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Biomarkers of acute kidney injury: a concise review of current literature

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ABSTRACT

Background: Acute kidney injury (AKI), a medical condition associated with increased hospitalization rates which requires interdisciplinary management, is a major health concern because of the burden it places on the health systems of different countries. Biomarkers represent the focus of recent years in furthering the early diagnosis of AKI, providing new opportunities for correct prophylaxis or early therapeutic intervention so that the evolution of patients with this pathology is favorable and the risk of life-threatening complications is negligible.

Methods: We performed an extensive literature search on PubMed and ScienceDirect databases, using keywords related to biomarkers for AKI. We searched for acute kidney injury (AKI), cystatin C (CYS-C), galectin-3 (GAL-3), kidney injury molecule-1 (KIM-1), neutrophil-gelatinase-associated lipocalin (NGAL), interleukin-8 (IL-8), and liver-type fatty acid-binding protein (L-FABP). We included a high number of papers, with an emphasis on more recent publications.

Results: Studies that analyzed the biomarkers for AKI show that CYS-C, GAL-3, KIM-1, NGAL, IL-8, calprotectin, and proteinuria were noted as potential biomarkers for early diagnosis of AKI.

Conclusions: Biomarkers represent the focus of recent years in furthering an early diagnosis of AKI, providing new opportunities for correct prophylaxis or early therapeutic intervention.

Keywords: acute kidney injury (AKI), biomarkers, cystatin C (CYS-C), liver-type fatty acid-binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL)

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INTRODUCTION

Acute kidney injury (AKI) is a life-threatening diagnosis that has led to many disputes in the past years while trying to better characterize it for a faster and more precise diagnosis. It is defined by fast impairment of the kidney function, both structural and functional, most commonly caused by extrarenal pathologies [1], and is associated with high mortality. Between 5% and 20% of the patients admitted to intensive care units (ICU) present an AKI episode whose severity is correlated with the mortality risk and hospitalization length [2,3]. Despite being frequently encountered, it remains a diagnosis dilemma and the cut-off values are still disputed.

AKI is a clinical syndrome characterized by a rapid loss of kidney function in a patient with previously normal renal function or in a patient known to have chronic kidney disease. The KDIGO guidelines for AKI are mostly preferred over the RIFLE classification [3-5]. However, these AKI staging systems have limitations that apply to both the KDIGO classification and the older classification systems (RIFLE and AKIN) (Table 1). These limitations rely on the determination of serum creatinine levels and the monitoring of urine output [5], as the diagnosis of kidney damage is still based on serum creatinine, a degradation product of creatine and phosphocreatine that is freely filtered by the glomeruli, as well as serum urea and diuresis. Serum creatinine is the most used worldwide biomarker of kidney damage and it has remained the gold standard for diagnosis for more than a century, despite its limitations [6].

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Table 1. Comparison of the classification systems for AKI

	RIFLE	AKIN	KDIGO
Serum creatinine level	>50 % which appears on the course of < 7 days	≥ 0.3 mg/dL or > 50% which appears in <48 hours	≥ 0.3 mg/dL which appears in < 48 hour; or >50 % which appears in < 48 h
Urinary flow	< 0.5 mL/kg/hour for > 6 hours	< 0.5 mL/kg/hour for > 6 hours	< 0.5 mL/kg/hour for > 6 hours

Studies show that an increase of 0.3 mg/dL above the known value of serum creatinine predicts an unfavorable prognosis, and the patient's condition worsens as the creatinine level rises with more than 0.3mg/dL. However, it is not considered a reliable diagnostic method for AKI in unstable patients, since its values vary with diet and body mass. Additionally, it is not considered specific and sensitive for AKI, but rather a late indicator of the condition [3,7,8], as it is not an indicator of tubular damage, rather a GFR indicator.

Using serum creatinine and urine output as tools for AKI diagnosis has disadvantages, as they do not predict mortality or the need for initiating renal replacement therapy (RRT). The duration of AKI persistence correlates better with mortality than with the peak value of serum creatinine because prolonged azotemia translates into a period when renal tubular injuries cannot recover, whereas short-term azotemia correlates with reversible renal injuries [5,9].

Proteinuria is a marker of renal impairment, routinely monitored in the clinical management of chronic kidney disease (CKD). In patients with CKD who present with proteinuria, its improvement is associated with a better long-term prognosis. Therefore, prescribed medications should aim to reduce urinary protein excretion [10,11]. Most often, these patients also suffer from hypertension, and antihypertensive treatments that impact proteinuria are preferred [11,12]. However, in CKD patients with proteinuria, it can also act as an important indicator of AKI risk in various clinical situations, such as post-surgical interventions. In this patient group, cardiac surgeries can precipitate the acute exacerbation of CKD, hence preoperative measurement of proteinuria is recommended to properly evaluate the patient's status and to establish a subsequent follow-up and treatment algorithm, aiming at minimizing the renal function decline as much as possible [13]. Focusing specifically on urinary albumin excretion, it should be noted that this is a useful marker for monitoring diabetic patients with renal impairment. Additionally, according to studies in the literature, microalbuminuria is present in cases of renal injury secondary to the administration of gentamicin or cisplatin. This is promising for clinical practice, but its low specificity and the occurrence of microalbuminuria in other conditions such as urinary tract infections, intense physical exercise, and dehydration limit its use in the early diagnosis of AKI [14].

For this reason, there has been a need to identify new biological entities that are produced by the kidney or that are produced under conditions of tubular damage. These new biomarkers should be able to be detected early in the evolution of AKI, and to suggest the site of injury, etiology and prognosis of kidney disease [6].

A biomarker is a biological parameter that can be quantified, an evaluator of physiological, biological, and pathological processes, or pharmacological responses following therapeutic interventions. The Food and Drugs Administration (FDA) considers a biomarker to be any diagnostic indicator that can be measured and provides information about the presence or risk of developing a disease [3,9]. An ideal biomarker for AKI should be easy to measure, accurate, reproducible, cost-effective, repeatable, able to determine the severity of kidney injury, determined early in the course of kidney injury to intervene therapeutically as soon as possible, specific to the kidney (addresses only the kidney), should have high sensitivity, and be easily interpreted by the clinician [3,4].

Objective and rapid quantification of the risk of a patient with obstructive kidney disease, with or without associated sepsis, to develop an AKI may lead to modification of the therapeutic attitude to prevent complications as well as to decrease mortality [15,16]. It is known that a prolonged evolution of AKI progresses to CKD. For example, kidney injury molecule-1 (KIM-1) and neutrophil-gelatinase-associated lipocalin (NGAL) are biomarkers associated with the transition from AKI to CKD [17].

In this narrative review, we would like to approach and summarize the most available worldwide and better-studied biomarkers in the past years and highlight their importance in the early detection of AKI in patients at risk and in the follow-up regimen, to obtain better management of this severe condition that may lead to irreversible kidney damage.

LITERATURE SEARCH STRATEGY

We searched a large medical database on PubMed and ScienceDirect, using keywords related to biomarkers for AKI. We searched for (AKI), cystatin C (CYS-C), galectin-3 (GAL-3), kidney injury molecule-1 (KIM-1), neutrophil-gelatinase-associated lipocalin (NGAL), interleukin-8 (IL-8), liver-type fatty acid-binding protein (L-FABP). We included a high number of papers with an emphasis on more recent publications.

RESULTS

Cystatin C (CYS-C)

The first publications regarding creatinine as a marker of kidney function started in 1926 with the publication of an article by Poul Brandt Rehberg: "Studies on kidney function. The rate of filtration and reabsorption in the human kidney" [18]. Since then, scientists have tried to improve and enlarge the spectrum of biomarkers used to assess renal function given the fact that creatinine varies upon different conditions and can be easily influenced by gender, age, or muscle mass, its limitations being highlighted almost 4 decades ago [19]. In 1981, the CYS-C amino acid sequence was discovered, leading to the uncovering of a new human protein superfamily, which is represented by 11 molecules [20].

CYS-C has a low molecular weight (13kDa) and is a member of the cysteine protease inhibitor family [4,21]. CYS-C has been seen as a potential biomarker since 1985. It is produced in all nucleated cells, and the renal glomeruli allow it to filter easily. The proximal tubules then reabsorb and catabolize it. Since its concentration in the serum is determined primarily by glomerular filtration, CYS-C is considered to be an endogenous indicator of GFR [22]. It is superior to serum creatinine in the early diagnosis of AKI, displaying increased levels earlier by 24-48 hours than creatinine. Studies suggest that CYS-C is useful in the early diagnosis and prognosis of contrast-induced nephropathy, both in patients with pre-existing renal disease and those without. Moreover, it has been shown that by using this biomarker, contrast-induced nephropathy can be diagnosed 24 hours earlier than when using serum creatinine [9,21].

A study by Herget-Rosenthal et al. which included 44 patients with acute renal failure showed that CYS-C presented higher serum levels by 1 to 2 days earlier than creatinine. Moreover, the results of their study revealed that CYS-C is a useful predictor of RRT and is a very useful tool in patients with critical illness [23]. Similar research that included 442 patients was conducted by Nejat et al. , showing that in the general ICU population, plasma levels of CYS-C were increased earlier than those of creatinine, thus proving to be an effective indicator of kidney injury [24]. Murty et al. performed a study that included 130 patients with AKI. The results revealed that serum creatinine levels were normal in the early stages of AKI in more than 50% of the cases, while CYS-C levels were increased. Moreover, serum creatinine showed large variations related to muscle mass and protein intake, including the fact that reduced GFR leads to increased tubular secretion. The free growth range of creatinine is the range where GFR is between 40-70 ml/min/1.73 m², during which serum creatinine does not yet begin to rise, but CYS-C is already elevated. This data indicates that CYS-C is a better and more relevant biomarker for AKI diagnosis than creatinine, not only in adults but also in children. Furthermore, it is now as influenced by muscle mass, age, or gender as creatinine [21]. A meta-analysis confirmed this conclusion for children with AKI, finding that this biomarker has elevated serum levels on the first day of admission [25]. Cystatin serum levels in patients diagnosed with AKI were also investigated in a study by Soto et al., confirming the conclusions of other studies [26-28] which identified this biomarker as an early predictor of AKI. Furthermore, it was able to redline prerenal azotemia and AKI. However, it did not show significant differences between AKI and CKD [29]. On the other hand, Bell et al. found a correlation between CYS-C levels and mortality in AKI patients, but also in non-AKI patients from ICU [26]. Furthermore, eGFR CYS-C was found to better reflect kidney function in patients with prolonged critical illness compared to creatinine, which was shown to be easily affected by the associated muscle loss [30]. Most studies have shown that there is no gender difference in the level of CYS-C. Regarding age, it appears that CYS-C levels increase with age over 50 years, as well as with decreased GFR. As for muscle mass, the serum level of CYS-C is not influenced by it. In the pediatric population, CYS-C levels are higher compared to those of the adults and decrease continuously until the age of one year, after which the same normal values as in adults apply (creatinine is low in very young children and then increases in direct proportion to the increase in muscle mass). The majority of authors agreed on using the same reference values for both men and women between the ages of one and 50 years. There is interest in using cystatin C as an index of adequacy in hemodialysis, but so far, it is only known that it is cleared six times faster than beta-2 microglobulin in hemodialysis and 1-2 times faster in peritoneal dialysis [3,4,21,31]. More information and studies are needed on this subject. Attempts are being made to use CYS-C in monitoring renal graft function in the immediate post-kidney transplantation period. All these studies emphasize that CYS-C could be a more reliable and sensitive predictor for AKI compared to serum creatinine.

Galectin-3 (GAL-3)

GAL-3 is a beta-galactosidase that binds to lectins, which are toxic proteins found in certain foods. It plays a role in regulating inflammation and tissue fibrosis. Studies have shown that GAL-3 levels increase in neoplasms and inflammatory diseases. It has been approved by the FDA as a useful marker in prognostic scores in patients with heart failure. In humans, the Framingham Heart Study

has shown that GAL-3 is elevated in individuals at high risk of developing CKD. Also, it can serve as a marker for AKI, even if commonly used markers for AKI are within normal cut-off values [31-33]. Moreover, a systematic review and meta-analysis highlighted the role of this family of proteins in diabetic nephropathy, promoting inflammation via NF-κB signaling pathway activation and leading to renal injury [34]. Similar results were found in other studies, as well [35]. In the kidney, GAL-3 has numerous roles: regulates inflammatory processes and is implicated in cell multiplication, growth, and proliferation. Also, it appears to stimulate macrophages that release pro-inflammatory cytokines, with a secondary release of oxygen species, thereby increasing the inflammatory response in the kidney [36]. Thus, acting on the GAL-3 gene or inhibiting the GAL-3 protein can impede renal fibrosis and reduce the effects of AKI [3]. Moreover, in animal studies, GAL-3 was linked to autophagy, playing a key role in cell response and survival [37].

A study was conducted on 1498 patients who underwent cardiac surgery between 2004 and 2007 in Maine, Vermont, and New Hampshire. The study aimed to determine the relationship between preoperative GAL-3 levels and the development of AKI after cardiac surgery. The study demonstrated a link between elevated preoperative GAL-3 levels and postoperative AKI in patients with preexisting renal dysfunction. GAL-3 was found to be a well-established biomarker for cardiac fibrosis, and ventricular dysfunction, useful in the diagnosis and prognosis of kidney diseases. It was the first study to demonstrate the link between GAL-3 as an inflammation/fibrosis marker and AKI in patients undergoing cardiac surgery, proposing GAL-3 as a biomarker for cardiac and renal fibrosis [31].

Horiuchi et al. performed a retrospective study that included 790 patients with acute heart failure, discovering that high GAL-3 levels were associated with kidney function impairment and they were positively correlated with the mortality risk [38]. In a translational study, GAL-3 was found to be a reliable diagnostic tool and a promising target for AKI induced by ischemic reperfusion [39].

Cisplatin is one of the most commonly used and effective chemotherapeutic agents, but AKI occurs in 30-40% of patients during treatment [9,31,30]. Cisplatin accumulates in renal tubular cells, inducing cellular damage and releasing cellular constituents that activate Toll-like receptor type 4 (TLR-4) in macrophages. This activation leads to the production of chemokines (creating a concentration gradient that guides other leukocytes, such as neutrophils, to the site of infection) and cytokines such as IFN-gamma and IL-17, causing renal cell injury and inflammation [8,31,33]. Cisplatin induces apoptosis in proximal tubular epithelial cells, while GAL-3 has anti-apoptotic effects. Deficiency of GAL-3 allows the accumulation of advanced glycation end products during cisplatin treatment, exacerbating renal injury, inflammation, and apoptosis. Studies in rodents have shown that mice treated with cisplatin and exhibiting reduced GAL-3 levels in the serum had high concentrations of proinflammatory cytokines in their serum [3,4,31,40]. Furthermore, in AKI induced by cisplatin, TLR2 activates autophagy via phosphatidylinositol 3-kinase (PI3K) protein kinase B (AKT)/mammalian target of rapamycin (PI3K/AKT/mTOR), a crucial signaling pathway that controls numerous cell events, which can be activated by GAL-3 [41-43]. On the other hand, in another study GAL-3 inhibition was also shown to suppress PKC-α (protein kinase C-α), thus inhibiting apoptosis of tubular cells in the kidneys and increasing the sensitivity of malignant tumors to cisplatin action [44]. In clinical practice, GAL-3 is a reliable and predictable tool for a faster and more accurate diagnosis of not only AKI but other important conditions and for sure it is a biomarker that needs further attention.

Kidney injury molecule-1 (KIM-1)

KIM-1, also known as T immunoglobulin or hepatitis A cellular receptor-1 (HAVCR-1), is a 90-kDa transmembrane glycoprotein that is expressed in the kidney, particularly in proximal convoluted tubule (PCT) cells following renal injury. In healthy kidneys, this glycoprotein is either not expressed or is expressed in very low amounts. It is used as a marker that increases following ischemic or nephrotoxic injury. Its level is not modified regardless of the CKD stage, urinary tract infections, or extrarenal azotemia [6]. Previously, increased levels of KIM-1 were associated with inflammation and fibrosis. However, in injured kidney cells, it regulates the phagocytosis of apoptotic cells [45]. This transmembrane glycoprotein is inserted into the tubular cells following renal injury caused by ischemia-reperfusion and persists in the epithelial cells until recovery. KIM-1 was found to be highly expressed in kidneys exposed to ischemia-reperfusion injury in studies conducted on rodents, as well as in rodents with induced AKI through the administration of toxic substances [3,33,40,46]. It has been demonstrated that the overexpression of this glycoprotein occurs in proximal tubule cells in both humans and rodents. KIM-1 increases in urine within the first hour of kidney injury secondary to nephrotoxicity or ischemia, well before serum creatinine [17].

Its level peaks 2-3 days after AKI and can be used to differentiate between extension of renal injury or recovery after AKI. In post-cardiac surgery AKI, the elevated level of KIM-1 increases at 6-12 hours and remains significantly elevated for over 48 hours. Increased urinary

levels of KIM-1 one day after cardiac surgery have been associated with a prolonged duration of AKI [9,46]. Moreover, it was found to be a predictor for transition from AKI to CKD [47].

In a study conducted at the University Hospital of Regensburg between March 2020 and February 2021, 80 patients with respiratory infections were enrolled. The patients were divided into two groups: a cohort group consisting of patients with positive SARS-CoV-2 RT-PCR tests and a control group consisting of patients with negative SARS-CoV-2 RT-PCR tests but other respiratory infections. KIM-1 levels were measured in urine collected at the emergency department. The study concluded that KIM-1 levels were elevated upon admission in COVID-19 patients who later developed AKI during hospitalization [46]. Moreover, KIM-1 was found to be a predictor of AKI development and intensive care unit (ICU) admission in patients with COVID-19 [46]. Cardiovascular diseases (CVDs) represent a serious health problem, where obesity, cigarette smoke and type 2 diabetes mellitus (T2DM) are major risk factors [48], which can further lead to kidney injury [49]. Therefore, Tonkonogi et al. detected increased KIM-1 urinary levels in diabetic patients with cardiovascular pathology [49].

A study by Brilland et al. which included 54 patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis with associated necrotizing glomerulonephritis showed that although KIM-1 did not correlate with glomerular involvement, it presented a positive correlation with the levels of acute tubular necrosis and atrophy, as well as with interstitial fibrosis, thus proving to be a potential biomarker for AKI [50]. Furthermore, urinary levels of this parameter were found to be a valuable tool for septic AKI diagnosis, as well as a predictor of the prognosis [51]. Nevertheless, this molecule that acts as a scavenger receptor was found to be more sensitive to kidney injury than creatinine and showed a negative correlation with eGFR. Moreover, it has already been included by the FDA and by the European Medicines Agency (EMA) on the list of evaluated biomarkers when reviewing new drugs [52]. KIM-1 appears in the urine after the first 48 hours after the onset of kidney injury, just before the maintenance phase, and has phagocytosis effects on both destroyed cells and cellular debris to achieve healing, which is why it has been proposed as a marker of prevention [53].

Neutrophil gelatinase-associated lipocalin (NGAL)

In response to an insult, tubular cells release specific injury proteins that are then found in the urine and the blood. NGAL, also known as LCN2 (lipocalin 2), a protein that belongs to the lipocalin family, is produced by the injured nephron. Urinary NGAL is more specific than plasma NGAL in terms of renal injury. Mouse studies have shown that NGAL appears earliest in renal injury, in TCD, compared to all other biomarkers found [54]. NGAL belongs to the lipocalin family, i.e., proteins that carry small hydrophobic molecules: steroids, retinoids, and lipids. Originally considered a component of neutrophil granules, it is also expressed in epithelial cells in response to inflammatory processes. This protein is produced in many cells, including the uterus, prostate, salivary glands, lungs, trachea, stomach, colon, and kidneys. In the kidney, NGAL is produced predominantly in the epithelial cells of the distal convoluted tubule but also in the cells of the proximal convoluted tubule. Elevated levels of NGAL in urine can be detected 3 hours after AKI, peaking at 6-12 hours, depending on the severity of AKI and the presence or absence of pre-existing chronic kidney disease. Elevated values may persist for up to 5 days depending on the severity of RKI [4,5,31,46,55]. A study of 71 children who underwent cardiac surgery demonstrated that 20 of those who developed AKI had elevated urinary NGAL levels at 2 hours postoperatively, meaning that this biomarker had increased predictability in AKI 1-3 days before serum creatinine levels increased [2,8]. Sepsis is a good example to demonstrate the usefulness of NGAL because it increases a few days before sepsis, causing an increase in creatinine and the need for TSFR. An important aspect is that NGAL increases when there is renal injury and it does not increase in e.g. rapidly reversible volume depletion. Therefore,o the usefulness of NGAL is that it separates AKI into two different entities: pre-renal and intrinsic, being able to establish the etiology at hospital admission. This has been demonstrated in studies of patients in emergency departments, distinguishing pre-renal from intrinsic AKI [7,13,20]. In particular, NGAL differentiates pre-renal AKI from acute interstitial tubular nephropathy (AITN). The same differentiation can also be made by calprotectin non-specifically, but for AKI [56].

Interleukin-8 (IL-8)

IL-8 is a cytokine generated by macrophages, other antigen-presenting cells, as well as PCT and collecting tube cells. It is also increased in renal ischemia and cisplatin-induced nephropathy. IL-8 is synthesized as an inactive precursor, which is intracellularly stagnant until cleaved by caspase-1 in response to external stimuli and subsequently secreted by monocytes/macrophages, inducing an inflammatory response. IL-18 is produced in renal tubular cells and released in the urine in a variety of pathological situations such as sepsis, neoplasia, and ischemia/reperfusion-induced renal injury. Urinary levels increase in the first six hours after AKI and peak at 12-18 hours [4]. Because of the plausibility of IL-18 in-

volvement in the development and progression of AKI, in animal studies, IL-18 is considered a biomarker of RAI. It appears that IL-18-deficient mice are protected from ischemia/reperfusion-induced RIA. It has also been shown that mice deficient in caspase-1 develop milder forms of RAI. Although the usefulness of IL-18 as a diagnostic biomarker is limited, anti-IL-18 therapy may become an important treatment for RAI in the future, so that patients with elevated urinary IL-18 levels may benefit from targeted immunomodulatory treatment [8,57]. This treatment could be performed with an exogenous protein that binds IL-18 and antagonizes it. However, this treatment could have its limitations, as such an IL-18-binding and antagonizing protein would have to be administered before the first six hours, thus before IL-18 is excreted in the urine [54,58,59].

Liver-type fatty acid-binding protein (L-FABP)

L-FABP is called liver-type fatty acid-binding protein and is a 15 kDa protein that selectively binds fatty acids and transports them to the mitochondria or peroxisomes where they are β-oxidized and participate in intracellular fat homeostasis. Circulating L-FABP appears to be filtered in the glomerulus and reabsorbed by proximal convoluted tubule cells. It also appears to be expressed in proximal convoluted tubule cells following renal injury. Because L-FABP is also produced by the liver, in liver disease, its levels increase [6]. It is part of the lipid-binding protein family, which includes members with specific distribution in different tissues. These molecules are implicated in intracellular transport. L-FABP is present in the liver, intestine, stomach, lungs, and kidneys, with the role of binding fatty acids and transporting them to mitochondria, where energy is formed and then used by tubular cells [32,55,60]. L-FABP also protects cells from oxidative stress, thus, L-FABP levels directly correlate with ischemia occurring in transplanted kidneys [32,33].

In AKI, L-FABP is a viable detection and prognostic marker of kidney dysfunction. In renal injury by ischemia/reperfusion, low renal perfusion causes increased oxidative stress; reactive oxygen species are produced in this situation in greater amounts that exceed the cellular clearance limit. These reactive oxygen species cause cell membrane destruction in a process called oxidative lipid degradation resulting in two lipid degradation products that accumulate and damage PCT cells [33,60]. L-FABP can disrupt this process by binding to excess fatty acids and lipid catabolic products which it transfers to the renal tubular lumen, secreting into the urine along with these metabolic products. L-FABP was discovered by Ockner in 1970 in intestinal mucosal cells while studying fatty acid metabolism in rodents. It has been identified in the liver, stomach, lung myocardium, adipose tissue, kidney, muscle, and other tissues [33,46]. In a study of 339 patients admitted to the ICU between 2008 and 2009 at Tokyo University Hospital, 5 urinary biomarkers (L-FABP, NGAL, IL-18, albumin, NAG) evaluated five biomarkers. The findings of the study were that all 5 biomarkers measured 12 hours after admission were increased in patients who developed AKI compared to those without AKI during admission [33]. It also appears that the dynamics of NGAL, IL-18, and L-FABP were more important (they were higher) than those of NAG and albumin in those patients who developed AKI while they were hospitalized or who were diagnosed with AKI since admission [31,60]. Thus, the new biomarkers were able to detect AKI as early as admission to inpatient therapy and predict its onset in a group of patients with heterogeneous pathology, while urinary L-FABP and NGAL were able to predict mortality earlier and with higher accuracy compared to serum creatinine. The biomarkers studied had as good mortality prediction ability as the APACHE II score [3,5,32].

In the first phase, proximal convoluted tubule injury occurs, resulting in a decrease of glomerular filtration rate. In the extension phase, eGFR continues to decrease due to hemodynamic alterations, inflammation, necrosis, and apoptosis of tubular epithelial cells. During the extension phase, AKI goes from moderate to severe, with IL-18 as the promoter, whose level peaks at this time. This occurs because of the proinflammatory effects of IL-18 [17,54]. Apoptosis represents important research directions and some indicators beneficial in evaluating apoptosis [61]. Also, NGAL and L-FABP are involved in the extension phase and have a renal protective role, in contrast to IL-18, as they have antiapoptotic and antioxidant effects. The oliguric phase is characterized by eGFR stabilization, proliferation, and migration of tubular epithelial cells that have survived the renal injury, and which will have the role of replenishing the damaged tubular epithelial cells. The repair phase is when renal function is restored. The last two phases do not start earlier than 2-3 days after the onset of kidney injury but they last for more than a week [17,54].

Calprotectin - possible marker in AKI evaluation

Another useful marker for early diagnosis of AKI and for differentiating between prerenal and intrinsic causes is calprotectin. Assigning this marker a pivot role in the diagnosis of AKI, substantially contributes to improving early diagnostic capabilities, thereby enhancing patient prognosis. This is due to its potential to be more easily included in the diagnostic panel alongside creatinine, compared to other markers described in the literature. Following renal injuries associated with inflammation (e.g., infections or other chronic conditions, including

chronic obstructions), as well as neoplastic damage, this protein, through its components S100A8/S100A9, is found in fluids such as urine or blood [62]. The increase in urinary calprotectin is not sustained in cases of AKI secondary to a prerenal mechanism, justifying the use of this marker to differentiate between prerenal AKI and renal AKI [63]. For current practice, it is useful to note that there is an increase in urinary calprotectin levels before it is detected in blood evaluations. Additionally, the higher sensitivity and specificity of this parameter compared to serum creatinine justify a future change in the etiological diagnosis of AKI cases [62]. The use of calprotectin for an accurate diagnosis of AKI is limited by the fact that its levels can also be elevated in other clinical conditions that do not involve the urogenital tract, such as inflammatory bowel diseases and rheumatoid arthritis [64].

CONCLUSIONS

AKI represents a major health problem characterized by impaired kidney function, with an increased mortality rate. Serum creatinine remains the most used parameter to predict kidney damage, according to international guidelines. Therefore, there is a great need to discover new biomarkers in clinical practice for the diagnosis and treatment of AKI. AKI-biomarkers should be used in early diagnosis of this condition to differentiate between different types of renal injury. CYS-C is an effective indicator of kidney injury because its serum levels increase earlier compared with serum creatinine. Elevated urinary levels of NGAL can be measured three hours after AKI and may persist for up to five days depending on the kidney injury. KIM-1 increases in urine within the first hour of kidney damage induced by nephrotoxicity or ischemia before serum creatinine.

Taking into consideration all these aspects, CYS-C, NGAL, KIM-1, GAL-3, IL-8, L-FABP, and calprotectin can be used as important tools for early AKI diagnosis and monitoring. Furthermore, they should be applicable in both adult and pediatric patients and be able to differentiate prerenal causes of AKI from intrinsic renal causes. Continuous medical efforts and assiduous research in this field are crucial forimproving the management and outcomes of AKI patients.

ABBREVIATIONS

AKI – acute kidney injury

ANCA – antineutrophil cytoplasmic antibodies

CKD – chronic kidney disease

Cys-C – cystatin C

eGFR – Estimated Glomerular Filtration Rate

FDA – Food and Drugs Administration

ICU – intensive care units

IL-8 – interleukin-8

KIM-1 – kidney injury molecule-1

L-FABP – liver-type fatty acid-binding protein

NGAL – neutrophil gelatinase-associated lipocalin

PCT – proximal convoluted tubule

AUTHORS' CONTRIBUTION

Conceptualization: IAV and IISS. Methodology and validation: DGB and LFSF. Resources: DM and LVC. Writing - original draft preparation: IAV, ISS, EC, and LFSF. Writing - review and editing: AEBS, DM, IISS, and LVC. Visualization: AEBS, DGB, and MG. Supervision: IAV. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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