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Novel biomarkers for detection of nephrotoxicity

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ABSTRACT

Nephrotoxicity is a significant clinical challenge and global public health issue. Kidney disease progresses over time and is silent due to exposure to nephrotoxicants and oxidative stress. Early detection of kidney injury is crucial for the treatment and nephroprotection. Conventional biomarkers such as blood urea nitrogen (BUN), creatinine, and urea are detected after 60% of kidney injury and they are not specific. The use of specific secondary novel biomarkers for the detection of kidney damage and evaluation of nephrotoxicity is a prerequisite for nephroprotection. Gene expression profiling is a potent technique for decoding pathways involved in nephrotoxicity. Targeting specific genes discovered through gene expression profiling can reduce severity. Nephrotoxicity is associated with the use of drugs such as cisplatin, and gentamycin. Second-generation biomarkers such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), clusterin, N-acetyl-β-d-glucosaminidase (NAG), β2-microglobulin, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) are proteins released from the renal tubules in response to kidney damage and helps in early detection of kidney injury. Evaluation of these novel parameters will help in early diagnosis of kidney injury.

Implication for health policy/practice/research/medical education:
Second-generation biomarkers of kidney injury have become a prerequisite and early detection of these markers is currently used for the evaluation of nephroprotection of synthetic drugs, plant extract and phytopharmaceuticals during pre-clinical assessment markers such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), clusterin, N-acetyl-β-d-glucosaminidase (NAG), β2-microglobulin, tissue inhibitor of matrix metallopro-teinase-1 (TIMP-1) are proteins released from the renal tubules in response to kidney damage. Upregulation of these markers can be detected in urine or blood samples. These second-generation biomarkers could be applied to assess the initial stages of kidney injury and early disease diagnosis helps in nephroprotection. In the current review, we are discussing recent de-velopments second generation biomarkers and their specificity in early detection of kidney damage as compared to conventional biomarkers.

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Introduction

The increase in acute and chronic kidney disease (CKD) is associated with the increase in patients with diabetes mellitus and hypertension. Diabetes mellitus is the leading cause of end-stage renal disease in the world, although various factors can trigger this physiopathology. Research in this area will help come out with an effective marker used to assess nephroprotection in diseased conditions.

To scientifically validate the potential of newly synthesized drugs, plant extracts or phytopharmaceuticals various markers are used for prediction of nephroprotective potential. The high number of affected individuals and the significant adverse impact of CKD should prompt enhanced efforts for better prevention, early detection, and nephroprotection in case of drug-induced nephropathy.

Kidney disorders progress over many years based on nephrotoxicants and oxidative stress. Early diagnosis of kidney damage is based on biomarkers used for the assessment of kidney injury. Conventional biomarkers such as glomerular filtration rate, serum creatinine, urea, and blood urea nitrogen (BUN) indicate kidney injury but expression is after major kidney damage. Novel second-generation biomarkers have shown promising results during the evaluation of kidney injury. This review aims to summarize second-generation markers used and their regulation in kidney damage.

Effective prevention of nephrotoxicity in drug development necessitates the identification of sensitive

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Review

and specific biomarkers, as traditional markers like BUN and serum creatinine have inherent limitations. Emerging biomarkers, such as urine albumin, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and others, offer the advantage of early detection of kidney damage (1,2). The amalgamation of secondary novel markers enhances the accuracy of assessments, guiding drug development in preclinical stages and aiding in the selection of safer therapeutics. This approach facilitates early detection, enabling timely intervention of nephrotoxicants during preclinical and clinical studies to enhance efficacy.

Long-term medication treatments contribute significantly to kidney damage, accounting for 60% of hospital cases related to kidney injury. Despite a 7% failure rate in animal testing during drug development, relying on animal models diminishes success rates, increasing both time and costs. Serum creatinine, the standard test for kidney issues, only detects harm after it has occurred. Therefore, the development of medications based on lab-testable biomarkers becomes imperative for early detection and intervention.

Genetic testing plays a pivotal role in identifying gene variations linked to hereditary kidney diseases. The Gene Network-Assisted Diagnostic Optimization approach, leveraging RNA-sequencing data, prioritizes potential disease genes based on the contribution of genetic variations to rare illnesses. This approach holds promise for diagnostic advancements in the realm of kidney diseases.

Scientists actively work towards identifying unique biomarkers like KIM-1, NGAL and clusterin affected by nephrotoxicants (3-5). Urinary levels of these proteins often indicate kidney injury at early stages as compared to conventional markers. Understanding the mechanisms of nephrotoxicity becomes essential, to understand the pathways involved.

Anticancer drugs such as cisplatin are widely used for the treatment of its potential but it has certain side effects associated with it after long-term use of the drug for example nephrotoxicity. Cisplatin-induced nephrotoxicity includes various pathways that lead to the release of some kidney proteins such as KIM-1, NGAL, and clusterin in blood and urine. In the untreated group, no traces of these markers are seen but in case of kidney damage, these are upregulated in urine and blood samples.

Toxicogenomic aims to create gene profiles for specific toxicities measurable on well-designed microarray platforms. The accuracy of gene alterations is assessed using techniques like a quantitative reverse transcriptase-polymerase chain reaction and microarray platforms using various probes to help analytically validate gene profiles.

Novel biomarkers for detection of nephrotoxicity

Clusterin

It is one of the glycosylated proteins involved in apoptotic and anti-apoptotic pathways, prevalent in vital organs in the human body the kidney. In humans, two isoforms of clusterin exist — a pro-apoptotic nuclear form and an anti-apoptotic secretory form. Within the kidney's tubules, clusterin exerts anti-apoptotic effects, leading to the protection of the kidney. Kidney damage leads to the regulation of the clusterin gene in case of drug-induced nephropathy. Notably, clusterin is an exclusive early detection marker for renal tubular cell damage detection in urine as it does not undergo glomerular filtration (6).

A comprehensive study involving animals such as Wistar rats, BALB mice examined nephrotoxicity markers, where urinary clusterin demonstrated superior performance over traditional markers like serum creatinine, uric acid, and BUN in identifying proximal tubular injury induced by various substances such as anticancer agents, antibiotics, anti-inflammatory and antidiabetic agents. Among all urinary biomarkers, clusterin, along with KIM-1, NGAL, and albumin, stood out as the perceptive and definite indicators of drug-induced kidney tubular injury in the early stages. Notably, urinary and serum KIM-1 and clusterin have proved to be highly sensitive biomarkers for detecting cisplatin-induced kidney damage, which can be correlated with hematoxylin and eosin (H&E) histopathological examination of kidney tissue of treated groups (7).

Clusterin emerges as a promising biomarker tool for evaluating kidney damage, particularly in the case of drug-induced nephrotoxicity. Its sensitivity in detecting proximal tubular injury, coupled with its ability to mirror damage across various nephron territories, positions it as a valuable tool for monitoring renal health and guiding targeted interventions in response to kidney damage (8).

The heightened expression of the clusterin gene in response to nephrotoxicity is part of an intricate cellular and molecular process aimed at safeguarding renal tissues from harm. Here is a detailed breakdown of the mechanisms involved:

- Cellular stress response; exposure to nephrotoxic agents induces stress within renal cells, triggering a sequence of molecular events geared toward adapting to and mitigating the adverse effects of the toxins.
- Activation of signaling pathways; cellular stress activates various signaling pathways involved in responding to injury.
- Transcriptional regulation; the clusterin gene, located on chromosome 8 in humans, undergoes transcriptional regulation in response to stress signals. Transcription factors bind to the gene's promoter region, initiating the synthesis of clusterin mRNA.
- mRNA translation; the transcribed mRNA undergoes processing and is transported to the cytoplasm for translation, resulting in the synthesis of clusterin protein on ribosomes.

- Glycosylation and post-translational modifications; being a glycosylated protein, clusterin undergoes post-translational modification involving the addition of sugar molecules, influencing its structure and function.
- Intracellular and extracellular functions; inside cells, clusterin contributes to anti-apoptosis, lipid recycling, and cellular protection. When secreted, clusterin plays a role in cell attachment, preventing aggregation, and overall maintaining renal integrity.
- Extracellular functions in the kidney; secreted clusterin exhibits protective effects in renal tubules, contributing to cell attachment and preventing aggregation, ultimately maintaining renal integrity.
- Detection in urine; As clusterin is not filtered through glomeruli, its presence in urine becomes an exclusive marker for tubular cell damage. The heightened clusterin gene expression leads to increased urinary excretion, making it a sensitive biomarker for tubular injury.
- Multiple territories of the nephron; importantly, clusterin reflects injury not only in proximal tubules but also in other nephron territories, including the distal tubule and collecting duct. This broader reflection enhances the utility of clusterin as a marker for various types of nephrotoxic insults.

In summary, the mechanism involves the activation of stress response pathways, transcriptional regulation of the clusterin gene, mRNA translation, glycosylation, and subsequent intracellular and extracellular functions, collectively contributing to the protection and surveillance of renal tissues in response to nephrotoxic challenges.

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin, a 25-kD protein belonging to the superfamily lipocalin, plays a vital role in sequestering iron kidney infection or damage, serving as a pivotal element of innate immunity against damage. Its expression is observed in renal tubular cells in case of initiation or early stages of kidney damage (9). NGAL protein is secreted mostly by kidney tubule cells in normal humans at low levels but kidney damage and inflammation lead to upregulation of NGAL levels. NGAL levels are increased in blood and urine in response to inflammation. NGAL serves as early detection biomarker of both chronic and acute kidney damage mainly in renal tubular cells. NGAL levels are helpful in the prediction of the progression of renal functions. Significant upregulation of NGAL gene products occurs in both the kidney and urine. Extensive research has focused on NGAL as a marker for cisplatin nephrotoxicity. In mouse models, NGAL has been detected in the urine during the early stages of gentamicin-induced, paracetamol-induced induced, and cisplatin-induced kidney damage. Similarly, NGAL has been identified as an early biomarker of cisplatin-induced acute kidney injury (AKI) in human subjects. The protein has also proven to be an early indicator of toxicity in animal studies involving aminoglycosides. Rats administered gentamicin over varying durations showed a dose-dependent increase in the levels of damage markers such as NGAL specifically and KIM accompanied by early detection of these markers' upregulation in urine. These findings extend to dogs and rats receiving gentamicin, where NGAL has been established as a sensitive urinary biomarker for AKI (10-12). These animal studies collectively suggest that NGAL holds promise as an early, sensitive, and noninvasive urinary biomarker for detecting kidney injury. In patients undergoing amphotericin B treatment, urinary NGAL has demonstrated its superiority by detecting AKI 3.2 days earlier than serum creatinine. This underscores the potential of NGAL as a valuable tool for the early detection of kidney injury in clinical settings. The elevation in NGAL production and release from tubular cells following exposure to various harmful stimuli is proposed to have a self-protective purpose. Iron transporting agents such as NGAL are released in response to kidney inflammation or injury. NGAL appears to play a crucial role in a defensive response to stress-induced kidney damage, contributing to its growth and differentiation while also serving as a predictive biomarker for the detection of nephroprotection of various compounds.

Kidney injury molecule-1

It is a protein present in an epithelial cell adhesion molecule distinguished by a unique immunoglobulin domain and predominantly located in proximal tubules, demonstrates minimal expression in healthy kidneys but undergoes a significant upregulation in response to kidney injury. Type 1 transmembrane protein such as KIM-1 which is highly upregulated and its ectodomain released from in the proximal tubule of the kidney after kidney injury. USFDA and EMA have qualified KIM 1 as a kidney injury novel biomarker to be used for the assessment of drug induced nephrotoxicity or kidney damage.

Review indicates up-regulation in KIM-1 levels in proximal tubules in response to kidney injury. As a noninvasive, swift, sensitive, and consistent biomarker, urinary KIM-1 proves effective in promptly detecting AKI induced by cisplatin in rats. Within just one day of administering cisplatin, there is a substantial three- to fivefold increase in urinary KIM-1 levels, without a corresponding rise in plasma creatinine, BUN, urinary N-acetyl-beta-glucosaminidase (NAG), glycosuria, or proteinuria. In a separate study involving various nephrotoxic agents such as folic acid, S-(1,1,2,2-tetrafluoroethyl)-l-cysteine (TFEC) and rise in KIM-1 expression were observed in proximal tubule epithelial cells in both tissue and urine samples. Further investigations by Zhou et al, where rats were injected with gentamicin, mercury, or chromium, demonstrated the heightened sensitivity and specificity of KIM-1 for

early AKI compared to conventional markers such as BUN and serum creatinine (13-15). Notably, in toxicity models associated with anticancer agents, antidiabetic agents, urinary KIM-1 consistently outperformed serum creatinine and BUN as an early indicator of toxicity.

In the context of cisplatin-induced AKI in humans, urinary KIM-1 consistently displays an increase prior to the elevation of serum creatinine levels, underscoring its potential as a dependable early marker for kidney injury.

KIM-1 plays a crucial role in nephrotoxicity. It serves as a sensitive biomarker closely associated with mild to moderate renal injury and subsequent repair. When the kidneys are exposed to toxic substances like certain drugs or chemicals, there is a noticeable increase KIM-1 expression. In cases of nephrotoxicity, KIM-1 stands out due to its consistent and measurable upregulation, positioning it as a predictive candidate biomarker for assessing renal damage. The elevated gene expression and the detection of urinary levels of soluble proteins like KIM-1 suggest its potential as a diagnostic indicator of kidney damage. KIM-1's involvement in dedifferentiation, migration, proliferation, and cellular function restoration highlights its significance in comprehending and monitoring nephrotoxicity.

To summarize, KIM-1 emerges as a pivotal factor in nephrotoxicity, functioning not only as a sensitive biomarker reflecting renal injury but also as a valuable tool for gauging the impact of nephrotoxic agents on kidney well-being. Monitoring KIM-1 expression provides valuable insights into the intricate processes of renal damage and recovery. KIM-1 is a transmembrane protein that undergoes upregulation in response to renal injury, playing a pivotal role in the mechanisms of nephrotoxicity. The following delineates the general mechanism of KIM-1 in nephrotoxicity:

- Upregulation in response to injury: In the absence of renal injury, KIM-1 remains unexpressed in healthy kidneys. However, it undergoes swift upregulation in renal epithelial cells when exposed to nephrotoxic insults like drugs or toxins.
- Dedifferentiation and repair processes: KIM-1 is associated with the dedifferentiation of renal tubular cells, a crucial aspect of the kidney's endeavor to repair and regenerate damaged tissue. KIM-1 expression is pivotal in facilitating the transition of renal epithelial cells to a reparative phenotype.
- Phagocytosis of apoptotic cells: KIM-1 is actively involved in the clearance of apoptotic cells. In instances where renal cells undergo apoptosis due to nephrotoxic insults, cells expressing KIM-1 can recognize and phagocytose these apoptotic cells, assisting in the removal of damaged cells and contributing to tissue repair.
- Urinary shedding: A distinctive feature of KIM-1 is its shedding into the urine. The extracellular domain of KIM-1 undergoes cleavage and is released into the urine, rendering it detectable in urine samples. This urinary shedding of KIM-1 serves as a non-invasive biomarker for kidney injury, facilitating monitoring and diagnosis.
- Involvement in inflammatory response: KIM-1 is closely associated with the inflammatory response in the kidneys. Its upregulation is often accompanied by an increased expression of pro-inflammatory cytokines, reflecting the inflammatory processes responding to nephrotoxic insults.
- Potential role in early detection; The early upregulation of KIM-1 in response to renal injury suggests its potential as an early marker for detecting nephrotoxicity, offering an advantage over traditional markers like serum creatinine that may show changes at a later stage.

KIM-1 plays a pivotal role in responding to nephrotoxic insults by contributing to tissue repair, facilitating apoptotic cell clearance, and serving as a biomarker for kidney injury. Understanding the mechanisms involving KIM-1 is instrumental in assessing and monitoring the impact of nephrotoxic agents on renal health.

Beta-2 microglobulin

Beta-2 microglobulin (B2M) is an amino acid protein which is mainly associated with glomeruli dysfunction. It undergoes free filtration by the glomerulus and complete reabsorption by proximal tubular cells. Tubular injury-induced impairment in uptake leads to an elevated urinary excretion of B2M, making it a direct indicator of tubular dysfunction.

Clinical study results were carried on cisplatin-treated ovarian cancer patients and followed for 24 weeks to assess kidney damage, each cisplatin administration results in upregulation of blood and urinary B2M levels. However, the study did not explore associations between the increase in B2M and subsequent clinical AKI development. In another study with cisplatin-treated patients, B2M exhibited a threefold increase by day 3, preceding observations with urinary KIM-1, TFF3, or calbindin. Notably, urinary B2M increased while serum B2M decreased.

Upregulation in urinary B2M is also observed after the administration of various anticancer, anti-inflammatory, and antidiabetic agents (16-20).

The following provides an overview of B2M's involvement in nephrotoxicity;

- Urinary release: in cases of kidney injury or dysfunction, there is an increased release of B2M into the urine. Elevated levels of B2M in urine act as an indicator of impaired renal function, making it a potential biomarker for nephrotoxicity.
- Tubular reabsorption: under normal conditions, the kidneys freely filter B2M, with almost all of it being reabsorbed and catabolized in the renal tubules. However, during nephrotoxic events, the tubular

reabsorption process may be compromised, leading to heightened levels of B2M in the urine.
- Diagnostic utility: the measurement of B2M levels in urine has been explored as a diagnostic tool for identifying early signs of nephrotoxicity. Elevated urinary B2M levels indicate renal tubular dysfunction, aiding in the early detection of kidney damage.
- Association with CKD: B2M has also been linked to CKD. In scenarios where nephrotoxicity contributes to the progression of CKD, monitoring B2M levels may provide insights into the severity of renal impairment.
- Inflammatory response: nephrotoxic insults can trigger an inflammatory response in the kidneys. B2M has been associated with inflammatory processes, and its involvement may contribute to the overall inflammatory environment observed in nephrotoxicity. In summary, B2M stands out as a relevant biomarker in the context of nephrotoxicity, with heightened urinary levels indicating compromised renal function. Monitoring B2M levels, particularly in urine, holds promise for diagnosing and assessing the impact of nephrotoxic agents on kidney health.

Fatty acid-binding protein 1

L-FABP, also recognized as fatty acid-binding protein 1 (FABP1), is a 14-kDa protein belonging to the extensive family of lipid-binding proteins. The encoding of L-FABP is governed by the FABP1 gene in humans. It falls within a category of carrier proteins responsible for overseeing the uptake and transport of fatty acids within cells. Its presence is not limited to the liver but extends to other organs, including the stomach, intestine, lung, and kidney. L-FABP plays a pivotal role in binding and transporting fatty acids to the mitochondria and peroxisomes, contributing to energy production through β-oxidation. Additionally, L-FABP serves a vital function in protecting cells by alleviating oxidative stress induced by H_2O_2. In the kidney, L-FABP is specifically situated in the proximal tubule, where it is subsequently excreted into the tubular lumen along with bound toxic peroxisomal products. Notably, increased expression of L-FABP and its urinary excretion have been observed before the rise in serum creatinine levels in various animal models of AKI, including instances involving ischemia-reperfusion and cisplatin-induced AKI. This highlights the potential of L-FABP as an early indicator of kidney injury in different AKI scenarios (21-22).

The involvement of liver-type fatty acid-binding protein (L-FABP) in nephrotoxicity encompasses several essential processes:

- Distribution in tissues: L-FABP is not confined solely to the liver; it is also present in various tissues, including the kidney. Specifically, L-FABP is localized in the proximal tubules within the kidney.
- Transport of fatty acids and energy generation: L-FABP functions as a carrier protein, facilitating the binding and transport of fatty acids. This transportation directs fatty acids to the mitochondria and peroxisomes in renal cells, contributing to energy production through β-oxidation.
- Cellular protection: L-FABP serves a protective role by counteracting oxidative stress induced by reactive oxygen species, notably hydrogen peroxide (H2O2). This protective function aids in shielding renal cells from potential damage.
- Specific localization in proximal tubules: L-FABP is specifically positioned in the proximal tubules of the kidney. This precise localization is noteworthy, given that the proximal tubule is frequently a target for nephrotoxic insults.
- Excretion of toxic substances: L-FABP is excreted into the tubular lumen along with bound toxic peroxisomal products. This excretion process assists in eliminating potentially harmful substances from renal tubules.
- Sensitivity as a biomarker: during nephrotoxic injury, heightened L-FABP expression and urinary excretion precede the elevation of traditional markers like serum creatinine. L-FABP functions as a sensitive biomarker, facilitating the early detection of nephrotoxicity.
- Defense against nephrotoxins: L-FABP exhibits protective effects against nephrotoxicity induced by various agents, including cisplatin. Its protective capabilities extend to different models of kidney injury.
- Free radical scavenging: the protective impact of L-FABP against nephrotoxicity, particularly in cisplatin-induced injury, is associated with its ability to scavenge free radicals. This implies that L-FABP contributes to diminishing oxidative stress linked with nephrotoxic results. In summary, L-FABP's role in nephrotoxicity involves facilitating fatty acid transport, promoting energy generation, and providing cellular protection. Its specific localization in the proximal tubules, sensitivity as a biomarker, and protective functions collectively establish L-FABP as a crucial element in the early detection of nephrotoxicity and the defense against renal damage.

Conclusion

Conventional biomarker such as serum creatinine, BUN, uric acid, urea are not specific for AKI factors such as age, gender, muscle mass, muscle metabolism and because of other disease conditions. The occurrence of drug-induced kidney injury presents a notable hurdle in the drug development process and increase in morbidity and mortality rates. Consequently, there is a growing

inclination among drug developers and regulatory bodies towards novel biomarkers capable of directly identifying glomerular or tubular damage. In response to this demand, both the US Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) have endorsed a panel of seven biomarkers for detecting nephrotoxicity in drug trials. This review primarily delves into some urinary biomarkers sanctioned by the FDA and EMEA, encompassing KIM-1, B2M, clusterin, NGAL, and FABL-1 which hold potential roles in nephrotoxicity studies. Many of these markers are upregulated in the early stages of kidney damage. Additionally, there is limited understanding regarding the connection between biomarker alterations and their long-term impact on kidney function. While these innovative biomarkers show promise for enhancing the effectiveness of preclinical and clinical trials, further exploration is imperative to fully comprehend their utility in evaluating drug-induced kidney toxicity.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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