PREDITORES PARA O DESENVOLVIMENTO DE DOENÇA ARTERIAL PERIFÉRICA NOS DOENTES SUBMETIDOS A TRANSPLANTE RENOPANCREÁTICO E IMPACTO NOS RESULTADOS

PREDICTORS FOR DEVELOPMENT OF PERIPHERAL ARTERIAL DISEASE IN PANCREAS-KIDNEY TRANSPLANT PATIENTS AND IMPACT ON OUTCOMES

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RESUMO

Introdução: O risco de doença arterial periférica (DAP) encontra-se significativamente aumentado nos doentes com diabetes mellitus tipo 1 que desenvolvem doença renal crônica. O transplante reno-pancreático assume-se como uma opção promissora para esses doentes, corrigindo ambas as disfunções. Os fatores de risco tradicionais para DAP estão bem definidos na população em geral. No entanto, em pacientes submetidos a transplante reno-pancreático a sua influência não se encontra caracterizada.

Objetivo: O objetivo deste estudo foi identificar fatores de risco que influenciassem o desenvolvimento e progressão da DAP em doentes submetidos a transplante reno-pancreático e avaliar os resultados nessa população.

Métodos: Estudo retrospetivo observacional de 229 doentes com diabetes mellitus tipo 1 e doença renal em estadio terminal submetidos a transplante simultâneo rim-pâncreas. Os dados demográficos, tempo de duração de diabetes antes do transplante, meses de diálise antes do transplante, tabagismo, medicação anti-hipertensora, estatinas, doença cerebrovascular, isquemia miocárdica, níveis de colesterol e níveis séricos de creatinina, cistatina C, proteína C reativa e albumina foram analisados. Foi realizada análise da sobrevida dos pacientes e dos enxertos renais e pancreáticos. Os dados foram analisados pelo SPSS versão 27 com significância em $p < 0,05$.

Resultados: Do total de 216 pacientes incluídos na análise com média de idade de 46,01 ± 0,48 anos, 32 doentes (14,8%) desenvolveram DAP sintomática e 23 pacientes (10,6%) isquemia crítica de membro. A taxa de amputação *major* neste subgrupo foi de 26,1%.
Os doentes com DAP foram caracterizados por níveis mais elevados de LDL-C antes do transplante ($p = 0,040$), que foram associados a um risco 1,011 vezes maior de desenvolver a doença. Níveis mais elevados de HbA1c 6 meses e 3 anos após o transplante também estavam presentes entre os doentes com DAP ($p = 0,033$ ep $= 0,022$), associados a um risco respectivamente 1,512 e 1,334 vezes maior de desenvolver a doença. Doentes com DAP foram também caracterizados por níveis mais elevados de cistatina C 5 anos após o transplante ($p = 0,015$), proporcionando um risco 2,405 vezes maior de desenvolver a doença. Além disso, a isquemia miocárdica também foi mais prevalente entre os doentes com DAP ($p = 0,037$), induzindo um risco 3,220 vezes maior de desenvolver a doença. A análise de sobrevida demonstrou uma tendência de menor sobrevida e menor sobrevida do enxerto renal em pacientes com DAP.

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Conclusão: O controle metabólico deficitário parece estar associado ao desenvolvimento de DAP sintomática nesta população. Níveis elevados de cistatina C também foram associados ao desenvolvimento de DAP, podendo ser um marcador independente de progressão da doença. Além disso, este estudo demonstrou que doentes com isquemia miocárdica apresentavam maior risco de desenvolver DAP.

Palavras-chave
Doença arterial periférica; Fatores de risco; Diabetes mellitus tipo 1; Transplante de pâncreas; Transplante de rim

ABSTRACT

Introduction: *The risk of peripheral arterial disease (PAD) is significantly increased in patients with type 1 diabetes mellitus who have developed chronic kidney disease. Pancreas kidney transplantation seems to be a promising option for these patients as it corrects both dysfunctions. The traditional risk factors for PAD are well defined in the general population. However, in patients undergoing simultaneous pancreas kidney transplant (SPKT) its influence is not well characterized.*

Objective: *The aim of this study was to identify possible risk factors that influence the development and progression of PAD in pancreas-kidney transplanted patients and assess the outcomes of PAD on this population.*

Methods: *We made a retrospective observational study of a group of 229 patients with type I diabetes mellitus and end stage renal disease who underwent pancreas-kidney transplantation. Demographic data, years of diabetes prior to transplant, months of dialysis prior to transplant, smoking, antihypertensive drugs intake, statins intake, cerebrovascular disease, myocardial ischemia, cholesterol levels and serum levels of creatinine, cystatin C, C-reactive protein and albumin were analyzed. Analysis of patients as well as kidney and pancreatic grafts survival was performed. Data were analyzed by SPSS version 27with significance at p < 0.05.*

Results: *Of the total of 216 patients included in the analysis with mean age of 46.01 ± 0.48 years, 32 patients (14,8%) developed symptomatic PAD and 23 patients (10,6%) critical limb ischemia. The major amputation rate in this subgroup was 26,1%. Patients with PAD were characterized by higher levels of LDL-C prior to transplant (p = 0.040), which were associated with a 1.011-fold higher risk of developing the disease. Higher levels of HbA1c 6 months and 3 years after transplant were also present among PAD patients (p = 0.033 and p = 0.022), associated with a respectively 1.512- fold and 1.334-fold higher risk of developing the disease. Patients with PAD had also higher levels of Cystatin C 5 years after transplant (p = 0.015) providing a 2.405-fold higher risk of developing the disease. Additionally, myocardial ischemia was also more prevalent among patients with PAD (p = 0.037) inducing a 3.220-fold higher risk of developing the disease. Survival analysis demonstrated a trend towards lower survival and lower renal graft survival in patients with PAD.*

Conclusion: *Poor metabolic control appears to be associated with the development of symptomatic PAD. Elevated levels of cystatin C were also associated with PAD and this can be an independent marker of progression of disease. Also, this study demonstrated that patients with myocardial ischemia were at higher risk of developing PAD.*

Keywords
Peripheral arterial disease; Risk factors; Type 1 diabetes mellitus; Pancreas transplantation; Kidney transplantation

INTRODUCTION

Peripheral arterial disease (PAD) affects more than 200 million people worldwide and its prevalence is increasing, especially in low-income countries[1]. The best-known risk factors include age, active smoking, diabetes mellitus (DM), arterial hypertension, dyslipidemia, and chronic kidney disease[2]. With the decrease in the prevalence of smoking habit in western countries, diabetes mellitus gains relevance as one of its major risk factors nowadays. It is known that the longer the duration of diabetes the greater the risk of developing peripheral arterial disease and thus patients with type 1 diabetes mellitus are particularly prone to this complication at an early age[3].

Pancreas-kidney transplantation has changed the course of type 1 DM patients with end-stage renal disease (ESRD) management. It provides a physiological mean of achieving normoglycemia with the advantage of keeping the ESRD patient free of dialysis[4]. A successful pancreas transplantation, by allowing the endocrine functions of the pancreas to be restored and by optimizing metabolic control, will intuitively slow the progression of diabetic micro and macrovascular complications. In fact, it has been reported that long-term normoglycemia following successful simultaneous pancreas kidney transplant (SPKT) significantly withstands improvement of the microangiopathic diabetic injuries, and that some of the already established injuries even have the potential to be reversed[5,6]. In contrast, data on the evolution of macroangiopathic diabetic injuries, as PAD, after SPKT is far from clear.

PAD is an independent predictor of cardiovascular events, affecting both the quality and expectancy of life. Early diagnosis and management of this disease is crucial to delay or avoid amputation and improve prognosis[7]. However, in patients undergoing SRKT, metabolic imbalance and renal disease represent the major burden for the development of the disease and the influence on other classical risk factors is still not well understood. Also, the characterization of the influence of PAD on overall survival is unknown in this group of patients.

METHODS

Study design and population

This research is a retrospective observational study, based on the electronic clinical records of 229 patients with type I Diabetes Mellitus and End Stage Renal Disease who underwent SPKT at Centro Hospitalar Universitário do Porto between May of 2000 and December of 2019. At our institution, SPKT indications include every fit for surgery patient with type I Diabetes Mellitus and End Stage Renal Disease requiring kidney transplant.

From the 229 patients, 13 patients were excluded from the study - 6 died at the time of transplant and 7 were lost in follow-up.

Risk factors and comorbidities

We conducted an extensive review of all patients' clinical records, and data describing their demographic and clinical features were collected, including sex, age, age at transplant, Body Mass Index (BMI), years of diabetes prior to transplant, months of dialysis prior to transplant, smoking, antihypertensive drugs intake, statins intake, cerebrovascular disease, myocardial ischemia, retinopathy, cholesterol levels (TC, LDL-C, HDL-C), triglycerides, HbA1c levels, creatinine, cystatin C, CRP, albumin and levels of neutrophils, lymphocytes, and platelets. To define the presence of dyslipidemia, we used HDL <40 mg/ dl in men and <50 mg/ dl in women, LDL > 120 mg/ dL, total cholesterol > 200 mg / dl and triglycerides ≥ 150 mg / dl, as criteria[8]. We also registered all follow-up periods, grafts' viabilities and grafts' survival time.

Peripheral arterial disease assessment

Due to the retrospective nature of our research and considering that the ankle brachial index was not systematically evaluated in all patients undergoing SRKT we only considered the presence of peripheral arterial disease in patients who were symptomatic: intermittent claudication or chronic limb threatening ischemia (CLTI) – rest pain and ulceration.

A detailed review of the presentation of patients with manifestations of PAD was performed according to the Rutherford scale[2]. The revascularization procedures were classified as endovascular, surgical or hybrid. The anatomical classification of the lesions was performed similarly to Dihem et al: aortoiliac (common, external and internal iliac arteries), femoropopliteal (common, superficial and deep femoral arteries, popliteal artery) and infrageniculate or distal (tibiofibular trunk, anterior and posterior tibial arteries, fibular artery) disease[9].

Considering the high frequency of aortoiliac disease found in patients with peripheral arterial disease, in disagreement with the known pathophysiology of diabetes mellitus typically associated with a more distal disease, a sub-analysis of these patients was carried out, investigating the technical aspects of transplantation surgery and as well as the detailed anatomical characterization of the disease.

Statistical analysis

The statistical analysis was performed using the IBM SPSS Statistics version 27.0.

The research results are presented in the form of mean ± standard deviation or median (interquartile range) for quantitative variables if they were normally or non-normally distributed, respectively. Qualitative variables are expressed as absolute numbers and percentages.

The study groups stratified as patients with PAD and patients without PAD were compared on clinical

characteristics using independent t-test for continuous normally distributed variables, Mann–Whitney test for continuous non-normally distributed variables and chi-square test for categorical variables.
The odds ratios (OR) for prevalent PAD associated with the cross-classification of LDL cholesterol, myocardial ischemia, HbA1c 6 months and 3 years after transplant and Cystatin C 5 years after transplant were calculated using logistic regression models.
A Kaplan-Meier survival analysis was performed to study the influence of PAD on the patients' survival, as well as on the of the pancreas and kidney grafts survival rates. For the statistical significance, a p-value < 0.05 was established. A confidence interval of 95% was used.

RESULTS

Characteristics

Our study was conducted on a group of 216 patients – 111 (51.4%) men and 105 (48.6%) women – with mean age of 46.01 ± 0.48 years and mean age at transplant of 35.54 ± 6.02 years. Mean follow-up time was 9 years. In 50 patients (23.15%) there was a need for reintervention in the same hospitalization because of different post-operative complications. During the follow-up period, the pancreatic graft remained functional in 174 (80.56%) patients, six patients with failed pancreas graft received a second pancreas transplant and it remained functional in only one patient. Regarding the kidney transplantation, the kidney graft remained functional in 192 (88.89%) patients Five of the patients with lost grafts were then re-transplanted and the rest started a hemodialysis program. Two of the retransplanted patients maintained a functioning graft whereas the 3 others lost the graft and begun hemodialysis. The post-operative complications as well as the causes of graft loss are detailed in TABLE I. The PAD characteristics of the 32 symptomatic patients are described in TABLE II. Eight patients (25%) presented with intermittent claudication and no revascularization procedures were performed. CLTI was targeted in 24 patients (75%) and 23 of these patients had undergone one or more surgical and endovascular revascularization procedures. In revascularized patients the rate of major amputation was 21% (n=6). One patient presented a small ulcer on the foot with Doppler ultrasound documenting hemodynamically significant occlusive disease of the infrapopliteal sector, however, he presented a favorable evolution of the lesion without the need for an invasive procedure for revascularization.

TABLE I Characterization of post-operative complications and causes of *graft* loss.

Post-operative complications, n		
Haemorrhage	22	
Infection	10	
Thrombosis and ischemia	8	
Intestinal Occlusion from surgical bandages	3	
Dehiscence of the surgical wound	2	
Pancreatitis	2	
Intestinal perforation	1	
Evisceration	1	
Urinary fistula	1	
Total	50	
Causes of graft failure, n	**Pancreas**	**Kidney**
Acute Rejection	4	1
Chronic Rejection	10	17
Vascular thrombosis	12	2
Haemorrhage	3	0
Infection	6	0
Non-*Hodgkin* lymphoma involving the *graft*	0	1
Unknown	7	3
Total	42	24

Aortoiliac arterial disease sub analysis

Twelve of the symptomatic patients had disease of the aortoiliac sector documented in diagnostic tests (TABLE III). Only in one patient the disease was limited to this anatomical sector, affecting multiple lower limb territories in all others. Four patients (33%) presented with complaints of intermittent claudication and 8 patients (67%) with chronic limb-threatening ischemia. In 9 patients (75%) the hemodynamically significant arterial disease was in the right iliac axis and in 3 patients (25%) in the left iliac axis. Six patients (50%) had hemodynamically significant lesion (stenosis or occlusion) in the transplant artery anastomosis: 5 patients with lesion in the right common iliac artery where the pancreatic transplant anastomosis was performed and 1 patient with lesion in the left external iliac artery where the renal transplant anastomosis was performed.

TABLE II Characterization of the symptomatic peripheral arterial disease

Rutherford classification at presentation	**n (%)**
1-3	8 (25)
4	1 (3)
5	11 (34)
6	12 (38)
Anatomical pattern	**n (%)**
Aortoiliac	12 (38)
Femoropopliteal	14 (44)
Infrageniculate	16 (50)
Revascularization procedures	**n (%)**
Endovascular	26 (60)
Hybrid	6 (14)
Surgical	11 (26)
Total	43
Outcomes	**n (%)**
Healing	11 (38)
Minor amputation	12 (41)
Major amputation	6 (21)

Analysis of predictive factors

Patient age, age at transplant, sex and BMI were not significantly different between the two groups.

The duration of diabetes mellitus prior to transplantation was mean 23.91 ± 5.75 years in the non- PAD group and mean 24.75 ± 5.40 years in PAD patients, with a non-significant difference. In non- PAD, all patients except 8 underwent hemodialysis as a replacement therapy for renal function before transplant with a median duration of hemodialysis of 21 (19) months. Whilst in PAD, only 1 patient did not undergo hemodialysis, with a median duration of hemodialysis 29 (27) months in this group. The duration of hemodialysis prior to transplant did not show any statistically significant difference between the groups.

Regarding smoking, we found no statistically significant difference between the two groups; although former and current smoking were slightly higher in the PAD patients. No association was found between antihypertensive therapy and statins intake and the prevalence of PAD.

There was an association found between PAD and myocardial ischemia (p = 0.037) with a higher risk of developing PAD of 3.220-fold among patients with myocardial ischemia. No association between PAD and cerebrovascular disease was found.

Patients with PAD were characterized by higher pre-transplant LDL-C levels (p = 0.040) and higher LDL-C levels were associated with a 1.011-fold higher risk of developing PAD. TC, HDL-C and triglycerides did not reveal any significant difference between the two groups. Regarding inflammation associated markers, no significant difference was found in CRP, NLR and PLR between groups.

HbA1c was significantly higher at 6 months (p = 0.033) and at 3 years after transplant (p = 0.022) in PAD patients, being associated with a 1.512- and a 1.334-fold higher risk of developing PAD, respectively. Besides that, at 1 and 5 years after transplant it was also higher in PAD patients, tending towards statistical significance 1 year after transplant (p = 0.068). Cystatin C was significantly higher in PAD patients 5 years after transplant (p = 0.015) and associated with a 2.405 higher risk of developing PAD. At 3- and 10-years' time although Cystatin C was also higher in PAD patients, the difference was not statistically significant. Regarding creatinine levels no significant difference was found.

In patients with no PAD symptoms, the mean duration of the pancreatic graft was 8.07 ± 5.27 years and of the kidney graft was 8.90 ± 5.03 years while in PAD patients it was 6.92 ± 5.89 years and 9.02 ± 4.55 years, respectively; no statistically significant difference was found.

Analysis of survival

Regarding the influence of PAD on pancreas and kidney grafts survival, using Kaplan Meieranalysis (FIGURES 1 AND 2), even though no statistically significant difference was found, we found an interesting trend towards lower graft survival in PAD patients, especially regarding kidney graft survival – FIGURE 2 .

Through the Kaplan-Meier survival analysis performed to evaluate the effect of PAD on patients survival, although the difference between the two groups was not statistically significant, PAD was clearly associated with lower survival time. Analyzing FIGURE 3, it is evident that from 10 years' time after transplant there is a much steep decline in survival among PAD patients compared to non- PAD patients.

TABLE III Characteristics of patients with aortoiliac significant hemodynamic disease.

Sex/ age	HBP	Dyslipi-daemia	Smoking	BMI	Rutherford class. at presentation	Anatomical patter of disease	Arterial anasto-mosis of pancreas/ kidney graft	Early rein-tervention	Retransplant previews to PAD	Aortoiliac revascularization	Outcome
F 44	Yes	No	No	19,53	1-3	Right EIA occlusion; FP and IP	Right CIA / Left EIA	Yes (bleeding)	No	None	-
M 42	Yes	Yes	Yes	21,63	1-3	Right CIA and EIA subocclu-sive stenosis	Right CIA / Left EIA	Yes (Pancreatic transplan-tectomy)	No	None	-
F 36	Yes	Yes	No	20,25	1-3	Right CIA subocclusive stenosis; FP and IP;	Right CIA / Left EIA	No	No	None	-
M 47	No	No	Yes	21,63	1-3	Right CIA and EIA suboclcu-sive stenosis	Right CIA / Left EIA	No	No	None	-
F 47	No	Yes	No	27,97	6	Left CIA subocclusive stenosis; FP and IP;	Right CIA / Left EIA	No	Yes (Kidney to Right EIA)	PTA and BES of left CIA	*Major* ampu-tation (below the knee)
M 48	No	Yes	No	19,77	4	Right EIA occlusion;	Right CIA / Left EIA	No	Yes (Pancreas to right EIA)	*ePTFE left to right femoro-femoral bypass*	-
F 51	Yes	Yes	Yes	20,89	5	Right EIA occlu-sion; FP and IP	Right CIA / Left EIA	Yes (enterohe-morrhagic pancreatitis)	No	*ePTFE left to right femoro-femoral bypass*	Helaing / Death (unrelated)
M 43	Yes	No	Yes	26,70	5	Right CIA stenosis; FP and IP	Right CIA / Left EIA	No	No	PTA and BES of right CIA	Healing
M 49	Yes	No	Yes	24,80	5	Right CIA occlu-sion; FP and IP	Right CIA / Left EIA	No	No	*PTA and stenting of CIA; ePTFE left to right femoral--femoral bypass*	Healing
F 38	No	No	No	21,93	6	Left CIA stenosis; FP and IP	Right CIA / Left EIA	No	Yes (Kidney to right EIA)	PTA and BES of CIA	Healing
F 36	Yes	Yes	No	27,43	6	Right EIA stenosis	Right CIA / Left EIA	No	No	PTA and SES of EIA	Healing
F 51	Yes	No	No	24,46	6	Left EIA stenosis; IP	Right CIA / Left EIA	Right CIA / Left EIA		PTA of EIA	

HBP - High Blood Pressure; BMI – Body Mass Index; EIA – External Iliac Artery; FP – femoropopliteal; IP – Infrapopliteal; CIA – Common Iliac Artery; PTA – Percutaneous Transluminal Angioplasty; BES - Balloon-Expandable Stents; ePTFE – Expanded Polytetrafluoroethylene; SES – Self-expanding Stent;

DISCUSSION

In this study, over the mean 9 years of follow up, the percentage of patients who developed symptomatic PAD was 14.81% which is an expressive value considering that the average age of our population was 46 years. In general population at age 45-49 years the prevalence of PAD is estimated to be 5.28% in women and 5.41% in men, mostly asymptomatic[10].

The duration of diabetes and hemodialysis prior to transplant did not show a significant role in the development of PAD in this population. Regarding smoking, one of most powerful predictor of large vessels PAD progression[11], no difference between the groups was found in our population.

The presence of myocardial ischemia associated with a 3.220-fold higher risk of developing PAD, which is in agreement with the systemic pathophysiology of

TABLE IV Comparison of clinical characteristics according to prevalent symptomatic PAD

Characteristics	Symptomatic Peripheral Arterial Disease		p-value
	No	Yes	
Male gender, n (%)	98 (53.3)	13 (40.6)	0.187
Age, years	45.89 ± 0.53	46.72 ± 1.10	0.537
Age at transplant, years	35.53 ± 6.04	35.63 ± 5.99	0.933
Pre-Transplant Data			
BMI, kg/m²	22.10 (3.34)	21.63 (5.27)	0.854
Duration of diabetes, years	23.91 ± 5.75	24.75 ± 5.40	0.444
Duration of dialysis, months	21 (19)	29 (27)	0.144
Smoking			0.423
Never, n (%)	122 (67.0)	19 (59.4)	
Past, n (%)	34 (18.7)	6 (18.8)	
Current, n (%)	26 (14.3)	7 (21.9)	
HbA1c, %	8.50 ± 1.62	8.57 ± 1.47	0.827
Total cholesterol, mg/ dL	166.00 (59)	179.50 (40)	0.242
LDL cholesterol, mg/ dL	**90.79 ± 33.86**	**104.31 ± 35.20**	**0.040**
HDL cholesterol, mg/ dL	48.00 (25)	51.50 (23)	0.618
Triglycerides, mg/ dL	122.50 (80)	126.00 (71)	0.463
Dyslipidemia, n (%)	122 (66.3)	21 (65.6)	0.940
Albumin, mg/ dL	3.89 ± 0.75	3.59 ± 0.50	0.077
CRP, mg/ dL	1.22 (3.40)	2.97 (13.01)	0.177
Neutrophiles, /µL	5.00 (2.21)	4.19 (2.69)	0.302
Lymphocytes, /µL	1.94 ± 0.76	1.85 ± 0.73	0.592
Platelets, /µL	262.00 (97)	279.00 (102)	0.140
Neutrophiles/ Lymphocytes Ratio	2.55 (1.60)	2.76 (2.16)	0.626
Platelets/ Lymphocytes Ratio	142.52 (74.01)	152.87 (135.41)	0.264
Antihypertensive drugs intake, n (%)	106 (91.4)	19 (95)	1.000
Statins intake, n (%)	71 (56.3)	12 (63.2)	0.576
Cerebrovascular Disease, n (%)	4 (2.3)	2 (6.3)	0.233
Myocardial ischemia, n (%)	**12 (6.9)**	**6 (19.4)**	**0.037**
Post-Transplant Data			
HbA1c at 6 months, %	**5.40 (0.70)**	**6.00 (2.70)**	**0.033**
HbA1c at 1 year, %	5.30 (0.63)	5.40 (1.70)	0.068
HbA1c at 3 years, %	**5.2 (0.70)**	**5.65 (3.20)**	**0.022**
HbA1c at 5 years, %	5.30 (0.60)	5.40 (3.20)	0.219
HbA1c at 10 years, %	5,70 (1,30)	5.50 (1.15)	0.759
Creatinine at 6 months, mg/ dL	1.11 (0.40)	1.08 (0.55)	0.943
Creatinine at 1 year, mg/ dL	1.12 (0.32)	1.10 (0.44)	0.716
Creatinine at 3 years, mg/ dL	1.11 (0.41)	1.24 (0.62)	0.313
Creatinine at 5 years, mg/ dL	1.14 (0.45)	1.41 (0.91)	0.218
Creatinine at 10 years, mg/ dL	1.22 (0.56)	1.29 (0.74)	0.246
Cystatin C at 1 year, mg/ L	1.13 (0.38)	0.97 (0.97)	0.688
Cystatin C at 3 years, mg/ L	1.18 (0.49)	1.43 (1.08)	0.199
Cystatin C at 5 years, mg/ L	**1.47 ± 0.65**	**2.01 ± 0.77**	**0.015**
Cystatin C at 10 years, mg/ L	1.58 ± 0.88	1.72 ± 0.72	0.623
Viable pancreas *graft*, n (%)	152 (82.6)	23 (71.9)	0.153
Duration of pancreas *graft* function, years	8.07 ± 5.27	6.92 ± 5.89	0.264
Viable kidney *graft*, n (%)	168 (91.3)	26 (81.3)	0.083
Duration of kidney *graft* function, years	8,90 ± 5.03	9.02 ± 4.55	0.894
Antihypertensive drugs intake, n (%)	83 (45.9)	17 (53.1)	0.448

BMI: Body Mass Index; HbA1c: Haemoglobin A1c; LDL: low-density lipoprotein; HDL: High-density lipoprotein; CRP: C-reactive Protein.
Data are presented as mean ± standard deviation, numbers (percentages) or median (interquartile range).

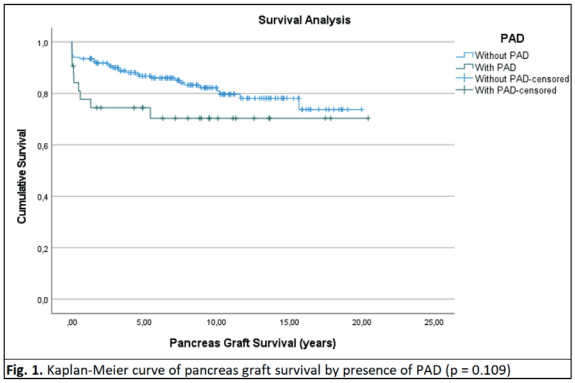

Fig. 1. Kaplan-Meier curve of pancreas graft survival by presence of PAD (p = 0.109)

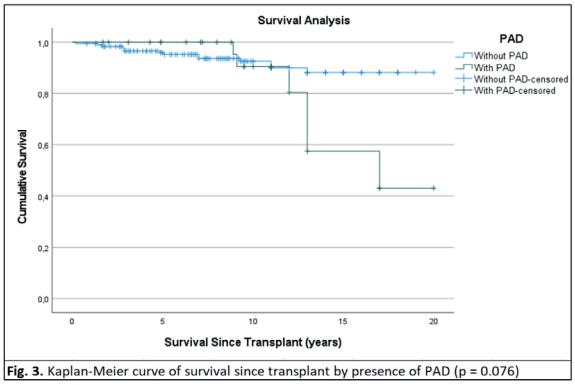

Fig. 3. Kaplan-Meier curve of survival since transplant by presence of PAD (p = 0.076)

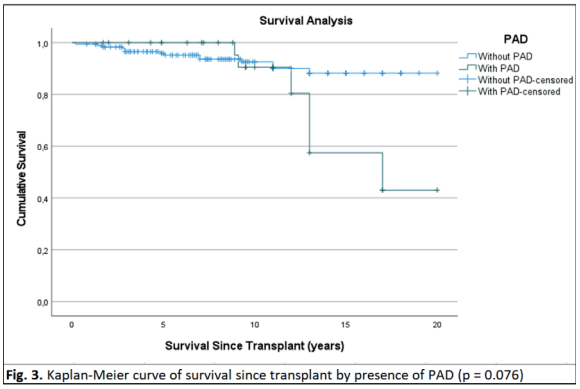

Fig. 3. Kaplan-Meier curve of survival since transplant by presence of PAD (p = 0.076)

atherosclerosis in multiple territories[12]. In contrast, in our study, we did not find any clear association between cerebrovascular disease and PAD.

The significance of high LDL-C as a major atherosclerotic risk factor and the importance of intensive LDL-C lowering in patients who are at high risk of atherosclerotic disease is well established[13]. Our results on LDL-C are is in agreement with these findings and proves that in SPKT population, metabolic control is crucial.
Also, in accordance with our findings regarding HbA1c, in the prospective Heinz Nixdorf Recall Study, diabetes with poor glycemic control (indicated by HbA1c≥7.0%) was strongly associated with incident PAD over a 5-year and 10-year follow-up[14]. It was also showed that a higher mean of HbA1c and a higher variability indicate an increased risk for PAD[15].
Several studies suggest that clinical markers associated with inflammation, such as CRP, lymphocytes and platelets, can be associated with the development of PAD[16,17]. However, in our study, none of those correlations were found.
Cystatin C is independently associated with incident PAD during long-term follow-up[18]. In our study, although there was a correlation between cystatin C elevation and the development of PAD, the same was not observed for creatinine, which suggests that this marker can have an impact on the development of PAD regardless of kidney dysfunction. Other studies also reported that elevated cystatin C concentration was found to be associated with future PAD procedure (bypass surgery, angioplasty, or amputation) among persons who did not have PAD at baseline[19].

Although some studies found association between the viability of the pancreas and kidney grafts and the development of PAD[20], in our study we did not find that association, which is possibly justified by the small number of lost grafts. However, the kidney graft survival seems to be lower in PAD patients which is shown in the analysis of the Kaplan-Meier curve in FIGURE *2. Also regarding the Kaplan-Meier survival analysis -* FIGURE *3 - it is evident that from 10 years' time after transplant there is a much steep decline in survival among PAD patients compared to non-PAD patients which comes in agreement with several studies that have already showed that PAD is a risk factor for all-cause mortality[7, 21].*

Another interesting finding of our study was the relative high prevalence of aortoiliac arterial disease (38% of all symptomatic patients) that would not be expected as DM is described in several studies by causing more distal atherosclerosis located mainly below the knee and because DM has been reported as the most obvious risk factor for atherosclerotic involvement of infragenicular arteries[9]. Possible explanations for this aortoiliac segment disease is the vascular clamp injury caused in the vessel at the time of transplant with subsequent intimal hyperplasia[22] and the hemodynamic impact of anastomosis performed at time of transplant. However, data in the literature are scarce regarding the development of iliac stenosis in long-term transplant patients.
This study has several limitations which may have compromised our results. Two limitations were that our study was a single center study, and it was retrospective.

CONCLUSION

Our study has come to agreement that the lack of metabolic control, namely the elevated levels of LDL cholesterol and HbA1c seem to contribute to the development of the PAD disease. Elevated levels of cystatin C were also associated with PAD and this can be an independent marker of progression of disease. Additionally, this study demonstrated that patients with myocardial ischemia were at higher risk of developing PAD. Besides the pathophysiology associated with diabetes mellitus and chronic kidney disease, our study suggests that vascular clamp injury may also play a role in the development of peripheral arterial disease in these patients. Also, the development of DAP could be associated with lower kidney graft and patient survivals rates, namely 10 to 15 years after the transplant surgery.

CONFLICT OF INTEREST

The authors declare no conflict of interest or financial support.

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