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REVIEW PAPER

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The significance of NGAL and KIM-1 proteins for diagnosis of acute kidney injury (AKI) in clinical practice

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ABSTRACT

Introduction. Despite advances in medical care AKI (*acute kidney injury*) is associated with high morbidity and mortality. The lack of adequate early renal injury biomarkers is often a problem for an early AKI diagnosis.

In recent years, numerous scientific studies have been carried out which reveal new urine and serum markers to assess the period of the kidney injury before revealing its late clinical effects.

In most clinical settings, AKI is due to acute renal tubular necrosis which results in protein accumulation in urine. Determination of the concentrations of proteins such as NGAL-(*neutrophil gelatinase-associated lipocalin*) and KIM-1 (*kidney injury molecule-1*) are of great significance in the diagnosis of AKI.

Aim. The purpose of the study was to review the literature about significance of NGAL and KIM-1 proteins for diagnosis of acute kidney injury (AKI) in clinical practice.

Materials and method. Analysis of Polish and foreign literature.

Keywords. NGAL proteins, KIM-1 proteins, acute kidney injury (AKI)

Introduction

Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) proteins have recently been used as biomarkers for renal injury. Their biological function is not fully understood. Both in a healthy kidney and in the urine, the level of these proteins is almost undetectable. As a result of renal ischaemia or the potentially nephrotoxic substances action, their expression and synthesis are intensified. Expression of NGAL like KIM-1 proteins are stimulated in damaged epithelial nephrons cells in the distal tubule and the S3 segment of the proximal tubule respectively.

Therefore, these are early, non-invasive markers of kidney injury detected especially in urine prior to the

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development of a full-blown AKI.-

Biochemical description of the NGAL protein

Neutrophil gelatinase-associated lipocalin also known as lipocalin-2, siderocalin, uterocalin and 24p3, is a 25 kDa protein belonging to the lipocalin superfamily.[1,2] The lipocalin protein family is a large group of small extracellular proteins.[3] Lipokalin can have different functions. They participate in the processes of regulating cell aging, differentiation and modeling of the immune response. In the human body, NGAL also influences the growth, development and differentiation of various cells.[4] A similar secondary and tertiary structure as well as the presence of ligand binding sites is a common feature of lipocalin. NGAL may exist in the form of a monomer, a dimer or in combination with other molecules, e.g. metalloproteinase-9 (*matrix metalloproteinase-9;* MMP-9), also called gelatinase B or collagenase type IV.[5]

Neutrophil gelatinase-associated lipocalin are endogenous and ubiquitous biomarker molecules that are secreted by various types of human tissues, including the gastrointestinal tract, respiratory tract and kidneys. In the kidneys, NGAL is secreted into the urine by the thick ascending limb of loop of Henle and collecting ducts of the kidney, with synthesis in the distal nephron.[6,7] Due to its small molecular size, the NGAL protein is freely filtered and can be easily detected in the urine. Neutrophil gelatinase-associated lipocalin in urine (uNGAL) appears in a very short time and its increased concentration is a result of acute kidney injury, diabetic nephropathy, nephritic syndrome, tubulointerstitial nephritis, and IgA nephropathy.[8,9,10]

Biochemical description of the KIM-1 protein

Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein with an ectodomain containing both an Ig-like and a mucin domain. It was discovered in renal tubular epithelial cells in a screen for molecules involved in the pathogenesis of AKI.[11]

The glycoprotein is located primarily on the apical surface of the proximal tubule of the nephron in the outer core layer. With the participation of metalloproteinases, the extracellular domain is cleaved and excreted into the urine. That ectodomain is a quantitative marker of kidney damage. The soluble KIM-1 has a molecular weight of around 90 kDa.[12,13]

During normal kidney function, KIM-1 is almost undetectable in the urine. Renal ischaemia, and also damage to various nephrotoxic factors induces its expression and synthesis. Therefore, the molecule is a quantitative biomarker of kidney injury.14 Clinical studies show that KIM-1 is upregulated in tubules of patients with focal segmental glomerulosclerosis, IgA nephropathy, or membranoproliferative glomerulonephritis and that it is associated with tubular injury and interstitial fibrosis. These results have led to the suggestion that KIM-1 may be a promising, non-invasive, easily detected in urine biomarker of chronic tubulointerstitial damage.15,16

The role of NGAL and KIM-1 proteins in AKI

current clinical diagnosis allows for detection of new biomarkers of renal tubular damage such as NGAL, KIM-1, interleukin 18 (IL-18), liver-type fatty-acid-binding protein (L-FABP), insulin-like-growth-factor-binding protein 7 (IGFBP7), and tissue inhibitor of metalloproteinase 2 (TIMP-2). Marking them by clinicians enables diagnosis of acute renal injury in the preclinical phase of the disease.[17]

Due to some renal complications, e.g. due to cardio-renal syndrome, attempts have been made to adapt several well-characterized markers for early diagnosis of kidney damage in patients treated for cardiovascular diseases. Among the large group of known markers, NGAL has the highest diagnostic significance due to the very fast response time to tubular lesions. This is particularly important because AKI complications during cardiac surgery are a cause of prolonged hospitalization and increased mortality.[18,19]

Neutrophil gelatinase-associated lipocalin seems to be a good biomarker of injury, due to the fact that the increase in the concentration of this protein both in plasma and in urine is observed already 2 hours after the kidney damaging factor action that significantly precedes serum creatinine elevation that occurs around 24-48 hours after kidney injury.

A large number of experimental studies confirm the usefulness of NGAL-1 gene in the diagnosis of AKI. In the ischemic and toxic AKI model, it was shown that the NGAL-1 gene was more expressed, and the protein encoded by it was one of the biomarkers of kidney damage synthesized in the largest amounts.[20,21] The usefulness of NGAL as "renal troponin" has also been confirmed in clinical trials.[22] Patients hospitalized in the intensive care unit with symptoms of acute renal failure were characterized by a significant increase in NGAL concentration, both in urine and plasma.[23]

It was noted that in adult patients who underwent cardiac surgery who developed post-operative AKI diagnosed on the third day after surgery evidenced by a 50% increase in serum creatinine in relation to its baseline, plasma NGAL concentration increased only 1-3 hours after surgery.[24] Similarly, it was observed among children operated on due to congenital heart disease who also developed AKI as a result of disorders of renal blood supply due to extracorporeal circulation.[25]

In a cohort of high-risk adult patients undergoing cardiac surgery, there was an increase in postoperative AKI and 1-year mortality in patients with higher preop-

erative serum NGAL. Those patients with serum NGAL above 220 ng/L had an estimated twofold increase risk of cardiovascular and all-cause mortality at 1 year following cardiac surgery.[26] In other studies of patients with acute nephropathy caused by radiographic contrast agents, urea and serum NGAL elevation were also observed.[27]

A meta-analysis summarizing the usefulness of the determination of NGAL in patients at risk of AKI after cardiac surgery during treatment in intensive care units after administration of contrast agents, clearly confirmed the reliability of the determination of NGAL concentration using standardized reagent kits. Based on a thorough review of the test results, covering over 2,500 patients, the predictive value of NGAL concentration was found to be higher than 150 ng/ml. Attention was also drawn to the higher predictive value of NGAL concentration in AKI in children.[28]

The high clinical utility of the marker NGAL can be demonstrated by the synthesis of lipocalin-2 and its use in relieving the symptoms of ischemic acute myocardial injury. In an established murine model of renal ischemia-reperfusion injury, intravenous NGAL administered before, during, or after ischemia resulted in marked amelioration of the morphologic and functional consequences, as evidenced by a significant decrease in histopathologic damage to tubules and in serum creatinine measurements. Neutrophil gelatinase-associated lipocalin-treated animals also displayed a reduction in the number of apoptotic tubule cells and an increase in proliferating proximal tubule cells after ischemic injury. The results indicate that NGAL may represent a novel therapeutic intervention in ischemic acute renal failure, based at least in part on its ability to tilt the balance of tubule cell fate toward survival.[29]

The therapeutic success of surgical treatment is largely associated with the lack of serious postoperative complications. Such postoperative complications include AKI, in which, depending on the type of surgery, mortality affects from 7-60% of patients.[30-32] Acute kidney injury markedly increases peri-operative mortality risk. However, despite the development of less invasive techniques, cardiac surgery remains the first option in many conditions such as severe coronary artery disease, valve diseases and complex interventions. Therefore, there is interest among cardiologists and cardiosurgeons in research on new markers of kidney damage. Numerous studies in the field of cardiology include issues of elevated serum NGAL levels, which are a consequence of cardiac surgery using extracorporeal circulation[18], as well as coronary bypass and coronary revascularization.[19]. The results of the study clearly show that the increase in lipocaline precedes the increase of serum creatinine concentration by 24-48 hours, which gives the opportunity to use serum and urinary NGAL determinations in monitoring kidney damage of patients after these procedures and rapid implementation of measures to protect the kidneys from progressive damage.[19]

Malyszko et al.[33] also see the usefulness of the determination of serum NGAL concentration in the diagnosis of kidney damage in the course of hypertension. Based on the concentration of NGAL, groups of patients at risk of early deterioration of renal function in the course of hypertensive nephropathy may be identified and appropriate treatment may be implemented.

A higher concentration of NGAL was found in the urine in patients with left ventricular hypertrophy in the course of primary hypertension[34], with atherosclerosis.[35] The prognostic significance of the NGAL concentration assessment in the urine and serum in renal syndrome[36] and in the assessment of acute renal failure in patients with acute congestive heart failure was also demonstrated.[37]

Studies show a positive correlation of higher levels of lipocalin-2 with a worse prognosis in patients with serum NGAL levels above 140 ng/ml at admission where seven times more often the deterioration of kidney function develops until failure. During long-term follow-up, shorter survival periods of patients with acute congestive heart failure have been demonstrated with initially higher levels of NGAL (above 215 ng/ml).[37,38]

Determination of NGAL levels in humans is used primarily in the assessment of AKI, but also in the diagnosis of the progression of chronic kidney diseases, e.g. obstructive nephropathy[39], IgA nephropathy[40] or progression of kidney damage in systemic diseases such as diabetes[41,42], arterial hypertension[43] or lupus erythematosus.[44] A positive effect of the determination of NGAL concentration for the evaluation of nephrotoxicity of contrast agents used in radiological diagnostics[45] and the nephrotoxicity of some drugs, e.g. cisplatin, was also demonstrated.[46]

The potential role of KIM-1 as a biomarker in various pathologies of the kidneys is still intensively studied, and in many analyses it has been shown that KIM-1 is a sensitive and specific marker of proximal tubular damage.[47] Any increase in KIM-1 in the urine indicates kidney damage, because the protein is not out of the kidney in an amount that can change its level in the urine. Both experimental and clinical studies indicate that KIM-1 is a biomarker of tubular lesions already appearing, similarly to NGAL-1, on the first hours after toxic or ischemic damage to the nephrons tubules.

Determination of this protein as a laboratory AKI index is also important in the assessment of the severity of this disease. Liangos et al.[48] embraced the study of 201 hospitalized AKI patients and found that those with the highest urinary KIM-1 level had a statistically 3-fold higher dialysis implementation frequency. A sim-

ilar relationship was found in a subsequent study evaluating the need renal replacement therapy and mortality among AKI development patients.[49]

Clearly increased KIM-1 concentrations were also observed in patients with acute tubular damage that developed due to previous cardiac surgery or with symptoms of acute renal failure in the course of sepsis.[50,51] In addition, it was observed that the risk of rejection of allogenic kidney transplant increases with elevating urinary KIM-1 concentration.[52,53] Increased KIM-1 secretion into the urine was also revealed in patients with clear cell renal carcinoma.[54]

Clinical usefulness of KIM-1 protein is not limited to the diagnosis of acute renal injury or failure. There are studies showing KIM-1 utility in diagnosing and monitoring of chronic kidney disease (CKD). Analysis of changes in the concentration of this marker in the urine may indicate the transition of AKI into the CKD.[55] Patients with chronic heart failure and cardiorenal syndrome were characterized by a higher concentration of KIM-1 in urine in relation to healthy people.[56]

This protein proves to be useful for identifying groups of patients with AKI or those at risk of its occurrence, especially those undergoing cardiac surgery. Early diagnosis and appropriate treatment may help reduce the number of patients requiring renal replacement therapy.

Conclusions

Biochemical diagnostics of AKI mainly based on classical laboratory parameters such serum creatinine or urea is still insufficient. There is a need to extend diagnostics with new protein biomarkers discussed briefly in this work. The use of NGAL and KIM-1 in combination with other biomarkers, i.e. cystatin C, nαKlotho protein or IL-18, allows an earlier and more reliable diagnosis of AKI in the preclinical phase of disease. Such knowledge will enable the rapid implementation of appropriate and effective therapeutic procedures.

There is hope that the determination of the protein biomarkers in the urine and plasma will become a routine diagnostic procedure in patients with AKI risk factors in clinical settings.

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