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Review article

Novel biomarkers of acute kidney injury and chronic kidney disease

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ARTICLE INFO

Article history:
Received 21 March 2016
Received in revised form
27 September 2016
Accepted 18 October 2016
Available online 11 November 2016

Keywords:
Acute kidney injury (AKI)
Chronic kidney disease (CKD)
Laboratory diagnosis
Biomarker

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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http://dx.doi.org/10.1016/j.poamed.2016.10.002
1230-8013/

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, tubulointerstitial 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

phenotype distribution in a population, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis, metabolic processes, substance abuse, pregnancy, cell line development, epidemiologic studies, etc.'[20]

According to the National Institute of Health (NIH) Biomarkers Definition Working Group, biomarker is a 'characteristic that is objectively measured and evaluated as an indicator of normal biological, pathologic processes or pharmacologic responses to a therapeutic intervention'.[21] In line with another, short and simple general definition proposed by Schiffl and Lang,[22] biomarker is a parameter of structural, biochemical, physiologic or genetic change that indicates the presence, severity or progress of a disease.

An ideal biomarker of renal dysfunction should have several features: be measurable and reproducible with a standardized and validated method, minimally invasively or non-invasively determined in urine or blood, i.e. possibly least burdensome for the patient, easy to interpret for clinicians, adequately sensitive and specific, non-expensive, changing rapidly and specifically in response to a kidney disease, correlating with the degree of kidney damage, suitable for risk stratification and establishment of prognosis, providing information on a possible mechanism of injury (e.g. pre-renal, post-renal), and non-interfering with implemented treatment. Importantly, an ideal biomarker should accurately predict clinical outcome and/or therapeutic response, and expedite drug development process.[23–25]

4.2. *Biomarkers of kidney damage*

Obviously, none of currently available markers satisfy all the criteria mentioned above. Moreover, most of the novel biomarkers of kidney damage is still in the phase of limited clinical trials. Hence, the long-term evaluation of their significance requires a longer observation after their introduction into general clinical practice.

However, still novel compounds are sought to be used in laboratory diagnosis of kidney disease, especially for determining the pathomechanism thereof. Another extremely important and desired feature of such novel biomarkers is their application for early detection of asymptomatic renal damage or early stages of kidney recovery.

Novel biochemical parameters used in nephrology are recently classified as the biomarkers of kidney regeneration and the biomarkers of renal damage progression, in line with a new conceptual framework for AKI course.[26] According to this concept, a subclinical phase of AKI may be identified using an early biomarker of kidney damage despite the lack of evidence of renal dysfunction. A similar concept can be used for CKD as well; while the presence of some recovery markers corresponds to normalization of renal function, their absence indicates a clinically silent, progressive loss of nephrons which is not reflected by abnormalities of sCr and urine output.[26]

Kidney biomarkers can be also classified according to the type of renal injury; such classification includes general clinical biomarkers (e.g. blood pressure and urine output), functional biomarkers (e.g. GFR), biomarkers of oxidative stress (a component of AKI and CKD pathogenesis), biomarkers of structural and cellular injury (e.g. tubular enzymes and upregulated proteins), biomarkers of immune response and fibrosis (with the last two categories typically used for CKD).[25,27] There is also a simpler classification, including biomarkers of kidney damage and biomarkers of kidney function.[28] Finally, kidney markers can be classified based on their origin (e.g. filtrated and non-resorbed, excreted by the tubules or cut from the renal cell membranes).[29] There is also an interesting classification proposed by Coca et al.[30] who distinguished three main categories of AKI biomarkers: used in the differential diagnosis in established AKI, in early detection and in determining AKI prognosis. Some of the markers can be assigned to each of these categories, which underlines their broad diagnostic significance. They are also mentioned in our Table 1 (e.g. cystatin C, neutrophil gelatinase-associated lipocalin-1 – NGAL-1, kidney injury molecule-1 – KIM-1, N-acetyl-β-glucosidase – NAG).

We have identified numerous publications presenting potential novel biomarkers suitable for the diagnosis and monitoring of both AKI and CKD. A short list of potential AKI biomarkers is presented in Table 1; an attempt was made to classify these compounds according to the abovementioned criteria. Potential novel biomarkers of CKD are listed in Table 2. Similar to some previously published papers, we grouped them into two categories: biomarkers of kidney function and biomarkers of renal damage. The latter group can be further divided according to the prevailing location and character of ongoing pathophysiological process. However, also another classification system exists, distinguishing between diagnostic markers of CKD and parameters used for monitoring of its progression.

4.3. *The most promising, novel biomarkers of kidney damage and the issue of the 'overlapping' of AKI and CKD markers*

Detailed description of all biomarkers listed in Tables 1 and 2 is out of the scope of this short review; more comprehensive characteristics of these compounds can be found in the references provided.

However, in our opinion, there are some publications presenting pathophysiological and clinical role of AKI[38–45] and CKD[46–48] biomarkers that deserve more attention.

Available evidence suggests that the most promising biomarkers of AKI are cystatin C, NGAL-1, KIM-1, liver-type fatty acid binding protein (L-FABP) and low-molecular-weight proteins. In turn, cystatin C, ADMA, fibrosis biomarkers and Klotho-FGF23 axis focus most interest of researchers as novel biomarkers of CKD. Specifically, a growing number of publications dealing with the dysregulation Klotho-FGF23 axis is worth emphasizing.[49–55]

Noticeably, some biomarkers (NGAL, KIM-1, NAG, L-FABP) can be used for both diagnosis and monitoring of AKI and CKD. Consequently, some compounds listed in Tables 1 and 2 reflect kidney dysfunction and damage in both acute and chronic conditions. This results from the fact that their presence in the blood or urine is determined by the mechanisms involved in the pathogenesis of both acute and chronic kidney damage – e.g. AKI and CKD share some common inflammatory pathways, but while the former is an acute condition, the latter has

Table 1 – Novel biomarkers of AKI.[30–34]

Biomarker	Origin and function	Biomarker property rationale	Detection time after renal injury, h	Clinical AKI settings studied
Cystatin C[a]	Cysteine protease inhibitor secreted by all nucleated human cells and released at constant rate into plasma, freely filtered in glomeruli, completely reabsorbed and degraded by proximal tubular cells	Plasma accumulation due to filtration decrease; impaired catabolism by the proximal tubules resulting in increase in urine	12–24	Intensive care unit patients, cardiopulmonary bypass, contrast, obstruction, nephrotoxin
Neutrophil gelatinase-associated lipocalin-1[a]	Glycoprotein produced by epithelial tissues, including proximal and distal tubules, freely filtered in glomeruli, undergoes complete reabsorption in healthy tubular cells, binds siderophores	Upregulated expression predominantly in proximal tubules after ischemic injury	2–4	Intensive care unit patients, cardiac surgery (both adults and pediatric), contrast, trauma, hemolytic uremic syndrome
Kidney injury molecule-1[a]	Transmembrane glycoprotein produced by proximal tubules, systemic non-detectable, confers phagocytic properties to tubular epithelia	Released into urine after ischemic or nephrotoxic damage of the proximal tubules and upregulated during dedifferentiation in response to injury	12–24	Cardiopulmonary bypass, contrast, transplant, nephrotoxin
Liver-type fatty acid binding protein	Cytoplasmic protein involved in fatty acid trafficking, produced in liver, pancreas, intestine, stomach, lung and proximal tubules, freely filtered in glomeruli and reabsorbed in proximal tubules	Plasma accumulation due to filtration decrease; increased urinary excretion after tubular cells damage (translocation from cytosol tubular lumen during ischemic injury)	1 after ischemic tubular injury	Coronary angiography, contrast, sepsis
Urinary low molecular weight proteins: • β-2 microglobulin • α-1 microgloblin • RBP	Produced by many tissues, filtered freely by glomeruli, resorbed, non-secreted	Filtered freely by glomeruli, resorbed, non-secreted	<12	β-2 microglobulin: cardiac surgery, intensive care unit patients, cisplatin, contrast, burn injury α-1 microgloblin: cardiac surgery, intensive care unit patients, contrast RBP: cardiac surgery, intensive care units, aminoglysosides, cisplatin
Urinary tubular enzymes: • NAG[a] • γGT • πGSH • αGSH • ALP • AAP	Expressed in almost all tissues, released from lysosomes and from the cytoplasm of proximal tubular cells	Urinary elevation imply tubular damage	12	NAG: cardiac surgery, cisplatin, intensive care unit patients, aminoglycosides, burn injury, amphotericin B, contrast AAP: cisplatin, contrast, aminoglycosides ALP: intensive care unit patients, contrast, extracorporeal shock wave lithotripsy αGSH, πGSH: cardiac surgery, intensive care units, amphotericin B γGT: intensive care unit patients, contrast, extracorporeal wave lithotripsy
Urinary inflammatory markers • interleukin-6 • interleukin-8 • interleukin-18 • calprotectin	Derived from neutrophils and macrophages, activators of the immune response, proinflammatory cytokines	Their presence is an evidence of an ongoing inflammatory reaction involving glomerulus and/or tubules	6–24	Intensive care unit patients, cardiopulmonary bypass, sepsis

Table 1 (*Continued*)

Biomarker	Origin and function	Biomarker property rationale	Detection time after renal injury, h	Clinical AKI settings studied
Osteopontin	Phosphorylated glycoprotein, mostly involved in mineralization of the extracellular matrices of bones and teeth, also participates in regulation of ectopic calcification, e.g. in kidneys	Increased release in both proximal and distal tubules after injury	No data available	Intensive care unit patients
Hepcidin	Peptide hormone produced in hepatocytes, kidney, heart and brain, freely filtered in glomeruli, undergoes almost complete reabsorption in healthy tubular cells	Plasma accumulation due to filtration decrease; impaired catabolism by the proximal tubules resulting in increase in urine	No data available	Cardiopulmonary bypass
Netrin-1	Protein found in lungs, pancreas, mammary glands, minimally expressed in proximal tubules, involved in axonal guidance, also developmental factor, renal function unclear	Highly expressed in injured proximal tubules	6	Cardiopulmonary bypass

Comments: RBP – retinol-binding protein, NAG – N-acetyl-β-glucosaminidase, γGT – γ-glutamyltranspeptidase, πGSH – π-glutathione S-transferase, αGSH – α-glutathione S-transferase, ALP – alkaline phosphatase, AAP – alanine aminopeptidase.
[a] A multifunctional marker used in differential diagnosis in established AKI, in early AKI detection and prognosis.

Table 2 – Novel biomarkers of CKD.[35–37]

	Biomarker	Origin and function	Biomarker property rationale	Clinical CKD settings studied
Kidney function				
Filtration	- Cystatin C - B2-M - BTP	Low molecular weight proteins, filtered, reabsorbed and mostly metabolized in proximal tubules	Plasma accumulation due to filtration decrease; impaired catabolism by the proximal tubules resulting in increase in urine. Indicators of reduced GFR	Both type 1 and 2 diabetes, kidney dysfunction with increased risk of heart failure, nephrectomy, renal artery stenosis
Kidney damage				
Glomerular injury	- Podocin - Nephrin - Podocalyxin	A renal filtration barrier compounds: podocin is a protein component of the filtration slits of podocytes; nephrin is a transmembrane protein that is a structural component of the slit diaphragm; podocalyxin is the major protein of the glycocalyx of podocytes in the glomerulus	The urinary presence of proteins structurally-associated with glomeruli is considered to be an evidence for glomerular injury	Elevated in diabetic nephropathy and active lupus nephritis, Ig-A nephropathy and post-streptoccocal glomerulonephritis
Tubulointestinal injury	- NGAL-1 - KIM-1 - NAG - L-FABP	See Table 1		Polycystic kidney disease, interstitial fibrosis in allografts, type 1 diabetes mellitus despite normal albumin excretion, HIV-associated nephropathy, primary focal segmental glomerulosclerosis, type 2 diabetic nephropathy

Table 2 (*Continued*)

	Biomarker	Origin and function	Biomarker property rationale	Clinical CKD settings studied
Endothelial dysfunction	- ADMA	Amino acid normally synthesized intracellularly and eliminated with the urine	ADMA is considered to be 'a missing link' between CKD and cardiovascular disease due to endothelial dysfunction – ADMA inhibits nitric oxide synthetases	Patients on hemodialysis, IgA nephropathy, polycystic kidney disease, type 2 diabetes
Kidney damage				
Oxidative stress	- Ox-LDL - AOPP - TBARS - MDA - AGE	In vivo oxidation of proteins, lipids, carbohydrates	Elevated oxidative stress occurs in early CKD and increases with CKD progress	Ox-LDL associated with endothelial injury and inflammation, AOPP and AGE associated with diabetic nephropathy development
Inflammation	- CRP - MCP-1 - PTX3 - Il-18	Commonly occurring mediators of inflammatory response	Inflammatory proteins, chemokines, released and upregulated by kidney glomerular and tubular cells	Increased in diabetic nephropathy and glomerulonephritis
Fibrosis	- TGF-β1 - CTGF - Tenascin - TIMP-1 - MMP-2, MMP-9	Tissue healing mediators (TGF-β1, CTGF); tenascin-matrix protein involved in interstitial tissue repair, MMP-2 and 9/TIMP-1 – enzymes and inhibitors involved in matrix rebuild and degradation	TGF-β and MMP-2 and -9 axis induce the epithelial-to-mesenchymal transition (EMT) and disruption of integrity of tubular basement membranes	High level in proteinuria and glomerulosclerosis
Kidney-associated metabolic disorders	- Klotho/FGF-23 axis - Adiponectin	FGF-23 – a phosphaturic, bone osteocytes-derived hormone, also decreasing calcitriol production and suppressing parathormone, Klotho is essential for FGF-23 to exert its phosphaturic effects in the kidney; adiponectin – a hormone secreted by adipocytes, inversely associated with obesity, improving insulin sensitivity	FGF-23 increases as Klotho decreases in CKD; the Klotho deficiency precludes the phosphaturic FGF-23 effect, resulting in hyperphosphatemia	Obstructive nephropathy, diabetic nephropathy, IgA nephropathy, chronic glomerulonephritis, rejected transplanted kidneys

Comments: B2-M – β2-microglobulin, BTP – β-trace globulin, NGAL-1 – neutrophil gelatinase-associated lipocalin-1, KIM-1 – kidney injury molecule-1, NAG – N-acetyl-β-glucosaminidase, L-FABP – liver type fatty acid binding protein, ADMA – asymmetric dimethylarginine, Ox-LDL – oxidized low-density lipoprotein, AOPP – advanced oxidation protein products, TBARS – thiobarbituric acid reactive substances, MDA – malondialdehyde, AGE – advanced glycation end product, CRP – C-reactive protein, MCP-1 – monocyte chemoattractant protein-1, PTX3 – pentraxin 3, Il-18 – interleukin 18, TGF-β1 – transforming growth factor-β1, CTGF – connective tissue growth factor, TIMP-1 – tissue inhibitor of metalloproteinases-1, MMP-2 – matrixmetalloproteinase-2, MMP-9 – matrixmetalloproteinase-9, FGF-23 – fibroblastic growth factor-23.

a chronic and progressive character. AKI eventually results in toxic or ischemic acute tubular necrosis; the latter may develop in various pathomechanisms: disruption of renal perfusion and renal vasoconstriction, tubular cell damage and death, loss of cytoskeletal integrity and polarity, cell desquamation, contributing to intratubular increase in hydrostatic pressure and imbalance of tubular-glomerular feedback. Therefore, early toxic or ischemic damage is associated with local inflammation and release of numerous pro-inflammatory mediators.[5,56] Inflammatory mechanisms are also involved in the pathogenesis of CKD, a condition resulting from progressive destruction of renal parenchyma, being a consequence of repeating AKI episodes or presence of chronic comorbidities (e.g. arterial hypertension, diabetes mellitus) that affect renal structure and contribute to loss of functional nephrons, compensatory growth and overload of the remaining ones. This eventually leads to kidney damage and fibrosis.[15,57,58]

Since some of the novel biomarkers are enzymes released by damaged tubular cells, proteins secreted in response to ischemia or toxic damage, indices of acute or chronic inflammation and fibrosis, they seem to be accurate measures of early renal impairment during the course of both AKI and CKD.

5. Conclusions

To summarize, there is a change in the approach to laboratory nephrology diagnostics: conventional, poorly specific markers of late renal impairment (creatinine, urea) are gradually replaced by novel, more accurate parameters

('troponin-like biomarkers') that reflect the pathophysiological nature of kidney damage. Probably, the biomarkers presented in this review will be soon used in routine clinical practice, providing broader insight into the course of renal pathologies, determining appropriate treatment and prognosis in these conditions.

Conflict of interest

None declared.

REFERENCES

1. Ostermann M. Diagnosis of acute kidney injury: Kidney Disease Improving Global Outcomes criteria and beyond. *Curr Opin Crit Care*. 2014;20(6):581–587.
2. Ferguson MA, Waikar SS. Established and emerging markers of kidney function. *Clin Chem*. 2012;58(4):680–689.
3. Uchino S. Creatinine. *Curr Opin Crit Care*. 2010;16(6):562–567.
4. Gowda S, Desai PB, Kulkarni SS, Hull VV, Math AAK, Vernekar SN. Markers of renal function tests. *North Am J Med Sci*. 2010;2(4):170–173.
5. Urbschat A, Obermuller N, Haferkamp A. Biomarkers of kidney injury. *Biomarkers*. 2011;16(suppl 1):S22–S30.
6. Lameire N, van Biesen W, Vanholder R. Acute renal failure. *Lancet*. 2005;365(9457):417–430.
7. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet*. 2012;380(9843):756–766.
8. Winterberg PD, Lu CY. Acute kidney injury: the beginning of the end of the dark ages. *Am J Med Sci*. 2012;344(4):318–325.
9. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis*. 2002;39(5):930–936.
10. Metcalfe W, Simpson M, Khan IH, et al. Acute renal failure requiring renal replacement therapy: incidence and outcome. *Q J Med*. 2002;95(9):579–583.
11. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204–R212.
12. Mehta RL, Kellum JA, Shah SV, Mehta RL, Palevsky P. Acute kidney injury network: report on an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.
13. Heung M, Chawla LS. Acute kidney injury: gateway to chronic kidney disease. *Nephron Clin Pract*. 2014;127(1–4):30–34.
14. Campbell D, Weir MR. Defining, treating and understanding chronic kidney disease – a complex disorder. *J Clin Hypertens (Greenwich)*. 2015;17(7):514–527.
15. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1):1–150.
16. Yamaguchi J, Tanaka T, Nangaku M. Recent advances in understanding of chronic kidney disease. *F1000Research*. 2015;4(F1000 Faculty Rev):1212. http://dx.doi.org/10.12688/f1000research.6970.1.
17. Cruz DN, Ricci Z, Ronco C. Clinical review: RIFLE and AKIN – time for reappraisal. *Crit Care*. 2009;13(3):211–220.
18. Ricci Z, Cruz DN, Ronco C. Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. *Nat Rev Nephrol*. 2011;7(4):201–208.
19. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int*. 2015;87(1):62–73.
20. Vasan RS. Biomarkers of cardiovascular disease. Molecular basis and practical considerations. *Circulation*. 2006;113(19):2335–2362.
21. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89–95.
22. Schiffl H, Lang SM. Update on biomarkers of acute kidney injury. Moving closer to clinical impact? *Mol Diagn Ther*. 2012;16(4):199–207.
23. Wasung ME, Chawla LS, Madero M. Biomarkers of renal function, which and when? *Clin Chem Acta*. 2015;438:350–357.
24. Devarajan P, Murray P. Biomarkers in acute kidney injury: are we ready for prime time? *Nephron Clin Pract*. 2014;127(1–4):176–179.
25. Tesch GH. Serum and urine biomarkers of kidney disease: a pathophysiological perspective. *Nephrology*. 2010;15(6):609–616.
26. Kashani K, Kellum JA. Novel biomarkers indicating repair or progression after acute kidney injury. *Curr Opin Nephrol Hypertens*. 2015;24(1):21–27.
27. Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. *Nephrol Dial Transplant*. 2014;29(7):1301–1311.
28. Martensson J, Martling CR, Bell M. Novel biomarkers of acute kidney injury and failure: clinical applicability. *Br J Anaesth*. 2012;109(6):843–850.
29. Pisitkun T, Johnstone R, Knepper MA. Discovery of urinary biomarkers. *Mol Cell Proteomics*. 2006;5(10):1760–1771.
30. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int*. 2008;73(9):1008–1016.
31. Waikar S, Bonventre JV. Biomarkers for the diagnosis of acute kidney injury. *Curr Opin Nephrol Hypertens*. 2007;16(6):557–564.
32. Thomas AA, Demirjian S, Lane BR, et al. Acute kidney injury: novel biomarkers and potential utility for patient care in urology. *Urology*. 2011;77(1):5–11.
33. Siew ED, Ware LB, Ikizler TA. Biological markers of acute kidney injury. *J Am Soc Nephrol*. 2011;22(5):810–820.
34. Ostermann M, Philips BJ, Forni LG. Clinical review: biomarkers of acute kidney injury: what are we now? *Crit Care*. 2012;16(5):233. http://dx.doi.org/10.1186/cc11380.
35. Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. *Kidney Int*. 2011;80(8):806–821.
36. Lopez-Giacoman S, Madero M. Biomarkers in chronic kidney disease, from kidney function to kidney damage. *World J Nephrol*. 2015;4(1):57–73.
37. Perco P, Pleban C, Kainz A, et al. Protein biomarkers associated with acute renal failure and chronic kidney disease. *Eur J Clin Invest*. 2006;36(11):753–763.
38. Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. *Annu Rev Pharmacol Toxicol*. 2008;48:463–493.
39. Edelstein CL. Biomarkers of acute kidney injury. *Adv Chronic Kidney Dis*. 2008;15(3):222–234.
40. Soni SS, Pophale R, Ronco C. New biomarkers for acute renal injury. *Clin Chem Lab Med*. 2011;49(8):1257–1263.
41. Abdallah E, Waked E, Al-Helal B, Asad R, Nabil M, Harba T. Novel troponin-like biomarkers of acute kidney injury. *Saudi J Kidney Dis Transpl*. 2013;24(6):1111–1124.
42. Obermüller N, Geiger H, Weipert C, Urbschat A. Current developments in early diagnosis of acute kidney injury. *Int Urol Nephrol*. 2014;46(1):1–7.
43. Ho J, Reslerova M, Gali B, et al. Urinary hepcidin-25 and risk of acute kidney injury following cardiopulmonary bypass. *Clin J Am Soc Nephrol*. 2011;6(10):2340–2346.

44. Lorenzen JM, Hafer C, Faulhaber-Walter R, et al. Osteopontin predicts survival in critically ill patients with acute kidney injury. *Nephrol Dial Transplant*. 2011;26 (2):531–537.
45. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P. Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Clin J Am Soc Nephrol*. 2010;5(3):395–401.
46. Devarajan P. The use of targeted biomarkers for chronic kidney disease. *Adv Chronic Kidney Dis*. 2010;17(6):469–479.
47. Khan Z, Pandey M. Role of kidney biomarkers of chronic kidney disease: an update. *Saudi J Biol Sci*. 2014;21 (4):294–299.
48. Breit M, Weinberg KM. Metabolic biomarkers for chronic kidney disease. *Arch Biochem Biophys*. 2016;589:62–80.
49. Hu MC, Kuro-o M, Moe OW. The emerging role of Klotho in clinical nephrology. *Nephrol Dial Transplant*. 2012;27(7): 2650–2657.
50. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. *Kidney Int*. 2012;82(7):737–747.
51. Heine GH, Seiler S, Fliser D. FGF-23: the rise of a novel cardiovascular risk marker in CKD. *Nephrol Dial Transplant*. 2012;27(8):3072–3081.
52. Olauson H, Larsson TE. FGF23 and Klotho in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2013;22(4):397–404.
53. Neyra JA, Moe OW, Hu MC. Fibroblast growth factor 23 and acute kidney injury. *Pediatr Nephrol*. 2015;30(11):1909–1918.
54. Donate-Correa J, Muros de Fuentes MM, Mora-Fernandez C, Navarro-González JF. Pathophysiological implications of fibroblast growth factor-23 and Klotho and their potential role as clinical biomarkers. *Clin Chem*. 2014;60(7):933–940.
55. Wong MG, Pollock CA. Biomarkers in kidney fibrosis: are they useful? *Kidney Int Suppl*. 2014;4(1):79–83.
56. Adiyanti SS, Loho T. Acute kidney injury (AKI) biomarker. *Acta Med Indones*. 2012;44(3):246–255.
57. Imig JD, Ryan MJ. Immune and inflammatory role in renal disease. *Compr Physiol*. 2013;3(2):957–976.
58. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. *Clin J Am Soc Nephrol*. 2011;6(11):2567–2572.