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KLOTHO PROTEIN, FIBROBLAST GROWTH FACTOR AND SCLEROSTIN IN CHRONIC HEART FAILURE

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Abstract: Chronic heart failure (CHF) is a global medical, social and economic problem. CHF is a syndrome caused by an imbalance in the neurohumoral regulation of the cardiovascular system, which is accompanied by a violation of the systolic and/or diastolic function of the heart. Currently, the search for and study of new biological markers that can ensure early diagnosis of CHF, serve as a laboratory tool for assessing the effectiveness of treatment, or be used as prognostic markers and risk stratification criteria continues.

Keywords: biological markers, cardiovascular diseases, Klotho protein.

INTRODUCTION

Chronic heart failure (CHF) is an important medical, social and economic problem [1, 2]. It represents a kind of finale of the cardiovascular continuum and is characterized by a significant increase in mortality [1]. Heart failure (HF) is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional abnormality of the heart and confirmed by an elevated level of natriuretic peptide (BNP) and/or objective signs of pulmonary or systemic congestion [3]. According to the left ventricular (LV) ejection fraction (EF), patients with HF are divided into those with HF with reduced EF (HFrEF; LVEF ≤40%), HF with moderately reduced EF (HFmrEF; LVEF 41–49%), HF with preserved EF (HFpEF; LVEF ≥50%), and HF with improved EF (HFimpEF; baseline LVEF ≤40%, increase from baseline LVEF by ≥10 points, second measurement of LVEF >40%) [3]. In recent decades, an increase in the prevalence of chronic kidney disease (CKD) has been recorded in patients with CHF [4]. On the one hand, CKD is a well-known comorbidity in CHF, which is associated with decreased survival; on the other hand, cardiovascular complications are the main cause of mortality in CKD [4].

MATERIALS AND METHODS

Klotho interacts with fibroblast growth factor receptors (FGFRs), most commonly FGFR1c, via its KL2 domain extension. FGF23 inserts into the groove formed by the KL1, KL2, and FGFR components [1]. Membrane-bound and soluble forms can both bind FGFR1c and function as co-receptors [2]. These molecular interactions create a high-affinity FGF23 binding site [3]. Activated FGFR signals are associated with several signaling pathways: ERK (extracellular signal-regulated protein kinase), MAPK (mitogen-activated protein kinase), PI3K (phosphoinositide 3-kinase), PKC (protein kinase) C, PL (phospholipase) Cγ [4].

RESULTS AND DISCUSSION

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Rodents with an insertional mutation in the promoter region of the Klotho protein gene have been shown to age prematurely [3]. Overexpression of the Klotho protein gene increased lifespan in rodents, suggesting that it may function as an aging suppressor gene [1]. Klotho expression declines with age; the decline in blood Klotho appears to be similar in men and women [2]. Low blood Klotho levels are associated with increased all-cause mortality [3]. Klotho deficiency is associated with many age-related diseases. Low Klotho levels are associated with hyperphosphatemia, chronic renal failure, multiple CVDs, neurodegenerative diseases, malignancies, pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), bone diseases and diabetes mellitus (DM) [3]. Klotho deficiency in vessels leads to their calcification. This is associated with FGFR/FGF23 resistance, which in turn leads to suppression of the anticalcifying effect of FGF23 [1]. Weakened Klotho expression in the vascular wall reduces nitric oxide (NO) production and increases the formation of reactive oxygen species (ROS) [2]. Thus, Klotho/FGF23 imbalance leads to oxidative stress and endothelial dysfunction. Klotho depletion is accompanied by increased pro-oxidative, pro-inflammatory, pro-apoptotic processes and damage to cardiomyocytes [3]. Klotho deficiency and its gene polymorphisms are risk factors for the development of CVD [4]. The occurrence of cardiac hypertrophy and its remodeling in Klotho deficiency is caused by oxidative stress. This is caused by the activation of the p38 (mitogen-activated protein kinase) and ERK1/2 (extracellular signal-regulated kinase 1/2) signaling pathways, as well as overexpression of transient receptor potential channel 6 (TRPC6) in the heart [2]. Klotho treatment reduces the severity of inflammation, as well as ROS formation, apoptosis, mitochondrial dysfunction, fibrosis and hypertrophy [3].

A study by X. Xiong et al. (2023) aimed to investigate the protective effect of Klotho on senescent cells. H9C2 cells were induced to undergo D-galactose (D-Gal) injury, followed by Klotho treatment in vitro. D-Gal treatment increased β-GAL (β-galactosidase) activity, decreased cell viability, increased oxidative stress, and decreased the expression of solute carrier family 7 member 11 (SLC7A11), glutathione peroxidase-4 (GPx4), and P53 (cell cycle-regulated transcription factor), which are the primary regulators of ferroptosis. Klotho delayed D-Gal-induced senescence, likely due to its ability to enhance the expression of ferroptosis-related proteins SLC7A11 and GPx4 [4]. J. Kresovich et al. [2] measured Klotho concentrations in 10,069 individuals aged 40–79 years included in the NHANES (National Health Interview Survey, a national survey conducted by the National Center for Health Statistics in the United States to provide a general assessment of the health and nutritional status of Americans) program from 2007 to 2014. Follow-up mortality data based on the National Death Index were obtained until 12/31/2015. On average, 616 deaths were recorded over 58 months (range 1–108 months). Low (<666 pg/mL) serum Klotho concentrations were associated with a 31% increased risk of death (compared with Klotho concentrations >985 pg/mL; odds ratio, OR=1.31, 95% CI 1.00–1.71, p=0.05). These results suggested that serum Klotho levels in adults may serve as a marker of mortality risk [4].

CONCLUSION

Research in the field of studying new laboratory biological markers should help in early diagnosis and selection of more effective therapy for patients with a cardiological profile. Analysis of biomarkers has thoroughly occupied its niche in oncology, but their use in the field of CVD is only in its infancy. Currently, there are available modern technologies for

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identifying new biomarkers, as a result of which it is advisable to develop a multi-biomarker model for diagnosing and predicting the course of cardiovascular pathology.

REFERENCES

1. Riccardi M., Sammartino A., Piepoli M., et al. Heart failure: an update from the last years and a look at the near future // ESC Heart Fail. 2022. Vol. 9, N 6. P. 3667–3693. doi: 10.1002/ehf2.14257. Erratum in: ESC Heart Fail. 2023. Vol. 10, N 3. P. 2143.

2. Golukhova E.Z., Alieva A.M. Clinical significance of determining natriuretic peptides in patients with chronic heart failure // Cardiology and cardiovascular surgery. 2007. No. 1. P. 45–51. EDN: HGTYXS

3. Bozkurt B., Coats A., Tsutsui H., et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure // J Card Fail. 2021. S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022. Epub ahead of print.

4. Szlagor M., Dybiec J., Młynarska E., et al. Chronic Kidney Disease as a Comorbidity in Heart Failure // Int J Mol Sci. 2023. Vol. 24, N 3. P. 2988. doi: 10.3390/ijms24032988