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Pre-existing and Postoperative Intimal Hyperplasia and Arteriovenous Fistula Outcomes

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Supplementary Material

Table S1: Associations between intimal thickness and clinical covariates on general linear regression analyses.

Table S2: Associations between intima-media ratio and clinical covariates on general linear regression analyses.

Table S3: Association between IH and primary unassisted patency using univariate Cox proportional hazards models.

Table S4: Association between postoperative IH and anatomic maturation failure by univariate logistic regression analysis.

Figure S1: Schematic representation of the two-staged brachio-basilic AVF surgery.

Figure S2: Microphotographs of an AVF section with advanced intimal lesion stained with antibodies against SMA and SM-MHC.

Figure S3: Matched pair analysis of vein and AVF from same patient showing change in medial thickness.

Item S1: Supplementary methods.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Supplementary Material Descriptive Text for Online Delivery

Supplementary Table S1 (PDF). Associations between intimal thickness and clinical covariates on general linear regression analyses.

Supplementary Table S2 (PDF). Associations between intima-media ratio and clinical covariates on general linear regression analyses.

Supplementary Table S3 (PDF). Association between IH and primary unassisted patency using univariate Cox proportional hazards models.

Supplementary Table S4 (PDF). Association between postoperative IH and anatomic maturation failure by univariate logistic regression analysis.

Supplementary Figure S1 (PDF). Schematic representation of the two-staged brachio-basilic AVF surgery.

Supplementary Figure S2 (PDF). Microphotographs of an AVF section with advanced intimal lesion stained with antibodies against SMA and SM-MHC.

Supplementary Figure S3 (PDF). Matched pair analysis of vein and AVF from same patient showing change in medial thickness.

Supplementary Item S1 (PDF). Supplementary methods.

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Abstract

Background—The contribution of intimal hyperplasia (IH) to arteriovenous fistula (AVF) failure is uncertain. This observational study assessed the relationship between preexisting, postoperative, and change in IH over time and AVF outcomes.

Study Design—Prospective cohort study with longitudinal assessment of IH at the time of AVF creation (pre-existing) and transposition (postoperative). Patients were followed-up for up to 3.3 years.

Setting & Participants—96 patients from a single center who underwent AVF surgery initially planned as a two-stage procedure. Veins and AVF samples were collected from 66 and 86 patients, respectively. Matched-pair tissues were available from 56 of these patients.

Predictors—Pre-existing, postoperative and change in IH over time.

Outcomes—Anatomic maturation failure was defined as an AVF that never reached a diameter greater than 6 mm. Primary unassisted patency was defined as the time elapsed from the second-stage surgery until first intervention.

Measurements—Maximal intimal thickness in veins and AVF and change in intimal thickness over time.

Results—Pre-existing IH (> 0.05 mm) was present in 98% of the patients. In this group, the median intimal thickness increased 4.40-fold (IQR, 2.17- to 4.94-fold) between the AVF creation and transposition. However, this change was not associated with the preexisting thickness ($r^2=0.002$; $p=0.7$). Ten of 96 AVFs (10%) never achieved maturation, while 70% of the vascular accesses remained patent at the end of the observational period. Postoperative IH was not associated with anatomic maturation failure using a univariate logistic regression. Pre-existing, postoperative, and change in IH over time had no effects on primary unassisted patency.

Limitations—The low number of patients from whom longitudinal tissue samples were available and the low incidence of anatomic maturation failure, which decreased the statistical power to find associations between end points and IH.

Conclusions—Pre-existing, postoperative, and change in IH over time were not associated with two-stage AVF outcomes.

Keywords

Intimal hyperplasia (IH); arteriovenous fistula (AVF); AVF creation; AVF transposition; failure; vascular access; stenosis; primary unassisted patency; intimal thickness; anatomic maturation failure; histology; vascular pathology; hemodialysis; outcomes; end-stage renal disease (ESRD)

The arteriovenous fistula (AVF) is the preferred vascular access for long-term hemodialysis.¹ Patients using an AVF have lower morbidity and mortality rates, and lower costs associated with maintenance of the vascular access compared to grafts and central venous catheters.^{2, 3} Despite the well-recognized advantages of AVFs, only 62% of dialysis-dependent patients

with end-stage renal disease (ESRD) in the United States are dialyzed through an AVF, and only 19% use this type of vascular access for hemodialysis initiation.⁴ These rates are lower than the 68% and 50% targets set by the Centers for Medicare & Medicaid Services (CMS) for prevalent use and initiation, respectively.⁴ The high frequency of AVF primary failure has been the most important barrier to reaching CMS goals.

Stenosis at the juxta-anastomotic venous segment is the main cause of AVF primary failure.⁵ It is believed that stenosis results from intimal hyperplasia (IH) and/or insufficient outward remodeling.⁶ However, the underlying mechanisms controlling development and hyperplastic expansion of the intima after vascular access creation are not well understood. The histological hallmark of this vascular pathology is the aggressive accumulation of myofibroblast-like cells in the inner layer of the vessel.⁷ It was only recently that the medial and adventitial origin of intimal cells in AVFs was elucidated.^{8, 9} Interestingly, pre-existing IH is frequently found in veins prior to vascular access creation,¹⁰ but its contribution to the pathogenesis of access failure is still controversial.^{11, 12} Since outward remodeling can compensate for the presence of IH and maintain an adequate luminal area, it is unclear whether IH is actually the main contributor of primary failure.

Using a prospective cohort of patients undergoing surgeries for two-stage AVF creation and transposition, which allowed the longitudinal collection of vein and AVF samples from the same individual, we assessed whether pre-existing, postoperative or change in IH over time had any association with AVF outcomes.

METHODS

Study Design

Patients aged 21 years and older scheduled for two-stage AVF creation (first-stage surgery) or AVF transposition (second-stage surgery) at Jackson Memorial Hospital and the University of Miami from 12/16/2011 through 01/25/14 were approached to participate in the study. The study consisted of collecting a segment of the pre-access vein or juxta-anastomotic area of the AVF for pathological evaluation. When vein and AVF samples from the same patient were available, a matched pair was formed to evaluate change in IH over time. Enrolled patients provided consent before the first- and second-stage surgeries. Clinical follow-up continued through 03/30/2015. Comorbidities, previous vascular access history and medications taken in the last 6 months prior to AVF creation (Tables 1 and 2) were obtained from the patient's electronic medical record. Ethnicity was defined as Hispanic and non-Hispanic blacks. All sections of the study were performed according to the ethical principles of the Declaration of Helsinki and regulatory requirements at both institutions. The ethics committee and Institutional Review Board at the University of Miami approved the study (IRB #20110645).

Figure S1 (provided as online supplementary material) depicts the overall surgical technique. A single surgeon (M.T.) performed all surgical procedures. Patients underwent venous and arterial mapping of the upper extremities prior to AVF creation. We followed the order of AVF preference as recommended by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI).¹³ A brachio-basilic AVF was chosen

when sizes of forearm and arm cephalic veins did not meet the size requirements for AVF creation by vessel mapping (89 patients). Five patients received brachio-brachial AVF due to the small size of the basilic vein (<3.5 mm). Any AVF with anatomic maturation failure (diameter ≤ 6 mm) underwent a short transposition or a graft extension during the second-stage procedure. Item S1 provides a detailed and complete description of the surgical procedures.

Definitions

Anatomic maturation failure was defined as an AVF that was created but never reached a diameter greater than 6 mm. Primary unassisted patency was defined as the time elapsed from the second-stage surgery until the first intervention. This patency definition for two-stage AVF avoids skewing this time-dependent variable with interpatient differences in the wait time between surgeries.

Specimen Collection and Tissue Processing

The circumferential vein and AVF biopsies consisted of a 1- to 2-mm sample collected at the site of transection during fistula creation (first-stage surgery) or transposition (second-stage surgery). The AVF biopsy was taken around 2 cm from the initial anastomosis if the length of the transected AVF was long enough to allow its transposition (Fig. S1). Vein and AVF biopsies were submerged in neutral formalin right after collection, and de-identified and labeled with a numerical code once in the research laboratory. Tissues were processed, paraffin-embedded, and sectioned for histology and immunohistochemistry.

Histological and Morphometric Analysis

Cross-sections were stained with Masson's trichrome and hematoxylin and eosin (H&E) stain for gross histopathological analysis. Myofibroblast/smooth muscle cells (SMCs) and contractile SMC were immunohistochemically stained with antibodies against α -smooth muscle cell actin (DAKO, Carpinteria, CA; clone 1A4) and SM-myosin heavy chain (Sigma Aldrich, clone hSM-V), respectively.¹⁴ Full digital images were acquired with a Visiontek digital microscope (Sakura, Torrance, CA). Maximal intimal thickness was defined as the maximal lineal distance from the internal elastic lamina to the endothelium as described by Lee et al.¹¹ Change in IH over time was calculated as the difference between the postoperative and pre-existing intimal thickness values. Measurements were performed using Image Pro Plus (Media Cybernetics, Rockville, MD). Additionally, the intima and media areas were determined in order to calculate the intima-media ratio. The cell (red) to collagen (blue) ratio was calculated from Masson's trichrome-stained sections using commercially available software and protocols for color segmentation. The final measurements represent the average of two independent measurements performed by two operators (?.?., ?.?.) blinded to the study data.

Statistical Analysis

Statistical analyses were performed using the SPSS software. Descriptive statistics were calculated for all variables. In all study groups, patients were stratified into low and high intimal thickness based on each group's median. Morphometric comparisons of longitudinal

samples from the same patient (matched pairs) were performed using paired t-tests with unequal variances. Normally distributed data were compared using t-test and expressed as mean $\pm$ standard deviation; otherwise, the Mann-Whitney test was used and data expressed as median and interquartile range (IQR). Comparisons between group frequencies were done using the chi-square test. Associations between clinical variables and maximal intimal thickness and intima-media ratios were assessed using a multivariate general linear regression adjusted for sex, age and diabetes. Linear regression analysis was used to explore relationships between continuous variables. The effect of post-operative IH on anatomic maturation failure was determined with a univariate logistic regression model. The impact of IH on primary unassisted patency was explored using Cox proportional hazards models after excluding maturation failures. Kaplan-Meier curves were generated with patient subgroups with low and high intimal thickness. Comparisons of Kaplan-Meier curves were performed by log-rank test.

RESULTS

Demographic, Clinical, and AVF Characteristics of Study Population

A total of 96 patients with planned two-stage AVF surgery were enrolled in the study. All patients underwent surgeries for AVF creation (first-stage) and transposition (second-stage). Three study groups were formed based on the availability of vein and AVF biopsies (Fig. 1). Sixty-six patients for whom veins were available were included in the first group, with the intention to discover the relationship between pre-existing IH and AVF outcomes. Nine patients were excluded due to poor tissue quality or loss of follow-up. The second study group, by which we aimed to reveal the impact of postoperative IH on AVF outcomes, was formed with 79 out of 86 individuals for whom the AVF biopsy was procured. Seven individuals had to be excluded from the analysis because of poor tissue quality and loss of follow-up. The third group included only those 56 patients with existing matched pair tissue samples (both the vein and AVF samples); after excluding five patients because one of the two tissues had poor quality, 51 patients remained to determine whether change in IH over time predicts AVF maturation and patency.

Table 1 describes the demographic, clinical and vascular access characteristics of the full cohort of 96 patients and the corresponding study groups. There were no significant differences between the three subgroups. The mean age of the entire patient cohort was 55.5 ± 12.4 (standard deviation) years. It comprised 34% non-Hispanic blacks and 66% Hispanics, of whom 39% were female. The majority of patients were hypertensive (95%) and 54% were diabetic. Approximately 20% of the study patients had a history of a previous AVF. A significant proportion of patients were taking statins (61%), antiplatelet agents (57%) and ACE inhibitors/ARBs (44%) prior to AVF creation. Two-stage brachio-basilic, brachio-brachial and aberrant radio-basilic AVFs were created in 93%, 5% and 2% of the study population, respectively. The median diameter of the basilic and brachial veins was 4.0 (IQR, 4.0–4.0) mm, while the median anastomosis diameter was 4.5 (IQR, 4.5–4.5) mm. Ten out of 96 AVFs (10%) never achieved anatomic maturation and required the creation of a short transposition or graft extension. The remaining 86 AVFs were patent for at least one month after transposition (second-stage surgery). Including anatomic maturation failures, by

the end of the observational period, 29 out of 96 AVF had required at least one endovascular or surgical intervention to maintain patency. Therefore, 70% of AVFs remained patent until the end of the study.

Pre-existing Intimal Hyperplasia

The association between pre-existing IH and AVF outcomes was studied in 57 patients from whom vein samples were available. Intima thickness in these tissues ranged from 0.05 to 0.66 mm, with concentric IH (>0.05 mm) observed in 98% of the patients. Table 2 shows the characteristics of patients with pre-existing intimal thickness above and below the median (0.18 [IQR, 0.10–0.20] mm). There were no differences between these two groups in terms of demographics, comorbidities, vascular access characteristics or concurrent medications (Table 2). Both mild and advanced lesions were populated by variable numbers of contractile (SM-MHC⁺ [smooth muscle–myosin heavy chain] SMA⁺ [α -smooth muscle cell actin]) and synthetic (SM-MHC[−] SMA⁺) SMCs (Fig. 2), with no specific pattern detected between both types of lesions. In contrast with the circumferential and longitudinal orientation of medial SMCs, contractile SMCs in the intima were randomly distributed. Collagen deposition was abundantly present in both the intima and the media, as detected by the blue staining in Masson's trichrome stain (Fig. 2A and D).

Pre-existing IH measured as maximal intimal thickness or intima-media ratio was not associated with age, sex or diabetes (Tables S1 and S2). The limited number of maturation failure events in this group ($n=5$ [9%]) prevented the assessment of the relationship between pre-existing IH and anatomic maturation failure. Pre-existing IH had no predictable value on primary unassisted patency as revealed by univariate Cox proportional hazards models (Table S3) and the Kaplan-Meier survival analysis (Fig. 3). In agreement with recent studies,¹² these results do not support a role for pre-surgical IH on subsequent AVF outcomes.

Postoperative Intimal Hyperplasia

The association between postoperative IH and AVF outcomes was studied in 79 patients from whom AVF samples were procured during transposition of the access. In contrast to IH in veins (Fig. 4A and D), the histological hallmarks of the lesion in AVF were the eccentric intima and atrophy of the vascular wall (Fig. 4B and E). The intima of AVF was mostly made up of synthetic SMCs that did not stain for SM-MHC (Fig. S2). Because of the remarkable loss of medial SMCs after first-stage surgery, the ratio of cell area to deposited collagen increased in the intima and decreased in the media (Fig. 4G and H). Postoperative IH ranged from 0.1 to 2.0 mm. Table 2 shows baseline characteristics of patients with postoperative IH above and below the group's median (0.62 [IQR, 0.38–0.86] mm). Both subgroups were similar with respect to demographics, comorbidities, vascular access characteristics, and medications. A positive effect of diabetes on postoperative IH was only evident with maximal intimal thickness but not with the intima-media ratio (Tables S1 and S2). Postoperative IH was not statistically associated with maturation failure (10 out of 79 AVFs) as determined with univariate logistic regressions despite the increased number of failures in the subgroup with higher IH (Table S4). This lack of association is further illustrated in Fig. 5, which shows AVF cross-sections with similar values of maximal intimal

thickness regardless of the different AVF outcomes. Similar to the pre-existing condition, postoperative IH had no predictable value on AVF primary unassisted patency (Fig. 6A and Table S3).

Change in Intimal Hyperplasia Over Time

Fifty-one patients from whom matched tissue pairs were available were used to determine whether change in IH over time modifies AVF outcomes. The longitudinal change in maximal intimal thickness ranged from -0.08 to 1.0 (median, 0.49 [IQR, 0.40 – 0.60]) mm.. There were no differences in terms of demographics, clinical factors, or vascular access characteristics between patients with low and high changes in IH (Table 2). The maximal intimal thickness in AVF increased 4.4-fold (IQR, 2.2- to 4.9-fold) with respect to the pre-existing condition after excluding one patient whose baseline thickness was > 0.05 (considered as zero) (Fig. 4C and F). The increase in medial thickness was also evident in the AVF compared to the corresponding vein at 1.8-fold (IQR, 1.3- to 1.9-fold; Fig. 4F and S3). The time interval between surgeries ranged from 14 to 413 (median, 63 [IQR, 43–84]) days (Table 1). here was no correlation between the time elapsed between surgeries and the thickness of the intima in the AVF ($r=-0.16$; $p=0.3$), suggesting a rapid IH development after AVF creation. There was also no correlation between pre-existing and postoperative intimal thickness ($r=0.04$; $p=0.7$) (Fig. 4I). Along with the eccentric formation of postoperative IH, this lack of association suggests a hyperplastic response of the vascular wall to upstream factors such as hemodynamics and surgical stress, and independent of pre-existing IH. There was no detectable association between sex, age or diabetes with the change in IH over time (Tables S1 and S2). As in the pre-existing group, the low number of failure events (5 out of 51) among pairs precluded the assessment of the relationship between change in IH and anatomic maturation failure. Nonetheless, the increment in IH between vein and AVF failed to predict loss of patency after excluding anatomic maturation failures (Fig 6B and Table S3).

DISCUSSION

Intimal hyperplasia is currently considered one of the main causes of AVF stenosis and failure. This assumption arose from histological observations of AVF collected at the time of access revision surgery, where intimal thickness appeared to compromise the critical luminal area required for high blood flow during dialysis.^{15, 16} Nonetheless, the presence of pre-existing IH in veins prior to AVF creation without an apparent association with failure¹² has led to a more careful scrutiny of this vascular lesion.

In this study, we comparatively characterized pre- and postoperative IH in the same patient by collecting venous tissue samples prior to and after AVF creation. Our findings suggest that: 1) the thickness of the pre-existing lesion does not predict the degree of postoperative IH, and 2) neither pre-existing nor postoperative IH are linked to anatomic maturation failure and loss of primary unassisted patency. However, the results do not rule out any potential pathological role of IH or its complications in secondary failure. Our study showed early histological changes in successful versus failed AVF before the confounding effect of frequent cannulations. In addition, we controlled for important variables such as vein and

anastomosis size, surgical technique, anatomical position of the fistula, and site of collection of the vein and AVF samples.

Contrary to the pre-existing intimal lesions that were concentric and rich in contractile SMC, the intima layer in AVF was eccentric and mostly populated by myofibroblasts. These findings suggest that intimal thickening occurs through different mechanisms in veins and AVFs. Pre-existing venous IH in chronic kidney disease patients may be the result of SMC migration from the media under the stimulus of uremic toxins¹⁷ and/or due to endothelial dysfunction.¹⁸ Intimal expansion in AVFs, on the other hand, occurs rapidly and involves the mobilization of cells from the media and adventitia as shown in experimental models.^{9, 19} In support of these different mechanisms, the thickness of the pre-existing vascular lesion did not correlate with the postsurgical expansion of the intima. Whether IH in veins and AVFs contributes to the adaptive response of the vessel to adverse physiological conditions remains enigmatic. While there is no doubt that intimal lesions are potentially obstructive for blood flow, it is also true that a thickened intima may promote hemostasis. Intimal myofibroblasts actively produce extracellular matrix components that could potentially contribute to the outward remodeling of the vein wall. A speculative theory would be that the intima acts as a natural barrier for circulating monocytes to help control inflammation. Assessing the real benefits and risks of having IH in veins and AVF warrants further research.

The most important finding of our study is the lack of an association between pre-existing, postoperative, and change in IH over time with AVF outcomes. In agreement with our results, studies by Allon et al. have also shown no correlation between pre-existing IH and stenotic events in AVF.¹² These results may imply that 1) the contribution of IH to early stenosis is minimal or none, 2) the balance between outward expansion and luminal narrowing due to IH is what ultimately determines stenosis,⁶ or 3) intimal thickness is not the aspect of the lesion that determines its impact on stenosis and AVF outcomes. Of note, luminal narrowing as observed in histological sections did not explain the differences in AVF outcomes (Fig. 5). These counterintuitive results may reflect the disparity between a presumptive functional interpretation of histological observations and the actual stenotic capacity of the intima. Intimal thickness is a static, two-dimensional variable that does not reflect the potential compressibility of the hyperplastic intima or the ability of a vessel to distend and increase volume (vascular compliance) under high flow rate and shear stress conditions. However, if IH does not predict AVF maturation, which biological factors are undermining AVF success? Based in our results, it is plausible to hypothesize that maladaptive-inward remodeling of the vein exacerbates the occlusive potential of IH, and therefore, causes failure. Unfortunately, the mechanisms that favor adaptive outward remodeling versus the maladaptive-response in AVF have been barely examined. The existing studies are limited to describing the role of elastin,²⁰ collagen²¹ and metalloproteinases during the reorganization of the vascular wall.^{22, 23} While there is not a definitive answer for this question yet, future research should aim to gain insights into the AVF remodeling process with the goal of identifying new therapeutic strategies that could improve fistula patency.

The limitations of our study are the limited number of matched tissue pairs and the younger age of our cohort, which is below the mean age of the US hemodialysis population.² In addition, our findings may not accurately reflect all vascular changes occurring in distal areas or in the arterial component of the vascular access. Moreover, the low incidence of anatomic maturation failure in our cohort decreased the power of our models to find meaningful associations between this end point and IH measurements. It is also important to note that our study was based on a racially skewed patient cohort that did not include Caucasians or Asians, and that only upper arm AVFs were assessed.

Despite these shortcomings, to our knowledge this is the first study of its type to provide direct evidence that neither pre-existing nor postoperative intimal thickness is associated with AVF stenosis. These results will need to be further confirmed in a larger and multicenter cohort. Nonetheless, this study fills an important gap in our understanding of AVF vascular biology, and sets the stage for a change in course from our current line of research to identify the actual causes of AVF failure and prevent loss of patency.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Flow diagram of the study design illustrating sample collection, exclusion criteria, and subsequent histopathological and statistical analysis.

Fig 2. Pre-existing intimal hyperplasia (IH) in veins

Representative basilic veins with low (A–C) and high pre-existing IH (D–I). The intimal thickness in first-stage veins oscillated between 0 to 0.66 (median, 0.18) mm (n=57). Intimal thickness was measured in Masson's trichrome stained sections (A, D, G). A significant number of intimal cells in the pre-fistula vein were smooth muscle cells that stained positive for α -smooth muscle cell actin (B, E, H) and smooth muscle myosin heavy chain (C, F, I). Microphotographs in G, H and I correspond to magnifications of boxed areas in D, E and F, respectively. I = Intima, M = Media.

Fig 3. Association between pre-existing intimal hyperplasia and primary unassisted patency
Kaplan-Meier curves for AVF with pre-existing intimal thickness above and below the group median of 0.20 mm after excluding anatomic maturation failures (n=52). Fistulas classified as anatomic maturation failure underwent a short transposition or graft extension and, therefore, had to be excluded from the analysis.

Fig 4. Intimal hyperplasia (IH) in matched pairs of veins and AVF

A–B. Representative matched tissue pair of a basilic vein (A) and AVF (B) collected before anastomosis and superficialization of a two-stage AVF from the same patient. Sections were Masson's trichrome stained. **C.** Matched pair analysis showing the change in intimal thickness in AVF with respect to the corresponding vein. AVF with anatomic maturation failure are shown in red. **D–E.** High magnification pictures of boxed areas in A–B, highlighting the media thickness and loss of smooth muscle cells (SMC) in the AVF. Arrows point to SMC stained in red. I = Intima, M = Media. **F.** Fold changes in medial and intimal thickness in AVF versus veins. **G–H.** Changes in the intima (G) and media (H) during remodeling. The relative areas of SMC (red) and collagen (blue) were quantified on Masson's trichrome stained sections. P values were calculated using a two-sample paired t-test with unequal variances. **I.** Linear regression analysis demonstrating the lack of correlation between pre-existing and postoperative IH in matched pairs.

Fig 5. Association between postoperative intimal hyperplasia and anatomic maturation failure
Representative sections of mature (A–C) and failed AVF (D–F). Sections were Masson's trichrome stained. The maximal intimal thickness is marked with a yellow arrow.

Fig 6. Association between postoperative and change in intimal hyperplasia (IH) with primary unassisted patency

A. Kaplan-Meier curves for AVF with postoperative intimal thickness above and below the group's median (0.57 mm, N=69). **B.** Kaplan-Meier curves for AVF with change in intimal thickness above and below the group's median (0.36 mm, N= 46).

Table 1

Baseline Characteristics of Patient Population and Study Groups of Intimal Hyperplasia

	All Patients (N=96)	Pre-Existing (Veins, n=57)	Postoperative AVFs, n=79	Change in IH (Pairs, n=51)	P-Value*
Demographics					
Age - y	55.5 ± 12.4	56.8 ± 12.4	56.4 ± 12.6	57.7 ± 12.4	0.9
Female Sex	37 (39)	21 (37)	32 (41)	20 (39)	0.9
Ethnicity					0.05
Non-Hispanic Black	33 (34)	24 (42)	28 (35)	29 (57)	
Hispanic	63 (66)	33 (58)	51 (65)	22 (43)	
Comorbidities					
Diabetes	52 (54)	30 (53)	39 (49)	27 (53)	0.9
Hypertension	92 (96)	55 (97)	75 (95)	49 (96)	0.9
CAD	20 (21)	11 (19)	17 (22)	11 (22)	0.9
COPD	7 (7)	5 (9)	6 (8)	5 (10)	0.9
CHF	6 (6)	3 (5)	8 (10)	6 (12)	0.5
Vascular Access					
AVF Type [†]					0.9
Brachio-Basilic	89 (93)	53 (93)	72 (91)	47 (92)	
Brachio-Brachial	5 (5)	3 (5)	5 (6)	3 (6)	
Aberrant Radial-Basilic	2 (2)	1 (2)	2 (3)	1 (2)	
Left Arm AVF	86 (90)	48 (84)	71 (90)	44 (86)	0.6
Anastomosis Size -mm	4.5 (4.5-4.5)	4.5 (4.5-4.5)	4.5 (4.5-4.5)	4.5 (4.5-4.5)	0.9
Vein Size - mm	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	0.9
AVF size - mm	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	0.9
Time Interval ^{**} - d	69 (52-119)	63 (49-94)	64 (54-119)	63 (43-84)	0.2
Previous Catheter	60 (63)	32 (56)	51 (65)	30 (59)	0.6
Previous AVF	19 (20)	9 (16)	15 (19)	10 (20)	0.9
Medications					

	All Patients (N=96)	Pre-Existing (Veins, n=57)	Postoperative AVFs, n=79	Change in IH (Pairs, n=51)	P-Value *
Antiplatelet Agents	55 (57)	34 (60)	42 (53)	29 (57)	0.7
Statins	59 (62)	36 (63)	46 (58)	31 (61)	0.8
ACE inhibitor/ARB	42 (44)	21 (37)	31 (39)	19 (37)	0.9

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AVF, arteriovenous fistula; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IH, intimal hyperplasia;

* P-value for the comparison of analysis groups.

[†] Created at or above the elbow.

** Time interval between first- and second-stage surgeries.

Table 2

Baseline Characteristics of Patients with Low and High Pre-existing, Postoperative and Change in Intimal Hyperplasia

	Pre-Existing – Veins			Postoperative – AVFs			Postoperative – AVFs		
	IH<0.18mm	IH>0.18mm	P	IH<0.62mm	IH>0.62mm	P	IH<0.49mm	IH>0.49mm	P
No. of patients	30	29		39	40		25	25	
Demographics									
Age - y	56.7 ± 12.6	57.9 ± 11.9	0.6	55.9 ± 14.5	56.9 ± 10.8	0.2	59.7 ± 12.6	55.5 ± 12.0	0.2
Female Sex	13 (43)	10 (35)	0.7	16 (41)	16 (40)	0.9	8 (31)	12 (48)	0.3
Ethnicity			0.2			0.08			0.3
Non-Hispanic Black	16 (53)	10 (35)		18 (46)	10 (25)		9 (35)	13 (52)	
Hispanic	14 (47)	19 (66)		21 (54)	30 (75)		17 (65)	12 (48)	
Comorbidities									
Diabetes	16 (53)	16 (55)	0.9	15 (39)	24 (60)	0.09	15 (58)	12 (48)	0.7
Hypertension	30 (100)	27 (93)	0.5	37 (95)	38 (95)	0.9	24 (92)	25 (100)	0.5
CAD	6 (20)	7 (24)	0.9	5 (13)	12 (30)	0.1	8 (31)	3 (12)	0.2
COPD	3 (10)	3 (10)	0.9	1 (3)	6 (15)	0.1	2 (8)	4 (16)	0.6
CHF	2 (7)	3 (10)	0.9	2 (5)	4 (10)	0.7	3 (12)	2 (8)	0.7
Vascular Accesses									
AVF Type *			0.3			0.7			0.5
Brachio-Basilic	27 (90)	28 (97)		36 (92)	37 (93)		23 (89)	24 (96)	
Brachio-Brachial	3 (10)	1 (3)		2 (5)	1 (3)		2 (8)	1 (4)	
Aberrant Radial-Basilic	0 (0)	0 (0)		1 (3)	2 (5)		1 (4)	0 (0)	
Left Arm AVF	27 (90)	23 (79)	0.4	34 (87)	37 (93)	0.7	21 (81)	23 (92)	0.4
Anastomosis size - mm	4.5 [4.5–4.6]	4.5 [4.5–4.5]	0.6	4.5[(4.5–4.5]	4.5 [4.5–4.5]	0.3	4.5 [4.5–4.5]	4.5 [4.5–4.5]	0.9
Vein size - mm	4.0 [4.0–4.0]	4.0 [4.0–4.0]	0.9	4.0 [4.0–4.0]	4.0 [4.0–4.0]	0.9	4.0 [4.0–4.0]	4.0 [4.0–4.0]	0.1
Previous Catheter	17 (57)	17 (59)	0.9	24 (62)	27 (68)	0.8	12 (46)	18 (72)	0.1
Previous AVF	4 (13)	7 (24)	0.5	8 (21)	16 (40)	0.1	3 (12)	7 (28)	0.3
Medications									
Antiplatelet Agents	20 (67)	16 (55)	0.4	18 (46)	24 (60)	0.3	14 (54)	15 (60)	0.9

	Pre-Existing – Veins		Postoperative – AVFs		Postoperative – AVFs	
	IH<0.18mm	IH>0.18mm	P	IH<0.62mm	IH>0.62mm	P
Statins	23 (77)	15 (52)	0.08	20 (51)	26 (65)	0.3
ACE inhibitor/ARB	9 (30)	14 (48)	0.2	11 (28)	20 (50)	0.08

Note: Table shows the characteristics of patients with pre-existing and postoperative intimal thickness above and below the medians (0.18 and 0.62 mm, respectively) and median longitudinal change in maximal intimal thickness (0.49 mm). Values for categorical variables are given as number (percentage); values for continuous variables, as mean $\pm$ standard deviation or median [interquartile range].

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AVF, arteriovenous fistula; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IH, intimal hyperplasia;

* Created at or above the elbow.