Allograft function and muscle mass evolution after kidney transplantation

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Abstract

Background  Advanced chronic kidney disease is associated with muscle wasting, but how glomerular filtration rate (GFR) recovery after kidney transplantation is associated with muscle mass is unknown.

Methods  We took advantage of the simultaneous measurement of GFR (using iohexol plasma clearance; ioGFR) and creatinine excretion rate (a surrogate marker of muscle mass; CER) performed 3 months after transplantation and at a later time point at our institution to investigate the interplay between allograft function, muscle mass, and outcome in kidney transplant recipients.

Results  Between June 2005 and October 2019, 1319 successive kidney transplant recipients (mean age 50.4 ± 14.6; 38.7% female) underwent GFR measurement at our institution 3 months after kidney transplantation. CER (CER₃) and ioGFR (ioGFR₃) were 7.7 ± 2.6 μmol/min and 53 ± 17.1 mL/min/1.73 m², respectively. Multivariable analysis identified female gender, older donor and recipient age, reduced body mass index, coronary disease, dialysis history, proteinuria, and reduced ioGFR₃ as independent predictors of low CER₃ (ioGFR₃: β coefficient 0.19 [95% confidence interval 0.14 to 0.24]). A total of 1165 patients had a subsequent CER measurement after a median follow-up of 9.5 months. Of them, 373 (32%) experienced an increase in CER > 10%, while 222 (19%) showed a CER decrease of more than 10%. Multivariable analysis adjusted for CER₃ and other confounders identified ioGFR₃ as an independent predictor of low CER₃ at follow-up (β coefficient 0.11 [95% confidence interval 0.07 to 0.16]). In multivariable Cox analysis, reduced CER at 3 months or at follow-up were consistently associated with mortality (hazard ratio [95% confidence interval] at 3 months: 0.82 [0.74 to 0.91]; at follow-up: 0.79 [0.69 to 0.99]) but not with graft loss.

Conclusions  Glomerular filtration rate recovery is a determinant of muscle mass variation after kidney transplantation. Early interventions targeting muscle mass gain may be beneficial for kidney transplant recipients.

Keywords  Kidney transplantation; Sarcopenia; Lean body mass; Creatinine; Measured glomerular filtration rate; Outcome

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**Introduction**

Kidney transplantation is the preferred treatment for end-stage kidney disease. While it offers an overall better quality of life and a longer life expectancy than dialysis, mortality remains a significant concern. Indeed, in western countries, up to 15% of the patients receiving a first renal allograft in the 21st century die within the first 5 years after transplantation. The notable progresses made in the management of immunosuppressive regimen and overall patients’ care have been partially mitigated by the shift towards proposing kidney transplantation to older and sicker patients. Identifying modifiable risk factors for death after kidney transplantation thus represents an important challenge.

Skeletal muscle accounts grossly for a third of the body mass. Beyond its role in locomotion, skeletal muscle also plays an essential role at the crossroad of proteostasis, energetic, and glucose metabolism. Multiple methods have been set up to quantitatively estimate skeletal muscle mass such as anthropometry, imaging techniques, assessment of whole body potassium or nitrogen, estimation of lean tissue mass using bio-impedance spectrometry, or measurement of creatinine excretion rate (CER). These approaches pinpointed low muscle mass as a risk factor for death in various conditions including cancer, cardiovascular disease, critical illness, or cirrhosis.

Chronic kidney disease (CKD) affects muscle health. Patients with end-stage kidney disease on maintenance dialysis are at high risk of muscle wasting. Concordant evidence indicates that even in CKD patients, who have not reached end-stage kidney disease, reduced glomerular filtration rate (GFR) is associated with a reduction in muscle mass, which represents an independent risk factor for mortality. Noteworthy, independent studies performed in non-CKD populations reported a significant inverse correlation between estimated glomerular filtration rate (eGFR) and parameters related to muscle mass.

Kidney transplantation drastically improves GFR, and GFR recovery is associated with a rapid improvement of multiple parameters affected by advanced CKD including cardiac, vascular, bone, parathyroid, and cognitive functions. In contrast, the impact of GFR recovery on muscle mass and its implication in terms of outcome has not been assessed.

Sarcopenia contributes to frailty phenotype, defined as an increased vulnerability to stressors with a decline in reserve and function of multiple physiologic systems. Frailty at transplantation is a predictor of adverse transplantation outcome. Limited evidence suggests that frailty improves in the majority of patient 3 months after transplantation, but our understanding of the element contributing to this amelioration is limited. In particular, the role of kidney function recovery has not been explored.

To date, only a single cross-sectional study investigated the factors associated with 24 h urinary creatinine excretion after kidney transplantation and its association with outcome. This study identified low creatinine excretion as an independent risk factor for both mortality and graft loss in stable kidney transplant recipients but did not find eGFR to be a predictor of CER, suggesting that GFR recovery does not impact muscle mass after kidney transplantation. Yet, 24 h urinary creatinine excretion has limitations, the most important being imprecisions in urinary collection. More importantly, unmeasured muscle mass affects eGFR accuracy and this point may obscure the relationship between kidney function and muscle mass.

Based on these considerations, we aimed to investigate the impact of GFR recovery on muscle mass in the first year following transplantation and its link with outcome. We studied a French monocentric cohort of kidney transplant recipients with simultaneous plasma iohexol clearance (ioGFR; a) and CER (as a surrogate of muscle mass) measurement, using rigorous timed collection, 3 months after transplantation. We combined distinct analyses. In a first approach, we performed a cross-sectional study to determine the factors associated with CER 3 months after kidney transplantation. Then, taking advantage of a subsequent measurement of CER and ioGFR that was performed in the majority of patients, we determined the baseline parameters predicting CER evolution at follow-up. Finally, we analysed the association between CER and transplantation outcomes.

**Material and methods**

**Study population**

All patients were adults transplanted and followed in the department of renal transplantation at Necker Hospital, Paris, France. According to our standard follow-up protocol, patients with a stable allograft function undergo GFR measurement 3 months, 1 year, and then every other year after transplantation. According to French law, anonymous retrospective data do not require the authorization from an institutional review board.

**Data collection**

The prospective database Données Informatiques Validées en Transplantation (DIVAT clinical prospective cohort, official website: www.divat.fr; registration number: 1016618) was used to collect data at specific points for each patient (3 months and at follow-up). The data include information concerning the donor (age, sex, deceased or living donor, and cold ischaemia time), the recipient (age, sex, and primary
cause of CKD), the transplantation procedure, the immuno-suppression regimen, the occurrence of delayed graft function (defined as the need for haemodialysis during the first week after transplantation), and the occurrence of death or graft loss as defined by re-transplantation or a return to long-term dialysis. Death or allograft loss was reported to the research assistant implementing the DIVAT database. Acute kidney rejection history was defined as an acute rejection requiring treatment occurring before GFR measurement. We prospectively collected height, body weight, blood pressure, and standard biochemical parameters at the time of GFR measurement.

Bio-impedance spectrometry

Since December 2019, body composition assessment with the Body Composition Monitor (BCM; Fresenius Medical Care) has been implemented to the protocoled follow-up of kidney transplant recipients at our institution. We compared lean body mass values obtained through this mean and urinary creatinine flow rate in the successive 69 kidney transplant recipients that were investigated from December 2019 to March 2020.

Glomerular filtration rate determination from iohexol plasma disappearance curves

Measured GFR was calculated from the plasma disappearance curve of iohexol with hourly plasma samples from 2 to 5 hours after iohexol injection using Jens Bröchner-Mortensen’s quadratic correction as previously described.27

Laboratory assays

Urinary and plasma creatinine measurement is routinely and stably performed with an IDMS traceable enzymatic assay (Multigent; Abbott) since February 2011. From 2005 to 2011, urinary and plasma creatinine was measured with a colorimetric assay. Contrary to plasma creatinine, previous studies have demonstrated an excellent agreement between colorimetric and enzymatic assays for the measurement of urinary creatinine in adult patients presumably because of the lack of interfering chromogens in urine.28 CER was determined as the mean of the values obtained on successive urine samples collected every hour for 5 h. Total calcium, phosphate, urea, standard plasma, and urine ion and protein concentration were measured by standard biochemical methods. Ionized calcium was measured on an ABL800 analyser (Radiometer). C-terminal fibroblast growth factor 23 (FGF23) plasma concentration was measured by ELISA (Immutopics). Serum parathyroid hormone concentration was measured with an immunochemiluminescent assay performed on the Elecsys analyser (RocheDiagnostics). Calcitriol and 25-hydroxy vitamin D (25-OH-vitD) concentrations were measured with radioimmunoassays (DiaSorin). Osteocalcin and beta-cross-laps were measured with Cobas® immunoassays (Roche). The assays were carried out in a single laboratory throughout the study.

Assessment of plasma creatinine stability

Plasma creatinine stability was evaluated by calculating the slope of the linear regression of plasma creatinine and time using the five-hourly measurement of plasma creatinine performed during GFR measurement.

Statistical analyses

Data were analysed using R Version 4.0.0 [R Core Team (2020). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/]. Data are expressed as mean ± SD for normally distributed continuous variables and as median (25th–75th percentiles) for continuous variables with a skewed distribution. Qualitative variables are reported as absolute number and percentage.

We calculated the correlation between mean urinary CER and lean tissue mass.

We analysed the association between mean CER and survival. Survival was compared between tertiles of CER with the log-rank test. We calculated the hazard ratio for death using CER as a continuous variable in a univariate Cox model. We designed multivariate Cox proportional hazards models for death. We included a maximum of 15 prespecified explanatory covariates in Cox models, which were selected on the basis of their reported association with outcome in other studies: ioGFR, gender, smoking, coronary artery disease, pre-emptive transplantation, donor age, donor type, diabetes, recipient age, systolic blood pressure at 3 months, height, and body mass index at 3 months. Missing data were omitted from the Cox models. The proportionality was tested for each covariate based on weighted residuals. All clinical and biologic parameters included in the multivariable models were measured/assessed at the inclusion of the patients in the study (i.e. at GFR measurement 3 months after kidney transplantation).

For allograft loss, death was considered as a competing risk, accounted for in the Fine and Gray models. The Fine and Gray models were adjusted on the same covariates as the Cox model for mortality.
Results

Patients

The cohort consisted of 1319 patients transplanted at Necker Hospital between June 2005 and October 2019, who were addressed for GFR measurement 3 months after the transplantation. The flow chart of patients included in the study is presented in Figure 1. The characteristics of the 130 excluded patients are presented in Supporting Information, Table S1. All included patients had simultaneous measurement of ioGFR and CER 3 months after kidney transplantation (ioGFR₃ and CER₃). The CER obtained through this approach showed a marked correlation with lean tissue mass measured by bio-impedance spectrometry that was performed in a subgroup of 69 patients (r = 0.81; P < 0.001). In comparison, 24 h urinary creatinine excretion showed a lower correlation with lean tissue mass (r = 0.60, P < 0.001). By simple linear regression, CER explained 65% of lean tissue mass variance, while 24 h urinary creatinine excretion explained 35% (Table S2 and Figure S1).

Characteristics of the 1319 patients by tertile groups of CER₃ are summarized in Table 1. The lowest tertile group of CER (Q1) consisted of older patients with a lower proportion of male recipients. Beyond all the differences attributable to gender and anthropometric characteristics, patients in the lowest tertile had a higher proteinuria and lower GFR and suffered more frequently from diabetes.

Association of measured and estimated glomerular filtration rate with creatinine excretion rate 3 months after transplantation

As we observed a significant correlation between ioGFR₃ and CER₃, we analysed if usual creatinine-based eGFR equations could also capture this association. We focused on the 807 patients with available IDMS-traceable enzymatic plasma creatinine measurement. In this subpopulation, CER₃ was significantly associated with ioGFR (slope: 0.032 [95% confidence interval (CI) 0.023 to 0.041], P < 0.001; Figure 2). In contrast, CER₃ showed no association with eGFR estimated by creatinine-based Modification of Diet in Renal Disease (MDRD; slope: −0.0010 [95% CI −0.010 to 0.008], P = 0.82) or Chronic Kidney Disease-Epidemiology (CKD-EPI; slope: 0.0024 [95% CI −0.006 to 0.011], P = 0.56) equation (Figure 2).

![Figure 1](image-url) Flow chart of included patients in the study. GFR, glomerular filtration rate.
Table 1 Characteristics of the cohort according to creatinine excretion rate 3 months after transplantation (CER<sub>3</sub>)

| Variable                        | Q1 (N = 440) | Q2 (N = 440) | Q3 (N = 439) | Total (N = 1319) | P-value |
|---------------------------------|--------------|--------------|--------------|------------------|---------|
| CER (μmol/min)                  | Mean (SD)    | 5.3 (1)      | 7.7 (0.6)    | 10.7 (2)         | 7.9 (2.6) | <0.001 |
| Recipient age (years)           | Mean (SD)    | 54.9 (14.6)  | 51.8 (14.2)  | 44.5 (13)        | 50.4 (14.6) | <0.001 |
| Gender (female)                 | N (%)        | 322 (73.2)   | 157 (35.7)   | 31 (7.1)         | 510 (38.7) | <0.001 |
| Initial nephropathy             | N (%)        |              |              |                  | 0.032    |
| Glomerulopathy                  |              | 98 (22.3)    | 93 (21.1)    | 135 (30.8)       | 326 (24.7) |
| Genetic cystic                  |              | 84 (19.1)    | 75 (17.7)    | 61 (13.9)        | 223 (16.9) |
| Unknown                         |              | 82 (18.6)    | 94 (21.4)    | 102 (23.2)       | 278 (21.1) |
| Genetic non-cystic              |              | 11 (2.5)     | 18 (4.1)     | 15 (3.4)         | 44 (3.3)  |
| Uropathy                        |              | 29 (6.6)     | 29 (6.6)     | 32 (7.3)         | 90 (6.8)  |
| Other                           |              | 40 (9.1)     | 43 (9.8)     | 29 (6.6)         | 112 (8.5) |
| Vascular                        |              | 30 (6.8)     | 29 (6.6)     | 25 (5.7)         | 84 (6.4)  |
| Diabetic                        |              | 45 (10.2)    | 39 (8.9)     | 27 (6.2)         | 111 (8.4) |
| Tox                             |              | 12 (2.7)     | 6 (1.4)      | 4 (0.9)          | 22 (1.7)  |
| Congenital                      |              | 9 (2.0)      | 11 (2.5)     | 9 (2.1)          | 29 (2.2)  |
| First transplantation           | N (%)        | 354 (80.5)   | 372 (84.7)   | 380 (86.8)       | 1106 (84.0) | 0.034 |
| Pre-emptive transplantation     | N (%)        | 57 (13.0)    | 63 (14.3)    | 73 (16.6)        | 193 (14.6) | 0.297 |
| Active smoking                  | N (%)        | 55 (12.5)    | 57 (13.0)    | 67 (15.3)        | 179 (13.6) | 0.439 |
| Diabetes                        | N (%)        | 85 (19.3)    | 66 (15.0)    | 56 (12.8)        | 207 (15.7) | 0.024 |
| Coronary disease                | N (%)        | 55 (12.5)    | 70 (15.9)    | 36 (8.2)         | 161 (12.2) | 0.002 |
| Living donor                    | N (%)        | 87 (19.8)    | 106 (24.1)   | 156 (35.5)       | 349 (26.5) | <0.001 |
| Donor age (years)               | Mean (SD)    | 56.3 (18)    | 54.2 (16.7)  | 50.2 (15.2)      | 53.6 (16.9) | <0.001 |
| Cold ischaemia duration (min)   | Median [Q1–Q3]| 1001.5 [506–1410]| 932.5 [238–1384]| 885 [131–1290]| 955 [180–1380] | 0.009 |
| Delayed graft function          | N (%)        | 142 (32.3)   | 136 (30.9)   | 133 (30.3)       | 411 (31.2) | 0.811 |
| History of treated acute rejection | N (%)  | 38 (8.6)     | 56 (12.7)    | 76 (17.3)        | 170 (12.9) | <0.001 |
| Systolic BP (mmHg)              | Mean (SD)    | 132.6 (16.5) | 132.5 (15.9) | 133.9 (14.4)     | 133 (15.6) | 0.346 |
| Missing                         | 6            | 7            | 7            | 4                | 17       |
| Diastolic BP (mmHg)             | Mean (SD)    | 73.8 (10.2)  | 75.5 (9.6)   | 79 (10.1)        | 76.1 (10.2) | <0.001 |
| Missing                         | 7            | 7            | 7            | 4                | 18       |
| Height (cm)                     | Mean (SD)    | 162 (8.8)    | 169.6 (7.4)  | 175.6 (7)        | 169.1 (9.6) | <0.001 |
| Weight (kg)                     | Mean (SD)    | 61.5 (13.2)  | 70.3 (12.5)  | 78 (13.1)        | 69.9 (14.6) | <0.001 |
| BMI (kg/m<sup>2</sup>)          | Mean (SD)    | 23.4 (4.8)   | 24.4 (4.1)   | 25.3 (4)         | 24.4 (4.4) | <0.001 |
| mGFR (ml/min/1.73 m<sup>2</sup>)| Mean (SD)    | 53 (17.1)    | 54.5 (15)    | 59.1 (13.9)      | 55.6 (15.6) | <0.001 |
| Creatinine (μmol/L)             | Mean (SD)    | 114.7 (47)   | 130.5 (43.9) | 137.6 (39.4)     | 127.6 (44.6) | <0.001 |
| Urinary Pcr (mg/mmol)           | Median [Q1–Q3]| 22 [14–35]| 17 [11–29.2] | 16 [10–29]       | 19 [12–31] | <0.001 |
| Missing                         | 28           | 20           | 28           | 76               |
| Urinary urea excretion (mmol/day)| Mean (SD) | 321 (139)    | 395 (162)    | 488 (171)        | 404 (144) | <0.001 |
| Missing                         | 79           | 91           | 103          | 273              |
| FGF23 C-ter (RU/mL)             | Median [Q1–Q3]| 95 [66–148]| 99 [63–149] | 98 [64–136]      | 98 [64–143] | 0.631 |
| Missing                         | 79           | 93           | 66           | 238              |
| 25OH vitamin D (ng/mL)          | Median [Q1–Q3]| 21 [14–29]| 20 [13–28] | 22 [14–28]       | 21 [14–28] | 0.296 |
| Missing                         | 45           | 53           | 53           | 151              |
| 1,25 OH vitamin D (pg/mL)       | Median [Q1–Q3]| 47 [30–68]| 45 [33–63] | 45.5 [33–66]    | 46 [32–66] | 0.552 |
| Missing                         | 31           | 30           | 27           | 88               |
| Osteocalcin (ng/mL)             | Median [Q1–Q3]| 35 [21–56]| 37 [22–61] | 40.2 [25–63]    | 37 [22–60] | 0.003 |
| Missing                         | 9            | 4            | 5            | 18               |
| Blood cross-laps (pmol/L)       | Median [Q1–Q3]| 6165 [3931–9126]| 6331 [4305–9610]| 7068 [4812–9842]| 6527 [4313–9610] | 0.010 |
| Missing                         | 6            | 5            | 6            | 17               |
| PTH (pg/mL)                     | Median [Q1–Q3]| 97 [61–162]| 105.8 [72–161]| 99.4 [66–158] | 100.3 [66–160] | 0.234 |
| Missing                         | 3            | 2            | 1            | 6                |

(Continues)
**Table 1** (continued)

| Variable | Q1 (N = 440) | Q2 (N = 440) | Q3 (N = 439) | Total (N = 1319) | P-value |
|----------|--------------|--------------|--------------|------------------|---------|
| Treatment |              |              |              |                  |         |
| Basiliximab induction | 240 (54.5) | 253 (57.5) | 276 (62.9) | 769 (58.3) | 0.043 |
| Corticosteroids | 416 (94.5) | 419 (95.2) | 420 (95.7) | 1255 (95.1) | 0.742 |
| Azathioprine | 0 (0.0) | 2 (0.5) | 2 (0.5) | 4 (0.3) | 0.373 |
| Mycophenolate mofetil | 389 (88.4) | 377 (85.7) | 389 (88.6) | 1155 (87.6) | 0.341 |
| Tacrolimus | 376 (85.5) | 366 (83.2) | 360 (82.0) | 1102 (83.5) | 0.370 |
| mTorc1 inhibitor | 44 (10.0) | 60 (13.6) | 44 (10.0) | 148 (11.2) | 0.141 |
| Ciclosporine | 58 (13.2) | 64 (14.5) | 67 (15.3) | 189 (14.3) | 0.672 |
| Belatacept | 1 (0.2) | 3 (0.7) | 0 (0.0) | 4 (0.3) | 0.173 |

BMI, body mass index; BP, blood pressure; CER, creatinine excretion rate; FGF23, fibroblast growth factor 23; OH, hydroxy; PCr, protein to creatinine ratio; PTH, parathormone.

**Figure 2** Correlation between muscle mass estimated from creatinine excretion rate measured 3 months after transplantation (CER₃) and glomerular filtration rate measured by iohexol plasma clearance (iGFR) (A), estimated from the creatinine-based CKD-EPI equation (B) or MDRD equation (C). These analyses were restricted to the subgroup of patients who underwent creatinine measurement with an enzymatic assay traceable to IDMS standards.
Table 2  Variables associated with creatinine excretion rate 3 months after transplantation (CER₃) in multivariable analysis (performed on the N patients with complete data)

| Model                        | Without urea excretion rate | With urea excretion rate | With urea excretion rate Excluding patients with an absolute plasma creatinine slope > 2.8 μmol/h |
|------------------------------|-----------------------------|--------------------------|---------------------------------------------------------------------------------|
| N                            | 1215                        | 1005                     | 868                                                                             |
| Variables of the multivariable model | β coefficient [95% CI] | P-value                  | β coefficient [95% CI] | P-value                  | β coefficient [95% CI] | P-value                  |
| Recipient age (years)        | −0.31 [−0.36 to −0.26]      | <0.001                   | −0.3 [−0.36 to −0.24]              | <0.001                   | −0.31 [−0.37 to −0.25]      | <0.001                   |
| Recipient female gender      | −0.27 [−0.32 to −0.22]      | <0.001                   | −0.27 [−0.33 to −0.21]              | <0.001                   | −0.25 [−0.31 to −0.19]      | <0.001                   |
| Pre-emptive transplantation  | 0.06 [0.01 to 0.1]          | 0.008                    | 0.06 [0.02 to 0.11]                | 0.008                    | 0.06 [0.01 to 0.11]          | 0.017                    |
| Coronary disease             | −0.07 [−0.11 to −0.03]      | 0.001                    | −0.06 [−0.11 to −0.02]              | 0.004                    | −0.05 [−0.1 to 0]           | 0.040                    |
| Diabetes                     | −0.05 [−0.09 to −0.01]      | 0.023                    | −0.06 [−0.1 to −0.01]               | 0.010                    | −0.05 [−0.1 to −0.01]       | 0.024                    |
| Living donor                 | 0.01 [−0.03 to 0.05]        | 0.699                    | −0.02 [−0.07 to 0.03]               | 0.469                    | 0.01 [−0.04 to 0.06]        | 0.655                    |
| Donor age                    | 0.09 [0.04 to 0.15]         | <0.001                   | 0.09 [0.04 to 0.15]                 | 0.001                    | 0.1 [0.04 to 0.16]          | 0.009                    |
| Delayed graft function       | 0.03 [−0.01 to 0.07]        | 0.119                    | 0.03 [−0.01 to 0.07]                | 0.162                    | 0.03 [−0.02 to 0.08]        | 0.269                    |
| History of rejection         | 0.04 [0 to 0.08]            | 0.059                    | 0.04 [−0.01 to 0.08]               | 0.090                    | 0.03 [−0.02 to 0.08]        | 0.196                    |
| Height (cm)                  | 0.41 [0.36 to 0.46]         | <0.001                   | 0.37 [0.31 to 0.43]                 | <0.001                   | 0.39 [0.32 to 0.45]         | <0.001                   |
| BMI (kg/m²)                  | 0.24 [0.2 to 0.28]          | <0.001                   | 0.23 [0.19 to 0.28]                 | <0.001                   | 0.23 [0.18 to 0.28]         | <0.001                   |
| ioGFR (mL/min/1.73 m²)       | 0.19 [0.14 to 0.24]         | <0.001                   | 0.18 [0.12 to 0.23]                 | <0.001                   | 0.17 [0.12 to 0.23]         | <0.001                   |
| Proteinuria > 20 mg/mmol     | −0.09 [−0.13 to −0.05]      | <0.001                   | −0.09 [−0.13 to −0.04]              | <0.001                   | −0.08 [−0.13 to −0.04]      | <0.001                   |
| Log(osteocalcin)             | −0.02 [−0.04 to 0.07]       | 0.571                    | −0.01 [−0.06 to 0.05]               | 0.847                    | 0 [−0.06 to 0.07]           | 0.961                    |
| Log(blood cross-laps)        | −0.04 [−0.09 to 0.01]       | 0.153                    | −0.01 [−0.07 to 0.05]               | 0.730                    | −0.03 [−0.09 to 0.04]       | 0.429                    |
| Urea excretion rate (mmol/24 h) | Not included               | 0.08 [0.04 to 0.13]       | <0.001                             | 0.09 [0.05 to 0.14]       | <0.001                             |
| R²                           | 0.55                        | 0.56                     | 0.55                               | <0.001                   | 0.55                               | <0.001                   |

BMI, body mass index; CI, confidence interval; ioGFR₃, glomerular filtration rate measured by iohexol plasma clearance 3 months after kidney transplantation.
Independent factors associated with creatinine excretion rate 3 months after transplantation

The results of the multivariable analysis investigating the factors associated with CER in the adjusted model are presented in Table 2. In addition to expected pre-transplantation factors such as anthropometric parameters, recipients age and gender, a history of diabetes or coronary artery disease, or the absence of dialysis history (pre-emptive transplantation), this analysis also identified donor age and post-transplantation GFR as predictors of CER. Improvement in kidney function following kidney transplantation is associated with modifications in the plasma level of three important mineral metabolism hormones, which have also been linked to muscle mass: parathormone (PTH), calcitriol, and FGF23.16,29 Further adjusting the model for the plasma level of these hormones did not modify the association between ioGFR and CER (Table S3). The correlation between urine creatinine excretion and muscle mass can be considered a reasonably reliable assumption only in the steady state conditions. To fully rule out that the associations we observed were obscured by patients with reduced or enhanced creatinine excretion caused by acute variation in kidney function, we took advantage of the repeated measurement of plasma creatinine over a 5 h period during GFR measurement. We computed the slope of the linear regression of plasma creatinine with time. The mean creatinine slope for the study population (14%) display an absolute slope above 2.8 μmol/l. Overall, 182 patients (14%) display an absolute slope above 2.8 μmol/l, a threshold corresponding to a retention or an elimination of 1 mmol urea/day in a patient with an extracellular fluid volume of 15 L. Sensitivity analysis excluding these patients showed similar results than those performed on the whole study population (Table 2).

Evolution of creatinine excretion rate after 3 months

A total of 1165 (88%) patients had a subsequent CER measurement after a median follow-up of 9.5 months (CERfu). Of them, 373 (32%) experienced an increase in CER > 10%, while 222 (19%) showed a CER decrease of more than 10%. Multivariable analysis adjusted for CER and other founders identified ioGFR as an independent predictor of CERfu (β coefficient 0.11 [95% CI 0.07 to 0.16]; Table 3). This analysis also identified male gender, younger age, higher body mass, and the absence of coronary artery disease as independent predictors of increased CERfu (Table 3). Including urinary urea excretion in the model did not change strength of the association between ioGFR and CER or CERfu (Tables 2 and 3).

Association of creatinine excretion rate with survival and graft loss

In Figure 3, we present the cumulative incidence of death (upper panels) and graft loss (lower panels) according to tertiles of CER measured at 3 months or at follow-up. In Table 4, we present the association between CER and mortality or graft loss. In the fully adjusted model, CER and CERfu remained significantly associated with all-cause mortality. CER was not associated with graft loss in the adjusted Fine and Gray model with death as a competing risk. In contrast, CERfu showed a significant association with graft loss in the same analysis. However, a sensitivity analysis restricted to the 929 patients who underwent GFR and CER determination specifically at 12 months did not show a consistent association of CER with graft loss (Table S4). In contrast, the association between CER and all-cause mortality remained significant in this analysis. Further sensitivity analyses excluding patients with an absolute creatinine slope above 2.8 μmol/h confirmed an independent association between CER and mortality at both time points (Table S5). In these sensitivity analyses, CER also associated with allograft loss.

Discussion

We evaluated for the first time the association of post-transplantation ioGFR with muscle mass following kidney transplantation in a large monocentric prospective cohort. We found that ioGFR independently associates with CER and predicts improved muscle mass at follow-up. In addition, we found CER to be an independent predictor of patients’ mortality at both time points.

This study is the first to demonstrate that restoration of GFR following kidney transplantation is associated with muscle recovery. We further confirmed a strong and consistent association of muscle mass with patients’ mortality but not with graft loss.

These findings were made possible by the use of appropriate methods for muscle mass and GFR evaluation. Indeed, the association of post-transplantation GFR with muscle mass would have been missed with creatinine-based eGFR. This predictable finding is obviously linked to the fact that both MDRD and CKD-EPI estimate creatinine production using gender and age. These parameters do not predict muscle mass with a sufficient accuracy to render eGFR independent of muscle mass.25 In addition, the use of timed collection rather than 24 h urine collection to assess CER provided a greater accuracy, reducing the fluctuation caused by inaccurate 24 h urine collection. This improved accuracy translates into a better appreciation of CER estimation. These two points may explain the absence of correlation between eGFR and 24 h CER previously reported in transplanted and non-transplanted CKD cohorts.24,32
Table 3  Baseline variables associated with creatinine excretion rate (CER) at follow-up (CERfu) in multivariable analysis (performed on the N patients with complete data)

| Variables of the multivariable model | Without urea excretion rate | With urea excretion rate | With urea excretion rate Excluding patients with an absolute plasma creatinine slope > 2.8 μmol/h |
|-------------------------------------|----------------------------|--------------------------|-------------------------------------------------------------------------------------|
| CER3                               | 0.37 [0.32 to 0.43]        | 0.34 [0.28 to 0.41]     | 0.32 [0.25 to 0.38]                                                                |
| Recipient age                       | –0.18 [-0.24 to -0.13]    | –0.2 [-0.26 to -0.14]   | –0.2 [-0.27 to -0.14]                                                             |
| Recipient female gender             | 0.21 [0.16 to 0.26]        | –0.23 [-0.29 to -0.17]  | –0.22 [-0.29 to -0.16]                                                            |
| Pre-emptive transplantation         | 0.04 [0 to 0.08]           | 0.03 [-0.02 to 0.07]    | 0.03 [-0.02 to 0.08]                                                              |
| Coronary disease                    | –0.05 [-0.09 to -0.01]    | –0.05 [-0.1 to -0.01]   | –0.05 [-0.1 to 0]                                                                 |
| Diabetes                            | –0.01 [-0.05 to 0.03]     | –0.02 [-0.06 to 0.03]   | 0.02 [-0.03 to 0.07]                                                              |
| Living donor                        | –0.02 [-0.06 to 0.02]     | 0.03 [-0.02 to 0.08]    | 0.03 [-0.07 to 0.08]                                                              |
| Donor age (years)                   | 0.04 [-0.01 to 0.09]      | 0.04 [-0.01 to 0.1]     | 0.06 [0.01 to 0.12]                                                               |
| Delayed graft function              | 0.03 [-0.01 to 0.07]      | 0.02 [-0.03 to 0.07]    | 0 [-0.05 to 0.05]                                                                 |
| History of rejection                | 0.01 [-0.03 to 0.05]      | 0.02 [-0.02 to 0.07]    | 0.01 [-0.04 to 0.06]                                                              |
| Height (cm)                         | 0.22 [0.16 to 0.28]       | 0.2 [0.14 to 0.26]      | 0.22 [0.15 to 0.29]                                                               |
| BMI (kg/m²)                         | 0.14 [0.09 to 0.18]       | 0.15 [0.1 to 0.2]       | 0.16 [0.1 to 0.21]                                                                |
| ioGFR3 (mL/min/1.73 m²)             | 0.11 [0.06 to 0.16]       | 0.1 [0.05 to 0.16]      | 0.12 [0.07 to 0.18]                                                               |
| Proteinuria > 20 mg/mmol            | 0 [-0.04 to 0.04]         | –0.01 [-0.05 to 0.04]   | –0.01 [-0.06 to 0.04]                                                             |
| Duration between CER3 and CERfu     | –0.07 [-0.1 to -0.03]     | –0.08 [-0.12 to -0.04]  | –0.07 [-0.11 to -0.02]                                                            |
| Urea excretion rate (mmol/24 h)     | Not included              | 0.05 [0 to 0.09]        | 0.06 [0.01 to 0.11]                                                               |
| Adjusted R²                         | 0.59                      | 0.58                    | 0.57                                                                              |
| P-value                             | <0.001                    | <0.001                  | <0.001                                                                           |

BMI, body mass index; CI, confidence interval; ioGFR3, glomerular filtration rate measured by iohexol plasma clearance 3 months after kidney transplantation.
The fact that post-transplantation GFR associates with muscle mass as early as 3 months after transplantation is notable. This overall association between recovery of kidney function and muscle mass is in line with experimental data showing that reduction of kidney function in mice led to muscle wasting within a few weeks. In mice, CKD muscle

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**Figure 3** Cumulative incidence of death (upper panels) or graft loss (lower panels) for tertiles of creatinine excretion rate measured 3 months after kidney transplantation (CER₃, left panels) or CERᶠᵤ (right panels).

**Table 4** Cox uni- and multivariable modelling of the association of CER₃ or CERᶠᵤ with transplantation outcome (performed on the N patients with complete data)

| Outcome of interest                                      | CER₃            | P-value | CERᶠᵤ           | P-value |
|---------------------------------------------------------|-----------------|---------|-----------------|---------|
| N                                                        | 1319            |         | 1149            |         |
| Outcome of all-cause mortality                           |                 |         |                 |         |
| Crude hazard ratio                                       | 0.77 (0.72–0.82) | <0.001  | 0.75 (0.69–0.81) | <0.001  |
| Adjusted hazard ratio                                    | 0.82 (0.74–0.91) | <0.001  | 0.79 (0.69–0.99) | <0.001  |
| Outcome of allograft loss with mortality as a competing risk |                 |         |                 |         |
| Crude hazard ratio                                       | 0.97 (0.89–1.05) | 0.400   | 0.93 (0.85–1.01) | 0.079   |
| Adjusted hazard ratio                                    | 0.97 (0.85–1.10) | 0.600   | 0.83 (0.71–0.97) | 0.013   |

CER, creatinine excretion rate; ioGFR, iohexol plasma clearance.

ªAdjusted for ioGFR₃, gender, smoking, coronary artery disease, pre-emptive transplantation, donor age, donor type, diabetes, recipient age, systolic blood pressure at 3 months, height, and body mass index at 3 months.

ªAdjusted for CERᶠᵤ, ioGFRᶠᵤ, gender, smoking, coronary artery disease, pre-emptive transplantation, donor age, donor type, diabetes, recipient age, systolic blood pressure at follow-up, height, and body mass index at follow-up.
wasting has been linked to excessive PTH signalling in adipocytes promoting adipose tissue browning and thereby energy and protein wasting. In contrast, we observed that, contrary to GFR, PTH is not associated with muscle mass after kidney transplantation.29 Furthermore, we did not observe consistent association of CER with the circulating level of FGF23, vitamin D, osteocalcin, or cross-laps. Other factors have been shown to promote muscle wasting in CKD such as myostatin,33 insulin resistance,34 inflammatory cytokines,35 or indoxyl sulfate.36 Unfortunately, these parameters were not measured in the present study.

Our study also unveiled that muscle mass recovery occurs in the first year after kidney transplantation in the majority of patients, yet to different levels. Interventions may improve kidney transplant recipients’ muscle mass and fitness. Physical exercise represents an obvious option as small randomized trials demonstrated beneficial effects of resistance or aerobic training on kidney transplant recipients’ physical performance.37,38 Our results indicating that both younger age and male gender are associated with muscle mass improvement at 12 months may suggest a role for androgens in muscle mass recovery. Androgen insufficiency is a frequent condition in male CKD patients and is associated with adverse outcome.39 To date, no trial investigated the impact of testosterone replacement therapy on kidney transplantation outcome.

Our study has limitations. As we estimated muscle mass from CER, we lack information regarding pre-transplantation muscle mass and we can only pinpoint that transplantation-related factor such as ioGFR₃ is associated with CER₃. This limitation however does not apply to the analyses investigating CER variation after 3 months, which allowed us to capture factors unambiguously associated with muscle mass recovery or wasting. The observational design does not permit the identification of a causative relation between muscle mass and mortality. Urinary creatinine excretion may not perfectly reflect muscle mass. We did not formerly control for protein intake that may impact urinary creatinine excretion in adults40 and children.41 We however included urea excretion rate as a surrogate marker for protein intake in our analyses. We did not measure muscle function, nutritional status, other markers of frailty, or bone mineral density. Yet, CER has been shown to correlate with handgrip strength in kidney transplant recipients in a recent prospective study.42 Last, the cumulative dose of corticosteroids during the first 3 months after kidney transplantation may directly have an impact on muscle mass. Unfortunately, this variable was not available. However, immunosuppressive treatment regimen was not significantly different between tertiles of muscle mass. Finally, kidney transplant recipients cohort of Necker Hospital includes a higher proportion of patients suffering from genetic kidney disease (mainly autosomal dominant polycystic kidney disease) and a lower proportion of patients suffering from diabetic nephropathy than usual kidney transplant recipients cohorts, which may limit the generalization of our findings. Due to French regulation, our database does not include information regarding patients’ ethnicity.

Our study has also important strengths, including the size of the studied kidney transplant recipients cohort, prospective data collection, simultaneous indoor measurement of ioGFR and CER using timed sampling, and the validation of CER against BCM in a subgroup of patients.

In conclusion, GFR restoration is associated with muscle mass increase in the first year following kidney transplantation. Along with demographic and anthropometric parameters, allograft function is a major determinant of muscle mass variation. Whether or not muscle mass increase would translate into improved outcome remains to be evaluated.

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Conflict of interest

None declared.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.
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