

## Drug-Induced Nephrotoxicity and Its Biomarkers

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### Abstract

Nephrotoxicity occurs when kidney-specific detoxification and excretion do not work properly due to the damage or destruction of kidney function by exogenous or endogenous toxicants. Exposure to drugs often results in toxicity in kidney which represents the major control system maintaining homeostasis of body and thus is especially susceptible to xenobiotics. Understanding the toxic mechanisms for nephrotoxicity provides useful information on the development of drugs with therapeutic benefits with reduced side effects. Mechanisms for drug-induced nephrotoxicity include changes in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Biomarkers have been identified for the assessment of nephrotoxicity. The discovery and development of novel biomarkers that can diagnose kidney damage earlier and more accurately are needed for effective prevention of drug-induced nephrotoxicity. Although some of them fail to confer specificity and sensitivity, several promising candidates of biomarkers were recently proved for assessment of nephrotoxicity. In this review, we summarize mechanisms of drug-induced nephrotoxicity and present the list of drugs that cause nephrotoxicity and biomarkers that can be used for early assessment of nephrotoxicity.

**Key Words:** Biomarker, Nephrotoxicity, Assessment

### INTRODUCTION

The kidney is an essential organ required by the body to perform several important functions including the maintenance of homeostasis, regulation of the extracellular environment, such as detoxification, and excretion of toxic metabolites and drugs (Ferguson *et al.*, 2008). Therefore, the kidney can be considered as a major target organ for exogenous toxicants. Nephrotoxicity is a kidney-specific feature in which excretion does not go smoothly owing to toxic chemicals or drugs (Finn and Porter, 2003; Galley, 2000). Approximately 20% of nephrotoxicity is induced by drugs, but medication of the elderly increases the incidence of nephrotoxicity up to 66% as the average life span increases. Chemotherapy or anticancer medicine has been of limited use due to nephrotoxicity (Kohli *et al.*, 2000; Naughton, 2008; Nagai and Takano, 2010).

Nephrotoxicity can be diagnosed through a simple blood test. Evaluation of nephrotoxicity through blood tests includes the measurements of blood urea nitrogen (BUN), concentration of serum creatinine, glomerular filtration rate and creatinine clearance. However, these assessments of nephrotoxicity are only possible when a majority of kidney function is damaged (Kirtane *et al.*, 2005; Rached *et al.*, 2008). Therefore, discovery and development of biomarkers that can detect kid-

ney dysfunction at the early stage are needed. In this review, we summarize the mechanisms of drug-induced nephrotoxicity and highlight their involvement in diseases. We also summarize and present the list of biomarkers for assessment of nephrotoxicity.

### MECHANISMS OF DRUG-INDUCED NEPHROTOXICITY

General mechanisms that cause nephrotoxicity include changes in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy (Zager, 1997; Schnellmann and Kelly, 1999; Schetz *et al.*, 2005; Ferguson *et al.*, 2008).

#### Changes in glomerular hemodynamics

For healthy young people, glomerular filtration rate (GFR) is 120 ml per minute. Kidneys can keep a constant filtration rate as well as maintain the displacement of urine through regulation of blood flow in afferent and efferent arteries for adjustments or maintenance of intraglomerular pressure. Circulation of prostaglandin is used for expansion of afferent arteries (Naughton, 2008). Anti-prostaglandin drugs such as

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nonsteroidal anti-inflammatory drugs (NSAIDs) or drugs having anti-angiotensin activity for prevention of blood pressure elevation including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) have been shown to induce nephrotoxicity in glomerulus (Olyaei *et al.*, 1999; Schoolwerth *et al.*, 2001; Palmer, 2002).

### Tubular cell toxicity

Because renal tubules, especially proximal tubule cells, are exposed to drugs in the process of concentration and reabsorption through the glomerulus, they are influenced greatly by drug toxicity (Perazella, 2005). Cytotoxicity occurs due to the damaged mitochondria in tubules, the disturbed tubular transport system, and the increase in oxidative stress by free radical generation (Zager, 1997; Markowitz and Perazella, 2005). The cytotoxicity inducing drugs include aminoglycoside antibiotics, antifungal agents such as amphotericin B, anti-retroviral drugs such as adefovir, anticancer drugs such as cisplatin and foscarnet (Markowitz *et al.*, 2003; Prezella, 2005; Markowitz and Perazella, 2005).

### Inflammation

Nephrotoxic drugs often induce inflammation in glomerulus, proximal tubules, and surrounding cellular matrix, and then fiberize the kidney tissue. Inflammation that disturb normal kidney functions and induce toxicity includes glomerulonephritis, acute and chronic interstitial nephritis. Glomerulonephritis has been shown to be closely related to proteinuria (Prezella, 2005). Acute interstitial nephritis, a type of drug-induced immune response, is induced by NSAIDs and antibiotic drugs such as rifampicin (Rossert, 2001). Chronic interstitial nephritis occurs frequently by long-term use of calcineurin inhibitors, lithium, some anticancer drugs or analgesics (Perneger *et al.*, 1994; Forel *et al.*, 2001; Isnard Bagnis, *et al.*, 2004; Rodriguez-Iturbe and Garcia Garcia, 2010). In case of chronic interstitial nephritis, early detection is especially important because it is difficult to diagnose until most of the functionality of the kidney is destroyed.

### Crystal nephropathy

Disorder in renal function is also affected by medications that make insoluble crystals in human urine (Perazella, 1999). The formation of insoluble crystals depends on the acidity of urine and drug concentration. Drugs that can cause crystal nephropathy are antibiotics such as ampicillin and antiviral agents such as acyclovir (Markowitz and Perazella, 2005; Perazella, 2005).

### Rhabdomyolysis

Rhabdomyolysis is a condition in which muscle fiber contents are released into the bloodstream when skeletal muscle is destroyed due to some injury. As renal muscle cells disintegrate due to damage in muscle tissue, myoglobin and serum creatine kinase are released into the blood. Released myoglobin degrades and depresses the function of filtration in kidney resulting the acute tubular necrosis or renal failure (Coco and Klasner, 2004). Major causes of rhabdomyolysis are drug abuses from heroin, methadone, methamphetamine, and statin as well as alcoholism (Coco and Klasner, 2004; Huerta-Alardin *et al.*, 2005).

### Thrombotic microangiopathy

Drug-induced thrombotic microangiopathy results from organ damage through inflammation or direct toxicity in renal epithelial cells (Pisoni *et al.*, 2001). Antiplatelet agents including cyclosporin, mitomycin-C and quinine have been shown to cause thrombotic microangiopathy (Pisoni *et al.*, 2001; Manor *et al.*, 2004).

## BIOMARKERS FOR ASSESSMENT OF NEPHROTOXICITY

Many pathophysiologic mechanisms mentioned above are directly related to the induction of nephrotoxicity. Because traditional standard markers such as BUN and serum creatinine have low sensitivity and specificity, the timing of the diagnosis and treatment are often delayed. Therefore, development of new biomarkers is needed for the specific diagnosis of nephrotoxicity at earlier stages (Ferguson *et al.*, 2008).

Biomarkers designate the biomolecules showing the relationship between exogenous toxic substances and diseases. Generally, biomarkers enable us to determine early damage to health caused by exposure to exogenous toxic substances, and provide an insight into the mechanism of the onset of these toxicants to adversely affect certain groups or individuals (Finn and Porter, 2003). The identification of biomarkers that can be determined from blood or urine resulted from exposure to a nephrotoxicant is a promising approach (Shao *et al.*, 2011). Especially, urine is regarded as attractive and efficient sample because it is non-invasive and easy to be obtained in considerable amounts (Wu *et al.*, 2010).

Biomarker candidates have been identified for the assessment of nephrotoxicity. Although some of them fail to confer specificity and sensitivity of biomarkers, several promising candidates have been proved for diagnosis of nephrotoxicity (Ferguson *et al.*, 2008; Bonventre *et al.*, 2010). List of biomarkers for nephrotoxicity assessment and drugs in different nephron segments is presented in Table 1.

### Urinary proteins with enzymatic activity

If there is acute or chronic kidney damage due to exposure to nephrotoxic substances, diabetic kidney disease, hypertension, renal ischemia, transplant, or glomerular diseases, the enzymes present in tubular epithelial cells are spilled into the urine and can be detected as nephrotoxic biomarkers. Biomarkers related with urinary proteins with enzymatic activity include alanine aminopeptidase, alkaline phosphatase,  $\alpha$ -glutathione-S-transferase,  $\gamma$ -glutamyl transpeptidase,  $\pi$ -glutathione-S-transferase, and N-acetyl-D-glucosaminidase (Ferguson *et al.*, 2008).

### Proteinuria

In normal conditions, the glomerulus restricts the migration of high molecular weight proteins from blood to nephron lumen by filtration (Finn and Porter, 2003). In some pathological states, however, high molecular weight proteins can be detected in the urine because the selective penetration through glomerulus is not functioning properly (Guder and Hoffman, 1992). High molecular weight proteins that can reveal kidney damage include albumin which can be used for early diagnosis of changed glomerular filtration and diabetes (Morgensen, 1971), transferrin which transports iron and represents glo-

**Table 1.** List of biomarkers for evaluation of nephrotoxicity

| Nephron segment | Drugs inducing nephrotoxicity   | Biomarkers  |
|-----------------|---|---|
| Glomerulus      | ACE inhibitor, ARB, NSAIDs, Mitomycin-C<br>Antiplatelet agents, Cyclosporin, Quinone  | Proteinuria<br>Albumin, Transferrin, Immunoglobulin G,<br>$\beta_2$ -microglobulin, $\alpha_1$ -microglobulin, Cystatin C<br>Retinol binding protein<br>Cytokines<br>Interferons, Interleukins, TNF, CSFs<br>Type IV collagen   |
| Proximal tubule | Aminoglycoside antibiotics<br>Amphotericin B, Adefovir<br>Cisplatin, Foscarnet<br>Contrast stain, Cocaine, Heroin, Methadone<br>Methamphetamine | Urinary proteins with enzymatic activity<br>$\alpha$ -GST, N-Acetyl-D-Glucosaminidase<br>Proteinuria<br>Albumin, Transferrin, Immunoglobulin G,<br>$\beta_2$ -microglobulin, $\alpha_1$ -microglobulin, Cystatin C<br>Retinol binding protein<br>Cytokines<br>Interferons, Interleukins, TNF, CSFs<br>KIM-1, NGAL, Clusterin, Osteopontin |
| Distal tubule   | Amphotericin B, Lithium<br>Acyclovir, Indinavir,<br>Sulfonamides  | NGAL, Clusterin, Osteopontin  |

ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, NSAIDs: nonsteroidal anti-inflammatory drugs, TNF: tumor necrosis factor, CSFs: colony-stimulating factors, GST: glutathione S-transferase

merular damage more sensitively (Prinsen *et al.*, 2001), and immunoglobulin G that shows structural damage in the glomerulus (Schurek *et al.*, 2000).

Low molecular weight proteins produced in other organs are filtered and reabsorbed in the glomerulus and not released from the proximal tubule. An increase of the filtered low molecular weight proteins represents that absorption in the glomerulus and proximal tubule is not adequate, which means there may be cell damage or overload (Bernard *et al.*, 1987). Therefore, kidney damage by toxicity can be detected earlier using measurements of proteins in urine.

Low molecular weight proteins that represent tubular damage are  $\beta_2$ -microglobulin (Herget-Rosenthal, *et al.*, 2004; Emeigh Hart, 2005),  $\alpha_1$ -microglobulin (Schaub *et al.*, 2005), retinol-binding protein which transports retinol from liver to other organs (Bernard *et al.*, 1987), and cystatin-C, an inhibitor of cysteine proteinase (Herget-Rosenthal *et al.*, 2004; Conti *et al.*, 2006).

### Kidney injury molecule-1 (KIM-1)

KIM-1 is a type I transmembrane glycoprotein and one of the gene families that form T-cell immunoglobulin mucin (Tim) and is known to have an immunoglobulin-like domain consisting of six unusual cysteine and topping a long mucin-like domain in extracellular region. It is also known as hepatitis A virus cellular receptor 1 (Vaidya *et al.*, 2008). When the kidney is exposed to toxic substances such as cisplatin or gets damaged by ischemia or reperfusion, KIM-1 can be used as a more sensitive biomarker than traditional nephrotoxic biomarkers such as BUN, serum creatinine, and proteinuria (Vaidya *et al.*, 2006). KIM-1 expression has been reported to correlate with proximal tubular injury, renal tubular regeneration and immune

response by nephrotoxicants. The mRNA and protein levels of KIM-1 are highly expressed in injured kidney. KIM-1 is exposed toward the tubular lumen and extracellular domain (or ectodomain) of KIM-1 is cut by matrix metalloproteinase and then finally excreted in urine (Bailey *et al.*, 2002). KIM-1 up-regulation appears rapidly and is easily detected in the urine upon nephrotoxicity. Because extracellular domain of KIM-1 is very stable and easy to be detected. KIM-1 has been considered as a non-invasive as a non-invasive biomarker for human renal proximal tubular damage (Ichimura *et al.*, 1998).

### Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a 25 kDa protein that binds to gelatinase in particular neutrophil granulocytes. It is synthesized in the maturation process of granulocytes (Borregaard *et al.*, 1995), and often induced in epithelial cells by inflammation or tumorigenesis (Nielson *et al.*, 1996). Because NGAL expression is increased in proximal tubule cells by drug-induced nephrotoxicity or ischemia, it is known as a sensitive biomarker for the early diagnosis of acute kidney injury. The concentration of NGAL in blood also increases in infection and inflammation (Xu *et al.*, 1995; Ohlsson *et al.*, 2003).

### Cytokines

Cytokines are polypeptides that regulate many important biological processes and act as mediators of inflammation and immune responses. Many cytokines are closely associated with the repair of damaged tissues. Among them, interferons (Baron *et al.*, 1991), interleukins (Horii *et al.*, 1993; Wada *et al.*, 1994), tumor necrosis factor, colony-stimulating factors, and several growth factors shown potential as biomarkers of nephrotoxicity because they are involved in glomerular and

tubular damage and repair (Finn and Porter, 2003).

### Clusterin

Clusterin, a sulfated glycoprotein with 426 amino acids, is present in the cytoplasm of proximal convoluted tubule or at the end of distal convoluted tubule (DCT) including connecting tubule in the kidney cortex. It can be used as a biomarker because it increases in various kidney diseases and is detected in the urine of patients with acute kidney injury. Interestingly, the depletion of clusterin worsens glomerulonephritis (Kharash *et al.*, 2006).

### Osteopontin

Osteopontin is a 44 kDa bone phosphoprotein also known as sialoprotein I, secreted phosphoprotein I, uropontin, and early T-lymphocyte activation-1 (Eta-1) (Oldberg *et al.*, 1986; Nomura *et al.*, 1988; Patarca *et al.*, 1989; Shiraga *et al.*, 1992). It is expressed most highly in epithelial tissue and bone, and can be detected at a high level in human urine ( $21.4 \pm 6.2$  mg/g of creatinine or  $1.9 \mu\text{g/ml}$ ) when the kidney is significantly damaged by gentamicin, cisplatin, cyclosporin, sevoflurane, angiotension II-induced tubulointerstitial nephritis, and puromycin-induced glomerulonephritis (Alchi *et al.*, 2005).

### Type IV collagen

Type IV collagen, a main component of the basement membrane, increases in the urine following damage of the glomerulus. Because it is too large to pass through the outer membrane of the glomerulus, its concentration in the urine is a sensitive indicator for glomerular changes in the structure of the extracellular matrix and thus an important biomarker of nephrotoxicity (Donovan *et al.*, 1994; Nerlich *et al.*, 1994).

## CONCLUSIONS

Drug-induced nephrotoxicity is closely associated with acute renal damage as well as with chronic kidney diseases. However, traditional nephrotoxicity assays such as measurement of the concentration of serum creatinine or BUN do not have the sensitivity and selectivity required to determine nephrotoxicity prior to the severe progression of renal damage. Recently identified biomarkers described in this review may provide useful information to diagnose nephrotoxicity earlier and more selectively.

Biomarkers make significant contributions to new drug development because they facilitate the process of toxicity assessment of drugs. Early diagnosis of drug-induced nephrotoxicity would be advantageous to reduce the economic costs losses during safety inspection of new drugs. Therefore, the need for the discovery and development of sensitive and selective biomarkers for nephrotoxicity has been increased. The present review presents recently identified biomarkers for kidney damage, providing useful information on the assessment of nephrotoxicity induced by drugs.

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