ASSESSMENT OF GAS6 IN VARIOUS CLINICAL VARIANTS OF CORONARY ARTERY DISEASE IN PATIENTS WITH CHRONIC HEART FAILURE AND CONCOMITANT METABOLIC PATHOLOGY

Borovyk K.

Kharkiv National Medical University, Kharkiv, Ukraine

https://doi.org/10.35339/ic.2025.12.4.bok

ABSTRACT

Background. Chronic Heart Failure (CHF) of ischemic origin is a significant medical problem, aggravated by concomitant Type 2 Diabetes Mellitus (T2DM) and obesity. Growth Arrest-Specific protein 6 (GAS6), a ligand for TAM (Tyro3, Axl, Mer) receptors family, is involved in apoptosis and myocardial fibrosis, making it a potential diagnostic marker.

Aim. To assess circulating GAS6 levels and establish correlations with various clinical variants of coronary artery disease in patients with chronic heart failure and concomitant type 2 diabetes mellitus and obesity.

Materials and Methods. The study involved 225 patients with ischemic heart failure, divided into groups according to metabolic disorders: Group 1 – 75 patients with Coronary Artery Disease (CAD), CHF, T2DM and obesity; Group 2 – 50 patients with CAD, CHF and T2DM; Group 3 – 50 patients with CAD, CHF and obesity; Group 4 – 50 patients with CAD and CHF without metabolic disorders. A Control Group included 30 healthy individuals. The patients were sub-divided in accordance with CAD form: stable angina, diffuse cardiosclerosis, and Post-Infarction CardioSclerosis (PICS). GAS6 levels were determined by Enzyme-Linked ImmunoSorbent Assay (ELISA). The data were analyzed using parametric and non-parametric methods via Statistica 14.0 (TIBCO Software Inc., USA). Group comparisons were performed using the Kruskal-Wallis H-test with post-hoc Mann-Whitney U-test with Bonferroni correction. The work was carried out within the framework of the author's dissertation.

Research Ethics. The study was approved by the Bioethics Commission of Kharkiv National Medical University and conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (1964–2024). All patients provided written informed consent to participate.

Results. The most pronounced and significant increase in circulating GAS6 levels was observed in patients of Groups 1 and 3 compared to the controls. The highest GAS6 level ([38.18±2.15] ng/ml) was found in Group 1 patients with PICS, significantly exceeding values in the diffuse cardiosclerosis subgroup ($p<0.008$). In Groups 2 and 4, GAS6 levels did not differ significantly from the Control Group ($p>0.008$). Correlation analysis revealed a strong positive correlation between GAS6 and obesity ($r=0.77$; $p<0.05$). A moderate significant positive correlation with PICS ($r=0.63$; $p<0.05$) and T2DM ($r=0.61$; $p<0.05$) was found. The correlation with stable angina was weak and insignificant ($r=0.26$; $p>0.05$).

Conclusions. Obesity is a key factor in GAS6 activation, reflecting systemic inflammation and profibrotic processes. Elevated GAS6 levels are reliably associated with post-infarction cardiosclerosis specifically in the presence of obesity, indicating its role in myocardial remodeling and fibrogenesis.

Keywords: *therapy, cardiovascular diseases, ischemic heart disease, type 2 diabetes mellitus, obesity, post-infarction cardiosclerosis.*

Corresponding Author:

Borovyk Kateryna – Candidate of Medical Sciences, Associate Professor, Department of Internal Medicine No.2 and Clinical Immunology and Allergology named after Academician L.T. Malaya, Kharkiv National Medical University, Ukraine.

✉ 4, Nauky ave., Kharkiv, 61022, Ukraine.

E-mail: km.borovyk@knmu.edu.ua

Introduction

Chronic Heart Failure (CHF) remains one of the most significant medical and social problems in modern cardiology, being the leading cause of hospitalization and significantly increasing mortality and disability rates among the population. In the vast majority of cases, the etiological basis of CHF is Coronary Artery Disease (CAD), which determines the complex and progressive nature of pathogenetic processes [1].

The clinical course and prognosis of CHF in patients with CAD is significantly aggravated by the presence of concomitant metabolic disorders, such as Type 2 Diabetes Mellitus (T2DM) and obesity [2–4]. These comorbid conditions create a multimorbid profile that exacerbates myocardial remodeling, promotes diffuse fibrosis and accelerates the progression of left ventricular dysfunction. This complex pathological cascade is caused by the activation of systemic inflammation, oxidative stress and endothelial dysfunction.

In the search for new diagnostic and prognostic markers that can reflect the degree of fibrosis and remodeling, the protein Growth Arrest-Specific protein 6 (GAS6) has attracted considerable attention. GAS6 is a vitamin K-dependent factor that is a ligand for the TAM (Tyro3, Axl, Mer) receptors family, which in turn are involved in the regulation of cell migration, apoptosis, and phagocytosis. In cardiology, GAS6 is considered a potential marker of atherosclerosis, thrombosis, and myocardial fibrosis. Its level correlates with the severity of cardiovascular disease and may reflect the activity of profibrotic processes [5; 6].

However, existing literature does not sufficiently cover the role of GAS6 in patients with ischemic heart failure against the background of combined T2DM and obesity [7; 8]. Of particular interest is the assessment of the levels of this protein in the context of different clinical variants of CAD (stable angina, diffuse cardiosclerosis, postinfarction cardiosclerosis). Establishing the relationship between GAS6 levels and specific forms of CAD in this cohort may broaden our understanding of the pathogenesis and have important prognostic significance.

The **aim** of study was to assess circulating GAS6 levels and establish correlations with various clinical variants of ischemic heart disease in patients with chronic heart failure and concomitant type 2 diabetes mellitus and obesity.

Materials and Methods

According to the study design, 225 patients undergoing treatment in the cardiology department of the Municipal Clinical Hospital No.27 of Kharkiv City Council were divided into groups depending on the metabolic disorders detected. Group 1 included patients with CHF against the background of CAD, T2DM and obesity (n=75). Group 2 consisted of patients with CHF, CAD and concomitant T2DM (n=50), and Group 3 consisted of patients with concomitant obesity (n=50). The comparison group (Group 4) consisted of patients who had signs of CAD of ischemic origin without metabolic disorders (n=50). The groups of examined patients were comparable in terms of age and gender. The Control Group consisted of 30 age- and gender-matched practically healthy individuals.

To achieve the goal, the patients were divided into subgroups depending on the clinical form of CAD: stable angina pectoris, Post-Infarction CardioSclerosis (PICS) and diffuse cardiosclerosis (*Table 1*). Analysis of Table 1 shows that all study groups were relatively comparable in terms of the distribution of clinical forms of CAD, which is important for comparative analysis. Thus, stable angina was the least common form of CAD in Group 1 (30.66%) and Group 2 (32.00%). In Groups 3 and 4, the proportion of stable angina was 34.00%. Diffuse cardiosclerosis was found in approximately one-third of patients in each group, ranging from 30.00% (Group 3) to 32.00% (Group 1, 2 and 4).

PICS had the highest frequency in Group 1 (33.33%), Group 2 (36.00%) and Group 3 (36.00%). In Group 4 its proportion was 34.00%.

Thus, in most groups (except for the fourth group, where all three forms were distributed almost evenly), chronic forms of CAD prevailed – diffuse cardiosclerosis and PICS, which together accounted for about [65–68]% of the total number of cases in each group. This confirms the chronic nature of the pathology in the study population.

The exclusion criteria were acute and chronic infectious diseases, newly diagnosed T2DM, autoimmune diseases and diffuse connective tissue diseases, exacerbation of chronic inflammatory processes or the presence of acute inflammatory diseases, diseases of the hypothalamus and pituitary gland, thyroid diseases, symptomatic hypertension, heart valve disease, chronic obstructive pulmonary disease, liver cirrhosis, moderate to severe anemia, acute stroke, acute left or right ventricular failure; cancer, drug addiction, alcoholism, concomitant mental illness, vascular dementia or other mnemonic disorders, inability to understand the content of informed consent, refusal to participate in the study for any reason, including economic reasons.

The standard patient examination procedure included clinical and laboratory-instrumental examinations in accordance with the recommendations of the European Society of Cardiology (ESC) 2021, the American Diabetes Association (ADA) 2019, and the International Diabetes Federation (IDF) 2018.

Table 1. Distribution of patients according to the clinical form of coronary artery disease, abs. (%)

Forms of CAD	CHF in CAD and type 2 diabetes mellitus and obesity (n=75)	CHF against the background of CAD with concomitant type 2 diabetes mellitus (n=50)	CHF against the background of CAD with concomitant obesity (n=50)	CHF of ischemic origin without metabolic disorders (n=50)
Stable angina pectoris	23 (30.67)	16 (32.00)	17 (34.00)	17 (34.00)
Diffuse cardiosclerosis	24 (32.00)	16 (32.00)	15 (30.00)	16 (32.00)
PICS	25 (33.33)	18 (36.00)	18 (36.00)	17 (34.00)

Notes: CAD – Coronary Artery Disease; PICS – Post-Infarction CardioSclerosis; CHF – Chronic Heart Failure.

Blood serum GAS6 level was determined by immunoenzyme method. For quantitative measurement, a commercial Human Growth arrest-specific protein 6 (GAS6) ELISA kit (Cusabio, USA) was used. The study was conducted on a Labline-90 immunoenzyme analyzer (Austria Lab Technologies, Austria) at the biochemical department of Central Research Laboratory of Kharkiv National Medical University.

Statistical analysis of the data was performed using parametric and non-parametric statistical methods. Mathematical computer processing of the results was performed using Statistica 14.0 (TIBCO Software Inc., USA) software package. The normality of data distribution was evaluated using the Shapiro-Wilk test. Descriptive statistics for normally distributed continuous variables were presented as mean and standard error of the mean (M±SEM). For non-normally distributed data, the median and interquartile range (Me [Q1; Q3]) were reported. To compare multiple independent groups (Groups 1–4 and Controls), the Kruskal-Wallis H-test was applied. In cases of significant differences ($p<0.05$), post-hoc pairwise comparisons were performed using the Mann-Whitney U-test with Bonferroni correction for multiple comparisons. The adjusted significance threshold was set at $p<0.008$ (based on 6 possible pairwise comparisons among 4 study groups). Correlation analysis was performed using Spearman's rank correlation coefficient (r). The significance of the correlation coefficients was assessed using Student's t-test.

Research Ethics

The study was carried out in accordance with the norms of WMA Declaration of Helsinki (1964–2024) and approved by the Bioethics Commission of Kharkiv National Medical University. All involved patients signed an informed consent.

Results

Analysis of circulating GAS6 levels (*Tables 2–5*) in patients with CHF against the background of various clinical variants of CAD showed that the most pronounced increase in this indicator was observed in patients with a combination of CAD, CHF, T2DM and obesity (Group 1). In this group, GAS6 levels were significantly higher than the control in all clinical variants of CAD ($p<0.008$). The highest concentration of GAS6 ([38.18±2.15] ng/ml) was recorded in the subgroup of patients who had suffered Myocardial Infarction (MI), where it significantly exceeded the indicators of the subgroup that included patients with diffuse cardiosclerosis ($p=0.003$).

A similar trend was observed in Group 3, where GAS6 levels in patients with PICS ([35.12± ±2.03] ng/ml) and diffuse cardiosclerosis significantly exceeded control values ($p=0.0018$). However, in this group, GAS6 levels in patients with stable angina did not differ significantly from the Control Group ($p>0.008$).

In contrast, in Group 2, no statistically significant differences in GAS6 concentration were found between clinical variants of CAD and the Control Group ($p>0.008$).

Group 4 showed the same trend as Group 2: no statistically significant differences in GAS6 concentration were found between the clinical variants of CAD and the Control Group ($p>0.008$). This emphasizes the role of obesity and its combination with other disorders as a key factor in GAS6 activation.

The results of the correlation analysis (Table 6) confirmed these findings, showing a strong positive correlation between GAS6 levels and obesity ($r=0.77$; $p<0.05$). A moderate significant positive correlation was also found with PICS ($r=0.63$; $p<0.05$) and T2DM ($r=0.61$; $p<0.05$). The correla-

Table 2. Circulating GAS6 levels in different clinical variants of coronary artery disease in patients of Group 1

	Diffuse cardiosclerosis	PICS	Stable angina	Control Group
	1	2	3	4
GAS6, ng/ml	27.44±2.23	38.18±2.15	30.46±2.41	19.03±1.29
p	p_{1-2}=0.0030 p_{1-3}=0.2920 p_{1-4}=0.0005	p_{2-3}=0.0050 p_{2-4}=0.0002	p_{3-4}=0.0006	

Note: p values were determined using the Kruskal-Wallis test followed by post-hoc Mann-Whitney U-tests with Bonferroni correction.

Table 3. Circulating GAS6 levels in different clinical variants of ischemic heart disease in patients of Group 2

	Diffuse cardiosclerosis	PICS	Stable angina	Control Group
	1	2	3	4
GAS6, ng/ml	22.37±2.21	24.07±2.14	23.27±2.19	19.03±1.29
p	p_{1-2}=0.523 p_{1-3}=0.631 p_{1-4}=0.217	p_{2-3}=0.696 p_{2-4}=0.276	p_{3-4}=0.201	

Note: p values were determined using the Kruskal-Wallis test followed by post-hoc Mann-Whitney U-tests with Bonferroni correction.

Table 4. Circulating GAS6 levels in different clinical variants of ischemic heart disease in patients in Group 3

	Diffuse cardiosclerosis	PICS	Stable angina	Control Group
	1	2	3	4
GAS6, ng/ml	26.49±2.17	35.12±2.03	22.45±2.26	19.03±1.29
p	p_{1-2}=0.0018 p_{1-3}=0.0330 p_{1-4}=0.0030	p_{2-3}=0.00074 p_{2-4}=0.00036	p_{3-4}=0.364	

Note: p values were determined using the Kruskal-Wallis test followed by post-hoc Mann-Whitney U-tests with Bonferroni correction.

Table 5. Circulating GAS6 levels in different clinical variants of ischemic heart disease in patients in Group 4

	Diffuse cardiosclerosis	PICS	Stable angina	Control Group
	1	2	3	4
GAS6, ng/ml	22.89±2.14	23.32±2.08	23.11±2.16	19.03±1.29
p	p_{1-2}=0.765 p_{1-3}=0.433 p_{1-4}=0.175	p_{2-3}=0.827 p_{2-4}=0.138	p_{3-4}=0.237	

Note: p values were determined using the Kruskal-Wallis test followed by post-hoc Mann-Whitney U-tests with Bonferroni correction.

tion with diffuse cardiosclerosis and stable angina pectoris was weak and statistically insignificant.

Table 6. Correlations between circulating GAS6 levels and clinical variants of ischemic heart disease and metabolic disorders (r_{crit}=0.41)

	GAS6	p
Stable angina	0.26	>0.05
PICS	0.63	<0.05
Diffuse cardiosclerosis	0.32	>0.05
T2DM	0.61	<0.05
Obesity	0.77	<0.05

Note: r – Spearman's correlation coefficient.

The results obtained demonstrate a significant association between increased levels of circulating GAS6 protein and the presence of concomitant metabolic disorders, especially obesity, in patients with CAD. The key conclusion of the study is that the most pronounced and statistically significant increase in GAS6 levels was observed in patients with combined CAD, T2DM and obesity, and in patients with CAD and obesity. Meanwhile, in patients with CAD and concomitant T2DM and patients with CAD without metabolic disorders, GAS6 levels did not differ from those in the Control Group. This fact is confirmed by the data of correlation analysis (Table 6), which revealed the strongest positive correlation between GAS6 levels and obesity (r=0.77; p<0.05). This is consistent with current understanding. It is known that obesity initiates systemic inflammation and metabolic dysregulation, leading to adverse myocardial remodeling [9]. Obesity is associated with the activation of profibrotic processes, in particular transforming growth factor β, which is a marker of fibrosis [10; 11]. The GAS6 protein, being a factor involved in inflammation and cell interaction, may act as a mediator or reflection of this inflammatory-fibrotic cascade induced by excess adipose tissue [6; 7]. Although T2DM also shows a moderate significant association with GAS6 (r=0.61; p<0.05), the absence of a significant increase in GAS6 in patients with CAD and concomitant T2DM indicates that obesity, rather than isolated T2DM, is a more powerful trigger for the activation of this protein, emphasizing the critical role of hypertrophied adipose tissue in the pathogenesis.

Discussion

The results of our study also confirm the association of elevated GAS6 levels with more pronounced structural myocardial damage [12; 13]. In Groups 1 and 3, which had significantly elevated GAS6, the highest protein concentrations were recorded in patients with PICS (*Tables 2, 4*), which is also confirmed by a moderate positive correlation (r=0.63; p<0.05). PICS is the result of a previous MI and is characterized by the formation of significant fibrous scarring, which is one of the main causes of systolic and diastolic dysfunction in CHF. Elevated GAS6 in this subgroup may indicate its involvement in remodeling and fibrogenesis processes after ischemic damage. This is consistent with experimental data showing that obesity and metabolic dysfunction can exacerbate and accentuate dilational remodeling after MI. The absence of a significant increase in GAS6 in stable angina, especially in Group 3 (*Table 4*), and the weak correlation (r=0.26) may indicate that GAS6 is a marker of chronic, structurally significant myocardial changes (cardiosclerosis) rather than just ischemic syndrome as such.

The established relationship between high GAS6 levels, obesity and PICS in patients with CHF suggests that GAS6 may serve as an additional biomarker for risk stratification in patients with CHF and metabolic syndrome, especially those with predominant fibrotic changes after MI [14; 15]. The results emphasize the need for aggressive treatment of obesity and associated metabolic disorders in this category of patients, as these factors contribute most to the increase in the profibrotic signal reflected through GAS6. Given that obesity is one of the most powerful independent predictors of cardiovascular risk, and that metabolic disorders can alter the fibrotic response to myocardial damage, our study points to GAS6 as a potential target or indicator of the effectiveness of therapeutic interventions aimed at reducing body weight and improving metabolic control.

Conclusions

1. A statistically significant increase in GAS6 levels associated with post-infarction cardiosclerosis is observed exclusively in patients with concomitant obesity, whereas in patients without obesity (Groups 2 and 4), GAS6 levels in PICS do not differ from controls.

2. Correlation analysis showed a moderate significant positive correlation between GAS6 levels and post-infarction cardiosclerosis (r=0.63; p<0.05), while the correlation with stable angina was statistically insignificant (r=0.26; p>0.05). The results

obtained indicate that GAS6 levels may be a biomarker for assessing profibrotic activity and a potential indicator of structural and functional changes in the myocardium caused by a combination of ischemia and metabolic dysfunction, especially in cases complicated by obesity and post-infarction cardiosclerosis.

Funding and Acknowledgments

The work was carried out within the framework of the dissertation research "Clinical and pathogenetic aspects of diagnosis, treatment and prognosis of the course of chronic heart failure in patients with coronary artery disease, obesity and type 2 diabetes mellitus", the topic of which was approved by the Academic Council of Kharkiv National Medical University (2020–2026 implementation years).

Declarations

Conflict of interest is absent.

The author has given her consent to the publication of the article, to the processing and publication of her personal data.

The author state that in the process of conducting research, preparing, and editing this manuscript, she did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the author.

References

1. Lavalle C, Mariani MV, Severino P, Palombi M, Trivigno S, D'Amato A, et al. Efficacy of Modern Therapies for Heart Failure with Reduced Ejection Fraction in Specific Population Subgroups: A Systematic Review and Network Meta-Analysis. Cardiorenal Med. 2024;14(1):570-80. DOI: 10.1159/000541393. PMID: 39284285.

2. Piché ME, Tchernof A, Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res. 22;126(11):1477-500. DOI: 10.1161/CIRCRESAHA.120.316101. Erratum in: Circ Res. 2020;127(3):e107. DOI: 10.1161/RES.0000000000000421. PMID: 32437302.

3. Hahn VS, Petucci C, Kim MS, Bedi KC Jr, Wang H, Mishra S, et al. Myocardial Metabolomics of Human Heart Failure with Preserved Ejection Fraction. Circulation. 2023;147(15):1147-61. DOI: 10.1161/CIRCULATIONAHA.122.061846. PMID: 36856044.

4. Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. Nat Rev Cardiol. 2021;18(4):291-304. DOI: 10.1038/s41569-020-00465-5. PMID: 33188304.

5. Ma T, Huang R, Xu Y, Lv Y, Liu Y, Pan X, et al. Plasma GAS6 predicts mortality risk in acute heart failure patients: insights from the DRAGON-HF trial. J Transl Med. 2023;21(1):21. DOI: 10.1186/s12967-022-03859-w. PMID: 36635690.

6. Lu C, Song Y, Wu X, Lei W, Chen J, Zhang X, et al. Pleiotropic role of GAS6 in cardioprotection against ischaemia-reperfusion injury. J Adv Res. 2025;70:481-97. DOI: 10.1016/j.jare.2024.04.020. PMID: 38653371.

7. Chen J, Wang Y, Li X, Guo X, Tian J, Zheng X, et al. IDHP Mitigates LPS-Induced Cardiomyocyte Injury via the GAS6/Axl-AMPK Axis: A Multi-Target Strategy Counteracting Inflammation, Oxidative Stress, and Apoptosis. Pharmaceuticals (Basel). 2025;18(8):1188. DOI: 10.3390/ph18081188. PMID: 40872581.

8. Zhao A, Lei W, Tian J, Wu X, Li M, Zhang Y, et al. Mangiferin Attenuates Myocardial Ischemia Reperfusion Injury by Regulating the GAS6/Axl Signalling Pathway. Phytother Res. 2025;39(3):1388-402. DOI: 10.1002/ptr.8423. PMID: 39780746.

9. Schleh MW, Caslin HL, Garcia JN, Mashayekhi M, Srivastava G, Bradley AB, Hasty AH. Metaflammation in obesity and its therapeutic targeting. Sci Transl Med. 2023;15(723):eadf9382. PMID: 37992150. DOI: 10.1126/scitranslmed.adf9382.

10. Yang X, Bhowmick K, Rao S, Xiang X, Ohshiro K, Amdur RL, et al. Aldehydes alter TGF-β signalling and induce obesity and cancer. Cell Rep. 2024 Sep 24;43(9):114676. DOI: 10.1016/j.celrep.2024.114676. PMID: 39217614.

11. Han X, Li W, He X, Lu X, Zhang Y, Li Y, et al. Blockade of TGF-β signalling alleviates human adipose stem cell senescence induced by native ECM in obesity visceral white adipose tissue. Stem Cell Res Ther. 2023;14(1):291. DOI: 10.1186/s13287-023-03525-y. PMID: 37807066.

12. Xiao H, Chen J, Duan L, Li S. Role of emerging vitamin K-dependent proteins: Growth arrest-specific protein 6, Gla-rich protein and periostin (Review). Int J Mol Med. 2021;47(3):2. DOI: 10.3892/ijmm.2020.4835. PMID: 33448308.

13. Chen W, Van Beusecum JP, Xiao L, Patrick DM, Ao M, Zhao S, et al. Role of Axl in target organ inflammation and damage due to hypertensive aortic remodelling. Am J Physiol Heart Circ Physiol. 2022;323(5):H917-33. DOI: 10.1152/ajpheart.00253.2022. PMID: 36083796.

14. Wu KS, Hung YJ, Lee CH, Hsiao FC, Hsieh PS. The Involvement of GAS6 Signaling in the Development of Obesity and Associated Inflammation. Int J Endocrinol. 2015;2015:202513. DOI: 10.1155/2015/202513. PMID: 25954309.

15. Li YH, Lu CH, Lin FH, Su SC, Liu JS, Hsieh CH, et al. Plasma Growth Arrest-Specific 6 Protein and Genetic Variations in the GAS6 Gene in Patients with Metabolic Syndrome. Metab Syndr Relat Disord. 2019;17(1):22-8. DOI: 10.1089/met.2017.0143. PMID: 30346880.

Received: 04 Oct 2025
Accepted: 29 Dec 2025
Published: 31 Dec 2025

Cite in Vancouver style as: Borovyk K. Assessment of GAS6 in various clinical variants of coronary artery disease in patients with chronic heart failure and concomitant metabolic pathology. Inter Collegas. 2025;12(4):7p. In press. https://doi.org/10.35339/ic.2025.12.4.bok