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NESFATIN-1 ACTIVITY IN THE BLOOD SERUM IN PATIENTS WITH CHRONIC HEART FAILURE OF ISCHEMIC ORIGIN AGAINST THE BACKGROUND OF TYPE 2 DIABETES MELLITUS AND OBESITY

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ABSTRACT

The aim: To study the nesfatin-1 activity in the blood serum of patients with chronic heart failure (CHF) of ischemic origin against the background of such metabolic disorders as type 2 diabetes mellitus (T2DM) and obesity.

Materials and methods: 154 patients with CHF were examined, and divided into 4 groups, according to the presence of metabolic disorders. Group 1 included patients with CHF on the background of coronary heart disease (CHD) and T2DM and obesity (n=42). The second group consisted of patients with heart failure on the background of CHD with concomitant T2DM (n=46), the third group - with concomitant obesity (n=36), the fourth group was formed from patients with signs of heart failure of ischemic origin without metabolic disorders (n=30). The control group (CG) included 30 practically healthy persons of comparable age.

Results: The mean level of serum nesfatin-1 was 1.64±0.27 ng/mL in the CHF group, 0.342±0.19 ng/mL in the CHF + T2DM + obesity group, 1.06±0.36 ng/mL in the obese + CHF group, 0.96±0.27 ng/mL in the CHF + T2DM group and 2.98±0.38 ng/mL in the CG. Significant correlation was found between the serum nesfatin-1 level and BMI ($r=-0.34$, $p<0.05$), HOMA ($r=-0.54$, $p<0.05$), insulin ($r=-0.41$, $p<0.05$). No significant correlation was found between the serum nesfatin-1 level and blood glucose level ($r=0.13$, $p=0.65$).

Conclusions: Thus, nesfatin-1 may play a significant role in the pathogenesis of both weight-related abnormalities and type 2 diabetes mellitus in patients with chronic heart failure of ischemic origin.

KEY WORDS: nesfatin-1, chronic heart failure, obesity, type 2 diabetes mellitus

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INTRODUCTION

In recent years, much attention has been paid to the study of markers of metabolic disorders, including nesfatin-1. Nesfatin-1 has a wide range of predominantly paracrine effects and plays a significant role in various physiological and pathophysiological processes, such as cardiovascular regulation, neuroendocrine control of stress hormone secretion, and participation in the mechanisms of formation of behavioral excitation reactions [1]. The given literary data regarding the biological action of nesfatin-1 provide grounds for the future practical application of the metabolic effects of this adipokine. According to Nikolaos P. E. Kadoglou [2] et al., nesfatin-1 may be useful for clinical practice in terms of two aspects.

Firstly, for the diagnostics of diseases accompanied by obesity, dysglycemia, and dyslipidemia [3-5]. It was established that an increase of nesfatin-1 level in blood serum is accompanied by a blood pressure increase, body weight decrease [6], and a glucose-dependent increase in insulin secretion by β-cells of the pancreas when the blood glucose level increases [7].

Secondly, nesfatin-1 represents a target model for the creation of therapeutic agents for the treatment of obese individuals, because systemic or local administration of drugs based on nesfatin-1 is able to improve the metabolic profile and reduce body weight in patients with obesity and metabolic syndrome [8].

The search for markers of early diagnosis of heart failure and endocrine disorders progression is especially relevant in wartime. After all, since February 24, 2022, most people with chronic diseases have faced considerable difficulties due to the restriction of access to quality drugs and medical care in general. Therefore, today the main goal of scientists and healthcare workers is to develop a qualitative strategy for the progression

and possible complications diagnosis of comorbid cardiovascular pathology.

THE AIM

The aim was to study the nesfatin-1 activity in the blood serum of patients with chronic heart failure (CHF) of ischemic origin against the background of such metabolic disorders as type 2 diabetes mellitus (T2DM) and obesity.

MATERIALS AND METHODS

During 2022 154 patients were examined, who were divided into 4 groups, according to the presence of metabolic disorders. Group 1 included patients with CHF with coronary heart disease (CHD) and T2DM and obesity (n=42). The second group consisted of patients with heart failure on the background of CHD with concomitant T2DM (n=46), the third group - with concomitant obesity (n=36), the fourth group was formed from patients with signs of heart failure of ischemic origin without metabolic disorders (n=30). The control group included 30 practically healthy persons of comparable age.

Pregnant women, patients with acute infectious and autoimmune diseases, diffuse connective tissue diseases, oncological diseases, diseases of the pituitary gland and hypothalamus, chronic renal failure with a decrease of GFR less than 35 ml/min/1.73 m^2, the presence of symptomatic hypertension, acute coronary syndrome, and acute cerebrovascular accident during the last 6 months, exacerbation of chronic or presence of acute inflammatory diseases; patients with a history of alcohol abuse, mental illness; patients who were expected to have a high probability of violating the research protocol and persons who are not citizens of Ukraine were not included in the study. Representatives of vulnerable population groups were also not involved in the project.

The standard method of examining the patient included clinical and laboratory-instrumental research according to the recommendations of the European Society of Cardiology (ESC) in 2021, the American Diabetes Association (ADA) in 2019, and the International Diabetes Federation (IDF) in 2018. Laboratory and instrumental studies were carried out on the basis of the City Clinical Hospital No.27.

The studies were approved by the commission on biomedical ethics of Kharkiv National Medical University (protocol №2, dated 12.10.2022) and conducted in accordance with the written consent of the participants and the principles of bioethics set forth in the Helsinki Declaration "Ethical Principles of Medical Research Involving Humans" and the "Universal Declaration on Bioethics and Human Rights (UNESCO)".

To determine the level of nesfatin-1 (ng/ml), an immunoenzymatic method was used using a set of Human Nesfatin-1 ELISA Kit reagents according to the instructions attached to the kit, on an immunoenzymatic analyzer «Labline-90» (Austria).

A statistical analysis of the data was carried out using the methods of parametric and non-parametric statistics.

Mathematical computer processing of the results was carried out using the software package «Statistica 6.0» (StatSoft Inc, USA). For the comparative analysis of the samples, a standard correlation analysis program was used to calculate the average arithmetic values: the received data is presented as mean value ± standard deviation (SD). Statistical significance was considered to be a discrepancy at $p<0.05$. When analyzing samples not subject to the laws of Gaussian distribution, the Mann-Whitney U-test for independent samples was used. The correlation coefficient (r) was used to assess the degree of relationship between the samples.

More than two groups were compared by one-way ANOVA, using the least significant difference as a post-hoc Tuckey test to compare individual groups. A p-value < 0.05 was considered to be statistically significant. Moreover, receiver operating curve (ROC) analysis was performed to compare the performance of the models.

For the implementation of laboratory and instrumental methods of research, we collaborated with the Central Scientific and Research Laboratory of Kharkiv National Medical University.

RESULTS

General study variables in the four study groups are summarized and compared in Table I. Accordingly, the four groups were comparable in terms of sex and age.

The mean level of serum nesfatin-1 was 1.64±0.27 ng/mL in the CHF group, 0.342±0.19 ng/mL in the CHF + T2DM + obesity group, 1.06±0.36 ng/mL in the obese + CHF group, 0.96±0.27 ng/mL in the CHF + T2DM group and 2.98±0.38 ng/mL in the CG (Fig.1).

The ROC curves of serum nesfatin-1 levels in groups are shown in Figure 2. The corresponding under-the-curve areas in CG, CHF, CHF + T2DM, CHF + obesity, CHF + T2DM + obesity were 0.79 (95% CI, 0.73-0.85, $p<0.001$), 0.81 (95% CI, 0.70-0.92, $p<0.001$), 0.814 (95% CI, 0.71-0.94, $p<0.001$), 0.89 (95% CI, 0.83-0.95, $p<0.001$) and 0.92 (95% CI, 0.86-0.98, $p<0.001$), respectively.

In the present study, the fasting serum nesfatin-1 level was measured in all groups consisting of CG, CHF, CHF + T2DM, CHF + obesity, and CHF + T2DM + obesity. According to our results, the mean level of serum nesfatin-1 was significantly higher in CHF than in CHF

Table I. General study variables in the four study groups (M±SD)

Parameter		CHF, n=30	CHF + T2DM + obesity, n=42	CHF + obesity, n=36	CHF+ T2DM, n=46	CG, n=30
Age		61.37±9.7	60.09±9.4	59.43±6.5	62.34±4.7	58.75±6.3
Sex	Female	17 (56.67)	24 (57.14)	20 (55.56)	26 (56.52)	17 (56.67)
	Male	13 (43.33)	18 (42.86)	16 (44.44)	20 (43.48)	13 (43.33)

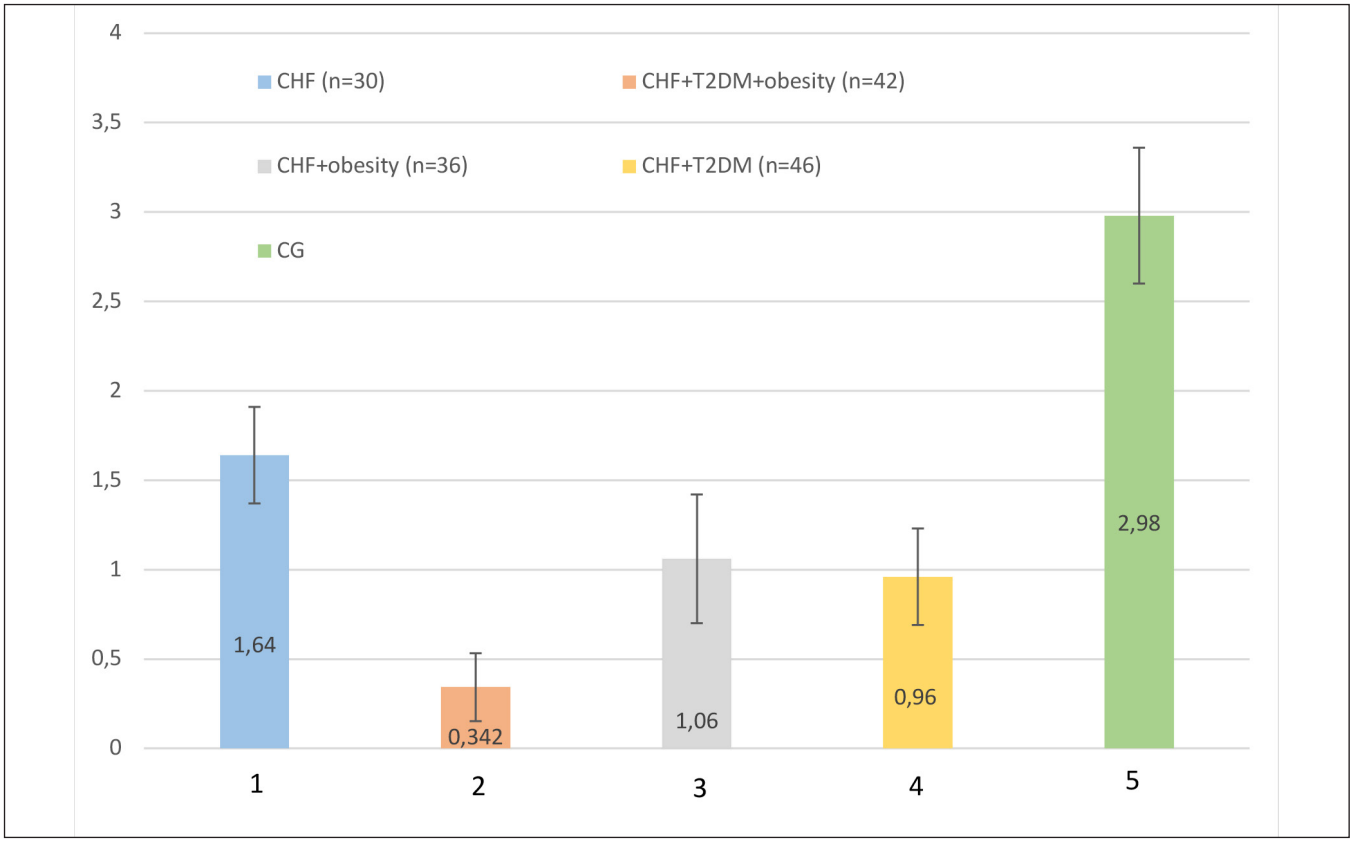

Fig. 1. The mean level of serum nesfatin-1 in the four study groups (M±SD)
Notes: $p_{1-2}<0.001$, $p_{1-3}<0.001$, $p_{1-4}<0.001$, $p_{1-5}<0.001$; $p_{2-3}<0.001$, $p_{2-4}<0.001$, $p_{2-5}<0.001$; $p_{3-4}>0.05$, $p_{3-5}<0.001$; $p_{4-5}<0.001$. Significant at $p < 0.05$

+ T2DM, CHF + obesity, and CHF + T2DM + obesity groups, but significantly lower than that in CG. At the same time, no significant difference was found between the obese and diabetic groups.

A significant correlation was found between the serum nesfatin-1 level and BMI (r=–0.34, p<0.05), HOMA (r=–0.54, p<0.05), and insulin (r=–0.41, p<0.05). No significant correlation was found between the serum nesfatin-1 level and blood glucose level (r=0.13, p=0.65) among all patients involved in the study.

DISCUSSION

A recent study by S. Mirakhor Samani et al. [9], showed that there are significant differences between normal-weight healthy subjects, healthy underweight persons, otherwise healthy obese people, and diabetic patients in terms of serum nesfatin-1 level. The results demonstrated the mean level of serum nesfatin-1 was significantly higher in normal-weight people than in both obese and diabetic groups, but significantly lower than that in underweight patients. At the same time, there was no significant difference between the obese and diabetic groups. In conformity with some previous reports in animal models and rare human studies, this peptide may play a pivotal role in the pathogenesis of both weight-related abnormalities and T2DM.

In a study by Shimizu et al. [5], they showed that nesfatin-1 plays a role in the development of insulin resistance and fat deposition in the liver, independent of effects on energy intake in rats.

The increased content in blood serum of the nesfatin-1 leads to remodeling of myocardium of the left ventricle (LV) in the form of a reduction of the ability of myocardium to a reduction in another report by Shaparenko O. et al. [10], who showed an increase of chambers and the LV sizes and can play a role in pathogenesis arterial hypertension in patients with obesity.

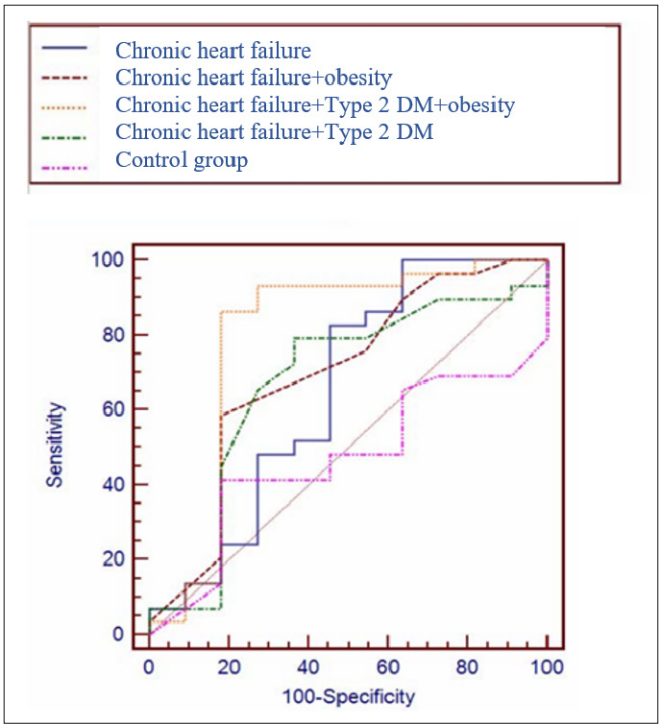

Fig. 2. Receiver operator characteristics curves of the mean serum nesfatin-1 levels in groups.

In recent research, Huang K. et al. [11] demonstrated serum nesfatin-1 as an important factor influencing insulin secretion in the development of T2DM, which may provide new insights for prospective research on the role of these factors in the pathogenesis of T2DM, as well as for active prediction and prevention of prediabetes before it develops into T2DM manifestation.

In another study, by Zhou et al., nesfatin-1 levels were measured in 50 CHF patients with T2DM and 50 CHF patients without T2DM. The results showed that nesfatin-1 levels were significantly higher in CHF patients with T2DM than in those without T2DM, and that nesfatin-1 levels were positively correlated with BMI, fasting glucose levels, and HbA1c levels. The authors suggested that increased nesfatin-1 levels may be a compensatory mechanism in response to T2DM-induced metabolic disturbances [12].

Based on the findings of the study by Luo et al. [13], the authors suggested that nesfatin-1 may play a role in the development of obesity-related cardiovascular complications in patients with chronic heart failure (CHF). They proposed that the elevated levels of nesfatin-1 in CHF patients with obesity may contribute to the pathogenesis of insulin resistance and metabolic dysfunction, which are commonly observed in obese patients with CHF. The authors also suggested that nesfatin-1 could potentially serve as a biomarker for the diagnosis and management of obesity-related cardiovascular disease in CHF patients. Further studies are needed to elucidate the precise mechanisms underlying the relationship between nesfatin-1, obesity, and CHF.

The prospects for the study of this marker also lie in the fact that under the conditions of military events, the number of patients with decompensation of both cardiovascular and metabolic diseases increases significantly. Thus, timely diagnosis aimed at preventing unfavorable consequences of these diseases is a priority for restoring economic stability in the field of medicine.

CONCLUSIONS

This study showed that there are significant differences in serum nesfatin-1 levels between the control group, chronic heart failure group, and chronic heart failure patients on the background of type 2 diabetes mellitus or obesity and with both metabolic disorders. In conformity with some previous reports in animal models and rare human studies, this peptide may play a pivotal role in the pathogenesis of both weight-related abnormalities and type 2 diabetes mellitus. Serum nesfatin-1 levels were negatively correlated with insulin, HOMA, and BMI.

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The Authors declare no conflict of interest.

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