В качестве фармакологической активной субстанцией в лечебных шампунях от перхоти используют кетоконазол, климбазол, пироктоноламин, соли цинка и селена, сера, пиритион цинка, салициловая кислота, пириктон, октопирокс, деготь, пироктоналамин, ундециленамидопропил триммониумметосульфат.

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CARDIAC REMODELING AND URINARY NAG LEVELS IN PATIENTS WITH CHF OF ISCHEMIC ORIGIN.

Abstract. The relationship between cardiac remodeling in patients with CHF with glomerular-tubular changes in the kidneys is still insufficiently studied, and the question of the relationship of urinary NAG with parameters of cardiac remodeling remains open. **The Aim:** To investigate the relationship between the biomarker of tubulo-interstitium NAG in urine with parameters of cardiac remodeling in patients with CHF of ischemic origin.

Materials and methods. The study enrolled 50 patients with CHF of ischemic origin II-IV FC. Patients were divided into 2 groups depending on the concentration of NAG. In the first group (n=29) the NAG concentration was greater than 37.7 ng/ml, in the second (n=21)- less than 37.7 ng/ml. Patients with CHF of ischemic origin without and with tubulo-interstitial injury (according to the concentration of NAG in urine) probably didn't differ in age (p=0,201), height (p=0,246), weight (p=0,690), body surface area (p=0.071). All patients underwent Doppler echocardiography on a device "Esaote MyLab Eight" (Italy) and enzyme-linked immunosorbent assay for urinary NAG (SEA 069 Hu, Cloud-Clone Corp., USA), sensitivity <0.54 ng/ml.

Results. The mean urine concentration of NAG in the first group was 48 (46; 88) ng/ml, in the second group - 22 (16; 29) ng/ml. Groups of the CHF patients with elevated and normal levels of urinary NAG didn't differ statistically in creatinine (0.110±0.023 mmol/l vs. 0.110±0.018 mmol/l (p=0.883)); glomerular filtration rate by CKD-EPI (p=0.791), MDRD (p=0.976), and Cockcroft-Gault (p=0.054), linear and volumetric parameters of the left and right ventricles, left atrium, wall thickness, and myocardial mass index, types of LV geometry, parameters of systolic and diastolic LV function. The vast majority of patients in both groups had eccentric hypertrophy (69% vs. 62%; p=0.608) and diastolic dysfunction by type of relaxation disorder (45% vs. 57%; p=0.406).

Conclusion. There are no significant changes in the structure and function of the heart in patients with CHF of ischemic origin associated with changes in the concentration of urinary NAG. Urinary NAG didn't show associative pathogenetic links with cardiac remodeling in patients with CHF of ischemic origin.

Key words: Cardiac remodeling, Chronic Heart Failure, urinary NAG, Cardiorenal syndrome, diastolic dysfunction.

Introduction. Cardiorenal syndromes (CRS) describe concomitant bidirectional heart and kidney dysfunction in which one organ initiates, prolongs perpetuates, and / or accelerates the deterioration of another. Classification, diagnosis and treatment of CRS with heart failure remains the focus of modern research [18].

Chronic heart failure (CHF) has been shown to lead to chronic kidney disease (CKD). Usually CHF and CKD coexist, and it is difficult to determine which of the two disease processes is primary. Damage to the renal tubules is observed in patients with CHF due to tubulo-interstitial injury by renal tissue hypoperfusion or due to a damaged glomerular filtration barrier [3].

The Digitalis Investigation Group trial found subclinical CKD in 45% of patients with CHF, which was associated with a higher level of hospitalization and mortality[7]. Renal dysfunction (RD) in heart failure causes adverse effects and often restricts aggressive diuretic therapy. The applying of cardiorenal biomarkers is useful not only in prognosis but also in optimizing treatment tactics, depending on the types of CRS and the phenotype of CHF [4].

Modern cardiorenal biomarkers provide valuable information on early signs of heart and kidney damage, recovery, and long-term consequences. Determination of creatinine changes falls to meet the criteria for early diagnosis of acute kidney injury (AKI) due to a significant time lag of 24 to 48 hours, and dependence on muscle mass and age of patients[5], which makes it impossible to carry out timely corrective therapeutic measures. [13].

N-acetyl-β-D-glucosamidase (NAG) - is a lysosomal enzyme with a molecular weight of 130-140 kDa, derived from proximal tubular cells, is not filtered through the glomeruli and indicates damage to the proximal tubules of the kidneys when detected in urine. Urine NAG is considered a relatively simple, inexpensive, rapid, and noninvasive reliable marker for detecting and monitoring renal tubular damage / function in a variety of settings. Urine NAG is evaluated in patients with acute kidney impairment, used to predict deterioration in renal function and mortality in patients with CHF. Cardiorenal biomarkers, especially NAG, are associated with higher mortality in patients with CHF, even with preserved glomerular filtration rate (GFR)[6]. However, the diagnostic potential of NAG to identify a particular phenotype of cardiorenal syndrome is limited because NAG levels also increase in diabetes mellitus and hypertension[14].

As a result, the issue of an involvement of tubulo-interstitial injury marker NAG in urine in the processes of cardiac remodeling in patients with chronic heart failure remains open.

The aim: To investigate the relationship of the biomarker of tubulo-interstitial injury NAG in urine with parameters of heart remodeling in patients with CHF of ischemic origin.

Materials and methods: The study was performed on the clinical basis of the Department of Propaedeutics of Internal Medicine, Radiation Diagnostics and Radiation Therapy ZSMU in the cardiology department of the City Hospital №6, Zaporizhzhya, in accordance with the standards of good clinical practice and principles of good clinical practice. The study protocol was approved by the Ethics Committee of Zaporizhia State Medical University. After signing the informed consent, 50 patients with CHF of ischemic genesis II-IV FC were enrolled into the study. The diagnosis of CHF of ischemic origin was established in accordance with the Recommendations for the diagnosis and treatment of chronic heart failure (2017) of the Association of Cardiologists of Ukraine and the Ukrainian Association of Heart Failure Specialists [16]. Doppler echocardiographic examination was performed on the device "Esaote MyLab Eight" (Italy) according to the standard method with the definition of baseline parameters [17]. Patients were divided into 2 groups depending on the concentration of NAG. For the level of NAG in urine, the cut-off point was> 37.7 ng/ml (area under the ROC curve 0.649; 95% CI 0.501-0.779; p = 0.133), sensitivity 63.6%, specificity 69.2%. In the first group (n = 29) the concentration of NAG was greater than 37.7 ng/ml, in the second (n = 21) - less than 37.7 ng/ml. The average concentration of NAG in urine in the first group was 48 (46; 88) ng/ml, in the second group - 22 (16; 29) ng/ml. Patients with CHF of ischemic origin with urine NAG greater or less than 37.7 ng / ml didn't differ significantly in age (p = 0.201), height (p = 0.246), weight (p = 0.690), body surface area (p = 0.071). The level of NAG in urine (ng/ml) was analyzed using an ELISA kit (enzyme-linked immunosorbent assay) (SEA 069 Hu, Cloud-Clone Corp., USA) following the manufacturer's instructions based on Diagnostic Center "Medlife-Bio" (Director - Ostashinskaya O.S.). The sensitivity was <0.54 ng/ml. The measurement range of the kit was 1.56 - 100 ng/ml with a variation of the internal analysis coefficient <10%.

Statistical processing of the material was performed using the software package Statistica 13.0 (StatSoft, USA), license number JPZ8041382130ARCN10-J. The normality of the distribution of quantitative traits was analyzed using the Shapiro – Wilk test. The parameters that had a normal distribution are given as the arithmetic mean and standard deviation (M ± SD). For indicators that had a distribution that differed from normal, descriptive statistics are given as the median and lower and upper quartiles - Me (Q25; Q75). Quantitative indicators in the groups were compared using Student's criteria (for the normal distribution of traits), Mann-Whitney (for the distribution of traits other than normal). The critical value of NAG was established by ROC analysis depending on the cumulative endpoint (death, ACS, stroke, gradient HF). The difference at p <0.05 was considered statistically significant. All tests were bilateral.

Results: We didn't find a significant difference between linear and volumetric parameters of the left and right ventricles, left atrium in groups of patients with CHF with and without injury of the tubulo-

interstitium depending on the concentration of NAG. The groups of patients with CHF with elevated and normal levels of NAG in urine didn't differ statistically in terms of wall thickness and left ventricular myocardial mass index. There were also no differences in the proportion of types of LV geometry (table 1). The vast majority of patients in both groups had eccentric hypertrophy (69% vs. 62%, (p = 0.0.608)).

Table. 1.

Types of LV geometry in patients with CHF with normal and elevated levels of NAG in urine

Types of LV geometry	Group of patients with CHF with a normal level of NAG in the urine, n=21	Group of patients with CHF with an elevated level of NAG in the urine, n=29	p
Normal geometry	10 % (3)	10 % (2)	1.0
Eccentric hypertrophy	69 % (20)	62 % (13)	0,608
Concentric hypertrophy	14 % (4)	24 % (5)	0,370
Eccentric remodeling	7 % (2)	5 % (1)	0,773
Concentric remodeling	0 % (0)	0 % (0)	1,0

Parameters of systolic function of the left ventricle (LV EF 50.71 ± 17.10% vs. 55.55 ± 17.73%, (p = 0.263); dP/dt 893.50 ± 505.40 mm Hg vs. 752,90 ± 280.49 mm Hg (p = 0.281); S 7.64 ± 3.00 cm/s vs. 5.50 ± 1.29 cm/s, (p = 0.203); S lat 8.75 ± 1.71 cm/s vs. 5.00 ± 1.30 cm/s, (p = 0.467); TEI LV 0.49 ± 0.19 ppm vs. 0.63 ± 0.28 ppm, (p = 0.432) in patients with CHF of ischemic origin with tubulo-interstitial injury (according to NAG in urine) didn't differ significantly from similar parameters in patients with CHF of ischemic origin without tubulo-interstitial injury. Groups of patients with CHF with elevated and normal levels of NAG in urine didn't have a statistically significant difference in LV diastolic function (E/e´ medial 13.86 ± 7.02 vs. 11.46 ± 6.13 (p = 0.829); E/e´ lat 8.37 ± 5.17 vs. 7.36 ± 2.27, (p= 0.992); mean E/e ´ 10.13 ± 6.59 vs. 8.65 ± 3.24, (p = 0.753); e´ medial 6.66 ± 2.59 cm/s vs. 5.81 ± 2.02 cm/s, (p = 0.149); e´ lateral 9.71 ± 3.48 cm/s vs. 8.10 ± 2.00 cm/s (p = 0.130)). The vast majority of the CHF patients with regardless of the level of urinary NAG had diastolic dysfunction by type of relaxation disorder (45 % vs. 57 % (p=0,406)), with a slight predominance of the proportion of "pseudonormal" diastolic filling of the left ventricle (38 % vs. 19 % (p=0,154)), in the CHF patients with elevated levels of NAG in the urine. (Table 2)

Table. 2.

Types of disorders of diastolic filling of the left ventricle in patients with CHF with normal and elevated levels of NAG in the urine.

Types of diastolic dysfunction of LV	Group of patients with CHF with a normal level of NAG in the urine, n=21	Group of patients with CHF with an elevated level of NAG in the urine, n=29	p
None	0 % (0)	0 % (0)	1,0
Type of relaxation disorder	45 % (13)	57 % (12)	0,406
"Pseudonormal" type	38 % (11)	19 % (4)	0,154
Restrictive type	17 % (5)	24 % (5)	0,544

Groups of CHF patients with elevated and normal levels of NAG in urine also didn't differ statistically in creatinine concentration (0.110± 0.023 mmol/l vs. 0.110 ± 0.018 mmol/l, (p = 0.883)); glomerular filtration rate by CKD-EPI (p = 0.791), MDRD (p = 0.976), and Cockcroft-Gault (p = 0.054).

Therefore, our research didn't identify significant changes in the structure and function of the heart in patients with CHF of ischemic origin associated with changes in the concentration of NAG in the urine. Like KIM-1, urinary NAG didn't show associative pathogenetic links with cardiac remodeling in patients with CHF of ischemic origin.

Discussion: Markers of urinary tubulointerstitial injury, such as kidney injury molecule 1 (KIM-1), neutrophilic gelatinase-associated lipocalin (NGAL), and NAG, are new urinary biomarkers that were initially identified and evaluated in patients with acute kidney injury (AKI). The Funabashi S. (2020) research found that the level of NAG in the urine during hospitalization can identify patients at high risk of further adverse events. These findings highlight the diagnostic role of NAG in urine in determining the long-term prognosis of patients with acute HF [6].

The GALLANT study showed that urinary NAG levels were significantly related to prognosis in CHF, whereas NGAL showed prognostic value along with natriuretic peptides in acute HF [12].

Also, the GISSI-HF study showed that the determination of NAG in urine can be useful in the

early diagnosis of tubulo-interstitial injury in patients with CHF with mild renal dysfunction(RD), which in such category of patients has an unfavorable prognostic value. Patients with RD and high NAG levels were twice as likely to die within 1.2 years compared with patients with low NAG and normal renal function [5].

Previous investigations of urinary NAG have focused on the diagnostic and prognostic potential of this marker in patients with acute kidney impairment. Urine NAG as a prognostic marker in people with chronic diseases has also been studied in patients with heart failure and diabetes. In two clinical trials in patients with CHF and normal renal function, urinary NAG was associated with left ventricular dysfunction and predicted all-cause mortality and rehospitalization in congestive heart failure [15].

According to Jungbauer C. G. (2016), increased NAG excretion was associated with CKD progression in patients with heart failure. The marker of tubulo-interstitial injury - NAG in urine was significantly increased in patients with symptoms of heart failure with NYHA above 2 functional class (FC) (against the control group P = 0.001, against NYHA ≤2 FC, P = 0.05). Patients with significantly decreased LV function (EF <40%) had higher NAG concentrations compared with patients with mild left ventricular dysfunction (LVD; EF ≥ 40%, P, 0.05)[8].

In the research [4], the authors concluded that in patients with CHF, NAG levels were significantly higher compared to healthy controls. In addition, patients with more significant LV dysfunction (EF <40%) have higher NAG levels compared with preserved LV EF. Although the increase in NAG levels is more pronounced in patients with HF and concomitant RD, defined as a decrease in GFR <60 ml / min / 1.73 m2, this marker was also increased in patients with HF without renal dysfunction.

In research Damman K. et al. (2013) [5] in 90 patients with heart failure, the level of NAG in the urine correlated with an increase in the level of NT-proBNP, an increase in the number of hospitalizations due to the progression of HF decompensation.

There is an evidence that urinary NAG is associated not only with nephropathy but also with vascular complications in type 2 diabetes, including retinopathy and macrovascular disease. In the investsgation of Kim S. R. (2017), the level of NAG correlated with an increase in the thickness of the intima-media complex of the carotid arteries, which proves the importance of this marker in the diagnosis of atherosclerosis in patients with type 2 diabetes [10].

A research by Allgaier R. (2020) showed the presence of a direct correlation between NAG and NT-proBNP concentration, and the functional class of CHF. The NAG marker has also been shown to be an independent predictor of ventricular arrhythmias, including heart failure [1].

In Diabetes Control and Complications Trial [9] the baseline of urinary NAG levels independently predicted macro- and microalbuminuria, identifying subjects with type 1 diabetes with a risk of developing nephropathy.

We didn't confirm the association of NAG in urine with cardiac remodeling, and although it is a recognized marker of acute renal tubulo-interstitial injury, it hasn't been shown to be clinically relevant in patients with CHF of ischemic origin in terms of structure and heart function.

In our exploration, no probable structural and geometric changes in the heart in patients with CHF of ischemic origin associated with changes in the concentration of NAG in the urine were found. The vast majority of patients in both groups had eccentric LV hypertrophy. Groups of patients with CHF with elevated and normal levels of NAG in urine didn't have a statistically significant difference in diastolic function, and the vast majority of patients with CHF with regardless of the level of NAG in urine had diastolic dysfunction by type of relaxation disorder, with a slight predominance of the proportion of "pseudonormal" diastolic filling of the left ventricle in patients with CHF with elevated levels of NAG in the urine.

The Bio-SHiFT trial demonstrated the role of NAG and KIM-1 as markers for determining the degree of renal tubular injury. In patients who reached the cumulative endpoint, NAG on average showed higher baseline levels, which increased even more as the endpoint approached. In patients who didn't reach the endpoints, NAG levels were lower and decreased during follow-up. NAG has also been shown to be a marker of tubular dysfunction that demonstrates early onset, while KIM-1 may serve as a quantitative marker of tubulo-interstitial injury, proving its greater prognostic value in CHF [3].

According to B. Beker (2018), the increase in NAG in urine in critically ill patients is a predictor of both AKI (AUC = 0.62) and mortality (AUC = 0.66). It was proved that patients with prerenal AKI had higher concentrations of NAG in the urine than patients with other types of AKI [2].

In the investigation by Lobato G.R. (2017) failed to demonstrate an association between urinary NAG levels and CKD progression or the development of adverse renal events. According to the authors, NAG doesn't work as well as KIM-1 or NGAL as a marker of progressive chronic kidney disease, but has proven to be an indicator of acute kidney injury after cardiac surgery [11].

In our exploration, the parameters of left ventricular systolic function in patients with CHF of ischemic origin with tubulo-interstitial injury (according to KIM-1 in urine) didn't differ significantly from similar parameters in patients with CHF of ischemic genesis without tubulo-interstitial injury.

Therefore, our research didn't identify significant changes in the structure and function of the heart in patients with CHF of ischemic origin associated with changes in the concentration of NAG in the urine. Like KIM-1, urinary NAG didn't show associative pathogenetic links with cardiac remodeling in patients with CHF of ischemic origin.

Conclusion: There are no significant changes in the structure and function of the heart in the CHF

patients of ischemic origin associated with changes in the concentration of NAG in the urine.

Conflicts of interest: authors have no conflict of interest to declare.

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