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Unlocking Hemodialysis Success: Navigating Arteriovenous Fistula Maturation Factors for Optimal Access

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Abstract

Background: Hemodialysis (HD) access related problems are called Achilles' heel, a term used to describe the weak point. Fistulas have the uppermost long-term patency rate of all HD access options. When the Arteriovenous Fistula (AVF) is developed and ready for use in HD, it is considered mature. Multiple factors take part in the functional maturation of AVFs, such as age, gender and blood markers. Older patients may have a higher burden of comorbid conditions, such as diabetes, hypertension, or cardiovascular disease, which can affect AVF outcomes and maturation. This study aimed to decide the prevalence of mature AVFs for HD access and evaluate the impact of demographic and medical factors on their maturation.

Patients and methods: One hundred patient were assessed with color Doppler ultrasonography for fistulas at post-operative day seven and day forty two of creation. Chi-square and ANOVA tests were used p-value was considered significant at level ≤ 0.05.

Results: The research showed that 71% of the fistulas were mature, while 29% were immature. Peripheral vascular disease was significantly associated with AVF maturation, but age, gender, body mass index, diabetes mellitus, hypertension, heart failure, ischemic heart disease and smoking did not show significant associations.

Conclusions: The study emphasizes the importance of early identification of vascular risk factors in dialysis patients and close monitoring to optimize AVF outcomes.

Keywords: Arteriovenous fistula; Maturation; Vascular access; Doppler ultrasound

Introduction

Hemodialysis access related problems are called Achilles' heel, a term used to describe the weak point [1]. Fistulas have the uppermost long-term patency rate of all HD access options. A native fistula created by the anastomosis of an artery to a vein, for example the Brescia-Cimino fistula, in which the cephalic vein anastomosed to the radial artery [2]. After 4-6 weeks, increased pressure transferred from the artery to the vein through the fistula causes distension and thickening of the vessel wall (arterialization) [2]. This facilitates its later use in the placement of large needles to access the circulation. The clinical features depend on the size and location of the fistula. The AVF for dialysis is considered less expensive to keep and with a longer life span. To date, more than 66% of continued patients and over 50% of all new patients on dialysis are using a fistula [3]. There are three main types of AVFs-radial-cephalic, brachial-cephalic and brachial-basilic transposition. Doppler monitoring is crucial for detecting stenosis and keeping adequate blood flow for effective dialysis. As patients requiring dialysis age and have co-morbidities, it becomes challenging to find suitable native vessels for creating AVFs [4]. Physical examination is usually dependable, but challenges arise with slow-maturing AVFs or obese patients [4,5]. Ultrasound (US) examination and hemodynamic parameter assessment, like AVF velocity, help determine AVF suitability for cannulation and identify potential thrombosis or low flow volume. The AVF requires time to heal and undergoes dilation to accommodate increased blood flow [6-7]. Doppler US is a correct method for finding arterial lesions and abnormalities [4]. There are different US criteria for defining AVF maturity, with varying sensitivity and specificity [8]. Maturation of AVF involves the development of physical characteristics suitable for venipuncture [9]. Regular monitoring and surveillance, including blood flow measurement, help maximize AVF survival by detecting complications early [4].

Meta-analysis shows that elderly patients may have an increased primary failure rate and reduced patency for brachiocephalic AVFs. Age-related changes in blood vessels, healing process and comorbid conditions can influence AVF maturation [9-11]. Gender-related differences in comorbid conditions and anatomical factors can affect AVF outcomes. Variations in cardiac output and blood flow dynamics between genders may influence AVF maturation [12]. Obesity is

associated with vascular changes that can hinder AVF maturation.

Diabetes Mellitus (DM)-related vascular changes and microvascular complications can delay or impede AVF maturation. DM can impair vein dilation and remodeling necessary for AVF development, leading to slower flow rate achievement [13]. Diabetic patients may be at a higher risk of AVF failure due to problems with vascular integrity, thrombosis, stenosis, and other complications [13-15]. Changes in blood vessels, including wall thickening and calcification, may affect the quality of vessels used for AVF creation [16].

Hypertension (HTN) can influence AVF maturation in patients requiring HD. Vascular changes and complications related to HTN can affect AVF development and functionality. Blood vessel wall thickening and stiffness caused by hypertension can hinder vein dilation and remodeling essential for AVF maturation [17]. Atherosclerosis and plaque formation due to hypertension can lead to stenosis or thrombosis within the AVF, reducing blood flow or causing AVF failure. Uncontrolled HTN can elevate pressures within the vascular system, affecting blood flow dynamics and the function of the AVF. Hypertension is also a risk factor for cardiovascular disease and other vascular complications, increasing the risk of AVF-related issues [17,18]. Heart failure can lead to reduced cardiac output, altered blood flow dynamics and increased venous pressure, all of which can hinder AVF maturation [19,20]. Fluid overload and medications used to manage HF can also influence vascular tone and blood flow, affecting AVF development and flow rates [19-21]. Peripheral vascular disease can limit blood flow in the arteries supplying the limbs, impacting AVF dilation and remodeling [22]. Impaired tissue repair and potential complications such as stenosis or thrombosis can also hinder AVF maturation [23]. Ischemic Heart Disease (IHD) can decrease blood flow in both coronary arteries and other vascular regions, potentially slowing AVF maturation [21-24]. Impaired endothelial function and increased risk of blood clot formation in IHD can further impact AVF development. Atherosclerosis and medications used to manage IHD may affect AVF integrity and healing processes [25,26]. Smoking can cause vasoconstriction, reduced blood flow and increased risk of blood clot formation, hindering the development of a well-functioning AVF [27]. It damages blood vessel linings, impairs endothelial function, triggers inflammation and weakens the immune system, all of which negatively affect AVF maturation [28]. The study aimed to decide the prevalence of mature AVFs and identify medical factors affecting their maturation through periodic Doppler ultrasound measurements.

Materials and Methods

This prospective cohort study conducted at two medical facilities in Karbala, Iraq, over six months, from November 2022 to May 2023. The study included 100 Iraqi patients with End-Stage Kidney Disease (ESKD) on Hemodialysis (HD) schedule, who recently had a new brachiocephalic Arteriovenous Fistula (AVF) created for HD access. The sample size was decided using Slovin's formula [29]. Patients with incomplete data, radio cephalic AVF, hemodynamic instability, noncompliance and disappearance of thrill during follow-up were excluded. Data collection included demographic characteristics, patient characteristics (such as DM, HTN, history of IHD or HF, PVD and smoking status) and Doppler assessment parameters of AVF velocity at postoperative day 7 and day 42. Doppler US was performed using specific machines with linear array probes and flow velocity was measured based on vessel diameter and time-averaged mean velocity. The AVF maturation was defined based on blood flow velocity measured by DUS at postoperative day 42 according to NKF-KDOQI guidelines [27] or University of Alabama at Birmingham (UAB) criteria [30]. Ethical approval was obtained and informed consent was obtained from all patients. Statistical analysis was performed using IBM SPSS software and p-value ≤ 0.05 was considered significant **(Figures 1 and 2).**

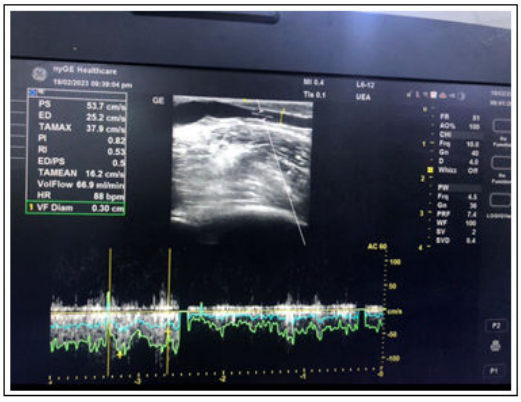

Figure 1: Flow measurement in arteriovenous fistula at day 7 (GE Healthcare LOGIC e machine). **Note:** PS: Peak Systolic; ED: End Diastolic; TAMAX: Time Average Maximum; PI: Pulsatility Index; RI: Resistive Index; HR: Heart Rate; VF: Vein Dimeter.

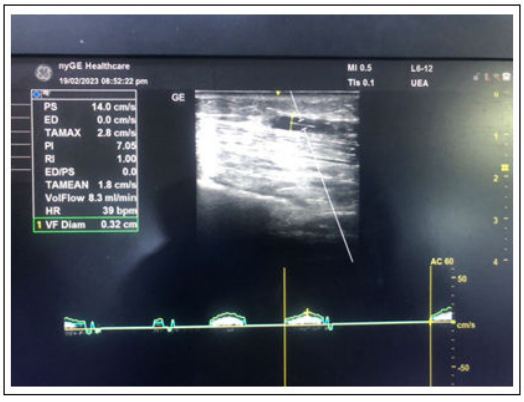

Figure 2: Flow measurement in native AVF at day 35 shows failure of maturation (Thrombosis) (GE Healthcare LOGIC e machine). **Note:** PS: Peak Systolic; ED: End Diastolic; TAMAX: Time Average Maximum; PI: Pulsatility Index; RI: Resistive Index; HR: Heart Rate; VF: Vein Dimeter.

Results

This study includes one hundred patients with CKD who underwent AVFs recently. Of the total one hundred patients, thirty-six patients were males (36%) and sixty-four were females (64%). The age of the patients included in this study ranging from 41-77 years, of which 8 (8%) were <50 years, 81 (81%) between 50-70 years and 11 (11%) were >70 years. Of the total one hundred patients, seventy-one with mature AVF and twenty-nine with failed AVF based on Qa 600 ml/min as cutoff point. At postoperative day 7 of AVF creation, the mean velocity of all patients was (82.15 ± 4.79) ml/min whereas at postoperative day 42, the mean velocity was (608.73 ± 97.07) ml/mi. The Qa3 is the difference between flow velocity at day 42 (Qa2) and flow velocity at day 7 (Qa1). The mean Qa3 of all patients were (525.96 ± 96.98) ml/min as shows in **Table 1.**

Table 1: Sample distribution according to flow velocity of AVF.

AVF flow velocity	AVF*		Mean (ml/min.) ± Standard deviation	N*	Mean (ml/min.) ± Standard deviation
(Qa1) at day 7**	Mature	71	82.38 ± 4.74	100	82.15 ± 4.79
	Failed	29	81.61 ± 4.94		
(Qa2) at day 42***	Mature	71	653.26 ± 49.61	100	608.73 ± 97.07
	Failed	29	499.70 ± 99.13		
(Qa3)****	Mature	71	569.64 ± 51.43	100	525.96 ± 96.98
	Failed	29	418.99 ± 99.76		
Note: *N: Total number of cases; AVF: Arteriovenous Fistula; **(Qa1): At day 7 flow velocity of AVF divided into mature and failed according to the fates of these fistulae after 42 days in retrospective manner. ***(Qa2): At day 42 flow velocity of AVF divided into mature and failed. ****(Qa3): Difference between (Qa2) and (Qa1).					

The relationship between patients' characteristics and AVF maturation were studied using chi-square test with a Qa cutoff point 600 ml/min and 500 ml/mi. There's a statistically significant effect of PVD on AVF maturation (p-value less than 0.05). There is no statistically significant association between other medical factor and maturation of the AVF (p-value more than 0.05) as shown in **Tables 2 and 3**.

Table 2: Association between medical factors and failure of maturation of AVF according to NFK-KDOQI criteria.

Medical factors		AVF*		Total	P. value*
		Failed**	Mature		
Age (years)	Below 50	4	4	8	0.394
	50 -70	22	59	81	
	Above 70	3	8	11	
Gender	Male	8	28	36	0.263
	Female	21	43	64	
Body mass index (kg/m^2)	<18.5	0	2	2	0.314
	18.5-24.9	12	41	53	
	25-29	13	21	34	
	≥ 30	4	71	11	
Diabetes mellitus	Positive	14	39	53	0.545
	Negative	15	32	47	
Hypertension	Positive	7	20	27	0.68
	Negative	22	51	73	
Heart failure	Positive	15	42	57	0.496
	Negative	14	29	43	
Peripheral vascular disease	Positive	19	3	22	0.004

	Negative	10	68	78	
Ischemic heart disease	Positive	16	38	54	0.88
	Negative	13	33	46	
Smoking	Positive	7	16	23	0.863
	Negative	22	55	77	

Note: *P-value estimated by using chi-square test; AVF: Arteriovenous Fistula; NKF-KDOQI: National Kidney Foundation-Kidney Disease Quality Initiatives. **Failed AVF with cutoff point 600 ml/min according to NKF-KDOQI guideline.

Table 3: Association between medical factors and failure* of maturation of AVF according to UAB** criteria.

Medical factors		**AVF****		**Total**	**P. value****
		Failed**	**Mature**		
Age (years)	Below 50	1	8	8	0.344
	50-70	5	81	81	
	Above 70	2	8	11	
Gender	Male	2	34	36	0.499
	Female	6	58	64	
Body mass index (Kg/m^2)	<18.5	0	2	2	0.344
	18.5-24.9	5	48	53	
	25-29	2	32	34	
	≥ 30	1	10	11	
Diabetes mellitus	Positive	5	48	53	0.575
	Negative	3	44	47	
Hypertension	Positive	3	51	51	0.329
	Negative	5	41	41	
Heart failure	Positive	3	54	57	0.245
	Negative	5	38	43	
Peripheral vascular disease	Positive	6	16	22	**0.003**
	Negative	2	76	78	
Ischemic heart disease	Positive	3	51	54	0.329
	Negative	5	47	46	
Smoking	Positive	3	20	23	0.31
	Negative	5	72	77	

Note: *Failed AVF with cutoff point 500 ml/min according to UAB criteria; **UAB: University of Alabama; ***P-value estimated by using chi-square test; AVF: Arteriovenous Fistula.

There is statistically significant association between the HTN, BMI and the AVF flow velocities at post-operative day 7, whereas the other medical factors were statistically not significant (p-value <0.05 by using ANOVA test). There is statistically significant association between PVD and AVF flow velocities at post-operative day 42, whereas the other medical factors were statistically not significant (p-value <0.05 by using ANOVA test) as shown in **Table 4.**

Table 4: Association between medical factors and AVF flow velocity at post-operative day 7 and day 42 (ANOVA test).

Medical factors		N	AVF* flow velocity at day seven Mean ± SD ml/min	P. value* (day 7)	AVF flow velocity at day 42 Mean ± SD ml/min	P. value* (day 42)
Age (years)	Below 50	8	84.35 ± 7.29	0.108	548.60 ± 121.06	0.126
	50 -70	81	82.26 ± 4.51		617.31 ± 83.06	
	Above 70	11	79.77 ± 4.18		589.23 ± 154.68	
Gender	Male	36	81.30 ± 4.54	0.185	622.06 ± 95.94	0.305
	Female	64	82.63 ± 4.90		601.23 ± 97.65	
Body mass index (Kg/m^2)	<18.5	2	79.80 ± 9.33	**0.043**	704.49 ± 136.20	0.542
	18.5-24.9	53	81.68 ± 4.97		610.65 ± 108.65	
	25-29	34	81.81 ± 3.98		603.16 ± 72.27	
	≥ 30	11	85.94 ± 4.41		599.27 ± 103.71	
Diabetes mellitus	Positive	53	82.88 ± 4.33	0.109	608.53 ± 107.23	0.983
	Negative	47	81.34 ± 5.19		608.95 ± 85.33	
Hypertension	Positive	27	83.97 ± 4.55	**0.020**	610.97 ± 87.61	0.889
	Negative	73	81.48 ± 4.73		607.90 ± 100.91	
Heart failure	Positive	57	82.12 ± 4.97	0.935	616.82 ± 81.52	0.34
	Negative	43	82.20 ± 4.60		598.00 ± 114.65	
Peripheral vascular disease	Positive	22	82.40 ± 5.00	0.783	507.01 ± 110.79	**0.00001**
	Negative	78	82.08 ± 4.76		637.42 ± 70.56	
Ischemic heart disease	Positive	54	81.70 ± 4.26	0.312	616.18 ± 92.90	0.408
	Negative	46	82.68 ± 5.35		599.98 ± 102.08	
Smoking	Positive	23	81.71 ± 6.12	0.614	591.26 ± 121.59	0.328
	Negative	77	82.29 ± 4.36		613.95 ± 88.74	

Note: *P-value estimated by using ANOVA test; AVF: Arteriovenous Fistula.

Discussion

The velocity of mature AVF can vary among individuals and depends on several factors including vessel size and technique used for creating the AVF. The overall vascular health of the individual and the presence of comorbidities such as DM, HTN, IHD, HF, PVD and smoking can influence AVF maturation. These conditions as well as hemodynamic factors may impair blood flow and delay the maturation process. To assess the maturation of AVF various criteria are considered in different studies. Each criterion depends on several parameters; the blood flow rate is one of these parameters which is measured by using DUS to consider the AVF suitability for hemodialysis [31]. This study finds a discrepancy for those with clinically mature AVF while their Qa1, Qa2 and Qa3 were more than 600 ml/min. On the other hand, some of patients in this study have a mature velocity by DUS definition while clinically their fistulae have non adequate blood flow for effective dialysis. The reason behind this is that AVF maturation is a multifactorial process influenced by numerous variables, such as vascular health, surgical technique, comorbidities, patient's age, gender, BMI and patient adherence to postoperative care [12,32]. This study utilized two different US criteria, like international standards. The NKF-KDOQI criteria used a Qa cutoff of 600 ml/min to define AVF maturity [27], while the UAB criteria used a Qa cutoff of 500 ml/min [31]. However, determining an optimal level of blood flow for AVF success remains challenging, as the hemodynamics of arteriovenous access are complex and a single measurement of flow may not provide sufficient information about the adequacy of the system. Other modifying factors need to be considered in addition to quantitative data before making decisions to intervene [32,33]. Currently, cutoff velocities of 500 ml/min or 600 ml/min are commonly used in DUS examinations to assess AVF maturation. However, it is important to note that the cutoff value for velocity indicating successful maturation can vary based on factors such as the AVF site, patient characteristics and study design. Regular monitoring and surveillance of AVFs are crucial to promptly identify potential complications and intervene when necessary. The study found some patients with clinically mature AVFs, but their Qa1, Qa2 and Qa3 were more than 600 ml/min. On the contrary, some patients had AVFs with mature velocity based on DUS definition,

but clinically, their fistulae did not have adequate blood flow for effective dialysis. This discrepancy highlights that AVF maturation is a multifactorial process influenced by various variables, such as vascular health, surgical technique, comorbidities, patient age, gender, BMI and patient adherence to postoperative care [33].

When using a cutoff velocity of 600 ml/min after 7 days of AVF operations was the only medical factor that significantly affected AVF maturation ($p<0.005$) [8]. The study highlights the importance of considering individual patient characteristics and surgical techniques in AVF creation, as these factors can play a crucial role in the maturation process. Additionally, the study population's heterogeneity may mask potential effects of certain factors on AVF maturation. Overall, the findings emphasize the significance of PVD as a critical factor influencing AVF maturation, while other medical factors and demographics did not show a statistically significant impact. According to the findings of this study, age did not have a significant adverse effect on AVF maturation (p-value=0.394). This aligns with a study by Lok et al. [27], which also did not find a negative impact of age on AVF maturation in their retrospective analysis of over 440 AVFs across different age groups. Similarly, this study did not show a significant effect of gender on AVF maturation (p-value=0.263). However, this contrasts with a study by Lee et al. [28], which suggested that females may have a worse outcome with AVF maturation. Differences in results between studies may be attributed to various factors such as sample size, patient heterogeneity, comorbidities, medications and individual patient characteristics, which can interact with gender and age, affecting AVF outcomes. Notably, gender-related differences in vascular health and endothelial function due to hormonal variations between men and women may influence AVF maturation. Additionally, differences in the prevalence of comorbid conditions like diabetes or cardiovascular disease between genders can impact AVF outcomes [29]. In summary, while age and gender might have varying degrees of influence on AVF maturation, their effects are not always consistent across studies, including the one at hand. Various factors contribute to these discrepancies and further research is needed to better understand the relationships between age, gender and AVF outcomes [12-14]. Obesity can potentially impact AVF maturation due to several factors, including alterations in vascular health, the presence of excess adipose tissue around the AVF site and increased cardiac output in large-bodied individuals, which can strain the AVF [29]. This is not consisting with this study due to variations in sample size, patient characteristics and study design. More research is needed to better understand the relationship between obesity and AVF maturation. According to the findings of this study, DM did not show an adverse effect on AVF maturation (p-value=0.545). This is consistent with a study by Konner et al. [32], which reported increased use of proximal fistulas in diabetic patients with primary access survival like that of non-diabetic patients. However, other studies disagreed with the current study's results and found potential delays in achieving functional AVF in diabetic patients due to impaired dilation and remodeling of fistula-related veins [16,17]. Diabetic patients may face adverse effects on vascular integrity, leading to a higher rate of thrombosis and stenosis of the fistula. Factors such as diabetic vascular wall thickening, fibrosis and calcification can also make them less suitable for long-term HD fistulas. As a result, early identification of potential vascular risk factors in diabetic patients and close monitoring are essential to address complications and optimize AVF outcomes. Regarding HTN, this study also showed no adverse effect on AVF maturation (p-value=0.680). This finding is consistent with a study by Carlo et al. [31], who performed a single-center cohort study and did not find any correlation between AVF maturation and HTN. The absence of an effect on maturation may be attributed to the controlled hypertensive patients in this and similar studies, where patients had recent-onset or controlled HTN through medication and lifestyle changes. In contrast, studies that did find an adverse effect of HTN on AVF maturation included patients with longstanding, uncontrolled HTN. The variability in patient response to hypertension could also explain why some hypertensive patients may experience a more significant impact on AVF maturation than others [18,19]. According to the results of this study, HF did not show an adverse effect on AVF maturation (p-value=0.496). This finding is consistent with a multi-center based prospective study by Arlon et al. [33]. However, studies by Roy-Chaudhury et al. and Herzog et al. [21,22] disagreed with these results and suggested that HF can potentially impact AVF maturation due to hemodynamic changes, reduced organ perfusion (including the kidneys), fluid retention, venous congestion, and medications commonly prescribed for HF patients, such as diuretics and vasodilators. The difference in findings between these studies and others, including the current study, regarding the impact of HF on AVF maturation is due to the complex relationship between HF and AVF. The severity of HF and individual patient factors can influence this relationship. It is important to note that even though HF may potentially affect AVF maturation, it does not necessarily mean that it will always lead to fistula failure or complications. The outcomes may vary based on individual patient characteristics and the management of HF [34]. Further research is needed to better understand the interplay between HF and AVF maturation and its implications for patient care. According to this study, there is an adverse effect for PVD on AVF maturation (p-value=0.004), which is consistent with findings from Ronald et al. and Allon et al. [35,36]. These studies emphasize the importance of optimal management of PVD to enhance AVF outcomes in patients requiring hemodialysis. On the other hand, this study shows no adverse effect for IHD on AVF maturation (p-value=0.880), which aligns with the findings of Yang et al. [37]. The reasons for the difference in results between studies regarding the relationship between AVF maturation and IHD may include sample size, variability in patient population, selection bias, study design, confounding variables, time frame assessment, publication bias and measurement errors. Inaccuracies in data collection or measurement methods can introduce noise into the data, making it harder to identify further significant associations. Additionally, a lack of statistical significance could be due to random chance, especially if the sample size is small [37]. Further research is needed to better understand the relationship between AVF maturation and IHD and to address potential confounding factors. This study shows no adverse effect for

smoking on AVF maturation (p-value=0.863), which is inconsistent with some previous research. The differences in findings could be attributed to various factors such as study design, variability in smoking habits among participants, confounding factors not adequately controlled for, publication bias, timing of assessment, regional differences in smoking prevalence and its impact on health outcomes [29-31]. It may be valuable to conduct a systematic review or meta-analysis to combine this study's results with other relevant studies to gain a broader perspective on the topic and better understand the relationship between smoking and AVF maturation.

Conclusion

This study found that the prevalence of mature AVF was 71%. AVF maturation is a complex process influenced by various medical factors, including vascular health, surgical technique, comorbidities, patient age, gender and BMI.

Recommendations

Conducting long-term follow-up studies on large cohorts of patients with AVFs can provide valuable insights into the factors that influence AVF maturation and long-term patency. This can help improve our understanding of the process and potentially lead to better strategies for optimizing AVF outcomes.

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