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Clinical Kidney Journal, 2021, vol. 14, no. 4, 1244–1254

doi: 10.1093/ckj/sfaa120
Advance Access Publication Date: 3 September 2020
Original Article

ORIGINAL ARTICLE

Less arterial stiffness in kidney transplant recipients than chronic kidney disease patients matched for renal function

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ABSTRACT

Background. Chronic kidney disease is associated with a high cardiovascular risk. Compared with glomerular filtration rate–matched CKD patients (CKDps), we previously reported a 2.7-fold greater risk of global mortality among kidney transplant recipients (KTRs). We then examined aortic stiffness [evaluated by carotid–femoral pulse wave velocity (CF-PWV)] and cardiovascular risk in KTRs compared with CKDps with comparable measured glomerular filtration rate (mGFR).

Methods. We analysed CF-PWV in two cohorts: TransplanTest (KTRs) and NephroTest (CKDps). Propensity scores were calculated including six variables: mGFR, age, sex, mean blood pressure (MBP), body mass index (BMI) and heart rate. After propensity score matching, we included 137 KTRs and 226 CKDps. Descriptive data were completed by logistic regression for CF-PWV values higher than the median (>10.6 m/s).

Results. At 12 months post-transplant, KTRs had significantly lower CF-PWV than CKDps (10.1 versus 11.0 m/s, P = 0.008) despite no difference at 3 months post-transplant (10.5 versus 11.0 m/s, P = 0.242). A lower occurrence of high arterial

Received: 17.4.2020; Editorial decision: 29.4.2020

stiffness was noted among KTRs compared with CKDps (38.0% versus 57.1%, $P < 0.001$). It was especially associated with lower mGFR, older age, higher BMI, higher MBP, diabetes and higher serum parathyroid hormone levels. After adjustment, the odds ratio for the risk of high arterial stiffness in KTRs was 0.40 (95% confidence interval 0.23–0.68, $P < 0.001$).

Conclusions. Aortic stiffness was significantly less marked in KTRs 1 year post-transplant than in CKDps matched for GFR and other variables. This observation is compatible with the view that the pathogenesis of post-transplant cardiovascular disease differs, at least in part, from that of CKD *per se*.

Keywords: cardiovascular risk, carotid-femoral pulse wave velocity (CF-PWV), chronic kidney disease, kidney transplantation

INTRODUCTION

Patients with chronic kidney disease (CKD) are at high risk of developing cardiovascular disease. Many studies reported an early, marked increase in arterial stiffness among CKD patients (CKDps), characterized by alterations in the viscoelastic properties of large arteries [1–4]. Carotid–femoral pulse wave velocity (CF-PWV) is the gold standard for the evaluation of aortic stiffness [5]. As a non-invasive and reproducible method, CF-PWV is considered as a marker of target organ damage in the guidelines of the European Society of Hypertension–European Society of Cardiology [6]. It has been shown to be an independent predictive factor for all-cause and cardiovascular mortality, coronary heart disease and fatal stroke in patients with diabetes [7], essential hypertension [8–10] and end-stage kidney disease (ESKD) [2, 11, 12] and kidney transplant recipients (KTRs) [13–16].

Kidney transplantation reduces the risk of lethal and non-lethal cardiovascular complications in selected patients relative to patients remaining on dialysis treatment [17–21]. The lower risk of mortality in KTRs than in chronic dialysis (ESKD) patients is partly due to the lower frequency of cardiovascular events [22]. However, even though kidney transplantation prolongs survival relative to chronic dialysis therapy, KTRs present a much higher mortality risk than healthy people. A European study reported a 14-fold higher risk of global mortality among KTRs than in an age-matched population with normal renal function during the first year post-transplantation and a 4-fold higher risk thereafter [23]. Recently we reported that beyond 1 year after transplantation, KTRs had a 2.7-fold greater risk of global mortality than non-transplant CKDps and a similar level of renal function. However, KTRs appeared to have more severe infections and there was no difference between the two groups in the incidence of cardiovascular events [24].

Data for a direct comparison of cardiovascular risk between KTRs and non-transplanted CKDp are lacking. We therefore decided to compare aortic stiffness and cardiovascular risk between KTRs and CKDps with similar renal function. To this end, we measured CF-PWV, a recognized intermediate endpoint, in KTRs and CKDps in a propensity score matching analysis including measured glomerular filtration rate (mGFR).

MATERIALS AND METHODS

Study design and participants

CKDps were recruited from two previously described observational cohort studies: the TransplanTest and the NephroTest [15, 25].

The TransplanTest cohort is a monocentric hospital-based cohort that included consecutive adult kidney graft recipients who attended the Division of Renal Physiology (Tenon Hospital, Paris, France) between June 2008 and January 2017 and were able and willing to be evaluated at 3 months and/or 1 year after transplantation. Eligible patients were 18–70 years of age and were recipients of a first living or cadaveric single kidney transplant. Non-inclusion criteria were cardiac arrhythmia, symptomatic lower limb arteriopathy and dual-kidney or combined organ transplantation. All participants signed a written informed consent and data collection was approved by the Commission nationale de l'informatique et des libertés according to French legislation (n°2065902v0). All kidney recipients received a standard immunosuppressive regimen including an induction therapy (methylprednisolone associated with basiliximab or anti-thymocyte globulin) followed by a triple therapy regimen with calcineurin inhibitors (CNIs) (mainly tacrolimus or ciclosporin), corticosteroids (tapered to 5 mg/day after 1 month) and mycophenolate mofetil. The primary study outcome of the cohort was the change in CF-PWV and its determinants after kidney transplantation.

The NephroTest study is a prospective hospital-based tricentric cohort (Physiology Departments of Tenon, Georges Pompidou and Bichat Hospitals, Paris, France) that enrolled 2084 consecutive adult CKDps of all stages from January 2000 to December 2012 [25]. Patients were referred by their nephrologists for an extensive workup in the Physiology Department, enrolling patients after a diagnosis of Stages 2–5 CKD. To be eligible, patients had to be >18 years old and neither on dialysis nor have received previously a kidney transplant. Pregnant women were excluded. All participants signed a written informed consent and a local ethics review board approved the study. The NephroTest study design was approved by an ethics committee (CCTIRS MG/CP09.503). The primary study outcomes of the cohort were measured showing a GFR decline, ESRD incidence and mortality. For the present study, we restricted the inclusion to patients evaluated for the first time at Tenon Hospital (609 patients), where CF-PWV was measured during the visit.

Data and measures

The NephroTest cohort CKDps were referred in a 1-day visit at the Renal Physiology Division of Tenon Hospital. The TransplanTest cohort patients (KTRs) were referred at 3 and 12 months after kidney transplantation for clinical and laboratory examinations to the same Renal Physiology Division. Data were retrospectively collected for KTRs and prospectively collected for CKDps. They included demographics, medical history, diagnosis of primary renal disease, body height and weight, resting blood pressure (BP) and medications. In the two cohorts and at each visit, mGFR was measured by chromium-51 ethylenediaminetetraacetic acid (^{51}Cr-EDTA) renal clearance, as reported previously [26]. In brief, 1.8–3.0 MBq of ^{51}Cr-EDTA (GE Healthcare, Velizy, France) were injected intravenously as a single bolus. The average renal ^{51}Cr-EDTA clearance was

determined over five to six consecutive 30-min clearance periods. Blood samples for creatinine measurements were obtained simultaneously. Serum creatinine was measured with an isotope dilution mass spectromtry–traceable enzymatic assay.

Biochemistry measurements were performed in the Physiology Department for both cohorts. Serum parathyroid hormone (PTH) was measured using second-generation two-site radio-immunometric assays [initially Allegro Intact PTH assay, then Allegro Calibrated Intact PTH Advantage assay (Nichols Institute Diagnostics, San Clemente, CA, USA) (normal range 10–58 pg/mL) and, since January 2004, Elecsys chemoluminescent assay from Roche (Indianapolis, IN, USA) (normal range 10–65 pg/mL)] that yielded quite similar results [27]. Plasma phosphate was measured by the colorimetric method (phosphomolybdate assay); blood ionized calcium, potassium and venous blood total carbon dioxideby specific electrodes (Beckman SX9; Beckman Coulter, Brea, CA, USA); plasma 25-hydroxyvitamin D [25(OH)D] by the radioimmunologic method (DiaSorin, Saluggia, Italy) recognizing both 25(OH)D_2 and 25(OH)D_3 with similar affinity (normal range 10–40 ng/mL) and plasma 1,25-dihydroxyvitamin D [1,25(OH)2D] by the radioimmunologic method (DiaSorin) (normal range 17–67 pg/mL).

BP and CF-PWV measurements

In the two cohorts, the same devices and methods were used to evaluate arterial stiffness. Patients were examined in a quiet, temperature-controlled room and measurements were performed by experienced operators. BP was measured after 15 min of rest in a supine position using a sphygmomanometer and a cuff of appropriate size. The average of five consecutive measurements was calculated. CF-PWV was measured along the descending thoraco-abdominal aorta with an automatic device (Complior, Artech Medical, Pantin, France). This method enables online pulse wave recording and automatic calculation of CF-PWV by dividing the distance between the carotid and femoral measurement sites by the transit time of the wave. Validation of this method and reproducibility have been previously reported, with intra- and interobserver repeatability coefficients of 0.94 and 0.89, respectively [28]. CF-PWV was defined as the mean of five determinations.

Study outcomes

The main study outcome was CF-PWV, the gold standard for large artery stiffness determinations. Aortic stiffness was compared between KTRs (at 3 months and 12 months post-transplant) and CKDps in a propensity score–matching analysis based on known determinants of CF-PWV, including age, sex, mean blood pressure (MBP), body mass index (BMI), heart rate and mGFR [28]. In addition, arterial stiffness determinants were sought by the evaluation of factors associated with the occurrence of high CF-PWV, defined as CF-PWV higher than the median.

Statistical analysis

We first created a study database by pooling the TransplanTest and NephroTest (Tenon Hospital) data. We then calculated propensity scores including the following variables: mGFR, age, sex, MBP, BMI and heart rate [28]. For KTRs, these variables were evaluated 12 months after transplantation.

The 168 KTRs were matched at a 2:1 ratio with the 609 CKDps and the closest propensity score. This provided propensity score-matched sets of 137 KTRs and 226 non-transplant CKDps (Figure 1). Propensity score matching was performed with a caliper, which enabled us to have no residual differences between the two groups for the variables used.

Patient characteristics were summarized as medians (interquartile ranges) or numbers (%) and the two groups were compared using Student's *t* test or Wilcoxon test for quantitative data and a chi-squared test or Mann–Whitney test for qualitative data, as appropriate.

Logistic regression models were used to estimate crude and adjusted odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for CF-PWV higher than the median. For multivariable analysis, we included in the models all clinically relevant vascular stiffness–associated factors selected based on literature and identified in univariate analysis ($P < 0.05$). Concerning covariates already used for propensity score matching, we included only those with standardized mean differences (SMDs) <0.10 [29]. Models were compared using log-likelihood statistics.

For sensitivity analyses, we repeated the matching, limited to only one mGFR matching, and repeated the analyses.

Missing data were managed by applying multivariate imputation with chained equations (MICE) before matching. The percentage of missing data among the patients before matching ($n = 777$) is given in Supplementary data, Table S1. We used the 'mice' package in R software (R Foundation, Vienna, Austria) [18] and the predictive mean matching method with five iterations. All statistical and graphic analyses were performed with R software and the R-Studio interface (version 3.3.2) [30].

RESULTS

Study population

Table 1 shows that there were no differences between the 137 KTRs and the 226 CKDps as regards mean mGFR and the majority of the other variables included in the propensity score.

Within the subgroup of KTRs, 'diabetes' included diabetic status prior to renal transplantation and not new-onset diabetes after transplantation. There were no differences between KTRs and CKDps as regards diabetes frequency (25.5% versus 32.3%, $P = 0.213$).

Regarding KTRs, 10.5% of them benefited from pre-emptive kidney transplantation. All the others were on dialysis an average of 3.7 years before kidney transplantation [median 2.8 years (IQR 1.6–4.7)].

There were no differences in hypertension frequency ($P = 0.547$), but treatments were different. KTRs more frequently received beta-adrenergic blockers (41.6% versus 22.6%, $P < 0.001$) or calcium channel blockers (59.9% versus 33.6%, $P < 0.001$), whereas angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were less frequently prescribed to KTRs (51.8% versus 79.2%, $P < 0.001$). Proteinuria (and albuminuria) was significantly lower among KTRs than CKDps. Prescription of diuretics was also less frequent among KTRs (13.1% versus 42.0%, $P < 0.001$).

As regards biochemistry parameters, there were several slight, although significant differences between groups. Blood ionized calcium concentration was higher among KTRs than CKDps, in association with higher serum PTH levels (57.0 versus 48.5 pg/mL, $P = 0.031$), despite significantly higher serum 1,25(OH)$_2$D levels and lower serum phosphate levels (0.98 versus 1.03 mmol/L, $P = 0.001$). Bone alkaline phosphatase serum levels (normal <25 and <22 μg/L for males and females, respectively)

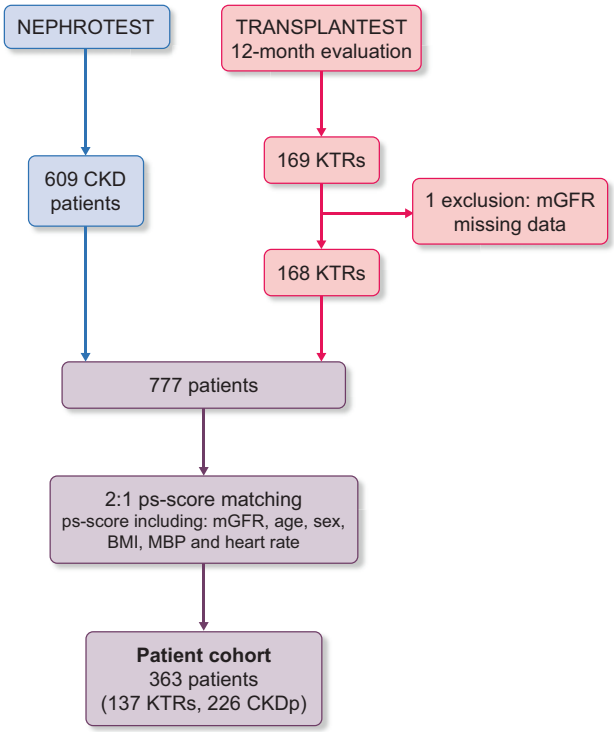

FIGURE 1: Flow chart.

were significantly higher among KTRs than CKDps (13.6 versus 11.6 μg/L, P = 0.031).

CF-PWV

Distribution and associated factors. KTRs had significantly lower median CF-PWV values than CKDps (10.1 versus 11.0 m/s, P = 0.008) at 12 months post-transplant, as shown in Figure 2 and Table 1. No such between-group difference was apparent at the 3-month time point post-transplant (Table 1). Figure 3 represents the CF-PWV distribution of CKDps compared with the distribution in KTRs at 12 months post-transplant. There was no association between CF-PWV and mGFR, even when analysing the two patient subgroups separately (Figure 4, $R^2 = -0.08$, P = 0.120 among all cohorts, $R^2 = -0.005$, P = 0.947 among KTRs and $R^2 = -0.10$, P = 0.125 among CKDps).

Interestingly, the KTR subgroup experienced a significant improvement in CF-PWV between Months 3 and 12 post-transplant (10.8 versus 10.6 m/s, P = 0.020).

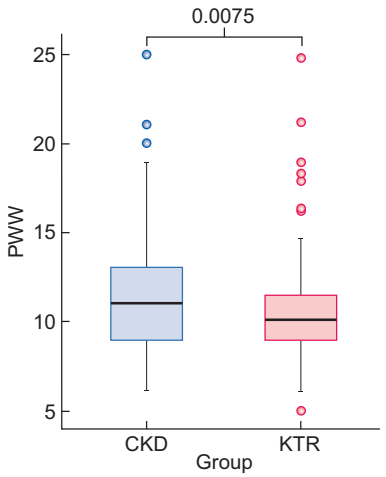

FIGURE 2: CF-PWV box plot in non-transplant CKDps and KTRs measured at 12 months post-transplant.

Arterial stiffness. When defining high arterial stiffness as CF-PWV values higher than the median CF-PWV value of the whole cohort (10.6 m/s), we found a significantly lower occurrence of arterial stiffness among KTRs as compared with CKDps [52 (38.0%) versus 129 (57.1%), P < 0.001].

Univariate logistic regression analysis (Table 2) showed that high aortic stiffness was associated with lower mGFR, older age, diabetic status (and diabetic nephropathy), current smoking and hypertension (and higher systolic BP, diastolic BP and MBP). All anti-hypertensive drug classes were significantly associated with greater arterial stiffness, with a greater number of anti-hypertensive medications.

Table 1. Characteristics of CKDp, quoted as the median (interquartile range) and the number (%)

Characteristics	Overall study population	Non-transplant CKDps	KTRs	P-value
N	363	226	137	
CF-PWV (KTRs, mo. 12)	10.59 (9.00–12.65)	11.00 (9.00–13.00)	10.09 (9.00–11.49)	0.008
CF-PWV (KTRs, mo. 3)	11.00 (9.00–13.00)	11.00 (9.00–13.00)	10.50 (9.23–12.14)	0.242
Quantitative data				
Age (years)	54.90 (44.10–63.15)	56.80 (42.60–65.12)	54.00 (45.00–61.00)	0.228
mGFR at inclusion (mL/min/1.73 m^2)	52.10 (36.60–66.18)	47.75 (33.82–68.80)	54.55 (44.37–64.24)	0.067
BMI (kg/m^2)	25.22 (22.22–29.11)	25.22 (21.88–29.31)	25.40 (22.72–28.68)	0.678
Systolic BP (mmHg)	130 (118–141)	130 (118–143)	130 (120–140)	0.936
Diastolic BP (mmHg)	73 (65–80)	72 (64–80)	73 (66–80)	0.541
MBP (mmHg)	92 (83–100)	90 (83–100)	93 (84–100)	0.682
Renal parameters				
Aetiology of kidney disease, *n* (%)				0.264
Diabetic	36 (9.9)	26 (11.5)	10 (7.3)	
Other	327 (90.1)	200 (88.5)	127 (92.7)	
Urinary protein:creatinine ratio (mg/mmol)	24 (11–69)	29 (14–79)	18 (9–53)	0.001
Urinary albumin:creatinine ratio (mg/mmol)	6 (2–32)	7 (2–37)	4 (2–19)	0.030
Conventional cardiovascular risk factors, *n* (%)				
Sex (male)	216 (59.5)	130 (57.5)	86 (62.8)	0.380
Diabetes	108 (29.8)	73 (32.3)	35 (25.5)	0.213
Hypertension	331 (91.2)	204 (90.3)	127 (92.7)	0.547
Current smoking	45 (12.4)	31 (13.7)	14 (10.2)	0.327
Medications, *n* (%)				
Diuretics	113 (31.1)	95 (42.0)	18 (13.1)	<0.001
Beta-adrenergic blockers	108 (29.8)	51 (22.6)	57 (41.6)	<0.001
Calcium channel blockers	158 (43.5)	76 (33.6)	82 (59.9)	<0.001
ACE inhibitors and/or ARBs	250 (68.9)	179 (79.2)	71 (51.8)	<0.001
Statins	138 (38.0)	87 (38.5)	51 (37.2)	0.897
Biochemical CKD-MBD parameters				
Serum calcium (mmol/L)	2.31 (2.23–2.41)	2.28 (2.20–2.36)	2.40 (2.29–2.48)	<0.001
Blood ionized serum calcium (mmol/L)	1.21 (1.17–1.25)	1.20 (1.17–1.23)	1.24 (1.20–1.27)	<0.001
Serum magnesium (mmol/L)	0.78 (0.71–0.85)	0.81 (0.75–0.87)	0.73 (0.65–0.79)	<0.001
Serum phosphate (mmol/L)	1.02 (0.20)	1.03 (0.92–1.19)	0.98 (0.85–1.09)	0.001
Serum PTH (pg/mL)	52.00 (34.00–90.00)	48.50 (29.00–91.50)	57.00 (39.00–89.00)	0.031
Serum 25(OH)D (ng/mL)	19.00 (13.00–27.50)	18.00 (12.00–28.00)	19.00 (14.00–26.30)	0.334
Serum $1,25(OH)_2D$ (pg/mL)	34.00 (24.00–49.00)	29.00 (20.25–41.00)	46.00 (33.00–63.00)	<0.001
Urinary calcium/creatinine (mM/mM)	0.06 (0.02–0.15)	0.04 (0.01–0.11)	0.10 (0.04–0.17)	<0.001
Serum bone alkaline phosphatase (μg/L)	12.10 (8.80–17.98)	11.60 (8.80–16.60)	13.60 (9.05–19.85)	0.031

Data include non-transplant CKDps from the NephroTest cohort and KTRs from the TransplanTest cohort. Values are presented as median (IQR) unless stated otherwise.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD-MBD, CKD-associated mineral and bone disorder; mo., months.

As to CKD-associated mineral and bone disorder biochemistry parameters, lower blood ionized calcium, PTH, 25(OH)D, 1,.25$(OH)_2$D and urinary calcium/creatinine levels were associated with a higher incidence of arterial stiffness in univariate analysis.

The KTR group had a lower risk of high arterial stiffness than the CKDp group [OR 0.46 (95% CI 0.30–0.71), $P < 0.001$]. This difference remained statistically significant after various adjustments (Table 3). In an analysis adjusted on mGFR, age, BMI, MBP, diabetes and serum PTH, the arterial stiffness risk OR for KTRs was 0.40 (95% CI 0.23–0.68, $P < 0.001$). Model 11 appeared to be the best statistical model.

Sensitivity analyses

Matching limited to mGFR alone. We found results similar to those obtained with propensity score analysis when matching by mGFR alone: KTRs had a 58% [OR 0.42 (95% CI 0.29–0.63), $P < 0.001$] reduced risk of having a CF-PWV greater than the median at 12 months post-transplant, as compared with the matched CKDps. This difference remained significant after various adjustments {for mGFR, age, BMI, MBP, diabetes and serum PTH [OR 0.58 (95% CI 0.36–0.94), $P = 0.029$], Model 6, Supplementary data, Table S4}.

DISCUSSION

Since CF-PWV is a well-recognized intermediate endpoint of cardiovascular events and cardiovascular mortality in the general population, as well as in CKDps [2, 11, 12], including KTRs [31], we hypothesized that there might be a difference in the degree of severity of CF-PWV between these two patient groups at comparable ages and GFRs. This was indeed the case. Relative to CKDps matched for age and mGFR, KTRs had a significantly lower CF-PWV and lower frequency of arterial stiffness at 1 year post-transplant. Interestingly, such a difference was not observed at 3 months post-transplant. This is compatible with a comparable cardiovascular status at baseline as regards CF-

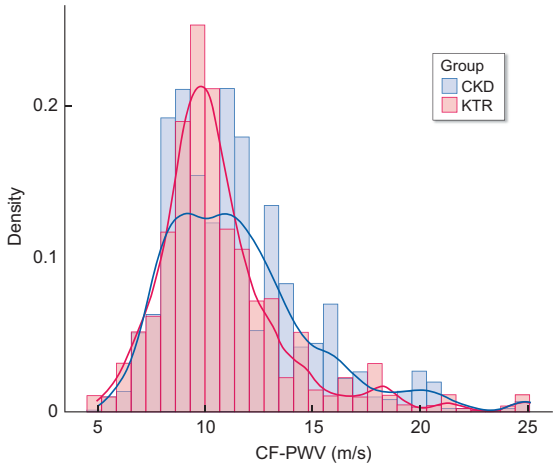

FIGURE 3: CF-PWV histogram plot in non-transplant CKDps and KTRs measured at 12 months post-transplant.

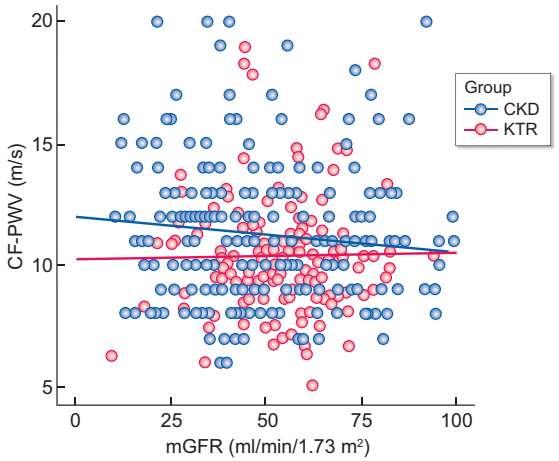

FIGURE 4: CF-PWV plot by mGFR according to renal transplantation (KTRs measured at 12 months post-transplant).

PWV and in favour of a slow improvement of CF-PWV post-transplant, which was the case between Months 3 and 12 post-transplant.

Compared with patients undergoing long-term dialysis therapy, KTRs present a lower global mortality risk [17–21], partly due to the lower frequency of cardiovascular events [22, 32]. In a recent personal study, KTRs had a higher global mortality risk than estimated glomerular filtration rate (eGFR)-matched CKDps [24], probably favoured by more severe infections, although there was no significant difference in the incidence of cardiovascular events, possibly due to a relatively small sample size [24].

Smulyan *et al.* [33] previously reviewed the impact of diabetes and hypertension on PWV in 329 patients. They found that in contrast to non-diabetic subjects, mean arterial pressure was not significantly associated with PWV among diabetic subjects. However, at comparable mean arterial pressures, arterial stiffness was significantly higher in diabetic than in non-diabetic patients (median 13.9 versus 11.5 m/s, respectively; $P < 0.0001$) and PWV was associated with diabetes duration and insulin resistance. It should be noted that diabetes duration was repeatedly found to be independently associated with aortic stiffness ($R^2 = 0.39$, $P < 0.0001$) after adjustment for age, heart rate, BP and metabolic syndrome [33–36].

Kidney transplantation was an independent determinant of arterial stiffness in the present study. An improvement of PWV was observed in KTRs, although most of them had experienced long-term dialysis and had a longer CKD history compared with CKDps. Therefore the latter would be predicted to have lower CF-PWV and lower cardiovascular risk than those on longer-lasting dialysis treatment. Better PWV values were observed in the KTR group despite the use of immunosuppressive drugs, such as calcineurin inhibitors (for almost all KTRs), which could theoretically interfere with beneficial post-transplant vascular effects [37]. This suggests the role of alternative mechanisms.

Several previous studies examined the impact of renal transplantation on vascular outcomes in KTRs. Delahousse *et al.* [38] reported in a prospective study on 74 KTRs from deceased donors a correlation between improved post-transplant aortic stiffness and donor age. In that study, CF-PWV (adjusted on MBP) decreased by 0.43 m/s (from 9.43 ± 1.48 to 9.00 ± 1.62 m/s)

Table 2. Univariate analysis with ORs for CF-PWV greater than the median among KTRs versus non-transplant CKDps

	Overall study population ($N = 363$)		KTRs ($n = 137$)		Non-transplant CKDps ($n = 226$)	
Characteristics	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
KTRs versus CKDp	0.46 (0.3–0.71)	<0.001				
Quantitative data						
Age (years)	1.1 (1.08–1.13)	<0.001	1.08 (1.04–1.12)	<0.001	1.11 (1.08–1.15)	<0.001
mGFR (mL/min/1.73 m^2)	0.99 (0.98–1)	0.023	0.98 (0.96–1)	0.061	0.99 (0.98–1.00)	0.134
BMI (kg/m^2)	1.09 (1.04–1.14)	<0.001	1.08 (1–1.18)	0.064	1.1 (1.04–1.16)	<0.001
Systolic BP (mmHg)	1.04 (1.02–1.05)	<0.001	1.01 (0.99–1.03)	0.312	1.06 (1.04–1.08)	<0.001
Diastolic BP (mmHg)	1.03 (1.01–1.05)	0.010	0.99 (0.96–1.02)	0.521	1.06 (1.03–1.09)	<0.001
MBP (mmHg)	1.04 (1.02–1.06)	<0.001	1.00 (0.97–1.03)	0.924	1.07 (1.05–1.1)	<0.001
Heart rate (bpm)	1.01 (1–1.03)	0.156	1.01 (0.98–1.03)	0.676	1.02 (1–1.05)	0.050
Extracellular fluid volume (L)	1.1 (1.04–1.17)	<0.001	1.1 (0.99–1.22)	0.071	1.13 (1.04–1.21)	0.002
Extracellular fluid volume (% body weight)	1.02 (0.98–1.07)	0.318	1.04 (0.96–1.12)	0.322	1.01 (0.95–1.08)	0.689
Diuresis	1.00 (0.99–1.01)	0.895	1.00 (0.99–1.01)	0.651	1 (0.99–1.01)	0.864
Renal parameters						
Aetiology of kidney disease (%)		<0.001		0.033		<0.001
Diabetes	7.32 (2.78–19.29)	<0.001	4.25 (1.05–17.25)	0.043	10.86 (2.5–47.17)	0.001
Other (reference)	–	–	–	–	–	–
Urinary protein:creatinine ratio (mg/mmol)	1.01 (0.99–1.00)	0.607	1.00 (0.99–1.01)	0.658	0.99 (0.99–1.00)	0.879
Urinary albumin:creatinine ratio (mg/mmol)	0.99 (0.99–1.00)	0.851	1.00 (0.99–1.01)	0.680	0.99 (0.99–1.00)	0.353
Conventional cardiovascular risk factors						
Sex (male)	1.11 (0.73–1.69)	0.623	0.81 (0.4–1.64)	0.550	1.43 (0.84–2.43)	0.193
Diabetes	4.65 (2.81–7.69)	<0.001	2.48 (1.13–5.44)	0.023	7.23 (3.53–14.81)	<0.001
Hypertension	6.13 (2.31–16.31)	<0.001	6.04 (0.74–49.13)	0.093	7.12 (2.32–21.81)	<0.001
Current smoking	0.46 (0.24–0.88)	0.020	0.24 (0.05–1.13)	0.072	0.49 (0.23–1.06)	0.070
Medications						
Diuretics	2.68 (1.69–4.26)	<0.001	2.29 (0.84–6.25)	0.105	2.27 (1.31–3.94)	0.004
Beta-adrenergic blockers	1.46 (0.93–2.3)	0.101	2.25 (1.11–4.56)	0.024	1.51 (0.79–2.88)	0.213
Calcium channel blockers	1.51 (1–2.3)	0.051	1.12 (0.55–2.27)	0.753	2.95 (1.62–5.4)	<0.001
ACE inhibitors and/or ARBs	2.24 (1.41–3.53)	<0.001	1.89 (0.93–3.81)	0.077	1.88 (0.98–3.6)	0.056
Anti-hypertensive medications		0.002		0.116		0.011
≤2 medications (reference)	–	–	–	–	–	–
>2 medications	1.94 (1.26–2.96)	0.002	1.76 (0.86–3.59)	0.120	2.02 (1.17–3.48)	0.011
CKD-MBD biochemistry parameters						
Serum total calcium (mmol/L)	0.38 (0.09–1.65)	0.197	0.96 (0.09–10.24)	0.975	0.95 (0.11–7.9)	0.961
Blood ionized calcium (mmol/L)	0.03 (0–0.62)	0.024	0.49 (0–58.11)	0.768	0.04 (0–3.03)	0.144
Serum magnesium (mmol/L)	1.46 (0.25–8.37)	0.673	0.27 (0.01–6.06)	0.408	0.56 (0.05–6.21)	0.636
Serum phosphate (mmol/L)	0.7 (0.25–1.96)	0.491	0.08 (0.01–0.66)	0.019	0.94 (0.26–3.41)	0.930
Serum PTH (pg/mL)	1.006 (1.00–1.01)	0.004	1.00 (0.99–1.01)	0.235	1.01 (1.00–1.02)	0.002
Serum 25(OH)D (ng/mL)	0.98 (0.97–1)	0.021	0.98 (0.95–1.01)	0.136	0.98 (0.97–1)	0.067
Serum 1,25$(OH)_2$D (pg/mL)	0.99 (0.98–1)	0.034	0.99 (0.97–1.01)	0.220	0.99 (0.98–1.02)	0.987
Urinary calcium/creatinine (mM/mM)	0.27 (0.08–0.94)	0.039	0.24 (0.04–1.61)	0.142	0.59 (0.11–3.27)	0.543
Serum bone alkaline phosphatase (μg/L)	1.00 (0.99–1.03)	0.426	1.02 (0.98–1.05)	0.324	1.01 (0.98–1.04)	0.420

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD-MBD: CKD-associated mineral and bone disorder.

between 3 and 12 months post-transplant in recipients of young donors (17–41 years) ($P = 0.028$), while it increased by 0.28 m/s (from 9.97 ± 1.70 to 10.25 ± 1.98 m/s) in recipients of older donors (53–70 years) ($P = 0.022$). In another study, Karras *et al.* [39] evaluated arterial stiffness by CF-PWV and vascular remodelling in 161 KTRs 3 and 12 months after transplantation. Three different groups were considered based on donor characteristics, namely recipients from living donors, recipients from standard criteria donors (SCDs) and recipients from extended criteria donors (ECDs). First, the maladaptive vascular remodelling observed in CKDps improved within 12 months post-transplant, independent of BP and renal function [39]. Second, mean PWV decreased from 10.8 m/s (95% CI 10.5–11.2) at Month 3 to 10.1 m/s (95% CI 9.8–10.5) at Month 12 ($P < 0.001$). The reduction of CF-PWV was more marked in patients with living donor allografts compared with those with deceased donor allografts ($P < 0.001$) after multivariable adjustment. Moreover, the change in CF-PWV differed significantly when comparing the SCD group [+0.1 m/s (95% CI −0.4–0.4)] to the extended criteria donor group [−0.7 m/s (95% CI −1 to −0.4), $P < 0.01$]. Thus improved PWV was independently associated with live organ donation and kidney graft characteristics. These findings suggest that graft quality, particularly renal donor characteristics, influence post-transplant vascular recovery [39]. In the present study, we did not focus on this specific issue.

It is well known that the high cardiovascular risk of CKDps results not only from traditional cardiovascular risk factors, but also from more CKD-specific factors such as abnormalities

Table 3. Multivariable models with ORs for CF-PWV greater than the median among KTRs at 1 year of follow-up versus non-transplant CKDps adjusted for other risk factors

Model	OR (95% CI)	P-value	LLH	LLH ratio test
Model 1: KTRs versus non-transplant CKDp	0.46 (0.3–0.71)	<0.001	−245	
Multivariate analysis				
Model 2: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg)	0.42 (0.25–0.71)	<0.001	−177	• Model 1 versus Model 2 • P < 0.001
Model 3: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes	0.43 (0.25–0.72)	0.001	−175	• Model 3 versus Model 2 • P = 0.025
Model 4: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Etiology of kidney disease	0.43 (0.25–0.73)	0.002	−173	• Model 4 versus Model 3 • P = 0.085
Model 5: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Current smoking	0.42 (0.25–0.72)	0.001	−175	• Model 5 versus Model 3 • P = 0.381
Model 6: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • ACE inhibitors and/or ARBs	0.47 (0.27–0.81)	0.006	−174	• Model 6 versus Model 3 • P = 0.143
Model 7: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Diuretics	0.45 (0.26–0.78)	0.004	−175	• Model 7 versus Model 3 • P = 0.492
Model 8: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Calcium channel blockers	0.41 (0.24–0.71)	0.001	−175	• Model 8 versus Model 3 • P = 0.608
Model 9: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Anti-hypertensive medications	0.42 (0.25–0.72)	0.001	−175	• Model 9 versus Model 3 • P = 0.515
Model 10: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes	0.48 (0.28–0.83)	0.008	−174	• Model 10 versus Model 3 • P = 0.180

(continued)

Table 3. Continued

Model	OR (95% CI)	P-value	LLH	LLH ratio test
• Blood ionized calcium (mmol/L)				
Model 11: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Serum PTH (pg/mL)	0.4 (0.23–0.68)	<0.001	−172	• Model 11 versus Model 3 • P = 0.018
Model 12: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Serum PTH (pg/mL) • Serum 25(OH)D (ng/mL)	0.4 (0.23–0.68)	<0.001	−171	• Model 12 versus Model 11 • P = 0.126
Model 13: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Serum PTH (pg/mL) • Serum 1,25$(OH)_2$D (pg/mL)	0.4 (0.22–0.71)	0.001	−172	• Model 13 versus Model 11 • P = 0.952
Model 14: KTRs versus non-transplant CKDps • mGFR (mL/min/1.73 m^2) • Age (years) • BMI (kg/m^2) • MBP (mmHg) • Diabetes • Serum PTH (pg/mL) • Urinary calcium/creatinine (mM/mM)	0.42 (0.24–0.72)	0.001	−172	• Model 14 versus Model 11 • P = 0.365

Data are presented as OR (95% CI) for KTRs versus non-transplant CKDps.
LLH, likelihood.

linked to the CKD-associated mineral and bone disorder [31, 40, 41]. In this study, serum PTH remained independently associated with the occurrence of high arterial stiffness. Even after a more or less successful correction of many CKD-related factors by renal transplantation, other non-traditional risk factors may favour cardiovascular morbidity and mortality, such as the effects of immunosuppressive drugs, antibiotics, the transplantation procedure itself and the persistent formation and retention of uraemic toxins [42, 43]. A variety of studies have linked cardiovascular morbidity to increased concentrations of uraemic solutes [44–48]. Barreto *et al.* [49] demonstrated positive associations of indoxyl-sulfate serum levels with vascular calcification, cardiovascular mortality and global mortality in a cohort of patients at different stages of CKD. The impact of an effective lowering of uraemic toxins post-transplant could explain the lower CF-PWV observed among KTRs compared with matched CKDps. Liabeuf *et al.* [43, 50] showed that serum-free and total indoxyl sulfate levels, measured at 12 months post-transplant, were significantly lower in KTRs than in CKDps matched for age, sex and eGFR, suggesting that kidney transplantation can be protective against the increase in indoxyl sulfate levels for a given degree of CKD. Other studies confirmed the normalization of this as well as other protein-bound uraemic toxins after kidney transplantation. Moreover, in contrast to observations in dialysis and pre-dialysis patients, indoxyl sulfate levels were not associated with cardiovascular disease, CKD progression and mortality among KTRs [49]. Determinations of uraemic toxin levels were not available among the two patient cohorts of the present study, preventing any conclusion regarding this issue.

Our study has several strengths. Based on two large cohorts of CKDps and KTRs, who were evaluated in a similar way, it combined two gold standard methods: aortic stiffness assessment by CF-PWV and mGFR measurement by ^{51}Cr-EDTA urinary clearance. Another strength of the study was the propensity score–based matching of KTRs with CKDps, including mGFR and BP, allowing us to better analyse the impact of renal transplantation *per se*, independent of CKD status. Limitations of the present study include a relatively limited sample size. However, if we estimated a difference between KTRs and CKDps of 0.2%, with a rate of CF-PWV higher than the median for KTRs at 40% and that of CKDpa at 60%, we would find that a study with 130 evaluable patients per group would have 90% power, with a one-sided type I error of 0.025. It appears that we had enough patients in the two groups to highlight such a difference. Limitations also include different time windows for the two cohorts (2000–12 and 2008–17) and also a lack of data on CF-PWV at baseline for KTRs and uraemic toxin concentrations.

CONCLUSION

KTRs had significantly lower CF-PWV 1 year after transplantation than mGFR-matched non-transplant CKDps of the same age and other comparable clinical characteristics, pointing to an improvement in arterial stiffness after kidney transplantation. The reason for this improvement remains unknown. Whether differences in the generation or elimination of uraemic toxins play a role remains to be seen. Our results are compatible with the hypothesis that the cardiovascular disease of KTRs may be partially due to different causes than that of non-transplant patients with a comparable degree of CKD.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

The NephroTest study group: Bichat University Hospital (Paris): Francois Vrtovsnik, Eric Daugas (Nephrology) and Martin Flamant and Emmanuelle Vidal-Petiot (Physiology); European Georges Pompidou University Hospital (Paris): Christian Jacquot, Alexandre Karras, Eric Thervet, Christian d'Auzac (Nephrology) and P. Houillier, M. Courbebaisse, D. Eladari and G. Maruani (Physiology); Tenon University Hospital (Paris): Jean-Jacques Boffa, Pierre Ronco, H. Fessi and Eric Rondeau (Nephrology) and Emmanuel Letavernier, Nahid Tabibzadeh, Marine Livrozet, Camille Saint-Jacques and Jean Philippe Haymann (Physiology); and INSERM (Villejuif): M. Metzger and B. Stengel. We thank nurses Martine Dapiedade, Catherine Fremy and Nathalie Dieu for their expert technical assistance.

CONFLICT OF INTEREST STATEMENT

Z.A.M. has received grants for the Chronic Kidney Disease–Renal Epidemiology and Information Network and other research projects from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp & Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka and the French government, as well as fees and grants to charities from Amgen, Astellas, Daichii and Sanofi-Genzyme. T.B.D. has received personal fees from Akebia, Amgen, Astellas, Chugai, F. Hoffman-La Roche, Fresenius Medical Care, GlaxoSmithKline, Kyowa Hakko Kirin and Vifor. L.C., J.P.H., S.L., N.T., E.L., J.-J.B., M.E. and M.D. have no competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this article. The results presented in this article have not been published previously in whole or part.

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