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Review article

Novel biomarkers of acute kidney injury and chronic kidney disease

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ABSTRACT

Introduction: Nowadays, laboratory evaluation of renal damage is based on conventional poorly-sensitive and poorly-specific markers, such as serum creatinine, urea and electrolyte levels. This stimulated continuous research on novel biochemical markers suitable for diagnosis and monitoring of acute kidney injury (AKI) and chronic kidney disease (CKD).
Aim: The aim of this paper was to review available evidence regarding novel biomarkers of kidney damage.
Material and methods: The review of available literature was conducted, using search terms 'kidney damage biomarker' and 'kidney injury biomarker.'
Results and discussion: Cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, liver-type fatty acid binding protein, selected urinary enzymes (e.g. N-acetyl-β-glucosidase) and low-molecular-weight proteins (e.g. β-2 microglobulin) seem to be the most promising biomarkers of both AKI and CKD. In turn, asymmetric dimethylarginine, inflammatory/fibrosis parameters (e.g. monocyte chemoattractant protein, transforming growth factor-β1) and Klotho-FGF23 axis raise most interest as the most selective markers of CKD.
Conclusions: Owing continuing progress in nephrology laboratory diagnostics, novel biomarkers of kidney damage are likely to be introduced in routine clinical practice.

1. Introduction

Renal function can be assessed with some traditional, commonly accepted and widely available methods, such as laboratory tests (e.g. serum creatinine, blood urea nitrogen, electrolyte profile, urine output and osmolality, fractional sodium excretion, urine microscopy – sediment analysis), renal histology and imaging studies (renal angiography, ultrasonography, TK/MRI).[1] The most useful and simplest method for biochemical estimation of kidney function is determination of serum creatinine (sCr) concentration; after

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substitution of this parameter to some equations proposed in literature (e.g. Cockcroft–Gault formula or Abbreviated Modification of Diet in Renal Disease (MDRD) equation), glomerular filtration rate (GFR) can be estimated.[2] Elevated serum creatinine is also considered an evident diagnostic marker of renal failure. However, interpretation of serum creatinine levels has some well-known limitations, as this parameter may be modulated by patient's muscle mass, physical activity and diet; furthermore, there is a time lag between the kidney injury and the increase is sCr. All these potential drawbacks of sCr have been reviewed elsewhere.[3,4] Owing the limitations mentioned above and poor sensitivity and specificity at early stages of either acute or chronic kidney dysfunction,[4,5] the routinely determined biochemical parameters should be mostly considered as surrogate biomarkers of renal function.

In line with widely accepted criteria, acute kidney injury (AKI), also referred to as acute renal failure (ARF), is a clinical condition characterized by an abrupt and sustained deterioration of renal function, resulting in nitrogenous and non-nitrogenous waste retention, oliguria progressing to anuria, disruption of water and electrolyte balance.[6–8] AKI is diagnosed in approximately 7.2% of all hospitalized patients. The most common causative factors of hospital-acquired renal insufficiency include decreased renal perfusion, pharmacotherapy, surgical treatment and administration of radiographic contrast agents; the risk of this condition may increase up to 25% in critically ill patients treated at intensive care units.[9,10] According to the pathophysiological criteria, AKI develops as a result of prerenal (decreased kidney perfusion of any etiology without alterations of renal parenchyma) or post-renal (impaired renal function resulting from urine flow obstruction, without concomitant changes in kidney parenchyma) disturbances, or as a consequence of direct kidney damage by various toxic, infectious and inflammatory factors (intrarenal AKI).[6–8]

Variety and inconsistency of published AKI definitions enforced introduction of unified, commonly accepted criteria for its progress and outcome. As a result, Risk-Injury-Failure-Loss-End Stage (RIFLE)[11] and Acute Kidney Injury Network (AKIN)[12] staging systems were developed and are both commonly used to diagnose AKI and to predict its outcome. Moreover, uniform AKI definition and diagnostic guidelines were published by the Kidney Disease Improving Global Outcomes (KDIGO) in 2012.[1,4]

In some cases, AKI leads to persistent structural and functional dysfunction which may eventually progress to chronic kidney disease (CKD).[13] However, CKD is usually a consequence of chronic and progressive disorders, especially those located in the kidneys (e.g. glomerulonephritis, tubule-interstitial inflammation, nephrolithiasis), or systemic conditions (hypertension, diabetes mellitus).[14] In line with the 2012 KDIGO definition, CKD is an abnormality of kidney structure or function present for more than 3 months and having implications for health.[14,15] Detailed diagnostic criteria of CKD include either a decrease in GFR to 60 mL/min/1.73 m^2 of body surface area for more than 3 months or an obvious evidence of kidney damage.[15,16] Potential underlying mechanisms of post-AKI CKD include loss of nephrons, glomerular hypertrophy, interstitial inflammation and fibrosis, tubular injury with the impairment of tubular cell renewal cycle, maladaptive tubular repair and inadequate cellular adaptation to microenvironmental conditions, such as hypoxia and oxidative stress.[16]

All published definitions of AKI and CKD (RIFLE, AKIN, KDIGO) include a common component, a decrease in glomerular filtration rate (GFR), reflecting lower urinary output and/or elevated sCr. However, also other biochemical parameters that could be used to diagnose AKI and CKD and to determine the severity thereof are a subject of ongoing debate. Moreover, some attempts are made to reconcile the existing consensuses and to introduce a single uniform definition of these conditions, based on other criteria than elevated sCr.[17,18] This results also from the limitations of existing laboratory markers (mainly sCR), especially their inability to determine the specific etiology of kidney damage and a relatively long time lag between the onset of GFR reduction and the initiation of kidney damage.[19]

All limitations inherent to currently used biochemical markers and the lack of an ideal, non-invasive method for accurate assessment of renal function justify research on novel laboratory tests that could be used for early, preclinical detection of kidney dysfunction.

2. Aim

The aim of this review was to identify novel laboratory biomarkers of kidney damage associated with AKI and CKD, that are likely to be introduced in clinical practice.

3. Material and methods

Using search terms 'kidney damage biomarker' and 'kidney injury biomarker', we searched Medline database (Ovid Medline 1946 to September week 1 2016) for articles published between 2000 and 2016. We have selected only full-text, English-language review papers related to humans. Specifically, we looked for generalized reviews related to AKI and CKD, excluding more specific papers, e.g. on the occurrence of these conditions in some age groups ('pediatric' or 'geriatric') or patients with isolated conditions (e.g. CKD in diabetic patients).

4. Results and discussion

Using the phrase 'kidney injury biomarker' and the above-mentioned search limits, a total of 884 publications were identified. For the term 'kidney damage biomarker' and similar search criteria, we found 816 potentially relevant titles.

Based on the review of literature published during recent 16 years, several potential biomarkers of kidney damage have been identified. They are briefly discussed below.

4.1. *What is a biomarker?*

Several definitions of 'biomarker' exist. According to one of the first definitions, a Medical Subject Heading (MeSH) published in 1989, biomarkers are 'measurable and quantifiable biological parameters (e.g. specific enzyme concentration, specific hormone concentration, specific gene

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