Changes in Plasma Cystatin C after Renal Transplantation and Acute Rejection in Adults

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Background: Cystatin C has recently been proposed as an alternative marker of glomerular filtration rate. The diagnostic value of plasma cystatin C for the longitudinal assessment of kidney function after renal transplantation, however, has not been addressed.

Methods: Renal function was evaluated in 30 adults receiving renal transplants (46 ± 9 years, mean ± SD) and in 56 healthy controls (38 ± 10 years) using cystatin C. Plasma cystatin C was determined daily starting the day of surgery and for 3 weeks after surgery by an immunonephelometric assay.

Results: Plasma concentration significantly decreased during the first week (−44% vs −29% for creatinine). Plasma cystatin C correlated with plasma creatinine (r = 0.741; P < 0.0001) and the reciprocal of the creatinine clearance estimated by the Cockcroft-Gault formula (r = 0.882; P < 0.001). In all three cases of acute renal impairment, the increase in plasma cystatin C values was more prominent than that of creatinine.

Conclusions: Plasma cystatin C is an alternative and accurate marker of allograft function in adult transplant patients. Increased sensitivity compared with creatinine for the detection of acute reduction in glomerular filtration rate allows in some cases a more rapid diagnosis of acute rejection or treatment nephrotoxicity.

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After renal transplantation, plasma (or serum) creatinine is the most common marker for assessment of allograft function. In a steady-state muscular mass balance, the plasma creatinine concentration is assumed to reflect glomerular filtration rate (GFR)4 (1). However, plasma creatinine is far from being an ideal marker of GFR, despite its convenience and low cost (2). Plasma creatinine suffers a high degree of interindividual variability related to sex, age, body composition, and dietary factors (3). With altered renal function, the plasma creatinine concentration increases only when the GFR is reduced by >50%. Furthermore, secretion or reabsorption of creatinine by the renal tubule is highly unpredictable, thus leading to under- or overestimation of GFR (2). Numerous drugs and endogenous substances also interfere with the measurement of creatinine by the Jaffé technique or enzymatic methods, leading to falsely high or low creatinine values (4).

Since the introduction of sensitive automated immunoassays, cystatin C has been proposed as an alternative marker of GFR (5). Human cystatin C is a 122-amino acid basic low-molecular weight protein (Mr, 13 300) that belongs to the superfamily of cysteine proteinase inhibitors (6). The product of a housekeeping gene (7), its plasma concentration in adults is relatively constant (~1 mg/L) and independent of gender and age, at least before the age of 50 years (8). Because of its low molecular weight and positive charge, cystatin C is freely filtered by the glomerular membrane before it is entirely catabolized in the proximal renal tubule (9,10). In adults suffering from renal diseases, cystatin C more sensitively reflects a reduction of GFR evaluated by 99mTc-diethylenetriamine pentaacetic acid (DTPA) or 51Cr-labeled EDTA filtration clearance than creatinine (5). The diagnostic value of plasma cystatin C as a marker of GFR in renal transplantation patients, however, has not been yet fully investigated (11).

In this prospective study, cystatin C was evaluated as a marker of allograft function during the early postoperative transplantation period. Plasma cystatin C was determined by a recently developed particle-enhanced immunonephelometric assay (12,13). Plasma cystatin C kinetics were compared with those of plasma creatinine used in our institution for estimation of GFR in transplant recip

4 Nonstandard abbreviations: GFR, glomerular filtration rate; DTPA, diethylenetriamine pentaacetic acid; DGF, delayed graft function; and UFC, ultrafiltration coefficient.
Patients. The results are discussed with the following clinical indicators of renal function: dialysis requirements, acute rejection, and treatment nephrotoxicity.

**Materials and Methods**

**PATIENTS**

Thirty consecutive patients with end-stage renal disease undergoing renal transplantation in our institution were included. Patients characteristics are presented in Table 1. Primary diagnosis was chronic interstitial nephropathy (n = 4), diabetic glomerulopathy (n = 3), polycystic kidney disease (n = 3), nephrosclerosis (n = 3), focal segmental glomerulosclerosis (n = 2), IgA nephropathy (n = 3), amyloidosis (n = 2), vascular nephropathy (n = 1), Goodpasture syndrome (n = 1), systemic lupus erythematosus (n = 1), uric acid nephropathy (n = 1), membranous glomerulonephritis (n = 1), mesangiocapillary glomerulonephritis (n = 1), and unknown (n = 4).

Immunosuppressive regimen included steroids (methylprednisolone at the initial dose of 500 mg, followed by 1 mg · kg⁻¹ · day⁻¹, progressively tapered) and cyclosporine (initial dose of 8 mg · kg⁻¹ · day⁻¹, and then adjusted according to blood concentrations) or FK506 in cases of cyclosporine intolerance (at the dose of 0.1 mg · kg⁻¹ · day⁻¹). Delayed graft function (DGF) was defined as a requirement for dialysis during the first 2 weeks after transplantation. All patients except one (peritoneal dialysis) were on conventional dialysis. Episodes of acute rejection diagnosed by renal biopsy were treated with 5 days of intravenous methylprednisolone.

This study was in accordance with the ethics standards of the Helsinki Declaration of 1975, as revised in 1983. Results obtained in transplantation patients were compared with those of 56 age- and sex-matched healthy subjects (28 males and 28 females; mean age, 38 ± 10 years).

**ANALYSIS**

**Sampling.** Allograft function was evaluated on a daily basis starting the day of surgery (day 0) and for 3 weeks thereafter or until hospital discharge, whichever occurred first. Blood (7 mL) was drawn by venipuncture in a Vacutainer® Tube with heparin as an anticoagulant (Becton Dickinson) before centrifugation (1500g at 20 °C for 15 min) and analyzed for creatinine. Before cystatin C analysis, samples were frozen at -20 °C, which is considered the best condition to store samples before cystatin C measurement (12, 13).

**Biochemical analysis.** Plasma creatinine was enzymatically assayed on a Vitros 750 apparatus (Ortho-Clinical Diagnostics). The sample volume was 10 µL, and the assay was performed at 37 °C; total analysis time was 7 min. In our hands, the interassay imprecision (CV; n = 31) was <3% (low control, 90 µmol/L; high control, 737 µmol/L).

Plasma cystatin C was measured using a latex particle-enhanced immunonephelometric assay on a BN100 nephelometer (Behring). The assay procedure has been described in detail recently by others (12, 13). Briefly, the assay is performed at room temperature with a six-point calibration covering the range of 0.23–7.25 mg/L. The calibrator used is a purified cystatin C from human urine (1.45 mg/L). The sample volume is 80 µL. The time for analysis is 6 min, each subsequent sample reading being available after 8 s. In our hands, the interassay CV (n = 20) was <4% for both the low (1.4 mg/L) and high (2.8 mg/L) controls.

**Calculations.** The percentage of discordant changes in plasma cystatin C and creatinine concentrations was calculated on a day-to-day basis after transplantation. A change in opposite direction (increase/decrease) of >10% between the two markers was considered as discordant. On hospital discharge or at the end of the 3-week period, creatinine clearance was estimated from plasma creatinine using the formula of Cockcroft and Gault (1). This formula developed for adults previously was validated against ⁹⁹mTc-DTPA-measured GFR in renal transplantation patients at steady-state renal function (14). Calculations of estimated clearance by this formula were not done for patients requiring hemodialysis during the last week of the study (n = 8). A cutoff of 80 mL/min was selected for normal estimated creatinine clearance (15).

**STATISTICAL ANALYSIS**

Data are presented as mean ± SD or as median and range when appropriate after checking for gaussian distribution. Differences between two groups were evaluated by the Wilcoxon signed-rank test. Multiple comparisons were performed by the Friedman repeated-measure ANOVA on ranks followed by the Dunn test. Correlation between techniques was evaluated by linear regression and ANOVA. Results with P <0.05 were considered statistically significant.

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**Table 1. Characteristics of renal transplant patients.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age, years</td>
<td>46 ± 9</td>
</tr>
<tr>
<td>Recipient gender, M/F</td>
<td>15/15</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65 ± 14</td>
</tr>
<tr>
<td>Time on dialysis, years</td>
<td>1–18</td>
</tr>
<tr>
<td>First/second transplantation, n</td>
<td>26/4</td>
</tr>
<tr>
<td>DGF, n</td>
<td>14</td>
</tr>
<tr>
<td>Acute rejection/treatment nephrotoxicity, n</td>
<td>4/1</td>
</tr>
<tr>
<td>Duration of hospital stay, days</td>
<td>23 ± 9</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SD.

DGF defined as a hemodialysis requirement during the first 2 weeks after transplantation.

1–10 hemodialysis sessions.
HEALTHY CONTROLS
The mean plasma creatinine and cystatin C concentrations were 83 ± 11 μmol/L and 0.70 ± 0.12 mg/L, respectively. Plasma cystatin C significantly correlated (r = 0.515; P < 0.0001) with creatinine (Fig. 1). Cystatin C plasma concentrations were not influenced by age (r = 0.230; not significant) or by gender (males, 7% higher vs females; not significant). The calculated reference interval (based on mean ± 1.96 SD) for creatinine was 0.46–0.94 mg/L. The calculated sex-specific reference intervals for plasma creatinine were 60–100 μmol/L for females and 64–109 μmol/L for males.

TRANSPLANT PATIENTS
In patients without DGF (n = 16), a significant decline in plasma concentration was more rapidly obtained for cystatin C (day 1: −62% vs day 0; P < 0.05) than for creatinine (day 1: −25%; not significant; Fig. 2). Starting on day 4 posttransplantation (and until the end of the study period), the decrease in the plasma concentration of patients without DGF was more pronounced for creatinine than for cystatin C (Fig. 2). In patients with DGF (n = 14), the reduction in the plasma concentration was not significant until day 14 (−34% vs day 0) for creatinine and day 18 (−22%) for cystatin C (Fig. 2). At the end of the 3-week study period, a 52% reduction from the initial plasma creatinine concentration was observed in patients with DGF vs 33% for cystatin C. The frequency of discordant daily changes in cystatin C and creatinine plasma values was significantly higher in patients with DGF (35%) than in those without DGF (19%; P < 0.01). Overall, plasma cystatin C significantly correlated with creatinine concentrations (r = 0.890; P < 0.0001; n = 255) than in those with DGF (r = 0.429; P < 0.0001; n = 275; Fig. 3).

There were four biopsy-documented acute rejection episodes (incidence, 13%) during the 3-week study period (at days 10, 14, 17, and 18 posttransplantation). In two cases, acute rejection was suspected by prolonged DGF, as demonstrated by persistent increases in both plasma creatinine and cystatin C concentrations (case 1; Fig. 4A). An acute rise in plasma creatinine was attributed to acute rejection in two patients, as illustrated in Fig. 4B (case 2). There was one case of acute treatment (FK506) nephrotoxicity at day 9 postsurgery, with a 44% increase of plasma creatinine over 2 days (Fig. 4C). Plasma cystatin C gradually rose (125%) during 7 days before diagnosis. Treatment nephrotoxicity regressed spontaneously.

At the end of the study (day 20 or hospital discharge), plasma creatinine was 180 μmol/L (79–602 μmol/L) vs 2.59 mg/L (1.04–6.54 mg/L) for cystatin C. Both markers were significantly correlated (r = 0.890; P < 0.001). Estimated creatinine clearance by the Cockcroft and Gault formula (1) in patients with stable renal function (no hemodialysis during the last week, n = 22) was 45 mL/min (18–76 mL/min), and no patient was within the reference interval (>80 mL/min). Plasma creatinine was within the reference interval for five patients (79–96 μmol/L) compared with none for cystatin C. The relation-

![Fig. 1. Correlation between plasma cystatin C and plasma creatinine in healthy adults.](Image)

![Fig. 2. Plasma cystatin C and creatinine kinetic in renal transplant patients.](Image)

Transplant patients (n = 30) were separated into two groups: normal course (absence of complications; n = 16) and DGF (n = 14), defined as requiring hemodialysis during the first 2 weeks after surgery. Three patients with DGF left the hospital within 20 days postsurgery (n = 13 at day 20). Nine of 14 patients with normal course had an hospital stay shorter than 21 days. Values are presented as medians. *, first day significantly different from the day of surgery (Friedman repeated-measure ANOVA on ranks followed by the Dunn test, P < 0.05). In patients without DGF, statistical analysis was not possible during the last postoperative week because of the number of missing values (hospital discharge).

(r = 0.741; P < 0.0001; n = 530; day 0 to day 20). The correlation was better in patients without DGF (r = 0.818; P < 0.0001; n = 255) than in those with DGF (r = 0.429; P < 0.0001; n = 275; Fig. 3).
Plasma creatinine and cystatin C concentrations were measured in 30 patients undergoing renal transplantation. Cystatin C and creatinine were determined on a daily basis starting on the day of surgery and for 3 weeks or until hospital discharge, whichever occurred first. DGF was observed in 14 patients. Data were analyzed by linear regression and ANOVA: patients without DGF ($r = 0.816; P < 0.0001; n = 255$) and those with DGF ($r = 0.429; P < 0.0001; n = 275$).

A significant correlation between estimated creatinine clearance and the reciprocal of plasma cystatin C ($r = 0.882; P < 0.001$).

**Discussion**

Sensitive and reliable recognition of changes in GFR is of primary importance in transplant patients. A DGF is an identified and independent risk factor for graft survival (16). Acute rejection is also an established risk factor for renal graft failure, defined as a return of patient to hemodialysis (16). Recent studies have suggested that cystatin C might be a potential better marker of GFR than plasma creatinine (5, 12, 13, 17, 18), such as in renal transplant patients (11).

During the last decade, substantial technical improvements, especially concerning sensitivity and practicability, have been made in the measurement of plasma cystatin C. In the present study, we measured the plasma cystatin C concentration with a fully automated latex particle-enhanced immunonephelometry assay (12, 13). This technique has been shown to correlate well with automated latex particle-enhanced immunoturbidimetry assays and displayed excellent analytical performance (12, 13). Turbidimetric assays (18, 19) and nephelometric assays are not subject to the same analytical interferences (such as bilirubin or hemolysis) as plasma creatinine. The analytical precision was excellent (CV < 4%), and the total analysis time was comparable to that of creatinine (~5 min); thus this assay is well suited for routine use in clinical laboratories. The cost of this assay is ~15-fold higher than that of creatinine determination by the Vitros technology, which in terms of cost-effectiveness remains acceptable if significant clinical benefits can be obtained with this new marker.

The mean cystatin C plasma concentration in our group of healthy adults was similar to that reported in a group of healthy subjects (n = 12; mean age, 40 years), using an immunoturbidimetric assay (0.65 ± 0.05 mg/L) (20). Slightly higher values (mean cystatin C, 0.80 mg/L) were reported by others (13) in a group of 52 adults with normal renal function (ages, 21–79 years). These data are in agreement with an increase in plasma cystatin C values with age, especially after the age of 50 years (8). Like others (8, 13, 20), we did not find the sex difference reported previously (21, 22). Plasma cystatin C correlated poorly with plasma creatinine, as reported previously in subjects with GFR > 80 mL/min (13) or GFR > 70 mL·min⁻¹·1.73 m²⁻² (11). These data suggest that different physiological factors (such as sex, dietary factors, or body composition) influence cystatin C and creatinine plasma concentrations in healthy adults.

In renal transplant patients, plasma cystatin C concentrations paralleled those of creatinine regardless of graft function (absence or presence of DGF). Consequently, plasma cystatin C and creatinine significantly correlated over the postoperative study period ($r = 0.741; P < 0.0001$), as observed previously in adult renal transplant patients (11) and subjects suffering from chronic renal disease (13). Some differences, however, were apparent in their respective plasma kinetics. During the first 4 days posttransplantation, the cystatin C plasma concentration decreased more rapidly than that of creatinine. Transmural leakage of the low-molecular weight (M, 100) creatine (23) has been reported in acute renal failure, thus leading to high plasma creatinine values. Starting on day 4 posttransplantation, the decrease in plasma concentration became more prominent for creatinine than for cystatin C, which might be attributable to an underestimation of GFR by plasma cystatin C, an overestimation of GFR by plasma creatinine, or both. A stronger correlation between cystatin C than between creatinine and the measured GFR has been reported in adults suffering from renal diseases (5, 19, 24). The sensitivity to detect a reduction in GFR is also better for cystatin C than for creatinine when cutoffs at 70 mL·min⁻¹·1.73 m⁻² (11), 72 mL·min⁻¹·1.73 m⁻² (16), or 80 mL·min⁻¹·1.73 m⁻² (13, 21) are considered. Better accuracy of plasma cystatin C for estimation of GFR would need to be confirmed by a gold standard technique for measuring GFR, such as ⁵¹Cr-labeled EDTA, or inulin clearance.

For patient follow-up, the ability to detect rapid changes in GFR is clinically more important than accuracy itself. With diminished GFR, a significant increase in plasma concentration of cystatin C and creatinine will depend on the rate of its accumulation in plasma, which depends on its production rate and distribution volume,
but also on its biological intraindividual variation. Repeated measures obtained in healthy subjects suggested that intraindividual variation might be more important for cystatin C (13.3%) than for creatinine (4.9%). If true, cystatin C would be less sensitive for the detection of acute rejection episodes for a given individual than creatinine. In all four episodes of acute rejection and one treatment acute nephrotoxicity in our study, the plasma cystatin C concentration broadly paralleled that of creatinine. Interestingly, the rise in the plasma cystatin C concentration was more prominent than that of creatinine. Diagnosis of acute rejection could have been anticipated by 3 days with cystatin C in patient 2 (Fig. 4B), and treatment acute nephrotoxicity could have also been detected earlier (patient 3; Fig. 4C).

After renal transplantation, hemodialysis was required in almost 50% of our patients. We found a higher degree of discrepancy (35% of discordant results; \( P < 0.01 \)) between cystatin C and creatinine plasma kinetics in patients requiring hemodialysis than in those with a normal course (19%). In addition, cystatin C and creatinine weakly correlated in hemodialyzed patients (\( r = 0.429 \)). The molecular weight of cystatin C is 13,300 with an Einstein-Stokes radius of 30–40 Å, which is much higher than creatinine (\( M_r 100 \) and 3 Å). In a large study of 112 patients on stable maintenance hemodialysis, a 30% reduction in serum cystatin C was observed after dialysis with mostly AN69 high-flux membranes (10). As expected, the elimination of cystatin C during dialysis increased with the ultrafiltration coefficient (UFC) of the membrane, an estimate of the permeability: 0% (vs 40% for creatinine) for UFC, 15 mL \( \cdot \) h \(^{-1} \) \( \cdot \) m\(^2\) \( \cdot \) mmHg and \( \sim 60\% \).

Fig. 4. Time course of plasma cystatin C and creatinine.

There were four episodes of acute graft rejection (confirmed by renal biopsy) during the 3-week study period in our group of 30 transplant patients. For purposes of simplification, plasma cystatin C and creatinine concentrations were normalized to the values obtained 10 days before renal biopsy (set at 100). (A), time course of plasma cystatin C and creatinine during acute rejection episode with dialysis. In this case, plasma cystatin C and creatinine concentrations at day 10 before acute rejection were 5.0 mg/L and 612 \( \mu \)mol/L, respectively. (B), time course of plasma cystatin C and creatinine during acute rejection episode without dialysis. In this case, plasma cystatin C and creatinine concentrations at day 10 were 1.7 mg/L and 128 \( \mu \)mol/L, respectively. (C), time course of plasma cystatin C and creatinine during immunosuppressive treatment nephrotoxicity. This case experienced FK506 toxicity. Plasma cystatin C and creatinine concentrations at day 9 were 1.2 mg/L and 101 \( \mu \)mol/L, respectively.
and Gault(1). No patient had a GFR within the reference interval (\( \text{mL/min} \)) was estimated at the end of the study period by the formula of Cockcroft of our study (n

than 21 days. Transplant patients who were hemodialyzed during the last week of discharge, whichever occurred first. Twelve patients had a hospital stay shorter

period (first 3 weeks). Limits to its routine use in trans-

planted patients include cost, which is much higher for an

adult transplantation. In some cases, a more prominent

rise in plasma cystatin C values allows a more rapid

diagnosis of acute rejection or treatment nephrotoxicity.

In conclusion, plasma cystatin C is as an alternative and

probably more accurate marker of GFR than creatinine in

adult transplantation. In some cases, a more prominent

rise in plasma cystatin C values allows a more rapid
diagnosis of acute rejection or treatment nephrotoxicity.
Cystatin C does not, however, appear clearly superior to
plasma creatinine, at least during the early postoperative
period (first 3 weeks). Limits to its routine use in trans-
plantation include cost, which is much higher for an
immunonephelometric assay than for a creatinine deter-
mination; absence of clearance measurements; and poorly
documented behavior during hemodialysis. Further pro-
spective studies are needed to evaluate this last issue and
the potential of plasma cystatin C in the long term
follow-up of graft function in renal transplantation.

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automated particle-enhanced turbidimetric method, is a better

Fig. 5. Relationship between plasma cystatin C, plasma creatinine, and GFR.

Transplant patients (n=30) were studied for 3 weeks or until hospital
discharge, whichever occurred first. Twelve patients had a hospital stay shorter
than 21 days. Transplant patients who were hemodialyzed during the last week
of our study (n=8) were excluded from our calculations. Creatinine clearance (in
mL/min) was estimated at the end of the study period by the formula of Cockcroft
and Gault (1). No patient had a GFR within the reference interval (<0.94 mg/L).

(as for creatinine) for UFC >15 mL · h⁻¹ · m² · mmHg (10).

Thus, removal of cystatin C by hemodialysis seems highly

dependent on the type of membrane selected. This is an

important issue in renal transplantation because it could

limit the use of plasma cystatin C as a marker of graft

function in patients with DGF. On the other hand, if

poorly filtered by dialysis membranes, plasma cystatin C

could be used by the nephrologist to monitor appropriate
duration of hemodialysis in patients with DGF. Prolonged

unnecessary hemodialysis could be avoided as soon as a

significant decrease in plasma cystatin C is obtained by

dialysis.

In conclusion, plasma cystatin C is as an alternative and

probably more accurate marker of GFR than creatinine in

adult transplantation. In some cases, a more prominent

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