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Renal Function Decline After Vascularized Composite Allotransplantation

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Background. Chronic kidney disease (CKD) is a common complication of nonrenal transplantation, influencing recipients' morbidity and mortality. The incidence of CKD varies depending on the transplanted organ. Recipients of vascularized composite allotransplantation (VCA) need lifelong immunosuppression similar to that of solid organ transplantation. This study investigated renal function in VCA recipients. **Methods.** We studied 70 recipients from 17 centers (median follow-up: 8 y): 59 upper extremity, 10 face, and 1 penis transplant. Pretransplant and posttransplant clinical data and sera were collected to calculate the estimated glomerular filtration rate (eGFR) using the CKD Epidemiology collaboration 2021 formula. **Results.** Pretransplantation, the median eGFR was 105.36 mL/min (range, 71.39–155.39 mL/min). By 3 mo posttransplant, the eGFR had significantly decreased to 78.42 mL/min (range, 32.49–130.74 mL/min; $P = 0.001$) before stabilizing. Despite higher tacrolimus levels at 3 mo, no correlation with eGFR was found. During follow-up, 17.1% of patients experienced a ≥50% eGFR decline, 10.9% progressed to CKD, and 4.7% developed end-stage kidney disease. Some risk factors were identified, but their responsibility could not be established with certainty because of the low number of severe renal outcomes. **Conclusions.** Renal function declines in the majority of VCA recipients, but the function loss is lower compared with nonrenal solid organ transplantation recipients. Although no statistically significant correlation could be established between tacrolimus exposure and renal function decline, strategies aiming at minimizing calcineurin inhibitor exposure and avoiding other nephrotoxic causes are recommended to preserve long-term kidney function.

(*Transplantation Direct* 2026;12: e1976; doi: 10.1097/TXD.0000000000001976.)

INTRODUCTION

Vascularized composite allotransplantation (VCA) is a continuously evolving area of modern transplant medicine, which refers to the transplantation of multiple tissues of different origins and antigenic properties as a functional unit.[1,2] Upper extremity allotransplantation (UET), face, uterus, abdominal wall, larynx, and penis transplantations are the most common VCAs.[3,4] VCA recipients need lifelong immunosuppression similar to that of solid organ transplantation (SOT) recipients[4] and are therefore at risk of developing the side effects reported after SOT.[5] Chronic kidney disease (CKD) is one of the most common complications developing in nonrenal transplant recipients,

Received 31 October 2025. Revision received 8 May 2026.

Accepted 13 May 2026.

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impacting their morbidity and mortality. The incidence of CKD varies depending on the transplanted organ (10%–80%): intestine and liver are more affected than heart and lung transplant recipients.[6-8] Although multiple risk factors have been reported, calcineurin inhibitors (CNIs) are considered the main cause.[6,8] Recently, 2 studies showed a decline in renal function after uterus transplantation (UTx), which is a "transient transplantation," as immunosuppression is discontinued after transplantectomy following 1–2 pregnancies.[9,10]

Herein, we report the results of a study performed to investigate renal function in other VCAs.

MATERIALS AND METHODS

Patients

The study included 70 patients from 17 centers performing VCA worldwide: 59 UET recipients (38 bilateral, 14 right-side, and 7 left-side UET), 10 recipients of face, and 1 of penis transplantation. The transplantations were performed between 1999 and 2021. The study included all patients transplanted for at least 1 y, and the recipients' data were collected for 10 y (median time of follow-up: 8 y).

A database was created, including the recipients' main pretransplant demographic data, which could increase the risk of CKD (hypertension, diabetes, smoking, gout, urinary infections, nephrolithiasis, chronic use of nonsteroid anti-inflammatory drugs, acute renal failure), and the immunosuppressive regimen at the transplantation and during the follow-up period. After the transplantation, the principal clinical data were collected, including graft loss and patient death.

Renal Function

Serum creatinine values were collected before the transplantation and at each time point of the follow-up after the transplantation (at 3 mo and then each year) to calculate the estimated glomerular filtration rate (eGFR) according to the CKD Epidemiology collaboration 2021[11,12] without adjusting for body surface, as it was challenging to take into account the addition of the graft weight, particularly in UET recipients.

End-stage kidney disease (ESKD) was defined as a glomerular filtration rate (GFR) <15 mL/min, according to the clinical practice guidelines of the National Kidney Foundation,[13] or the onset of dialysis therapy, or preemptive kidney transplantation. On the basis of the GFR criteria suggested by Kidney Disease: Improving Global Outcomes 2024,[14] the marker used to define kidney damage was a decreased GFR (GFR <60 mL/min per 1.73 m^2 for at least 3 mo; GFR categories G3a–G5). GFR categories included: G1: GFR >90 mL/min; G2: GFR = 60–89 mL/min; G3a: GFR = 45–59 mL/min; G3b: GFR = 30–44 mL/min; G4: GFR = 15–29 mL/min; and G5 <15 mL/min. In young adults, neither G1 nor G2 fulfills the criteria for CKD. Moreover, urinary albumin, urinary albumin-to-creatinine ratio, and/or urinary protein-to-creatinine ratio were available for 20 patients. On the basis of the criteria suggested by Kidney Disease: Improving Global Outcomes 2024,[14] albuminuria is considered another marker of kidney damage and albuminuria categories are considered albuminuria >300 mg/d, albuminuria/creatinine ratio ≥300 mg/g, or proteinuria/creatinine ratio ≥500 mg/g as severely increased (A3).

The tacrolimus blood trough level was collected at the same time points of the follow-up.

The main outcomes included a decline in eGFR of at least 50% on 2 consecutive time points of the follow-up compared with the pretransplantation value, a posttransplantation eGFR value <29 mL/min, and the occurrence of ESKD.

Statistical Analysis

The descriptive analysis was conducted using percentages for categorical variables and median values, along with a minimum–maximum range for continuous variables. The changes in GFR values during follow-up were analyzed using the Wilcoxon test for paired data. The correlation between the blood level of tacrolimus and the eGFR at any follow-up time point was explored using the Spearman rank correlation coefficient. Univariate and multivariable logistic regressions were performed to investigate risk factors (age, body mass index [BMI], sex, pretransplantation and posttransplantation diabetes and arterial hypertension, smoking status, history of acute renal failure before transplantation, and at least 1 episode of acute renal failure after transplantation) associated with a decline in renal function, defined as an eGFR decline of at least 50% on 2 consecutive follow-up points or an eGFR <29 mL/min or ESKD.

The analyses were carried out using IBM SPSS Statistics, Version 29.0.1.0. A *P*-value of 0.05 or less was considered statistically significant.

Institutional Review Board Statement

The clinical data used for the analyses were retrospectively collected and anonymized from each of the participating transplant centers and stored in a central database. All procedures adhered to the ethical standards set by the Declaration of Helsinki. The Institutional Review Board waived the need for consent.

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The authors declare no funding or conflicts of interest.

G.O., J.K., E.M., and P.P. designed the study, collected the patients' data, created the database, and wrote the article. C.S. contributed to the epidemiological design and performed the statistical analyses. L.B., O.T., A.G., and C.G. contributed to the research design and writing the article. All the other authors contributed to creating the database by reporting their patients' data and to writing the article.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001976

TABLE 1.

Characteristics of the VCA recipients before transplantation

Recipient characteristics	All VCA recipients (n = 70)	UET (n = 59)	Face Tx (n = 10)	Penis Tx (n = 1)
Median age (minimum–maximum), y	34 (19–69)	34 (21–69)	38 (19–59)	33
Sex (M/F)	58/12	49/10	8/2	1/0
Median BMI (minimum–maximum)	24.5 (15–68)	24.4 (15.5–68.5)	21.0 (18.4–30.0)	25.0
Arterial hypertension	5	4	0	1
Diabetes	2	2	0	0
Smoking	9	6	3	0
History of acute renal failure	4	4	0	0
History of urinary tract infection	1	1	0	0
History of gout	2	1	1	0
History of nephrolithiasis	3	3	0	0
Chronic use of NSAIDs	4	4	0	0

BMI, body mass index; F, female; M, male; NSAIDs, nonsteroid anti-inflammatory drugs; Tx, transplantation; UET, upper extremity transplantation; VCA, vascularized composite allotransplantation.

Institutional Review Boards of the main transplant center are as follows:

UET (for the first 7 bilateral transplantations): CCPRB AN/FL-99047/126A (April 29, 1999), then 99176.

Double Allogreffe des Membres supérieurs : Intervention et Evaluation clinique : étude pilote de 5 cas (DAMIE) project (bilateral arm transplantation): national number ID-RCD 2014-A01372-45; ANSM (14124OB-62; ANSAM authorization on March 13, 2015).

Face transplantation: National number 2006-A00110-51 (CCP Nord-Ouest n. 2006/14, February 8, 2007, and n. 061101, January 8, 2007).

RESULTS

The baseline characteristics of the recipients are shown in Table 1. The patients included 58 men and 12 women. Their median age was 34 y (range, 19–69 y), and their median BMI was 24.49 (range, 15.5–68.5). Before transplantation, 15% of the patients were smokers, 8% had arterial hypertension, and 3% had diabetes. A history of nephrolithiasis was reported in 6% of the patients, gout in 4%, and urinary tract infections in 2%. Eight percent of the patients chronically used nonsteroid anti-inflammatory drugs after the trauma that caused amputation or disfigurement. Acute renal failure occurred in 8% of the patients following the events that caused their amputation or disfigurement.

The induction therapy (short-term course ranging from 5 to 7 d) consisted of antithymocyte globulin (64% of patients), Campath-1 (16% of patients), and basiliximab (19% of patients). All recipients received tacrolimus in their maintenance therapy in the first year after transplantation. A few patients (5/70) were switched to a CNI-free regimen. Tacrolimus was discontinued in 2 other patients, but it was later reintroduced into their regimen. The blood trough levels of tacrolimus at the different time points of the follow-up are shown in Table 2.

During the follow-up, 18% of the recipients developed de novo posttransplant diabetes, and 20% of them developed de novo arterial hypertension. Graft loss (because of graft vasculopathy) and patient's death (with no graft removal) occurred in 14% and 13% of cases, respectively (the leading cause of death was malignancy; no cardiovascular causes were reported).

Before the transplantation, the median creatinine value was 75 µmol/L (range, 31.68–114.95 µmol/L), and the median eGFR was 105.36 mL/min (range, 71.09–155.39 mL/min). Eighty-three percent of the recipients were category G1 and 17% were G2 (eGFR >60 mL/min in both groups). Table 3 presents the patients' median eGFR values at each follow-up time point.

Figure 1 illustrates the evolution of renal function, as indicated by the eGFR for each patient during follow-up. Figure 2 shows the median eGFR values and the median tacrolimus blood trough level of all patients during the follow-up.

In the present study, 7 of 41 patients (17.1%) showed an eGFR decline of at least 50% on 2 consecutive follow-up points.

Category G4 (eGFR <29 mL/min) was evidenced in 7 of 64 (10.9%) recipients during the follow-up (Table 4). Three recipients (4.7%) underwent dialysis and then received a kidney graft at 7, 96, and 107 mo after the VCA, respectively. All patients with ESKD were UET recipients.

No significant difference in eGFR decrease was observed between UET and the other types of VCA at 3 mo after transplantation ($P = 0.114$ by the Mann-Whitney test). At 3-mo posttransplantation, 30% of the patients were category G1, 50% were G2, 13% were G3a, and 5% were G3b. In contrast, before transplantation, 83% of the patients were G1 and 17% were G2. At 1 y after transplantation, 1 patient in G2 before transplantation was G3a, and 21 patients who were in category G1 showed a decline in their renal function: 16 were in category G2, 3 were in G3a, 1 was in G3b, and 1 in G4. Thereafter, the eGFR values remained stable in the majority of patients, and no significant decrease was observed at subsequent follow-up time points (Figure 3).

Analysis of the different categories during follow-up revealed that the decline in renal function occurred early after transplantation, as shown in Table 4.

The univariate logistic models detected female sex (odds ratio [OR], 5.6; $P = 0.11$), smoker or ex-smoker status (OR, 9.5; $P = 0.05$), posttransplant diabetes (OR, 17.2; $P = 0.01$), and at least 1 episode of acute renal failure after transplantation (OR, 15.3; $P = 0.01$) as risk factors.

The multivariable logistic model suggested a potential role of these risk factors, although the low number of severe renal outcomes limited the certainty.

TABLE 2.

Tacrolimus trough levels (ng/mL) during follow-up

Years after transplantation	Median	Minimum	Maximum
0.25	12.5	6.1	44.9
1	9.05	0.8	14.9
2	7.85	4.2	14.5
3	7.55	3.3	17.3
4	7.9	3.2	10.9
5	7.4	2.6	13.5
6	7.05	3.6	15.9
7	6.7	2.6	12.5
8	7.5	4.2	20.0
9	7.1	3.5	14.5
10	6.9	2.8	9.4

TABLE 3.

eGFR mL/min values before transplantation and during follow-up

	eGFR		
Time from transplantation	Median	Minimum	Maximum
Pretransplantation	105.36	71.09	155.39
3 mo after Tx	78.42	32.49	130.74
1 y after Tx	82.61	42.10	124.78
2 y after Tx	77.52	51.44	136.55
3 y after Tx	79.92	39.30	140.72
4 y after Tx	78.16	39.21	129.03
5 y after Tx	79.19	36.22	126.74
6 y after Tx	78.90	16.14	130.55
7 y after Tx	79.86	19.54	123.84
8 y after Tx	79.82	16.74	120.27
9 y after Tx	86.48	42.11	118.84
10 y after Tx	80.81	42.21	120.52

eGFR, estimated glomerular filtration rate; Tx, transplantation.

There was no significant correlation (Spearman rank-order correlation coefficient) between the blood trough levels of tacrolimus and the eGFR at any time point of the follow-up, although at 3 mo the tacrolimus level was higher (median, 12.5 ng/mL).

Among the 20 patients with reported values of urinary albumin, urinary albumin-to-creatinine ratio, and/or urinary protein-to-creatinine ratio, 2 were in category A3 and developed ESKD. Two other patients in category A3 (1 of them at 1 and 10 y and the second one at 8 y after transplantation) showed a decrease in eGFR compared with pretransplantation values (progression from category G1 to G3a). Only 1 of them had received mammalian target of rapamycin inhibitors in her immunosuppressive treatment.

DISCUSSION

It is well known that transplantation of nonrenal organs is often complicated by CKD.[6-8] The incidence of chronic renal failure reportedly ranges from 7% to 21%, depending on the type of transplanted organ, recipients of liver and small bowel transplantations being those with the highest incidence. Indeed, in Wiseman's study,[15] the 5-y risk of chronic renal failure varied according to the type of organ transplanted—from 6.9% among recipients of heart-lung transplants[16] to 21.3% among recipients of intestinal transplants. In other studies, it ranged from 7% after heart transplantation to 18% after liver transplantation at 5 y.[15-17]

The present study included 70 recipients (59 with UETs, 10 with face, and 1 with penis transplantations) who received lifelong immunosuppression, such as SOT. A decrease in renal function was not considered an exclusion criterion. Remarkably, the majority of VCA patients were young (their median age was 34 y) and healthy (8% of the recipients had arterial hypertension and 3% of them had diabetes before transplantation), and they had a median eGFR of 105.36 mL/min before transplantation. In the present study, 10.9% of VCA recipients developed CKD (G4) and 4.7% developed ESKD during the first 10 y of follow-up, whereas this was reported in up to 20% of the other nonrenal SOTs (NRSOTs).[6,8,15] Seventeen percent of VCA recipients showed an eGFR decline of at least 50% at 2 consecutive follow-up points.

The young age and healthy state could explain the lower incidence of severe function loss among recipients after a median follow-up time of 8 y. However, the majority of VCA recipients developed a decline in renal function early after transplantation, regardless of the type of VCA, although 59 of them were UET, that is, they had grafts heavier than other VCA types. There was a significant decrease in eGFR values (78.42 L/min) at 3 mo after transplantation compared with the pretransplantation values (median eGFR, 105.36 mL/

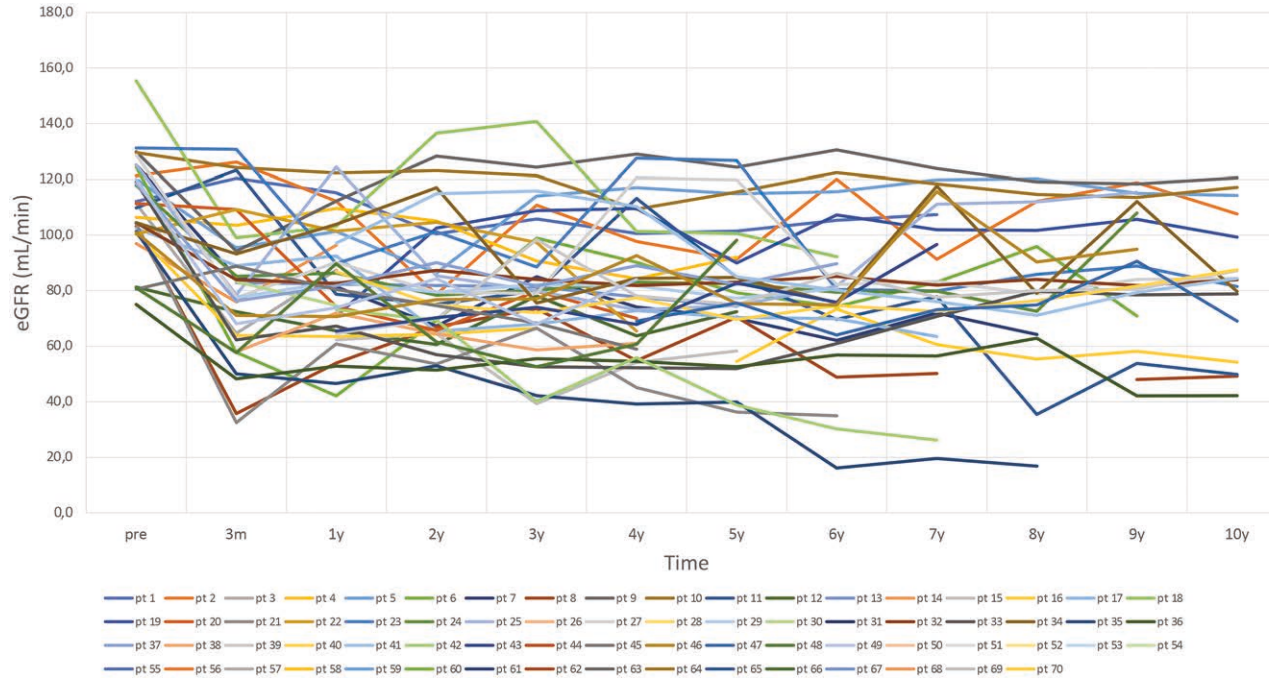


FIGURE 1. Progression of renal function, expressed as eGFR (mL/min), of all patients included in the study before transplantation and during follow-up. Before transplantation, all patients had eGFR >60mL/min. eGFR, estimated glomerular filtration rate; pt, patient.

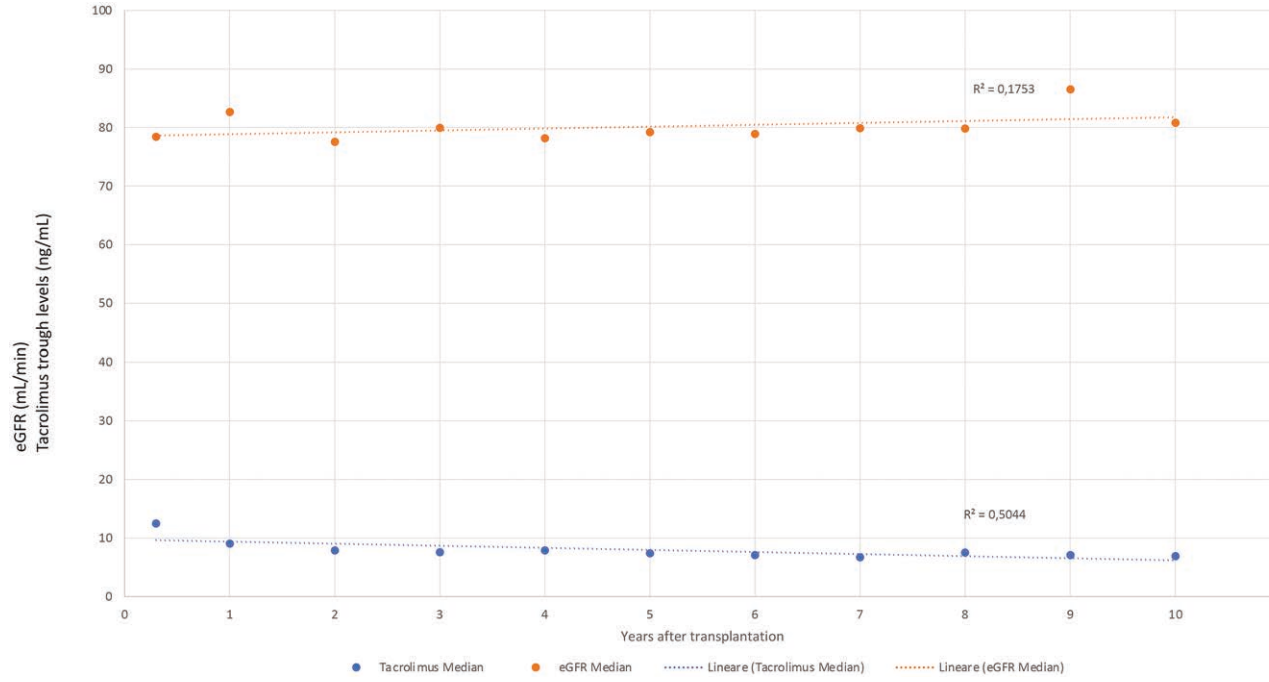


FIGURE 2. Evolution of eGFR (median values expressed as mL/min) and tacrolimus (median blood trough levels expressed as ng/mL) at each time point of follow-up. eGFR, estimated glomerular filtration rate.

min; $P = 0.001$ by the Wilcoxon test). However, eGFR values remained stable thereafter in the majority of patients during follow-up.

Urinary albumin and/or proteinuria were reported in merely 20 patients. Interestingly, 4 of these patients had high values (A3): 2 of them developed ESKD and 2 others had a significant decline in their renal function (they progressed from G1 to G3a). In all cases, this occurred several years after the transplantation. Albuminuria and proteinuria were unfortunately tested and reported by the majority of teams only when the recipients developed signs of CKD.

In other NRSOTs, the clinical course from transplantation to ESKD ranges from rapid deterioration to slow progression, with long periods of functional stability.[7] However, the most frequent pattern is a biphasic curve, with a 50% decrease in the GFR during the first posttransplant year, followed by

TABLE 4.

GFR categories before and after VCA during follow-up

GFR categories	Pre-Tx	3 mo	1 y	2 y	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y
No. of pts	60	40	49	41	41	40	36	33	27	24	24	24
G1	50 (83%)	12 (30%)	19 (39%)	12 (29%)	12 (29%)	13 (33%)	11 (30%)	8 (24%)	9 (33%)	8 (33%)	11 (46%)	6 (25%)
G2	10 (17%)	20 (50%)	24 (49%)	25 (61%)	22 (54%)	19 (48%)	18 (51%)	20 (61%)	14 (52%)	12 (50%)	8 (33%)	11 (46%)
G3a	0	5 (13%)	4 (8%)	4 (10%)	4 (10%)	7 (18%)	4 (11%)	2 (6%)	2 (7%)	1 (4%)	4 (17%)	5 (21%)
G3b	0	2 (5%)	1 (2%)	0	3 (7%)	1 (3%)	3 (8%)	2 (6%)	0	1 (4%)	1 (4%)	2 (8%)
G4	0	1 (3%)	1 (2%)	0	0	0	0	1 (3%)	2 (7%)	2 (8%)	0	0
G5	0	0	0	0	0	0	0	0	0	0	0	0

The total number of recipients is indicated at each time point of the follow-up, as well as the recipients' number and percentage of patients for each category (G1–G5).
GFR, glomerular filtration rate; pts, patients; Tx, transplantation; VCA, vascularized composite allotransplantation.



FIGURE 3. Renal function (eGFR, mL/min) pretransplantation and during follow-up for 18 patients with at least 1 eGFR value <60 mL/min, grouped by severity of renal function decline. Green = no renal function decline, blue = moderate renal function decline, and red = severe renal function decline. eGFR, estimated glomerular filtration rate; n, number of patients.

stabilization, and a subsequent slow but relentless decline until ESKD, as reported by Greenberg et al[16] in a cohort of 228 heart allograft patients and by Pattison et al[17] in a cohort of 67 heart-lung transplant recipients.

A previous study on renal function in VCA recipients also reported a similar biphasic decline.[18] Interestingly, in our study this decrease was significant only in the early posttransplant period, following which renal function remained stable during the follow-up (median time 8 y) in the vast majority of patients.

An early decline in kidney function has also been reported by Ekberg et al.[9] In their study, all 7 UTx recipients showed a decrease in renal function, with only 2 of them returning to baseline values after transplantectomy and discontinuation of immunosuppression.[9] In another international cohort of 18 UTx recipients, alterations in renal function were first observed early after transplantation and, for some patients, persisted throughout pregnancy and into the early postpartum period.[10] Also, in this cohort of patients, discontinuation of immunosuppression did not uniformly result in an immediate improvement in renal function. It should be remembered that UTx recipients have a higher risk of renal dysfunction because, in about 30% of women with Mayer-Rokitansky-Kuster-Hauser syndrome, uterine agenesis may be associated with congenital renal abnormalities. In addition, 28% of UTx recipients developed preeclampsia.[10]

In NRSOT recipients, the overall risk of chronic renal failure is associated with several variables, such as the patient's age, BMI, race, sex, pretransplantation GFR and the presence of pretransplantation arterial hypertension, diabetes, or hepatitis C infection.[6,7]

The multivariable logistic regression analysis showed an association between sex, smoking, posttransplant diabetes, and at least 1 episode of acute renal failure after transplantation and the decline in renal function (defined as an eGFR ≥50% reduction on 2 consecutive follow-up time points, or an eGFR < 29 mL/min, or ESKD); however, because of the relatively limited number of patients with renal function decline, this association has to be considered with caution. We found no correlation between GFR categories and the pretransplant acute renal failure episodes that occurred in 8% of the patients following their disfigurement or amputation, as suggested recently by Zuo et al[19] in those recipients who developed acute renal failure because of sepsis.

In the present study, although the most prominent decrease in eGFR was observed within the first 3 posttransplant months with correlating tacrolimus trough levels, which were too high in the immediate posttransplant period (median, 12.5 ng/mL), we found no statistically significant correlation (by the Spearman rank-order correlation coefficient) between the blood trough levels of tacrolimus and the eGFR during the follow-up. Moreover, in the present study, tacrolimus was included in the maintenance therapy of all recipients during the first posttransplant year. Thereafter, a minority of patients were switched to a CNI-free regimen. For this reason, although it is well known that CNIs, such as tacrolimus, can be nephrotoxic,[20,21] it was not possible to detect a correlation between the decline in renal function and the immunosuppressive regimen.

Two forms of tacrolimus nephrotoxicity are distinguished: acute and chronic.[20] Acute nephrotoxicity is functional, dose-dependent, and usually completely reversible after dose reduction. It is associated with alterations of intrarenal hemodynamics and a reduced GFR that occurs soon after treatment initiation. Tacrolimus causes vasoconstriction of the afferent and efferent glomerular arterioles because of an increase in vasoconstrictor mediators (such as sympathetic tone, the renin-angiotensin system, and endothelin-1) and a decrease in vasodilator mediators (such as prostaglandins and nitric oxide).[20-22] The vasoconstriction of renal microcirculation results in hypoperfusion and parenchymal ischemia, causing functional renal impairment that improves with the reduction of tacrolimus dosages.[20-22]

Chronic tacrolimus nephrotoxicity (CTN) is chronic, structural, progressive, and irreversible, but its mechanisms are poorly understood. Several studies suggest that tacrolimus can generate reactive oxygen species and disrupt antioxidant defense in the proximal tubules.[20-23] CTN affects all 3 compartments of the kidneys: vessels (arteriolar hyalinosis), tubulo-interstitium (tubular atrophy and interstitial fibrosis), and glomeruli (thickening and fibrosis of Bowman's capsule and focal segmental or global glomerulosclerosis). Vascular involvement manifests as nodular hyaline deposits in the media of afferent arterioles, also called arteriolar hyalinosis, a hallmark of CNI nephrotoxicity. Remarkably, however, when renal biopsies were performed in NRSOT, many patients had no overt histological evidence of CNI toxicity.[23] Therefore, a diagnosis of CNI nephrotoxicity can only be established by renal biopsy, with histological evidence of nodular arteriolar hyalinosis, associated with striped interstitial fibrosis, in the absence of another primary renal disease. In the present study, only 1 patient underwent a renal biopsy before renal transplantation; this showed extensive arteriosclerosis but no signs of acute or CTN (data not shown).

Increased blood pressure at 1 y was recently described as an independent risk factor for GFR decline between 1 and 5 y after liver and heart transplantation.[7,8,24]

Tighter blood pressure control is at least equally important as tacrolimus minimization or avoidance in the long-term management of NRSOT patients[8,15] and VCA recipients. Limiting all nephrotoxic insults might also be a helpful strategy for VCA recipients, as recommended by Bloom and Reese[8] for NRSOT patients.

Our study has strengths. For the first time, information on the renal function of 70 VCA recipients from 17 centers was directly collected and reported with a median follow-up time of 8 y. Limitations of our study include missing data for some follow-up points in some patients (ie, pretransplantation eGFR in several patients) and incomplete proteinuria assessments (available for only 20 patients), which restricts the interpretation of the results.

In conclusion, our study reveals a decline in renal function in VCAs, such as UET, face, and penis transplantations, but it also shows that the incidence of severe function decline (G5) and a decline in eGFR of at least 50% are lower compared with NRSOT recipients.

VCA is a non–life-saving procedure, and as reported in the present study, the recipients are young and healthy, with normal renal function before transplantation (GFR >60 mL/min). For these reasons, renal function has to be carefully monitored before transplantation and during the follow-up, and every effort has to be made to limit the risk factors that might cause renal dysfunction.

Based on our findings, we recommend avoiding an overdose of tacrolimus, particularly in the first posttransplant period,[20] and minimizing CNI exposure in the long-term follow-up. Nevertheless, a complete withdrawal of CNI must be implemented with caution, considering the high risk of rejection. Minimizing the tacrolimus dose, given in association with another immunosuppressant, such as belatacept, could be a strategy to prevent acute and/or chronic rejection.[25] In addition, limiting all nephrotoxic insults (above all, arterial hypertension, nephrotoxic drugs, and contrast imaging products) should be implemented as a valuable strategy to prevent renal function decline in VCA recipients.

ACKNOWLEDGMENTS

The authors thank Mrs Céline Dagot for her precious assistance in collecting the patients' data.

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