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Clinical features and burden of new onset diabetic foot ulcers post simultaneous pancreas kidney transplantation and kidney only transplantation

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ABSTRACT

Background: Patients with diabetes and kidney disease are at risk of diabetes-related foot ulcers (DFU). Whether this risk is modified post simultaneous pancreas-kidney (SPK) or kidney only (KO) transplant is unknown.
Methods: We evaluated the incidence of new onset DFU post SPK and KO transplant in 235 patients with diabetic kidney disease and diabetic neuropathy. In total 90 (51% male) SPK patients and 145 KO (66% male, 26% Type 1 DM) were evaluated in a single centre retrospective study. Median (range) follow up was 6 (3 to 13) years for both cohorts.
Results: We observed that 16 (17%) of SPK and 22 (15%) KO patients respectively developed a DFU during follow up. In both cohorts a history of peripheral arterial disease [37.5% vs. 4%] and pre-transplant history of DFU were associated with post transplant DFU ($p \ll 0.05$).
In KO cohort, patients who developed a DFU were more likely to have T1DM than T2DM (29% vs. 10%), $p \ll 0.05$. There was no impact of DFU on SPK transplant failure. In contrast patients with DFU post KO transplant had more than five fold increased hazard ratio (HR) of transplant failure as compared to those without DFU independent of other risk factors [HR 5.19 95% CI (2.05 to 13.18) $p = 0.001$].
Conclusion: Nearly 1 in 7 patients develop a new onset DFU post KO or SPK transplantation and DFU also significantly increases risk of failure of the transplanted kidney. Our results highlight the need for greater awareness of regular foot examination, DFU prevention and risk evaluation in post-transplant patients.
Research in context: **Evidence before this study**
Patients with diabetes and kidney disease are at enhanced risk of diabetic foot ulcers (DFU). Whether this risk is modified post successful kidney only (KO) or simultaneous pancreas and kidney (SPK) transplantation is unknown. Small case series and studies with short term follow up report varied rates of incidence and are from historical cohorts before the use of modern anti-transplant medications and treatments. Short term studies also suggest that post SPK the resultant normoglycaemia may reverse some features and risk markers of DFU. There are no long term studies on the incidence and impact of diabetic foot ulcers in patients with diabetic kidney disease post SPK or KO transplantation.
Added value of this study
We report the long term follow up results on DFU incidence, clinical features and related impact on transplant viability in 235 patients with diabetic kidney disease and neuropathy post successful SPK and KO transplant at a single centre. We observed that nearly 1 in 7 patients developed a DFU during follow up and that in patients who received KO transplant onset of DFU was associated with more than 5 fold increase of transplant failure.
Implications of all the available evidence
Our results highlight the need for greater awareness of regular foot examination, DFU prevention and risk evaluation in post-transplant patients. Despite normoglycaemia post SPK there is a residual burden and risk of DFU. Our work establishes a clinical rationale for further research to explore putative mechanisms that could explain the association between DFU and renal transplant dysfunction.

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1. Introduction

Patient with diabetes and kidney disease are at enhanced risk of diabetes-related foot ulceration (DFU) with a 2 to 7 fold higher risk compared to patients with preserved renal function.[1]

Moreover, impaired renal function is associated with worse DFU outcomes in advanced stages of chronic kidney disease (CKD).[1,2] This enhanced risk may be in part explained by uraemia, anaemia and hypoalbuminemia which can aggravate and accelerate the onset of DFU and impair healing as well as the increased prevalence of other diabetes related vascular complications [eye disease, peripheral arterial disease, cardiovascular disease (CVD)] and peripheral and autonomic neuropathy in patients with diabetes and CKD.[2,3]

Whether this enhanced risk of DFU is modified after kidney only (KO) or simultaneous pancreas-kidney (SPK) transplantation is unknown. Several studies have demonstrated that SPK transplantation improves certain markers of neuropathy whilst not significantly impacting others.[4,5] Recent data using corneal confocal microscopy, a small nerve fibre marker, suggests that at 12 months post SPK transplantation nerve regeneration and increased nerve fibre density can be observed in individuals with diabetic neuropathy, however established loss of protective sensation is not fully reversed nor is there significant improvement in neurophysiological measures, quantitative sensory testing, or intraepidermal nerve fibre density in the foot.[6]

The natural history, risk factors and healing rates for new onset DFU post SPK or KO transplant remains poorly described and there is a paucity of information on the impact of DFU on transplant viability in this population.

Our hypothesis was that post SPK or KO there would be a residual risk of DFU and that onset of DFU may impact on transplant survival.

We therefore studied the incidence, clinical features and long term impact of new onset DFU in individuals undergoing SPK or KO transplantation.

2. Methods

2.1. Study design

This was a retrospective study performed at a single large university teaching hospital which is a regional transplant centre. We analysed the electronic medical records of patients with Type 1 Diabetes Mellitus (T1DM) or Type 2 Diabetes Mellitus (T2DM) and diabetic kidney disease who underwent a successful kidney only (KO) or simultaneous kidney-pancreas (SPK) transplantation between 2004 and 2014 with complete follow-up data.

We only included those patients with SPK or KO having regular follow up in our centre. No formal sample size calculation was performed. This observational study was designed to generate pilot data and determine sample size and feasibility for future studies.

All patients had a clinical diagnosis of diabetic kidney disease and neuropathy documented in their hospital records. Patients with non-diabetic kidney disease or new onset post transplant diabetes were excluded. We defined 'successful' transplantation as documentation of a fully functioning graft at 6 months post-transplantation in the absence of acute rejection, thrombosis or severe infection.

2.2. Data collection

Pre-selected parameters including demographic values (age, gender, ethnicity, body mass index [BMI]); the presence of retinopathy, neuropathy, peripheral arterial disease (PAD); transplantation demographics (date of transplantation, age at transplantation, duration of diabetes at transplantation and adequacy of transplantation); pre-transplantation [defined as most recent available data (≪12 weeks) before transplant] clinical measures and laboratory data and post-transplantation DFU characteristics (DFU free days, severity, infection, and need for amputation) were collected from patient records and cross-checked by two independent researchers for each individual patient.

We divided patients undergoing KO and SPK into two cohorts. DFU was defined as a 'full thickness lesion which is present at a level distal to the malleolus' and severity of DFU was evaluated by the SINBAD score,[7] which is based on analysing variables including site, ischaemia, neuropathy, bacterial infection, area and depth of each ulcer. A score ≥ 3 is classified as a severe DFU. The SINBAD score was used as this index of DFU severity is recorded in our clinical unit and it also enables comparison with the United Kingdom National Diabetes Footcare Audit (NDFA). Minor amputations were defined as resections distal to the ankle. Major amputations were defined as resections proximal to the ankle. DFU free days were defined as the number of days between date of transplantation and first documentation of DFU post-transplantation. Kidney transplant failure was defined as commencement of dialysis post-transplantation and pancreatic graft failure was defined as requirement for insulin treatment post-transplantation. DFU was deemed to have 'healed' if there was documented evidence of "intact skin and complete epithelialisation of previously ulcerated site" and no further dressings were necessary as per the definition of the International Working Group on the Diabetic Foot (IWGDF), Diabetic Foot: Definitions and Criteria.[8]

2.3. Statistical analysis

Descriptive statistics were used to define baseline and foot specific demographic characteristics. For continuous variables, the mean and standard deviation (SD) were calculated. The median and interquartile range (IQR) was used to describe non-parametric continuous data. Categorical variables were described using proportions and frequencies. To assess for statistical significance between groups, the χ^2 test was implemented for categorical variables and the independent *t*-test for continuous variables. The Fisher's exact test was used for categorical variables with low cell numbers (<5). The Mann-Whitney *U* test was employed for non-parametric continuous data which was not normally distributed. Odds ratios (95% CI) were used as an additional measure of association. To assess whether DFU was independently associated with transplant failure, Cox regression analysis was performed and hazard ratio and 95% CIs were reported. Cox regression assumptions and related residual methods were checked for and adhered to. To build the regression model, we included variables in the model that were significantly different at baseline between those patients with and without a DFU during follow up. We also included variables that were significantly different between patients with and without transplant failure during follow up.

Statistical significance was defined as a p value $\ll 0.05$. All analyses were performed using SPSS (version 25.0; SPSS, Chicago, IL).

3. Results

We studied 235 (90 post SPK and 145 post KO) transplant patients with a median (range) follow up of 6 (3 to 13) years for both cohorts.

In the SPK cohort, of the 90 (51% male) patients evaluated, median (range) age was 49 (28 to 69) years and duration of diabetes 32 (10–56) years. In the SPK cohort during the follow up period 16 (17%) patients developed a new DFU. Patients with a new DFU were of similar age, duration of diabetes, and had similar pre-transplant haemoglobin, HbA1c and estimated glomerular filtration as compared to those without a DFU (Table 1). There were no significant differences in the use of anti-diabetic or other medications between groups.

Patients who developed a DFU were more likely to have history of PAD (37.5% vs. 4%) $p \ll 0.05$ (Table 1). Of the cohort, 8 patients had a history of DFU pre-transplant and all 8 developed a new onset DFU post SPK transplant. A pre-transplant history of amputation was noted in 1 of the 8 patients with history of DFU.

Of the 6 patients in the SPK cohort with a new DFU post-transplant, who had a history of PAD pre-transplant, 4 had undergone superficial femoral artery angioplasty and stenting.

Median (range) duration of healing was 7 (2–27 weeks). SINBAD classification score was ≪3 (the cut off for less severe DFU) in 10 of the 16 DFU cases. Nearly 60% of DFU occurred within 500 days post-transplant (Fig. 1). In our cohort only 1 out of 16 DFU needed treatment with a minor amputation and there were no major amputations. Post-transplant immunosuppression regimes were similar in those with and without subsequent DFU. There was no statistically significant difference in transplant failure between those with and without DFU (31% vs. 23.3%).

In the KO cohort of 145 (66% male, 26% Type 1 DM) patients, median (range) age was 62 (28 to 80) years and duration of diabetes 23 (7–60) years. In this cohort 22 (15%) patients developed a new DFU. Patients with a DFU were of similar age, body mass index, diabetes duration and had similar pre-transplant haemoglobin, as compared to those without a DFU (Table 2).

Patients who developed a DFU were more likely to have Type 1 DM than T2DM (29% vs. 10%), history of PAD [32% vs. 8%], had modestly higher pre-transplant HbA1c, mean ± standard deviation (7.5 ± 1.2% vs. 6.8 ± 1.4%) $p \ll 0.05$ for all (Table 2). However the clinical significance of this modest difference in HbA1c in the context of patients in end stage renal disease with concurrent use of iron and erythropoietin treatment is unclear. There were no significant differences in anti-diabetic or other medication use between groups. Of the 7 patients with new DFU and history of PAD pre-transplant, 2 had undergone revascularisation (one femoral artery bypass and one angioplasty and stent of femoral artery).

In the KO cohort 8 patients had a history of DFU pre-transplant and all 8 developed a new onset DFU post-transplant. A pre-transplant history of amputation was noted in 4 of the 8 who developed new DFU post-transplant.

Median (range) duration of healing was 5 (1–26) weeks. SINBAD score was ≪3 in 14 of the 22 DFU cases. Nearly 50% of all DFU occurred within the first 1000 days post-transplant (Fig. 1). Of the 22 cases, 6 needed a minor amputation; no major amputations were documented.

Review of the available microbiology results of new onset DFU post-transplant demonstrates that the organisms most commonly cultured were, in descending order, *Staphylococcus aureus*, Pseudomonas Species, Group B Streptococcus and *Enterobacter cloacae* and Citrobacter Koseri. Post-transplant immunosuppression medications and regimes were similar in those with and without subsequent DFU.

There was no significant difference in mortality between patients with DFU compared without DFU (27.3% vs. 20.3% $p = 0.25$). We did not observe any significant association between side of kidney transplant and subsequent side where DFU occurred in either KO or SPK cohorts.

We observed that KO patients with a new onset DFU had more than two-fold increased risk of transplant failure as compared to those without DFU (50% vs 23.3% $p = 0.02$). Patients who developed transplant failure as compared to those who did not, were of similar age (mean ± SD 61.9 ± 11.6 vs. 60.7 ± 10.9 years), duration of diabetes (17.1 ± 11.6 vs 17.4 ± 11.0 years and pre transplant BMI (26.6 ± 5.1 vs. 27.3 ± 4.8 kg/m2). There was a numerically greater prevalence of PAD (18.8% vs. 9.7% $p = 0.16$) and T1DM (T1DM 34% vs. 24% $p = 0.23$) in those with transplant failure. The only significant differences between the two groups were a lower proportion of patients of Afro-Caribbean ethnicity (9% vs 32) and new onset of DFU (34.4 vs 9.7%) in those who develop transplant failure $p \ll 0.05$ for both. In multivariable analyses the enhanced risk of transplant failure persisted after adjusting cox regression for baseline factors associated with increased risk of DFU or risk of transplant failure including, age, gender, type of diabetes, previous history of DFU, ethnicity, and PAD (Table 3 and Fig. 2).

Table 1
Demographic, clinical and laboratory characteristics of 90 patients with diabetes who had simultaneous pancreas-kidney (SPK) transplant with or without post-transplant diabetes foot ulcer.

Variable	No diabetic foot ulcer $n = 74$	Diabetic foot ulcer $n = 16$	p-Value
Age (years)	48.7 ± 9.0	48.9 ± 9.6	0.93
Gender (male %)	38 51	8 (50%)	0.53
Caucasian (%)	58 (76%)	10 (62%)	
Afro-Caribbean	10 (13%)	5 (31%)	0.22
Other	8 (11%)	1 (7%)	
Diabetes duration (years)	33.9 ± 10.0	29.7 ± 9.0	0.13
Peripheral arterial disease n (%)	3 (4%)	6 (38%)	0.001
Pre-transplant diabetic foot ulcer	0	8 (50%)	0.000
Transplant failure	14 (19%)	5 (31%)	0.52
Diabetic foot ulcer on same side as renal transplant (%)		Right 55% Left 40%	0.41
Pre-transplant BMI (kg/m^2)	26.0 ± 4.0	25.8 ± 4.9	0.92
Pre-transplant HbA1c	7.7 ± 1.9	7.9 ± 2.4	0.71
Pre-transplant Haemoglobin	11.3 ± 1.6	11.2 ± 2.1	0.85
Pre-transplant type of renal replacement therapy			
Haemodialysis	29 (40%)	6 (37%)	0.45
Peritoneal dialysis	45 (60%)	10 (63%)	

4. Discussion

We describe for the first time a high incidence of DFU post SPK and KO transplantation and describe the clinical features, timelines and consequences of DFU in this population. Our results demonstrate that post SPK transplant 1 in 6 patients develop a new DFU and similarly 1 in 7 post KO transplant patients develop DFU. We also observed that patients who develop a DFU post KO transplant have a ≫5 fold increased risk of transplant failure as compared to those without DFU. Our results indicate that ≫50% of DFU occur within first 500 days post-transplant. We also observed that a pre-transplant history of PAD and DFU was associated with increased risk of new onset post-transplant DFU in both KO and SPK cohorts.

To our knowledge this is the first study in such a large SPK and KO cohort that has evaluated the incidence and risk factors for new onset DFU and the impact of ulcers on transplant viability.

Previous studies have been in smaller cohorts predominantly post SPK or pancreas only transplant with limited documentation of DFU healing rates, severity and outcomes. In a small study of 9 (mostly T1DM) patients, those with a KO transplant had two fold longer time to heal of their plantar ulcers as compared to those without a renal transplant (47 vs. 111 days) suggesting that immunosuppression may contribute to delayed healing.[9] In 27 patients post KO transplant, Nyberg et al. reported that during a mean follow-up of 51 months, 6 of 27 subjects (22%) underwent amputation for foot ulceration.[10]

In a SPK transplant cohort of 87 subjects over median (range) follow-up of 8 (1–15) years, 16 of 87 subjects (18%) with SPK underwent lower extremity amputation.[11] In a larger study of 200 post SPK transplant patients, 19 (19.5%) had amputation (majority ~two thirds were minor amputations) during follow up of 5 years. The authors commented that longer duration of haemodialysis pre-transplant or previous amputation was associated with enhanced risk.[12]

However these studies did not describe the severity of the DFU, healing rates/times of ulcer nor the associated impact on transplant viability. Furthermore, many of these studies were published ≫15 years ago when multidisciplinary foot care teams were not standard practice and transplant pre-assessment and immunosuppression protocols were different to current practice and also less standardised.

In a more recent study of 218 Korean patients, majority with a pancreas only transplant (T1DM 86%, 30% SPK and 70% pancreas only), 15 patients (6.9%) developed DFU over mean follow up of 4.3 years. Mean (range) time to DFU was 14 (2–56) months. The authors did not

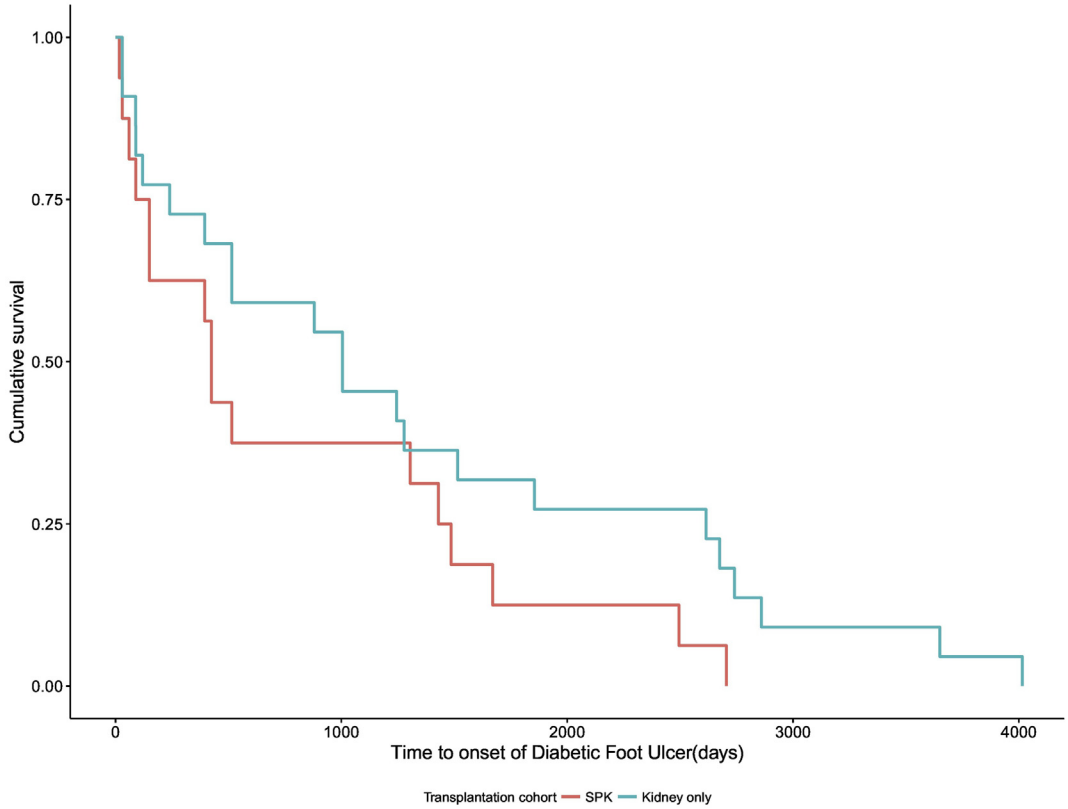

Fig. 1. Time course for new onset of diabetic foot ulcer post simultaneous pancreas-kidney or kidney only transplantation.

report the specific features of SPK cohort separately but did note that higher pre-transplant creatinine was associated with more foot complications.[13] Mean time to DFU development was 420 days. However, DFU characteristics, DFU healing metrics or the impact on transplant viability were not described.

There are several strengths and limitations of our study. One major strength was that we studied a well characterised clinical cohort attending one centre over a long duration of follow up. Second, we report DFU severity using a validated measure, SINBAD, which is also used in the United Kingdom National Diabetes Foot Audit.[14] Third, all patients had standardised pre-transplant evaluation and post-transplant care and those that developed DFU received multi-disciplinary foot care in a contemporary real-world clinical setting.

Limitations of the work include the retrospective observational study design and hence causality in terms of DFU and its association with transplant failure cannot be confirmed. The association we observed in KO cohort between DFU and increased risk of transplant failure appears to be independent of traditional markers of transplant viability. Whether there are other factors that predispose to both DFU and transplant failure or if patients who get DFU have features/co-morbidities that predispose to subsequent transplant failure cannot be excluded.

Table 2
Demographic, clinical and laboratory characteristics of 145 patients with diabetes who had kidney only (KO) transplant with or without post-transplant diabetes foot ulcer.

Variable	No diabetic foot ulcer $N = 123$	Diabetic foot ulcer $N = 22$	p-Value
Age (years)	60.6 ± 11.6	61.7 ± 9.3	0.612
Gender (male %)	82 (67%)	15 (68%)	0.53
T1DM (%)	26 (21%)	11 (50%)	0.008
T2DM (%)	97 (79%)	11 (50%)	
Caucasian (%)	54 (43%)	12 (54%)	
Afro-Caribbean (%)	33 (27%)	6 (27%)	0.45
Other (%)	36 (30%)	4 (19%)	
Diabetes duration (years)	24.8 ± 11.6	27.1 ± 12.1	0.39
Peripheral arterial disease n (%)	10 (8%)	7 (32%)	0.005
Pre-transplant diabetic foot ulcer	0	8 (36%)	0.000
Transplant failure	21 (17%)	11 (50%)	0.002
Diabetic foot ulcer on same side as transplant (%)		Right 80% Left 42%	0.21
Pre-transplant BMI (kg/m^2)	27.4 ± 5.2	26.0 ± 3.2	0.23
Pre-transplant HbA1c	7.5 ± 1.2	6.8 ± 1.4	0.04
Pre-transplant Haemoglobin	11.1 ± 1.5	11.1 ± 1.5	0.95
Pre-transplant type of renal replacement therapy			
Haemodialysis	85 (69%)	17 (77%)	0.48
Peritoneal dialysis	40 (31%)	5 (23%)	

Table 3
Unadjusted and adjusted (for other risk factors) multivariable cox regression analysis models that demonstrate the relationship between post transplant diabetic foot ulcer and transplant failure in 145 patients with diabetes and kidney only transplant.

	Hazard Ratio	95% CI	p-value
Model 1 Unadjusted model DFU only	5.42	2.55–11.52	≪0.001
Model 2 Adjusted for DFU and type of diabetes	6.41	2.85–14.40	≪0.001
Model 3 Adjusted for DFU, type of diabetes, PAD	6.38	2.80–14.48	≪0.001
Model 4 Adjusted for DFU, type of diabetes, previous DFU (pre-transplant), PAD	5.19	2.05–13.18	≪0.001
Model 5 Adjusted for DFU, type of diabetes, previous DFU (pre-transplant), PAD, ethnicity	7.74	2.72–22.07	≪0.001

Abbreviations DFU - diabetic foot ulcer, PAD - peripheral arterial disease.

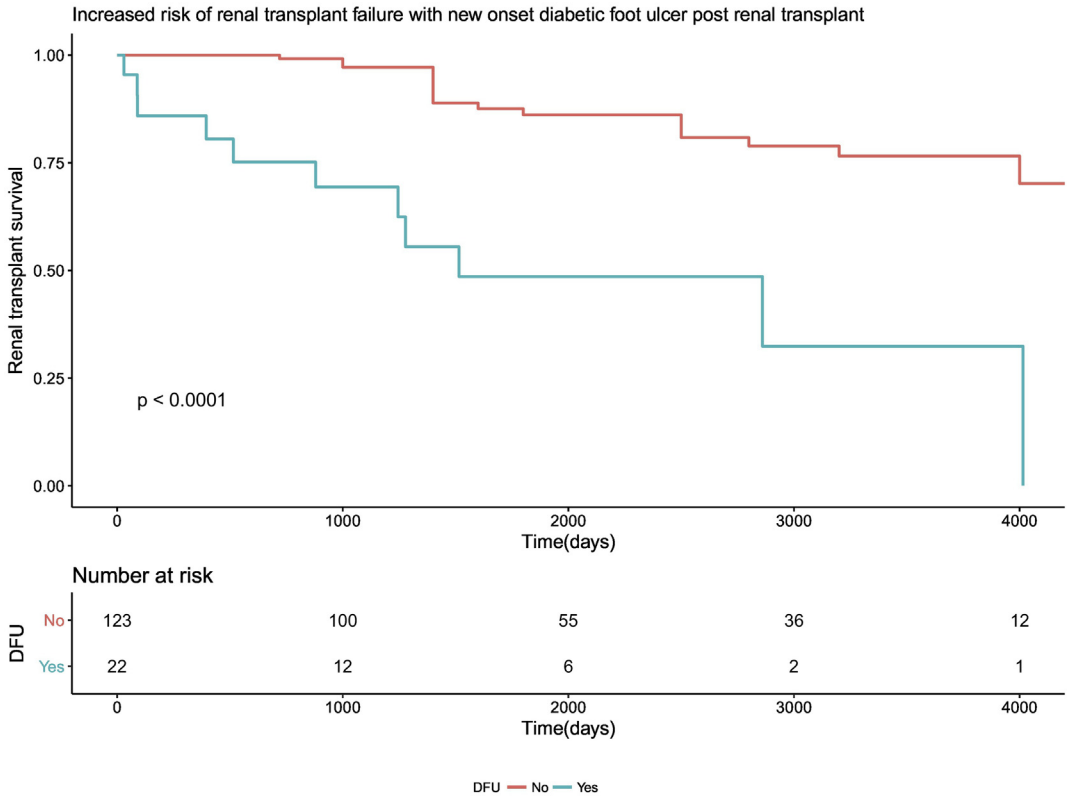

Fig. 2. Increased risk of renal transplant failure in patients with new onset diabetic foot ulcer post renal transplant.

The data we report was collected from one centre and therefore further larger multi-centre studies are needed to confirm our findings. We are also unable to comment on the mechanisms that link the above observation however our study establishes the scientific rationale for further work to better understand the pathophysiological pathways and mechanisms between DFU and renal transplant failure.

In our transplant centre, as in many others, patients who are deemed eligible for transplant have comprehensive vascular assessments with patients with advanced PAD or CVD often excluded from surgery until these risk factors are deemed non-severe. This leads to a potential 'selection bias' where a cohort at 'lower PAD risk' receive transplants as compared to patients with severe CVD and or PAD who may be deemed ineligible for transplantation. In CKD patients CVD and advanced PAD are known risk factors for a higher DFU incidence and worse healing.[1] Despite this potential 'bias' we still observed that patients with a pre-transplant history of DFU or diagnosis of PVD had a higher risk of post-transplant DFU.

Our results also confirm that despite resolution of hyperglycaemia and renal dysfunction post SPK or KO transplantation, there is residual risk for new DFU. This clinical observation is consistent with studies that demonstrate some improvement on neurological disease markers but no reversal/resolution of the diabetic neuropathic deficits or lesions.[4,9,13,15]

In the post-transplant setting immunosuppressive regimens may increase the risk of neuropathy and case series and reports suggesting delayed healing of DFU.[9,15–17] However in our study DFU healing rates observed were superior to the United Kingdom National Diabetic Foot Audit (63% of ulcers in our cohort had healed at 12 weeks vs 49% in national data set, and similarly at 24 weeks (87% vs 66%) and there was also a lower proportion of severe DFU at presentation (SINBAD ≫ 3; 35% vs 46%).[18] This may be due to the more intensive medical review and follow up transplant patients receive, as this greater 'attention' may enable earlier detection of DFU. There is a significant association between higher DFU severity at presentation and greater time to first expert assessment with negative DFU prognosis.[19] Our findings support the notion that despite the immunosuppression (and continued impact of neuropathy and coexistent PAD, when present), excellent DFU outcomes may be achieved in this group. Furthermore, these results support the importance of a multi-disciplinary team approach that is needed for managing patients with DFU and emphasises the importance of foot surveillance and education for prevention of DFU. We would recommend that in such SPK and KO transplant cohorts (who often have a long duration diabetes, advanced CKD and neuropathy) a greater awareness of the need for regular foot evaluation post-transplant has to better communicated to health care professionals involved in the care of be transplant patients. Our findings also emphasise the importance of screening for DFU in patients who have normoglycaemia post successful pancreas transplant, a patient group who may be incorrectly missed from the required screening/surveillance.

In summary our results highlight a residual high burden and risks of DFU post KO or SPK transplantation. We hope our findings will alert clinicians and patients to be more aware of risk of DFU and our results emphasises the importance of foot surveillance and education for prevention of DFU post KO and SPK transplantation.

Author contributions

Angelica Sharma data collection and analyses, interpreted the data and writing

Siew Cohen data collection

Nikoloas Fountoulakis helped with data collection and analyses

Tejal Patel helped with data collection

Stephen Thomas interpreted the data and analysis

Prashant Vas designed the study, interpreted the data and writing article

Janaka Karalliedde designed the study, interpreted the data and writing article

Conflict of Interest Statement

The authors declare that there is no duality of interest associated with the manuscript.

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