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NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN DETERMINATION IN CARDIOVASCULAR DISEASES

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Previous studies of neutrophil gelatinase-associated lipocalin levels have focused on studying its changes in various pathological conditions. These studies have demonstrated the high sensitivity of this marker in tubulointerstitial kidney injury. The aim of the work was to study the current state of the diagnostic and prognostic significance of the neutrophil gelatinase-associated lipocalin biomarker in cardiovascular diseases according to experimental and clinical investigations. An analysis of literary sources from the Pubmed and Web of Science databases over the last 5 years was conducted. It has been established that neutrophil gelatinase-associated lipocalin deficiency contributes to the development of atherosclerotic changes in vessels in the initial stages of the disease and accelerates the progression of atherosclerosis. A significant increase in serum neutrophil gelatinase-associated lipocalin levels has been noted in patients with angiographically confirmed ischemic heart disease and the number of affected vessels. Increased neutrophil gelatinase-associated lipocalin expression has been identified in hypertension and heart failure, but the pathogenetic mechanisms of these changes continue to be studied. Elevations of this biomarker in the blood are associated with adverse early and long-term outcomes in acute myocardial infarction and heart failure.

Key words: neutrophil gelatinase-associated lipocalin, lipocalin 2, ischemic heart disease, arterial hypertension, myocardial infarction, heart failure, prognosis.

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ВИЗНАЧЕННЯ ЛІПОКАЛІНУ, АСОЦІЙОВАНОГО З ЖЕЛАТИНАЗОЮ НЕЙТРОФІЛІВ, ПРИ СЕРЦЕВО-СУДИННИХ ЗАХВОРЮВАННЯХ

Попередні дослідження з використанням ліпокаліну, асоційованого з желатиназою нейтрофілів, були сфокусовані на вивченні його змін при різних патологічних станах та доказана висока чутливість при тубулоінтерстиціальному ушкодженні нирок. Метою роботи було вивчити сучасний стан діагностичної та прогностичної значущості біомаркеру ліпокаліну, асоційованого з желатиназою нейтрофілів, при серцево-судинних захворюваннях за даними експериментальних та клінічних досліджень. Проведено аналіз літературних джерел бази даних Pubmed та Web of Science за останні 5 років. Встановлено, що дефіцит ліпокаліну, асоційованого з желатиназою нейтрофілів, сприяє розвитку атеросклеротичних змін в судинах на початкових стадіях захворювання та прискорює розвиток атеросклерозу. Відмічено значне зростання рівнів сироваткового ліпокаліну, асоційованого з желатиназою нейтрофілів, у пацієнтів з ангіографічно підтвердженою ішемічною хворобою серця та кількістю уражених судин. Визначено підвищення експресії ліпокаліну, асоційованого з желатиназою нейтрофілів, при артеріальній гіпертензії, серцевій недостатності але патогенетичні механізми цих змін продовжують вивчатись. Підвищення цього біомаркеру у крові асоціюються з несприятливими ранніми та довгостроковими результатами при гострому інфаркті міокарда та серцевій недостатності.

Ключові слова: ліпокалін, асоційований з желатиназою нейтрофілів, ліпокалін 2, ішемічна хвороба серця, артеріальна гіпертензія, інфаркт міокарда, серцева недостатність, прогноз.

The work is a fragment of the research project "To determine the features of immuno-cytokine imbalance in comorbid patients with hypertension and type 2 diabetes and cardiovascular and renal complications", state registration No. 0123U101711.

Recently, among the researches of basic and applied medicine, the search for new compounds that could reflect the improvement of diagnostics of pathological conditions, including cardiovascular diseases, their complications, definition of the personalized treatment strategy and prognosis continues [21]. Such compounds are called biomarkers, and their appearance in the patient's body may indicate the development of the disease long before its clinical manifestations. Thus, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic states or pharmacological responses to therapeutic intervention [30].

Previous studies on the determination of neutrophil gelatinase-associated lipocalin (NGAL) have focused on the possibilities of using it as a biomarker in various pathological conditions of internal organs and have proven the possibility of using NGAL as a sensitive indicator of tubulointerstitial kidney damage [9, 49].

The purpose of the study was to establish the current state of the diagnostic and prognostic significance of the neutrophil gelatinase-associated lipocalin biomarker in cardiovascular diseases according to experimental and clinical studies.

An analysis of literary sources from the Pubmed and Web of Science databases over the past 5 years was conducted.

Lipocalins are a family of usually small extracellular proteins, 160–180 amino acids long, with a characteristic secondary structure [31]. It has been found that amino acid sequence similarity between members of the lipocalin family is very low, but their three-dimensional structure includes 8 antiparallel peptide regions that form a cylindrical cup with a "closed-end" on one side and an "open end" on the opposite side. The latter provides access to the central cavity for internal ligand binding. Previously, it was believed that lipocalins transport or store a number of small hydrophobic molecules (prostaglandins, steroid hormones, fatty acids, vitamins, etc.) [31]. Currently, multilevel biological functions in the modulation of cell proliferation, differentiation, apoptosis, and aging have been established [13].

NGAL (also known as lipocalin-2, oncogene protein 24p33, mouse uterocalin, unbound rat lipocalin) is a small 25 kDa glycoprotein of the lipocalin superfamily, comprising 178 amino acid residues [37]. It was first identified as a protein isolated from specific granules of neutrophils [23], and later it was proved that it is covalently bound to neutrophil gelatinase (an enzyme of the group of matrix metalloproteinases – collagenase IV contained in neutrophils). In addition to production by activated neutrophils, NGAL can also be released in small concentrations in various human tissues and organs [6]. It has been established that in response to various types of stress, such as inflammation, ischemia, infection, proliferation of tumor cells, etc., NGAL is expressed by various types of cells: endothelial, smooth muscle, epithelial cells, renal tubular cells, as well as cardiomyocytes, cardiac fibroblasts, neurons, macrophages, dendritic cells and various populations of immune cells, adipocytes [35], hepatocytes [20].

NGAL is especially actively synthesized by the cells of the tubular epithelium of the kidneys, hepatocytes, immune cells, as well as the epithelium of the respiratory and digestive tracts. Thus, in the lung, NGAL secretion by immune cells such as neutrophils and macrophages, as well as airway epithelial cells, is induced during the inflammatory response. NGAL secretion by various cell types also occurs in response to oxidative stress [29].

NGAL expression has been shown to be induced by many pro- and anti-inflammatory cytokines and factors, such as lipopolysaccharides, tumor necrosis factor-α (TNF)-α, interleukins: IL-1β, IL-6, and IL-17, etc. [37].

NGAL can be secreted in three different forms: as a monomer, a homodimer, or as a heterodimer with matrix metalloproteinase (MMP-9). The secreted conformation usually depends on the type of cell that secretes it [40].

Five NGAL receptors are known: megalin, 24p3R (Slc22a17), melanocortin receptor 4 (MC4R), melanocortin receptor 1 (MC1R) and melanocortin receptor 3 (MC3R), which are described in more detail in a review [13].

Physiological role of NGAL.

NGAL is involved in the inflammatory response in many diseases and during infections. It is an important part of natural antibacterial immunity. Bacteriostatic properties of NGAL are determined by attachment to bacterial siderophores, due to which it prevents bacteria from obtaining iron from the environment [24].

It was established that NGAL recruits polymorphonuclear leukocytes to the site of inflammation [13]. It has been experimentally established that in conditions of metabolic inflammation, type 2 diabetes or nonalcoholic steatohepatitis, increased expression of NGAL promotes inflammation through the recruitment of inflammatory cells, such as neutrophils, and the induction of proinflammatory cytokines [17, 20]. It has been demonstrated that NGAL-deficient (Lcn2−/−) mice exhibit higher levels of TNF-α and IL-6 compared to wild-type control animals under conditions of bacterial infection [8]. Consequently, NGAL is released from neutrophils in response to inflammatory cytokines, including TNF-α, interleukin-1β, and interleukin-6.

It has been demonstrated that NGAL can regulate iron homeostasis by binding to siderophores (iron-transporting animal and bacterial proteins). It was established that during infection, bacteria obtain most of the iron from the host by synthesizing siderophores, which absorb iron and transport it to the pathogen. The host's innate immune system can prevent bacteria from acquiring iron by producing NGAL, which sequesters bacterial siderophores in response to Toll-like receptor (TLR) activation. It has been established that upon encountering invading bacteria, Toll-like receptors on immune cells stimulate the transcription, translation, and secretion of NGAL, which limits bacterial growth by sequestering an iron-rich siderophore [20]. NGAL has also been shown to enhance pro-inflammatory signaling pathways [13].

On the other hand, NGAL is able to promote anti-inflammatory, alternatively activated or "M2-like" polarization of macrophages. Thus, in an experiment [41] it was shown that NGAL weakens the early

inflammatory response and impairs the clearance of bacteria, which leads to a deterioration in the survival of mice suffering from pneumococcal pneumonia. NGAL induced IL-10 production by macrophages, distorting macrophage polarization in a STAT3-dependent manner. During bacterial pneumonia in humans, lung NGAL levels were remarkably elevated, suggesting a deleterious outcome of pneumonia caused by Gram-positive bacteria. The authors emphasize the importance of macrophage deactivation for the outcome of pneumococcal infections and emphasize the role of NGAL and IL-10 as determinants of macrophage efficiency in the airways [41].

In addition, NGAL is able to limit inflammatory responses by regulating the expression of regulatory T- cells [25].

Plasma NGAL is freely filtered through the glomerular membrane and almost completely reabsorbed by endocytosis in the proximal tubule. Detection of NGAL in urine is possible only when the proximal tubule has been damaged and thus reabsorption is impaired, or when de-novo synthesis of NGAL is markedly increased. Increased production of NGAL in the cells of the proximal tubules is detected in ischemia of the kidney parenchyma and under the influence of nephrotoxins [43]. In addition, decreased tubular reabsorption after acute kidney injury may lead to a further increase in urinary NGAL concentration. NGAL has been considered an early marker of renal tubular injury in patients, which is why it is called “renal troponin” [39].

When the renal endothelium is damaged during the first hours, NGAL in increased quantities enters the lumen of the renal tubules and is excreted in the urine (the concentration of NGAL in the urine increases 25–1000 times). In acute kidney injury, there is an increase in NGAL mRNA expression, mainly in the liver and lungs. Next, NGAL enters the circulating blood. Also, NGAL enters the systemic bloodstream from neutrophils and monocytes [16]. A decrease in the glomerular filtration rate (GFR) due to impaired kidney function leads to a decrease in the renal clearance of NGAL and its subsequent increase in the blood. But the participation of these mechanisms in the increase of NGAL levels in the blood plasma has not yet been established.

Since NGAL specifically binds siderophores, it can be an iron donor, which in case of kidney damage has a nephroprotective effect [43]. However, NGAL also inhibits erythropoiesis by inducing apoptosis and delaying the differentiation of erythropoietic progenitor cells [33].

Recently, evidence has accumulated that NGAL is involved in a wide range of cellular and pathophysiological processes, such as insulin demand, tumor cell proliferation, and apoptosis [14]. Serum LCN2 protein levels were significantly increased in patients with type 2 diabetes or impaired glucose tolerance, as well as in obese women [17].

Damage to the gastric mucosa is a lesser-known complication of obesity. Experimentally, a significant increase in pro-inflammatory factors and an increase in the number of apoptotic cells in gastric tissue sections in obese groups was established [46]. NGAL expression secreted by parietal cells has been shown to be increased in obese individuals and to protect against obesity-related gastric damage by inhibiting apoptosis and ameliorating inflammation [46].

NGAL can promote the differentiation and proliferation of vascular HMCs, cardiac fibroblasts, and some other cell types by acting as a growth factor.

A large body of evidence suggests that elevated NGAL levels may contribute to inflammatory responses and early acute injury in cardiovascular disease.

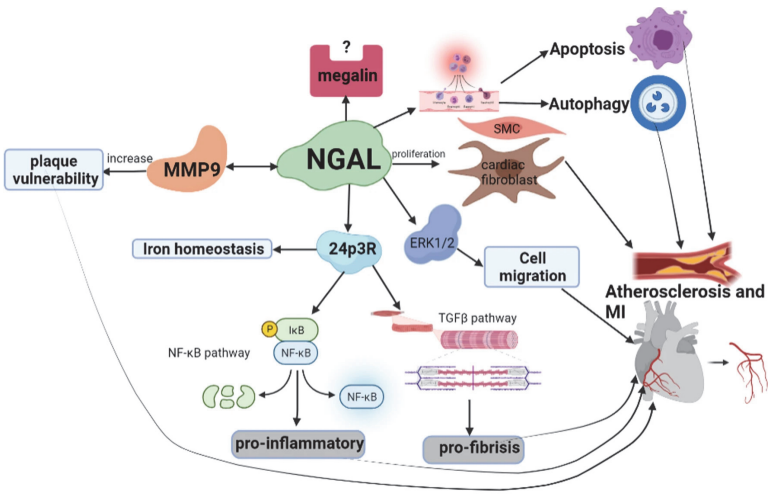

Fig.1. The roles and mechanisms of NGAL in ischemic heart disease.[48].

NGAL content is measured in plasma, urine and other body fluids. Since the release and increase of NGAL occurs first in the urine, the content of NGAL measured in urine is considered to be superior to that in plasma. The advantages of determining the content of NGAL in blood plasma are the availability of the analysis at any time (it does not depend on urine output) and is considered more accurate in patients with anuria or oliguria [9].

The summary effects of NGAL are presented in Fig. 1.

Atherosclerosis.

Recently, NGAL has attracted increasing attention as a valuable biomarker of atherosclerosis and coronary heart disease (CHD). In an experimental study [12], the effect of NGAL on the state of endothelial cells in conditions of hypoxia was studied. NGAL has been shown to induce endothelial cell damage (inflammation, redox imbalance, and apoptosis) even under normal oxygen conditions. The indicated effects increased in conditions of hypoxia. It has also been shown that NGAL-induced endothelial cell damage is realized through eNOS-NO-NRF2-mediated redox regulation in endothelial cells. There is a decrease in endothelial nitric oxide synthase (eNOS) signaling to nitric oxide (NO), which reduces the expression and nuclear translocation of nuclear factor erythroid-related factor-2 (NRF2), that was confirmed by overexpression of NRF2 [12].

In the experimental study [47] established that NGAL induces monocyte migration, macrophage polarization, as well as foam cell formation and thus participates in the main initial events of atherosclerotic plaque development.

In a Japanese experimental study [40], it was shown that NGAL accelerates the development of atherosclerosis. The expression of NGAL in monocytes and macrophages was determined on the THP1 cell line model of human aortic smooth muscle cells and human umbilical vein endothelial cells. The established effects of NGAL are increased monocyte adhesion, upregulation of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin associated with upregulation of nuclear factor-κB (NF-κB) in human umbilical vein endothelial cells. It was also shown in the THP1 model that NGAL significantly enhanced human umbilical vein endothelial cell proliferation and oxidized LDL-induced foam cell formation. In addition, long-term infusion of NGAL in Apoe-/- mice significantly accelerated the development of atherosclerotic lesions of the aorta, which was accompanied by increased intracellular monocyte/macrophage infiltration and expression of pentraxin-3 and collagen-1 [40].

Coronary heart disease.

A Chinese study [47] of 261 patients (169 men and 92 postmenopausal women) who underwent coronary angiography (188 with confirmed CHD and 73 without CHD) evaluated the relationship between serum NGAL levels and CHD. Serum NGAL levels were found to be significantly higher in male patients than in female patients. Moreover, significant differences were observed only in men with CHD compared to men without CHD.

Another study in patients undergoing angiography for the first time with suspected CHD showed a significant increase in serum NGAL levels in patients with angiographically confirmed CHD compared with patients with normal coronary arteries, and statistically significant correlations between serum NGAL levels and by the number of affected vessels [45].

In a study of patients with angiographically documented coronary artery disease, analysis of blood plasma samples revealed a correlation between plasma NGAL levels and the severity of coronary angiography [47].

Acute coronary syndrome.

In the study of Tran A.V. et al. [44] assessed the contribution of serum NGAL, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), high-sensitivity tropinin (hsTnT) and GRACE score to predicting all-cause mortality in patients with ACS. Patients with kidney disease were not included in the study. Assessment of the relative risk of mortality after 3 months of follow-up showed a high level of NGAL (≥154.55 ng/ml), NT-proBNP (≥10.02 ng/ml), hsTnT concentration (≥2.14 ng/ml) and GRACE score (≥140.50) associated with deaths in patients with ACS (OR from 11.1 to 49.0; p≤0.013). Multivariate logistic regression analysis showed the ability to predict mortality for all markers, the highest for NGAL and the lowest for GRACE [44].

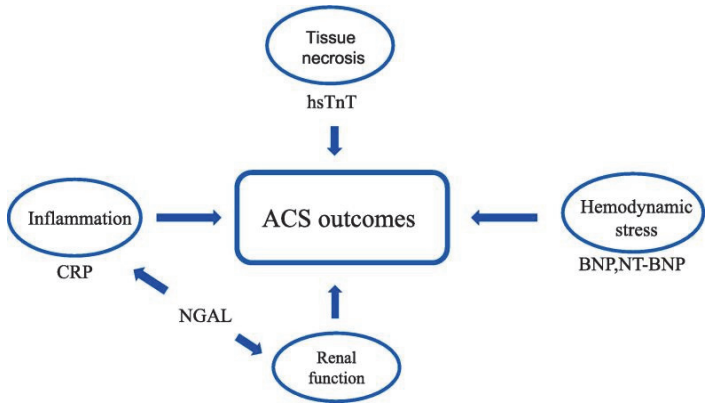

Fig. 2. Utilization of biomarkers in acute coronary syndromes (ACS); hsTnT-high sensitive troponin, CRP-C reactive protein, BNP-brain natriuretic peptide, NT-BNP- N terminal BNP,NGAL-neutrophil gelatinase associated lipocalin [39].

Fig. 2 schematically presents the place of NGAL and other known biomarkers in ACS.

Myocardial infarction.

In the experimental part of the study [2], it was shown that NGAL is one of the key mediators of cardiac injury after myocardial infarction (MI). Thus, 3 months after MI, NGAL knockout mice had lower levels of interstitial fibrosis and left ventricular (LV) inflammation, better LV contractility and compliance, and higher stroke volume and cardiac output than wild-type MI mice. Furthermore, aldosterone was shown to increase NGAL expression in cultured human cardiac fibroblasts and increase type I collagen production. This effect was prevented by treatment with the mineralocorticoid receptor antagonist finerenone (1 mg/kg/day) or by NGAL knockdown. This NGAL-mediated activity depends on the activation of NFκB (nuclear factor-κB), which was confirmed using the NFκB-specific inhibitor BAY11–7082, which prevented the effects of both aldosterone and NGAL on type I collagen.

Direct interaction between NGAL and MMP-9 may be one of the mechanisms underlying the regulatory role of NGAL after MI. NGAL has been shown to induce apoptosis in cultured cardiomyocytes by inhibiting autophagy and increasing intracellular iron accumulation [23]. NGAL-siderophore-iron complexes have been shown to increase the generation of reactive oxygen species (ROS) and reduce oxidative phosphorylation in mitochondria, which may cause cardiomyocyte damage [39].

It has been demonstrated that NGAL overexpression increased MMP-9 expression in macrophages, and NGAL knockout decreased MMP-9 expression in post-MI. The innate immune protein CARD9 has been shown to regulate NGAL expression through activation of nuclear factor-κB (NF-κB) in macrophages, which in turn increased MMP-9 expression, promoting lesion enlargement and adverse remodeling [27]. Thus, NGAL may mediate cardiac injury after MI by regulating cardiomyocyte apoptosis and MMP-9 expression.

Plasma NGAL levels were found to be significantly higher in patients with ST-segment elevation MI (STEMI) than in patients with stable angina and controls [28]. The results of a multivariate regression analysis, according to which plasma NGAL levels were independently associated with high SYNTAX scores [OR=1.109, (95 % CI: 1.104–1.114), P<0.001], allow the potential consideration of this biomarker for risk stratification in patients with CHD [28].

In a study of plasma NGAL levels in patients with ST-segment elevation MI (STEMI), it was shown that the increase in this indicator in the group with reduced left ventricular ejection fraction (LVEF) compared with the group with preserved LVEF did not reach statistical significance [1]. However, the authors showed that plasma NGAL levels can be used to predict cardiovascular mortality in patients with STEMI [1].

Ziv-Baran T. et al. [50] analyzed the prognostic value of elevated NGAL levels for assessing clinical outcomes in patients with ST-elevation MI. The study population included 273 patients with ST-elevation MI who were evaluated for a composite outcome of newly diagnosed heart failure, left ventricular ejection fraction <45 %, and 30-day mortality. High NGAL levels (within the 4th quartile) were independently associated with adverse outcomes. These findings were further enhanced after propensity score matching. The discriminatory power of NGAL to identify adverse outcomes was significantly superior to that of high-sensitivity troponin T, C-reactive protein, white blood cell count, and neutrophil/lymphocyte ratio.

A study [39] of post-MI patients showed that both higher baseline NGAL levels and greater increases in serum NGAL levels during follow-up were significantly associated with lower 6-month recovery of LV ejection fraction as assessed by cardiac magnetic resonance imaging.

Freitas IA. et al. [10] analyzed new biomarkers of kidney damage in the context of their association with atherosclerotic coronary artery disease. The authors showed that the evidence presented in the literature suggests that increased NGAL levels are associated with a better prognosis after cardiac arrest and with concomitant kidney damage.

Højagergaard MA et al. [16] studied the prognostic value of plasma NGAL in patients with ST-elevation MI. Plasma NGAL was measured in 1624 patients at admission and in consecutive subgroups 6–12 hours (n = 163) and 12–24 hours (n=222) after admission. They demonstrated that plasma NGAL at admission was independently associated with a higher risk of all-cause mortality within 30 days, and the prognostic value of NGAL was highest 6–24 hours after admission.

In a study [19], NGAL concentration predicted long-term mortality in patients with NSTEMI (hazard ratio [HR]=2,02, 95 % CI: 1.50–2.72, P<0.001), but not in patients with STEMI (HR=1,32, 95 % CI: 0.95–1.83, P=0.100). In all patients, the combination of NGAL concentration and GRACE score yielded an HR of 5.56 (95 % CI: 4.37–7.06, P<0.001) for q4/q4 for both variables. Thus, measuring circulating NGAL concentration may help identify patients, especially with NSTEMI, who require closer follow-up after MI.

Arterial hypertension.

It has been established that pressure overload in arterial hypertension (AH) stimulates inflammatory pathways, namely the secretion of cytokines, chemokines and growth factors by innate immune cells and resident cardiomyocytes, which are involved in the activation of cardiac fibroblasts and cardiac remodeling [26]. Thus, MMP-9 is one of the potential biomarkers of cardiac remodeling, which is involved in changes in the interstitial matrix [36], which is stimulated by the NGAL protein and is related to the degradation of the extracellular matrix as part of cardiac remodeling during the development of hypertrophy [2]. An experimental study [32] established direct cellular effects of NGAL in cultured cardiomyocytes: increased expression of NGAL determines the effects of proliferation and hypertrophy of cardiomyocytes, which may explain cardiac hypertrophy and probably reflects chronic activation of inflammatory pathways.

Studies [3, 4] have shown a significant increase in serum NGAL levels in patients with hypertension compared with healthy individuals. In another study [25], in patients with hypertension, increased urinary NGAL was associated with increased LV myocardium mass in low-risk patients with hypertension and early diagnosis of cardiac damage in hypertension.

In the study by Gharishvandi F. et al. [11], the diagnostic value of NGAL was compared with cystatin C and creatinine for assessing renal function in patients with hypertension. It was found that in patients with hypertension, the content of NGAL in blood plasma demonstrated a higher diagnostic value for detecting renal damage in the early stages of chronic kidney disease (CKD) compared with cystatin C and creatinine (sensitivity and specificity for NGAL were 96 % and 100 %, for cystatin C – 92 % and 60 %, for creatinine – 76 % and 47 %, respectively). In the study by Zhang C. et al. [49], the relationship between morning blood pressure elevation and NGAL in patients with hypertension was studied. It has been demonstrated that the morning peak of systolic blood pressure in hypertension is an important factor causing kidney damage, and early NGAL screening has important clinical significance for the early prevention and treatment of kidney damage in patients with hypertension.

Heart failure.

It is assumed that NGAL may participate in the pathogenesis of heart failure (HF). Thus, neutrophil activation and subsequent secretion of NGAL may potentially participate in the development of inflammatory reactions in the pathogenesis of HF. Left ventricular remodeling, which leads to the development and progression of HF, is a very complex process that includes changes not only in cardiomyocytes, but also in the extracellular matrix. Important mediators in this process are activated metalloproteinases.

Clinical data suggest that elevated serum NGAL levels are found in acute and chronic HF [18]. Increased myocardial NGAL expression has also been shown in clinical and experimental HF, supporting the role of innate immune responses in the pathogenesis of HF. In a study [14] of patients with acute post-infarction HF and patients with chronic HF, serum NGAL levels were shown to be closely correlated with clinical indicators of chronic HF severity and neurohormonal abnormalities. Histochemical studies in laboratory rats with post-infarction HF showed that massive NGAL synthesis occurs in cardiomyocytes of the non-ischemic part of the left ventricle. It was found that initial serum NGAL levels were closely associated with adverse outcomes [38].

Renal damage and dysfunction are commonly associated with HF, which can lead to an unfavorable prognosis. The prognostic value of NGAL levels for the short-term and long-term outcome of patients with HF has been established. Thus, in a study [34] involving 46 elderly patients with chronic HF of varying degrees, blood NGAL levels were significantly higher than in healthy subjects (458.5 vs. 37.8 ng/mL; $p=0.0001$) and increased in parallel with the clinical severity of HF [according to the NYHA classification], with the highest levels in patients with class IV ($p=0.0001$). And patients with higher baseline NGAL concentrations also had significantly higher mortality at 2-year follow-up.

Chronic HF, accompanied by a decrease in GFR and an increase in urinary albumin excretion, is associated with a decrease in survival. In a study by Damman K. et al. [7], which included 90 patients with chronic HF and a control group of 20 healthy people, it was found that the mean urinary NGAL levels were significantly increased in patients with chronic HF compared with the control group (175 (70–346) vs. 37 (6–58) μg/gCr, $p<0.0001$). In addition, patients with chronic HF had a significantly reduced eGFR (64±17 vs. 90±12 mL/min/1.73 m2) and increased urinary albumin excretion. Therefore, renal failure in patients with chronic HF is characterized not only by a decrease in eGFR and an increase in urinary albumin excretion, but also by the presence of tubular damage, which is determined by an increase in the concentration of NGAL in the urine.

In a study [5] of patients with HF, urinary NGAL concentration was strongly associated with the composite endpoint of all-cause mortality and HF-related hospitalizations during a 3-year follow-up. And

even in patients with normal estimated GFR, urinary NGAL levels were also associated with worse outcome.

In a study [42] evaluated the prognostic value of plasma NGAL in patients with HF with or without renal dysfunction and compared it with 2 commonly used biomarkers of chronic kidney disease (glomerular filtration rate (GFR) and cystatin C). Higher plasma NGAL levels were independently associated with an increased risk of all-cause mortality in patients with and without chronic kidney disease. It has also been found that NGAL is a stronger predictor of mortality than the established markers of kidney function eGFR and cystatin C.

A scientific research [22] found that in patients with acute decompensated heart failure, elevated urinary NGAL levels on the first day of hospitalization were independently associated with poor prognosis.

Numerous studies have shown that N-terminal B-type pronatriuretic peptide (NT-proBNP) is a marker for diagnosis and determination of short-term prognosis in patients with acute HF. A research [30] of patients with acute HF showed that NGAL was even better than NT-proBNP in predicting 30-day outcome in patients with acute HF. Patients with high NT-proBNP and NGAL values had the worst outcomes; while patients with low NT-proBNP and high NGAL values were at significant risk, and the risk of other patients was low, suggesting that NGAL provides additional information to NT-proBNP in risk classification.

Deterioration of renal function during aggressive diuresis for the treatment of acute CH may reflect damage to the renal tubules or simply indicate hemodynamic or functional changes in glomerular filtration. The Renal Optimization Strategies Evaluation-Acute Heart Failure (ROSE-AHF) study [15] examined the mechanisms of renal function deterioration during aggressive diuresis in acute heart failure, using high-dose loop diuretics in all patients. The study aimed to determine whether biomarkers of tubular injury were associated with renal function deterioration during aggressive diuresis and their association with prognosis. The biomarkers of renal tubular injury included N-acetyl-β-d-glucosaminidase, NGAL, and kidney injury molecule 1, which provide quantitative estimates of the extent of renal tubular injury. Per protocol, biomarkers of tubular injury were assessed at baseline and 72 hours after study entry. Renal impairment was defined as a ≥20 % decrease in glomerular filtration rate as assessed by cystatin C. Patients received a mean of 560 mg IV furosemide equivalents (interquartile range 300–815 mg), which induced a diuresis of 8425 mL (interquartile range 6341–10528 mL) during the 72-hour intervention period. N-acetyl-β-d-glucosaminidase and kidney damage molecule 1 levels were not altered by aggressive diuresis (both $P>0.59$), whereas NGAL levels were slightly decreased (interquartile range 169 to 35 ng/mg; $P<0.001$). Deterioration in renal function occurred in 21.2 % of patients and was not associated with increases in any marker of renal tubular injury. Increased levels of NGAL, N-acetyl-β-d-glucosaminidase, and kidney injury molecule 1 were paradoxically associated with improved survival (adjusted hazard ratio 0.80 per 10 percentile increase; 95 % confidence interval 0.69–0.91; $P=0.001$) [15]. Renal tubular injury is not associated with GFR in the context of aggressive diuresis in patients with acute HF. These results support the idea that the mild to moderate deterioration in renal function that is often seen with aggressive diuresis is distinct from traditional causes of acute kidney injury.

Thus, NGAL is currently the most promising biomarker that is being actively studied in clinical trials. Research data indicate the effectiveness of using NGAL in clinical practice as part of a diagnostic evaluation, especially for more complex cases of acute kidney injury. Changes in NGAL content are actively studied in cardiovascular diseases, diabetic nephropathy, etc. It has been established that an increase in this biomarker in heart failure is a strong predictor of an unfavorable prognosis. At the same time, NGAL testing is usually much more expensive than other biomarkers of kidney function and is not covered by health insurance, which makes it difficult to use NGAL for routine measurement in outpatients. Further research should be aimed at studying NGAL levels in various diseases and identifying their specific application as biomarkers of renal diseases with maximum benefit for patients.

Conclusions

1. It has been experimentally established that NGAL deficiency contributes to the development of atherosclerotic changes in vessels in the initial stages of the disease and accelerates the development of atherosclerosis.

2. Clinical studies have shown a significant increase in serum NGAL levels in patients with angiographically confirmed ischemic heart disease and the number of affected vessels.

3. Changes in NGAL levels have been shown to be a biomarker for early prediction of mortality in patients with acute coronary syndrome. Elevated plasma NGAL levels are associated with adverse early and long-term outcomes (higher mortality, and death from cardiovascular disease).

4. Increased NGAL expression has been identified in hypertension, but the pathogenetic mechanisms of these changes continue to be studied. Increased NGAL expression in heart failure reflects the involvement of the innate immune response in the pathogenesis of heart failure. It has been established that an increase in this biomarker in serum in heart failure is an independent predictor of adverse prognosis.

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