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The closure of arteriovenous fistula in kidney transplant recipients is associated with an acceleration of kidney function decline

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ORIGINAL ARTICLE

ABSTRACT

Background. The creation of arteriovenous fistula (AVF) may retard chronic kidney disease progression in the general population. Conversely, the impact of AVF closure on renal function in kidney transplant recipients (KTRs) remains unknown.

Methods. From 2007 to 2013, we retrospectively categorized 285 KTRs into three groups: no AVF (Group 0, $n = 90$), closed AVF (Group 1, $n = 114$) and left-open AVF (Group 2, $n = 81$). AVF closure occurred at 653 ± 441 days after kidney transplantation (KTx), with a thrombosis:ligation ratio of 19:95. Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease equation. Linear mixed models calculated the slope and intercept of eGFR decline versus time, starting at 3 months post-KTx, with a median follow-up of 1807 days (95% confidence interval 1665–2028).

Results. The eGFR slope was less in Group 1 (−0.081 mL/min/month) compared with Group 0 (−0.183 mL/min/month; $P = 0.03$) or Group 2 (−0.164 mL/min/month; $P = 0.09$). Still, the eGFR slope significantly deteriorated after (−0.159 mL/min/month) versus before (0.038 mL/min/month) AVF closure ($P = 0.03$). Study periods before versus after AVF closure were balanced to a mean of 13.5 and 12.5 months, respectively, with at least 10 observations per patient ($n = 99$).

Conclusions. In conclusion, a significant acceleration of eGFR decline is observed over the 12 months following the closure of a functioning AVF in KTRs.

Keywords: arteriovenous fistula, GFR, graft function, kidney transplantation, MDRD

INTRODUCTION

Arteriovenous fistula (AVF) is considered the best vascular access for chronic haemodialysis in patients with end-stage renal disease (ESRD) [1]. After kidney transplantation (KTx), the AVF remains functional in most patients. There is limited literature regarding management of a functioning AVF, i.e. surgical ligation versus watchful preservation, in kidney transplant recipients (KTRs) [2]. Vajdic *et al.* [3] retrospectively showed that the persistence of a functional AVF at 1 year post-KTx was associated with a lower estimated glomerular filtration rate (eGFR) and an increased risk for graft loss. Additionally, a cardioprotective impact of AVF closure has been reported in a few prospective studies including a limited number of patients [4–6]. In contrast, others concluded that AVF persistence for prolonged periods of time post-KTx had minor consequences on cardiac morphology and function [7–9]. Hence, on the basis of these controversial findings, AVF closure is not routinely recommended in KTRs with stable renal allograft function. Moreover, the creation of a new AVF in case of ESRD in KTRs may be extremely difficult and not always feasible when peripheral veins are exhausted. Surgical ligation is usually performed in patients with specific indications, including high-flow fistula, high-risk cardiovascular status or cosmetic reasons.

Very recently, the creation of an AVF has been suggested to retard chronic kidney disease (CKD) progression in the general

non-transplant population [10, 11]. These intriguing observations may be partly explained by the pathophysiological cascades of remote ischaemic preconditioning [12]. An AVF causes brief but repeated periods of local ischaemia, thereby inducing systemic protection against tissue underperfusion. An AVF also adds a low-resistance venous compartment to the central arterial system, which may attenuate arterial stiffness and arterial pressure [13].

In the present retrospective monocentric study including 285 KTRs, we investigate whether the closure of a functioning AVF significantly impacts the eGFR slope in KTRs.

MATERIALS AND METHODS

Patient population

All KTRs were retrospectively identified from 1 January 2007 to 31 December 2013 using the computerized prospective database of the University of Liège Hospital (ULg CHU) in Liège, Belgium. Patients with a follow-up post-KTx of <12 months were excluded. Medical files were systematically reviewed and patients were categorized into three groups: no AVF (Group 0), closed AVF (Group 1) and left-open AVF (Group 2). After 12 months post-KTx, the decision to close the AVF or not was at the discretion of the physicians in charge. This study was approved by the institutional ethics committee.

Statistics

Linear mixed models (Proc Mixed) were used to calculate the slope and intercept of the eGFR decline versus time. The eGFR was determined using the Modification of Diet in Renal Disease (MDRD) equation [14]. The MDRD equation is based on serum creatinine (SCr) with the following formula: $175 \times \text{SCr (mg/dL)}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if woman) $\times$ 1.21 (if African American) [14]. The MDRD equation is currently regarded as the most accurate estimation of GFR in KTRs [15]. We excluded eGFR values within the first 3 months post-KTx in order to avoid the usual fluctuations of renal function in the immediate post-KTx period. Separate regressions of MDRD eGFR on time (in months post-KTx) for each AVF subgroup (where AVF = 1 was further subdivided into 'before' and 'after' AVF closure) were fitted. For the latter, time was balanced before versus after AVF closure, with at least 10 observations per patient. Evidence that regressions differed among AVF subgroups was obtained by comparing eGFR slopes and intercepts. Analysis of variance (ANOVA) or χ^2 test was used, as appropriate, to compare the clinical characteristics of patients belonging to the three groups. All analyses were done with SAS 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

From 1 January 2007 to 31 December 2013, we listed 345 KTRs. Sixty patients were excluded because of inadequate follow-up. Thus, our cohort included 285 KTRs (Table 1) with a median follow-up of 1807 days (95% confidence interval 1665–2028). The mean age was 50.2 ± 14.3 years, with a female:male ratio of 118:167. The mean cold ischaemia time reached 700 ± 333 min, with a global rate of delayed graft function (DGF) of 18%. Expanded criteria donors (ECDs) were 22% of all KTxs.

The KTR cohort ($n = 285$) was further categorized into three groups based on their AVF status during post-KTx follow-up (Table 1). Group 0 included 90 patients with no AVF: 31 patients under peritoneal dialysis (PD) before KTx, 38 patients under catheter-mediated chronic haemodialysis (HD) and 21 patients with pre-emptive KTx (Supplementary data, Table S1). Group 1 included 114 patients in whom the AVF was closed after KTx. AVF closure occurred after a mean time of 653 ± 441 days post-KTx, with a thrombosis:ligation ratio of 19:95. Spontaneous AVF thrombosis occurred after a mean time of 733 ± 419 days post-KTx, whereas surgical ligation of a functioning AVF took place after a mean time of 638 ± 420 days post-KTx (P = 0.25). Finally, Group 2 included 81 patients in whom the physicians in charge decided not to close the operative AVF. ANOVA highlighted statistically significant differences between the groups concerning (i) age of the recipient and donor, (ii) body mass index (BMI) of the recipient, (iii) proportion of ECDs and (iv) rate of DGF (Table 1). Indeed, patients in whom the AVF was left open (Group 2) were significantly older and heavier, with a higher incidence of DGF, compared with patients in whom the AVF was closed (Group 1). Furthermore, at 3 months post-KTx, the mean eGFR in Group 2 was significantly lower than in Group 1. The eGFR slope was less in Group 1 (−0.081 mL/min/month) compared with Group 0 (−0.183 mL/min/month; P = 0.03) or Group 2 (−0.164 mL/min/month; P = 0.09) (Figure 1).

Focusing on Group 1, we first matched the time of exposure before versus after AVF closure in every single patient in order to elude the unavoidable long-term decline of eGFR in KTRs. Of methodological note, the period before AVF closure was longer than the period after AVF closure in most KTRs of the present cohort, which required censoring some of these data. We only considered patients with a least 10 available eGFR values. Hence, 99 KTRs were included, with study periods before and after AVF closure of 13.5 and 12.5 months, respectively (Figure 2). No difference was found between the corresponding intercepts (57.2 ± 1.5 mL/ versus 57.6 ± 1.5 mL/min/1.73 m^2; P = 0.85). In contrast, eGFR slopes were significantly different before (0.038 mL/min/month) versus after (−0.159 mL/min/month) AVF closure (P = 0.029).

DISCUSSION

Our present observations based on a retrospective monocentric cohort of 285 KTRs suggest that the decline of eGFR is significantly accelerated over the 12 months following the closure of a functioning AVF. Although the dilemma to keep or not to keep a functioning AVF in KTRs after a successful KTx is ongoing, very few studies have questioned the impact of AVF closure on hard clinical outcomes, e.g. blood pressure (BP) control, heart function or CKD progression [2]. In a prospective study

Table 1. Clinical characteristics

	Whole cohort	No AVF (Group 0)	Closed AVF (Group 1)	Left-open AVF (Group 2)	P-values	
					ANOVA or χ^2	(1) versus (2)
n	285	90	114	81		
Recipient						
Age (years)	50.2 ± 14.3	48.5 ± 16.0	48.8 ± 13.0	54.2 ± 13.7	0.01	0.01
Gender (F/M)	118/167	50/40	40/74	28/53	0.36	0.88
BMI at KTx (kg/m^2)	24.9 ± 4.7	24.4 ± 5.3	24.5 ± 4.8	25.9 ± 4.0	0.06	0.04
Donor						
Age (years)	44.3 ± 14.5	42.5 ± 14.6	42.5 ± 14.8	48.1 ± 14.0	0.01	0.01
Gender (F/M)	125/160	40/50	49/65	36/45	0.97	0.89
BMI (kg/m^2)	25.2 ± 6.9	24.6 ± 4.1	26.1 ± 12.9	25.0 ± 3.6	0.44	0.39
DBD/DCD/LD (%)	65/26/9	72/14/14	68/23/10	56/41/4	0.0004	0.01
ECD (%)	22	17	23	28	0.03	0.02
Transplant						
CIT (min)	700 ± 333	653 ± 332	705 ± 340	743 ± 325	0.22	0.43
DGF (%)	18	13	16	26	0.07	0.08
eGFR at 3 months post-KTx (mL/min, MDRD)	56 ± 21	62 ± 29	57 ± 17	48 ± 18	0.001	0.01
eGFR slope (mL/min/month, MDRD)	−0.143 ± 0.034	−0.183 ± 0.035	−0.081 ± 0.031	−0.164 ± 0.037	<0.05	0.09

Data are expressed as mean ± standard deviation. eGFR slopes are expressed as mean ± standard error.
BMI, body mass index; LD, living donor; DCD, donor after circulatory death; DBD, donor after brain death; ECD, expanded criteria donor; CIT, cold ischaemic time; DGF, delayed graft function; eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease (MDRD) formula; KTx, kidney transplantation.

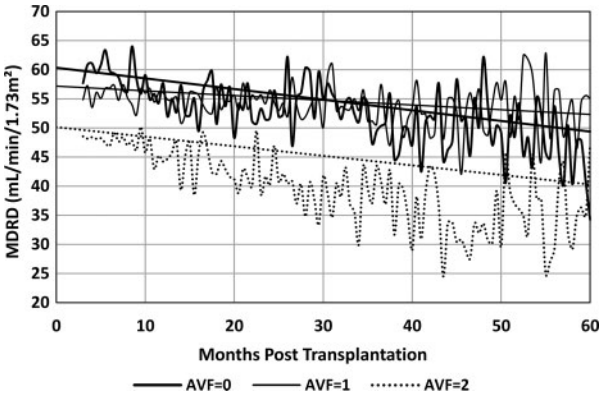

FIGURE 1: eGFR slopes of kidney transplant recipients based on the status of their arteriovenous fistula (AVF). Groups 0, 1 and 2 include kidney transplant recipients with no AVF ($n = 90$, black line), closed AVF ($n = 114$, grey line) and left-open AVF ($n = 81$, dotted line), respectively. The means of the MDRD eGFR per time point in each group were exported and plotted against months after kidney transplantation (KTx). The straight line corresponds to the linear mixed model: MDRD eGFR = Slope × Months post-KTx + Intercept.

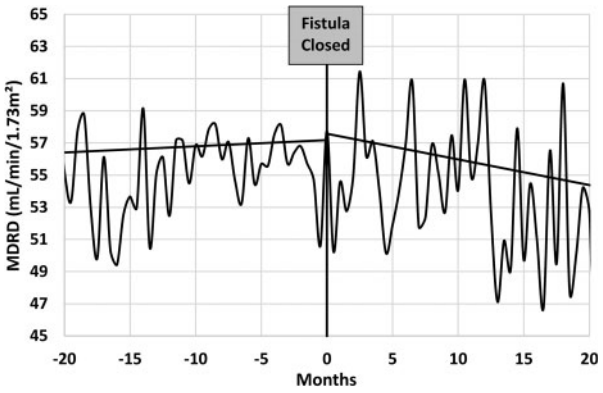

FIGURE 2: eGFR slopes of kidney transplant recipients before versus after closure of the arteriovenous fistula (AVF). The means of the MDRD eGFR per time point between −20 and +20 months with respect to the time of AVF closure were exported and plotted against time. The straight line that fits the data before AVF closure corresponds to the formula: MDRD eGFR = 57.18 + 0.03853 × Months, with Months varying from −20 to 0. The straight line that fits the data after AVF closure corresponds to the formula: MDRD eGFR = 57.57–0.1595 × Months, with Months varying from 0 to +20. The slopes are significantly different from each other (P = 0.0299).

including 16 KTRs, the mean 24-h diastolic BP significantly increased at 1 month after surgical AVF ligation, without systolic changes [5]. Such an increase in diastolic BP correlated with the reduction of left ventricle (LV) mass. Similarly, an improvement in LV hypertrophy after AVF ligation was reported in two prospective studies including 20 and 17 KTRs with stable allograft function [4, 6]. Conversely, the preservation of functional AVF has been independently associated with an increased aortic augmentation index [16]. Aortic augmentation and peripheral pulse waveforms were noninvasively assessed using pulse wave analysis. Therefore, on the basis of these observations, AVF closure has been advised in KTRs with a well-functioning allograft and persistent LV dilatation [6]. However, such a protective impact of AVF ligation on long-term cardiac function was not confirmed in other prospective and retrospective trials including 30 and 61 patients [9, 17]. Residual concentric LV remodelling, as well as increased diastolic BP, may indeed blunt the putative cardioprotection. In addition, AVF blood flow may vary among patients, which in turn may lead to dissimilar impacts on cardiac output and peripheral vascular resistance following AVF closure. Of note, the Vascular Access Society has defined a high-flow access as one with a flow (Qa) of 1–1.5 L/min or a Qa that is >20% of the cardiac output [18].

Concerning the impact on kidney function, a historical cohort of 311 KTRs showed that patients with a functional AVF

at 1-year post-KTx (69 ± 21 mL/min/1.73 m^2; $n = 239$) had significantly lower eGFR values than those with a spontaneously closed AVF (74 ± 19 mL/min/1.73 m^2; $n = 72$). Furthermore, adjusted analyses suggested that AVF persistence was associated with an increased risk of allograft loss [3]. Note that this retrospective cohort only considered patients with a functional AVF at the time of KTx and excluded 91 KTRs because of early graft loss, nonfunctioning kidneys, technical failures or deaths during the first year post-KTx. Kidney graft function was transversally compared at 1-year post-KTx, with no consideration for eGFR slopes. The main limitation of observational historical cohorts, including ours, concerns the retrospective design *per se*, which limits the complete identification of inequities between groups. Hence, our present data show major confounding by indication within the analyses. Indeed, KTRs with left-open AVFs (Group 2) are basically older and heavier than patients in whom the AVF was closed (Group 1). The incidence of DGF, as well as eGFR values at 3 months post-KTx and the long-term eGFR slope, were significantly worse in Group 2 than in Group 1. Figure 1 depicts the large inter-individual variability in eGFR slope. These retrospective observations most probably suggest that the physicians in charge biasedly decided not to close the AVF in patients at higher risk for CKD progression and ESRD. Similarly, statistical comparisons between Group 0 and Group 1 are difficult since Group 0 included a heterogeneous population of KTRs with a different medical history prior to KTx (Supplementary data, Table S1).

The mean long-term eGFR slope of our cohort reached −0.143 ± 0.034 mL/min/month. Still, a focus on the critical period of AVF management shows that the eGFR slope is rapidly and significantly impacted by AVF closure. Indeed, the mean eGFR slope before AVF closure is close to zero (0.038 ± 0.062 mL/min/month), whereas it reaches the level of those observed in Groups 0 and 2 following AVF ligation (−0.159 ± 0.066 mL/min/month). It should be noted that the periods of observations were appropriately matched before versus after AVF closure for every patient. Furthermore, each patient longitudinally acts as his/her own control since eGFR slopes are compared using a linear mixed model that takes into account repeated data from the same patients. Our observations suggest that the loss of a functioning AVF may be a factor short-term eGFR decline. Such a statement is based on eGFR, as we do not have access to measured GFR in our cohort, which may limit its interpretation. Indeed, Gera *et al.* [19] demonstrated that eGFR underestimates graft functional loss, especially in the early post-KTx period. The—unlikely—impact of changes in body composition (oedema-free weight and surface) on eGFR assessments before versus after AVF closure remains to be studied [20, 21].

From a pathophysiological point of view, an AVF creates a low-resistance, high-compliance compartment along the arterial system [12]. Lobo *et al.* [22] recently demonstrated in an open-label, multicentre, prospective, randomized controlled trial that implanting a central iliac arteriovenous coupler in patients with uncontrolled hypertension produced a marked reduction in the average 24-h ambulatory BP and significantly reduced hypertensive complications. Additionally, AVF-mediated venous return necessarily favours pulmonary flow, which may in turn recruit larger lung areas and increase arterial oxygen content [23]. One may thus advocate that an AVF favourably influences CKD progression by improving oxygen delivery to the kidney, thereby attenuating the vasoconstrictive renal chemoreflex [12, 24]. Recently, Golper *et al.* [10] retrospectively observed in a series of 123 CKD patients that the creation of an AVF was associated with a slowing of eGFR slope decline from 5.9 to 0.5 mL/min/year. These intriguing observations were confirmed in a nationwide cohort of 3026 CKD US veterans: a significant deceleration of eGFR decline was observed following AVF creation (from −5.6 to −4.1 mL/min/1.73 m^2/year) [11].

In conclusion, while the creation of a pre-dialysis AVF in the general population with advanced CKD may delay the onset of dialysis initiation, the ligation of a functioning AVF in KTRs with stable allograft kidney function may accelerate eGFR decline. Conversely, an improvement in LV hypertrophy after AVF ligation has been reported in two prospective studies, while the preservation of a functional AVF has been independently associated with an increased aortic augmentation index. Randomized clinical trials are urgently needed to assess the causal link between AVFs and the progression of chronic kidney and heart diseases. These would definitely help identify KTRs who will benefit from AVF preservation versus ligation.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

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