Underestimated effect of antiphospholipid antibodies on arteriovenous fistula maturation in hemodialysis patients

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Abstract

Background: Arteriovenous fistula delay or absence of maturation is a common problem in hemodialysis. The prevalence of antiphospholipid antibody is higher among hemodialysis patients compared to the general population and is inconsistently associated with arteriovenous fistula thrombosis or stenosis. However, the effect of antiphospholipid antibodies on delayed or absence of maturation of the arteriovenous fistula has never been studied.

Methods: We retrospectively identified 103 hemodialyzed patients with arteriovenous fistula whether used or not. We collected the clinical and biological data potentially involved in arteriovenous fistula maturation and investigated the association between antiphospholipid antibody positivity and arteriovenous fistula maturation failure according to KDOQI guidelines.

Results: In our cohort, the prevalence of arteriovenous fistula maturation failure was of 45.8%. The prevalence of antiphospholipid syndrome was of 7.8 %, whereas only 10.7% of patients fulfilled only antiphospholipid laboratory criteria. The persistent positivity of antiphospholipid antibody was a risk factor for arteriovenous fistula maturation failure. In multivariate analysis, this association was independent of stenosis.

Conclusions: To our knowledge, we report for the first time, a statistically significant association between arteriovenous fistula maturation failure, antiphospholipid antibody persistent positivity and antiphospholipid syndrome. This association was independent of arteriovenous stenosis. Our data suggests a potential non-stenotic and/or non-thrombotic mechanism of antiphospholipid antibody related arteriovenous fistula maturation failure in hemodialysis patients.

Background

End-stage kidney disease (ESKD) is characterized by the need of initiating renal replacement therapy to control clinical, biological, and hemodynamic complications. Renal transplantation, peritoneal dialysis, and hemodialysis (HD) are currently the treatment options in ESKD. The latter technique requires the creation of a vascular access such as an arteriovenous fistula (AVF) or the placement of a hemodialysis catheter. Both should allow high blood flow rates for adequate hemodialysis. Compared to catheters, native AVF is considered as a preferred vascular access since it is associated with lower morbidity and mortality (1).

AVF creation consists in performing a surgical or endovascular anastomosis of an artery to an adjacent vein (1). This outflow vein will be exposed to an arterial oxygen-rich flow with a higher blood pressure. This vein will therefore be exposed to wall shear stress (2). All these changes will lead to a complex vascular remodeling process called “maturation” process characterized by diameter and thickness changes of the vein. This process usually takes place in about 6 weeks and is crucial for routine use of the AVF (3, 4). According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines AVF maturation can be assessed by ultrasonography (US) (5). AVF is considered matured 6 weeks after its

creation if: (a) its diameter is at least 6.0 mm, (b) its depth less than 6.0 mm, (c) blood flow rate is at least 600 ml/min and (d) its length is at least 6.0 cm in order to allow a two-needle cannulation. KDOQI guidelines defined AVF maturation failure (AVFMF) as a delay or absence of maturation (1, 5). AVFMF is a major complication affecting more than half of the AVF (1, 6).

Antiphospholipid syndrome (APS) is an autoimmune disease, characterized by a prothrombotic state affecting both arterial and venous vasculature, and is also associated with obstetrical complications (7). APS is defined by the combination of at least one clinical criterion (thrombotic or obstetrical) along with the persistent positivity of antiphospholipid antibodies (aPL) as described in the Sydney classification criteria. Are included the following antibodies : lupus anticoagulant (LA); IgG or IgM anti-cardiolipin antibody (aCL); or IgG or IgM anti β2 glycoprotein I (aβ2-GPI) (7). Confirmation of a positive assay is mandatory at 12 weeks, to confirm the biological criterion. In the absence of a clinical criteria, aPL does not allow the diagnosis of APS. However, this biological entity is of definite importance since it is associated with an increased thrombotic risk in the general population and in lupus patients (8, 9). Among hemodialysis patients, up to 37% have persistent aPL (10). In retrospective studies, aPL positivity has been associated with vascular access thrombosis (10, 11). However, according to our knowledge, the relationship between aPL and AVFMF has never been reported in the literature.

Methods

Study design and patients: This is a monocentric retrospective study. Institutional Review Board authorization was obtained from our local ethics committee (Ethics Committee of Brugmann University Hospital), reference number: CE 2018/117.

We have identified all patients in the hemodialysis department of our hospital between 01/01/2019 and 01/08/2019, who have had a native AVF confection, whether used or not. Exclusion criteria were: (a) the absence of antiphospholipid antibody (aPL Ab) assay or uninterpretable assays (concomitant anticoagulant therapy, inflammatory state, or acute thrombosis), (b) the absence of AVF and (c) the presence of innate thrombophilia other than APS.

Study groups

We classified patients according to Sydney's classification criteria (7) into *aPL group* when only biological criterion was met and *APS group*. In addition, we also studied another *group of unknown significance (UnK aPL)* representing patients with only one antiphospholipid antibody (aPL Ab) positive assay either without confirmation at 12 weeks, or one positive aPL Ab among 2 assays (positive becoming negative or the opposite). Control group included patients with only negative aPL Ab assay.

Data: All collected data were anonymized and stored in a password-protected database. We recorded histories of AVF maturation status, thrombosis or stenosis incidence from patient medical records but also completed with direct questioning. Other data related to vascular access were collected such as: clinical signs (pain, edema, aneurysmal dilatation, hematoma, prolongation of post dialysis bleeding

time), pre-pump arterial and post-pump pressure and dialyzer circuit thrombosis. We also reviewed the laboratory reports and collected demographic and clinical data, including patients' treatment. Data from the hemodialysis technique were also collected: hydration status using bio-impedancemetry (Body Composition Monitor® (BCM), Fresenius), Urea Kt/V, Urea Reduction Ratio (URR), weekly dialysis time, dialysis technique (HD or hemodiafiltration (HDF)), type of dialyzer, time since HD initiation, residual urine outflow.

Criteria for arteriovenous fistula maturation: AVF maturation was defined according to the Kidney Disease Outcomes Quality Initiative recommendations (5) Doppler ultrasound examination : AVF flow > 600 ml/min, outflow vein diameter > 6 mm over a length ≥ 6 cm and a depth ≥ 6 mm, at ≥ 6 weeks of its creation.

Detection of antiphospholipid antibodies: The aPL Ab assays were performed at the beginning of the HD session before administration of anticoagulation. Lupus anticoagulant (LA) positivity was assessed by using a three-step diagnostic procedure: screening, mix and confirmation procedures using diluted-Russell-viper venom (dRVVT-Siemens®) and Silica Clotting time (SCT-Werfen®). Results were expressed as screening to confirmation ratios. LA was confirmed if one of the two functional coagulation assays (dRVVT or SCT) was positive in terms of Screening to confirmation ratio, using a citrated plasma sample (3.2%) in accordance with current pre-analytical and analytical recommendations (12, 13). The determination of aCL and aβ2GPI was performed by a chemiluminescence immunoassay (HemosIL Acustar aCL IgM/IgG Kit and aβ2GPI IgM/IgG kit- Werfen®). According to the standards of our laboratory the results were interpreted as positive (> of the 99th percentile) or negative when the IgG or IgM titers were respectively > 20 U/ml or ≤ 20 U/ml.

Statistical analysis

Data are described as mean and standard deviation for variables with a normal distribution, and median and the interquartile range for variables with a non-normal distribution. Groups were compared using Pearson's Chi-square test, or Fischer's exact test if necessary. Student's t-test was used to compare the means of the quantitative variables following a normal distribution by group. The Mann-Whitney Wilcoxon test was used to study the variation between two groups of variables following an asymmetric distribution. The significance level of the tests was 0.05 with odds ratios and 95% confidence intervals of odds ratio. Multivariate models were proposed through logistic regression for variables showing statistically significant differences between groups. All statistical analyses were performed using Stata/IC 15.1 software.

Results

Hundred and seventy HD patients were identified between 01/01/2019 and 01/08/2019 in our institution. Sixty-seven were excluded because of the absence of aPL Ab assay (n = 39), the absence of AVF (n = 11) or uninterpretable aPL Ab assays (n = 17). No patients had innate thrombophilia in our cohort. Hundred and three patients were included for analysis (Flowchart summarized in Fig. 1). Also, 10.7% (11/103) had

APS, whereas 7.8% (8/103) had aPL. UnK aPL represented 32% (33/103) and negative aPL Ab represented 49.5% (51/103). Figure 2 summarizes aPL Ab distribution.

All AVF were native AVF and 61.5% were distal forearm AVF whereas 38.5% were proximal AVF. Tables 1 and 2 show demographic and hemodialysis related data. The mean age was 59.1 years, and male/female ratio was 74/29. The mean BMI was 16.1 kg/m². The prevalence of smokers, diabetes, hypertension, HIV, and hepatitis C virus (HCV) were 29.1%; 48.5%; 83.5%; 6.8% and 15.5% respectively. With respect to patient's treatment: 55.3% of patients were treated with antiplatelet therapy, 27.2% with statins, 53.4% with ACE inhibitors and 68% with phosphate binders. The mean aPTT value was 32.6 ± 4.8 sec (reference range: 21.6–28.7 sec), the mean platelet count was 227.7 ± 83.9 x10³/μL (reference range: 15–440 x10³/μL) and the mean Hb level was 10.2 ± 1.5 g/dL (reference range: 13–18 g/dl).

Table 1
Demographics and baseline characteristics of the population

Demographics	**n**	**Laboratory test**	**n**
Gender		aPTT	32.6 ± 4.8 s
Male	74/103 (71.8%)	Platelets	227.7 ± 83.9 x10^3/μL
Female	29/103 (28.2%)	Hemoglobin	10.2 ± 1.5 g/dL
Mean age	59.7 ± 15 years	Total Cholesterol total	156.1 ± 37.0 mg/dl
BMI	26.12 ± 5.3 Kg/m²	LDL-Cholesterol	89.4 ± 51.8 mg/dl
Smokers	30/103 (29.1%)		
Comorbidities		**Antiphospholipid status**	
Diabetes mellitus	50/103 (48.5%)	APS	11/103 (10.7%)
Hypertension	86/103 (83.5%)	aPL	8/103 (7.8%)
Autoimmune disease	7/103 (6.8%)	Lupus anticoagulant	18/103 (17.5%)
HIV	7/103 (6.8%)	aβ2GP I	1/103 (1%)
Anti-HBc antibody	27/103 (26.2%)	aCL	2/103 (1.9%)
HCV	16/103 (15.5%)	Double positivity	0/103 (0%)
		Triple positivity	1/103 (1%)
Treatment		**Thrombotic events**	
Statins	28/103 (27.2%)	Venous thrombosis	13/103 (12.6%)
Antiplatelet therapy	57/103 (55.3%)	Arterial thrombosis	35/103 (34%)
ACE/ARBs	55 (53.4%)	Coronary artery disease	22/103 (21.4%)
Phosphate binders	70/103 (68%)		

aCL: anticardiolipin antibodies, **aβ2GP I**: anti beta2 glycoprotein I antibodies, **aPL**: antiphospholipid antibodies, **APS**: antiphospholipid syndrome, **aPTT**: activated partial thromboplastin time, **BMI**: Body mass index, **HCV**: hepatitis C virus, **HIV**: human immunodeficiency virus, **ACE**: Angiotensinogen converting enzyme inhibitors, **ARBs**: Angiotensin II receptor blockers, **LDL**: low density lipoprotein.

Table 2
Hemodialysis parameters and vascular access complications

	n
Hemodialysis vintage (years)	3.46 (2.04–6.20)
Histological proof of renal disease (n, %)	24/103 (23.3)
Urinary outflow > 300 ml (n, %)	33/103 (32.0)
BCM overload (liter)	− 0.41 ± 2.3[1]
HD modality (n, %)	44/103 (42.7)
HD	59/103 (57.3)
HDF	
Dialyser membranes (n, %)	25/103 (24.3)
Polysulfone (FX 80®)	52/103 (50.5)
Polysulfone (FX 800®)	20/103 (19.4)
Polyarylethersulfone and polyvinylpyrrolidone (Theranova 400®)	6/103 (5.8)
Polymethylmetacrylate (Torray®)	
Kt/V	1.75 ± 0.3
URR (%)	76.6 ± 6.5
AVF type (n, %)	76/103 (73.8)
Currently used	5/103 (4.9)
Maturation process ongoing	22/103 (21.4)
Not used (lost AVF)	48/78 (61.5)
Distal AVF	30/78 (38.5)
Proximal AVF	
AVF thrombosis or stenosis (n, %)	61/95 (64.2)
Thrombosis	21/95 (22.1)
Stenosis	52/95 (54.70
AVF maturation failure (n, %)	38/83 (45.8)

Values for continuous variables are presented as mean (standard deviation) or median (P25-P75 interquartile range)

BCM: Body composition Monitor ®, **HD**: Hemodialysis, **HDF**: Hemodiafiltration, **URR**: Urea reduction ratio, **AVF**: Arteriovenous fistula,

	n
Hematoma (n, %)	24/88 (27.3)
Prolonged blood clotting time avec HD (n, %)	8/87 (9.2)
Dilated AVF outflow vein (n, %)	6/89 (6.7)
Oedema (n, %)	7/90 (7.8)
Pain (n, %)	16/87 (18.4)
Values for continuous variables are presented as mean (standard deviation) or median (P25-P75 interquartile range)	
BCM: Body composition Monitor ®, **HD**: Hemodialysis, **HDF**: Hemodiafiltration, **URR**: Urea reduction ratio, **AVF**: Arteriovenous fistula,	

The average vintage of dialysis was 3.46 years. Primary nephropathy was confirmed histologically in only 23.3%. Most patients were anuric (68%) and on average dehydrated (BCM − 0.41 ± 2.3l). HDF was the technique of choice (57.3%). Ppolysulfone (Fx80®), polysulfone (Fx800®), polyarylethersulfone and polyvinylpyrrolidone (Theranova®) and polymethylmetacrylate (Toray®) dialyzer membranes were used in respectively 24.3; 50.5; 19.4 and 5.8% of the patients. Urea Kt/V and URR averaged 1.7 ± 0.3 and 76.6 ± 6.5. In our cohort, 90% of the patients had an AVF and in 73.8% of the patients AVF was used. The prevalence of AVF thrombosis/stenosis was 64.3% (22.1% thrombosis and 54.7% stenosis), the prevalence of AVFMF was 45.8%.

Tables 3 and 4 show the univariate analysis, assessing the association between AVF thrombosis/stenosis or AVFMF and demographic parameters or HD related parameters. Risk factors for AVFMF at univariate analysis were: aPL, UnK aPL, LA positivity, unknown primary renal disease, AVF thrombosis or stenosis, AVF stenosis, altered arterial/venous pressures, and dilatation, oedema, or pain at the site of AVF. After logistic regression, considering age, smoking and the presence of AVF stenosis, aPL remains an independent risk factor for AVFMF (adjusted OR = 6.8, 95% CI: 1.80, 20.51; p-value 0,004). No association between the presence of aPL and Kt/V, blood volume or residual diuresis was found, however, aPL was associated with lower URR (72.2 ± 8.4% versus 77.7 ± 5.4%; p = 0.02).

Table 3
Risk factors for AVF maturation failure.

	Maturation failure n = 38	No maturation failure n = 45	p-value
Gender	27/38 (71.1)	30/45 (66.7)	0.67
Age	55.7 (14.8)	60.8 (15.4)	0.13
BMI	26.7 (5.7)	26.0 (4.2)	0.54
Smokers	7/38 (18.4)	17/45 (37.8)	0.053
Diabetes mellitus	18/38 (47.4)	21/45 (46.7)	0.95
Hypertension	33/38 (86.8)	37/45 (82.2)	0.56
Neoplasia	7/38 (18.4)	4/45 (8.9)	0.33
AID	2/38 (5.3)	5/45 (11.1)	0.44
HIV	4/38 (10.5)	3/45 (6.7)	0.70
HBV	11/38 (28.9)	11/45 (24.4)	0.64
HCV	8/38 (21.1)	6/45 (13.3)	0.35
APT	20/38 (52.6)	22/45 (48.9)	0.73
ACE / ARBs	18/38 (47.4)	23/45 (51.1)	0.73
Phosphate binders	27/38 (71.1)	28/45 (62.2)	0.40
Statins	9/38 (23.7)	15/45 (33.3)	0.33
Hb	9.9 (1.7)	10.4 (1.4)	0.18
aPTT	32.9 (5.0)	32.2 (4.6)	0.52
Platelets	227.3 (73.3)	223.0 (99.2)	0.83
Total Cholesterol	151.4 (38.2)	159.8 (36.3)	0.31
LDL Cholesterol	82.2 (30.3)	88.1 (32.8)	0.40
APS	5/38 (13.2)	2/45 (4.4)	**0.01**
aPL	6/38 (15.8)	1/45 (2.2)	**0.04**

APS: antiphospholipid syndrome, **aPL**: antiphospholipid antibody persistent positivity, **LA**: Lupus anticoagulant, **AID**: autoimmune disease, **aPTT** : activated partial thromboplastin time, **BMI** : Body mass index, **HBV**: Hepatitis B virus, **HCV** : hepatitis C virus, **HIV** : human immunodeficiency virus, **AVK**: antivitamin K, **APT** : antiplatelets therapy, **ACE**: Angiotensinogen converting enzyme inhibitors, **ARBs** : Angiotensin II receptor blockers, **LDL** : low density lipoprotein, **HDL**: high density lipoprotein, **Hb**: hemoglobin

	Maturation failure n = 38	No maturation failure n = 45	p-value
UnK aPL	18/38 (47.4)	7/45 (15.6)	**0.002**
Negative	9/38 (23.7)	35/45 (77.8)	**< 0.001**
LA	11/38 (28.9)	3/45 (6.7)	**< 0.001**

APS: antiphospholipid syndrome, **aPL**: antiphospholipid antibody persistent positivity, **LA**: Lupus anticoagulant, **AID**: autoimmune disease, **aPTT** : activated partial thromboplastin time, **BMI** : Body mass index, **HBV**: Hepatitis B virus, **HCV** : hepatitis C virus, **HIV** : human immunodeficiency virus, **AVK**: antivitamin K, **APT** : antiplatelets therapy, **ACE**: Angiotensinogen converting enzyme inhibitors, **ARBs** : Angiotensin II receptor blockers, **LDL** : low density lipoprotein, **HDL**: high density lipoprotein, **Hb**: hemoglobin

Table 4
Hemodialysis parameters and vascular access complications in patients with or without AVF maturation failure.

	Maturation failure **n = 38**	**Absence of maturation failure** **n = 45**	**p-value**
Unknown primary renal disease (n/%)	24/38 (63.2)	39/45 (86.7)	**0.01**
Urinary outflow > 300ml (n/%)	12/38 (31.6)	15/45 (33.3)	0.87
Kt/V	1.76 (0.21)	1.75 (0.33)	0.81
URR (%)	76.3 (5.0)	77.3 (6.6)	0.43
BCM overload (liter)	-0.99 (2.43)	-0.27 (2.35)	0.18
Distal AVF (n/%)	18/27 (66.7)	24/39 (61.5)	0.67
HD vintage (years)	3.31 (1.73–5.51)	3.54 (1.88–6.54)	0.60
HD / HDF (n/%)	14/38 (36.8)	21/45 (46.7)	0.37
Membrane	5/38 (13.2)	14/45 (31.1)	0.22
FX 80 (n/%)	20/38 (52.6)	21/45 (46.7)	
FX 800 (n/%)	9/38 (23.7)	8/45 (17.8)	
Theranova (n, %)	4/38 (10.5)	2/45 (4.4)	
Torray (n, %)			
Arterial thrombosis (n, %)	12/38 (31.6)	14/45 (31.1)	0.96
Venous thrombosis (n, %)	7/38 (18.4)	3/45 (6.7)	0.17
AVF thrombosis/stenosis (n, %)	31/38 (81.6)	24/45 (53.3)	**0.007**
Thrombosis (n, %)	11/38 (28.9)	8/45 (17.8)	0.23
Stenosis (n, %)	28/38 (73.7)	19/45 (42.2)	**0.004**
Hematoma (n, %)	6/33 (18.2)	14/45 (31.1)	0.20
Prolonged blood clotting time avec HD (n, %)	4/33 (12.1)	3/44 (6.8)	0.45
Dilated AVF outflow vein (n, %)	0/34	5/45 (11.1)	**0.07**
Oedema (n, %)	4/35 (11.4)	0/45	**0.03**

BCM: Body composition Monitor ®, **HD**: Hemodialysis, **HDF**: Hemodiafiltration, **URR**: Urea reduction ratio, **AVF**: Arteriovenous fistula,

	Maturation failure n = 38	Absence of maturation failure n = 45	p-value
Pain (n, %)	11/33 (33.3)	3/44 (6.8)	**0.006**

BCM: Body composition Monitor ®, **HD**: Hemodialysis, **HDF**: Hemodiafiltration, **URR**: Urea reduction ratio, **AVF**: Arteriovenous fistula,

We found a higher prevalence of AVFMF in UnK aPL, aPL and APS groups. However, there was no difference between these groups with respect to AVFMF (Fig. 3).

UnK aPL is significantly associated with non-AVF thrombosis (p = 0.04), non-AVF arterial thrombosis (p = 0.03), coronary artery disease (p = 0.003) and AVF stenosis (p = 0.04).

Discussion

The prevalence of aPL and APS in our hemodialysis population with native AVF was 18.4%, which is similar to the prevalence reported by others (11–37%) (10). The prevalence of AVFMF was of 45.8%, which is also consistent with the literature. In fact, up to 60% of AVF will fail maturation after they are created (14).

The pathophysiology of AVFMF is complex and multifactorial. It mainly involves intimal hyperplasia, endothelial dysfunction, oxidative stress, and inflammation. Uremia itself promotes inflammation, endothelial dysfunction as well as a hypercoagulability state and platelet dysfunction. In addition, arterial or venous stenosis and hypoxemia are factors influencing the maturation process. Uremia, atherosclerosis, and hyperlipidemia on the one hand, and on the other hand vascular damage induced by surgical interventions, favor AVFMF (15–17). Finally, patients' age, chronic low blood pressure, smoking, female gender, diabetes mellitus, and the presence of a thrombophilia are additional risk factors for AVFMF (16, 17). Figure 4 summarize the pathogenesis of AVFMF.

To our knowledge, we report for the first time a statistically significant association between AVFMF and aPL (p = 0.04) or APS (p = 0.01). We also found this association with LA positivity alone (p < 0.001). In 2013, Birgitta Salmela et al. performed a prospective observational study, following 219 patients with underlying thrombophilia and assessing primary and functional primary patency defined respectively as the time of AVF creation or first AVF cannulation, until the need for the first vascular access intervention. Eleven percent of these patients (n = 23) had aPL, but the latter was not associated with patency failure. AVF maturation was not analyzed in this specific group (17).

The high prevalence of aPL and APS in the hemodialysis population is currently well established, however its association with AVF thrombosis and stenosis remains uncertain (18, 19). Thrombosis and stenosis both may influence AVF maturation (14), but they cannot always be distinguished. As expected, our study found an association between AVFMF and stenosis or thrombosis (p = 0.007), but

independently of thrombosis, only stenosis was associated with AVFMF. In the multivariate analysis, aPL and stenosis were independent risk factors for AVFMF (adjusted OR = 6.8, 95% CI: 1.80, 20.51; p-value 0.004). This suggests that there is a non-thrombotic or non-stenotic mechanism of AVFMF.

A common cause of stenosis is intimal hyperplasia (IH), which is well-described in AVFMF (14, 20). IH is more likely to occur at the anastomotic level and involves endothelial cells activation (21). IH has also been reported in aPL-associated disorders such as aPL-associated nephropathy and is referred to as aPL-associated Vasculopathy and is a non-thrombotic manifestation of APS. Its pathophysiology involves the activation of the mammalian Target of Rapamycin (mTOR) pathway (18, 22). One of the pathophysiological hypotheses that may explain AVFMF in aPL patients, is that endothelial cells activation and intimal proliferation under the influence of aPL will lead to IH, stenosis and/or thrombosis and thus maturation failure. Whether this phenomenon is mediated by mTOR pathway is not yet studied. Interestingly, when looking for aPL, APS and UnK aPL all together, anastomotic stenosis was found in 10.4% versus 4.2% in aPL negative patients. This was even more predominant when considering only APS and aPL subgroups (16.7% vs 4.2%). It would be interesting to explore more specifically IH by Doppler ultrasonography or histology and given our low prevalence of anastomotic stenosis, to confirm this on a larger cohort.

Furthermore, aPL has been associated with accelerated atherosclerosis, arterial vascular disease such as cardiovascular disease and peripheral artery disease (23, 24). Thus, an atherogenic hypothesis has been proposed by some authors and may explain the link between aPL and fistula occlusion (19). Furthermore, atherosclerosis with thickened vessels, and vascular calcification could also lead to an impaired remodeling process, to stenosis and/or thrombosis and therefore to AVFMF. We did not find an association between the aPL, APS and thrombosis or stenosis in our study, as it has been previously described in some studies (18).

Endothelial dysfunction has been reported in APS patients (25). Nitric oxide (NO), which is generated by endothelial NO synthase, has a vasodilatation effect, as well as anti-inflammatory and antiplatelet properties and has been shown to be crucial in AVF maturation (26). Impaired NO formation seems to be a major aspect of the aPL-induced endothelial dysfunction (27, 28). This may lead to insufficient vascular remodeling process of the outflow vein (14, 29). Figure 4 summarize our pathophysiological hypotheses of AVF maturation failure considering the involvement of aPL.

Interestingly, we studied a group of unknown significance (UnK aPL group), which was also associated with AVFMF and stenosis when compared to the negative group (p = 0.002 an p = 0.04 respectively). This group merged patients with one positive antiphospholipid antibody assay without confirmation (either absence of confirmation assay (11.7%) or negative (20.4%)). These patients do not fulfill the diagnosis criteria for APS of aPL, however, this group represents 32% of our cohort and therefore is of interest in terms of clinical outcomes. Antiphospholipid antibody negativation or fluctuation have been described in about 10% of APS patients, with uncertain clinical impact (30, 31). In a cohort of 472 patients of APS ACTION, 11% of patients with clinically meaningful aPL at baseline were unstable at a median follow-up

of 5 years (32). Follow up of these patients is crucial, and confirmation of their antiphospholipid antibody status should be performed.

The literature also suggests a role for platelet activation in the maturation of AVF (33). The 2019 ERA-EDTA Clinical practice guidelines on peri- and postoperative care of AVF and grafts for hemodialysis in adults suggest the administration of antiplatelet therapy during the first two months after AVF creation, in order to favor its maturation (3). Our study did not find an association between AVF maturation and antiplatelet therapy. Moreover, AVFMF was not associated with statins, ACE inhibitors or phosphate binder use. Age was associated with AVFMF in the literature (16) but we did not find such association in our cohort. This can be explained by the relatively young age of our HD population (34). In our cohort, we did not find an association between AVFMF and URR, Kt/V, BCM overhydration status. However, aPL was associated with lower URR ($p = 0.02$).

This study has several limitations: first, it a retrospective monocentric study involving a limited number of patients. Also, the definition of AVFMF by Doppler ultrasound is operator dependent and this may have influenced our results. Finally, not all clinical and anamnestic data were systematically reported, and other data such as utilization of erythropoietin (10), ultrasound mapping before AVF creation (35), the AVF location (36) and AVF geometric parameters (37) could not be collected in this study.

Conclusions

We report for the first time a statistically significant association between aPL/APS positivity and AVFMF. aPL and stenosis were independent risk factors for AVFMF. We hypothesize that aPL may cause AVF non maturation by two mechanisms: 1) either stenosis/thrombosis related or 2) a stenosis /thrombotic unrelated mechanism, possibly through endothelial dysfunction, intimal hyperplasia, accelerated atherosclerosis. Prospective studies are needed to confirm our hypothesis. We suggest that aPL could be an underestimated biomarker-candidate that could help clinicians identify at-risk patients for AVFMF.

Declarations

Ethics approval and consent to participate

This study has been performed in accordance with the Declaration of Helsinki. Institutional Review Board authorization was obtained from our local ethics committee (Ethics Committee of Brugmann University Hospital), reference number: CE 2018/117. The requirement for informed consent was waived by the Ethics Committee of Brugmann University Hospital because of the retrospective nature of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy considerations but are available by the corresponding author upon reasonable request.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' contributions

MT, AD, MM, FC, YD, JN and AP were involved in the conception and design of the study. MT did the data collection wrote the first draft of the manuscript. AD, MM, FC, YD, JN and AP revised the manuscript. AD did the laboratory workup, and the antiphospholipid assays. All authors were involved with the analysis and the interpretation of data and participated in the writing. FC and AP contributed equally to the supervision of this work and are to be considered as co-senior authors.

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Figures

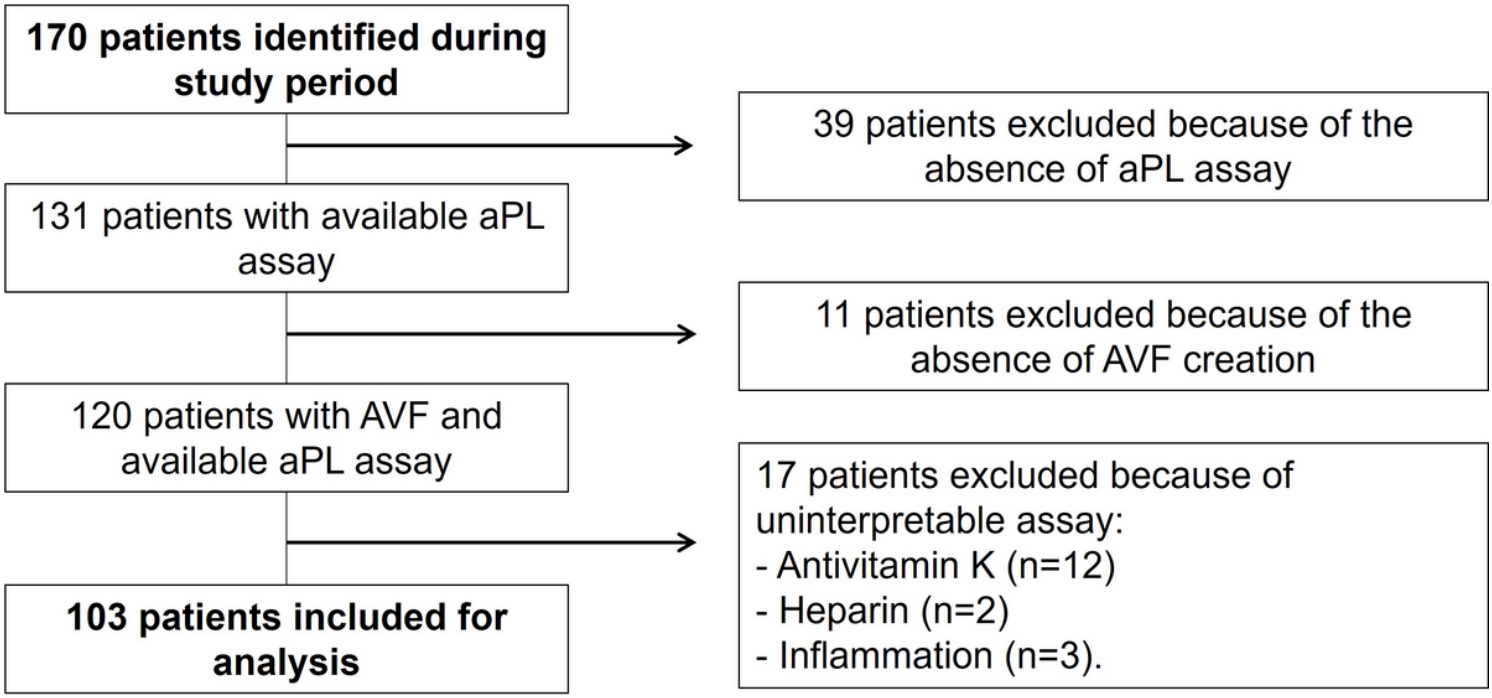

Figure 1

Study flowchart

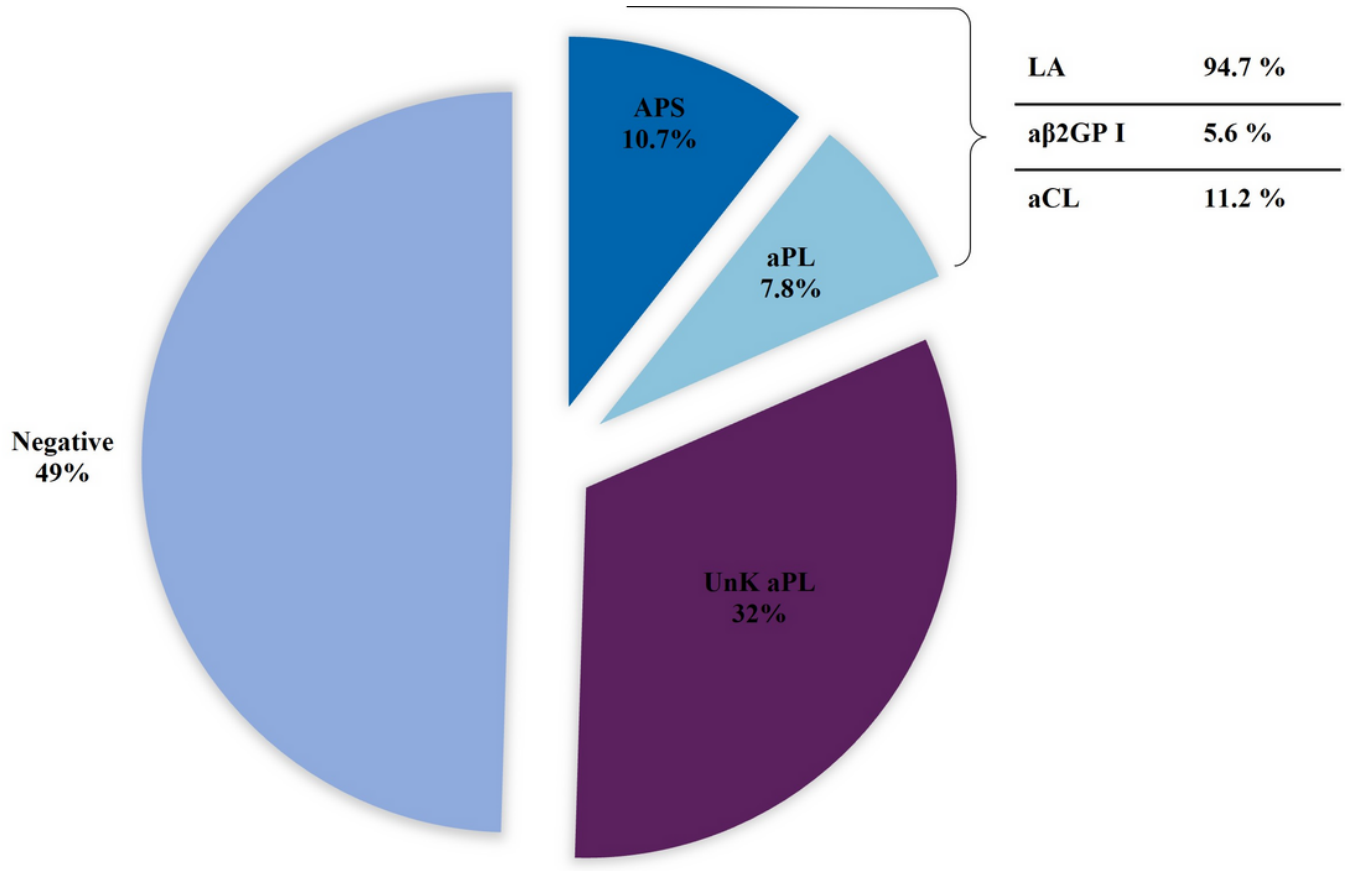

Figure 2

Antiphospholipid antibodies distribution among the 103 hemodialysis patients.

aPL and APS and negative groups are defined according to the Sapporo diagnosis criteria (13). UnK aPL consists in one positive value (patients with only one aPL Ab positive assay either without confirmation at 12 weeks, or one positive aPL Ab among 2 assays (positive becoming negative or the opposite)).

aCL: anticardiolipin antibodies, **aPL**: antiphospholipid antibody persistent positivity, **APS**: antiphospholipid syndrome, **aβ2GP I**: anti beta2 glycoprotein I antibodies, **LA**: lupus anticoagulant, **UnK aPL**: *group of unknown significance*

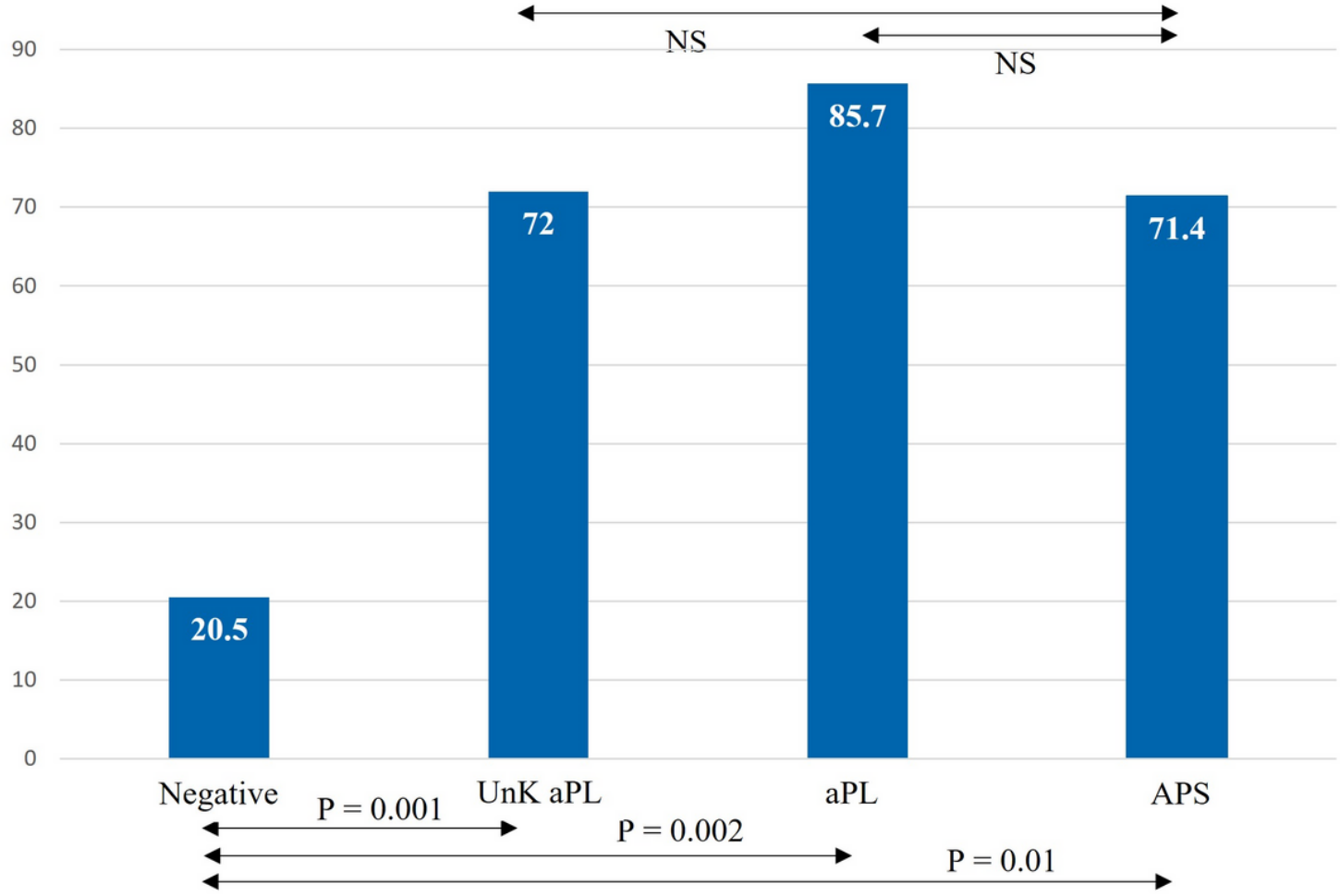

Figure 3

Prevalence of AVFMF in our cohort (%), according to the antiphospholipid antibody status.

aPL: antiphospholipid antibody persistent positivity, **APS**: antiphospholipid syndrome, **NS**: statistically not significant, **UnK aPL**: *group of unknown significance.*

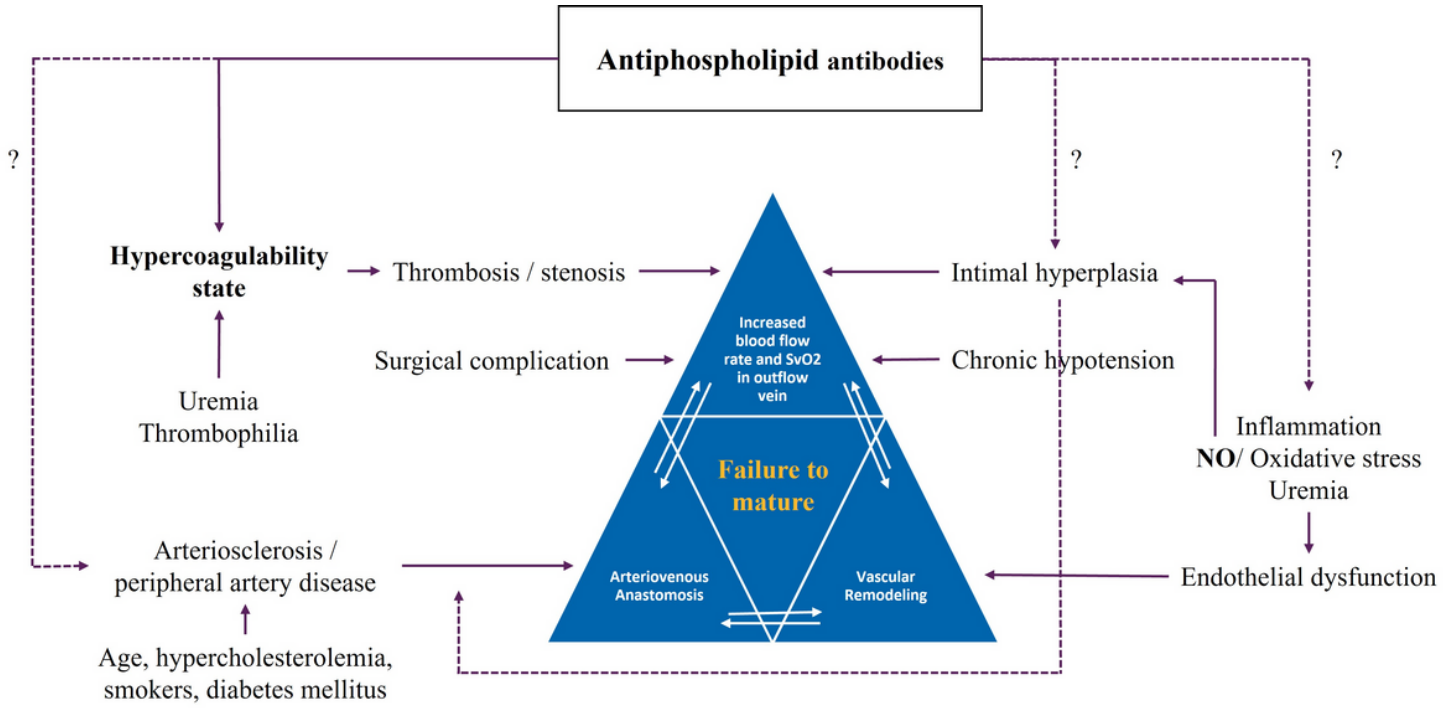

Figure 4

Proposed pathophysiology of AVF maturation failure considering the involvement of aPL/APS. According to (14,15,17).

Triangle represents the pathophysiology of AVF maturation failure.