Cytokine elevation and transaminitis after laparoscopic donor nephrectomy

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Yap S, Park SW, Egan B, Lee HT. Cytokine elevation and transaminitis after laparoscopic donor nephrectomy. Am J Physiol Renal Physiol 302: F1104–F1111, 2012. First published January 18, 2012; doi:10.1152/ajprenal.00543.2011.—Acute kidney injury frequently occurs in critically ill and often progresses into multiorgan dysfunction syndrome, resulting in high mortality. We previously showed that nephrectomized mice had increased interleukin (IL)–6 and tumor necrosis factor (TNF)–α that directly contributed to systemic inflammation and hepatic injury. In this study, we examined whether patients undergoing laparoscopic donor nephrectomy have increased postoperative cytokine levels with injury to the liver and whether the remaining kidney sustains injury. Serial serum and urine samples were collected from 32 patients undergoing laparoscopic donor nephrectomy and 17 patients undergoing nonrenal laparoscopic surgery. Serum IL-6, IL-18, TNF-α and monocyte chemotactic protein-1 (MCP-1) (markers of systemic inflammation) and urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), MCP-1, and IL-18 (markers of acute kidney injury) were quantified by enzyme-linked immunosorbent assay. We also analyzed serum creatinine, aspartate transaminase (AST), and alanine transaminase to assess liver injury. Patients who underwent donor nephrectomy not only demonstrated increased serum creatinine but also had significant increases in serum IL-6, MCP-1, and AST. Serum TNF-α also trended upward in donor nephrectomy patients. Finally, the donor nephrectomy group showed increased urinary NGAL but not KIM-1 at 24 h. Taken together, our findings of increased serum IL-6, MCP-1, and AST after donor nephrectomy suggest that an acute reduction of kidney function induces systemic inflammation and may have distant effects on the liver. Further studies are needed to correlate increased urinary NGAL after donor nephrectomy both as a potential marker for renal tubular stress and/or hypertrophy in the contralateral kidney.

acute kidney injury; interleukin-6; neutrophil gelatinase-associated lipocalin; tumor necrosis factor-α

ACUTE KIDNEY INJURY (AKI) is a frequent occurrence in critically ill with 5% to 20% of patients experiencing an episode of AKI during their intensive care unit stay (46). Mortality in critically ill patients with AKI remains high and is estimated to be >50% (54). Even when controlled for the severity of illness, AKI confers an independent risk for mortality regardless of whether AKI is mild or treated with renal replacement therapy (30). Hence, understanding the specific extrarenal effects of AKI in propagating or exacerbating multiorgan dysfunction is essential, since it may lead to new therapies in decreasing mortality after AKI.

In animal models, it is increasingly clear that AKI is not an isolated event and induces distant organ dysfunction to the lungs, heart, liver, and brain through a mechanism that involves neutrophil migration and elevated cytokine levels (14).

In particular, hepatic injury associated with AKI has important clinical implications, since the liver plays a vital metabolic role in critical illness, including protein synthesis, drug metabolism, and detoxification (35). In mice, nephrectomy results in early onset of inflammation, apoptosis, and tissue damage in hepatocytes with increased tumor necrosis factor-α (TNF-α) (13), interleukin (IL)-6, and monocyte chemotactic protein-1 (MCP-1), which contributes to transaminitis and periportal necrosis (41). To directly implicate cytokines in distant organ injury, we showed that IL-6- and TNF-α–deficient mice, as well as wild-type mice treated with IL-6 and TNF-α–neutralizing antibodies, were protected against hepatic injury after nephrectomy. In addition, IL-18 was demonstrated to be a key mediator of acute tubular necrosis in a mouse model of renal ischemia reperfusion, inducing both neutrophil and monocyte infiltration of the renal parenchyma (51).

Here, we studied healthy donor patients undergoing laparoscopic nephrectomy as a correlate to animal models of unilateral nephrectomy to determine the distant organ effects of an acute decrease in renal function in humans. We measured perioperative levels of inflammatory markers such as IL-6, IL-18, MCP-1, and TNF-α and evaluated for distant injury to the liver by measuring transaminites levels. Injury to the contralateral kidney is also of clinical interest, since the remaining kidney is potentially subjected to elevated cytokine levels in the setting of heightened metabolic demand secondary to glomerular hyperfiltration (20). We measured several markers of kidney injury, including neutrophil gelatinase-associated lipocalin (NGAL) (37), MCP-1 (38), IL-18 (40), and kidney injury molecule-1 (KIM-1) (16). We hypothesized that, after laparoscopic donor nephrectomy, cytokine and chemokine levels increase with transaminitis and injury to the contralateral remaining kidney.

MATERIALS AND METHODS

Patient recruitment. This study protocol was approved by the Columbia University Medical Center Institutional Review Board. Thirty-two patients undergoing left-sided laparoscopic donor nephrectomy and 17 patients undergoing other types of nonrenal laparoscopic surgery were recruited, and informed consent was obtained. Patients with chronic inflammatory disease, infection, malignancy, and kidney or liver disease were excluded from the study. Patients receiving right-sided nephrectomy were also excluded due to intraoperative hepatic retraction and dissection. All surgeries were performed under general anesthesia with volatile anesthetic (sevoflurane and isoflurane) supplemented with midazolam and opioids.
Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donor Nephrectomy (n = 32)</th>
<th>Control Laparoscopy (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>41.2 ± 1.90</td>
<td>45.6 ± 2.8</td>
<td>0.20</td>
</tr>
<tr>
<td>Male sex no. (%)</td>
<td>15 (47)</td>
<td>5 (29)</td>
<td>0.24</td>
</tr>
<tr>
<td>BMI*</td>
<td>27.0 ± 0.8</td>
<td>33.3 ± 5.2</td>
<td>0.06</td>
</tr>
<tr>
<td>American Society of Anesthesiology Class</td>
<td>1.3 ± 0.1</td>
<td>1.6 ± 0.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Operative time, min</td>
<td>216.1 ± 8.04</td>
<td>212.2 ± 17.5</td>
<td>0.84</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr, mg/dl</td>
<td>0.79 ± 0.03</td>
<td>0.77 ± 0.05</td>
<td>0.77</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>107.1 ± 4.3</td>
<td>105.7 ± 5.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Serum IL-6, pg/ml</td>
<td>9.6 ± 2.8</td>
<td>4.2 ± 1.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum IL-18, pg/ml</td>
<td>40.0 ± 40.0</td>
<td>391.5 ± 204.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Serum TNF-α, pg/ml</td>
<td>21.4 ± 9.4</td>
<td>5.9 ± 4.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Serum MCP-1, pg/ml</td>
<td>172.2 ± 26.2</td>
<td>174.0 ± 26.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Urine NGAL, ng/ml</td>
<td>8.1 ± 1.5</td>
<td>7.1 ± 1.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Urine MCP-1, pg/ml</td>
<td>21.1 ± 4.1</td>
<td>55.8 ± 7.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urine IL-18, pg/ml</td>
<td>84.6 ± 15.0</td>
<td>55.8 ± 17.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Urine KIM-1, pg/ml</td>
<td>630.2 ± 93.7</td>
<td>1,104.9 ± 217.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Intraop fluids, ml</td>
<td>4,515.6 ± 107.0</td>
<td>2,429.4 ± 219.46</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Results shown are means ± SE; n, no. of subjects. Cr, creatine; GFR, glomerular filtration rate; IL, interleukin; TNF, tumor necrosis factor; MCP, monocyte chemotactic protein; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1. *The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

At our institution, laparoscopic donor nephrectomy is typically performed using one 12-mm port and two 5-mm ports. After mobilization of the kidney, the 12-mm port is removed, and the incision is extended to ~5 cm to allow for extraction of the kidney via an endoacath bag (43). Patients undergoing control laparoscopic surgery required between three and six small incisions for laparoscopic ports.

Analyses of serum and urine. Serum and urine were collected immediately after induction of anesthesia and again at 5 and 24 h after completion of surgery. Specimens were separated into aliquots and stored at −80°C for a maximum of 3 mo. Serum was analyzed by Quest Laboratories (Teterboro, NJ) for common metabolic profile, albumin, and bilirubin. Serum creatinine and transaminase levels were measured using the Chronic Kidney Disease-Epidemiology Equation at a point where creatinine glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease-Epidemiology Equation. Estimated GFR, creatinine, transaminase, cytokine, and urine biomarker values were comparable between both groups. However, the donor nephrectomy group received significantly more intraoperative fluids (lactated Ringer). The donor nephrectomy group had lower urine MCP-1 compared with controls. However, urine MCP-1 levels in both groups were within the range of measured values among apparently healthy patients (38). In the control group, nine patients underwent laparoscopic hysterectomy. The remaining control patients received distal pancreatectomy with or without spleenectomy, uterine myomectomy, Nissen fundoplication, small bowel resection, and laparoscopic gastric banding. Control laparoscopy was performed with more laparoscopic ports (donors: 3.00 ± 0.03 ports vs. controls: 4.00 ± 0.22 ports, P < 0.001) and mildly higher insufflation pressure (donors: 15.0 ± 0.07 cmH2O vs. controls: 17.7 ± 0.7 cmH2O, P < 0.001). Thirteen out of 32 donor nephrectomy patients received mannitol (range: 12.5–37.5 grams). No additional diuretic was administered to either donor or control groups. Similarly, no albumin or other colloids were administered.

Serum creatinine and GFR. After nephrectomy, serum creatinine increased and neared plateau 24–48 h later (Fig. 1). At 48 h, creatinine had stabilized in the nephrectomy group and was increased by 0.61 ± 0.04 mg/dl, or 76.5 ± 4.0% above baseline (P < 0.001). There were no significant changes in baseline (baseline: 107.1 ± 4.3 ml/min, 48 h: 55.8 ± 2.4

![Fig. 1. Serum creatinine. Serum creatinine was measured at baseline and at 5, 24, and 48 h after surgery for donor nephrectomy (n = 32) and control laparoscopy (n = 17). # P < 0.005 vs. control. ** P < 0.005 vs. baseline. *** P < 0.0005 vs. baseline. Data are presented as means ± SE.](http://ajprenal.physiology.org/DownloadedFrom)
ml/min, P < 0.001). GFR for the control group showed no significant changes after surgery compared with baseline (baseline: 105.7 ± 5.6 ml/min, 48 h: 94.6 ± 12.5 ml/min, P = 0.76).

Intraoperative fluid balance and serum albumin. Large volumes of intravenous fluids (lactated Ringer) were administered to both donor patients and control laparoscopy patients (donor: 4.5 ± 0.1 liters, control: 2.4 ± 0.2 liters, P < 0.01). Intraoperative increase in extracellular fluid volume was calculated for donor nephrectomy patients (3.4 ± 0.2 liters) and control patients (1.3 ± 0.3 liters) by subtracting urine output and estimated blood loss multiplied by a factor of three from the total volume of intraoperative fluids given. Extracellular fluid volume was not calculated in the postoperative period because oral fluid intake was not measured. Serum albumin showed normal levels in either nephrectomy (baseline: 40.0 ± 3.2 g/dl, 24 h: 32.6 ± 3.4 g/dl) and control group (baseline: 4.01 ± 0.1 g/dl, 5 h: 3.74 ± 0.11 g/dl, 24 h: 3.49 ± 0.09 g/dl). None of the study subjects received perioperative albumin or colloid fluids.

Serum cytokines and chemokines. After control laparoscopic surgery, we found stable serum IL-6 at 5 h (baseline: 4.2 ± 1.7 pg/ml, 5 h: 15.8 ± 3.7 pg/ml, P > 0.05 vs. baseline) and at 24 h (13.1 ± 3.2 pg/ml, P > 0.05 vs. baseline) (Fig. 2A). In contrast, donor nephrectomy resulted in increased IL-6 at 5 h (baseline: 9.6 ± 2.8 pg/ml, 5 h: 36.4 ± 5.8 pg/ml, P < 0.01 vs. baseline) that continued to increase at 24 h (53.0 ± 10.6 pg/ml, P < 0.001 vs. baseline) and was significantly higher compared with the control laparoscopy group (P < 0.0002).

TNF-α also showed a similar increase that was highest at 24 h after nephrectomy compared with baseline (baseline: 21.4 ± 11.6 pg/ml, 24 h: 70.8 ± 33.5 pg/ml, P = 0.12) but did not reach statistical significance because of variance and sample size (Fig. 2B).

MCP-1 showed a delayed increase in the donor nephrectomy group (baseline: 172.2 ± 26.2 pg/ml, 5 h: 206.9 ± 28.4 pg/ml, 24 h: 278.7 ± 41.1 pg/ml, P < 0.05 at 24 h vs. baseline) (Fig. 2C). In contrast, control laparoscopic surgery showed no significant deviation from baseline (baseline: 174.0 ± 26.4 pg/ml, 5 h: 180.4 ± 21.8 pg/ml, 24 h: 195.7 ± 31.1 pg/ml, P > 0.05).

Serum IL-18 did not change significantly nor increase above normal levels in either nephrectomy (baseline: 40.0 ± 40.0 pg/ml, 5 h: 300.2 ± 129.7 pg/ml, 24 h: 122 ± 86.3 pg/ml, P > 0.05 vs. baseline) and control (baseline: 391.5 ± 204.0 pg/ml, 5 h: 171.1 ± 94.7 pg/ml, 24 h: 723.7 ± 361.3 pg/ml, P > 0.05 vs. baseline) (Fig. 2D). Enzyme-linked immunosorbent assay for IL-18 was validated with serum from 40 apparently healthy volunteers demonstrating a mean serum IL-18 level of 393.4 pg/ml, ranging from undetectable to 732.7 pg/ml.

Urine cytokines. At baseline, urine IL-6, TNF-α, and IL-18 were comparable between the two groups (Table 2). At 5 h, both nephrectomy and control groups had transiently increased urine IL-6 concentration that trended back toward baseline at 24 h. Concentration of IL-6 in the urine was significantly elevated at 5 h compared with baseline (P < 0.01) when normalized by urine creatinine, but renal excretion of IL-6 per hour was unchanged (P = 0.34) in the nephrectomy group. Increased serum IL-6 at 24 h was significantly correlated with normalized urine IL-6 (Pearson’s r = 0.415, P = 0.049) and renal excretion (Pearson’s r = 0.45, P = 0.031). Urine TNF-α concentration trended higher (P = 0.06) and renal excretion of TNF-α per hour was significantly higher (P < 0.05) after donor nephrectomy at both 5 and 24 h compared with the control group. For both donor and control groups, urine IL-18 approximated the lowest reference level at baseline and decreased to undetectable levels postoperatively. Urine MCP-1 increased significantly from baseline in the donor nephrectomy group at 5 and 24 h. The control group showed similar increase but did not achieve significance because of higher variance and was not statistically different from the donor group.
Table 2. Urine cytokines and chemokines

<table>
<thead>
<tr>
<th></th>
<th>Urine IL-6</th>
<th>Urine TNF-α</th>
<th>Urine MCP-1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>5 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Concentration, pg/ml</td>
<td>4.6 ± 2.8</td>
<td>1.7 ± 1.2</td>
<td>14.0 ± 8.8</td>
</tr>
<tr>
<td>Normalized, 10^10</td>
<td>35.2 ± 9.7</td>
<td>35.4 ± 9.7</td>
<td>82.6 ± 20.6</td>
</tr>
<tr>
<td>Renal excretion, pg/h</td>
<td>NC</td>
<td>1,248</td>
<td>409</td>
</tr>
</tbody>
</table>

Results shown are means ± SE. Urine cytokines and chemokines were measured for donor nephrectomy (n = 32) at baseline and 5 h, and control laparoscopy (n = 17) at baseline and 5 h. AST increased significantly at 24 h after donor nephrectomy (P < 0.05 vs. baseline). Urine KIM-1 did not show significant changes in either the donor (baseline: 0.08 ± 0.01 × 10^-5, 5 h: 0.15 ± 0.05 × 10^-5, 24 h: 0.39 ± 0.16 × 10^-5, P < 0.05 at 24 h vs. baseline). Urine TNF-α and MCP-1 excretion was increased at 24 h after donor nephrectomy. Serum transaminase. AST and ALT were measured as markers of hepatic injury. Compared with baseline, normalized AST increased significantly at 5 and 24 h after donor nephrectomy, whereas no significant change was noted after control laparoscopy (Table 3). ALT trended higher (P = 0.11) after donor nephrectomy. Increases in ALT correlated with increases in serum IL-6 (Pearson’s r = 0.32, P = 0.04) and TNF-α (Pearson’s r = 0.35, P = 0.02).

Urine biomarkers. To determine whether the remaining contralateral kidney sustains injury, we measured sensitive markers for renal tubular injury, including NGAL and KIM-1. After control laparoscopy, urinary NGAL remained unchanged postoperatively (baseline: 0.11 ± 0.02 × 10^-5, 5 h: 0.19 ± 0.07 × 10^-5, 24 h: 0.21 ± 0.08 × 10^-5, P > 0.05) (Fig. 3A). In contrast, patients who underwent donor nephrectomy showed significantly higher urinary NGAL at 24 h compared with baseline (baseline: 0.08 ± 0.01 × 10^-5, 5 h: 0.15 ± 0.05 × 10^-5, 24 h: 0.39 ± 0.16 × 10^-5, P < 0.05 at 24 h vs. baseline). Urine KIM-1 did not show significant changes in either the donor (baseline: 680.8 ± 85.1 × 10^-5, 5 h: 349.3 ± 96.4 × 10^-5, 24 h: 251.4 ± 46.0 × 10^-5, P > 0.05) or control (baseline: 1,842.2 ± 400.2 × 10^-5, 5 h: 1,431.2 ± 292.6 × 10^-5, 24 h: 1,696.8 ± 261.7 × 10^-5, P > 0.05) (Fig. 3B) group and approximated normal values measured in apparently healthy subjects (7).

DISCUSSION

The major findings of this study are that laparoscopic donor nephrectomy results in increased systemic inflammation with increased IL-6 and MCP-1, and subclinical transaminitis. Compared with the most commonly used AKI classification systems, laparoscopic donor nephrectomy resulted in an acute decline of renal function that is between the risk and injury categories as defined by the RIFLE criteria (2), and between the stage I and stage II categories according to the AKI Network Criteria (35). We found that, despite a nearly 50% decrease in renal function, urine IL-6 concentration was unchanged, and TNF-α excretion was increased at both 5 and 24 h, suggesting that elevated cytokine levels may be due in part to increased endogenous production. We also found increased urine NGAL after donor nephrectomy.

The findings of this study offer a clinical correlation to previously published animal studies demonstrating the extrarenal effects of AKI to the lungs, heart, liver, and brain characterized by elevated cytokine levels and neutrophil recruitment (14). In the lungs, animal models of bilateral nephrectomy show increased TNF-α and IL-6, which lead to uncontrolled systemic inflammation, neutrophil infiltration, and impaired vascular permeability resulting in pulmonary edema (27). Renal ischemia reperfusion in rats leads to increased TNF-α, IL-1, and intercellular adhesion molecule-1 mRNA and myeloperoxidase activity in the heart, resulting in left ventricular dysfunction at 48 h after reperfusion (25). Furthermore, mice models of AKI describe cytokine-mediated cerebral edema, gliosis, pyknosis, and increase in glial fibrillary acidic protein in the brain (32). The results of this study validate key findings previously published by our laboratory which demonstrates that animal models of nephrectomy AKI result in increased TNF-α, IL-6, and MCP-1 expression that mediates transaminitis and periportal necrosis. The major implication of these
findings is that AKI may initiate or aggravate conditions of cytokine dysregulation such as systemic inflammatory response syndrome (4), thus enhancing our understanding how AKI directly increases mortality and leads to earlier onset of multiorgan dysfunction among the critically ill.

IL-6 is a proinflammatory cytokine that plays a major role in the acute phase response (17) and increases vascular permeability (34). Additionally, IL-6 has been shown to induce a delayed expression of MCP-1 that mediates the transition from an innate immune response characterized by neutrophil infiltration to an acquired immune response with increased macrophage infiltration (23, 44, 52). In this study, we demonstrated that IL-6 rapidly increased after nephrectomy, with a delayed increase in MCP-1 at 24 h. Our findings correlate with recently published clinical research showing increased IL-6 levels after laparoscopic donor nephrectomy (26). However, because the objective of Kielstein et al. (26) was to evaluate the relationship between asymmetric dimethylarginine and inflammation, no control group was enrolled. Hence, it was not possible to determine whether IL-6 elevation after donor nephrectomy is distinct from other types of intraperitoneal laparoscopic surgery that typically occur from activation of neutrophils, monocytes, and fibroblasts in the surgical field (24).

However, there is controversy whether serum cytokine elevation after AKI is due to increased endogenous production and/or decreased renal excretion (3, 19). Our results, which suggest that renal excretion of IL-6 is maintained, imply that elevated serum IL-6 is due predominantly to increased endogenous production as opposed to decreased renal excretion. Moreover, increased renal excretion of TNF-α may explain why increased serum TNF-α levels did not achieve statistical significance.

It is unknown why serum IL-6 increases after nephrectomy. Uremia stimulates cytokine production and may explain rapid cytokine elevation after bilateral nephrectomy in mice (18, 41). However, this is unlikely in human kidney donors, since blood urea nitrogen decreased postoperatively due to aggressive intravenous fluid administration and postoperative diuresis. Increased IL-6 is likely due to extrarenal production compounded by decreased GFR. The liver is a possible source, since IL-6, TNF-α and MCP-1 mRNA expression increased in the liver after nephrectomy in mice (41).

Our experimental findings showed significantly elevated AST with ALT trending higher after donor nephrectomy. Clinically, AST is a more sensitive marker than ALT for injury to the liver and, to a lesser extent, heart and skeletal muscle (12). This is likely due to the higher AST concentration in zone 3 of the hepatic acinus, which is the most vulnerable region of the liver to ischemic and toxic injury (45, 47). Insults to the liver, especially those that are characteristic of hepatic necrosis, generally show earlier and higher elevation of AST compared with ALT (12).

Increases in AST after donor nephrectomy, although statistically significant after normalization for hemodilution, were an order of magnitude less than that observed in mice after unilateral nephrectomy (41). Further studies could potentially demonstrate that patients who sustain more severe forms of renal injury such as bilateral nephrectomy, prolonged ischemia-reperfusion (>30 min), or renal artery occlusion may show more overt clinical signs of liver injury. However, it is difficult to test this hypothesis in a healthy patient population, since renal ischemia times at our institution rarely exceed 15 min and bilateral nephrectomy is rarely performed for indications other than end-stage renal failure or bilateral renal malignancies.

The smaller change demonstrated in humans after unilateral nephrectomy may also reflect interspecies differences. It may also reflect the anti-inflammatory effects of medications given intraoperatively such as isoflurane, sevoflurane, and dexamethasone (given for nausea and vomiting prophylaxis). We previously demonstrated that mice anesthetized with volatile anes-

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**Table 3. AST and ALT**

<table>
<thead>
<tr>
<th></th>
<th>AST, U/l</th>
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<th>ALT, U/l</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>5 Hr</td>
<td>24 Hr</td>
<td></td>
</tr>
<tr>
<td>Donor nephrectomy</td>
<td>19.5 ± 1.0</td>
<td>22.9 ± 1.8</td>
<td>23.9 ± 2.6</td>
<td>17.3 ± 1.3</td>
</tr>
<tr>
<td>Control laparoscopy</td>
<td>20.5 ± 1.6</td>
<td>20.5 ± 1.0</td>
<td>22.2 ± 1.1</td>
<td>16.8 ± 1.3</td>
</tr>
</tbody>
</table>

Results shown are means ± SE. AST, aspartate transaminase; ALT, alanine transaminase. Liver function tests were measured for donor nephrectomy (n = 32) and control laparoscopy (n = 17). Adjustments for hemodilution using albumin correction are shown in italics. *P < 0.05 vs. baseline. **P < 0.01 vs. baseline.
thetics had attenuated levels of IL-6 and hepatic injury after septic peritonitis compared with those anesthetized with pentobarbital (28). In addition, dexamethasone has been shown to modulate expression of IL-6 in mast and basophilic cell lines stimulated with phorbol 12-myristate,13-acetate (31).

Both donor and control laparoscopy patients had significant increases in extracellular fluid volume during their perioperative course. This is due to large positive perioperative fluid balance that resulted in an ~10–20% increase in extracellular fluid volume (this approximation may underestimate the actual increase, since the quantity of oral fluid intake was not available for the majority of patients). This is consistent with an ~13% decrease in serum albumin observed in both nephrectomy and control groups. The increase in extracellular fluid volume leads to dilution of liver function tests. For example, patients on hemodialysis have been found to have a nearly 50% increase in serum transaminase levels after hemodialysis with removal of up to 5 liters of extracellular fluid (33). As a result, serum cytokines, MCP-1, and transaminases were normalized to change in serum albumin. The concentrations of urine cytokines and biomarkers are also influenced by the concentration of urine, which is affected by hydration, diuresis, or, potentially, renal injury. It appears that different methods of quantifying urine markers have unique advantages. While absolute concentrations of biomarkers best diagnose AKI, normalized concentrations best predict outcomes such as death or dialysis, whereas the rate of renal excretion was associated with increased severity (42).

We measured urinary biomarkers to assess for renal injury to the contralateral kidney after unilateral nephrectomy, since the remaining kidney is subjected to cytotoxicity from elevated cytokine levels in the setting of increased metabolic demand. NGAL showed an increase at 24 h, but this value was below the cutoff NGAL value of 150 ng/ml (15) commonly used to define AKI to optimize sensitivity and specificity. This, in addition to negative findings in other biomarkers (urinary KIM-1, IL-18, and MCP-1), is consistent with long-term retrospective epidemiological studies of kidney donors suggesting no evidence of increased risk of hemodialysis compared with the general population (11, 21).

However, the delayed onset of statistically significant urinary NGAL among kidney donors in the absence of any increase in the control group is unexpected especially because these patients are presumably healthy with excellent baseline renal function. NGAL has been shown recently to have a dose-dependent relationship with tubular stress and injury, and is primarily expressed by the thick ascending limb (39). Glomerular hyperfiltration after nephrectomy exacerbates metabolic demand on the distal tubules, which are responsible for generating an osmotic gradient by active transport of sodium. This is in contrast to KIM-1 and IL-18, which are preferentially expressed in the proximal tubules (10, 16) and are specific for injury to the proximal tubules such as acute tubular necrosis (8, 16, 40). Hence, the presence of increased NGAL in the absence of KIM-1 and IL-18 may underscore the vulnerability of the distal tubules as opposed to the proximal tubules in the setting of glomerular hyperfiltration (5, 6, 20). It may also reflect the decreased specificity exhibited by NGAL, since Munshi et al. (38) recently demonstrated that NGAL increased in response to a variety of insults, including proximal tubular, prerenal, and postrenal injury, as well as azotemia. Last, delayed increase in NGAL may be a result of the ongoing renal hypertrophy, a process that begins soon after nephrectomy and is nearly completed 1 wk thereafter (1). In animal models of nephrectomy, increase in DNA expression in tubular cells has been demonstrated within 6 h after nephrectomy with cellular division peaking 2 days later (49). Delayed expression of NGAL after nephrectomy may originate from proliferating tubular cells, since NGAL plays a critical role in the conversion of undifferentiated kidney cells into epithelia and tubular cells (53). Unfortunately, because of the limited study length of 24 h after nephrectomy, the duration or peak level of NGAL expression is indeterminable.

One of the limitations of this study is the design of the control group. This reflects the unique circumstances surrounding kidney donation in that the patients are rigorously screened for preexisting medical conditions such as hypertension and diabetes and undergo elective surgery without an underlying pathology and without medical indication. In contrast, the vast majority of patients undergoing laparoscopic surgery at our institution were excluded for underlying pathology of inflammatory, infectious, or malignant nature, which may result in altered cytokine homeostasis (9). Therefore, the control group consists of patients receiving laparoscopic surgery for underlying medical reasons that were thought to have the least effect on baseline cytokine levels such as fibroids, menorrhagia, and pancreatic cysts.

Taken together, these findings show that donor nephrectomy results in elevated serum IL-6 levels because of increased endogenous production. Increased cytokine levels correlated with transaminitis, suggesting that acute reduction in renal function due to unilateral nephrectomy may have direct effects on distal organs such as the liver. Establishing IL-6 as a mediator in the extrarenal effects of AKI is clinically important, since it may lead to use of cytokine-binding proteins and other anti-inflammatory agents to improve outcome beyond what current supportive renal measures can offer. Last, increased NGAL after nephrectomy may be indicative of underlying renal hypertrophy or tubular stress from increased metabolic demand secondary to glomerular hyperfiltration.

GRANTS
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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

REFERENCES
Cytokine elevation after nephrectomy


