsis N, Manning E, Wei Y, Velazquez OC, Liu ZJ, Goldschmidt-Clermont PJ, Salman LH, Asif A, Vazquez-Padron RI: Origin of neointimal cells in arteriovenous fistulae: Bone marrow, artery, or the vein itself? *Semin Dial* 24: 242–248, 2011 https://doi.org/10.1111/j.1525-139X.2011.00870.x
78. Hall MR, Yamamoto K, Protack CD, Tsuneki M, Kuwahara G, Assi R, Brownson KE, Bai H, Madri JA, Dardik A: Temporal regulation of venous extracellular matrix components during arteriovenous fistula maturation. *J Vasc Access* 16: 93–106, 2015 https://doi.org/10.5301/jva.5000290
79. Chan CY, Chen YS, Ma MC, Chen CF: Remodeling of experimental arteriovenous fistula with increased matrix metalloproteinase expression in rats [published correction appears in *J Vasc Surg* 45: 1293, 2007]. *J Vasc Surg* 45: 804–811, 2007 https://doi.org/10.1016/j.jvs.2006.12.063
80. Kohler TR, Toleikis PM, Gravett DM, Avelar RL: Inhibition of neointimal hyperplasia in a sheep model of dialysis access failure with the bioabsorbable vascular wrap paclitaxel-eluting mesh. *J Vasc Surg* 45: 1029–1037, discussion 1037–1038, 2007 https://doi.org/10.1016/j.jvs.2007.01.057
81. Terry CM, Li L, Li H, Zhuplatov I, Blumenthal DK, Kim SE, Owen SC, Kholmovski EG, Fowers KD, Rathi R, Cheung AK: In vivo evaluation of the delivery and efficacy of a sirolimus-laden polymer gel for inhibition of hyperplasia in a porcine model of arteriovenous hemodialysis graft stenosis. *J Control Release* 160: 459–467, 2012 https://doi.org/10.1016/j.jconrel.2012.03.011
82. Rotmans JI, Pattynama PM, Verhagen HJ, Hino I, Velema E, Pasterkamp G, Stroes ES: Sirolimus-eluting stents to abolish intimal hyperplasia and improve flow in porcine arteriovenous grafts: A 4-week follow-up study. *Circulation* 111: 1537–1542, 2005 https://doi.org/10.1161/01.CIR.0000159332.18585.B5
83. Kelly B, Melhem M, Zhang J, Kasting G, Li J, Krishnamoorthy M, Heffelfinger S, Rudich S, Desai P, Roy-Chaudhury P: Perivascular paclitaxel wraps block arteriovenous graft stenosis in a pig model. *Nephrol Dial Transplant* 21: 2425–2431, 2006 https://doi.org/10.1093/ndt/gfl250
84. Rotmans JI: Animal models for studying pathophysiology of hemodialysis access. *Open Urol Nephrol J* 7: 14–21, 2014 https://doi.org/10.2174/1874303X01407010014
85. Kokozidou M, Katsargyris A, Verhoeven ELG, Schulze-Tanzil G: Vascular access animal models used in research. *Ann Anat* 225: 65–75, 2019 https://doi.org/10.1016/j.aanat.2019.06.002
86. Bao YW, Yuan Y, Chen JH, Lin WQ: Kidney disease models: Tools to identify mechanisms and potential therapeutic targets. *Zool Res* 39: 72–86, 2018 https://doi.org/10.24272/j.issn.2095-8137.2017.055
87. Yang HC, Zuo Y, Fogo AB: Models of chronic kidney disease. *Drug Discov Today Dis Models* 7: 13–19, 2010 https://doi.org/10.1016/j.ddmod.2010.08.002
88. MacRae JM, Dipchand C, Oliver M, Moist L, Lok C, Clark E, Hiremath S, Kappel J, Kiaii M, Luscombe R, Miller LM; Canadian Society of Nephrology Vascular Access Work Group: Arteriovenous access failure, stenosis, and thrombosis. *Can J Kidney Health Dis* 3: 2054358116669126, 2016 https://doi.org/10.1177/2054358116669126
89. Ginsburg M, Lorenz JM, Zivin SP, Zangan S, Martinez D: A practical review of the use of stents for the maintenance of hemodialysis access. *Semin Intervent Radiol* 32: 217–224, 2015 https://doi.org/10.1055/s-0035-1549844
90. Dolmatch BL, Tio FO, Li XD, Dong YH: Patency and tissue response related to two types of polytetrafluoroethylene-covered stents in the dog. *J Vasc Interv Radiol* 7: 641–649, 1996 https://doi.org/10.1016/S1051-0443(96)70822-9
91. Jones RG, Willis AP, Tullett K, Riley PL: Results of stent graft placement to treat cephalic arch stenosis in hemodialysis patients with dysfunctional brachiocephalic arteriovenous fistulas. *J Vasc Interv Radiol* 28: 1417–1421, 2017 https://doi.org/10.1016/j.jvir.2017.06.023
92. Swinnen JJ, Hitos K, Kairaitis L, Gruenewald S, Larcos G, Farlow D, Huber D, Cassorla G, Leo C, Villalba LM, Allen R, Niknam F, Burgess D: Multicentre, randomised, blinded, control trial of drug-eluting balloon vs sham in recurrent native dialysis fistula stenoses. *J Vasc Access* 20: 260–269, 2019 https://doi.org/10.1177/1129729818801556
93. Karnabatidis D, Kitrou PM, Ponce P, Chong TT, Pietura R, Pegis JD, Ko PJ, Lin CH; Lutonix AV Global Registry Investigators: A multicenter global registry of paclitaxel drug-coated balloon in dysfunctional arteriovenous fistulae and grafts: 6-Month results. *J Vasc Interv Radiol* 32: 360–368.e2, 2021 https://doi.org/10.1016/j.jvir.2020.11.018
94. Kocaaslan C, Oztekin A, Bademci MS, Denli Yalvac ES, Bulut N, Aydin E: A retrospective comparison analysis of results of drug-coated balloon versus plain balloon angioplasty in treatment of juxta-anastomotic de novo stenosis of radiocephalic arteriovenous fistulas. *J Vasc Access* 21: 596–601, 2020 https://doi.org/10.1177/1129729819893205
95. Lookstein RA, Haruguchi H, Ouriel K, Weinberg I, Lei L, Cihlar S, Holden A; IN.PACT AV Access Investigators: Drug-coated balloons for dysfunctional dialysis arteriovenous fistulas. *N Engl J Med* 383: 733–742, 2020 https://doi.org/10.1056/NEJMoa1914617
96. Liao MT, Chen MK, Hsieh MY, Yeh NL, Chien KL, Lin CC, Wu CC, Chie WC: Drug-coated balloon versus conventional balloon angioplasty of hemodialysis arteriovenous fistula or graft: A systematic review and meta-analysis of randomized controlled trials [published correction appears in *PLoS One* 15: e0233923, 2020]. *PLoS One* 15: e0231463, 2020 https://doi.org/10.1371/journal.pone.0231463
97. Rokoszak V, Syed MH, Salata K, Greco E, de Mestral C, Hussain MA, Aljabri B, Verma S, Al-Omran M: A systematic review and meta-analysis of plain versus drug-eluting balloon angioplasty in the treatment of juxta-anastomotic hemodialysis arteriovenous fistula stenosis. *J Vasc Surg* 71: 1046–1054.e1, 2020 https://doi.org/10.1016/j.jvs.2019.07.075
98. Yan Wee IJ, Yap HY, Hsien Ts'ung LT, Lee Qingwei S, Tan CS, Tang TY, Chong TT: A systematic review and meta-analysis of drug-coated balloon versus conventional balloon angioplasty for dialysis access stenosis. *J Vasc Surg* 70: 970–979.e3, 2019 https://doi.org/10.1016/j.jvs.2019.01.082
99. Abdul Salim S, Tran H, Thongprayoon C, Fülöp T, Cheungpasitporn W: Comparison of drug-coated balloon angioplasty versus conventional angioplasty for arteriovenous fistula stenosis: Systematic review and meta-analysis. *J Vasc Access* 21: 357–365, 2020 https://doi.org/10.1177/1129729819878612

100. Granada JF, Stenoien M, Buszman PP, Tellez A, Langanki D, Kaluza GL, Leon MB, Gray W, Jaff MR, Schwartz RS: Mechanisms of tissue uptake and retention of paclitaxel-coated balloons: Impact on neointimal proliferation and healing. *Open Heart* 1: e000117, 2014 https://doi.org/10.1136/openhrt-2014-000117
101. Speck U, Häckel A, Schellenberger E, Kamann S, Löchel M, Clever YP, Peters D, Scheller B, Trog S, Bettink S: Drug distribution and basic pharmacology of paclitaxel/resveratrol-coated balloon catheters. *Cardiovasc Intervent Radiol* 41: 1599–1610, 2018 https://doi.org/10.1007/s00270-018-2018-9
102. Murphy GJ, Johnson TW, Chamberlain MH, Rizvi SI, Wyatt M, George SJ, Angelini GD, Karsch KR, Oberhoff M, Newby AC: Short- and long-term effects of cytochalasin D, paclitaxel and rapamycin on wall thickening in experimental porcine vein grafts. *Cardiovasc Res* 73: 607–617, 2007 https://doi.org/10.1016/j.cardiores.2006.11.015
103. Yang H-M, Cho H-J, Park K-W, Cho H-J, Kang H-J, Koo B-K, Sohn D-W, Oh B-H, Park Y-B, Kim H-S: Paclitaxel itself induces drug-resistance to paclitaxel in vascular smooth muscle cells and reduces its effect of suppression of neointimal hyperplasia after angioplasty. *J Am Coll Cardiol* 57: E2053, 2011 https://doi.org/10.1016/S0735-1097(11)62053-6
104. Wiskirchen J, Schöber W, Schart N, Kehlbach R, Wersebe A, Tepe G, Claussen CD, Duda SH: The effects of paclitaxel on the three phases of restenosis: Smooth muscle cell proliferation, migration, and matrix formation: An in vitro study. *Invest Radiol* 39: 565–571, 2004 https://doi.org/10.1097/01.rli.0000133815.22434.55
105. Sollott SJ, Cheng L, Pauly RR, Jenkins GM, Monticone RE, Kuzuya M, Froehlich JP, Crow MT, Lakatta EG, Rowinsky EK: Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest* 95: 1869–1876, 1995 https://doi.org/10.1172/JCI117867
106. Blagosklonny MV, Demidenko ZN, Giovino M, Szynal C, Donskoy E, Herrmann RA, Barry JJ, Whalen AM: Cytostatic activity of paclitaxel in coronary artery smooth muscle cells is mediated through transient mitotic arrest followed by permanent post-mitotic arrest: Comparison with cancer cells. *Cell Cycle* 5: 1574–1579, 2006 https://doi.org/10.4161/cc.5.14.3113
107. Blagosklonny MV, Darzynkiewicz Z, Halicka HD, Pozarowski P, Demidenko ZN, Barry JJ, Kamath KR, Herrmann RA: Paclitaxel induces primary and postmitotic G1 arrest in human arterial smooth muscle cells. *Cell Cycle* 3: 1050–1056, 2004 https://doi.org/10.4161/cc.3.8.986
108. DeVita MV, Khine SK, Shivarov H: Novel approaches to arteriovenous access creation, maturation, suitability, and durability for dialysis. Kidney Int Rep 5: 769-778, 2020
109. Conte MS, Nugent HM, Gaccione P, Guleria I, Roy-Chaudhury P, Lawson JH: Multicenter phase I/II trial of the safety of allogeneic endothelial cell implants after the creation of arteriovenous access for hemodialysis use: The V-HEALTH study. *J Vasc Surg* 50: 1359–68.e1, 2009 https://doi.org/10.1016/j.jvs.2009.07.108
110. Conte MS, Nugent HM, Gaccione P, Roy-Chaudhury P, Lawson JH: Influence of diabetes and perivascular allogeneic endothelial cell implants on arteriovenous fistula remodeling. *J Vasc Surg* 54: 1383–1389, 2011 https://doi.org/10.1016/j.jvs.2011.05.005
111. Hye RJ, Peden EK, O'Connor TP, Browne BJ, Dixon BS, Schanzer AS, Jensik SC, Dember LM, Jaff MR, Burke SK: Human type I pancreatic elastase treatment of arteriovenous fistulas in patients with chronic kidney disease. *J Vasc Surg* 60: 454–461.e1, 2014 https://doi.org/10.1016/j.jvs.2014.02.037
112. Peden EK, Leeser DB, Dixon BS, El-Khatib MT, Roy-Chaudhury P, Lawson JH, Menard MT, Dember LM, Glickman MH, Gustafson PN, Blair AT, Magill M, Franano FN, Burke SK: A multi-center, dose-escalation study of human type I pancreatic elastase (PRT-201) administered after arteriovenous fistula creation. *J Vasc Access* 14: 143–151, 2013 https://doi.org/10.5301/jva.5000125
113. Chemla E, Velazquez CC, D'Abate F, Ramachandran V, Maytham G: Arteriovenous fistula construction with the VasQ™ external support device: A pilot study. *J Vasc Access* 17: 243–248, 2016 https://doi.org/10.5301/jva.5000527
114. Palumbo R, Dominijanni S, Centi A, D'Urso G, Tatangelo P, Floccari F, Smedile G, Niscola P, Londrino F, Di Daniele N: Hemodynamic impact of VASQ device in vascular access creation [published online ahead of print December 21, 2020]. *J Vasc Access* 10.1177/1129729820983153
115. Chemla E, Tavakoli A, Nikam M, Mitra S, Malete T, Evans J, Roy-Chaudhury P: Arteriovenous fistula creation using the Optiflow™ vascular anastomotic connector: The OPEN (Optiflow PatEncy and MaturatioN) study. *J Vasc Access* 15: 38–44, 2014 https://doi.org/10.5301/jva.5000169
116. Nikam M, Chemla ES, Evans J, Summers A, Brenchley P, Tavakoli A, Roy-Chaudhury P, Mitra S: Prospective controlled pilot study of arteriovenous fistula placement using the novel Optiflow device. *J Vasc Surg* 61: 1020–1025, 2015 https://doi.org/10.1016/j.jvs.2014.11.082
117. Leonardi G, Campagna M, Pellicanò V, Guarena C, Bergamo D, Lavacca A, Fop F, Biancone L: Implanted blood vessel external support device (VasQ™) for creation of hemodialysis arteriovenous fistula: A single-center experience [published online ahead of print November 12, 2020]. *J Vasc Access* 10.1177/1129729820971533
118. Shahverdyan R, Meyer T, Matoussevitch V: Patency and functionality of radiocephalic arteriovenous fistulas with an external support device (VasQ™): Real-world single-center experience. *J Vasc Access* 22: 166–172, 2021 https://doi.org/10.1177/1129729820904599
119. Benedetto F, Spinelli D, Derone G, Cutrupi A, Barillà D, Pipitò N: Initial single-center experience with a new external support device for the creation of the forearm native arteriovenous fistula for hemodialysis [printed online ahead of print March 16, 2021]. *J Vasc Access* 10.1177/11297298211002570
120. Wan Q, Yang S, Li L, Chu F: Effects of far infrared therapy on arteriovenous fistulas in hemodialysis patients: A meta-analysis. *Ren Fail* 39: 613–622, 2017 https://doi.org/10.1080/0886022X.2017.1361835
121. Hadimeri U, Wärme A, Stegmayr B: A single treatment, using Far Infrared light improves blood flow conditions in arteriovenous fistula. *Clin Hemorheol Microcirc* 66: 211–217, 2017 https://doi.org/10.3233/CH-170254
122. Desai S, Mitra A, Arkans E, Singh TM: Early application of an intermittent pneumatic compression device is safe and results in proximal arteriovenous fistula enlargement. *J Vasc Access* 20: 24–30, 2019 https://doi.org/10.1177/1129729818773295
123. Sullivan B, Desai S, Singh TM, Mitra A: Early application of an intermittent pneumatic compression device assists dilation of radiocephalic fistulas. *J Vasc Access* 20: 146–152, 2019 https://doi.org/10.1177/1129729818787717
124. Io H, Nakata J, Aoyama R, Inoshita H, Nakano T, Ishizaka M, Fukui M, Tomino Y, Suzuki Y: Far-infrared therapy for secondary vascular access patency of hemodialysis patients. *Ren Replace Ther* 5: 31, 2019 https://doi.org/10.1186/s41100-019-0224-9

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