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Skin disorders indicating peripheral arterial occlusive disease and chronic venous insufficiency in organ transplant recipients

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ABSTRACT

Background: Peripheral arterial occlusive disease (PAOD) and chronic venous insufficiency (CVI) in organ transplant recipients (OTR) can lead to harmful outcomes. We made an inventory of cutaneous manifestations of PAOD and CVI in OTR in relation with diabetes and other potential risk factors.
Methods: A prospective study in a single center was performed. OTR ($n = 112$) were included at the outpatient clinic to investigate clinical signs of PAOD and CVI. The most commonly associated risk factors were determined.
Results: PAOD had been diagnosed in 15.6% and CVI in 30.0% of the patients. Diabetes was the cause of organ failure in 9.8% of the patients. Type 1 diabetes had been diagnosed in 8.9% and type 2 diabetes in 21.4% (59.1% new-onset diabetes after transplantation). Type 1 diabetes showed an increased risk for PAOD and limb amputation with hazard ratios of 11.0 (95%CI 3.0–40.2) and 9.1 (95%CI 1.4–58.6). Type 2 diabetes showed no increased risk.
Conclusions: Patients with a history of type 1 diabetes were at high risk for PAOD even years after a simultaneous pancreas kidney transplantation and they should remain under close observation for PAOD even though they are supposedly "cured" from their diabetes to prevent a harmful outcome.

1. Introduction

Skin disorders are a well-known complication in organ transplant recipients (OTR).[1,2] Most commonly described are cutaneous malignancies (cumulative incidence 20–70%) and skin infections (prevalence 55–97%).[2–4] About 10% of all OTR develop a cutaneous malignancy within 10 years and 40% within 20 years after the transplantation.[2] Therefore, patients are advised to visit specialized dermatology clinics in order to get regularly checked for skin cancer.[3] Regarding skin infections, the spectrum and post-transplant time period varies, dependent on the type of the infection.[5] About 70% of all severe skin infections occur during the first 3 months after transplantation.[1] Diabetes is a common complication in OTR either as new-onset diabetes after transplantation caused by the chronic corticosteroid treatment or as a cause of kidney failure which has led to the transplantation.

Besides skin malignancies and infections, skin conditions related to peripheral arterial occlusive disease (PAOD) in OTR are also occasionally reported with an estimated incidence of 2–8%.[2,6–9] The cutaneous manifestations of PAOD, in particular ulcers of the lower extremities, necrosis of the skin and gangrene often have a severe clinical course with limb amputation as one of the most severe complications.[6] In general, PAOD has an estimated prevalence of 25% in all patients with end-stage renal failure.[7] Besides well-known risk factors for PAOD, such as hypertension and diabetes, Sung et al. implicate that the development of PAOD after transplantation can also be a possible consequence of immunosuppressive therapy.[9] This therapy can induce or exacerbate hypertension and hyperglycemia, and therefore contribute to vascular complications.[6,7,9]

Several studies have indicated that PAOD after solid organ transplantation has a negative impact on allograft and patient survival. A higher all-cause mortality in OTR has been demonstrated in those who have undergone major limb amputation.[6–10] Screening programs are important to prevent serious cardiac and cerebral complications of PAOD, but

Abbreviations: ABI, Ankle-brachial index; CI, Confidence interval; CEAP, Clinical, Etiological, Anatomical and Pathophysiological (classification system); CRT, Capillary refill time; CVI, Chronic venous insufficiency; DM, Diabetes mellitus; HR, Hazard ratio; METC, Medical Ethical Committee; OTR, Organ transplant recipients; PAOD, Peripheral arterial occlusive disease; SPK, Simultaneous pancreas kidney; WMO, Medical Research Involving Human Subjects Act.

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better knowledge about PAOD in OTR may also help clinicians to develop preventive programs for patients at risk for developing skin ulcers, skin necrosis and limb amputation after transplantation.

2. Materials and methods

A prospective study was performed to make an inventory of the percentage of OTR presenting with cutaneous manifestations of vascular disease and to determine risk factors, such as diabetes, that predispose for these cutaneous manifestations.

2.1. Patients

All OTR who visited the specialized OTR skin clinic located at the Department of Dermatology of the Leiden University Medical Center (LUMC) in the 3-month period between November 2018 and February 2019 were included. In this specialized OTR skin clinic kidney, simultaneous pancreas kidney (SPK) and liver transplant recipients are followed. All patients who visited the specialized OTR skin clinic had an independently set appointment, most commonly for a routine check-up for cutaneous malignancies. Patients were included by the principal investigator (PI) of the study. Inclusion criteria were age ≥ 18 years and OTR. Exclusion criteria were severe mental or psychiatric disorder and/or insufficient knowledge of the Dutch or English language.

Each patient willing to participate was physically examined, focused on cutaneous signs of PAOD and chronic venous insufficiency (CVI) and a brief questionnaire based on symptoms of these diseases was taken. Additional diagnostic measures (ankle-brachial index (ABI) and duplex ultrasound) to confirm the diagnosis of PAOD in patients presenting with signs/symptoms of the disease were not used because of limited time. An information letter about the study was given to all patients who participated. Since inclusion in the study required only one-time participation, no follow-up for this study was scheduled.

Permission for the study was granted by the Medical Ethical Committee (METC) of the LUMC by a declaration of no objection (METC reference number: N19.012), since this research was not subjected to the Medical Research Involving Human Subjects Act (WMO) informed consent was given orally.

2.2. Data collection

The following baseline characteristics were recorded for each patient: date of birth, sex, weight, height, cause of organ failure, type of transplantation(s), date of transplantation(s). Details of the following variables were collected: PAOD, CVI, lymphedema, skin ulcer, skin necrosis and amputation (minor and major). PAOD was defined as the presence of one or more clinical signs (e.g. claudication) confirmed by diagnostic testing (ABI or duplex ultrasound).[11] The following symptoms of PAOD were scored: resting/night pain; dullness; cold hands and feet; claudication (less or >100 m); or a combination of these symptoms. Similarly, clinical signs of PAOD were scored: abnormal peripheral pulsations (defined as absent peripheral pulsations of the tibialis anterior and/or dorsalis pedis artery); prolonged capillary refill time (CRT); cold feet/toes; cyanosis and ulceration.

CVI was defined as the presence of venous skin disorders (e.g. varicose veins, edema, pigmentation, eczema, lipodermatosclerosis, atrophie blanche and (healed) ulcer), with or without the presence of edema.[12] Symptoms of CVI were scored: pain; tiredness/heaviness; cramps; swelling; or a combination of these symptoms. The following clinical signs were documented: telangiectasia/reticular veins; edema; and pigmentation/eczema. In the presence of solitary edema, CVI was included as the main cause only if registered as the final diagnosis.

In addition, variables indicating possible risk factors were obtained: diabetes mellitus (DM), diabetic complications, acute myocardial infarct (AMI), smoking status, alcohol consumption and hypertension. Hypertension was defined as a repeatedly elevated blood pressure exceeding 140 over 90 mmHg. All data collection was performed at the department of Dermatology at the LUMC. Data were collected from patient charts through the electronic patient record system of the LUMC (HiX, Chipsoft).

Data were completed with the information obtained at the specialized OTR skin clinic. PAOD was classified according to the Fontaine classification.[13] CVI was staged using the Clinical, Etiological, Anatomical and Pathophysiological (CEAP) classification system.[14] Because the OTR were only screened for clinical signs, CVI was staged from C_1 to C_6.

2.3. Statistical analysis

Continuous variables were analyzed with Student's *t*-test and categorical variables using the Chi-squared test. Univariate and multivariable Cox proportional hazard regression models were used to estimate the hazard ratio (HR) for each subcategory of peripheral vascular disease. For the start of the analysis, the date of first transplantation was used and dates of onset of the vascular disorder, death or last follow-up were indicated as the end of the analysis. Only clinical signs of PAOD or CVI that occurred after the first transplantation were included in the final analyses. *P*-values < 0.05 were considered statistically significant. IBM SPSS Statistics for Windows, Version 23 was used for all analyses.

Table 1
Baseline characteristics of included patients.

Variable	Patients ($n = 112$)
Type of first transplantation, no. (%)	
Kidney	88 (78.6)
Simultaneous pancreas/kidney	7 (6.3)
Liver	17 (15.2)
Cause of organ failure, no. (%)[c]	
Glomerulonephritis	22 (21.6)
ADPKD	16 (15.7)
Diabetes mellitus	10 (9.8)
Hypertension	4 (3.9)
Urological disease	23 (22.5)
Congenital disease	1 (1.0)
Liver cirrhosis	13 (12.7)
Other	13 (12.7)
Year of transplantation (range)	1969–2018
Age at first transplantation, years, median (25;75%)	46.4 (35.1;59.8)
Men, no. (%)	78 (69.6)
BMI at time of inclusion, median (25;75%)	24.6 (22.5;27.1)
Diabetes mellitus at any time, no. (%)	
No DM	78 (69.6)
DM type 1	10 (8.9)
DM type 2	24 (21.4)
Diabetic complications at any time, no. (%)	
None	19 (17.0)
Retino- or neuropathy	5 (4.5)
Nephropathy[a]	0 (0)
Retino- or neuropathy AND nephropathy	10 (8.9)
N.A. (no DM)	78 (69.6)
AMI, no. (%)	14 (12.5)
Ever smoker, no. (%)	59 (52.7)
Hypertension, no. (%)[b]	82 (75.2)
Age at time of follow-up, years, median (25;75%)	66.2 (58.8;71.5)

%, valid percent; SD, standard deviation; no., number; BMI, body mass index; ADPKD; autosomal dominant polycystic kidney disease; N.A., not applicable; DM, diabetes mellitus; AMI, acute myocardial infarct.

[a] When documented in the patient records as a complication of diabetes.
[b] As documented in the patient records (Blood Pressure > 140/90).
[c] Missing values: 10.

3. Results

Of all patients presenting at the specialized OTR skin clinic from November 2018 until February 2019 ($n = 133$), 21 patients were not included because they refused to participate or because of time pressure during the consultations, resulting in a total of 112 patients, 88 kidney, 7 simultaneous and 17 liver transplant recipients, to be analyzed.

Patient characteristics are listed in Table 1. Of all OTR, 30.3% had been diagnosed with DM, with 9.8% having DM as the cause of organ failure. Most of the patients with DM had type 2 diabetes and 59.1% of type 2 diabetes was new-onset diabetes after transplantation. Hypertension was frequently observed.

3.1. Inventory of cutaneous manifestations of vascular disease

Of all patients included at the specialized OTR skin clinic, 51.8% had no PAOD or CVI reported in the electronic patient records. CVI was more prevalent than PAOD (Table 2). The first skin ulcers as clinical signs of PAOD appeared 13.0 ± 10.4 years, skin necrosis 15.2 ± 11.0 years and amputation 19.8 ± 11.4 years after transplantation. The diagnosis of CVI was made 11.8 ± 9.8 years after transplantation.

Table 3 shows the Fontaine stages of PAOD and the CEAP classification of CVI at the time that the OTR presented in our hospital with their first clinical presentation of PAOD and/or CVI. If patients were already diagnosed with PAOD and/or CVI before visiting the specialized OTR skin clinic, the first symptom ever documented in the patient records (post-transplantation) was used. Table 3 shows that most patients with PAOD and CVI were diagnosed at a relatively early stage. Nine out of 13 (69%) OTR with PAOD had Fontaine stage I or II and 15 (88%) out of 17 OTR with CVI had CEAP classification C1, C2 or C3 (8.3% and 13.4% respectively). This means, however, that 4 out of 13 (31%) of all patients with PAOD were diagnosed for the first time at an already advanced stage.

All signs and symptoms of PAOD at time of presentation at the specialized OTR skin clinic are listed in Table 4. In case of more than one symptom or sign, the most severe presentation is provided. Almost all described signs were seen on the lower legs of the patients. 70% of the patients had ≥1 symptoms of CVI. Swelling/edema was the most frequent sign/symptom of CVI, besides the presence of varicose veins. Symptoms of PAOD were described by 39.3% of all patients and almost half of the patients (45.9%) showed clinical signs of PAOD, with the most frequent sign being abnormal peripheral pulsations. Thirteen patients (12%) had cyanosis of the feet and lower legs, which indicates microvascular insufficiency, mostly in combination with other signs of PAOD.

3.2. Risk factors for PAOD and CVI

For the final analysis, the diagnosis of PAOD and CVI was only used when confirmed in the electronic patient records, because of the lack of objective diagnostic testing in the specialized OTR skin clinic.

Table 2
Peripheral arterial occlusive disease (PAOD) and chronic venous insufficiency (CVI), reported in the electronic patient records.

Type and symptoms of PAOD and CVI	Patients ($n = 112$)[a]
No PAOD or CVI, no. (%)	58 (51.8)
PAOD, no. (%)	17 (15.6)
Skin ulcer, no. (%)	13 (11.9)
Skin necrosis, no. (%)	6 (5.6)
Amputation, no. (%)	9 (8.1)
CVI, no. (%)	33 (30.0)
Lymphedema, no. (%)	1 (0.9)

%, valid percent.
[a] Patients can have both PAOD and CVI and also multiple symptoms of PAOD and CVI.

Table 3
Classification of peripheral arterial occlusive disease (PAOD) and chronic venous insufficiency (CVI) at first presentation, reported in the electronic patient records.

Type of peripheral vascular disease	Patients ($n = 112$)
Fontaine stage (PAOD), no. (%)	
N.A.	95 (88.0)
I, asymptomatic	1 (0.9)
II, claudication	8 (7.4)
III, ischemic rest pain	1 (0.9)
IV, gangrene or ulcer	3 (2.8)
CEAP classification (CVI), no. (%)	
C_0, no visible or palpable signs	79 (70.5)
C_1, telangiectasia or reticular veins	–
C_2, varicose veins	7 (6.3)
C_3, edema	8 (7.1)
C_4, pigmentation and/or eczema, lipodermatosclerosis and/or atrophie blanche	2 (1.8)
C_5/C_6, active venous ulcer	–

%, valid percent; N.A., not applicable.

Table 5 displays all studied risk factors for PAOD in OTR. In agreement with the non-immunosuppressed population, increasing age was also a risk factor for PAOD in the studied OTR. A history of DM type 1 showed an eleven-fold increased risk for PAOD. Hypertension and smoking suggested an increased risk, although these results were statistically non-significant (Table 5).

Table 4
Symptoms and signs of peripheral arterial occlusive disease (PAOD) and chronic venous insufficiency (CVI) at time of presentation at the specialized OTR skin clinic.

Symptoms and signs[a]	Patients ($n = 112$)
Symptoms of PAOD, no. (%)	
None	68 (60.7)
Resting/night pain	1 (0.9)
Dullness	4 (3.6)
Cold hands and feet	14 (12.5)
Claudication >100 m	5 (4.5)
Claudication <100 m	1 (0.9)
Multiple symptoms	19 (17.0)
Signs of PAOD, no. (%)	
None	60 (54.1)
Abnormal peripheral pulsations	21 (18.9)
Prolonged CRT	3 (2.7)
(Severe) cold feet/toes	14 (12.6)
Cyanosis	1 (0.9)
Cyanosis with signs of PAOD[b]	12 (10.8)
Ulceration	–
Symptoms of CVI, no. (%)	
None	36 (32.1)
Pain	2 (1.8)
Tiredness/heaviness	3 (2.7)
Cramps	15 (13.4)
Swelling	19 (17.0)
Multiple symptoms	37 (33.0)
Use of compression stockings, no. (%)	22 (19.6)
Signs of CVI, no. (%)	
None	17 (15.7)
Telangiectasia/reticular veins	30 (27.8)
Varicose veins	23 (21.3)
Edema[c]	27 (25.0)
Pigmentation/eczema	16 (14.8)

%, valid percent; CRT, capillary refill time.
[a] Patients can have multiple symptoms/signs. Most severe symptom/sign is described.
[b] One or more sign of PAOD as mentioned above.
[c] In combination with other cutaneous manifestations of CVI.

Table 5
Possible risk factors for peripheral arterial occlusive disease (PAOD) in patients included in the final analysis ($n = 109$).[c]

	No PAOD ($n = 92$)	PAOD ($n = 17$)	Univariate HR (95% CI)	Multivariable HR (95% CI)[a]
Age at first transplantation, mean	46.2	45.2	1.7 (1.1;2.6)[b]	1.9 (1.1;3.4)[b]
Gender, no. (%)				
Women	28 (30.4)	4 (23.5)	1	1
Men	64 (69.6)	13 (76.5)	1.8 (0.49;6.3)	1.9 (0.49;7.0)
Diabetes mellitus, no. (%)				
No DM	67 (72.8)	8 (47.1)	1	1
DM type 1	5 (5.4)	5 (29.4)	10.1 (3.0;34.7)	11.0 (3.0;40.2)
DM type 2	20 (21.7)	4 (23.5)	2.2 (0.45;10.7)	1.5 (0.28;7.7)
BMI, mean	24.9	25.7	1.1 (0.94;1.2)	1.0 (0.93;1.2)
Hypertension, no. (%)	67 (73.6)	15 (88.2)	2.2 (0.50;10.0)	2.5 (0.55;11.4)
Smoking status, no. (%)				
Non-smoker	47 (51.1)	5 (29.4)	1	1
Current smoker	4 (4.3)	1 (5.9)	2.4 (0.27;21.7)	2.4 (0.25;22.2)
Ex-smoker	41 (44.6)	11 (64.7)	3.2 (0.98;10.4)	2.1 (0.63;7.2)
Alcohol consumption, no. (%)				
None	49 (53.3)	10 (58.8)	1	1
Normal	41 (44.6)	6 (35.3)	0.84 (0.28;2.5)	0.90 (0.30;2.8)
Excessive	2 (2.2)	1 (5.9)	3.4 (0.41;28.8)	2.4 (0.28;20.7)
AMI, no. (%)	9 (9.8)	4 (23.5)	1.9 (0.52;6.8)	1.5 (0.40;5.8)

DM, diabetes mellitus; BMI, body mass index; AMI, acute myocardial infarct.
[a] Corrected for the following variables: age at first transplantation, gender, and BMI.
[b] Calculated per 10 years of age.
[c] Patients included only when PAOD was registered as a diagnosis in the electronic patient records.

For skin ulcers, a history of DM was the main risk factor. Patients with DM type 1 and 2 had an eighteen-fold and a five-fold increased risk for developing ulcers, respectively (Table 6).

A history of DM type 1 showed an adjusted hazard ratio with 95% confidence interval (CI) of 59.7 (95%CI 3.8–934) in patients with skin necrosis. DM type 1 and 2 also showed an increased risk for amputation with adjusted hazard ratios of 9.1 (95%CI 1.4–58.6) and 6.0 (95%CI 1.3–27.0), respectively. All other risk factors for skin manifestations of PAOD were not statistically significant or could not be determined because of small patient numbers.

Smoking was associated with CVI with an adjusted hazard ratio of 8.2 (95%CI 2.3–29.5) for current smokers and 1.7 (95%CI 0.7–3.8) for ex-smokers. The development of CVI was not influenced by DM with an adjusted hazard ratio of 0.7 (95%CI 0.16–3.1) for DM type 1 and of 1.3 (95%CI 0.52–3.4) for DM type 2.

4. Discussion

4.1. Principal findings

This study shows that 45.9% of our study group had signs of PAOD at clinical investigation. If we compare this with the percentage of 15.6% in the patients who were actually diagnosed with PAOD in the electronic patient records, we can state that PAOD is probably an underdiagnosed disease in our patient population. The same accounts for CVI with 84.3% of patients who had

Table 6
Possible risk factors for developing skin ulcers in patients included in the final analysis ($n = 109$).[c]

	No ulcer ($n = 96$)	Ulcer ($n = 13$)	Univariate HR (95% CI)	Multivariable HR (95% CI)[a]
Age at first transplantation, mean[b]	45.9	47.7	1.7 (1.0;2.8)	1.8 (1.0;3.3)
Gender, no. (%)				
Women	27 (28.1)	5 (38.5)	1	1
Men	69 (71.9)	8 (61.5)	0.59 (0.18;2.0)	0.58 (0.15;2.3)
Diabetes mellitus, no. (%)				
No DM	71 (74.0)	4 (30.8)	1	1
DM type 1	5 (5.2)	5 (38.5)	13.6 (3.4;54.8)	17.4 (4.0;75.7)
DM type 2	20 (20.8)	4 (30.8)	4.4 (1.0;20.1)	4.9 (0.96;27.3)
BMI, mean	25.3	23.3	0.88 (0.74;1.0)	0.86 (0.70;1.1)
Hypertension, no. (%)	71 (74.7)	11 (84.6)	1.7 (0.37;7.9)	1.7 (0.36;7.8)
Smoking status, no. (%)				
Non-smoker	46 (47.9)	6 (46.2)	1	1
Current smoker	5 (5.2)	0 (0)	–	–
Ex-smoker	45 (46.9)	7 (53.8)	1.56 (0.47;5.1)	0.70 (0.37;4.4)
Alcohol consumption, no. (%)				
None	51 (53.1)	8 (61.5)	1	1
Normal	43 (44.8)	4 (30.8)	0.68 (0.19;2.4)	0.83 (0.23;3.1)
Excessive	2 (2.1)	1 (7.7)	4.1 (0.48;34.6)	4.9 (0.52;45.9)
AMI, no. (%)	13 (13.5)	0 (0)	–	–

DM, diabetes mellitus; BMI, body mass index; AMI, acute myocardial infarct.
[a] Corrected for the following variables: age at first transplantation, gender and BMI.
[b] Calculated per 10 years of age.
[c] Patients included only when ulcer was registered as a diagnosis in the electronic patient records.

signs of CVI at clinical investigation compared to 30.0% in the electronic patient records.

A history of DM type 1 was found as a significant risk factor for PAOD, but not for CVI. Among patients with a history of DM, patients with DM type 1 were the most susceptible for developing ulcers, compared to patients with DM type 2. Diabetics and former diabetics were at high risk of developing PAOD, even years after a SPK transplantation when they were supposedly "cured" from their diabetes. Our findings suggest a significantly increased risk of CVI in the smoking population.

4.2. Interpretation of findings

This study shows a high prevalence of PAOD and CVI in OTR. The percentages in the general population are 10–29% for PAOD and 1–40% for CVI, respectively.[15–17] These percentages are in line with the percentages of 15.6% for PAOD and 30.0% for CVI as reported in the electronic patient records, but much lower than the percentages found at clinical investigation.

Our study also suggests that OTR with a history of DM, in particular type 1, are at high risk of developing PAOD. Diabetics are often held at close surveillance for diabetic complications before transplantation, however when the DM is supposedly "cured" by a SPK transplantation, PAOD as a late complication of DM can still occur. Our results are comparable with previous studies, which indicate that a successful SPK transplantation does not necessarily diminish the progression of PAOD, and can even lead to severe cutaneous manifestations.[6,8,18] Conflicting results have been described recently by Boggi et al., who stated that a SPK transplantation has a positive impact on the development of PAOD.[19] Their study reported not only improvement of PAOD after transplantation, but also a slower progression of long-term complications of diabetes. However, this also means that a long follow-up in these patients is needed to tackle these problems.[19]

Consensus about this subject has not yet been reached. Recommendations are written in order to maintain post-transplant DM type 2 stable with regular blood glucose measurements.[20] However, standard protocols containing guidelines to keep former type 1 diabetics under surveillance after SPK transplantation are not commonly available. Sharma et al. also encounters the need for regular follow-up and greater awareness for diabetic foot ulcers post transplantation.[21] Patients who have undergone a SPK transplantation are considered as "cured" from DM, and are usually not included in national guidelines.[22] Therefore, early detection of PAOD in these patients can be challenging.

4.3. Limitations of this study

We acknowledge the risk of information bias, since we were dependent on the information in the patient files. Not all PAOD were described as detailed as required for this study. This was certainly the case for CVI. We used edema as a sign of CVI. This particular clinical finding can be difficult to distinguish from edema caused by renal insufficiency, immunosuppressive therapy or other co-morbidities.[23,24] This can possibly result in an overestimation of CVI, although we tried to prevent this with searching for other signs such as varices to confirm venous insufficiency. Similar to this, the percentage of PAOD observed at the specialized OTR skin clinic can also be an overestimation, since we were not able to confirm the diagnosis by additional diagnostic tests.

Secondly, a relative small cohort was used. Larger studies should be formed to compare incidences of PAOD and CVI with the normal population.

Lastly, not all possible risk factors were included due to a limited study period. Important risk factors such as type, duration and dose of immunosuppressive therapy should also have been investigated. This can be taken in consideration for further studies in the future.

4.4. Conclusion

Vascular skin disorders in OTR are an underreported problem that requires the clinician's attention. Skin manifestations are one of the most objective and straightforward tools to indicate the presence of PAOD and CVI. Knowledge about these vascular skin disorders cannot only help dermatologists, but also other clinicians to detect PAOD in the OTR whom they take care of. OTR are often on dermatological surveillance for skin cancer, but not specifically for vascular skin disorders. Patients with DM who require a SPK transplantation are at high risk for developing, or worsening of PAOD, even with normal glucose levels after transplantation. It is important to maintain these patients under close cardiovascular risk management to prevent a severe outcome such as limb amputation, transplant failure or even death.

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Authorship page

Maren Buntinx, Adriana P.M. Lavrijsen and Jan N. Bouwes Bavinck participated in research design, in the writing of the paper, the performance of the research and the data analysis. Johan W. de Fijter, Marlies E.J. Reinders, and Abbey Schepers participated in the writing of the paper.

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