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# NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) AS A MARKER OF RENAL DAMAGE IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES MELLITUS*

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Arterial hypertension (AH) is currently regarded as one of the leading medical and social challenges of modern medicine, given its high prevalence in the general population and its substantial impact on mortality and disability rates. Numerous epidemiological studies have shown that elevated blood pressure is observed in approximately one-third of adults and, in some populations, nearly one-half of adults. At the same time, a considerable proportion of patients with AH present with concomitant metabolic disorders, particularly type 2 diabetes mellitus (T2DM). The combination of these two pathological conditions creates a complex comorbid profile that markedly increases the risk of cardiovascular complications, promotes the accelerated development of chronic kidney disease, and is associated with a less favourable clinical prognosis [1, 2].

The development of target organ damage in arterial hypertension is mediated by a complex set of pathophysiological mechanisms, among which endothelial dysfunction, activation of the oxidative stress response, persistence of low-grade chronic inflammation, and alterations in intrarenal hemodynamics are important. When AH is combined with T2DM, these pathological mechanisms are further aggravated by prolonged hyperglycemia, insulin resistance, and stimulation of pro-inflammatory signalling pathways. Renal damage in patients with such comorbid pathology often remains clinically silent for a long time, which complicates its early diagnosis and the timely implementation of preventive measures aimed at slowing the progression of nephropathy [3–7].

Given the high prevalence of target organ damage in cardiovascular and metabolic dis-

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orders, one of the important tasks of modern clinical medicine is to identify biological markers that reflect early functional and structural changes in renal tissue and blood vessels before clinically overt abnormalities develop. In this context, particular interest has focused on molecular indicators that may signal the early stages of kidney injury. Among these biomarkers, neutrophil gelatinase-associated lipocalin (NGAL), a low-molecular-weight lipocalin, is considered particularly promising. It is synthesized by various cell types, including neutrophils, renal tubular epithelial cells, endothelial cells, and vascular smooth muscle cells [8, 9].

NGAL is involved in a number of important biological processes, including the regulation of inflammatory responses, the formation of immune responses, the control of apoptosis, and tissue remodeling. Under conditions of ischemic, toxic, or metabolic injury to renal tissue, the expression of this protein increases substantially, which makes it a potential early indicator of both acute and chronic kidney injury. In addition, elevated NGAL levels have been associated with an enhanced systemic inflammatory response, progression of atherosclerotic changes in the vascular wall, and an increased risk of cardiovascular complications.

Several clinical studies have demonstrated elevated levels of neutrophil gelatinase-associated lipocalin in patients with arterial hypertension. However, the factors that may influence the variability of this biomarker remain insufficiently investigated, and available findings remain inconsistent. Information on the role of various clinical and metabolic characteristics in determining NGAL levels in patients with concomitant AH and T2DM is particularly limited. Therefore, the relationship between this biomarker and clinical parameters and the metabolic profile of hypertensive patients, depending on the presence or absence of T2DM, warrants further investigation [10-12].

In view of the above, studying the factors associated with changes in NGAL levels in patients with AH, both with and without T2DM, is relevant and clinically important. The results obtained may contribute to improving approaches to the early detection of target organ damage, to more accurate individual risk assessment, and to the optimization of personalized treatment strategies for this patient group.

Based on the above, the aim of the study was to investigate clinical and laboratory, immunological, biochemical, and hemodynamic factors and to determine their relationships with neutrophil gelatinase-associated lipocalin (NGAL) concentration in patients with arterial hypertension with and without type 2 diabetes mellitus.

## MATERIALS AND METHODS

The study was conducted in accordance with the ethical and legal requirements set forth in the Charter of the Ukrainian Association of Bioethics, as well as international standards of Good Clinical Practice (GCP, 1992) and Good Laboratory Practice (GLP, 2002). The study also took into account the provisions of the Declaration of Helsinki on ethical principles for medical research involving human subjects, as well as the Council of Europe Convention on Human Rights and Biomedicine. The study protocol was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University.

The study included 136 patients with diagnosed AH. All participants were divided into two clinical groups. The first group consisted of 64 patients with isolated AH, including 30 men and 34 women; the mean age was 55.8 ± 8.31 years. The second group included 72 patients with concomitant AH and T2DM (34 men and 38 women), with a mean age of 51.98 ± 6.44 years.

The control group comprised 20 apparently healthy individuals in whom no signs of cardiometabolic pathology were detected during examination.

Patients with acute infectious or autoimmune diseases, malignancies, and chronic kidney disease stage ≥ 3b (glomerular filtration rate < 35 mL/min/1.73 m²) were excluded from the study. Additional exclusion criteria included secondary hypertension, severe T2DM, type 1 diabetes mellitus, pregnancy, various forms of addiction, and acute inflammatory conditions.

All study participants underwent a comprehensive clinical, laboratory, and instrumental examination. Biochemical blood analysis included assessment of lipid profile parameters,

namely total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TG). Renal function was assessed by serum creatinine and urea levels, as well as by estimated glomerular filtration rate (eGFR) calculated using generally accepted methods. To characterize carbohydrate metabolism, serum insulin and glycated haemoglobin (HbA1c) levels were determined using enzyme-linked immunosorbent assay (ELISA). ELISA was also used to determine the levels of neutrophil gelatinase-associated lipocalin (NGAL), leptin, cystatin C (Cys C), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and insulin using certified commercial kits according to the manufacturers' instructions.

To assess immune system status, peripheral blood lymphocyte subpopulations were analyzed. The study used an immunoperoxidase method with monoclonal antibodies against cell-surface markers, and the relative proportions of these markers were determined. The proportions of total T lymphocytes ($CD3^+$), T helper cells ($CD4^+$), T cytotoxic/suppressor lymphocytes ($CD8^+$), and activated T cells ($CD16^+$) were determined. The obtained results were compared with reference values: $CD3^+$ 50–80 %, $CD4^+$ 33–46 %, $CD8^+$ 17–30 %, and $CD16^+$ 12-23 %. In addition, the immunoregulatory index (the $CD4^+/CD8^+$ ratio, or Th/Ts ratio), which characterizes the balance between helper and suppressor components of cellular immunity, was calculated; values of 1.5–2.5 were considered normal.

The structural and functional state of the heart was assessed by echocardiography using an Ultima PA ultrasound system (Radmir, Ukraine) equipped with a sector phased-array transducer operating at 2-3 MHz, in accordance with the recommendations of the American Society of Echocardiography. During the examination, the dimensions of the cardiac chambers (aorta, left and right atria, right and left ventricles), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT) were measured. Left ventricular myocardial mass (LVMM) and its index (LVMMI), relative wall thickness (RWT), left ventricular ejection fraction (LVEF), and diastolic function parameters, including early (VE) and late (VA) diastolic filling velocities, their ratio (VE/VA), and isovolumic relaxation time (IVRT), were also calculated.

Statistical data analysis was performed using Statistica 14.0 (StatSoft Inc., USA) and Microsoft Excel 2013. The distribution pattern of quantitative variables was assessed using the Shapiro-Wilk W test. For normal distributions, results were presented as mean ± standard deviation (M ± SD). Regression analysis was used to assess the influence of various factors on NGAL concentration, thereby determining the strength and direction of relationships among the studied variables.

## RESULTS AND THEIR DISCUSSION

The study included a comprehensive assessment of clinical, laboratory, and structural-functional parameters in patients with isolated AH and in those with AH combined with T2DM. Comparative analysis revealed systemic differences between the study groups, reflecting the specific metabolic, immunological, and cardiohemodynamic changes associated with comorbidity (Table 1).

It was found that patients with concomitant AH and T2DM had a more unfavourable anthropometric profile, characterized by a tendency toward higher BMI. At the same time, SBP and DBP levels did not differ significantly between the groups.

Analysis of lipid profile parameters demonstrated a more pronounced atherogenic profile in patients with comorbid pathology, as evidenced by elevated total cholesterol, triglycerides, and atherogenic coefficient levels, with no substantial changes in individual lipoprotein fractions.

The immunological profile of patients with the combined course of these diseases was characterized by activation of the cellular arm of immunity. This was accompanied by an increase in $CD3^+$ cells, their major subpopulations, and the $CD4^+/CD8^+$ ratio against the background of decreased circulating immune complex (CIC) levels, which may indicate an imbalance in the immune response.

Table 1

**Comparative characteristics of clinical, laboratory, and structural and functional parameters in patients with isolated arterial hypertension and in those with arterial hypertension combined with type 2 diabetes mellitus**

| Parameter | AH group | AH + T2DM group | p-value |
|---|---|---|---|
| Age, years | 55.8 ± 8.31 | 51.98 ± 6.44 | 0.0030 |
| Body mass index, kg/m$^3$ | 27.86 ± 2.30 | 32.55± 6.00 | 0.0000 |
| Systolic blood pressure, mmHg | 143.09 ± 11.24 | 140.02 ± 22.09 | 0.3092 |
| Diastolic blood pressure, mmHg | 87.42 ± 8.94 | 84.94 ± 13.78 | 0.2113 |
| HbA1c, % | 6.97 ± 1.58 | 7.33 ± 1.66 | 0.1773 |
| Total cholesterol, mmol/L | 5.49 ± 1.30 | 6.29 ± 1.65 | 0.0047 |
| Triglycerides, mmol/L | 1.86 ± 0.80 | 3.13 ± 2.17 | 0.0002 |
| HDL-C, mmol/L | 1.18 ± 0.31 | 1.13 ± 0.26 | 0.3868 |
| LDL-C, mmol/L | 3.44 ± 1.29 | 3.69 ± 1.07 | 0.3223 |
| VLDL-C, mmol/L | 0.96 ± 0.68 | 1.07 ± 0.43 | 0.3463 |
| Atherogenic coefficient (AC) | 3.64 ± 1.44 | 4.94 ± 2.74 | 0.0054 |
| Circulating immune complexes (CIC), units | 96.47 ± 9.74 | 31.08 ± 8.55 | 0.0001 |
| T-lymphocytes, % (CD39$^+$) | 65.29 ± 3.76 | 149.83 ± 21.66 | 0.0001 |
| T-helper cells, % (CD4$^+$) | 38.76 ± 3.07 | 53.15 ± 4.08 | 0.0001 |
| T-suppressor cells, % (CD8$^+$) | 21.77 ± 1.91 | 29.84 ± 3.57 | 0.0001 |
| Activated T-lymphocytes, % (CD25$^+$) | 7.18 ± 1.36 | 24.08 ± 3.89 | 0.0001 |
| Immunoregulatory index (CD4$^+$/CD8$^+$) | 1.84 ± 0.28 | 11.40 ± 2.72 | 0.0001 |
| Blood urea, mmol/L | 5.60 ± 1.40 | 6.08 ± 1.65 | 0.0904 |
| Creatinine, mmol/L | 96.39 ± 16.26 | 99.10 ± 23.30 | 0.4745 |
| Cystatin C, mg/L | 150.21 ± 33.51 | 131.10 ± 26.70 | 0.0293 |
| Leptin, ng/mL | 21.70 ± 11.16 | 25.03 ± 9.18 | 0.0486 |
| NGAL, pg/mL | 17.67 ± 4.52 | 17.03 ± 4.37 | 0.3827 |
| NT-proBNP, pg/mL | 413.39 ± 130.84 | 453.49 ± 141.46 | 0.0791 |
| Insulin, μIU/mL | 21.11±14.98 | 22.48 ± 12.62 | 0.5475 |
| Aortic root diameter, cm | 3.28 ± 0.25 | 3.79 ± 0.09 | 0.0001 |
| Left atrial diameter, cm | 3.61 ± 0.27 | 4.47 ± 0.12 | 0.0001 |
| Right atrial diameter, cm | 3.84 ± 0.24 | 4.23 ± 0.11 | 0.0001 |
| LVEDD, cm | 4.53 ± 0.43 | 5.90 ±0.09 | 0.0001 |
| LVESD, cm | 3.33 ± 0.46 | 4.19 ± 0.12 | 0.0001 |
| Right ventricular diameter, cm | 1.73 ± 0.08 | 1.35 ± 0.06 | 0.0001 |
| IVST, cm | 1.25 ± 0.07 | 1.32 ± 0.07 | 0.0001 |
| LVPWT, cm | 1.26 ± 0.04 | 1.20 ± 0.05 | 0.0001 |
| LVMM, g | 205.52 ± 30.91 | 261.72 ± 17.83 | 0.0001 |
| LVMMI, g/m$^2$ | 121.87 ± 16.74 | 136.08 ± 9.00 | 0.0001 |
| RWT | 0.53 ± 0.05 | 0.49 ± 0.03 | 0.0001 |
| LVEF, % | 57.47 ± 3.67 | 48.53 ± 3.14 | 0.0001 |

| Parameter | AH group | AH + T2DM group | p-value |
|---|---|---|---|
| VE, cm/s | 62.49±8.33 | 64.01±7.92 | 0.2734 |
| VA, cm/s | 72.98±8.33 | 83.22±6.59 | 0.0001 |
| VE/VA | 0.86±0.13 | 0.79±0.12 | 0.0012 |
| IVRT, ms | 105.40±10.97 | 117.04±11.30 | 0.0001 |

*Notes:*

HDL-C — high-density lipoprotein cholesterol;
LDL-C — low-density lipoprotein cholesterol;
VLDL-C — very-low-density lipoprotein cholesterol;
NGAL — neutrophil gelatinase-associated lipocalin;
NT-proBNP — N-terminal pro-B-type natriuretic peptide;
LVEDD — left ventricular end-diastolic diameter;
LVESD — left ventricular end-systolic diameter;
IVST — interventricular septal thickness;
LVPWT — left ventricular posterior wall thickness;
LVMM — left ventricular myocardial mass;
LVMMI — left ventricular myocardial mass index;
RWT — relative wall thickness;
LVEF — left ventricular ejection fraction;
VE — early diastolic filling velocity;
VA — late diastolic filling velocity;
IVRT — isovolumic relaxation time.

Overall, renal functional parameters did not show fundamental intergroup differences; however, individual biomarkers reflected moderate changes associated with metabolic burden. At the same time, patients with concomitant T2DM showed elevated leptin levels as a marker of metabolic disturbances.

It should be noted that patient stratification in the study was based on the presence of a verified clinical diagnosis of T2DM in accordance with current ADA (American Diabetes Association, 2024) and EASD (European Association for the Study of Diabetes, 2023) guidelines, rather than solely on HbA1c levels. The relatively elevated HbA1c values observed in the group of patients with isolated AH may reflect the presence of subclinical disturbances of carbohydrate metabolism and insulin resistance, which is consistent with the concept of the cardiometabolic continuum. At the same time, HbA1c was not used as the sole classification criterion due to its limitations, including its integrative nature, susceptibility to non-metabolic influences, and inability to differentiate prediabetes without additional testing.

The HbA1c values obtained in the non-diabetic group reflect the metabolic heterogeneity of patients with AH and do not indicate incorrect stratification; rather, they highlight the presence of early metabolic alterations relevant for the assessment of NGAL as a marker of subclinical target organ damage.

According to echocardiographic data, patients with combined pathology exhibited more pronounced cardiac remodeling, characterized by chamber enlargement, increased left ventricular myocardial mass (LVMM), and changes in cardiac geometry. In addition, a decrease in left ventricular systolic function was observed. Analysis of diastolic function revealed a more pronounced impairment of myocardial relaxation in patients with comorbidity, as evidenced by changes in transmitral blood flow parameters and prolongation of the isovolumic relaxation time (IVRT).

Thus, the combination of AH and T2DM is associated with more profound metabolic, immunological, and cardiac disturbances, with important clinical significance for risk stratification and optimization of therapeutic approaches.

Following the generalization of the results, the next stage of our study involved a more detailed analysis of the parameters, accounting for the distribution of patients by NGAL biomarker level. For this purpose, a comparative

analysis of clinical, laboratory, immunological, and echocardiographic parameters was performed in groups formed according to the median NGAL level (16.35 pg/mL): patients with NGAL < 16.35 pg/mL (n = 68) and those with NGAL > 16.35 pg/mL (n = 68) (Table 2).

As shown in the presented data, the groups were comparable with respect to the main demographic and anthropometric characteristics, as well as blood pressure levels and parameters of carbohydrate and lipid metabolism. This indicates their baseline homogeneity and allows for a more accurate interpretation of the observed differences. Particular attention should be paid to the parameters for which statistically significant differences were identified between the study groups. Specifically, patients with higher NGAL levels demonstrated a significant increase in leptin concentration, which may indicate more pronounced disturbances in metabolic regulation and a potential association with adipose tissue-related inflammatory mechanisms. Given leptin's pro-inflammatory adipokine role, these findings may suggest that

Table 2

**Clinical, laboratory, immunological, and echocardiographic characteristics of patients stratified according to the median level of neutrophil gelatinase-associated lipocalin (NGAL)**

| Parameter | NGAL < 16.35 n = 68 | NGAL > 16.35 n = 68 | p-value |
|---|---|---|---|
| Arterial hypertension | n = 35 | n = 29 | — |
| Arterial hypertension + type 2 diabetes mellitus | n = 33 | n = 39 | — |
| Age, years | 54.19 ± 6.12 | 52.93 ± 8.64 | 0.311 |
| Body mass index, kg/m$^3$ | 30.01 ± 4.62 | 30.98 ± 5.86 | 0.267 |
| Systolic blood pressure, mmHg | 142.00 ± 18.85 | 140.74 ± 17.54 | 0.675 |
| Diastolic blood pressure, mmHg | 86.49 ± 11.90 | 85.57 ± 112.02 | 0.641 |
| HbA1c, % | 7.26 ± 1.58 | 7.09 ± 1.72 | 0.536 |
| Total cholesterol, mmol/L | 6.09 ± 1.53 | 5.91 ± 1.52 | 0.515 |
| Triglycerides, mmol/L | 2.73 ± 2.31 | 2.55 ± 1.29 | 0.611 |
| HDL-C, mmol/L | 1.15 ± 0.30 | 1.16 ± 0.28 | 0.942 |
| LDL-C, mmol/L | 3.69 ± 0.99 | 3.43 ± 1.36 | 0.309 |
| VLDL-C, mmol/L | 0.99 ± 0.53 | 1.04 ± 0.62 | 0.696 |
| Atherogenic coefficient (AC) | 4.48 ± 2.78 | 4.12 ± 1.66 | 0.446 |
| Circulating immune complexes (CIC), units | 59.46 ± 34.14 | 60.20 ± 33.72 | 0.898 |
| T-lymphocytes, % (CD3$^+$) | 112.85 ± 45.63 | 112.99 ± 44.98 | 0.986 |
| T-helper cells, % (CD4$^+$) | 47.01 ± 8.14 | 46.71 ± 8.01 | 0.823 |
| T-suppressor cells, % (CD8$^+$) | 26,24 ± 1.91 | 26.39 ± 4.82 | 0.863 |
| Activated T-lymphocytes, % (CD25$^+$) | 17.32 ± 9.59 | 16.04 ± 8.23 | 0.399 |
| Immunoregulatory index (CD4$^+$/CD8$^+$) | 7.21 ± 5.28 | 7.20 ± 5.10 | 0.964 |
| Blood urea, mmol/L | 5.98 ± 1.70 | 5.81 ± 1.43 | 0.528 |
| Creatinine, mmol/L | 97.07 ± 24.00 | 98.01 ± 17.93 | 0.802 |
| Cystatin C, mg/L | 124.81 ± 22.47 | 127.82 ± 36.53 | 0.548 |
| Leptin, ng/mL | 21.70 ± 7.61 | 25.68 ± 11.93 | 0.011 |
| NGAL, pg/mL | 13.95 ± 1.69 | 20.66 ± 3.74 | 0.0001 |
| NT-proBNP, pg/mL | 447.76 ± 120.80 | 447.25 ± 134.94 | 0.981 |
| Insulin, μIU/mL | 24.79 ± 16.15 | 18.96 ± 19.98 | 0.009 |
| Aortic root diameter, cm | 3.63 ± 0.33 | 3.56 ± 0.30 | 0.631 |
| Left atrial diameter, cm | 4.07 ± 0.46 | 4.04 ± 0.49 | 0.610 |

| Parameter | NGAL < 16.35 n = 68 | NGAL > 16.35 n = 68 | p-value |
|---|---|---|---|
| Right atrial diameter, cm | 4.06 ± 0.25 | 4.03 ± 0.28 | 0.622 |
| LVEDD, cm | 5.26 ± 0.76 | 5.25 ±0.75 | 0.926 |
| LVESD, cm | 3.82 ± 0.53 | 3.75 ± 0.56 | 0.454 |
| Right ventricular diameter, cm | 1.52 ± 0.08 | 1.54 ± 0.20 | 0.485 |
| IVST, cm | 1.29 ± 0.08 | 1.29 ± 0.07 | 0.780 |
| LVPWT, cm | 1.22 ± 0.04 | 1.23 ± 0.05 | 0.529 |
| LVMM, g | 235.52 ± 30.91 | 24.62 ± 39.06 | 0.888 |
| LVMMI, g/m$^2$ | 130.71 ± 16.74 | 128.06 ± 15.68 | 0.302 |
| RWT | 0.50 ± 0.05 | 0.51 ± 0.05 | 0.330 |
| LVEF, % | 57.47 ± 3.67 | 52.74 ± 5.78 | 0.947 |
| VE, cm/s | 63.07 ± 8.33 | 63.50 ± 8.51 | 0.751 |
| VA, cm/s | 78.67 ± 8.33 | 78.08 ± 9.25 | 0.705 |
| VE/VA | 0.82 ± 0.12 | 0.83 ± 0.13 | 0.726 |
| IVRT, ms | 112.26 ± 13.21 | 110.83 ± 11.94 | 0.506 |

*Notes:*
abbreviations see Table 1.

metabolic inflammation contributes to elevated NGAL levels. In addition, the group with higher NGAL levels showed a statistically significant decrease in insulin concentration, suggesting changes in insulin secretion or tissue insulin sensitivity. This pattern may indicate more complex disturbances in carbohydrate metabolism that do not always directly correlate with HbA1c levels.

As expected, the NGAL level itself differed significantly between the groups, confirming the correctness of their allocation and the validity of the chosen stratification approach.

At the same time, most of the other investigated parameters, including lipid profile indices, renal function markers, immune status parameters, and echocardiographic characteristics, did not show statistically significant differences between the groups. This may indicate that, at this stage, an increase in NGAL is not accompanied by pronounced changes in the structural and functional state of the heart or in the basic indicators of the immune response, or alternatively, that it reflects earlier, subclinical abnormalities.

Thus, the results indicate that elevated NGAL levels are primarily associated with metabolic changes, particularly the adipokine profile and insulin homeostasis, which may be important for understanding its role as an early biomarker of cardiometabolic risk.

Against the background of the identified intergroup differences, the next stage of the study involved an analysis of the independent determinants of NGAL levels using stepwise multiple regression analysis.

Influence of various factors on NGAL levels in patients with arterial hypertension: stepwise regression analysis ($R^2 = 0.31$, $F = 3.15$, $p < 0.0139$)

In patients with AH, the developed model was statistically significant ($R^2 = 0.31$; $F = 3.15$; $p < 0.0139$) and demonstrated moderate explanatory power for NGAL variability. Independent predictors included parameters of carbohydrate metabolism, renal function, and hemodynamic indices. In particular, the strongest inverse association of NGAL was observed with HbA1c levels (Fig. 1) and urea concentrations (Fig. 2), while strong relationships were also observed with insulin levels and diastolic blood pressure, suggesting the complex nature of the metabolic regulation of this biomarker. The negative association with insulin may potentially reflect the relationship between NGAL and insulin resistance, whereas the association with renal function parameters confirms its role as a marker of early nephropathic changes.

**Effect of various factors on NGAL levels in patients with arterial hypertension: stepwise regression analysis ($R^2 = 0.31$, $F = 3.15$, $p < 0.0139$)**

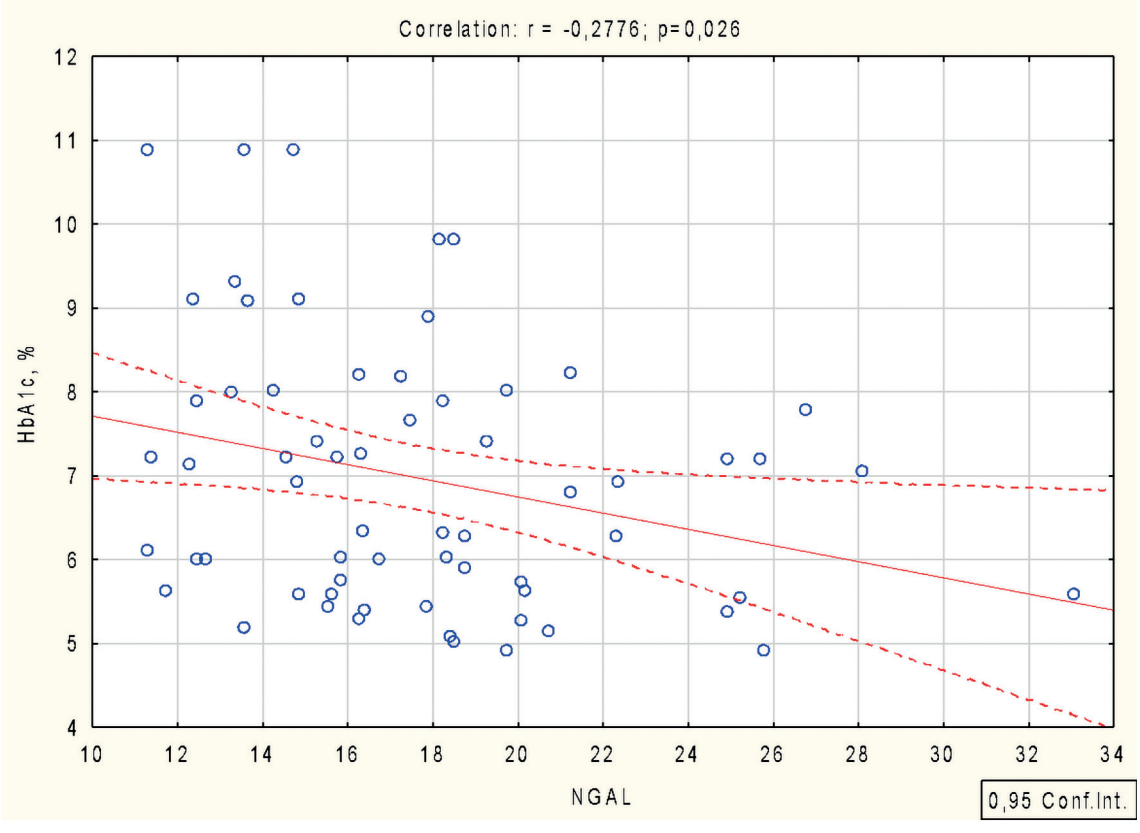


Fig. 1. Correlation between NGAL and HbA1c levels in patients with arterial hypertension.

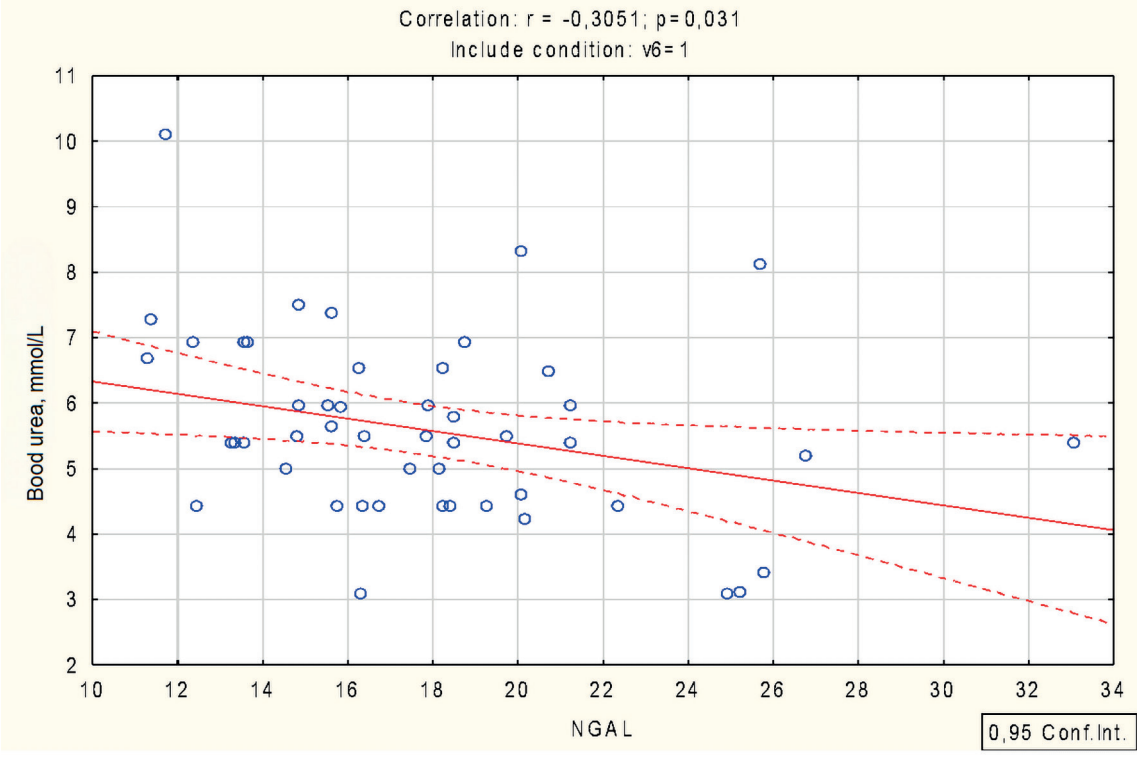


Fig. 2. Correlation between NGAL and blood urea levels in patients with arterial hypertension.

Y(NGAL) = 47.46 – 0.99HbA1c (X1) – 0.90Urea (X2) – 0.06Insulin (X3) – 2.80RA (X4) – 0.07DBP (X5)

**Effect of various factors on NGAL levels in the examined patients with arterial hypertension and type 2 diabetes mellitus (stepwise regression analysis) ($R^2 = 0.37$, $F = 1.99$, $p < 0.035$).**

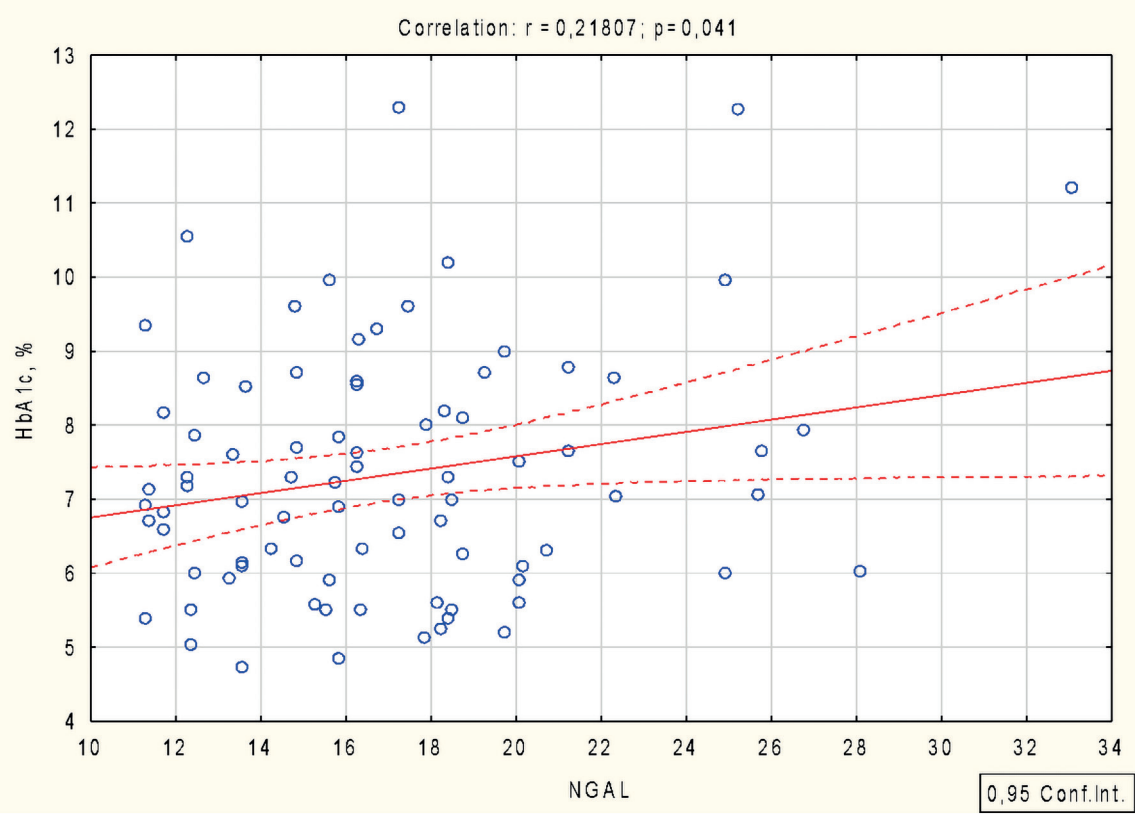


Fig. 3. Correlation between NGAL and HbA1c levels in patients with AH+T2DM.
Y(NGAL) = –7.51 + 0.57HbA1c (X1) + 9.38IVST (X2) – 0.29CD25 (X3) + 1.46LDL-C (X4) + + 0.10VE (X5) – 0.15CD4 (X6) + 21.13LV RWT (X7) + 0.23LVEF (X8) + 0.13BMI (X9) + 0.04LVMM (X10)

In the group of patients with concomitant AH and T2DM, the model demonstrated somewhat greater explanatory power ($R^2 = 0.37$; $F = 1.99$; $p < 0.035$), indicating a more pronounced multifactorial influence on NGAL levels. The model structure included both metabolic factors (HbA1c, BMI, lipid parameters) and immunological markers ($CD25^+$, $CD4^+$), as well as echocardiographic parameters, including indices of diastolic function and left ventricular remodeling. A direct correlation between HbA1c and NGAL levels was identified ($r = 0.218$; $p = 0.041$) (Fig. 3), suggesting a tendency toward increased NGAL levels with worsening glycemic control. In the stepwise regression analysis, HbA1c showed a positive association with NGAL variability ($\beta = 0.22$; $B = 0.57$; $p = 0.056$), suggesting a possible influence of chronic hyperglycemia on NGAL levels. The observed associations indicate NGAL's integrative role as a marker reflecting the interactions among metabolic disturbances, immune activation, and structural and functional myocardial changes.

Of note, in patients with comorbid pathology, the spectrum of predictors was broader, including indicators of immune response and cardiac remodeling, suggesting systemic inflammation and cardiovascular remodeling as mechanisms underlying elevated NGAL levels.

All patients with T2DM received contemporary standard glucose-lowering therapy, including a combination of metformin (1000 mg/day) and a sodium–glucose cotransporter 2 inhibitor (dapagliflozin 10 mg/day), in accordance with current recommendations for the management of patients at high cardiometabolic risk. This approach is clinically justified given the well-established cardio- and nephroprotective effects of these agents. The study had an observational design and did not include a comparative analysis of different antidiabetic treatment

regimens; however, the relative uniformity of therapy allowed minimization of the impact of therapeutic heterogeneity on the studied parameters. Importantly, in the performed regression analysis, independent associations between NGAL levels and parameters of carbohydrate metabolism, particularly HbA1c and insulin, were preserved, indicating their independent pathophysiological significance regardless of the pharmacotherapy used.

The results of the stepwise regression analysis confirm that NGAL levels are shaped by a complex of interrelated factors, and that its clinical significance increases under conditions of concomitant AH and T2DM, where it may be considered an integral biomarker of cardiometabolic risk and subclinical target organ damage.

In summary, the comprehensive analysis performed in this study demonstrated consistency between descriptive and analytical approaches to the assessment of NGAL levels. The identified associations with metabolic parameters, together with the results of regression modelling, indicate that NGAL reflects not isolated abnormalities but rather the integrated impact of interrelated pathophysiological processes. This is particularly evident in patients with concomitant AH and T2DM, in whom a more complex profile of determinants is formed, including metabolic, immunological, and cardiohemodynamic components.

In our previous work, we demonstrated that patients with comorbid AH and T2DM exhibit significantly elevated NGAL levels, which correlate with early markers of renal damage, supporting its role as a biomarker of subclinical renal dysfunction [12]. The present findings are consistent with these observations and further expand the understanding of NGAL as an integral biomarker of cardiometabolic risk.

Furthermore, the obtained data are conceptually aligned with the current paradigm of the renal–metabolic continuum, according to which NGAL (lipocalin-2) and Cys C act not only as early markers of tubulointerstitial kidney injury but also as integrative indicators of metabolic dysregulation, including insulin resistance and albuminuria, reflecting the early stages of chronic kidney disease progression [13].

Thus, the present results not only confirm the findings of other researchers [14–17], but also extend current understanding of the pathophysiological role of NGAL as an integral biomarker of early target-organ damage and cardiometabolic risk, supporting its further investigation in the context of patient stratification and disease progression prediction.

## CONCLUSIONS

1. Patients with concomitant arterial hypertension and type 2 diabetes mellitus were found to have significantly more pronounced metabolic, immunological, and cardiohemodynamic disturbances compared with patients with isolated arterial hypertension. This was manifested by significantly increased body mass index, total cholesterol, triglyceride levels, and atherogenic coefficient ($p < 0.01$), as well as activation of the cellular immune response (increased $CD3^+$, $CD4^+$, $CD8^+$, and $CD25^+$; $p < 0.0001$) and more pronounced myocardial remodeling accompanied by reduced left ventricular systolic function ($p < 0.0001$).
2. The level of neutrophil gelatinase-associated lipocalin (NGAL) did not differ significantly between patients with arterial hypertension and those with arterial hypertension and type 2 diabetes mellitus ($p > 0.05$), suggesting its relative independence from diabetes at this stage of the disease. At the same time, stratification according to NGAL level revealed significant associations with metabolic parameters, namely increased leptin levels ($p = 0.011$) and decreased insulin levels ($p = 0.009$), suggesting a relationship between NGAL and disturbances in adipokine regulation and insulin homeostasis.
3. According to a stepwise multiple regression analysis, NGAL levels in patients with arterial hypertension were determined by a combination of metabolic and functional parameters, including glycated haemoglobin, urea, insulin, and diastolic blood pressure ($R^2 = 0.31$; $p < 0.0139$). In patients with concomitant arterial hypertension and type 2 diabetes mellitus, the model demonstrated greater explanatory power ($R^2 = 0.37$; $p < 0.035$) and included a broader spectrum of deter-

minants, namely metabolic, immunological ($CD25^+$, $CD4^+$), and echocardiographic parameters (indices of left ventricular remodeling and function).

4. The obtained data confirm that NGAL is an integral biomarker whose level is shaped by a complex of interrelated pathophysiological processes. Its clinical significance increases in the presence of comorbidities, where it reflects interactions among metabolic, immune, and cardiac disturbances, making NGAL a promising marker of early subclinical target-organ damage and a tool for cardiometabolic risk stratification.

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## NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) AS A MARKER OF RENAL DAMAGE IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES MELLITUS


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**Introduction.** The combination of arterial hypertension (AH) and type 2 diabetes mellitus (T2DM) is associated with an increased risk of target organ damage, particularly renal injury, which necessitates the search for early biomarkers of subclinical damage. Neutrophil gelatinase-associated lipocalin (NGAL) is considered a promising marker of early nephropathic and cardiometabolic changes; however, its relationships with clinical and metabolic parameters in AH, especially when combined with T2DM, remain insufficiently studied.

**Aim.** To investigate clinical, laboratory, immunological, biochemical, and hemodynamic factors and to determine their association with NGAL levels in patients with arterial hypertension with and without type 2 diabetes mellitus.

**Materials and Methods.** The study included 136 patients with AH, divided into two groups: the first group comprised patients with isolated AH (n = 64), and the second group comprised patients with AH combined with T2DM (n = 72). The control group consisted of 20 apparently healthy individuals. All participants underwent clinical, biochemical, immunological, and instrumental examinations, including assessment of lipid profile,

HbA1c, insulin, cystatin C, leptin, NT-proBNP, and NGAL by ELISA; evaluation of lymphocyte subpopulations, renal function indices, and echocardiographic parameters. Statistical analysis was performed using correlation and stepwise multiple regression.

**Results.** Patients with combined AH and T2DM demonstrated a more unfavourable metabolic profile, with increased BMI, total cholesterol, triglycerides, and atherogenic coefficient, as well as activation of the cellular immune response and more pronounced myocardial remodeling. NGAL levels did not differ significantly between the groups ($p > 0.05$). Stratification by the median NGAL level showed a significant increase in leptin ($p = 0.011$) and a decrease in insulin ($p = 0.009$) in patients with higher NGAL values. According to stepwise regression analysis, independent predictors of NGAL in patients with AH were HbA1c, urea level, insulin level, and diastolic blood pressure ($R^2=0.31$; $p<0.0139$). In patients with AH + T2DM, the model demonstrated greater explanatory power ($R^2 = 0.37$; $p < 0.035$) and included metabolic, immunological, and echocardiographic parameters.

**Conclusions.** NGAL levels in patients with arterial hypertension are shaped by a complex set of metabolic, immunological, and hemodynamic factors. In the presence of concomitant type 2 diabetes mellitus, the spectrum of determinants expands to include indicators of myocardial remodeling and immune activation. NGAL is associated with disturbances in adipokine regulation and insulin homeostasis and may be considered an integral biomarker for early subclinical target-organ damage and for cardiometabolic risk stratification.

Keywords: arterial hypertension, type 2 diabetes mellitus, NGAL, cardiometabolic risk, HbA1c, insulin.

## ЛІПОКАЛІН, АСОЦІЙОВАНИЙ З ЖЕЛАТИНАЗОЮ НЕЙТРОФІЛІВ (NGAL), ЯК МАРКЕР НИРКОВОГО УШКОДЖЕННЯ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ ТА ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

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**Вступ.** Поєднання артеріальної гіпертензії (АГ) та цукрового діабету 2 типу (ЦД2) асоціюється з підвищеним ризиком ураження органів-мішеней, зокрема нирок, що потребує пошуку ранніх біомаркерів субклінічного ушкодження. Ліпокалін, асоційований з желатиназою нейтрофілів (NGAL), розглядається як перспективний маркер ранніх нефропатичних та кардіометаболічних змін, однак його взаємозв'язки з клініко-метаболічними показниками при АГ, особливо у поєднанні з ЦД2, залишаються недостатньо вивченими.

**Мета.** Дослідити клініко-лабораторні, імунологічні, біохімічні та гемодинамічні чинники і визначити їх взаємозв'язок із рівнем NGAL у пацієнтів з артеріальною гіпертензією за наявності та відсутності цукрового діабету 2 типу.

**Матеріали і методи.** У дослідження включено 136 пацієнтів з АГ, які були розподілені на дві групи: до першої групи увійшли хворі з ізольованою АГ (n = 64), до другої групи – пацієнти з АГ у поєднанні з ЦД2 (n = 72). Контрольну групу становили 20 практично здорових осіб. Усім обстеженим проводили клінічне, біохімічне, імунологічне та інструментальне дослідження, включаючи визначення ліпідного спектра, HbA1c, інсуліну, цистатину С, лептину, NT-proBNP та NGAL методом ІФА, оцінку субпопуляцій лімфоцитів, показників функції нирок та ехокардіографічних параметрів. Статистичний аналіз виконували з використанням кореляційного та покрокового множинного регресійного аналізу.

**Результати.** У пацієнтів із поєднанням АГ та ЦД2 виявлено більш несприятливий метаболічний профіль із підвищенням ІМТ, загального холестерину, тригліцеридів і коефіцієнта атерогенності, а також активацію клітинної ланки імунітету та більш виражене ремоделювання міокарда. Рівень NGAL не відрізнявся між групами ($p > 0,05$). Стратифікація за медіанним рівнем NGAL показала достовірне підвищення лептину ($p = 0,011$) та зниження інсуліну ($p = 0,009$) у пацієнтів із вищими значеннями NGAL. За результатами покрокового регресійного аналізу у хворих з АГ незалежними предикторами NGAL були HbA1c, рівень сечовини, інсуліну та діастолічний артеріальний тиск ($R^2 = 0,31$; $p < 0,0139$). У пацієнтів із АГ+ЦД2 модель мала більшу пояснювальну здатність ($R^2 = 0,37$; $p < 0,035$) і включала метаболічні, імунологічні та ехокардіографічні показники.

**Висновки.** Рівень NGAL у пацієнтів з артеріальною гіпертензією формується під впливом комплексу метаболічних, імунологічних та гемодинамічних факторів. При поєднанні артеріальної гіпертензії з цукровим діабетом 2 типу спектр детермінант розширюється та включає показники ремоделювання міокарда й імунної активації. NGAL асоціюється з порушеннями адипокінової регуляції та інсулінового гомеостазу і може розглядатися як інтегральний біомаркер раннього субклінічного ураження органів-мішеней та стратифікації кардіометаболічного ризику.

Ключові слова: артеріальна гіпертензія, цукровий діабет 2 типу, NGAL, кардіометаболічний ризик, HbA1c, інсулін.