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Original article

Low level of neutrophil gelatinase-associated lipocalin (NGAL) in patients with chronic heart failure and multivessel coronary atherosclerosis

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Abstract: *Rationale* — Several biomarkers are used to determine the prognosis of patients with heart failure (HF), including neutrophil gelatinase-associated lipocalin (NGAL, Lipocalin-2). We investigated NGAL serum levels in patients with HF and coronary artery disease (CAD).
Methods — Fifty-three patients with chronic HF and stable multivessel CAD were included in the study. Patients were grouped on the basis of the NGAL level: low NGAL group (NGAL<37 ng/mL, n=19) and normal NGAL group (NGAL ≥37 ng/mL, n=34).
Results and Discussion — The main findings from our study of patients with HF and multivessel CAD were: 1) Plasma NGAL levels were below reference values in 35.8% of cases. 2) We detected a strong positive correlation between neutrophil count and NGAL level (0.573, p<0.001). 3) Neutropenia was present in 15.8% of patients in the low NGAL group and in none in the group with a normal NGAL level (p=0.041). 4) Postinfarction left ventricular aneurysms were more often diagnosed in patients of the first group (15.8%) and in none of patients in the second group (p=0.041).
Conclusion — Low NGAL has been associated with neutropenia in patients with heart failure and multivessel atherosclerotic CAD. Left ventricular aneurysms were diagnosed in 15.8% (n=3) patients with low NGAL and in none with normal NGAL levels. These changes may be due to maladaptive remodeling of the heart after myocardial infarction, but further research is needed.

Keywords: Neutrophilic gelatinase-associated lipocalin, NGAL, chronic heart failure, multivessel coronary atherosclerosis.

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Introduction

Chronic heart failure (HF) is a severe progressive clinical syndrome [1-3]. Several biomarkers are used to determine the prognosis of patients with heart failure [3-9]. Neutrophil gelatinase-associated lipocalin (NGAL, Lipocalin-2) is one of such biomarkers [10]. It is synthesized in hepatocytes, cardiomyocytes, neurons, smooth muscle, renal, endothelial, and various populations of immune cells (e.g., neutrophils) [11]. Early clinical and experimental studies discovered NGAL levels closely associated with acute and chronic kidney disease [12-14]. Also, there is evidence that NGAL may be involved in the development of atherosclerotic vascular disease [15]. For example, NGAL content increased in patients with vulnerable carotid atherosclerotic plaques [16]. Other studies demonstrated that high NGAL levels were associated with vascular aneurysm rupture [17-18]. Also, NGAL could play a potential role in the development of abdominal aortic aneurysms [19]. High NGAL levels were associated with the development of early complications and mortality in patients with ST-segment elevation myocardial infarctions (STEMI) [20], along with acute and chronic heart failure [21-23]. In summary, most studies reported augmented levels of NGAL in patients with cardiovascular diseases, compared with healthy people. At the same time, some studies did not show NGAL as a predictor of clinical events in multivariate models following adjustment for renal function and brain natriuretic peptide (BNP) level [24-25]. However, there is a lack of clinical data on association low NGAL levels with cardiovascular pathology. Moreover, in a preclinical model, low NGAL was linked to adverse postinfarct remodeling of the left ventricle [26]. Therefore, we sought to investigate NGAL serum levels in patients with HF and coronary artery disease (CAD), scheduled for coronary artery bypass grafting (CABG).

Material and Methods

Study Design and Population

Fifty-three patients with chronic heart failure and stable multivessel CAD who were hospitalized for elective CABG were sequentially included in the study. The eligibility criteria were as follows: 1. Patients with chronic heart failure. 2. Triple vessel CAD revealed by invasive coronary angiography: atherosclerotic plaques ≥ 50% of the lumen of the vessel in the anterior descending, circumflex and right coronary arteries, or the presence of stenosis of the left coronary artery in combination with damage to the right coronary artery.

The exclusion criteria were as follows: severe respiratory failure (exacerbation of chronic obstructive pulmonary disease, uncontrolled course of bronchial asthma), diagnosed cancer, acute infection, exacerbation of chronic infectious disease, myocardial infarction, or progressive angina less than three months ago.

All patients were examined in accordance with a unified algorithm before surgery: review of anamnesis, clinical examination with determining body mass index (ratio of body weight in kilograms to the square of the body height in meters), symptoms and signs of heart failure. The instrumental examination included 12-lead electrocardiography (ECG), 24-hour Holter monitoring, and transthoracic echocardiography [27].

In addition, routine blood tests, including the absolute neutrophil count (reference values of neutrophils were 2-5.5×10^9/L, according to the local laboratory) were performed. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Coronary angiography was performed according to clinical indications within two months of inclusion in the study. The local institutional review board approved the study, and all patients provided written informed consent.

Table 1. The clinical characteristics and medical history of patients with chronic heart failure and multivessel atherosclerosis of the coronary arteries vs. NGAL level

Parameter	*Low NGAL group (NGAL<37 ng/mL; n=19)*	*Normal NGAL group (NGAL 37-106 ng/mL; n=34)*	*p-value*
Men / women, n (%)	16/3 (84.2/15.8)	26/8 (76.5/23.5)	0.385
Age, years, Median (Q25; Q75),	67.0 (61.0; 68.0)	59.0 (55.0; 63.0)	0.019
Past myocardial infarction, n (%)	14 (73,7)	20 (58.8)	0.218
Time since last myocardial infarction Median (Q25; Q75), months	18.0 (5.0; 36.0)	12.0 (3.37; 78.0)	0.572
Hypertension, n (%)	19 (100)	32 (94.1)	0.407
Diabetes mellitus, n (%)	6 (31.6)	13 (38.2)	0.429
Arrhythmias, n (%)	12 (63.1)	13 (38.2)	0.072
Angina pectoris, n (%)	17 (89.5)	34 (100.0)	0.124
Dyspnea, n (%)	19 (100)	32 (94.1)	0.407
Palpitations, n (%)	12 (63.2)	7 (20.6)	0.003
Lower extremity edema, n (%)	2 (10.5)	6 (17.6)	0.395
Fatigue, n (%)	8 (42.1)	10 (29.4)	0.262

NGAL, neutrophil gelatinase-associated lipocalin; (Q25; Q75), interquartile range; p, significance level.

Table 2. Characterization of patients with heart failure

Parameter	Low NGAL group (NGAL<37 ng/mL; n=19)	Normal NGAL group (NGAL 37-106 ng/mL; n=34)	p-value
NT-proBNP, pg/ml, Median (Q25; Q75)	428(208;621)	397(219;580)	0.261
I NYHA, n (%)	0	3 (8.8)	0.255
II NYHA, n (%)	10 (52.6)	22 (64.7)	0.284
III NYHA, n (%)	9 (47.4)	9 (26.5)	0.108
IV NYHA, n (%)	0	0	
HFpEF, n (%)	11 (57.9)	21 (67.7)	0.504
HFmrEF, n (%)	1 (5.3)	3 (8.8)	0.547
HFrEF, n (%)	7 (36.8)	8 (23.5)	0.236

NGAL, neutrophil gelatinase-associated lipocalin; NYHA, New York Heart Association functional classification; HFpEF, heart failure with preserved ejection fraction (≥50%); HFmrEF, heart failure with midrange ejection fraction (40-49%); HFrEF, heart failure with reduced ejection fraction (<40%); (Q25; Q75), interquartile range; p, significance level.

Table 3. Medical therapy in patients with chronic heart failure and multivessel atherosclerosis of the coronary arteries

Parameter	Low NGAL group (NGAL<37 ng/mL; n=19)	Normal NGAL group (NGAL 37-106 ng/mL; n=34)	p-value
Angiotensin-converting enzyme inhibitors, n (%)	7 (36.9)	15 (44.1)	0.413
Angiotensin II type receptor antagonists, n (%)	8 (42.1)	12 (35.3)	0.420
Beta-blockers, n (%)	15 (78.9)	33 (97)	0.106
Mineralocorticoid receptor antagonist, n (%)	6 (31.6)	2 (5.9)	0.019
Acetylsalicylic acid, n (%)	12 (63.2)	24 (70.6)	0.398
Clopidogrel, n (%)	6 (31.6)	12 (35.3)	0.510
Statins, n (%)	16 (84.2)	25 (73.5)	0.297

NGAL, neutrophil gelatinase-associated lipocalin; p, significance level.

Table 4. Echocardiographic parameters in patients with chronic heart failure and multivessel atherosclerosis of the coronary arteries, depending on the level of NGAL

Parameter	*Low NGAL group (NGAL<37 ng/mL; n=19)*	*Normal NGAL group (NGAL 37-106 ng/mL; n=34)*	*p-value*
Left ventricular ejection fraction, %; Median (Q25; Q75)	50.0 (30.0;66.0)	61.5 (39.0;64.0)	0.385
Left ventricular aneurysm, n (%)	3 (15.8)	0 (0.0)	0.041
Left atrial volume index, mL/m^2; Median (Q25; Q75)	46.8 (31.20;59.50)	35.25 (30.75;47.60)	0.151
Left ventricular end-diastolic volume, mL; Median (Q25; Q75)	130.5 (104.0;191.0)	117.5 (108.25;147.0)	0.939
Left ventricular end-systolic volume, mL; Median (Q25; Q75)	44.0 (37.0; 123.0)	51.0 (38.5; 84.5)	0.722
Stroke volume, mL Median (Q25; Q75)	67.0 (56.0;72.0)	69.5 (65.0; 74.5)	0.233
Left ventricular mass index, g/m^2; Median (Q25; Q75)	97.0 (91.0;123.0)	95.5 (88.25;101.75)	0.470
E/A ratio; Median (Q25; Q75)	0.88 (0.57; 1.81)	0.87 (0.75; 1.23)	0.956
E/e' ratio; Median (Q25; Q75)	8.18 (6.67;14.25)	9.25 (7.11; 11.18)	0.736
Moderate and severe mitral regurgitation, n (%)	1 (5.3)	3 (8.8)	0.547
Moderate and severe tricuspid regurgitation, n (%)	0	2 (5.9)	0.407

NGAL, neutrophil gelatinase-associated lipocalin; (Q25; Q75), interquartile range; p, significance level.

Table 5. Laboratory parameters in patients with chronic heart failure and multivessel atherosclerosis of the coronary arteries, depending on the level of NGAL

Parameter Median (Q25; Q75)	*Group 1 (NGAL<37 ng/mL; n=19)*	*Group 2 (NGAL 37-106 ng/mL; n=34)*	*p-value*
Hemoglobin, g/L	150.0 (137.0;162.0)	153.0 (142.0;166.0)	0.160
Red blood cell count, 10^{12}/L	4.58 (4.22; 5.33)	4.94 (4.65;5.42)	0.083
Leukocytes, 10^9/L	6.5 (5.30;7.75)	8.15 (6.82; 9.32)	0.004
Neutrophil cell count, 10^9/L	2.74 (2.26;3.46)	4.03 (3.13;5.17)	0.001
Neutrophils, %	41.0 (36.22; 52.40)	49.7 (36.4; 51.7)	0.097
Monocytes, %	9.9 (8.95;11.32)	9.25 (8.0; 10.07)	0.107
Platelets, 10^9/L	202.5 (159.0; 225.25)	213.0 (190.75;258.0)	0.147
Total bilirubin, umol/L	17.25 (14.07;19.32)	17.55 (13.5;23.45)	0.860
Alanine aminotransferase, u/L	20.55 (15.17;27.90)	22.75 (16.40;26.45)	0.430
Aspartate aminotransferase, u/L	21.1 (18.00;24.60)	20.0 (15.7; 26.3)	0.682
Creatinine, mg/L	10.86 (9.67; 12.5)	10.86 (9.4; 11.99)	0.495
Blood urea, mg/dL	6.0 (4.9; 6.9)	5.9 (4.9; 6.5)	0.575
Glomerular filtration rate (CKD-EPI), ml/min/1.73m^2	69.0 (61.0; 71.5)	70.0 (60.0; 74.0)	0.602
Sodium, mmol/L	142.3 (140.15; 143.85)	142.1 (140.1; 144.00)	0.719
Potassium, mmol/L	4.56 (4.45;5.15)	4.62 (4.21;4.88)	0.712
Protein, g/L	70.5 (68.05; 76.3)	72.4 (68.55;76.75)	0.904
Total cholesterol, mg/dL	3.86 (3.21; 4.55)	4.23 (3.72; 5.93)	0.297
Triglycerides, mg/dL	1.22 (1.04; 1.68)	1,78 (1.19;2.60)	0.002
Low-density lipoprotein, mg/dL	2.14 (0.91; 3.55)	2.72 (1.6; 4.03)	0.112
High-density lipoprotein, mg/dL	1.16 (1.03; 1.48)	1.15 (1.08; 1.24)	0.903
C-reactive protein, mg/L	4.3 (3.95;7.95)	4.5 (4.05;8.05)	0.423

NGAL, neutrophil gelatinase-associated lipocalin; (Q25; Q75), interquartile range; p, significance level.

Biomarker Quantification

The concentration of serum NGAL was determined by enzyme-linked immunosorbent assay technique using Human NGAL Rapid ELISA Kit (KIT 037) (BioPorto Diagnostics, Denmark). Reference ranges of NGAL were 37-106 ng/mL, as per the manufacturer's instructions (the limit based on the median value of plasma NGAL level in healthy individuals) [28].

Statistical Analyses

Data were analyzed with the use of STATISTICA 10.0 and R programming language in R studio software. Continuous variables were presented as median and interquartile range (IQR), considering the non-normal distribution parameters. Categorical data were presented in absolute and relative values: n (%). Continuous variables in the independent samples were analyzed using the Wilcoxon rank-sum test. The statistical significance of differences for categorical variables was determined using the two-sided Fisher's exact test. The correlation between metrics was evaluated by calculating the Spearman correlation coefficient. A value of $p<0.05$ was considered statistically significant.

Results

The median serum concentration of NGAL was 41.6 (33.2; 51.7) ng/mL. There were no values greater than the upper reference value (106 ng/mL). Patients were grouped on the basis of the NGAL level: low NGAL group (NGAL<37 ng/mL, n=19) and normal NGAL group (NGAL≥37 ng/mL, n=34). Patients in the low NGAL group were older (on average, 67 vs. 59 years old, p=0.019) with no difference in sex ratio (*Table* 1). Previous myocardial infarctions were recorded in 58.8% of patients in the normal NGAL group and 73.7% in the low NGAL group (p=0.218).

The severity of heart failure symptoms and exercise tolerance (sensu NYHA classification) were comparable between the groups (*Table* 2). There was no significant baseline difference in the main classes of cardiovascular medications (*Table* 3).

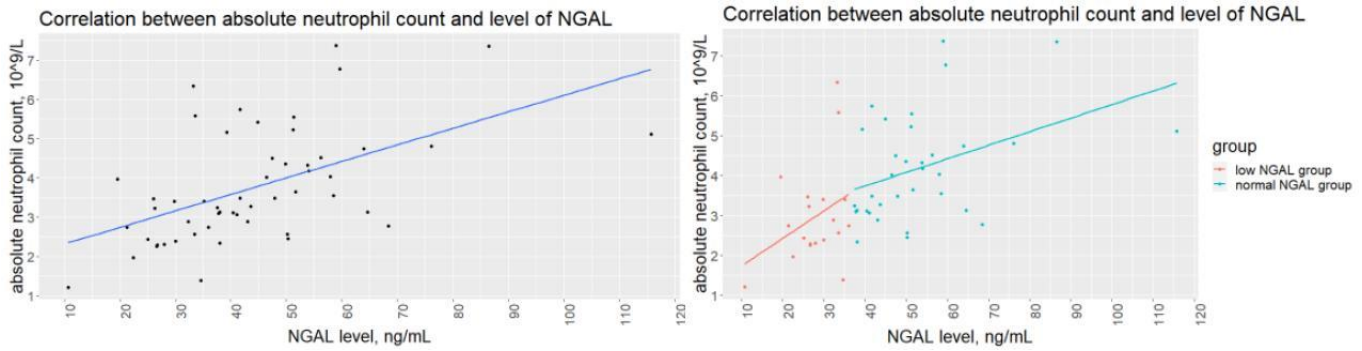

Figure 1. Correlation between absolute neutrophil count and level of NGAL.

Postinfarction left ventricular aneurysms were more often diagnosed in patients of the first group (15.8%) and in none of patients in the other group (p=0.041) (*Table* 4).

According to the results of a blood test, nearly every fifth patient with a low NGAL level (15.8%) was diagnosed with neutropenia, whereas in the group with normal NGAL values, the neutrophil level in all patients was within the reference range (p=0.041). Neutrophil level was missing in one patient. The absolute neutrophil count significantly differed between the groups as well: 2.74 (2.26; 3.46) and 4.03 (3.13; 5.17); p=0.001. There was a positive correlation between absolute neutrophil count and NGAL (r=0.573, p<0.001) (*Figure* 1).

However, we did not find differences in the eGFR between the groups: 69.0 (61.0; 71.5) mL/min/1.73 m^2 and 70.0 (60.0; 74.0) mL/min/1.73 m^2 (p=0.602) (*Table* 5).

Discussion

Our data represented the pioneering study of NGAL and cardiac structure/function in patients with heart failure and multivessel coronary atherosclerosis, who were scheduled for CABG. Previous studies in a similar cohort focused predominantly on renal outcomes in patients with different levels of NGAL after CABG [29-32].

The main findings from our study of patients with HF and multivessel CAD undergoing CABG were: 1) Plasma NGAL levels did not exceed reference values; moreover, NGAL levels were below reference values in 35.8% cases. 2) Since the NGAL level could be associated with the neutrophil count [33], we tested this association in our study and found a strong positive correlation between neutrophil count and NGAL level (0.573, p<0.001). 3) Neutropenia was present in 15.8 % of patients in the group with a low NGAL and none in the group with a normal NGAL level (p=0.041). 4) Postinfarction left ventricular aneurysms were more often diagnosed in patients of the first group (15.8%), and in none of patients in the other group (p=0.041), which could result from maladaptive remodeling of the heart after myocardial infarction [26]. It should be noted that the proportion of patients who had a history of myocardial infarction did not differ between the groups.

Earlier studies of NGAL demonstrated that low NGAL was more closely associated with neutropenia than with proinflammatory cytokines, procalcitonin and nutritional status, especially in patients with low levels of systemic inflammation while maintaining renal function [33].

Neutrophils matter in the healing process after myocardial infarction and subsequent remodeling of the heart. Yet, the exact role of neutrophils is ambiguous since both overactivation and insufficient activation may contribute to pathological remodeling of the heart and heart failure [34-38]. Mouse models demonstrated that neutrophil depletion during myocardial infarction led to excessive fibrosis, an increase in the left ventricular end-systolic volume, a significant decrease in left ventricular ejection fraction and cardiac output, which ultimately resulted in progressive deterioration of cardiac function [26]. One of the processes, required for adequate repair and cardiac remodeling, is macrophage efferocytosis, and its effectiveness depends on the level of NGAL [26, 39].

Accordingly, our results are consistent with experimental data on the association of low level of NGAL with features of post-infarction cardiac remodeling and development of heart failure. To date, there are no other convincing clinical studies demonstrating the association of low levels of NGAL with the clinical characteristics and medical history of patients with multivessel coronary atherosclerosis.

The main limitation of our study was its small sample size. Also, we had only cross-sectional data; and lack of follow-up information impaired our ability to draw conclusions about the interrelationship of NGAL and cardiac remodeling. Also, we did not know NGAL level at the time of acute myocardial infarction, leading to precipitating heart failure. Finally, clinical outcomes were not collected.

Conclusion

Low NGAL has been associated with neutropenia in patients with heart failure and multivessel atherosclerotic CAD. Left ventricular aneurysms were diagnosed in 15.8% (n=3) patients with low NGAL and in none with normal NGAL levels. These changes could be due to maladaptive remodeling of the heart after myocardial infarction, but further examination is needed. Further histological correlation between myocardial properties and NGAL, as well as study of the biomarker dynamics of NGAL after CABG, are needed.

Compliance with Ethical Standards

All performed procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with 1975 Declaration of Helsinki, year 2000 revision. Signed informed consent was obtained from all patients included in the study. The study was approved by the local institutional review board.

No animal studies were carried out by the authors for this article.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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