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Lower Extremity Peripheral Arterial Disease and Its Relationship with Adverse Outcomes in Kidney Transplant Recipients: A Retrospective Cohort Study

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Abstract: The purpose of the study was to characterize lower extremity peripheral arterial disease (LEPAD) in a series of kidney transplant patients and to assess the impact on adverse outcomes. A retrospective cohort study was conducted including kidney transplant recipient patients who underwent screening for LEPAD. The outcomes evaluated were classified as perioperative and post-transplant, including cardiovascular events, amputation, mortality, and loss of the graft. A total of 141 renal transplant patients screened for LEPAD were identified, with an average follow-up of 3 years. LEPAD occurred in 14.2% (20/141). No differences in cardiovascular risk factors were found between the groups, except for smoking (45% vs. 24%, $p < 0.05$). In the group with LEPAD, the most compromised anatomical segment was the infrapopliteus, with no iliac involvement found. The Cox proportional hazards model indicated that the variables age, gender, and weight were significant in patients with LEPAD. There were no differences between the groups in terms of graft loss and death. The infrapopliteal segment is the area of greatest stenosis in kidney transplant patients with LEPAD. Together with smoking, they can explain the presence of major amputations in kidney transplant patients; however, they had no impact on graft functionality or death.

Keywords: peripheral arterial disease; photoplethysmography; kidney transplant; ankle-brachial index; toe-brachial index; amputation

1. Introduction

Lower extremity peripheral arterial disease (LEPAD) is common in patients older than 80 years, diabetics, or with chronic kidney disease [1,2], with a prevalence of up to 25% [3]. This carries a three to five times increased risk of cardiovascular events [4,5]. LEPAD is generally diagnosed by measuring the Ankle Brachial Index (ABI) [6,7], which is associated with higher mortality in this group of patients [8,9]. However, the occurrence of LEPAD in patients without risk factors for atherosclerosis and under 50 years is low. Information from population-based cohort reports described an occurrence of 1% of irregular resting ABI in patients under 50 years [3]. Thus, a lower extremity vascular physiological assessment through ABI must be considered during the pre-transplant evaluation [6,9].

LEPAD has a high incidence in transplant patients. In a cohort study of 43,427 patients, it occurred in 20% of diabetics [10]. In other studies, its most severe presentation, defined as the presence of intermittent claudication, the need for revascularization of the limb (surgical and/or endovascular), or major amputation, had an incidence of 4.2% and 5.9%, at 5 and 10 years of follow-up of transplant recipients [11]. Moreover, it is related to poor outcomes in this group of patients [12,13]. One study found that transplant patients with LEPAD had up to a twofold risk of post-transplant death, independent of the absence or presence of diabetes [10]. In another cohort of 819 kidney transplant recipients with LEPAD, defined by an ABI < 0.9 or $\geq$1.4, a twofold increased risk of mortality and a threefold increased risk of graft failure were observed at the 5-year follow-up [14].

Because LEPAD is a risk factor for death, amputation, and graft failure, as indicated by studies since 1990 [15,16], transplant centers routinely screen patients with a history of diabetes who present intermittent claudication, or pulse deficits in the extremities, focusing mainly on iliac compromise, considering that it is the place of implantation of the transplant [17,18].

Contemplating that hemodynamic studies are recommended in patients with chronic kidney disease, due to the greater presence of arterial stiffness, and considering that few investigations use this type of non-invasive hemodynamic studies of the lower limbs, this research aims to explore the relationship between the LEPAD with adverse outcomes in patients undergoing kidney transplantation in a high complexity center.

2. Materials and Methods

A retrospective observational study was carried out in a cohort of patients. All patients over 14 years of age who underwent renal transplantation (patients under 14 years of age belong to the pediatric program and are cared for in another section of the hospital), and who underwent screening for LEPAD, in the period between January 2013 and December 2019 were included. The screening was performed through a non-invasive hemodynamic study (arterial photoplethysmography) of lower limbs, within the pre-kidney transplant study protocol, to patients over 14 years of age who had diabetes mellitus (DM) as a cardiovascular risk factor, or in all those over 50 years of age with risk factors other than DM. Those with a lack of information in the clinical history about the study variables were excluded.

2.1. Kidney Transplant Technique

Renal graft implantation was routinely performed on the right side over the iliac fossa, using the external iliac artery, through an end-to-side anastomosis with 5.0 polypropylene. The location was modified to the left side in the scenario of not presenting patency of the external iliac vein or evidence in the photoplethysmography of the protocol occlusive arterial disease of any arterial segment of the right lower limb, associated with intermittent claudication or critical ischemia of the extremity (rest pain or ulcers). No type of revascularization or endarterectomy was performed during graft implantation. Only those patients who had bilateral critical ischemia were revascularized in the pre-transplant period, and before entering the waiting list. Claudicants did not undergo revascularization. Routine ureteroneocystostomy was an extravesical technique. Thymoglobulin was used as induction therapy, and maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone.

2.2. Study Variables

Demographic data and clinical, epidemiological, and hemodynamic characteristics of the patient's lower extremities were obtained from the clinical records reviewed by the investigators. Data entry was performed by two independent operators, with subsequent reconciliation of the data by the principal investigator. A follow-up was verified in the patient's outpatient records.

2.3. LEPAD Definition

Patients with LEPAD were identified according to the diagnosis made by the interpretation of the non-invasive hemodynamic study of the lower limbs by the internist or vascular surgeon, following the institutional protocol, defined as follows: (a) patients with ankle-brachial index (ABI) ≤ 0.9, and (b) patients with ABI between 0.91–1.29 or $\geq$1.3 plus alteration in the variables toe-brachial index (TBI) < 0.7, segmental pressures, arterial Doppler wave, waves of volume by plethysmography, and waves of photoplethysmography.

The 2 extremities of each patient were considered independent, thus, everyone contributed 2 ABI and 2 TBI, for the diagnosis.

2.4. Outcomes

The main outcomes evaluated were major amputation, defined as amputation above the ankle, graft functionality (excellent function, delayed function, graft loss), stroke, cardiovascular event (defined as acute myocardial infarction and/or heart failure), and perioperative death. In postoperative (outpatient) follow-up, the outcomes to be evaluated were graft loss, death, and major amputation (secondary results).

2.5. Statistical Analysis

The information was entered into a database in Excel (Microsoft) and then exported to the statistical package SPSS v. 24 (IBM) for analysis. Continuous quantitative variables were summarized using the median and interquartile range (IQR) based on the observed data distribution (Kolmogorov–Smirnov test), while qualitative variables were summarized using proportions. A bivariate analysis was performed to adjust and balance the clinical variables that behaved as risk factors for both LEPAD and the study outcomes. This was carried out by comparing the proportions for the qualitative variables, using the χ^2 tests or Fisher's exact. Hypothesis contrast tests were performed for the difference in means, as student-t, and Mann–Whitney and Wilcoxon U tests, for the difference in ranges and medians, to adjust the comorbidities that cause the outcomes with LEPAD.

To explore the association of LEPAD with some outcomes in transplant patients, the risk ratio (RR) was calculated with its corresponding confidence interval. Furthermore, a Cox proportional hazards model was used to determine independent risk factors for LEPAD, and patient survival curves were also constructed by the method of Kaplan and Meier. For this study, the value of $p < 0.05$ was taken as the level of statistical significance.

2.6. Bioethical Aspects

The study protocol was approved by the Research Ethics Committee of the Hospital San Vicente Fundación, Rionegro, Colombia (Record 05-2020). Moreover, the bioethical recommendations of the Declaration of Helsinki were followed.

3. Results

A total of 586 clinical records were reviewed between January 2013 and December 2019, of which 225 patients were screened for LEPAD and 141 patients were transplanted (Figure 1).

Of the 141 transplant recipients, 20 (14.2%) had LEPAD. Ninety-nine patients were male (70.2%) with a median age of 58 years (IQR 10.5). The sociodemographic, clinical, and hemodynamic characteristics of patients with or without adjusted LEPAD are presented in Table 1. The most frequent comorbidities in transplant recipients were arterial hypertension (91.5%), diabetes (44.7%), and dyslipidemia (38.2%). In transplant recipients with LEPAD, the main comorbidities were arterial hypertension (100%) and diabetes (60%). Smoking was observed in 45% of them.

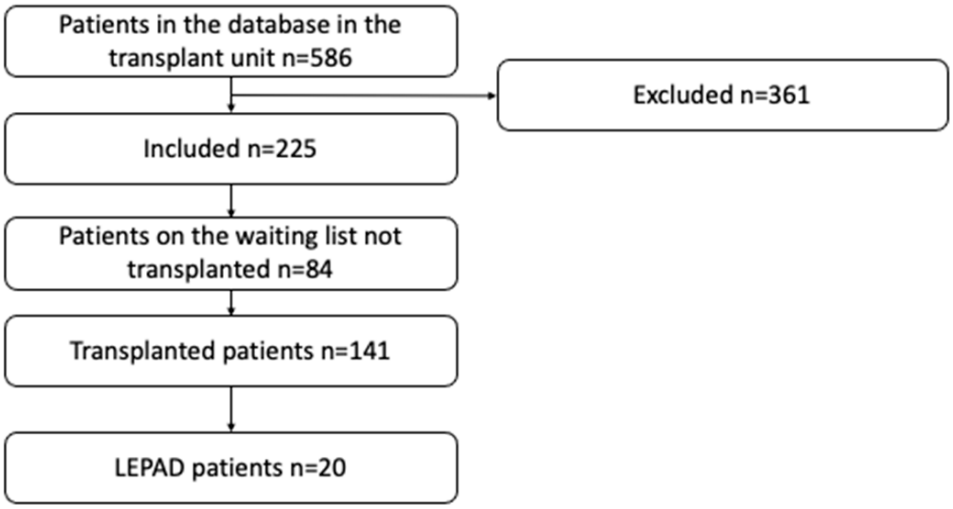

Figure 1. Flow chart of study collection and analysis groups.

Table 1. Adjusted comparison of the sociodemographic and clinical characteristics of the patients who received a transplant, discriminated by exposure or not to LEPAD.

Baseline Clinical Characteristics		LEPAD (*n* = 20)		Non-LEPAD (*n* = 121)		Total (*n* = 141)		*p* Value
		N	%	N	%	N	%	
Gender	Male	17	(85)	82	(68)	99	(70.2)	0,19
	Female	3	(15)	39	(32)	42	(29.8)	
Age	-	58	IQR (10.5)	58	IQR (10.5)	58	IQR (10.5)	0.97
Days of hospitalization	-	9	IQR (6)	9	IQR (6)	9	IQR (6)	0.56
Coronary heart disease	Yes	6	(30.0)	14	(11.6)	20	(14.2)	0.22
	Not	14	(70)	107	(88.4)	121	(85.8%)	
Arterial hypertension	Yes	20	(100)	109	(90)	129	(91.5%)	0.13
	Not	-	(-)	12	(10)	12	(8.5%)	
Diabetes mellitus	Yes	12	(60)	51	(52)	63	(44.7)	0.92
	Not	8	(40)	70	(48)	78	(55.3)	
Chronic heart failure	Yes	1	(5)	3	(2.1)	4	(2.8)	0.86
	Not	19	(95)	118	(97.9)	137	(97.2)	
Smoking	Yes	9	(45)	29	(24)	38	(27)	0.05
	Not	11	(55)	92	(76)	103	(73)	
Retinopathy	Yes	9	(45.0)	29	(23.9)	38	(27)	0.74
	Not	11	(55.0)	92	(61.2)	103	(73)	
Dyslipidemia	Yes	7	(35)	47	(38.8)	54	(38.2)	>0.99
	Not	13	(65)	74	(61.2)	87	(61.8)	
Cerebrovascular disease	Yes	1	(5.0)	5	(4.1)	6	(4)	1.00
	Not	19	(95.0)	116	(95.9)	135	(96.4)	
Body Mass Index	Underweight < 18.5	1	(5.0)	1	(0.8)	2	(2)	0.46
	Normal 18.5–24.9	9	(45.0)	48	(39.7)	57	(40)	
	Overweight 25–29.9	8	(40.0)	54	(44.6)	62	(44)	
	Obesity > 30	2	(5.0)	18	(14.9)	20	(14)	

In transplant patients with LEPAD, 40% (8) had an ABI $\leq$ 0.9, and 72.2% (13) had a TBI < 0.7. Of these patients, 20% (4/20) presented intermittent claudication. None with critical limb ischemia. The most compromised anatomical segment was the infrapopliteus (55% right lower extremity and 45% left lower extremity), 45% bilaterally [9], and there was no aortoiliac involvement (Table 2).

Table 3 summarizes the bivariate analysis of the outcomes of interest. There were statistically significant differences in major amputation in out-of-hospital follow-up, being higher in the group of transplant recipients with LEPAD [15% (3 patients) vs. 1.7% (2 patients), $p < 0.04$; RR: 9.1 (95% CI, 1.6–51)]. Most of the amputations were performed

on the side of the transplanted kidneys (90%). One patient (5%) died in the perioperative period after the transplant in the group with LEPAD. There were no statistically significant differences between graft loss and delayed function. Only one major cardiovascular event occurred in each group at the time of transplantation.

Table 2. Presence of claudication affected anatomical segments, and hemodynamics of transplant patients with LEPAD.

Variable		LEPAD (n = 20)	
		N	%
Claudication	Yes	4	(20)
	Not	16	(80)
Compromised limb	Right	4	(20)
	Left	7	(35)
	Bilateral	9	(45)
Aortoiliac right	Yes	-	-
	Not	20	(100)
Iliofemoral right	Yes	1	(5)
	Not	19	(95)
Femoropopliteus right	Yes	2	(10)
	Not	18	(90)
Infrapopliteal right	Yes	11	(55)
	Not	9	(45)
Metatarsus right	Yes	10	(50)
	Not	10	(50)
Aortoiliac left	Yes	-	-
	Not	20	(100)
Iliofemoral left	Yes	-	-
	Not	20	(100)
Femoropopliteus left	Yes	2	(10)
	Not	18	(90)
Infrapopliteal left	Yes	9	(45)
	Not	11	(55)
Ankle-brachial index right	Altered high $\geq$ 1.3	4	(20)
	Normal 1.0–1.29	5	(25)
	Bordering 0.91–0.99	3	(15)
	Altered low $\leq$ 0.9	8	(40)
Ankle-brachial index right	Altered high $\geq$ 1.3	4	(20)
	Normal 1.0–1.29	9	(45)
	Bordering 0.91–0.99	2	(10)
	Altered low $\leq$ 0.9	5	(25)
Index toe-brachial right	<0.7 abnormal	12	(66.7)
	$\geq$0.7 normal	6	(33.3)
Index toe-brachial left	<0.7 abnormal	13	(72.2)
	$\geq$0.7 normal	5	(27.8)

Moreover, a Cox proportional hazards model was performed to adjust for critical factors such as age, gender, weight, smoking, and DM status. The variables age, gender, and weight were significant in the model (Table 4).

Figure 2 presents the survival curve of patients with LEPAD, indicating that LEPAD Does not seem to have an impact on patient mortality.

Table 3. Renal transplant outcomes in patients with and without LEPAD.

Baseline Clinical Characteristics		LEPAD (n = 20)		Non-LEPAD (n = 121)		Total (n = 141)		p-Value	RR CI 95%
		N	%	N	%	N	%		
Perioperative Outcomes									
Major cardiovascular event	Yes	1	(5.0)	1	(0.8)	2	(1.4)	NA	NA
	Not	19	(95.0)	120	(99.2)	139	(98.6)		
Cerebrovascular disease	Yes	-		-		-		NA	NA
	Not	20	(100)	121	(100)	141	(100)		
In-hospital mortality	Yes	-	-	-		-		NA	NA
	Not	20	(100)	121	(100)	141	(100)		
Functionality graft	Yes	1	(5)	-		-	(0.7)	NA	NA
	Not	19	(95)	121	(100)	140	(99.3)		
	Excellent	16	(80)	89	(73.6)	105	(74.5)	0.74	NA
	Retarded	4	(20)	30	(24.8)	34	(24.1)		
	Lost	-	-	2	(1.7)	2	(1.4)		
Posthospital Outcomes									
Graft loss	Yes	1	(5)	7	(5.8)	8	(5.7)	>0.99	0.86 (0.11–6.65)
	Not	19	(95)	114	(94.2)	133	(94.3)		
Amputation	Yes	3	(15)	2	(1.7)	5	(3.5)	0.04	9.1 (1.6–51)
	Not	17	(85)	119	(98.3)	136	(96.5)		
Death	Yes	-		3	(2.5)	3	(2.1)	1.00	NA
	Not	20	(100)	118	(97.5)	138	(97.9)		

Table 4. Cox proportional hazards model adjusted for critical factors.

Factor	Coefficient	Hazard Ratio	95% Confidence Interval	p-Value
Age	0.063	1.065	1.004–1.130	0.036
Gender	−1.983	0.138	0.031–0.605	0.009
Weight	−0.081	0.922	0.873–0.973	0.003
Diabetes Mellitus	−0.826	0.438	0.169–1.133	0.089
Smoking	−0.006	0.994	0.383–2.580	0.990

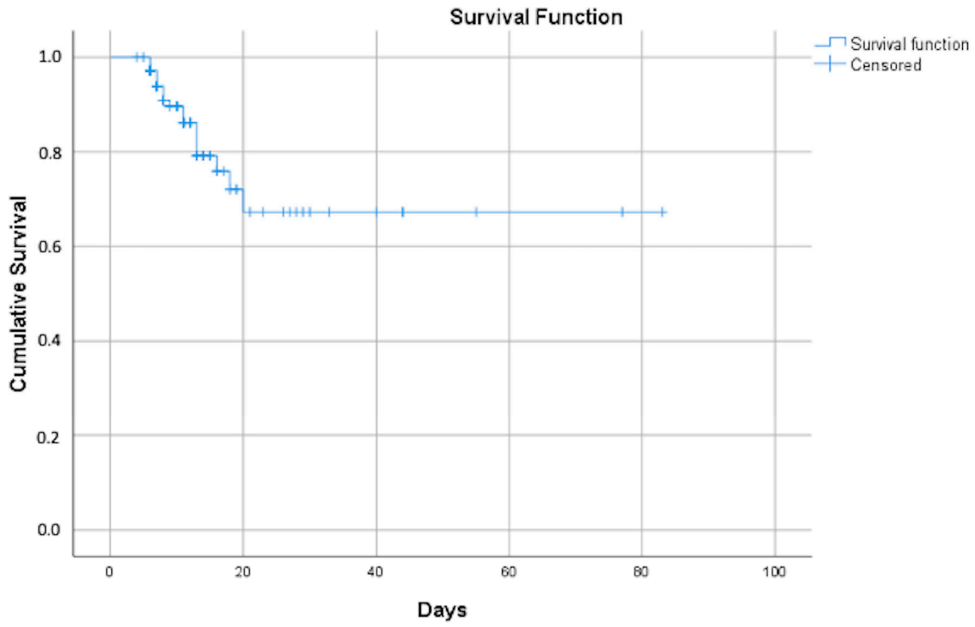

Figure 2. Kaplan–Meier patient survival estimates of patients with LEPAD.

4. Discussion

LEPAD is linked to adverse outcomes in kidney transplant patients. Chronic kidney disease is related to enhanced atherosclerosis including LEPAD. Patients with LEPAD present a superior quantity of cardiovascular incidents and important functional damage [14]. Renal transplant recipients are at risk of LEPAD from underlying conditions even before the commencement of immunosuppression. A considerable quantity of patients is transplanted for chronic renal failure secondary to diabetic or hypertensive nephropathy, disorders that are evidently related to enhanced atherosclerosis [11].

This is the first study in our country where the correlation of this pathology with adverse outcomes, anatomical characteristics, and prevalence in renal transplant patients was carried out. Its prevalence in this study was 14.2%, which is lower than that reported in the literature (20–25%) in the highest-risk groups [1,6]. This can be explained by the different definitions of LEPAD used in the studies, which may even overestimate it [15,19]. For its diagnosis, this pathology requires a comprehensive evaluation of multiple hemodynamic variables to assess perfusion, due to the greater presence of arterial stiffness in patients with end-stage chronic kidney disease [20,21]. In our institution, per protocol, a global interpretation of different hemodynamic variables (ABI, TBI, segmental pressures, volume waves by plethysmography) is used to establish the diagnosis in patients older than 50 years or diabetics. This makes it possible to increase sensitivity and specificity to identify this group and optimize it at the time of transplantation. Specifically, ABI is a precise manner to estimate the permeability of the lower extremity arterial system and is a suitable guide for the occurrence of LEPAD [14]. Some researchers are only interested in detecting iliac calcification, using different diagnostic approaches, such as pelvic radiography or tomography, to decide the place of kidney implantation [17,22] while others point out that only aortoiliac stenosis has a higher risk of perioperative morbidity and mortality, lower graft, and patient survival [23,24].

The most compromised arterial segment in transplant patients was the bilateral infrapopliteal segment. This compromise is very similar to that of elderly, Black, and Asian patients, adjusted for a history of diabetes [3].

Herein, it was observed that in patients with LEPAD the percentage of amputation was 15%, corroborating the results described in the literature [14,15]. It is noteworthy that in this group there was a greater history of smoking, with a statistically significant difference compared to the non-LEPAD group (45% vs. 24%, $p < 0.05$). In this regard, it has been indicated that the remnants from the cigarette cause malfunction of endothelial, smooth muscle cell transformation and macrophage phenotypic renovation across numerous molecular means. These uncontrolled alterations are the molecular source for the manifestation and progress of peripheral vascular illnesses [25].

On the other hand, it is important to note that the non-LEPAD group also presented amputations (almost 2%). This result corroborates previous findings about post-transplant amputations in patients without LEPAD (2.1%) [26]. This result can be explained by the presence of DM as a constant factor in both groups and is correlated with previous reports [10].

No major amputation occurred in the perioperative period. This can be explained by the fact that no patient with hemodynamically significant aortoiliac involvement was transplanted, and only one with iliofemoral involvement contralateral to the implant site. Although 45% of transplant recipients with LEPAD had low infrapopliteal involvement and ABI (25%), the events were not generated early. This indicates the presence of other cardiovascular risk factors, or poor control over time such as diabetes, the only constant factor that did not present statistically significant differences between the comparison groups. Furthermore, in most cases, although infrapopliteal lesions were susceptible to revascularization, they presented poor DM control, increasing the probability of amputations after revascularization. The only group presented in the perioperative period of the transplanted patients was the LEPAD group, and it corresponded to a smoker with several comorbidities, including DM, arterial hypertension, and being overweight. These

findings are consistent with the results of different published studies [15,16]. It is important to highlight that it has been widely reported that hypertension is one of the main risk factors for LEPAD due to the structural and functional changes it causes in the vascular tree [14–16].

Unfortunately, in medical records, we do not have information related to the pre-transplant dialysis methods or the times that dialysis was performed prior to the transplant. However, the type of dialysis or time may be an atherosclerotic factor, time does not preclude admission to the waiting list; therefore, evaluation by means of a hemodynamic study such as plethysmography is essential to define whether the patient is admitted to the list of waits. In the present study, we focused mainly on the arterial plethysmography data to define whether the patient should be transplanted and to assess the possible risk to the extremities. According to the presence of intermittent claudication or critical limb ischemia, the need for pre-transplant revascularization of the compromised limb was evaluated. On the other hand, patients with delayed function graft underwent hemodialysis through the contralateral femoral catheter or through the arteriovenous fistula, until the graft recovered normal diuresis.

In a study conducted over 10 years, adverse outcomes were found to be more frequent in patients with LEPAD. Reduced ABI was found to be an independent and significant factor in graft loss, mortality, and secondary outcomes [16]. This indicates that the diagnostic criteria for LEPAD screening of the present study is appropriate for detection, and adequately correlates with the described findings associated with the secondary outcome (major amputation). However, no statistically significant differences were found concerning other cardiovascular outcomes, graft loss, or death.

On the other hand, it is important to note that ABI examination is inexpensive, particularly when the expenses are linked with the costs related to the transplant itself or with the prices of caring for patients with modest transplant results. Consequently, assessment for LEPAD would be valuable in recognizing patients who are at elevated risk for complications regarding kidney transplants and designing treatments to modify risk factors [14]. TBI is a noninvasive examination that is convenient to assess for LEPAD in individuals with noncompressible arteries, which produce an artificial increase in the ABI [3]. A TBI $\leq$0.70 is anomalous and diagnostic of LEPAD since the digital arteries are infrequently noncompressible [3]. Patients with established DM or progressive chronic kidney disease present an elevated occurrence of noncompressible arteries. Consequently, TBI evaluation permits the diagnosis of LEPAD in these patients with noncompressible arteries that present description or physical inspection outcomes indicative of LEPAD [3]. For symptomatic patients in whom ABI/TBI corroborates LEPAD and in whom revascularization is contemplated, supplementary imaging with duplex ultrasonography, computed tomography angiography (CTA), or magnetic resonance angiography (MRA) is convenient to plan personalized management, incorporating support in the choice of vascular access places, recognition of important lesions, and decision of the possibility of a procedure for invasive handling. These noninvasive imaging approaches present noble sensitivity and specificity in comparison to invasive angiography [3]. Kidney functionality does not disturb the security of duplex ultrasonography, despite duplex presenting lesser spatial resolution than CTA and MRA in the location of arterial calcification. Moreover, the tomographic information from CTA and MRA provides the 3D reconstruction of the vessels scanned [3]. In this investigation, a non-invasive hemodynamic study of lower limbs was performed. In this regard, it has been indicated that diagnostic methods including noninvasive examinations or angiography are indicated for symptomatic patients or for individuals with satisfactory iliac inflow to a probable kidney transplant is questionable [11].

LEPAD with iliac involvement presents worse outcomes in patients undergoing kidney transplantation. A meta-analysis reported that kidney transplant recipients with prior aortoiliac calcification (AC) had a significantly increased risk of death at 1 and 5 years. Moreover, the risk of graft loss in one year was three times higher in recipients with AC [RR 3.15 (CI 1.30–7.64)] [24]. The present study had no patients with this compromise;

only one patient with stenosis of the contralateral iliofemoral segment was found who was claudicant and not a candidate for revascularization. Despite the above, the protocol research group transplants patients with lesions with critical ischemia after resolving this stenosis (before entering the waiting list), because it has been indicated that endarterectomies or revascularizations during transplantation have a negative impact on the survival of the graft [27,28]. In the case of claudicants, using the side of the compromised extremity can trigger decreased flow in the extremity when implanting the graft, generating steal syndrome, and increasing the risk of amputation [29,30]. On the other hand, no statistically significant differences were found in renal graft loss. Cardiovascular outcomes were very low, one in each group, but the frequency was higher in the LEPAD group (5%) versus (0.8%), which marks the trend shown by different studies [11,24].

It is important to note that it has been described that the frequency of manifestation of de novo LEPAD following transplantation does not vary over time, which indicates that the increasing results of immunosuppression had no effect on the acceleration/deceleration of the disease considering the phase prior to transplant placement. The progression of LEPAD changes over time, which makes it difficult to consider the effect of transplantation as such, from the outcomes of pretransplant aspects and features after graft failure on sickness evolution. It has been described that patients who had signs of LEPAD regarding transplantation are probable to have presented some grade of atherosclerosis at the phase of transplantation. Certainly, the occurrence of LEPAD before transplantation was the greatest risk factor for LEPAD after transplantation [11]. Moreover, transplant recipients with LEPAD after transplantation present an augmented possibility of mortality with a functioning graft. Nonetheless, this does not indicate that transplantation certainly accelerates fatality in patients with previous LEPAD, considering that this condition has an augmented menace of mortality in the general population [31]. Although this was not the case in the present study, in a series of patients with a background of LEPAD, it was described as an augmented but not important possibility of death, most were successfully transplanted and remained alive at the period of final evaluation [11]. Consequently, the presence or development of LEPA after transplantation does not conduct unavoidably to patient mortality and should not exclude probable recipients merely on this base. Nevertheless, these patients are undoubtedly at an elevated risk, and all possible transplant aspirants with LEPAD must have a laborious cardiac valuation before registering for transplantation. The control of diabetes and smoking interruption, though unconfirmed in avoidance of LEPAD in this population, can help delay the progress of sickness in the patients [32,33], and are valuable targets for other health motives [11].

Thymoglobuline is commonly used as an induction therapy in solid organ transplantation to prevent organ rejection by suppressing the recipient's immune system. The use of induction therapy with thymoglobuline can vary depending on the specific transplantation protocol, the organ being transplanted, the patient's medical history, and the preferences of the transplant team [34]. However, it is important to note that medical practices and protocols can change over time, and individual patient cases may vary. For example, the use of basiliximab has also been recommended; however, a recent study found no difference in acute rejection events or graft survival when thymoglobulin or basiliximab were used in mild-to-moderate immunological risk living donor kidney transplant recipients on tacrolimus and mycophenolate-based immunosuppressive regimens [35]. Therefore, the decision to use thymoglobuline or any other induction therapy is typically made by the transplant team based on the patient's unique circumstances and medical needs.

As has been indicated, recognized risk factors for LEPAD in the general population and in end-stage renal disease patients including age, smoking, and diabetes [11] were also relevant in the present investigation, illustrating the impact of pretransplant features. However, the Cox regression analysis only presented statistical significance in the age, gender, and weight variables, an issue that may be due to the sample size of this research. Another important aspect to consider is that LEPAD after renal transplantation disturbs kidney graft survival through inconsistent patient attrition. LEPAD is one expression of

generalized atherosclerosis, and most patients with this condition present concomitant cardiovascular disorder [31,32].

Patients with LEPAD must have a complete program of "guideline-directed management and therapy" (GDMT), counting systematized training and lifestyle adjustment, to decrease cardiovascular ischemic incidents and increase functional status. Smoking interruption is a fundamental factor of attention for patients with LEPAD. An agenda of pharmacotherapy to decrease cardiovascular ischemic incidents and limb-related occurrences must be recommended for each patient with LEPAD and are tailored to specific risk factors, such as if the patient also presents DM. Preceding investigations have described that patients with LEPAD are less probable to obtain GDMT than individuals with other types of cardiovascular diseases, such as coronary artery disease [33].

It is recommended that a group of specialists denoting diverse disciplines contribute to the assessment and supervision of the patient with LEPAD. For the attention of patients with claudication, the interdisciplinary group should incorporate clinicians trained in endovascular revascularization, surgical revascularization, wound curative treatments, foot surgery, and medical valuation and care [3].

Finally, three priorities have been proposed to promote health care for patients with LEPAD. ABI is recommended as the primary diagnostic exam to determine the diagnosis of LEPAD in patients with the description or physical assessment findings allusive to LEPAD. It is of fundamental relevance to ensure admission to controlled exercise schedules for persons with LEPAD. While large high-quality evidence endorses controlled exercise plans to develop functional status and quality of life, just a minority of individuals with LEPAD partake in these agendas because of the nonexistence of repayment by insurers. It is recognized that the demand for the inclusion of patient-centered results is in the development of regulatory agreements for innovative medical treatments and revascularization tools. For revascularization automation, regulatory authorization is focused principally on information on angiographic efficiency and care endpoints. The context of the functional restriction related to LEPAD permits the inclusion of patient-centered results, including functional factors and quality of life, into the efficacy results for the approval process [3].

This study has the limitations of its retrospective nature. Thus, a direct causal relationship cannot be evidenced; however, this study considered a series of elements provided by different clinical guidelines to guarantee the performance of an unbiased study. Moreover, it is important to recognize that the low frequency of outcomes may be due to the absence of iliac involvement and a low prevalence of LEPAD. Although Cox regression analysis was performed to adjust for confounding variables, only the variables age, gender, and weight were statistically significant. It is possible that the sample size of the present study influenced the regression results. Moreover, the average follow-up duration was three years, which might not be long enough to fully assess the impact of LEPAD on adverse outcomes post-transplant, especially considering the potential long-term implications of a kidney transplant. Therefore, the generalizability of the results of this study is limited. Thus, future studies could benefit from a prospective design where data collection can be standardized, and causal relationships better explored.

5. Conclusions

In transplant patients with LEPAD, the main vascular compromise was infrapopliteal segment stenosis, presenting a higher frequency of major amputations during outpatient follow-up, possibly due to smoking, the predominant risk factor in the LEPAD group. However, this variable was not significant in the regression model, as were age, gender, and weight. LEPAD does not seem to have an impact on graft loss or patient mortality, possibly due to the lack of involvement of the aortoiliac segment in the photoplethysmography of the patients in this study. The main anatomic compromise of these patients was infrapopliteal segment stenosis, independent of known risk factors such as diabetes, establishing the hypothesis that chronic kidney disease and arterial hypertension alone could cause this compromise.

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