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**Urinary neutrophil gelatinase-associated lipocalin (NGAL) for the detection of acute kidney injury after orthotopic liver transplantation**

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Acute kidney injury (AKI) is a frequent complication after orthotopic liver transplantation (OLT). The incidence of post-operative AKI according to acute kidney injury network criteria can be estimated to be as high as 60% of all patients after liver transplantation [1–3]. Besides increasing morbidity and length of hospitalization, graft survival is significantly reduced, even with only modest increase of serum creatinine (> 0.5 mg/dL, AKIN Stage 1) [3,4]. Post-operative AKI is also an independent risk factor for mortality during the first year after transplantation [1].

The development of AKI following liver transplantation is multifactorial and influenced by numerous pre-, intra- and post-operative factors. During the preoperative period, conditions predisposing for post-operative AKI can be present. The most commonly observed preoperative renal dysfunction is due to the hepato-renal syndrome characterized by arterial vasodilatation mainly in the splanchnic vessel area and severe renal vasoconstriction. Intraoperative factors include long periods of vascular crossclamping, hypotension, high doses of vasoressors and large volume load. Post-operative hypotension and calcineurin inhibitors such as cyclosporine and tacrolimus also support conditions potentially culminating in AKI [4].

Currently, there are no effective measures or treatment strategies available for the prevention or treatment of AKI. The development of effective interventions is hampered by the limited ability of early detection of AKI [5,6]. In order to develop and evaluate strategies for the prevention and treatment of AKI, there is a great need for early biomarkers.

In this issue of *Nephrology Dialysis Transplantation*, Wagener et al. [7] propose increased urinary neutrophil gelatinase-associated lipocalin (NGAL)/creatinine ratio as an early predictor of AKI following OLT. The data source is a prospective cohort study of 92 patients undergoing OLT at a single centre between 2008 and 2010 (18 living related, 74 deceased). Patients underwent OLT for different reasons (hepatitis C, hepatitis B, nutritive toxic liver cirrhosis, primary sclerosing cholangitis) and showed a modified end stage liver disease score of 21.9 ± 7.4 prior to surgery. Patients did not require renal replacement therapy preoperatively and apparently had intact kidney function according to the serum creatinine (0.99 ± 0.64 mg/dL).

Urine samples were collected after induction of anaesthesia prior to incision, immediately after portal reperfusion of the liver graft and then 3, 18 and 24 h later. To compensate for possible urinary dilution or concentration, the results of the NGAL measurements are given as urinary NGAL/creatinine ratio. AKI was defined according to the RIFLE criteria [7].

NGAL compared to serum creatinine for the diagnosis of AKI after OLT. Interestingly, in patients with AKI, NGAL...
already declined between 3 and 18 h after OLT and there was no significant difference between the AKI and non-AKI group after 24 h. This time course suggests that the increase in urinary NGAL/creatinine is specific for the kidney injury during OLT. Just before transplantation, and immediately after reperfusion, there were no differences in urinary NGAL/creatinine concentration between patients with AKI and those without AKI. The investigators conclude that urinary NGAL/creatinine ratio is an early marker of AKI after liver transplantation, which, because of its high sensitivity and specificity, might be a useful surrogate end point of AKI in clinical trials.

Urinary NGAL might be a more sensitive marker for AKI, especially in patients after liver transplantation, than serum creatinine because unlike serum creatinine, it is not dependent on drugs, muscle mass or liver metabolism [8]. Urinary NGAL is mainly produced by the distal nephron after injury and is immediately secreted into the urine. In contrast, plasma NGAL is a product of multiple sources. Nevertheless, AKI also triggers increasing amounts of messenger RNA in other tissues than the distal nephron including liver and lung [9]. This might explain why both urinary and plasma NGAL proved to be reliable markers for AKI in children after cardiac surgery with an AUC–ROC of >0.9 [14]. But also in patients with AKI after liver transplantation, it was shown to be of benefit. In a prospective study of 59 patients undergoing liver transplantation between 2007 and 2008, plasma NGAL was measured [11]. Forty-five of these patients had a preserved preoperative renal function (serum creatinine <1.5 mg/dL without renal replacement therapy). More than 50% (24 patients) fulfilled this study’s definition of AKI (≥250% increase in serum creatinine compared to baseline). A single measurement of plasma NGAL 2 h after reperfusion was a fairly good marker for the development of AKI with an AUC–ROC of 0.79 at a cut-off value of 139 ng/mL. However, in other studies with different cohorts, NGAL performed less well and the range of the reported specificity and sensitivity is quite large (AUC–ROC between 0.61–0.96) [9]. This was ascribed to more confounding variables in adults such as age and pre-existing (latent) chronic kidney disease. This is probably the reason why NGAL measurement performs better in patients with baseline eGFR >60 mL/min [12]. A way to minimize the confounding factor of pre-existing tubular damage might be to report the data as a difference to baseline measurements [11]. Additionally, plasma NGAL might not be specific for renal damage since NGAL is produced at a low level in many different tissues. Besides by renal cells, it is secreted especially by injured epithelial cells of the colon, liver and lung and as a product of many cancers [9] and as an acute-phase protein by activated neutrophils and other cells [11]. A prospective observational study analysed NGAL levels in patients in an intensive-care setting. A significant increase in plasma NGAL was shown in patients affected by AKI and sepsis in comparison to patients with non-septic AKI [13]. This suggests that plasma NGAL might be a good biomarker for inflammation, but in the context of a systemic inflammatory reaction, it loses power to predict the development or prognosis of AKI. The use of urinary NGAL might be a possibility to increase the specificity of the detection of renal damage in the context of inflammation.

To our knowledge, the study by Wagener et al. included the largest cohort for diagnosing AKI using urinary NGAL in patients undergoing liver transplantation so far. In an observational study on novel biomarkers in patients undergoing liver transplantation, Portal et al. collected data on 95 patients for AKI. But mainly due to many patients with anuria, they were able to collect urine in 46 of 95 patients only [10]. This might be a reason why urinary NGAL—although being a powerful predictor for AKI and presenting better results than serum creatinine—was outperformed by plasma NGAL in this study.

Opinions are diverse concerning normalization of urinary NGAL to urine creatinine concentration as presented by Wagener et al. This illustrates the attempt to compensate for possible urinary dilution or concentration [7]. On the other hand, adjustment for urine creatinine implicates a steady state for urine creatinine during the development of AKI, which is clearly not the case. However, studies normalizing for urine creatinine show slightly higher AUC–ROC values and increased statistical significance [9].

A very important feature of the study of Wagener et al. is that the measurement of urinary NGAL was performed very early (3 h after the insult). This might enhance the specificity of urinary NGAL compared to plasma NGAL; unfortunately plasma NGAL was not measured in this study. Nevertheless, although not applicable in the state of anuria, one would assume that measurement of urinary NGAL could be a more “pure” predictor of AKI with less confounding variables and being more restricted to tubular damage.

For future development of effective tools against AKI, early predictors are necessary. Urinary NGAL seems to be a promising novel biomarker. But clearly, more studies are needed to understand the origin of urinary NGAL and the mechanisms of renal NGAL secretion in response to the renal insult. Therefore, larger multicentre studies with well-defined patient cohorts and uniform mechanisms of renal injury are needed. This would not only give us valuable information of the usefulness of NGAL as a biomarker for AKI but would also allow us to study the impact of different renal injury mechanisms on the diagnostic performance of NGAL.

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(See related article by Wagener et al. Urinary neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after orthotopic liver transplantation. Nephrol Dial Transplant 2011; 26: 1717–1723)

References

Congenital solitary functioning kidneys: which ones warrant follow-up into adult life?

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Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of paediatric end-stage renal failure (ESRF) \cite{1,3}. The clinical spectrum of CAKUT includes a variety of malformations of the urinary tract. Understanding the rate of progression for the different CAKUT categories and predicting long-term outcome is critical for a correct clinical management of these patients and for the transition of care from paediatric to adult nephrology.

Among CAKUT categories, congenital solitary functioning kidney (SFK) has been the object of debate whether it constitutes a benign condition or presents a significant risk of progression to ESRF \cite{2–14}.

In the present issue of Nephrology Dialysis and Transplantation, Westland \textit{et al.} report on the results of the KIMONO-study (REF ID pending). The authors analysed a large cohort of 206 children with SFK of congenital origin to identify indicators of renal injury. Among them, 116 had a primary congenital solitary functioning kidney (pSFK) and 90 had a secondary solitary functioning kidney (sSFK) after unilateral nephrectomy due to congenital anomalies of the kidney or urinary tract. Ipsilateral CAKUT was present in \sim 30\% of children from both groups. Among the patients with pSFK (which encompasses unilateral renal agenesis and multicystic dysplastic kidney), ipsilateral anomalies were significantly more frequent in cases with renal agenesis. Similarly, high blood pressure was present in comparable proportions between pSFK and sSFK, and it was significantly higher in the subgroup with renal agenesis. About 20\% of children were using renoprotective agents and \sim 12\% had albuminuria. Overall, >30\% of patients with SFK showed evidence of renal injury. These data indicate that a significant fraction of children with congenital solitary kidney show evidence of renal parenchyma damage early in life and can potentially progress to ESRF in adulthood. These numbers are consistent with our previous report on long-term outcome in CAKUT patients, in which 50\% of children with solitary kidney reached ESRF by the age of 30 \cite{11}. Westland \textit{et al.} explored the rate of progression by generalized estimated