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Kidney Dysfunction After Vascularized Composite Allotransplantation

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Background. Kidney dysfunction is a major complication after nonrenal solid organ transplants. Transplantation of vascularized composite allografts (VCA) has yielded successful midterm outcomes despite high rates of acute rejection and greater requirements of immunosuppression. Whether this translates in higher risks of kidney complications is unknown. **Methods.** Ninety-nine recipients of facial or extremity transplants from the Brigham and Women's Hospital (BWH) and the International Registry on Hand and Composite Tissue Transplantation (IR) were reviewed. We assessed immunosuppression, markers of renal function over time, as well as pretransplant and posttransplant renal risk factors. **Results.** Data were obtained from 10 patients from BWH (age at transplant, 42.5 ± 13.8 years) and 89 patients (37.8 ± 11.5 years) from IR. A significant rise in creatinine levels (BWH, $P = 0.0195$; IR, $P < 0.0001$) and drop in estimated glomerular filtration rate (GFR) within the first year posttransplant was observed. The BWH and IR patients lost a mean of 22 mL/min GFR and 60 mL/min estimated GFR in the first year, respectively. This decrease occurred mostly in the first 6 months posttransplant (BWH). Pretransplant creatinine levels were not restored in either cohort. A mixed linear model identified multiple variables correlating with renal dysfunction, particularly tacrolimus trough levels. **Conclusions.** Kidney dysfunction represents a major complication posttransplantation in VCA recipients early on. Strategies to mitigate this complication, such as reducing calcineurin inhibitor trough levels or using alternative immunosuppressive agents, may improve long-term patient outcomes. Standardizing laboratory and data collection of kidney parameters and risk factors in VCA patients will be critical for better understanding of this complication.

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The importance of preserving renal function is well recognized and described in nonrenal solid organ transplantation (NRSOT). Although the introduction of calcineurin inhibitors (CNI) to the immunosuppression regimens of transplant recipients reduced the rates of rejection and improved graft survival, it also contributed to increased risks of developing chronic kidney disease (CKD).[1,2] Other risk factors, such as systemic hypertension, cardiovascular disease, and both pretransplant and posttransplant diabetes mellitus (DM), which are traditionally associated with renal disease, further affect renal function in NRSOT.[3]

Vascularized composite allografts (VCA) refers to the transplantation of a vascularized functional unit of multiple tissues, such as muscle, nerve, bone and skin (eg, hand, face,

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etc), from a deceased donor to a matching recipient. In select patients, VCA offers improved functional and cosmetic outcomes compared with conventional reconstructive techniques.[4] However, VCA recipients must submit to lifelong immunosuppression to prevent rejection of their transplants despite the absence of a life-threatening disease. These immunosuppression regimens can cause unfavorable effects to kidney function.

Death with a functioning graft is one of the leading causes of allograft loss in solid organ transplant, with cardiovascular mortality being a major culprit. Renal dysfunction is a major risk factor for cardiovascular complications.[3,5,6] Minimizing the degree of renal dysfunction posttransplantation is therefore crucial to improve outcomes. Indeed, those patients with better renal function have a significant reduction in cardiovascular mortality posttransplantation.[7]

The development of CKD in NRSOT recipients is well described, but there is no literature on CKD in VCA recipients. In this study, we aimed to evaluate renal function in our VCA cohort, as well as in an international VCA cohort to quantify the prevalence of renal dysfunction and identify the most pertinent risk factors for renal dysfunction.

MATERIALS AND METHODS

Source of Data

For this retrospective cohort study, we used the hospital information system of the Brigham and Women's Hospital (BWH), Boston, MA. The hospital information system database contains documentation of all in-house visits and respective blood chemistry and urine analyses, as well as scanned documentation of outpatient visits in other institutions, when available. We obtained clinical and laboratory data from 10 patients that received VCA and followed-up at the BWH.

We also included deidentified data from the International Registry on Hand and Composite Tissue Transplantation (IR), which compiles patient data from 24 participating international VCA centers.[8] Data include pretransplant history and demographic characteristics, as well as surgical information, immunosuppressive induction therapy, and maintenance regimens. The VCA centers that subscribe to the registry update the information on their transplant recipients on an annual and voluntary basis.

Study Subjects

The BWH cohort consisted of all 10 patients that received VCA at BWH, namely, 3 upper-extremity recipients and 7 face transplant recipients.

The IR cohort also included recipients of upper-extremity (60 patients) or facial transplantation (29 patients).

Variables Examined and Outcomes Measured

We collected demographics and information about type and level of the transplant in the BWH cohort. To account for potential covariates, we recorded pretransplant medical history data that indicated potential risk factors for kidney injury, such as comorbidities, drugs, and vital signs. To assess the effect of graft mass, we calculated a size score for upper-extremity transplants. We assigned a number to transplants depending on the size (1, hand only; 2, upper extremity below elbow and including hand; 3, upper extremity above elbow and including hand) and then summed the values for left and right sides for each patient, which yielded a single number between 1 and 6 representing the mass of transplanted grafts. We gathered detailed information on induction and maintenance immunosuppression as well as drug trough levels and parameters of renal function. The IR data included creatinine levels beyond baseline *only* for extremity transplant recipients and *not* for face transplant recipients. We calculated the estimated glomerular filtration rate (eGFR) and age adjusted for every assessed time point using the Modified Diet in Renal Disease (MDRD) equation:

$$\mathrm{eGFR}\left(\mathrm{mL/\,min\ per\ 1.73m^2}\right) = 175 \times (\mathrm{S_{cr}})^{-1.154} \times (\mathrm{age})^{-0.203} \times (0.742\ \text{if female}) \times (1.212\ \text{if African American})$$

MDRD has been shown to more precisely reflect GFR over other metrics, such as Chronic Kidney Disease Epidemiology Collaboration, in transplantation.[3,9] Our primary points of interest were the relationship between immunosuppressive regimens and kidney function as measured in creatinine levels as well as in changes in eGFR over time at 1, 3, and 5 years.

Statistical Analysis

Data were gathered in Excel (Microsoft Inc., Redmond, WA). Changes in eGFR over time were calculated with a Wilcoxon rank-sum test for continuous nonparametric variables, as well as with Mann-Whitney *U* test for unpaired nonparametric values in Prism 7.0 (Graphpad, La Jolla, CA). Further data were analyzed with SPSS Statistics Version 22 (IBM, Armonk, NY). MDRD was log transformed to satisfy normality assumption which was assessed with QQplot. Long-term trends were only assessed in patients in which continuous variables were available. Clinical parameters (**Table S1, SDC,** http://links.lww.com/TXD/A98) that showed *P* values less than 0.2 in bivariate correlation analysis using Pearson and Spearman correlation coefficients were selected for further analysis. Univariate linear mixed-effects models with acute rejection (AR) [1] covariance structure were used to study the effects of these preselected parameters on MDRD. Those parameters with *P* values less than 0.05 in the univariate analysis were then included in a multiple linear mixed-effects model. All *P* values were considered to indicate statistical significance when $\alpha \leq 0.05$ and were reported 2-sided.

RESULTS

Baseline Characteristics

The baseline characteristics of the BWH cohort are summarized in Table 1A. Seventy percent of the BWH cohort subjects were recipients of facial allografts, and 30% were upper-extremity graft recipients. The average age at the time of transplant was 42.5 years with 41.3 in face transplants and 45.3 in upper-extremity transplants. Comorbidities at the time of transplantation were present only in the face transplant group, and included DM (28.6%), hypertension (28.6%), and hepatitis C virus infection with detectable viral load at time of transplant (14.3%; genotype 3a). Mean estimated GFR before transplantation was 119.3 (±46.2) mL/min per 1.73 m^2. Estimated GFR was not less than 60 mL/min per 1.73 m^2 before transplantation in any patient, and no patient had been treated with dialysis pretransplant. Time since transplantation varied between 0.5 and 7 years, with 4 face

TABLE 1.

Baseline characteristics of patients with vascularized allografts included in the study

	(A) BWH			(B) International Registry		
Characteristics	**All (N = 10)**	**Face (n = 7)**	**UE (n = 3)**	**All (N = 89)**	**Face (n = 29)**	**UE (n = 60)**
Age, y	42.5 (SD ± 13.8)	41.3 (SD ± 13.2)	45.3 (SD ± 17.6)	37.8 (n = 83) (SD ± 11.5)	38.4 (n = 28) (SD ± 10.9)	37.6 (n = 55) (SD ± 11.8)
Male sex, n (%)	8 (80.0%)	5 (71.4%)	3 (100.0%)	75 (84.3%)	23 (79.3%)	52 (86.7%)
White race, n (%)	10 (100.0%)	7 (100.0%)	3 (100.0%)	—	—	—
Height, cm	165.5	175.9	141.3	—	—	—
Weight, kg (pretransplant)	73.8 (SD ± 24.2)	76.6 SD ± 29.1)	67.3 (SD ± 1.7)	78.43 (N = 74)(SD ± 25.82)	72.12 (N = 24) (SD ± 24.1)	80.65 (N = 50) (SD ± 26.08)
Hypertension pretransplantation, n (%)	2 (20%)	2 (28.6%)	0 (0%)	—	—	—
DM pretransplantation, n (%)	2 (20%)	2 (28.6%)	0 (0%)	—	—	—
Positive for HBsAg, n (%)	1 (10%)	1 (14.3%)	0 (0%)	—	—	0 (0)
Positive for HCV Ab, n (%)	1 (10%)	1 (14.3%)	0 (0%)	—	—	1 (1.67)
Any dialysis requirement before transplantation, n (%)	0 (0%)	0 (0%)	0 (0%)	—	—	—
Pretransplantation eGFR (MDRD), n				N = 64	N = 18	N = 46
(%)	6 (60%)	3 (42.9%)	3 (100%)	48 (75.0%)	15 (83.3%)	33 (71.7%)
>60	4 (40%)	4 (57.1%)	0 (0%)	15 (23.4%)	3 (16.7%)	12 (26.1%)
30-59	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	1 (2.2%)
<29	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CNI during initial hospitalization for transplantation, n (%)						
Tacrolimus	10 (100%)	7 (100%)	3 (100%)			

The cohort of the BWH (A) as well as the cohort of the IR (B) are displayed.

UE, upper extremity; HBsAg, hepatitis B surface antigen as marker for hepatitis B infection; HCV antigen, hepatitis C virus antigen as marker for hepatitis C virus infection.

transplant recipients and 1 upper extremity having reached the 5-year time point at the time of analysis. Size and dimension of grafts are shown in Table 2, and immunosuppressive regimens in Table 3.

The baseline characteristics of the IR cohort are summarized in Table 1B. Of the total 89 patients available for analysis, 29 (32.6%) had received a face transplant and 60 (67.4%) had received an upper-extremity transplant. The overall mean age was 37.8 years, and 84% of the recipients were male, with little variation between face and upper-extremity recipients. Pretransplant comorbidities were not uniformly reported among registry participants. Initial eGFR were not available for all patients, but mean eGFR was 113.2 (±42.2) mL/min per 1.73 m^2 in 64 patients. Only 1 patient had eGFR of less than 60 mL/min per 1.73 m^2 (33.4 mL/min) at the time of transplant. Mean follow-up time was 3.8 years (0.3-17 years).

Renal Function Over Time

In the BWH cohort, creatinine levels increased within the first year posttransplant ($P = 0.0195$). This rise in creatinine correlated with a reduction in eGFR over time (Figure 1A). The most prominent increase of creatinine levels was seen within the first 6 months posttransplant with correlating tacrolimus trough levels, which were highest in the period immediately posttransplant (11.3 ± 3.0 ng/mL) (Figure 1B). **Figure S1 (SDC,** http://links.lww.com/TXD/A97) shows a trend in creatinine over time for individual patients of the BWH cohort, and this trend also correlated with rejection events and uptitration of immunosuppression.

When calculating the decline of eGFR in mL/min per year, a mean drop of 22 mL/min (±27.9) occurred within the first year for all VCA patients (Figure 1C). Specifically, for face and upper-extremity recipients, there was a drop of 25.1 mL/min (±32.6) and 21.3 mL/min (±8.1), respectively (Figure 1D). The subsequent years show a considerably smaller decline of eGFR.

A similar trend was observed in the IR cohort. There was a significant increase in creatinine ($P < 0.0001$) in the first year after transplantation, and a correlating decrease in eGFR ($P < 0.0001$) (Figure 1E). Between the first and the third postoperative years, a partial improvement in renal function (Figure 1E) was observed, although renal function did not return to baseline pretransplant levels. Higher tacrolimus trough levels (13.3 ± 3.9 ng/mL) were present initially and correlated with higher creatinine levels (Figure 1F). A yearly decline in eGFR is shown in Figure 1G, which demonstrates a loss of a mean of 60.2 mL/min (±36.4) in the first year, with rates of 8.9 (±28.9) in the second year, and 11.3 mL/min in the third year. Given that consecutive data on renal parameters for face transplant recipients were not available in this cohort, these effects are solely attributed to upper-extremity recipients.

TABLE 2.

Graft characteristics of VCA recipients in the cohort of BWH

Face	**7 (100%)**
Soft tissue	5 (71%)
Soft tissue + bone	2 (29%)
Upper extremity (grafts)	6 (100%)
Above elbow	3 (50%)
Below elbow	3 (50%)

TABLE 3.

Characteristics of induction and immunosuppressive regimen in the cohort of BWH and the IR

	BWH			International Registry		
	All (N = 10)	Face (n = 7)	UE (n = 3)	All (N = 89)	Face (n = 29)	UE (n = 60)
Induction						
ATG	10 (100.0%)	7 (100.0%)	7 (100.0%)	54 (60.7%)	22 (75.9%)	32 (53.3%)
Tacrolimus	10 (100.0%)	7 (100.0%)	7 (100.0%)	66 (74.2%)	18 (62.1%)	48 (80.0%)
MMF	10 (100.0%)	7 (100.0%)	7 (100.0%)	54 (60.7%)	16 (55.2%)	38 (63.3%)
Prednisone	10 (100.0%)	7 (100.0%)	7 (100.0%)	61 (68.5%)	19 (65.5%)	42 (70.0%)
Immunosuppression						
Year 1	n = 9	n = 7	n = 2	n = 52	n = 14	n = 38
Tacrolimus	8 (88.9%)	6 (85.8%)	2 (100.0%)	41 (78.8%)	11 (78.57%)	30 (78.95%)
MMF	9 (100%)	7 (100.0%)	2 (100.0%)	38 (73.08%)	11 (78.57%)	27 (71.05%)
Prednisone	3 (33.3%)	2 (28.6%)	1 (50.0%)	34 (65.38%)	8 (57.14%)	26 (68.42%)
Year 3	n = 6	n = 5	n = 1	n = 35	n = 12	n = 23
Tacrolimus	6 (100.0%)	5 (100.0%)	1 (100.0%)	29 (82.9%)	9 (75.0%)	20 (86.9%)
MMF	6 (100.0%)	5 (100.0%)	1 (100.0%)	30 (85.7%)	9 (75.0%)	21 (91.3%)
Prednisone	1 (16.7%)	1 (20.0%)	0	28 (80.0%)	8 (66.7%)	20 (86.9%)
Year 5	n = 5	n = 4	n = 1	n = 25	n = 6	n = 19
Tacrolimus	5 (100%)	4 (100%)	1 (100%)	21 (84.0%)	3 (50.0%)	18 (95.7%)
MMF	5 (100%)	4 (100%)	1 (100%)	19 (76%)	4 (66.7%)	15 (78.9%)
Prednisone	3 (60%)	3 (75%)	0	19 (76%)	4 (66.7%)	15 (78.9%)

ATG, anti-thymocyte globulin.

Risk Factors for Kidney Dysfunction

To assess for potential factors affecting posttransplant renal function, we used a mixed linear model with parameters derived from the medical history (**Table S1, SDC,** http://links.lww.com/TXD/A98).

All BWH upper-extremity recipients had a size score of 5, whereas upper-extremity recipients from the IR had size scores ranging between 1 and 4 (2.6 ± 1). These variations were included in the model. Several factors demonstrated significant effects in a univariate mixed linear model of BWH patient data (Table 4). Metabolic factors, such as posttransplantation body mass index (BMI), pretransplant and posttransplant DM, pretransplant and posttransplant hypertension and hypertensive treatment showed a positive correlation with eGFR, as did age. In terms of immunosuppression, both induction and maintenance doses of tacrolimus, as well as prednisone induction doses, had a significant correlation with renal function. None of these factors remained significant in the multivariate mixed model.

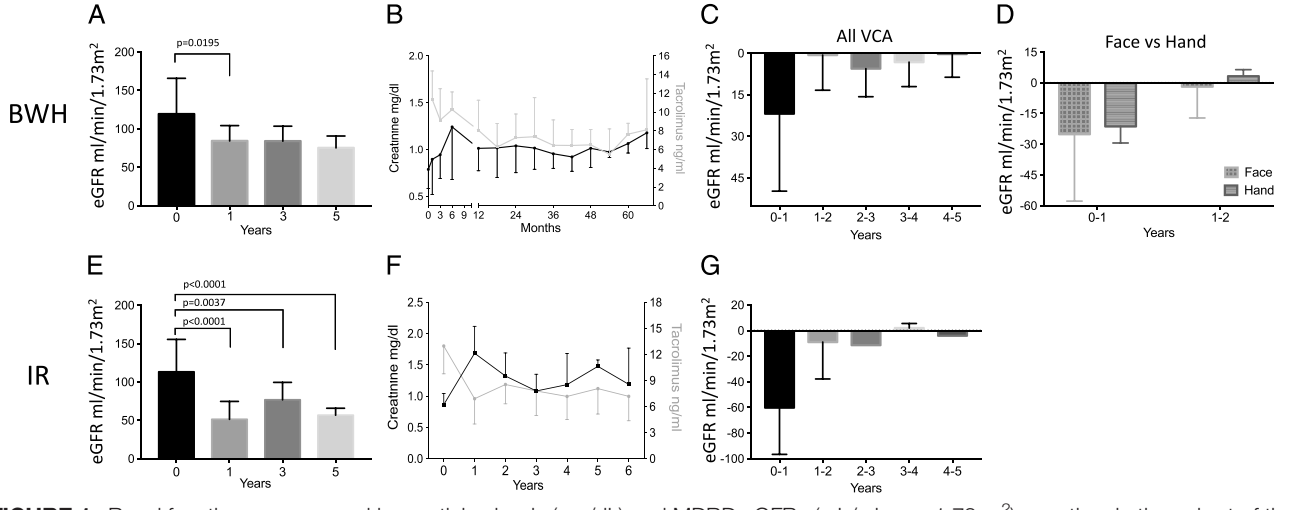

FIGURE 1. Renal function as measured in creatinine levels (mg/dL) and MDRD eGFRs (mL/min per 1.73 m^2) over time in the cohort of the BWH and in the IR. Panels A and E demonstrate changes in eGFR at 0, 1, 3, and 5 years after transplantation, with a clear decrease in renal function, particularly in the first year. Creatinine levels (mg/dL) and tacrolimus trough levels (ng/mL) of the 2 VCA cohorts at the BWH and the IR are shown for up to 6 years posttransplant. IR data only include data of upper-extremity recipients. A distinct increase in creatinine levels in the first year, particularly in the first 6 months, can be seen in the BWH cohort (B), which also appears in the IR cohort (F). Mean levels of early tacrolimus doses at time of transplantation are high in both cohorts—11.3 ng/mL BWH and 13.3 ng/mL in IR. After a substantial decrease in the first years, these levels seem to mimic the creatinine levels over time (B and F). Panel F shows more granular data of eGFR over time, pointing to a major loss of function within the first 6 months (B). Yearly loss of GFR in mL/min over time is demonstrated in panels C and G, with the losses of 22 mL in the BWH and 60.2 mL in IR, respectively. More detailed analysis shows greater loss of mL in the facial subgroup at BWH (D), whereas IR data (G) could only be calculated from upper-extremity recipient, because no continuous creatinine levels were documented for face transplant recipients.

TABLE 4.

Effects of correlated covariates (*P* < 0.2) on logMDRD in a mixed-linear model in the BWH's cohort

Parameters	Estimate	Std. error	*df*	*t*	*P* univariate MLM
Proteinuria			14.7107		0.6505
Age	–0.0077	0.0036	15.0745	–2.1560	**0.0476**
Sex			14.1402		0.1339
Type of VCA			15.6882		0.0975
Post-Tx BMI	0.0161	0.0065	19.7115	2.4879	**0.0219**
Pre-Tx weight	–0.0024	0.0027	14.7987	–0.8783	0.3938
Pre-Tx HTN			14.7572		**0.0256**
Post-Tx HTN			14.8564		**0.0439**
Anti-HTN treatment			14.8564		**0.0439**
Sepsis			14.1240		0.0773
Pre-Tx DM			14.7572		**0.0256**
Post-Tx DM			14.7572		**0.0256**
Smoking			14.7068		0.4082
Creatinine at 1 mo	0.0688	0.1642	13.6165	0.4188	0.6819
Tac induction dose	–0.0452	0.0203	12.8970	–2.2249	**0.0446**
Prednisone induction dose	–0.0006	0.0003	13.9254	–2.3423	**0.0346**
Tac maintenance dose	0.0299	0.0095	93.2753	3.1491	**0.0022**
Prednisone maintenance dose	0.0003	0.0007	41.4735	0.4374	0.6641

Right columns showing *P* values of univariate and multivariate mixed linear model analysis.

Categorial variables shown with estimates, standard deviation, degrees of freedom and *P* value; continuous variables shown with degrees of freedom and *P* value.

Statistically significant *P* values are in bold.

Using data from the International Registry (Table 5), we identified tacrolimus trough levels, Campath-1H and anti-thymocyte globulin as having a significant correlation with renal function in the univariate mixed-linear model. Upper-extremity size score was also significant in explaining the variance in eGFR. None of these factors remained significant in the multivariate mixed model.

DISCUSSION

This study revealed significant worsening in renal function over time in VCA recipients both in the BWH and the IR cohorts, most pronounced within the first year after transplantation. Univariate factor analysis indicated that tacrolimus dose and levels were the major contributors for this decrease in renal function. Early posttransplant tacrolimus trough levels were high (above 10 ng/mL) in both cohorts; a reduction after 1 year was accompanied by parallel slight improvement in renal function. Even so, renal function remained below pretransplant baseline levels.

There is no consensus across the literature on the reported cumulative incidence of CKD in NRSOT, with wide variance, ranging from 2% to 18% after liver, heart, or lung transplants.[10-13] Some studies report prevalence as high as 83%.[6] These inconsistencies can be partially attributed to fundamental differences between studies, such as the type of organ, the duration of the follow-up period, and the definition of CKD.[6] Moreover, the rate of progression of CKD

TABLE 5.

Effects of correlated covariates (*P* < 0.2) on logMDRD in a mixed-linear model in the IR's upper-extremity cohort

Parameters	Estimate	Std. error	*df*	*t*	*P* single MLM
Tacrolimus through level	0.0724	0.0120	71.7407	6.0427	**<0.0001**
Proteinuria			2.9074		0.2824
No. AR			36.3715		0.7590
Age	–0.0058	0.0041	79.8061	–1.4273	0.1574
Pre-Tx BMI	–0.0031	0.0055	37.6143	–0.5540	0.5828
Pre-Tx Weight	–0.0029	0.0016	42.8812	–1.8294	0.0743
UE size score	0.1128	0.0537	60.8810	2.1001	**0.0399**
Campath 1H			30.5658		**0.0035**
Daclizumab			34.9450		0.3439
ATG			71.5237		**<0.0001**
Basiliximab			65.3197		0.1903
Prednisone Maintenance	–0.0079	0.0061	47.7341	–1.2917	0.2027
Sirolimus through level	–0.1187	0.0497	1.9313	–2.3884	0.1440

Face transplant recipients were excluded due to missing renal data. Right columns showing *P* values of univariate mixed linear model analysis. Categorial variables shown with estimates, standard deviation, degrees of freedom and *P*-value; continuous variables shown with degrees of freedom and *P* value.

Tx, transplantation; UE size score, upper extremity size score; HTN, hypertension; ATG, anti-thymocyte globulin.

Statistically significant *P* values are in bold.

and the manifestation of the ultimate outcome of renal failure can vary even between individuals. More specifically, the incidence of CKD with an eGFR below 29 mL/min is estimated as 11% after heart transplant and 18% after liver transplant at 5 years after transplantation.[6]

We observed a marked decrease in the mean eGFR in the first year (22 mL/min) posttransplant in our BWH patient cohort. Greenberg et al[14] reported a biphasic decline in renal function in a cohort of 228 cardiac allograft patients, with a rapid deterioration especially within the first 24 months, and a slower decline until 7 years postoperatively. Pattison et al[15] also reported a biphasic decline in renal function in a cohort of 67 heart-lung transplant recipients. Our findings in the BWH and IR cohorts suggest a similar biphasic declining trend in renal function. The first decline is observed during the first year and the second after 3 to 4 years. In between both declines, there is a period of intermittent improvement.

In our study, decreased eGFR correlated with tacrolimus trough levels. Immediately posttransplant, tacrolimus trough levels were highest and accompanied by a parallel trend in creatinine levels. However, not all the BWH and IR patients included in the study had reached the postoperative end time point of 5 years, and continuous documentation of renal function and tacrolimus trough level over the time of observation was not available for some IR patients. These limiting factors make it difficult to assess the decline in renal function for all patients combined. Although renal function seemed to slowly recover over time, it never returned to baseline values measured before transplant within the period of observation. Thus, there was an everlasting reduction in renal function in all patients in this study.

The majority of recipients in the IR had received upper-extremity grafts, which comprise significantly more muscle mass than facial allografts, and therefore had the potential of generating more creatinine after transplant leading to higher creatinine levels despite no actual changes in eGFR. Our mixed-linear model suggested that the upper-extremity size score had a significant effect on creatinine levels with higher scores leading to a greater rise in creatinine. We were not able to assess this correlation in the 3 BWH upper-extremity recipients, because they all had the same upper-extremity size score. We did not have data on the weight of the allografts; however, according to de Leva,[16] the mass of a forearm is 3 times that of a hand (**Table S2, SDC,** http://links.lww.com/TXD/A99). Considering that increased muscle mass translates into increased total daily creatinine production, we can speculate that the mass of the allograft may directly contribute to the variance in renal function, although further studies are required to assess this factor in more detail.

We performed a combined mixed-linear model evaluating all the potential risk factors before transplantation that could affect renal function in the posttransplant follow-up period. Some of the covariates that significantly affected the eGFR postoperatively were age, pretransplant BMI, history of pretransplant hypertension, use of antihypertensive medications, and history of DM. Postoperatively, both the tacrolimus induction and maintenance doses burdened renal function. In the International Registry's cohort in particular, immunosuppressive agents correlated with impaired renal function. Calcineurin inhibitors, indispensible in post-VCA immunosuppression, were one of the major predictive factors of renal function deterioration. Due to potential multicollinearity, single significant covariates can lose significance in a multivariate analysis because of larger standard errors, which may explain lack of significance of single factors in our combined mixed linear model. As the majority of the patients in our cohorts had pretransplant eGFR within normal ranges (the majority had eGRF >60), the major factors associated with postoperative declines in renal function were tacrolimus doses and individual risk factors. Considering the normal renal function pretransplant of VCA recipients, the size of the effect of CNI on eGFR is striking.

The available literature is discrepant regarding the statistically significant risk factors correlated with the development of CKD in NRSOT. Many studies agree on age, female sex, hypertension, and hepatitis C as preoperative risk factors.[2,6,17,18] In contrast, others showed no correlation between hypertension, DM, hepatitis C seropositivity, and CKD.[10,19] Two studies suggested an association between increased BMI with CKD manifestations and specifically the development of secondary glomerulosclerosis.[19,20] It may very well be that increased patient weight contributes to renal damage through multiple pathways and should be kept in mind for transplant recipients both preoperatively and postoperatively. In any case, the small cohort reported here prevents any definitive conclusion and another limitation is the fact that pretransplant comorbidities, which could potentially contribute to changes in renal function posttransplant, were not uniformly reported in the IR cohort.

Calcineurin inhibitors have been traditionally correlated with acute kidney injury through vasoconstriction of the afferent arterioles and reduction of GFR, and this effect had been linked to a dose dependent reduction of GFR.[21] However, CNIs have also been described to have a causal relationship to CKD through arteriolar hyalinosis, tubular toxicity, and/or interstitial fibrosis.[22] However, not all kidney injuries can be solely attributed to CNI toxicity based on the literature of kidney transplantation, in which arterial hyalinosis was present in up to 65% of kidney recipients that had never received CNI.[23] Other kidney risk factors, such as diabetes, hypertension, and chronic inflammation, may also contribute to chronic kidney damage.[3,24]

Based on our findings, we should consider minimizing CNI exposure posttransplant. Few possibilities include complete withdrawal of CNI or reduction of CNI dose with addition of mammalian target of rapamycin inhibitor or belatacept.[25] The Nordic Everolimus (Certican) Trial in Heart and Lung Transplantation study by Arora et al[26] showed a significant improvement in renal function in both high and moderate renal impairments (20-29 and 30-59 mL/min per 1.73 m^2), within 1 year after conversion to everolimus and CNI reduction in thoracic transplant recipients. Gullestad et al[26,27] showed similar effects with everolimus in 282 heart and lung recipients; both studies indicated better results with earlier conversions. However, in upper-extremity transplantation, a recent study by Grahammer et al[28] suggested caution in the conversion of CNI to belatacept without continuation of CNI at low doses, as 1 of 4 patients converted to belatacept developed a severe rejection, requiring graft amputation. One of our BWH patients was started on belatacept and continued on low dose CNI to prevent rejection with good midterm success.[29] These preliminary findings suggest that complete CNI withdrawal is probably not a reasonable strategy in VCA based on the high rates of AR, which is up to 100% in most cohorts.[30] Calcineurin inhibitor dose reduction with additive immunosuppression with either mammalian target of rapamycin

TABLE 6.

Overview of potential renal risk factors in vascularized composite allotransplant recipients

Pretransplant	Peritransplant	Posttransplant
Identify patients with risk for CKD[a]	Minimize use of nephrotoxic agents	Minimize tacrolimus exposure
Treat existing renal conditions	Avoid hypovolemia	Treat hypertension
Avert hypo/hypertension	Limit ischemia time	Treat hyperglycemia
Limit nephrotoxic drugs		Treat dyslipidemia
Manage weight and hyperglycemia		Avoid IV contrast
Limit IV contrast		Limit potentially nephrotoxic drugs such as NSAIDS

[a] Diabetes, hypertension, heart disease, advanced age.

NSAIDS, nonsteroidal anti-inflammatory drugs.

inhibitor or belatacept are potential strategies to mitigate the risk of rejection.

Based on the recommendations of the Kidney Disease Outcomes Quality Initiative for CKD in the general population, Bloom et al[3] made specific recommendations for the protection of kidney function in NRSOT recipients. Among others, these recommendations comprise limiting nephrotoxic insults before transplantation as well as avoiding hypotension and optimization of renal perfusion. Posttransplant recommendations suggest aggressive treatment of hypertension, hyperglycemia, and dyslipidemia. Minimization of nephrotoxic agents, such as nonsteroidal anti-inflammatory drugs and avoidance of perioperative risk factors for kidney injury, should be attempted. Furthermore, we advocate limiting the use of IV contrast whenever possible (Table 6).

All conclusions in this study must be interpreted within the limited context of the study design. Documentation in the IR by the participating VCA centers is voluntary, and therefore, documentation is incomplete. We also could not verify the calibration assays for creatinine measurements on individual centers. Consistent reporting according to the registry's guidelines would empower the entire VCA research community by enriching the knowledge around complications posttransplant. No detailed data blood pressure, DM, or on urine proteinuria was available to help stratify patients according to CKD stages.

In sum, this study quantifies for the first time the highly prevalent kidney dysfunction after VCA, highlighting the importance of aggressively tracking and managing kidney risk factors to prevent long-term CKD in VCA recipients. Critical assessment of tacrolimus dosage/levels immediately after transplantation seems warranted. We encourage more VCA groups to monitor renal function and proteinuria closely early on, reduce CNI trough levels as soon as possible, advise patients about potentially nephrotoxic drugs and report on the postoperative course of their cohort to broaden our understanding of this important part of VCA patient care.

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