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COMMENTARY

Are recently reported biomarkers helpful for early and accurate diagnosis of acute kidney injury?

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Abstract

Over the past few years and with the use of innovative genomic and proteomic tools, several molecules that their urinary concentration is modified during acute kidney injury have been identified and proposed as biomarkers. Among the most studied biomarkers are neutrophil gelatinase-associated lipocalin-2, kidney injury molecule-1, interleukin-18, cystatin C, N-acetyl-β-D-glucosaminidase, liver fatty-acid binding protein, and heat shock protein 72. Here, we reviewed and compared the sensitivity and specificity of each biomarker for the appropriate diagnosis of acute kidney injury, as well as its ability to stratify renal injury and to monitor a renoprotective pharmacologic strategy.

Keywords: NGAL, IL-18, Kim-1, Hsp72, cystatin C, NAG, L-FABP

Introduction

The major causes of acute kidney injury (AKI) are ischaemia/reperfusion (I/R) and nephrotoxic injuries (Friedewald & Rabb 2004). Nearly 15% of hospitalized patients are at risk of developing AKI; however, its incidence increases to 40–60% in patients admitted to the intensive care unit (Kelly 2006). During AKI, many alterations occur at the cellular and molecular levels that finally lead to renal dysfunction and structural injury (Sharfuddin & Molitoris 2011). Despite recent advances in the understanding of AKI pathophysiology, the mortality rate remains elevated mainly because of the lack of effective therapies and early detection of AKI (Wu & Parikh 2008). Furthermore, early treatment of AKI might be correlated with a better prognosis; therefore, the identification of successful biomarkers for early diagnosis, would improve the effectiveness of therapeutic strategies (Yamamoto et al. 2007). In addition, it is imperative to find biomarkers that can correctly stratify the extent of renal injury that each patient suffered because patients who undergo renal dysfunction and tubular damage during AKI are at a high risk of developing chronic kidney disease (CKD) (Siew et al. 2012). The identification of these at-risk patients would allow the clinicians to make an appropriate intervention to ameliorate their prognosis and reduce the risk of a requirement for renal replacement therapy or renal transplant.

Conventional biomarkers for detection of AKI

For many decades, the diagnosis of AKI has been based on an elevation of serum creatinine and blood urea nitrogen (BUN) or the presence of oliguria (Mehta & Chertow 2003). These traditional biomarkers, however, have several shortcomings in establishing an early and sensitive diagnosis of AKI (Bagshaw & Gibney 2008). In the case of creatinine, many factors that modify serum creatinine concentration are not linked to renal injury, such as muscular activity, body weight, age, gender, race, and protein intake. In addition, the elevation of serum creatinine usually occurs from 48 to 72 h after the renal injury has occurred; thus, an early diagnosis based on creatinine elevation is unlikely to be feasible (Coca &

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Parikh 2008). Moreover, a large proportion of the renal tissue may be injured before serum creatinine rises, an outcome that is evidenced in the renal transplantation context, where the kidney donor loses 50% of the total kidney mass without changes in serum creatinine (Herrera & Rodriguez-Iturbe 1998). BUN is also an insensitive AKI marker because its concentration may be altered by non-renal factors, such as a high-protein diet, glucocorticoid therapy or trauma. In addition, in a great number of patients, AKI is developed without loss of excretory function; thus, oliguria might underestimate the number of patients with acute tubular damage (Ronco et al. 2010). In this regard, the identification of novel biomarkers of AKI that would allow for the establishment of an early AKI diagnosis is needed. Once a new biomarker is found, its sensitivity as a reliable and early marker of AKI must be assessed in five critical phases: (i) experimental studies identifying the molecules of which expression or concentration is modified during experimental AKI in mice or rat; (ii) the identification of a reliable and reproducible method to quantify the biomarker in urine samples; (iii) clinical assays to detect the proposed biomarker in samples from patients with clinical AKI and evaluations of the biomarker's ability to detect AKI prior to diagnosis with the conventional methods; (iv) large-scale validation to determine the biomarker's properties, such as sensitivity and specificity; and (v) screening the population with the new biomarker throughout disease treatment, disease evolution and improvement of outcomes (Siew et al. 2011).

Novel biomarkers of AKI

Over the past few years, many studies have focused on the development of early and sensitive biomarkers for AKI. With the use of innovative genomic and proteomic tools, several molecules of which their serum or urine concentration is modified during AKI in experimental models and humans have been identified and proposed as biomarkers. From these studies, nearly 20 molecules have been proposed to serve as biomarkers of AKI. Among the most studied and promising biomarkers are neutrophil gelatinase-associated lipocalin-2 (NGAL), kidney injury molecule-1 (Kim-1), interleukin-18 (IL-18), cystatin C, N-acetyl-β-D-glucosaminidase (NAG), liver fatty-acid binding protein (L-FABP), and heat shock protein 72 (Hsp72).

Neutrophil gelatinase-associated lipocalin-2

NGAL is a 25-kDa protein that is covalently bound to gelatinase from neutrophils and is expressed at low levels in several human tissues, including lung, stomach, colon, and epithelial cells located in the proximal tubule (Cowland & Borregaard 1997; Flower et al. 2000). NGAL is one of the fastest up-regulated proteins after an ischaemic insult in the rat (2 h) as is shown in Table 1 (Mishra et al. 2003). Mori et al. (2005) found that the NGAL concentration displayed a significant increase in plasma and urine by 10-fold and 100-fold, respectively, in patients who suffered from AKI in the intensive care unit (ICU) compared with control humans. These findings indeed showed a substantial elevation of NGAL during an AKI episode. There is also an evidence that NGAL is an early AKI biomarker. Mishra et al. (2005) showed, in a population of children with cardiopulmonary bypass who developed AKI, a 10-fold elevation of NGAL in the urine and plasma 2–6 h after the surgery, whereas the elevation of serum creatinine was observed 1–3 days after the surgery. These observations have also been corroborated in adult populations subjected to cardiopulmonary bypass (CBP) (Parikh et al. 2011a;Tuladhar et al. 2009). As shown in Table 2, NGAL has been extensively studied for the early diagnosis of AKI after cardiac surgery, showing a 100% efficiency in diagnosing AKI at 2 h post-surgery (Bennett et al. 2008; Torregrosa et al. 2012; Matsui et al. 2012). Other studies, however, have reported a lower effectiveness (Han et al. 2002; Wagener et al. 2008; Koyner et al. 2010; Parikh et al. 2011b; Parikh, 2011a; Pechman et al. 2009). Wagener et al. (2009) found that urinary NGAL was consistently elevated after cardiac surgery (1, 3, 8, and 24 h). Unfortunately, NGAL was also elevated in non-AKI patients. The poor effectiveness of NGAL in these patients was evidenced by the low area under the curve (AUC), sensitivity, and specificity (0.67, 69, and 65%, respectively) 3 h after surgery. In the transplantation setting, NGAL seems to show a better performance (Nauta et al. 2011; Jochmans et al. 2011). In a cohort of transplanted patients, NGAL predicted delayed graft function (DGF) at a cut-off value of 1000 ng/mg creatinine with 90% sensibility, 83% specificity, and an AUC of 0.9 (Parikh et al. 2006a). Consequently, the ability of NGAL to predict AKI before serum creatinine elevation has been evaluated in ICU patients (Prabhu et al. 2010; Makris et al. 2009). In a study performed by de Geus et al. (2011), urinary NGAL assessed at ICU admission was able to predict the development of severe AKI with similar efficacy as serum creatinine-derived *estimated glomerular filtration rate* (GFR). Moreover, plasma NGAL quantified in patients in the ICU was a good diagnostic tool for AKI development, with an AUC of 0.78 and with a diagnosis window of 48 h before creatinine-based

Table 1. Comparison of biomarkers performance in: early detection of AKI, renal injury stratification, pharmacological intervention monitoring, recovery of kidney injury and prognosis prediction.

Biomarker	Early Detection	Injury Severity	Pharmacological intervention	Recovery	Prognosis
NGAL	✓	✓	N.D.	✓	✓
Kim-1	x	✓	✓	x	✓
IL-18	✓	✓	N.D.	N.D.	✓
Cystatin C	✓/x	N.D.	N.D.	N.D.	✓
NAG	✓	N.D.	N.D.	N.D.	✓
L-FABP	✓	✓	N.D.	✓	✓
Hsp72	✓	✓	✓	✓	N.D.

Hsp, heat shock protein; IL, interleukin; Kim, kidney injury molecule; L-FABP, liver fatty-acid binding protein; NAG, N-acetyl-β-D-glucosaminidase; N.D., not determined; NGAL, neutrophil gelatinase-associated lipocalin-2.

Table 2. Performance comparison among the biomarkers reviewed in different clinical settings by using the area under the curve reported for each biomarker.

Biomarker	Cardiac surgery (adults)	Cardiac surgery (pediatric)	ICU	Kidney transplantation (DGF)	Nephrotoxic (AKI)
NGAL	0.5/0.57/0.6/0.65/0.77/0.88/0.95/0.98	0.71/0.91	0.77/0.82/0.86/0.86/0.97	0.63/0.85/0.9	0.91/0.92
Kim-1	0.68/0.78/0.91	N.D.	0.9/0.95	0.74	N.D.
IL-18	0.61/0.66/0.72	0.72/0.84	0.62/0.73	0.83/0.9	N.D.
Cystatin C	0.5/0.76/0.86	N.D.	0.62/0.7/0.7/0.72/0.8/0.92	0.74/0.83	0.48
NAG	0.62/0.63/0.75	N.D.	0.84	0.75	N.D.
L-FABP	0.72/0.86	0.77/0.81	0.95	N.D.	N.D.
Hsp72	N.D.	N.D.	N.D.	N.D.	N.D.

DGF, delayed graft function; Hsp, heat shock protein; ICU, intensive care unit; IL, interleukin; Kim, kidney injury molecule; L-FABP, liver fatty-acid binding protein; NAG, N-acetyl-β-D-glucosaminidase; N.D., not determined; NGAL, neutrophil gelatinase-associated lipocalin-2.

diagnosis (Cruz et al. 2010). The ability of NGAL to detect AKI induced by cisplatin has also been evaluated in mice (Mishra et al. 2004). NGAL was up-regulated in the kidney 3 h after a high dose of cisplatin, and interestingly, urinary NGAL concentrations correlated with the dose and duration of cisplatin administration. NGAL urinary concentration can also provide prognostic value for some clinical outcomes, such as initiation of dialysis and mortality (Parikh et al. 2011a). In addition, urinary NGAL level performed well in detecting AKI induced by nephrotoxic agents in humans (Hirsch et al. 2007). An interesting study reported by Haase et al. showed that a cohort of NGAL-positive but normal creatinine patients were 16-fold more likely to undergo dialysis, 3-fold more likely to die during hospitalization, spent 3 more days in the ICU and spent 8 more days at hospital compared with NGAL-negative patients or patients with creatinine elevation (Haase et al. 2011). These findings suggest that NGAL concentration is a biomarker that is capable of detecting subclinical AKI; however, whether subclinical AKI affects prognosis and or long-term effects remains unknown. One disadvantage of the use of this biomarker in the clinical setting is that non-renal NGAL is elevated in response to systemic stress, and thus, urinary NGAL excretion is increased in other pathological conditions or in patients with chronic renal injury without reflecting the presence of AKI (Soni et al. 2010). In fact, serum NGAL is elevated in patients with acute bacterial infections (Alpizar-Alpizar et al. 2009). Although NGAL is an early AKI biomarker, its reduced specificity limits its consistency as an ideal biomarker of AKI.

Kidney injury molecule-1

Kim-1 is a trans-membrane glycoprotein with immunoglobulin and mucin domains. This protein is a phosphatidylserine receptor that recognizes apoptotic cells and confers on epithelial cells the capacity to recognize and phagocytize dead cells that are present after renal ischaemia (Ichimura et al. 2008). Kim-1 is expressed minimally in normal adult rat kidney and is dramatically over-expressed in the S3 segment of the proximal tubule cells after ischaemia/reperfusion (I/R) or nephrotoxic injuries in rat kidneys (Vaidya et al. 2006, 2010). Kim-1 is thought to be expressed in dedifferentiated cells after AKI, as it is also expressed in patients with renal cell carcinoma, a condition that displays cell dedifferentiation (Han et al. 2005). Fortunately, a proteolytically processed ectodomain is easily detected in the urine, facilitating assessment of Kim-1 urinary concentration (Zhang et al. 2007). In fact, in several clinical studies, urinary Kim-1 is higher in patients with AKI than other types of kidney injury, such as CKD (Han et al. 2002; Liangos et al. 2009). Importantly, in patients with recognized AKI, the AUC is 0.90 as is shown in Table 2. However, one study evaluating Kim-1 as an early biomarker reported a poor performance for this protein as is depicted in Table 1 (Han et al. 2008). In spite of the inability of urinary Kim-1 to predict the outcomes after AKI, it has been showed that the urinary Kim-1 and NAG levels could predict the odds for dialysis requirement or hospital death (Liangos et al. 2007). In a population of patients who underwent cardiac surgery, urinary Kim-1 increased significantly compared with non-AKI patients at 2 h after surgery, and after 24 h, the AUC ranged between 0.78 and 0.91 (Table 2). However, Kim-1 performed better in patients with established acute tubular necrosis, with an AUC ranging from 0.9 to 0.95 (Huang & Don-Wauchope 2011). The ability of Kim-1 to predict DGF after kidney transplant has been evaluated by Kim-1 immunohistochemistry. Unexpectedly, the authors did not find any significant correlation between Kim-1 staining and the occurrence of DGF (Schroppel et al. 2010). However, Malyszko et al. (2010) reported that urinary Kim-1 after transplantation provides prognostic information, such as the rate of renal function decline over time, suggesting that although Kim-1 is not an early predictor of DGF, in a long-term context, it may be useful to predict renal dysfunction progression. Kim-1 has also proven successful for diagnosing AKI induced by nephrotoxic agents. In fact, a recent report showed that Kim-1 outperformed serum creatinine, BUN and urinary NAG in multiple rat models of nephrotoxicity, with the best results being observed with cisplatin, gentamicin and kancomycin exposure, suggesting that urinary Kim-1 may facilitate

accurate prediction of human nephrotoxicity in preclinical drug studies (Vaidya et al. 2010). Finally, Kim-1 levels are also valuable for monitoring a renoprotective strategy in an experimental model of chronic cyclosporine nephrotoxicty (Perez-Rojas et al. 2007). Together, these findings indicate that Kim-1 is a better biomarker for diagnosing established AKI than for ascertaining an early diagnosis.

Interleukin-18

IL-18 is a pro-inflammatory cytokine that is up-regulated and cleaved in the proximal tubule during AKI. It is expressed in the intercalated cells of the late distal convoluted tubule, connector and collecting duct. IL-18 is co-expressed with P2X7 and caspase-1, which convert the pro-IL-18 into its active form. Subsequently, IL-18 leaves the cell, and the IL-18 in the tubular epithelium enters the urine (Melnikov et al. 2001; Fantuzzi et al. 1998). Urinary IL-18 level is sensitive in diagnosing established AKI, as its urinary concentration was elevated in patients with acute tubular necrosis, with an AUC of 0.95. However, no elevation is observed in CKD, urinary tract infection, nephrotic syndrome or pre-renal azotaemia (Parikh et al. 2004). For early diagnosis, IL-18 seems to have a low sensitivity but high specificity. However, as is shown in Table 2, inconsistent results have been observed for the ability of IL-18 to predict AKI in post-cardiac surgery patients (Haase et al. 2008; Parikh et al. 2006b; Torregrosa et al. 2012; Parikh et al. 2005; Siew et al. 2010). In a cohort of 1219 adults undergoing cardiac surgery, urinary IL-18 peaked 6 h after the surgery, and the highest urinary IL-18 levels were associated with 6.8-fold increased odds of AKI development, longer hospital and ICU stays and higher risk for dialysis requirement or death (AUC of 0.76 for AKI diagnosis) (Parikh et al. 2011a). The ability of IL-18 to predict DGF was evaluated in 91 transplant patients, in whom DGF was classified as slow graft function or immediate graft function. The median levels of urinary NGAL and IL-18, but not Kim-1, were different between the groups at all time points studied (Hall et al. 2011a). Little is known about the ability of IL-18 to detect AKI induced by nephrotoxic agents. One study reported that IL-18 identified contrast-induced nephropathy (CIN) 24 h earlier than SCr elevation (Ling et al. 2008). All of these data suggest that IL-18 is a suitable biomarker for established AKI but cannot predict AKI after cardiac surgery due to low sensitivity.

Cystatin C

Cystatin C is a cysteine protease inhibitor that is produced by all nucleated cells, is released into the blood at a relatively constant rate, and apparently is not influenced by factors other than GFR. Cystatin C is often considered a marker of GFR because it possesses the main characteristics of an ideal GFR marker: it is freely filtered, completely reabsorbed and not secreted into the renal tubules. In contrast to creatinine, cystatin C levels are not significantly affected by age, gender, race, or muscle mass (Herget-Rosenthal et al. 2004). However, although it is more often recognized as a GFR marker, it seems to be a marker of AKI as well, as renal dysfunction is a main feature of AKI (Zhang et al. 2011; Haase et al. 2009; Nejat et al. 2010; Hall et al. 2011b; Hall et al. 2011a). Indeed, serum cystatin C has been a useful AKI marker in hospitalized patients 24–48 h earlier than serum creatinine elevation but 10 h later than NGAL. Herget-Rosenthal et al. (2004) reported that cystatin C may predict AKI 2 days before serum creatinine elevation in the ICU context. In a post-cardiac surgery paediatric population, increased cystatin C, 6 h after surgery predicted stage 1 and 2 AKI. Moreover, higher cystatin C predicted longer ventilation and ICU stay (Zappitelli et al. 2011). The urinary excretion of cystatin C has shown the ability to predict the requirement for renal replacement therapy in patients with established AKI 2 days earlier than creatinine clearance reduction, with an AUC of 0.72 (Royakkers et al. 2011). However, similar findings were not observed in a paediatric population of kidney transplant recipients because cystatin C was not superior to creatinine for the detection of DGF (Slort et al. 2012). Finally, cystatin C did not show a better performance than serum creatinine in detecting contrast-induced nephropathy (Ribichini et al. 2012). Therefore, cystatin C seems to perform better than serum creatinine in predicting AKI but in lesser proportion than other recently described biomarkers.

N-acetyl-β-D-glucosaminidase

NAG is a lysosomal enzyme found in proximal tubules, and increased activity of this enzyme in the urine suggests injury to tubular cells. Therefore, NAG can serve as specific urinary marker for damaged tubular cells. NAG has proven to be effective for the diagnosis of nephrotoxic renal injury, delayed renal allograft function, chronic glomerular disease, diabetic nephropathy and cardiopulmonary bypass earlier than creatinine elevation (Bazzi et al. 2000; Katagiri et al. 2012). Moreover, higher urinary NAG has been associated with poor outcomes, such as dialysis requirement or death (Liangos et al. 2007). Unfortunately, urinary NAG activity is inhibited by endogenous urea as well as by a number of industrial solvents and heavy metals. Furthermore, increased NAG has been reported in a variety of conditions in the absence of clinically significant AKI, including rheumatoid arthritis, impaired glucose tolerance and hyperthyroidism (Erdener et al. 2005; Tominaga et al. 1989). The insensitivity and non-specificity of NAG may limit its use as a biomarker of AKI. In addition, NAG was reportedly unable to predict the odds of delayed graft function in the transplant context (Moers et al. 2010), but NAG performed better for CIN diagnosis. Ren et al. (2011) reported that amongst 590 patients undergoing diagnostic coronary angiography, a significant increase in urinary NAG was found in 33 patients who developed CIN; this increase occurred 1 or 2 days before serum creatinine elevation. In addition, in an experimental

model of AKI induced by cadmium, Kim-1 increased after 6 weeks of cadmium treatment and continued to increase until 12 weeks; however, no increase of NAG was observed until after 12 weeks of cadmium treatment. Thus, in comparison with Kim-1, NAG performs poorly for diagnosing AKI induced by cadmium (Prozialeck et al. 2009).

Liver fatty acid-binding protein

FABPs are small cytoplasmic proteins of 14 kDa that are abundantly expressed in tissues with active fatty acid metabolism. Two types of FABPs have been isolated from the human kidney: heart-type FABP and liver-type FABP (L-FABP). L-FABP is normally found in the cytoplasm of human proximal tubular cells (Veerkamp et al. 1991). It binds to fatty acids and transports them to mitochondria or peroxisomes, where the fatty acids are β-oxidized, and L-FABP participates in intracellular fatty acid homeostasis. L-FABP is reabsorbed by the proximal tubule via megalin-domain endocytosis and is localized in the cytoplasm of proximal tubular cells, liver cells and small intestine cells (Oyama et al. 2005; Maatman et al. 1992). Recent studies performed in rats have shown that L-FABP is a sensitive biomarker in ischaemic AKI (Negishi et al. 2009). In a cardiovascular surgery setting, Matsui et al. (2011) showed that L-FABP is an early biomarker of AKI and that it is elevated faster than NGAL and NAG, see Table 1. These findings were confirmed by Portilla et al. (2008) in children undergoing cardiac surgery. The increase in urinary L-FABP occurred within 4 h after cardiac surgery and predicted subsequent AKI development with an AUC of 0.81. In the transplant context, urinary L-FABP level correlated well with the ischaemic time of the transplanted kidney and with the length of hospital stay in living related-donor renal transplant recipients (Yamamoto et al. 2007). In addition, Nakamura et al. (2006) reported that baseline urinary L-FABP was significantly higher in those patients who developed contrast nephropathy after coronary angiography; however, the authors did not evaluate the diagnostic performance of urinary L-FABP in predicting AKI. Moreover, a significant elevation of urinary L-FABP was found to exist in established AKI of a variety aetiologies, including acute tubular necrosis, sepsis, and nephrotoxic exposure (Ferguson et al. 2010). In contrast, urinary L-FABP increased proportionally to the dose of cisplatin administrated to the mice and correlated with the tubular injury score.

Heat shock protein 72

Heat shock proteins (Hsps) are up-regulated in response to alterations in cellular homeostasis, as occurs during AKI (Csermely et al. 2007). Particularly, the Hsp70 subfamily are composed of four isoforms: Hsc70 (constitutive isoform), Hsp72 (inducible isoform), mHsp75 and Grp78. Hsp72 is highly induced during AKI such that it constitutes up to 15 % of total cellular protein (Hernadez-Pando et al. 1995; Kelly 2002; Kelly et al. 2001; Molinas et al. 2010). Indeed, Zhang et al. (2008a) reported that Hsp72 is one of the most up-regulated proteins among 30,000 studied proteins in the I/R rat model. This protein is induced in renal tubular cells during AKI, and many of these cells are detached and projected into the urinary space in response to AKI. In a previous study from our laboratory, we reasoned that Hsp72 could be an early and sensitive biomarker to detect AKI (Barrera-Chimal et al. 2011). For this purpose, in rats undergoing different durations of ischaemia (10, 20, 30, 45 or 60 min) to induce different degrees of renal injury, Hsp72 expression progressively increased with the duration of ischaemia. Moreover, in the urine of these animals, Hsp72 concentration increased proportionally to the degree of renal injury, showing a high correlation with the histological injury score, which is the gold standard for monitoring the renal injury induced by I/R. Furthermore, we explored the performance of Hsp72 as an early biomarker of AKI. Rats undergoing to 30 min of ischaemia were randomly sorted into groups of different durations of reperfusion (3–120 h). Urinary Hsp72 was elevated at 3 h of reperfusion, peaked at 18 h and reached normal values at 72 h of reperfusion. Interestingly, this Hsp72 behavior strongly correlated with the histo-pathological findings: starting at 3 h of reperfusion, there was evidence of tubular injury, which peaked at 18 h and began healing after 72 h of reperfusion. These results provide evidence that Hsp72 is an early biomarker of AKI and that it may help in monitoring the regeneration process after AKI. Because we had previously shown that mineralocorticoid receptor blockade with spironolactone or adrenal gland removal is an effective strategy to prevent renal injury induced by spironolactone, we also evaluated the effectiveness of Hsp72 to detect a pharmacological strategy to prevent AKI. A group of animals were pre-treated with different doses of spironolactone 3 days before renal injury induced by renal bilateral ischaemia. Hsp72 was able to monitor the degree of renoprotection conferred by the different doses of spironolactone. In our study, the ability of Hsp72 to monitor the renal injury was compared with NGAL, Kim-1 and IL-18, and we found that Hsp72 was a superior biomarker for the early detection and stratification of AKI, at least in the AKI model induced by renal ischaemia in the rat. Finally, we also showed that Hsp72 seems to be an early biomarker of AKI in humans, because amongst critically ill patients, urinary Hsp72 elevation occurred 24–48 h earlier than serum creatinine elevation in those patients who developed AKI (Barrera-Chimal et al. 2011). Although more clinical studies with more patients are required, Hsp72 seems to be a promising biomarker to detect AKI.

Other biomarkers with potential application in AKI detection

It has been reported that the monocyte chemoattractant protein-1 (MCP-1), a molecule that participates in mediating injury during AKI, can be detected in the urine of mice with AKI induced by maleate and in 10 patients

diagnosed with AKI, in particular this biomarker did not show an overlapping between AKI and no AKI patients (Munshi et al. 2011).

Pro-inflammatory cytokines such as IL-6 and IL-8 were reported to be elevated in serum from patients developing AKI after cardiac surgery and predicted prolonged mechanical ventilation (Liu et al. 2009). In addition, in 25 paediatric patients subjected to CBP, urinary IL-6 increased 6 h after surgery in those patients whom developed AKI with a sensitivity of 88% (Dennen et al. 2010).

Netrin-1 a laminin-like molecule; was observed to be excreted in the urine of mice subjected to I/R or after cisplatin, endotoxin or folic acid nephrotoxicity and in most of the AKI patients included in the study (Reeves et al. 2008). Ramesh et al. (2010) reported that netrin-1 increased 2 h after CBP in patients that developed AKI. The duration and severity of AKI correlated with netrin-1 levels after 6 h of the surgery.

Finally α-Glutathione-S-transferase (α-GST) that is localized in the proximal tubule in the rat and human, was found in the urine of rats after cisplatin induced AKI (Gautier et al. 2010) This enzyme was also assessed in a population of patients after cardiac surgery and it was found that urinary α-GST levels were able to predict the development of AKIN 1 and 3 (Koyner et al. 2010).

Similarity of the performance of various biomarkers in detecting AKI

An ideal biomarker for AKI should exhibit the following characteristics: (i) detect renal injury early, (ii) stratify the degree of renal injury, (iii) screen the effectiveness of a renoprotective intervention and regeneration process, and (iv) help with prognosis prediction. Table 1 compares the performance of the biomarkers discussed here in detecting AKI. Despite many advances in our knowledge about these biomarkers, many features remain to be determined. However, this evaluation allows us to discern how closely the biomarkers fit the ideal performance for detecting AKI. Although Kim-1 seems to be a poor biomarker for early diagnosis of AKI and for monitoring the recovery after renal injury, it appears to be a good biomarker of established AKI. Many issues remain unexplored for IL-18, cystatin C and NAG. Moreover, some studies have shown contradictory results, e.g. regarding cystatin C as an early biomarker of AKI. Although NGAL and L-FABP have shown promise, their ability to monitor a renoprotective intervention remains to be determined. The sensitivity and specificity of each biomarker are variable in the same and in different clinical settings. These discrepancies may be due to the lack of guidelines for cut-off values and standardized testing methods, the timing of the measurements and sample storage protocols. In addition, the AUC analysis sometimes over-estimates a biomarker's performance as a result of its normalisation to urinary creatinine concentration, which is differentially altered under AKI. A summary of the biomarker studies reporting the AUC-ROC analysis in several clinical settings is presented in Table 2. This analysis showed the high variability observed when the same biomarker is used to diagnose AKI in the same clinical context. This issue is reflected in the AUC reported for NGAL in diagnosing AKI after a cardiac surgery, which ranges from 0.5 to 0.95. Despite the variability in AUCs, NGAL seems to be a helpful biomarker because of its early elevation in the patients who will further develop AKI after cardiac surgery and in hospitalized patients in the ICU, as well as its performance in the prediction of DGF after kidney transplant. The performance of the other biomarkers in the early diagnosis of AKI after cardiac surgery seems to be poor compared with NGAL. In the ICU setting, Kim-1 and L-FABP perform well, with AUCs ranging from 0.9 to 0.95. In the kidney transplant field, only one study has reported a low AUC (0.74) for Kim-1. However, other reports studying Kim-1 expression by immunohistochemistry after kidney transplantation have reported opposite results (Schroppel et al. 2010). Zhang et al. (2008b) found that Kim-1 expression correlated with renal function after transplantation whereas Schroppel et al. (2010) showed that Kim-1 did not correlate well. In this regard, IL-18 seems to better predict DGF, and this ability may be due to the inflammatory nature of this clinical condition. Finally, for nephrotoxic AKI, NGAL seems to perform the best. Although other biomarkers have also been studied in different clinical settings, their AUCs were not reported.

All of these studies showed that due to the aetiological diversity, a panel of biomarkers to diagnose AKI may be a better strategy than using a single one. However, cost-effectiveness analyses are also needed to establish whether a panel of biomarkers can be implemented with a favorable clinical-to-economical balance for healthcare systems. Because one of the goals of developing a biomarker is to reduce the extra costs that AKI represents to the health care system in each country (Srisawat et al. 2011). One concern about the sensitivity that a biomarker should have arises from the fact that all biomarkers that display a high sensitivity might identify more patients who are suffering some degree of renal injury (subclinical AKI), but the long-term prognostic value of biomarker results have not been assessed. Thus, the clinical significance of detecting subclinical AKI remains to be determined. Nevertheless, AKI is a risk factor for developing CKD, which underscores the relevance of studying subclinical AKI, given the pandemics of CKD observed in the last few years.

Declaration of interest

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