Original Articles

Urinary neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after orthotopic liver transplantation

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Abstract

Background. Urinary neutrophil gelatinase-associated lipocalin (NGAL) is a novel, sensitive and specific biomarker that is rapidly released after kidney injury. It predicts acute kidney injury (AKI) in multiple clinical scenarios. We hypothesized that urinary NGAL can predict AKI after liver transplantation.

Methods. Urine was collected in 92 patients undergoing liver transplantation (18 living-related and 74 deceased) before surgery, after reperfusion of the liver graft and then 3, 18 and 24 h later. NGAL was analyzed with enzyme-linked immunosorbent assay and corrected for dilution/concentration by calculating urinary NGAL/urine creatinine ratios. AKI was defined by Risk-Injury-Failure-Loss-Endstage stage kidney disease (RIFLE)-risk criteria (increase of serum creatinine by >50%).

Results. Urinary NGAL/urine creatinine ratio was low prior to surgery and increased immediately after reperfusion, peaked 3 h later and remained elevated at 18 and 24 h. Urinary NGAL/urine creatinine ratios were higher in patients with post-operative (post-OP) AKI defined by RIFLE—risk criteria 3 and 18 h after reperfusion. The area under the curve of the receiver operator characteristics curve of urinary NGAL/urine creatinine ratio to predict AKI was 0.800 (95% CI: 0.732–0.869, P < 0.0001) 3 h and 0.636 (95% CI: 0.551–0.720, P < 0.005) 18 h after reperfusion.

Conclusions. We conclude that urinary NGAL/urine creatinine ratio is able to predict post-OP AKI 3 and 18 h after transplantation with good discrimination.

Keywords: living-related liver transplantation; renal biomarkers; renal failure; renal injury

Introduction

Acute kidney injury (AKI) after liver transplantation is a frequent complication and associated with a substantial increase in morbidity, length of stay and mortality [1–4]. The incidence of AKI after liver transplantation is estimated to be between 14 and 78% depending on the definition [1]. The cause of AKI after liver transplantation is multifactorial and multiple insults and risk factors are required for AKI to progress to renal failure requiring renal replacement therapy. Pre-operative (pre-OP) renal dysfunction and hepatorenal syndrome, caval cross-clamping with renal vein outflow obstruction, intra- and post-OP hypotension, high vasopressor requirements and large volume transfusions and the post-OP use of calcineurin inhibitors all contribute to renal injury that may cumulate to lead to AKI [1,5].

Serum creatinine, the commonly used marker for renal injury, is slow and insensitive. It is a marker of function and not injury and is unable to detect subtle injuries or delineate a single cause of renal injury. Serum creatinine is diluted by large-volume transfusions and may take days after injury to increase. Therefore, an increase of serum creatinine reflects the sum of injuries in the preceding days and cannot identify the effect of a single renal insult or subtle differences between groups of patients.

Urinary neutrophil gelatinase-associated lipocalin (NGAL) is a novel biomarker that is detectable very early after renal injury. It is upregulated by renal distal tubular cells within minutes after ischemia-reperfusion injury and secreted in the urine [6,7]. It is protease resistant and easily detectable using enzyme-linked immunosorbent assay (ELISA). Urinary NGAL is the most promising among a panel of renal biomarkers that are currently under investigation [8,9]. NGAL was found to be a good predictor of AKI in many clinical scenarios of renal injury, for example after cardiac surgery [10–12] or emergency room admissions [13], in septic shock [14] or with contrast induced nephropathy [15]. Plasma NGAL has recently been described as a good predictor of acute kidney after liver transplantation [16] but urinary NGAL after liver transplantation has not been studied to date. This study evaluates urinary NGAL/urine creatinine ratios after liver
transplantation and their ability to predict AKI after liver transplantation.

Subjects and methods

Patients

All adult patients undergoing liver transplantation (deceased or living related) at Columbia University Medical Center were eligible for inclusion into this study. Patients with pre-OP renal failure requiring renal replacement therapy were excluded. The Institutional Review Board of Columbia University waived the requirement to obtain written informed consent for the collection of urine as this is considered minimal risk by New York State and US Federal regulations.

Surgical technique

All patients underwent liver transplantation using a subcostal incision and midline extension. In the case of deceased liver transplantation, the liver was dissected and then removed after total inferior vena cava occlusion. For living-related liver transplant, the right hepatic lobe graft was inserted using the piggyback technique with only partial caval occlusion. No veno-venous bypass was used in any of these cases.

Sample collection and processing

Fifteen microliters of urine was collected on 92 orthotopic liver transplants after induction of anesthesia prior to incision, immediately after portal reperfusion of the liver graft and then 3, 18 and 24 h later. The urine was immediately spun at 2000 g and the supernatant was frozen at −80°C. Urinary NGAL was determined using a commercially available ELISA (Antibodyshop, Gentofte, Denmark) by the Irving Institute for Clinical and Translational Research of Columbia University. The limit of detection for this assay is 0.5 and 4.0 pg/mL and intra-assay variation in the urine is 2.1% (range: 1.3–4.0).

Urine creatinine levels were determined by a colorimetric method [17] using a commercially available kit (Fisher Diagnostics, Middletown, VA). All NGAL results were normalized to urine creatinine concentrations and presented as urinary NGAL/urine creatinine ratio to compensate for possible urinary dilution or concentration. Urinary NGAL (nanograms per microliter)/urine creatinine (micrograms per deciliter) ratios are unitless and were multiplied by 1000. For example, a urinary NGAL concentration = 30 ng/mL and a urine creatinine = 60 mg/dL results in a urinary NGAL/urine creatinine ratio = 0.5 (×10−3).

AKI was defined as an increase of serum creatinine of >50% compared to pre-OP values as described by the Acute Dialysis Quality Initiative as a Risk-Injury-Failure-Loss-Endstage stage kidney disease (RIFLE)-risk classification [18]. Additionally, we used the injury (>100% increase of serum creatinine) and failure (>200% increase of serum creatinine) definitions of the RIFLE criteria to evaluate the performance of urinary NGAL/urine creatinine ratios. We did not include the urine output criteria of the RIFLE classification since >70% of all patients received diuretics in the post-OP period (Table 1).

Data collection

Basic demographic data were collected prospectively. We determined the number of intensive care unit (ICU)- and hospital-free days defined as the number of days a patient was not in the ICU or the hospital within the first 30 days after surgery. By definition, patients who died within 30 days after surgery were considered to have no ICU- and hospital-free days.

Serum creatinine and AKI after liver transplantation

Thirty-seven patients (40.2%) developed AKI defined by the RIFLE-risk criteria. Pre-OP estimated creatinine clearance was higher in patients with post-OP AKI (123.8 ± 44.6 mL versus 93.1 ± 37.0 mL/min, <0.01) when the formula by Cockcroft–Gault was used but not with the MDRD formula. Pre-OP serum creatinine was similar in both groups (1.03 ± 0.40 versus 0.94 ± 0.88 mg/dL, ns). Both MDRD and Cockcroft–Gault have also been known to overestimate creatinine clearance in patients with liver disease [21] (Table 1).

Serum creatinine increased significantly in all patients on post-OP Days 1, 2 and 3 compared to pre-OP serum creatinine (from 0.99 ± 0.63 mg/dL to 1.27 ± 0.65 mg/dL on post-OP Day 1; P < 0.05, to 1.30 ± 0.76 mg/dL on post-OP Day 2; P < 0.01 to 1.23 ± 0.70 mg/dL on post-OP Day 3; P < 0.01). In patients with post-OP AKI, serum creatinine increased significantly on post-OP Day 1 and peaked on Day 2. There was no significant difference in serum creatinine in patients with and without AKI on post-OP Day 0 and Day 1; only from Day 2 on was serum creatinine higher in patients with post-OP AKI. (Figure 1).

Urinary creatinine and AKI after liver transplantation

Urinary NGAL was low prior to surgery, increased immediately after reperfusion of the liver graft, peaked 3 h later and remained elevated 18 and 24 h after reperfusion when compared to pre-OP values (Figure 2, panel A). Urine creatinine decreased immediately after reperfusion and 3 h later and was elevated again at 18 and 24 h after reperfusion when compared to pre-OP values (Figure 2, panel B). When correcting urinary NGAL for urinary dilution or concentration, urinary NGAL/urine creatinine ratios were low prior to surgery (0.52 ± 1.07) and increased immediately after reperfusion (2.61 ± 4.40, P < 0.0001 com-
paring post-OP with pre-OP values), peaked 3 h later (6.5 ± 13.52, P < 0.0001 comparing 3 h with pre-OP values) and were still elevated 18 (1.83 ± 5.55, P < 0.0001) and 24 h later (2.19 ± 28.04, P < 0.0001) (Figure 2, panel C).

Urinary NGAL/urine creatinine ratio and AKI after liver transplantation

Urinary NGAL/urine creatinine ratio was similar in patients with and without post-OP RIFLE-R AKI prior to surgery, immediately after reperfusion and at 24 h. Urinary NGAL/urine creatinine ratios were significantly higher in patients with RIFLE-R AKI 3 and 18 h after reperfusion (Figure 2, panel C and Table 2). When using the RIFLE injury (RIFLE-I) and failure (RIFLE-F) categories for AKI urinary NGAL/urine creatinine ratios were higher 18 and 24 h after reperfusion (Table 2).

The area under the curve of the receiver operator characteristics (ROCs) curves of urinary NGAL/urine creatinine ratio to predict AKI defined by RIFLE-risk criteria was 0.800 (95% CI: 0.732–0.869, P < 0.0001) at 3 h and 0.636 (95% CI: 0.551–0.720, P < 0.005) at 18 h (Figure 3).

We defined the best cutoff value that maximizes sensitivity and specificity as the point on the ROC curve that is closest to sensitivity = specificity = 100%. Three hours after reperfusion, the best cutoff value for the urinary NGAL/urine creatinine ratio was 0.74 with a sensitivity = 83.5% (95% CI: 74.2–90.4%) and a specificity = 67.5% (95% CI: 56.1–77.6%). Eighteen hours after reperfusion, the best cutoff was 0.35 with a sensitivity = 68.1% (95% CI: 57.5–77.5%) and a specificity = 59.7 (95% CI: 47.9–70.8%, Figure 3).

Table 1. Demographicsa,b

<table>
<thead>
<tr>
<th>Metric</th>
<th>All OLT n = 92</th>
<th>No RIFLE-R n = 55</th>
<th>RIFLE-R n = 37</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-OP Age/years</td>
<td>54.3 ± 11.6</td>
<td>54.4 ± 12.8</td>
<td>54.2 ± 9.7</td>
<td>ns</td>
</tr>
<tr>
<td>Sex = female (%)</td>
<td>32 (34.8%)</td>
<td>15 (27.3%)</td>
<td>17 (45.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1 ± 6.8</td>
<td>25.7 ± 6.0</td>
<td>29.1 ± 7.5</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hepatitis C</td>
<td>39 (42.4%)</td>
<td>21 (38.2%)</td>
<td>18 (48.6%)</td>
<td></td>
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<tr>
<td>Hepatitis B</td>
<td>5 (5.4%)</td>
<td>4 (7.3%)</td>
<td>1 (2.7%)</td>
<td></td>
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<tr>
<td>ETOH</td>
<td>10 (10.9%)</td>
<td>7 (12.7%)</td>
<td>3 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>PSC</td>
<td>8 (8.7%)</td>
<td>6 (10.9%)</td>
<td>2 (5.4%)</td>
<td></td>
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<tr>
<td>With HCC</td>
<td>28 (30.4%)</td>
<td>16 (29.1%)</td>
<td>12 (32.4%)</td>
<td></td>
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<tr>
<td>INR</td>
<td>1.52 ± 0.66</td>
<td>1.48 ± 0.76</td>
<td>1.57 ± 0.46</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.99 ± 0.64</td>
<td>1.03 ± 0.40</td>
<td>0.94 ± 0.88</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine clearance (CG), mL/min</td>
<td>105.4 ± 42.8</td>
<td>93.1 ± 37.0</td>
<td>123.8 ± 44.6</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Creatinine clearance (MDRD), mL/min</td>
<td>95.7 ± 40.9</td>
<td>88.9 ± 44.9</td>
<td>105.8 ± 36.8</td>
<td>ns</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>136.2 ± 4.3</td>
<td>135.9 ± 3.8</td>
<td>136.6 ± 4.8</td>
<td>ns</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>5.32 ± 7.4</td>
<td>4.56 ± 7.41</td>
<td>6.48 ± 7.54</td>
<td>ns</td>
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<tr>
<td>MELD score</td>
<td>21.9 ± 7.4</td>
<td>22.5 ± 7.9</td>
<td>20.9 ± 6.5</td>
<td>ns</td>
</tr>
<tr>
<td>Intra-OP Cold ischemic time, h</td>
<td>7.0 ± 5.1</td>
<td>7.1 ± 5.7</td>
<td>6.8 ± 4.0</td>
<td>ns</td>
</tr>
<tr>
<td>Warm ischemic time, min</td>
<td>41.9 ± 7.3</td>
<td>40.5 ± 10.2</td>
<td>42.1 ± 7.1</td>
<td>ns</td>
</tr>
<tr>
<td>Deceased transplant (%)</td>
<td>74 (80.4%)</td>
<td>45 (81.8%)</td>
<td>29 (78.4%)</td>
<td></td>
</tr>
<tr>
<td>Length of surgery, h</td>
<td>8.4 ± 2.4</td>
<td>8.4 ± 2.2</td>
<td>8.5 ± 2.7</td>
<td>ns</td>
</tr>
<tr>
<td>Fresh frozen plasma, U</td>
<td>10.9 ± 12.8</td>
<td>9.4 ± 10.7</td>
<td>13.2 ± 15.1</td>
<td>ns</td>
</tr>
<tr>
<td>Red blood cells, U</td>
<td>9.8 ± 11.4</td>
<td>9.2 ± 11.5</td>
<td>10.5 ± 11.4</td>
<td>ns</td>
</tr>
<tr>
<td>Estimated blood loss, mL</td>
<td>3298 ± 3654</td>
<td>3085 ± 3563</td>
<td>3633 ± 3822</td>
<td>ns</td>
</tr>
<tr>
<td>Intra-OP diuretic use (%)</td>
<td>66 (71.7%)</td>
<td>38 (69.1%)</td>
<td>28 (75.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Intra-OP urine output, mL</td>
<td>1242 ± 973</td>
<td>1405 ± 1092</td>
<td>1000 ± 711</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Intra-OP urine output/bodyweight, mL/kg</td>
<td>17.3 ± 17.6</td>
<td>20.5 ± 20.3</td>
<td>12.6 ± 11.2</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Post-OP Hospital-free days/30 days</td>
<td>16.8 ± 9.2</td>
<td>17.1 ± 10.1</td>
<td>16.4 ± 7.9</td>
<td>ns</td>
</tr>
<tr>
<td>ICU-free days/30 days</td>
<td>25.2 ± 6.6</td>
<td>25.4 ± 6.8</td>
<td>24.8 ± 6.5</td>
<td>ns</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>3 (3.3%)</td>
<td>1 (1.8%)</td>
<td>2 (5.4%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*aOLT, orthotopic liver transplant; BMI, body mass index = weight (kilograms)/height (square meter); ETOH, alcohol-induced hepatic cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepato-cellular carcinoma; INR, international normalized ratio.  
*To convert serum creatinine from milligrams per deciliter into micromoles per liter, multiply with 88.4.

Fig. 1. Serum creatinine before and after liver transplantation comparing with (RIFLE-R) and without (no RIFLE-R) AKI defined by RIFLE-risk criteria (increase of serum creatinine by >50% compared to pre-OP values); mean ± SEM; *P < 0.05.
Deceased versus living-related liver transplantation

Patients who underwent deceased liver transplants had similar serum creatinine levels prior to surgery and but higher serum creatinine on post-OP Days 0–2 (Figure 4) compared to patients receiving living-related liver transplant. Twenty-nine of 74 patients undergoing deceased liver transplantation (39.2%) compared to 8 of 18 patients (44.4%) undergoing living-related liver transplantation developed AKI (not significant). Patients undergoing deceased liver transplants had similar urinary NGAL/urine creatinine ratios prior to surgery compared to living-related liver transplants but significantly higher urinary NGAL/urine creatinine ratios at all time points after surgery. Urinary NGAL/urine creatinine ratios increased significantly only in deceased liver transplants after surgery but not in living-related liver transplants. The greatest difference of urinary NGAL/urine creatinine ratio between deceased and living-related liver transplants was 3 h after reperfusion (urinary NGAL/urine creatinine ratio at 3 h: 7.64 ± 14.51 versus 0.67 ± 0.177, P < 0.0001; Figure 5).

Discussion

This study evaluated a novel biomarker for renal injury, urinary NGAL, after liver transplantation. We demonstrated that patients undergoing liver transplantation sustain substantial renal injury evidenced by an increase in urinary NGAL/urine creatinine ratios hours after reperfusion and by an increase of serum creatinine days after surgery. The discriminatory power of urinary NGAL/urine creatinine ratios to predict AKI as indicated by the area under the curve of the ROC curve was very good 3 h after reperfusion of the liver graft and good 18 h later. There was, however, no difference immediately after reperfusion and 24 h later. We further showed that deceased liver transplants sustain more severe renal injury than patients undergoing living-related liver transplants indicated by higher post-OP serum creatinine and higher urinary NGAL/urine creatinine ratios.

The predictive power of urinary NGAL/urine creatinine ratios is very similar to what was previously described of plasma NGAL 2 h after liver transplantation by Nieman et al. [16]. Plasma NGAL may be advantageous as a marker because there is no need to compensate for urinary dilution with the use of diuretics and the marker can be detected even if the patient is anuric. However, NGAL is released by many cell types from several organs and plasma NGAL may therefore derive from organs other than the kidney [22,23]. In most clinical scenarios, urinary NGAL is 5–10 times higher than plasma NGAL after renal injury and may therefore be easier to detect and have higher precision. The urinary NGAL levels we measured were lower than the plasma NGAL levels described by Niemann et al. but different ELISA kits were used and there is currently no uniformly accepted method of measuring NGAL.

Methods to standardize the detection of NGAL detection and create clinical platforms that allow rapid and reliable detection of NGAL in the blood [24] or urine [25] are currently being evaluated. We will need larger prospective studies to measure simultaneous urine and plasma renal

**Table 2.** Urinary NGAL/urine creatinine ratios (×10⁻³) before and after reperfusion of the liver graft when using different definitions of AKI

<table>
<thead>
<tr>
<th></th>
<th>No RIFLE-R</th>
<th>RIFLE-R</th>
<th>P-value</th>
<th>No RIFLE-I</th>
<th>RIFLE-I</th>
<th>P-value</th>
<th>No RIFLE-F</th>
<th>RIFLE-F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>n = 55</td>
<td>n = 37</td>
<td></td>
<td>n = 78</td>
<td>n = 14</td>
<td></td>
<td>n = 87</td>
<td>n = 5</td>
<td></td>
</tr>
<tr>
<td>Pre-OP</td>
<td>0.54 ± 1.23</td>
<td>0.50 ± 0.79</td>
<td>ns</td>
<td>0.50 ± 1.08</td>
<td>0.63 ± 1.03</td>
<td>ns</td>
<td>0.47 ± 1.03</td>
<td>1.45 ± 1.42</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Post-reperf.</td>
<td>2.75 ± 4.71</td>
<td>2.40 ± 3.94</td>
<td>ns</td>
<td>2.34 ± 4.08</td>
<td>4.14 ± 5.82</td>
<td>ns</td>
<td>2.64 ± 4.51</td>
<td>2.14 ± 1.86</td>
<td>ns</td>
</tr>
<tr>
<td>3 h</td>
<td>4.06 ± 7.26</td>
<td>10.17 ± 19.06</td>
<td>&lt;0.05</td>
<td>6.64 ± 12.74</td>
<td>11.38 ± 17.19</td>
<td>ns</td>
<td>6.18 ± 13.20</td>
<td>12.63 ± 20.20</td>
<td>ns</td>
</tr>
<tr>
<td>18 h</td>
<td>0.80 ± 2.07</td>
<td>3.53 ± 8.46</td>
<td>&lt;0.05</td>
<td>1.24 ± 4.13</td>
<td>5.81 ± 10.71</td>
<td>&lt;0.05</td>
<td>1.19 ± 3.91</td>
<td>26.04 ± 2.42</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24 h</td>
<td>0.71 ± 1.17</td>
<td>4.14 ± 12.02</td>
<td>ns</td>
<td>1.37 ± 4.53</td>
<td>7.25 ± 18.40</td>
<td>&lt;0.05</td>
<td>1.30 ± 4.30</td>
<td>22.76 ± 31.72</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*RIFLE-R: risk definition of the RIFLE criteria defined as an increase of serum creatinine by >50% when compared to baseline. RIFLE-I: injury definition of the RIFLE criteria defined as an increase of serum creatinine by >100% when compared to baseline. RIFLE-F: risk definition of the RIFLE criteria defined as an increase of serum creatinine by >200% when compared to baseline. Post-reperf., immediately after reperfusion of the liver graft.

**Fig. 2.** Urinary NGAL (panel A), urine creatinine (panel B) and urinary NGAL/urine creatinine ratios (panel C) before and after reperfusion of the liver graft comparing with (RIFLE-R) and without (no RIFLE-R) AKI defined by RIFLE-risk criteria (increase of serum creatinine by >50% compared to pre-OP values); mean ± SEM; *P < 0.05.
biomarkers in the same population to decide if urine or plasma biomarkers or a combination of both are best suited to predict AKI.

During the last several years, multiple new biomarkers of renal injury have been proposed and tested for the early detection of renal injury [9,26]. Using rapid sensitive biomarkers may have a similar impact on the diagnosis and treatment of AKI as the discovery of troponin-I on the diagnosis of myocardial infarction. Markers such as Kidney Injury Molecule-1 (KIM-1) or N-acetyl-beta-D-glucosaminidase (NAG) have already undergone some clinical evaluation. Newer markers such as soluble CD-73 [27] and netrin [28] demonstrated encouraging results in preclinical trials not only as an indicator of renal injury but also as potential nephroprotective interventions. The most promising biomarker of all, urinary NGAL, a 23-kDa protein, is secreted by distal nephrons in response to ischemic or nephrotoxic injury [7,29]. In diabetic nephropathy, urinary NGAL is increased not because of increased secretion but due to less reuptake in proximal tubular cells. We assume that the NGAL we measured derived from distal nephrons as a response to renal ischemia-reperfusion injury and not from decreased reuptake (or systemic secretion from the liver graft) but we will need further studies to elucidate the origin of urinary NGAL after liver transplantation.

After pediatric cardiac surgery, NGAL showed an excellent performance as a predictor of AKI [10]. It was much less sensitive and specific when predicting AKI after complex adult cardiac surgery but NGAL correlated better with indicators of intra-OP renal injury such as cardiopulmonary bypass time than change in serum creatinine [11]. This is further evidence that serum creatinine (and any definition of AKI that is based on change in serum creatinine) is much less sensitive to detect renal injury than urinary NGAL.

Fig. 3. ROC's curves of urinary NGAL/urine creatinine ratios to predict AKI defined by RIFLE-risk criteria (increase of serum creatinine by >50% compared to pre-OP values). Panel (A) urinary NGAL/urine creatinine ratio 3 h after reperfusion of the graft: area under the curve = 0.800 (95% CI: 0.732–0.869), P < 0.0001. Best cutoff value (the point closest to sensitivity = specificity = 1): 0.740 with a sensitivity = 83.5% (95% CI: 74.2–90.4%) and a specificity = 67.5% (95% CI: 56.1–77.6%). Panel (B) urinary NGAL/urine creatinine ratio 18 h after reperfusion of the graft: area under the curve = 0.636 (95% CI: 0.551–0.720), P < 0.001. Best cutoff value (the point closest to sensitivity = specificity = 1): 0.350 with a sensitivity = 68.1% (95% CI: 57.5–77.5%) and a specificity = 59.7% (95% CI: 47.9–70.8%).

Fig. 4. Serum creatinine before and after liver transplantation comparing deceased (CAD) with living-related liver transplants; mean ± SEM; *P < 0.05.

Fig. 5. Urinary NGAL/urine creatinine ratios before and after reperfusion of the liver graft comparing deceased (CAD) with living-related liver transplants; mean ± SEM; *P < 0.05.
renal injury with biomarkers such as urinary NGAL is the ability to evaluate new drugs for potential nephrotoxic effects much faster and with fewer study subjects. It took years and large multicenter studies to discover that tacrolimus is similarly nephrotoxic as cyclosporine [30]. Using novel sensitive biomarkers as an end point may expedite drug development and the recognition of nephrotoxic adverse effects. Early detection of renal injury may allow for preventive intervention with clinically novel therapies. For example, Grenz et al. have demonstrated that activation of endogenous adenosine 2B receptors produce powerful renal protection [31].

We demonstrated that patients undergoing living-related liver transplants sustained less renal injury than patients receiving deceased liver transplants. This may be due to lower MELD scores of living-related liver transplant recipients (they undergo transplantation earlier in the disease process). The piggyback technique used with living-related liver transplants avoids the occlusion of renal venous outflow, which may reduce renal injury during the anhepatic phase [32]. Patients undergoing living-related liver transplants also have markedly lower pre-OP and post-OP levels of inflammatory markers [33,34]. Inflammation (as well as prolonged hepatic ischemia [35]) causes renal injury. The differences in the inflammatory state and the duration of hepatic ischemia may therefore also be responsible for the difference in renal injury between living-related and deceased liver transplants detected with urinary NGAL. Further studies will need to evaluate if there is a direct correlation between inflammatory state and NGAL.

The relatively low number of subjects did not allow us to detect differences with regard to post-OP mortality or morbidity such as graft survival or the requirement for renal replacement therapy. The limitations of slow and insensitive change of serum creatinine to detect renal injury are well known and therefore future studies will have to correlate urinary NGAL not only with serum creatinine but also with established markers of renal injury and function such as urine microalbuminuria, fractional excretion of sodium or measured glomerular filtration rate. Without these large outcome studies, we cannot establish urinary NGAL as a clinical tool for the detection of renal injury after liver transplantation that replaces or supplements serum creatinine.

In conclusion, we found that urinary NGAL/urine creatinine ratio 3 h after liver transplantation is a very good marker of AKI after liver transplantation. We will need larger trials before NGAL (or a combination of novel markers) can supplement or replace serum creatinine in clinical practice. However, its ability to detect subtle renal injuries with high sensitivity and specificity already allows us to use it as a useful surrogate end point of renal injury in clinical trials.

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Conflict of interest statement. None declared.

(See related article by Feldkamp et al. Urinary neutrophil gelatinase-associated lipocalin (NGAL) for the detection of acute kidney injury after orthotopic liver transplantation. Nephrol Dial Transplant 2011; 26: 1456–1457)

References

Attitudes towards medication non-adherence in elderly kidney transplant patients

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Abstract

Background. Non-adherence to the post-transplant regime is a common problem in kidney transplant patients and may lead to rejection or even graft failure. This study investigated attitudes towards the post-transplant regime of immunosuppressive medication among the ever growing population of elderly kidney recipients.

Methods. Q methodology was used to explore attitude profiles. Participants (>65 years) were asked to rank-order opinion statements on issues associated with (non-)adherence. The rankings were subject to by-person factor analysis, and the resulting factors were interpreted and described as attitudes.

Results. Twenty-six elderly renal transplant recipients participated in the study. All passed the Mini-Mental State Examination. Two attitude profiles were found: (i) satisfied and easy-going (attitude A), and (ii) reserved and concerned (attitude B). Elderly patients with attitude A want to enjoy the new life following their kidney transplant, are not very concerned about having to recommence dialysis, now and then even forget their regime, and do not really worry about their kidney transplant, are fairly concerned over issues like rejection or going back on dialysis, and try to adapt their way of life to the regime. One-third of these elderly patients forget their medication at least once a month, but there was no difference between attitude groups.

Conclusions. Attitudes about the post-transplant regime differ among elderly patients, implying different needs.