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REVIEW ARTICLE

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) - NOVEL DIAGNOSTIC BIOMARKER OF SEPSIS AND KIDNEY INJURY

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Abstract: Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of cellular stress, released from various tissues as a result of neutrophil activation. According to literature data, the detection of NGAL is applicable in cardiological conditions, metabolic disorders such as diabetes or dyslipidemia. Moreover, NGAL is recognised as one of the biomarkers of sepsis. Up to 70% of acute kidney injury (AKI) cases may be related to the development of sepsis. Renal tissue injury associated with inflammation, hypoxia or exposure to toxins leads to an increase in plasma NGAL concentration earlier than other commonly used biochemical markers, even as soon as two hours after injury. Studies have demonstrated the utility of NGAL in early diagnosis of AKI, prediction of chronic kidney disease progression, and assessment of graft function following kidney transplantation. Aviators exposed to hypobaric hypoxia, i.e. high altitude hypoxia, are at risk of injury to several organs, including the kidneys. Novel biomarkers can indicate structural kidney damage before renal function deteriorates. The use of NGAL to identify specific sites of renal tissue injury represents an additional area of investigation, as well as a potential target for therapeutic intervention. The aim of the study is to review the current medical knowledge regarding NGAL biomarker, with particular emphasis on its use in the diagnosis of kidney injury and sepsis.

Keywords: NGAL, biomarker, kidney injury, sepsis

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INTRODUCTION

Neutrophil gelatinase-associated lipocalin (NGAL,) also known as lipocalin-2 (LCN-2) or siderocalin, described by Kjeldsen et al. in 1993, is a marker of cellular stress, released from various tissues as a result of neutrophil activation [10,19,43]. In addition to neutrophiles, other known sources of NGAL are macrophages, dendritic cells, adipocytes, epithelial cells, and tubular cells in the kidney, heart, liver, stomach, lung, colon. NGAL exists in several forms: a 25kDa monomer released by renal tubules, a 45kDa homodimer released by activated neutrophiles and 145kDa complex of NGAL and matrix metalloproteinase-9 [19,35].

NGAL is an acute phase protein that plays a role in antibacterial, antiviral and antifungal immune responses [2,11,35]. As a siderophore-binding protein preventing bacterial acquisition of iron, NGAL has a bacteriostatic role, limiting growth and multiplication of pathogens. In addition, NGAL acts as a chemoattractant for neutrophils, affecting neutrophile maturation, adhesion and extravasation, promoting phagocytosis. Furthermore, NGAL is possibly involved in modulating cell-mediated immunity, by participating in activation of T lymphocytes [25,31]. According to Miharada et al. increased secretion of NGAL during infections, particularly in chronic inflammatory diseases, involves apoptosis of hematopoietic progenitors of red blood cells, that contribute to anemia development [29].

The utility of NGAL as a biomarker is related to its biological function. NGAL levels could be measured primarily in plasma and urine, but also it is also detectable in peritoneal effluent, cerebrospinal fluid, saliva, tears, human breast milk, vaginal fluid, bronchoalveolar fluid and amniotic fluid [4,35,45,50].

Elevated level of NGAL can be detected and used as a marker and predictor in a number of cardiological conditions such as hypertension, atherosclerosis, acute and chronic heart failure and myocardial infarction. Studies have shown that patients suffering from chronic heart failure and elevated levels of serum NGAL have a higher mortality rate, indicating that NGAL may serve as a potential prognostic marker of survival in this population [5,35]. Similarly, in myocardial infarction increased concentrations of serum NGAL have been associated with worse outcomes [12]. According to Lindberg et al., NGAL is an independent predictor of major adverse cardiovascular events and mortality following ST-elevation myocardial infarction (STEMI) [16].

NGAL concentration may also correlate with metabolic disorders such as diabetes, insulin resistance, obesity and dyslipidemia. The measurement of urinary NGAL may serve as an early marker of diabetic nephropathy [32].

NGAL could affect cell stimulation and differentiation as well as play a role in carcinogenesis of breast, thyroid, prostate, stomach and esophageal cancers [8,9,17,21,37,44]. There potential for research into the use of NGAL as a diagnostic marker and a therapeutic target. Intensive chemotherapy protocols, particularly those involving nephrotoxic agents and systemic complications such as severe infections, highlight the need for markers allowing early detection of organ damage. This would facilitate the timely identification of at-risk patients, the implementation of preventive measures and the initiation of appropriate treatment. Moreover, oncology patients undergoing chemotherapy, struggling with its side effects such as nausea and vomiting, diarrhea, receiving numerous additional drugs such as antibiotics and painkillers, and undergoing imaging tests with intravenous contrast agents are at risk of developing AKI. Shinke et al., found that NGAL may serve as an early biomarker of AKI in patients treated with cisplatin-based chemotherapy protocols [41]. According to Latoch et al., exposure to nephrotoxic chemotherapy such as methotrexate, cyclophosphamide, high doses of glycocorticosteriodes and radiotherapy results in elevated NGAL levels, even years after treatment [22].

Sepsis

NGAL is an inherent component of the inflammatory process. Tissue injury associated with infection leads to an increase in plasma NGAL concentration [35]. By participating in the pathogenesis of inflammation, NGAL may serve as a biomarker of sepsis.

Sepsis is a dynamic condition which could rapidly progress to severe sepsis, septic shock and death, if not promptly recognized [13]. Unfortunately, the lack of specific symptoms hinder rapid diagnostics, therefore, sepsis remains a cause of high of morbidity and mortality worldwide. The qSOFA (quick Sequential Organ Failure Assessment Score) and SIRS (Sytemic Inflammatory Response Syndrome) criteria used in the diagnosis of sepsis demonstrate sensitivities and specificities of 70% and 73% for qSOFA and 88% and 34% for SIRS, respectively [1]. Similarly, commonly used markers such as C-reactive protein (CRP) and procalcitonin (PCT) also exhibit low sensitivity and specificity [2]. Furthermore, in one-third of the blood cultures tested, no growth of pathogens

responsible for disease development is observed [3]. Rapid and early diagnosis and initiation of appropriate treatment improves outcomes in septic patients. Elevated NGAL levels correlate with other known inflammatory markers such as interleukine-6 (IL-6), interleukine-10 (IL-10), vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), tumor necrosis factor alpha (TNF- α), the C-reactive protein and leukocytes account [26].Plasma NGAL levels appear to have a stronger correlation with absolute neutrophil count than with other inflammatory cytokines, although NGAL can still be detected in patient with neutropenia and systemic inflammation, albeit at lower levels. Nevertheless, urinary NGAL levels may be significantly elevated in patients with AKI and neutropenia [34].

The kinetics of the biomarker responses may affect diagnostic and prognostic accuracy, particularly in rapidly progressing diseases [23]. According to Wang et al., monitoring the activity of TNF-α, NGAL, and IL-6 may contribute significantly to the diagnosis and assessment sepsis severity [46]. The correlation between NGAL and other sepsis markers may also aid in distinguishing patients with severe sepsis from those with more benign clinical course [27]. In a study by Shapiro et al., a biomarker panel comprising NGAL, interleukin-1 receptor antagonist (IL-1Ra) and C-reactive protein was predictive of severe sepsis, septic shock and mortality among emergency department patients with suspected sepsis [39].

Moreover, Chang et al. described plasma NGAL as a reliable predictor of 28- day mortality in severe sepsis [6]. Research by Wu et al. has shown that serum NGAL and lactate may serve as independent risk factors for 28-day mortality in sepsis patients [49] Lentini et al. found that elevated plasma NGAL levels in patients with sepsis and AKI is associated with severity of the systemic inflammatory response [24]. Although NGAL is a significant biomarker for AKI in sepsis, it has been reported to be elevated in sepsis independently of renal injury [52]. Sepsis contributes to more than 20% of AKI cases in intensive care unit (ICU) patients, with cases severe enough to require renal replacement therapy [24].

Kidney failure

One of the most extensively researched areas of NGAL utility is the diagnosis of renal disorders. Numerous studies have demonstrated the role of NGAL in early diagnosis in AKI, predicting of progression in chronic kidney disease (CKD), and assessment of graft function following kidney transplantation. NGAL concentrations are elevated in various types of CKD. Its diagnostic value has been tested in differentiating between primary inflammatory and non-inflammatory etiologies of CKD. Furthermore, NGAL can replace serum ferritin in the assessment of iron status in CKD patients, even those requiring renal replacement therapy [7,14,18,30,38].

In the kidneys, NGAL is secreted by epithelial cells of the loop of Henle, as well as the proximal and distal tubules, and its level increases in proportion to the degree of renal tubular injury, whether ischemic, nephrotoxic, inflammatory or septic in nature [27,44,48].

Research by Mellor showed that NGAL levels rise in response to prolonged hypobaric hypoxia and this increase may occur without concomitant acute kidney injury [28]. The development of proteinuria or acute kidney injury may be associated with rapid ascent to high altitudes. According to a study by Xiaoshan, the hypoxic and hypobaric environment at high altitudes may cause podocyte damage, promoting proteinuria and it is considered to play significant role in the development and progression of CKD [15,51]. Aviators exposed to gravitational forces are at risk of multiple organ injury, including the kidneys. In a study by Noddeland, aviators examined without anti- gravitational suits demonstrated proteinuria and the presence of hyaline casts [33]. Chang et al. demonstrated that pilots, particularly flying fighter aircraft, are at risk of developing hypertension, which may accelerate glomerular damage, inflammation and lead to a reduced number of glomeruli, affecting kidney structure and function and contributing to CKD [6].

Commonly used markers of kidney function, such as serum creatinine and blood urea nitrogen, reflect changes in the glomerular filtration rate, which typically occur as a manifestation of distinct kidney damage [42]. Novel biomarkers can indicate structural kidney damage before renal function begins to deteriorate. NGAL can be detected in plasma within two hours of AKI, with peak concentration after six hours [35]. Elevated plasma NGAL levels are observed for five days before gradually declining [47]. Urinary NGAL is also elevated in AKI. Both plasma and urinary NGAL can be detected earlier, even 24 hours prior to an increase in creatinine levels [30]. Elevated serum NGAL levels result from neutrophil and monocyte activation during the inflammatory response and from decresed renal function, which leads to the accumulation of plasma NGAL [14].

Sepsis with Acute Kidney Injury (AKI)

Up to 70% of AKI cases may be related to sepsis, which is strongly linked to adverse outcomes. Sepsis-associated AKI (SA-AKI) is defined as the occurrence of AKI within seven days of the onset of sepsis, diagnosed according to the criteria of the Kidney Disease: Improving Global Outcome (KDIGO) and Sepsis 3 [10]. SA-AKI is categorized into early, occurring within the first 48 hour of sepsis, and late, occurring between 48 hour and seven days after the onset of sepsis. SA-AKI is associated with a poorer prognosis among patients with sepsis [20]. Moreover, critically ill patients with sepsis, electrolyte imbalances, nephrotoxic drugs and hemodynamic instability are at higher risk of persistent AKI [36,40].

In addition to urine output and serum creatinine levels, which are components of AKI definition, several serum and urinary diagnostic and prognostic biomarkers have also been developed. These include interleukins 6, 8 and 18, osteoprotegerin, galectin-3, presepsin, cystatin C, NGAL, proenkephalin A, Chemokine (C-C motif) ligand (CCL-14), tissue inhibitor of metalloproteinases 2 (TIMP-2) and liver fatty acid-binding protein (L-FABP) [51]. Compared to creatine, NGAL has greater predictive value for AKI in sepsis patients [49].

The use of biomarkers may help overcome the limitations of current diagnostic standards for AKI and sepsis [10]. Although the mechanisms of action of these markers are not yet fully understood, they appear to increase predictive accuracy in the diagnosis of sepsis and AKI, particularly when used in combination with other known markers. Further research is needed to establish reference ranges for NGAL concentrations under various conditions. Moreover, the use of NGAL to identify specific sites of kidney tissue damage as well as its potential role in targeted therapy represent a promising area of investigation. The diagnostic accuracy of NGAL in sepsis and AKI requires further research.

AUTHORS' DECLARATION:

Study Design: Agnieszka Podgórska, Grzegorz Kade, Janusz Hałka. **Data Collection:** Agnieszka Podgórska, Grzegorz Kade, Janusz Hałka. **Manuscript Preparation:** Agnieszka Podgórska, Grzegorz Kade, Janusz Hałka.

The authors declare that there is no conflict of interest.

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