International Journal of Endocrinology

Оригінальні дослідження
Original Researches

UDC 616.12-008.46:616.12-005.4:616.379-008.64:616-056.5 DOI: https://doi.org/10.22141/2224-0721.22.1.2026.1669

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GAS6 as an indicator of carbohydrate metabolism disorders in patients with ischaemic heart failure and comorbid metabolic disorders

For citation: Mìžnarodnij endokrinologìčnij žurnal. 2026;22(1):15-20. doi: 10.22141/2224-0721.22.1.2026.1669

Abstract. ***Background.*** *Comorbid obesity and type 2 diabetes mellitus significantly worsen the global burden of chronic heart failure with coronary artery disease, accelerating myocardial dysfunction and diffuse fibrosis via chronic systemic inflammation. The growth arrest-specific protein 6 (GAS6) acts as a key link in this complex cardiometabolic continuum, actively contributing to insulin resistance by altering insulin receptor signaling. Its involvement in inflammation and the fibrotic cascade makes evaluating GAS6 crucial for risk stratification. The purpose was to evaluate and verify the level of circulating GAS6 as an independent indicator of the severity of carbohydrate metabolism disorders and a predictor of unfavourable course of heart failure in patients with coronary artery disease against the background of concomitant type 2 diabetes mellitus and obesity.* ***Materials and methods****. A clinical study was conducted on 225 patients with ischaemic chronic heart failure, divided into four main groups based on the combination of type 2 diabetes and/or obesity, and a healthy control group (n = 30). Serum GAS6 levels were measured using ELISA. Carbohydrate metabolism was assessed by glucose, insulin, HbA1c, and the HOMA-IR index. Statistical analysis utilised correlation coefficients (r) with* r_{crit} *= 0.39 to assess relationships.* ***Results.*** *Patients in group 1 (with comorbid type 2 diabetes mellitus and obesity) exhibited the most severe abnormalities in the carbohydrate profile, including hyperinsulinemia and high HOMA-IR. GAS6 levels were highest in group 1 (32.03 ± 2.06 ng/ml) and group 3 (with concomitant obesity), significantly exceeding the control group (19.03 ± 1.29 ng/ml) (p < 0.05). Correlation analysis in group 1 revealed the strongest positive link between GAS6 and body mass index (r = 0.68; p < 0.05). Significant correlations were also found with insulin (r = 0.49; p < 0.05) and HbA1c (r = 0.43; p < 0.05).* ***Conclusions.*** *The presence of obesity is the key factor activating circulating GAS6 in patients with ischaemic chronic heart failure. GAS6 acts as a potential integral biomarker reflecting the degree of metabolic inflammation and profibrotic activity. The strong association between high GAS6 levels, body mass index suggests its utility for risk stratification, particularly in patients with obesity.*

Keywords: *chronic heart failure; coronary artery disease; type 2 diabetes mellitus; obesity; growth arrest-specific protein 6; carbohydrate metabolism*

Introduction

Chronic heart failure (CHF) of ischaemic origin remains one of the modern medicine global pandemics, being the leading cause of hospitalisation, disability and significantly affecting mortality rates worldwide [1, 2]. The prognosis and quality of life of these patients critically depend on the successful control of comorbid metabolic disorders, the prevalence of which is steadily increasing. In particular, type 2 diabetes mellitus (T2DM) and obesity are recognised not only as concomitant diseases, but also as powerful pathogenetic factors that accelerate the progression of CHF and worsen its clinical course [3, 4]. Patients with a combination of coronary artery disease (CAD), CHF and metabolic disorders show increased myocardial remodelling, diffuse fibrosis and chronic systemic inflammation. These processes create a complex cardiometabolic continuum that prevents effective risk stratification using only classical biomarkers (e.g., natriuretic peptides) [5, 6]. There

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is an urgent need to find new molecular indicators capable of reflecting the degree of interaction between metabolic dysfunction and heart damage.

Among the potential biomarkers, Growth arrest-specific protein 6 (GAS6), a vitamin K-dependent secretory protein that is a ligand for TAM (Tyro3, Axl, MerTK) family receptors, occupies a special place. GAS6 is involved in the regulation of cell proliferation, apoptosis, phagocytosis and, most importantly, myocardial fibrosis and vascular remodelling [7–9].

Recent studies highlight a direct link between GAS6 and carbohydrate metabolism disorders. In particular, high levels of GAS6 have been shown to be associated with obesity and insulin resistance (IR) in adults and adolescents, as GAS6 can affect the insulin signalling pathway through its Axl receptor, thereby contributing to the development of T2DM [10]. At the level of the cardiovascular system, GAS6/Axl activation is associated with pro-inflammatory activity, the development of atherosclerosis and fibrogenesis after ischaemic myocardial damage [11, 12]. GAS6 is also considered a mediator that reflects integrated cardiometabolic stress [13].

Despite the significant amount of data available, there is still no consensus on which component of metabolic disorders — obesity or T2DM — is the leading factor in the activation of GAS6 in the context of existing CHF and CAD.

The purpose of this study was to evaluate and verify the level of GAS6 as an independent indicator of the severity of carbohydrate metabolism disorders and a predictor of unfavourable chronic heart failure in patients with coronary artery disease against the background of concomitant type 2 diabetes mellitus and obesity.

Materials and methods

The clinical study involved 225 patients with CHF of ischemic origin who were undergoing inpatient treatment in the cardiology department of the Municipal Clinical Hospital 27 of the Kharkiv City Council. Patients were divided into four main groups based on the presence or combination of concomitant metabolic disorders, as well as one control group. The groups of examinees were comparable in terms of age and gender of patients. The data are presented in Table 1.

The level of GAS6 protein in blood serum was determined by enzyme-linked immunosorbent assay (ELISA). 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 immunoassay analyser (Austria Lab Technologies, Austria) at the biochemical department of the Central Research Laboratory of the Kharkiv National Medical University of the Ministry of Health of Ukraine. To control carbohydrate metabolism, glucose levels were determined using the glucose oxidase method; the content of glycated haemoglobin (HbA1c) in whole blood was determined by a photometric method based on the reaction with thiobarbituric acid using a commercial test system from Reagent (Ukraine); insulin concentration was determined by ELISA using a commercial test system Insulin ELISA Kit (Monobind, USA). IR was assessed using the IR index calculated according to the HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) model using the formula:

$$HOMA\text{-}IR = insulin\ (mU/ml) \times \frac{blood\ glucose\ (mmol/l)}{22.5}.$$

Patients were considered insulin resistant if their HOMA-IR index was > 2.77. To diagnose abdominal obesity, anthropometric indicators (waist and hip circumference) and body mass index (BMI) (Quetelet index) were determined, which was calculated using the formula:

$$BMI = \frac{m}{h^2},$$

where m is body weight (kg), h is height (m).

The results of the study were statistically processed using parametric and non-parametric analysis methods. Data accumulation, correction, systematisation and visualisation were performed in Excel 2010 spreadsheets (Microsoft, USA). The conformity of quantitative indicators to normal distribution was assessed using the Kolmogorov-Smirnov criterion. When the normality of distribution was confirmed, the data were described using the arithmetic mean (M) and the standard deviation (m). Fisher's criterion (F) was used to assess the differences between the studied indicators. Spearman's rank correlation coefficient (r) was used to assess the degree of correlation between samples. The critical level of significance (p) in testing statistical hypotheses was taken to be 0.05.

The study was approved by the Ethics and Bioethics Committee of the Kharkiv National Medical University and conducted in accordance with the principles of bioethics set out in the Declaration of Helsinki ("Ethical Principles for Medical Research Involving Human Subjects") and the Universal Declaration on Bioethics and Human Rights (UNESCO). All patients provided informed consent to participate in the study.

Table 1. Distribution of patients involved in the study into groups

Group	Clinical characteristics	Number of patients
Group 1	CHF with CAD + T2DM + obesity	75
Group 2	CHF with CAD + T2DM	50
Group 3	CHF with CAD + obesity	50
Group 4	CHF in CAD without metabolic disorders	50
Control group	Healthy individuals	30

Results

When assessing carbohydrate metabolism indicators in patient groups (according to Table 2), a number of statistically significant differences were found. In particular, fasting blood glucose levels in patients with CHF against a background of CAD with combined T2DM and obesity (group 1) and in patients with concomitant T2DM (group 2) were significantly higher than in group 3 — by 37 and 35.7 %, respectively ($p < 0.05$). A similar pattern was observed when comparing these two groups with group 4: glucose levels in group 4 were 43 and 41.8 % lower than in groups 1 and 2, respectively ($p < 0.05$). In addition, when comparing group 1 and 2 with the control group, a significant excess of glucose was found — by 46.6 and 45.5 %, respectively ($p < 0.05$). At the same time, no significant differences in glucose le-

Table 2. Carbohydrate metabolism indicators and serum GAS6 levels in patients with chronic heart failure of ischaemic origin with concomitant obesity and type 2 diabetes mellitus, M ± m

Indicator, units	Observation groups				Control group (n = 30)
	Group 1 (n = 75)	Group 2 (n = 50)	Group 3 (n = 50)	Group 4 (n = 50)	
Blood glucose, mmol/l	7.51 ± 0.34	7.36 ± 0.25	4.73 ± 0.09	4.28 ± 0.07	4.01 ± 0.12
p		$p_{1–2} > 0.05$ $p_{2–3} < 0.05$ $p_{2–4} < 0.05$ $p_{2–4} < 0.05$	$p_{1–3} < 0.05$ $p_{3–4} > 0.05$	$p_{1–4} < 0.05$ $p_{4–5} > 0.05$	
Insulin, mU/ml	33.46	30.41 ± 0.43	16.67 ± 0.38	7.59 ± 0.33	7.11 ± 0.26
p		$p_{1–2} > 0.05$ $p_{2–3} < 0.05$ $p_{2–4} < 0.05$	$p_{1–3} < 0.05$ $p_{3–4} < 0.05$	$p_{1–4} < 0.05$ $p_{4–5} > 0.05$	
HOMA-IR index	11.17 ± 0.42	9.95 ± 0.51	3.51 ± 0.07	1.44 ± 0.05	1.37 ± 0.08
p		$p_{1–2} > 0.05$ $p_{2–3} < 0.05$ $p_{2–4} < 0.05$	$p_{1–3} < 0.05$ $p_{3–4} < 0.05$	$p_{1–4} < 0.05$ $p_{4–5} > 0.05$	
HbA_{1c}, %	9.23 ± 0.36	8.58 ± 0.27	6.12 ± 0.04	5.69 ± 0.03	5.27 ± 0.06
p		$p_{1–2} < 0.05$ $p_{2–3} < 0.05$ $p_{2–4} < 0.05$	$p_{1–3} < 0.05$ $p_{3–4} > 0.05$	$p_{1–4} < 0.05$ $p_{4–5} > 0.05$	
GAS6, ng/ml	31.64	24.95 ± 1.43	26.98 ± 1.77	23.87 ± 2.05	19.03 ± 1.29
p		$p_{1–2} < 0.05$ $p_{2–3} > 0.05$ $p_{2–4} > 0.05$ $p_{2–5} = 0.003$	$p_{1–3} < 0.05$ $p_{3–4} < 0.05$ $p_{3–5} < 0.001$	$p_{1–4} < 0.05$ $p_{4–5} < 0.05$	$p_{1–5} < 0.001$

vels were found between group 1 and 2, as well as between group 3, 4 and the control group ($p > 0.05$).

The assessment of insulin concentration in blood serum showed similar dynamics. Hyperinsulinemia was detected in group 1: insulin levels exceeded those in group 3 by 50.2 %, in group 4 by 77.3 % and in the control group by 78.8 % ($p < 0.05$). In group 2, insulin levels also differed significantly from those in group 3, 4, and the control group, exceeding them by 45.2, 75, and 76.6 %, respectively ($p < 0.05$). Even in group 3, insulin concentration was higher than in group 4 and the control group by 54.5 and 57.3 %, respectively ($p < 0.05$). No significant difference in insulin concentration was found between group 1 and 2 ($p > 0.05$).

Similar results were obtained when analysing the HOMA-IR index. The differences between group 1 and 2, as well as between group 4 and the control group, did not reach statistical significance ($p > 0.05$). However, in group 1, the HOMA index was higher than in group 3 by 68.6 %, group 4 by 87.1 % and the control group by 87.7 % ($p < 0.05$). Patients in group 2 also had a significant excess of the HOMA-IR index: by 64.7, 85.5 % and 86.2 % compared to group 3, 4 and the control group, respectively ($p < 0.05$). In addition, in group 3, the IR index significantly exceeded the values of group 4 and the control group by 59 and 61 %, respectively ($p < 0.05$). The results obtained give grounds to assert that obesity, T2DM, hyperinsulinemia, and IR have a common pathogenetic mechanism in patients with cardiovascular pathology, and the polymorbidity of these conditions leads to the accumulation and intensification of cardiovascular risk.

Correlation analysis also demonstrated a relationship between serum GAS6 levels and carbohydrate metabolism indicators in patients with CAD against a background of concomitant type 2 diabetes mellitus and obesity. The study of the nature of the relationships between the indicators studied in the research groups (Tables 3–6) demonstrated the following connections.

Thus, in the group of patients with ischaemic heart disease against the background of combined metabolic pathology in the form of type 2 diabetes mellitus and obesity, GAS6 demonstrated reliable positive correlations of moderate strength with BMI ($r = 0.68$; $p < 0.05$), insulin ($r = 0.49$; $p < 0.05$) and HbA1c ($r = 0.43$; $p < 0.05$).

Table 3. Correlations between serum GAS6 levels and carbohydrate metabolism indicators in patients with chronic heart failure of ischaemic origin accompanied by obesity and type 2 diabetes mellitus ($r_{crit} = 0.39$)

Parameter	r	p
Glucose	0.19	> 0.05
Insulin	0.49	< 0.05
HOMA-IR index	0.23	> 0.05
HbA1c	0.43	< 0.05
BMI	0.68	< 0.05

Table 4. Correlations between serum GAS6 levels and carbohydrate metabolism indicators in patients with chronic heart failure of ischaemic origin with concomitant type 2 diabetes mellitus ($r_{crit} = 0.39$)

Parameter	r	p
Glucose	0.36	> 0.05
Insulin	0.41	< 0.05
HOMA-IR index	0.28	> 0.05
HbA1c	0.40	< 0.05
BMI	0.31	> 0.05

Table 5. Correlations between serum GAS6 levels and carbohydrate metabolism indicators in patients with chronic heart failure of ischaemic origin with concomitant obesity (r_{crit} = 0.39)

Parameter	r	p
Glucose	0.29	> 0.05
Insulin	0.51	< 0.05
HOMA-IR index	0.61	< 0.05
HbA1c	0.41	< 0.05
BMI	0.54	< 0.05

Table 6. Correlations between serum GAS6 levels and carbohydrate metabolism indicators in patients with chronic heart failure of ischemic origin without concomitant metabolic pathology (r_{crit} = 0.39)

Parameter	r	p
Glucose	0.26	> 0.05
Insulin	0.23	> 0.05
HOMA-IR index	0.19	> 0.05
HbA1c	0.17	> 0.05
BMI	0.31	> 0.05

In the group of patients with CHF in CAD with concomitant T2DM, GAS6 had significant correlations of moderate strength with insulin ($r = 0.41$; $p < 0.05$) and HbA1c ($r = 0.40$; $p < 0.05$).

Significant correlations were also found in the group of patients with coronary artery disease and concomitant obesity. GAS6 had a significant moderate correlation with BMI ($r = 0.54$; $p < 0.05$), insulin ($r = 0.51$; $p < 0.05$) and HbA1c ($r = 0.41$; $p < 0.05$) and the HOMA-IR index ($r = 0.61$; $p < 0.05$).

No significant correlations were found in the group of patients with isolated ischaemic CHF.

These results suggest that GAS6 is a potential integral biomarker reflecting the degree of metabolic inflammation and profibrotic activity closely associated with hyperinsulinemia and obesity in the structure of comorbid cardiometabolic pathology.

Discussion

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 ischaemic CAD. The key finding 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. This fact is consistent with current beliefs that obesity initiates systemic inflammation and metabolic dysregulation, leading to adverse myocardial remodelling [14, 15]. Thus, in their study, J. Chylikova et al. consider the role of M1 macrophages in adipose tissue in the synthesis of pro-inflammatory cytokines (TNF-α, interleukin IL-6 and MCP-1) and their role in the development of insulin resistance [16], while T.S. Larsen et al. consider systemic inflammation and metabolic dysregulation as triggers of insulin signalling dysfunction and inefficient oxidation of substrates (mainly fatty acids) in the heart muscle, which ultimately leads to a decrease in the functional efficiency of the heart [17]. The review by S. John et al. [18] summarises the results of many years researches examining obesity in the context of the activation of profibrotic processes, in particular transforming growth factor β, which is a marker of fibrosis. The GAS6 protein, as 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 [19, 20]. Although T2DM also shows a moderate significant association with GAS6, the absence of a significant increase in GAS6 in patients with CAD and isolated T2DM suggests that obesity, rather than isolated T2DM, is a more potent trigger for the activation of this protein [21]. This highlights the critical role of hypertrophied adipose tissue in pathogenesis.

Studies show that GAS6, acting through its AXL receptor, actively contributes to the development of insulin resistance. C. Schott et al. found that the GAS6/AXL complex interacts with the insulin receptor, altering signalling pathways and enhancing endocytosis of insulin receptors in muscle cells, which essentially reduces the sensitivity of cells to insulin [10].

Elevated levels of circulating GAS6 and soluble AXL are often observed in patients with obesity and metabolic syndrome, confirming that excess adipose tissue is a powerful trigger for the activation of this biomarker. GAS6 may be involved in adipose tissue remodelling and inflammatory processes associated with obesity.

The results of the study also confirm the association of elevated GAS6 levels with more pronounced structural myocardial damage, which correlates with studies investigating the role of GAS6/AXL in the cardiovascular system. Thus, the works of T. Ma et al. [22, 23] show that GAS6 levels increase significantly in hypertrophied myocardium and in the presence of signs of heart failure. Experimental models demonstrate that blocking or "turning off" GAS6 can reduce the degree of myocardial hypertrophy and fibrosis, as well as improve contractile function [24].

According to P. Petsophonsakul et al., GAS6 is also involved in the processes of vascular wall remodelling and smooth muscle cell proliferation, which are key in the development of atherosclerosis and hypertension — the main components of CAD [25]. Thus, GAS6 is a marker not only of metabolic but also of structural and functional changes in the cardiovascular system.

Current research considers GAS6 to be a molecular bridge between metabolic dysfunction and the progression of CHF due to its direct effect on the deterioration of cell sensitivity to insulin and its probable involvement in fibrogenesis and adverse myocardial remodelling.

Therefore, high GAS6 levels in patients with a combination of T2DM and obesity reflect an increased degree of metabolic risk and serve as a signal of the active involvement of profibrotic and inflammatory mechanisms that worsen the prognosis in ischaemic CHF.

The results emphasise the need for aggressive treatment of obesity and associated metabolic disorders, as these factors contribute most to the increase in the profibrotic signal re-

flected through GAS6. GAS6 thus indicates a potential target or indicator of the effectiveness of therapeutic interventions aimed at reducing body weight and improving metabolic control.

Conclusions

1. Patients with chronic heart failure against a background of ischaemic heart disease in the presence of concomitant metabolic pathology in the form of type 2 diabetes mellitus and obesity demonstrated the most pronounced carbohydrate profile abnormalities. This is confirmed by hyperglycaemia, hyperinsulinaemia and insulin resistance. Such polymorbidity indicates an increase in chronic inflammation and glucotoxicity, which cumulatively exacerbates tissue damage and functional insufficiency of the cardiovascular system.

2. It has been established that the presence of obesity in the structure of polymorbid pathology is a key factor in the activation of the circulating protein GAS6 in patients with ischemic heart failure. The highest average GAS6 level was recorded in patients with chronic heart failure that developed against the background of coronary artery disease, type 2 diabetes mellitus and obesity (32.03 ± 2.06 ng/ml), which is significantly higher than in the control group (19.03 ± 1.29 ng/ml) ($p < 0.05$). This fact is also confirmed by a strong positive correlation between GAS6 levels and body mass index ($r = 0.68$; $p < 0.05$), as well as a moderate correlation with insulin ($r = 0.49$; $p < 0.05$) and HbA1c ($r = 0.43$; $p < 0.05$). Thus, GAS6 is a potential integral biomarker that reflects the degree of metabolic inflammation and profibrotic activity closely associated with hyperinsulinemia and the presence of obesity in the structure of comorbid cardiometabolic pathology.

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Received 24.10.2025
Revised 22.12.2025
Accepted 16.01.2026

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Conflicts of interests. Author declares the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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GAS6 як індикатор порушень вуглеводного обміну в пацієнтів з ішемічною серцевою недостатністю та коморбідними метаболічними розладами

Резюме. ***Актуальність.*** Коморбідний перебіг ожиріння та цукрового діабету 2-го типу (ЦД2) значно погіршує загальний тягар хронічної серцевої недостатності з ішемічною хворобою серця, пришвидшуючи дисфункцію міокарда й дифузний фіброз через хронічне системне запалення. Білок GAS6 виступає ключовим ланцюгом у цьому складному кардіометаболічному континуумі, активно призводячи до інсулінорезистентності шляхом зміни сигналінгу інсулінових рецепторів. Його участь у запаленні та профібротичному каскаді робить оцінку GAS6 значущою для стратифікації ризику. ***Мета:*** оцінити та перевірити рівень циркулюючого GAS6 як незалежного показника тяжкості порушень вуглеводного обміну і предиктора несприятливого перебігу хронічної серцевої недостатності в осіб з ішемічною хворобою серця на тлі супутнього цукрового діабету 2-го типу й ожиріння. ***Матеріали та методи.*** До дослідження були залучені 225 пацієнтів з ішемічною серцевою недостатністю, розділені на чотири основні групи залежно від поєднання ЦД2 та/або ожиріння, а також контрольна група здорових осіб (n = 30). Рівень GAS6 у сироватці крові визначали імуноферментним методом. Вуглеводний обмін оцінювали за вмістом глюкози, інсуліну, HbA1c та індексом HOMA-IR. Для статистичного аналізу використовували коефіцієнти кореляції (r) із r_{crit} = 0,39 для оцінки взаємозв'язків. ***Результати.*** Пацієнти групи 1 (із супутнім ЦД2 та ожирінням) мали найсерйозніші порушення вуглеводного профілю, включаючи гіперінсулінемію та високий індекс HOMA-IR. Рівень GAS6 також був найвищим у групі 1 (32,03 ± 2,06 нг/мл) та групі 3 (із супутнім ожирінням), значно перевищуючи показник контрольної групи (19,03 ± 1,29 нг/мл) ($p < 0,05$). Кореляційний аналіз у групі 1 продемонстрував найсильніший позитивний зв'язок між GAS6 та індексом маси тіла ($r = 0,68$; $p < 0,05$). Також було виявлено значущі кореляції з рівнем інсуліну ($r = 0,49$; $p < 0,05$) та HbA1c ($r = 0,43$; $p < 0,05$). ***Висновки.*** Наявність ожиріння є ключовим фактором, який активує циркуляцію GAS6 у пацієнтів із хронічною серцевою недостатністю ішемічного генезу. GAS6 діє як потенційний інтегрований біомаркер, що відображає ступінь метаболічного запалення й профібротичної активності. Сильний зв'язок між високим рівнем GAS6 та індексом маси тіла свідчить про його корисність для стратифікації ризику, особливо в пацієнтів з ожирінням.

Ключові слова: хронічна серцева недостатність; ішемічна хвороба серця; цукровий діабет 2-го типу; ожиріння; білок GAS6; вуглеводний обмін