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Adipocytokine levels in patients with atherosclerosis and high triglyceride – glucose index

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ABSTRACT

Aim. To study the levels of adipocytokines and their associations with stable and unstable atherosclerotic plaques in patients with a high triglyceride – glucose (TyG) index.

Materials and methods. The study included 109 men aged 38–79 years (mean age 62.28 ± 8.19 years) with atherosclerosis hospitalized for coronary artery bypass grafting (CABG). After microscopy of the intima – media layer, the type of atherosclerotic plaque was determined: stable / unstable. The TyG index ≥ 4.49 was considered as high. Fifty-eight (60%) men had stable plaques in the CA (28 (56%) of them had TyG ≥ 4.49); 39 (40%) men had unstable plaques in the CA (15 (39%) had TyG ≥ 4.49). Blood adipocytokine level was studied using the multiplex assay and the Human Metabolic Hormone Panel V3.

Results. The final analysis included 97 patients. The level of glucose-dependent insulinotropic polypeptide (GIP) was 1.53 times greater in patients with TyG ≥ 4.49 (34.16 [18.71; 54.98] vs. 22.34 [15.02; 34.77], $p = 0.004$). In patients with TyG < 4.49, the adipsin level was 1.2 times higher in patients with unstable plaques than in patients with stable ones. In patients with stable plaques and TyG ≥ 4.49, the GIP level was 1.88 times higher than in patients with TyG < 4.49 (42.13 [25.34; 68.95] vs. 22.39 [17.00; 28.60], $p = 0.003$). In patients with unstable plaques and TyG ≥ 4.49, the level of peptide tyrosine – tyrosine (PYY) was 1.46 times greater than in patients with TyG < 4.49 (46.14 [30.49; 70.66] vs. 31.53 [24.71; 43.01], $p = 0.048$).

Conclusion. Men with atherosclerosis and TyG ≥ 4.49 had higher blood levels of GIP and PYY. Blood adipsin levels were higher in patients with unstable plaques without insulin resistance.

Keywords: TyG index, atherosclerosis, unstable atherosclerotic plaque, glucose-dependent insulinotropic polypeptide, peptide tyrosine – tyrosine, adipsin

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committees at Research Institute of Internal and Preventive Medicine and E.N. Meshalkin National Medical Research Center (Protocol No. 2 of 05.06.2011).

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Уровни молекул, секретируемых жировой тканью, у пациентов с коронарным атеросклерозом и высоким триглицерид-глюкозным индексом

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РЕЗЮМЕ

Цель – изучение уровней адипоцитокинов, а также их ассоциаций со стабильными и нестабильными атеросклеротическими бляшками у пациентов с высоким триглицерид-глюкозным индексом (TYG).

Материалы и методы. Исследование включало 109 мужчин 38–79 лет (средний возраст 62,28 ± 8,19 лет) с атеросклерозом коронарных артерий (КА), госпитализированных на операцию коронарного шунтирования (КШ). После микроскопического исследования фрагментов интима-медиа определялся тип атеросклеротической бляшки: стабильная/нестабильная. Высоким считался TYG ≥ 4,49. Имели стабильные бляшки в КА 58 (60%) мужчин (у 28 из них (56%) TYG ≥ 4,49), 39 (40%) имели нестабильные бляшки в КА (у 15 (39%) TYG ≥ 4,49). Адипоцитокины в крови изучались при помощи мультиплексного анализа и панели Human Metabolic Hormone V3.

Результаты. В итоговый анализ вошли 97 пациентов. Уровень глюкозозависимого инсулинотропного полипептида (GIP) был в 1,53 раза выше у пациентов с TYG ≥ 4,49 (34,16 [18,71; 54,98] против 22,34 [15,02; 34,77], p = 0,004). У пациентов с TYG менее 4,49 уровень адипсина был выше у пациентов с нестабильными бляшками, чем у пациентов со стабильными, в 1,2 раза. У пациентов со стабильными бляшками и с TYG ≥ 4,49 уровень GIP был в 1,88 раза выше, чем у пациентов с TYG менее 4,49 (42,13 [25,34; 68,95] против 22,39 [17,00; 28,60], p = 0,003). У пациентов с нестабильными бляшками и TYG ≥ 4,49 уровень пептида тирозин-тирозин (PYY) был в 1,46 раза выше, чем у пациентов с TYG менее 4,49 (46,14 [30,49; 70,66] против 31,53 [24,71; 43,01], p = 0,048).

Заключение. У мужчин с коронарным атеросклерозом и TYG ≥ 4,49 в крови более высокие уровни GIP и PYY. Уровень в крови адипсина более высокий с нестабильными АСБ у пациентов без ИР.

Ключевые слова: индекс TYG, коронарный атеросклероз, нестабильная атеросклеротическая бляшка, глюкозозависимый инсулинотропный полипептид, пептид тирозин-тирозин, адипсин

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальными комитетами по этике НИИТПМ – филиал ИЦиГ СО РАН и НМИЦ им. ак. Е.Н. Мешалкина (протокол № 2 от 05.06.2011).

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INTRODUCTION

The study of atherosclerosis and unstable atherosclerotic plaques is of great importance because of their key role in the pathogenesis of cardiovascular events. Atherosclerosis is a chronic inflammatory disease characterized by the emergence of atherosclerotic plaques in the walls of arteries, leading to stenosis and impaired blood flow. In particular, unstable atherosclerotic plaques are of clinical importance because they are prone to rupture, blood clots, and subsequent acute cardiovascular events. Recent studies have focused on the role of inflammation, lipid metabolism, and plaque destabilization mechanisms in the progression of atherosclerosis and the development of unstable plaques, emphasizing the importance of further research in this area to address the global burden of cardiovascular diseases [1–3].

Abdominal obesity is a well-established risk factor for the development and progression of atherosclerosis, largely due to the release of proinflammatory adipokines and cytokines from visceral adipose tissue, resulting in chronic low-grade inflammation and endothelial dysfunction, which play a key role in the pathogenesis of atherosclerosis [4]. Moreover, insulin resistance, a hallmark of the metabolic syndrome that often accompanies abdominal obesity, can further exacerbate atherosclerosis, contributing to dyslipidemia, oxidative stress, and inflammation, which together contribute to the formation and progression of atherosclerotic plaques [5].

It was found that the TyG index, a new marker of insulin resistance, is closely associated with atherosclerosis and cardiovascular risk, mainly due to its close relationship with dyslipidemia and impaired glucose metabolism, which play a key role in the pathophysiology of atherosclerosis [6]. Understanding the complex relationship between abdominal obesity, insulin resistance, and the TyG index is important for developing targeted strategies for the prevention of atherosclerosis and related cardiovascular complications.

The aim of our research was to study the levels of adipocytokines (C-peptide, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), interleukin-6 (IL-6), leptin, monocytic chemoattractant protein-1 (MCP-1), pancreatic polypeptide (PP), peptide tyrosine – tyrosine (PYY), tumor necrosis factor alpha (TNFa), plasminogen activator inhibitor-1 (PAI-1), lipocalin, ghrelin, glucagon, adiponectin, adipsin, resistin, omentin, visfatin) and their associations with stable and unstable atherosclerotic plaques in patients with insulin resistance (IR) using the triglyceride – glucose (TyG) index.

MATERIALS AND METHODS

The study was conducted as part of joint research of the Research Institute of Internal and Preventive Medicine – branch of the Institute of Cytology and Genetics of SB RAS and E. Meshalkin National Research Medical Center of the Ministry of Health of the Russian Federation. After patients signing a written consent to participate in the study, we collected their data and blood samples. The study was approved by the local Ethics Committees at both institutions (Protocol No.2 of 5.06.2011). The study was carried out with the financial support of the state assignment No. FWNR-2024-0004 and the RSF grant No. 24-25-00079.

The study included 109 men aged 38–79 years (mean age 62.28 ± 8.19 years) who were diagnosed with stable FC II–III angina pectoris and atherosclerosis of the coronary arteries (CA) following coronary angiography findings, did not have acute coronary syndrome (ACS), and were hospitalized at the clinic of E. Meshalkin NRMC from 2011 to 2023 for coronary artery bypass grafting (CABG).

The inclusion and exclusion criteria and the stages of data collection, examination, and histologic examination of samples were described in detail in previous articles [7].

After microscopy of the intima – media layer (sampled during CABG), we determined whether atherosclerotic plaques were stable or unstable [8].

After CABG, 6 patients dropped out of the study because they developed complications, signed a voluntary waiver or it was impossible to contact them. It was not possible to determine the type of a plaque in 6 patients. The final analysis included 97 patients. Insulin resistance in patients was determined using the TyG index (ln [triglycerides (mg / dl) x glucose (mg/dl)] / 2.). The optimal cut-off point was 4.49, with the sensitivity of 82.6% and specificity of 82.1% (AUC = 0.889, 95% CI: 0.854–0.924) [9].

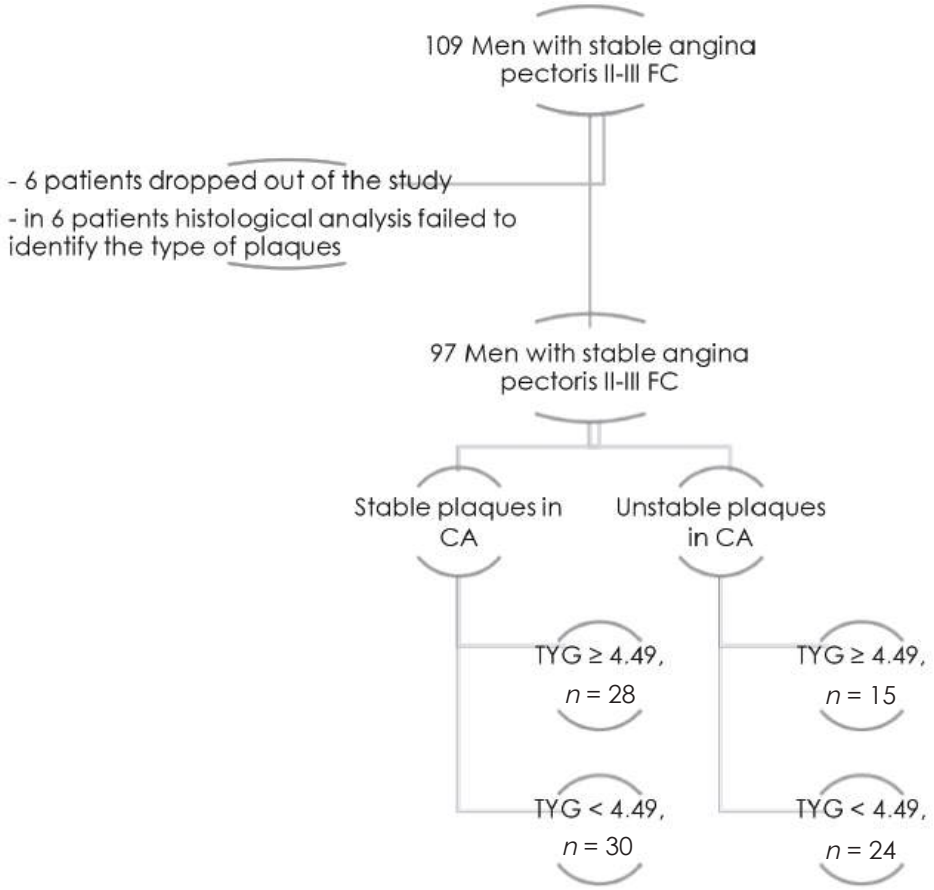

Fig. 1. Research design. CA – coronary arteries, FC – functional class, TyG – triglyceride – glucose index

In the study group, 58 (60%) men had stable plaques in CA (28 (56%) of them had TyG index ≥ 4.49, which, according to studies, is associated with insulin resistance [9]), and 39 (40%) men had unstable plaques in CA (15 (39%) had TyG index ≥ 4.49).

Biochemical studies were carried out using the enzymatic method on the Konelab 30i analyzer (Thermo, Finland). We applied the Luminex MAGPIX multiplexing system and the multiplex assay using the Human Metabolic Hormone Panel V3 (MILLIPLEX, Germany) to determine the levels of the following parameters: C-peptide, GIP, GLP-1, IL-6, leptin, MCP-1, PP, PYY, TNFa, PAI-1, lipocalin, ghrelin, glucagon, adiponectin, adipsin, resistin, omentin, and visfatin.

The statistical analysis was carried out using the SPSS 13.0 software package. The Kolmogorov – Smirnov test was used to estimate the distribution of variables. Since the distribution of quantitative variables was nonparametric, we used the median of the interquartile range *Me* (Q_{25}; Q_{75}). The Mann – Whitney *U*-test (for two independent samples) and the Kruskal – Wallis test were used to compare the samples. The Spearman's rank correlation coefficient (r_s) was applied to analyze the dependence of quantitative features of individual data from data aggregates. Qualitative variables were presented as absolute values *n* and fractions in %. The Pearson's χ^2 test was used to assess the differences between qualitative variables. The results were considered statistically significant at $p < 0.05$.

RESULTS

Table 1 presents data from patients with high and low TyG index and stable or unstable plaques. Type 2 diabetes mellitus was more common in patients with unstable plaques and TyG ≥ 4.49 than in patients with stable plaques and TyG ≥ 4.49 (53% vs. 11%, $p = 0.006$) (Table 1). All patients were diagnosed with essential hypertension and received antihypertensive therapy to achieve the target blood pressure values.

Dyslipidemia in patients of both groups was determined by an increase in the level of lipoproteins and lipids above the optimal value [1].

The patients included in the study had a very high cardiovascular risk, so dyslipidemia was determined at LDL-C levels > 55 mg / dl and at TG levels > 150 mg / dl. All patients with coronary artery disease received statin therapy at maximum tolerated doses, regardless of the presence of dyslipidemia.

Table 1

Characteristics of patient groups depending on TyG index and plaque type (stable/unstable)

Parameter	Patients with stable plaques and TyG ≥ 4.49, *n* = 28	Patients with unstable plaques, TyG ≥ 4.49 *n* = 15	*p*	Patients with stable plaques, TyG < 4.49, *n* = 30	Patients with unstable plaques, TyG < 4.49, *n* = 24	*p*
Average age	63.00 [57.00; 67.50]	59.00 [54.00; 65.00]	0.338	64.00 [57.25; 70.75]	62.00 [56.25; 68.00]	0.567
BMI, kg / m^2	29.84 [26.97; 32.14]	29.72 [26.83; 31.70]	0.899	26.67 [25.35; 30.12]	29.11 [25.97; 32.74]	0.169
WC more than or equal to 94 cm	16 (57.1%)	9 (60.0%)	0.856	10 (33.3%)	8 (33.3%)	0.933
WC, cm	92.00 [88.00; 100.00]	93.50 [89.00; 100.50]	0.530	89.00 [82.75; 99.50]	88.00 [84.50; 94.00]	0.864
SBP, mmHg	130.00 [121.25; 140.00]	125.00 [120.00; 142.00]	0.691	135.00 [127.00; 148.33]	137.00 [132.00; 143.00]	0.535
DBP, mmHg	80.50 [80.00; 89.50]	80.00 [78.33; 81.67]	0.301	80.00 [75.00; 90.00]	80.00 [80.00; 89.50]	0.485
Smoking status, abs. %	17 (61%)	10 (67%)	0.784	24 (80%)	22 (92%)	0.230
T2DM, abs. %	3 (11%)	8 (53%)	0.006	4 (13%)	4 (17%)	0.732
Cholesterol, mmol / l	4.17 [3.46; 4.88]	4.50 [3.57; 5.09]	0.628	3.92 [2.51; 4.46]	3.51 [3.13; 4.42]	0.862
Triglycerides, mmol / l	1.09 [1.02; 1.32]	0.86 [0.77; 1.44]	0.177	0.69 [0.58; 0.86]	0.62 [0.49; 0.78]	0.246
HDL-C, mmol / l	0.59 [0.47; 0.71]	0.61 [0.53; 0.70]	0.655	0.61 [0.52; 0.80]	0.70 [0.53; 0.89]	0.293
LDL-C, mmol / l	2.98 [2.47; 3.74]	3.46 [2.26; 3.79]	0.760	2.85 [1.67; 3.39]	2.41 [1.98; 3.40]	0.947
Glucose, mmol / l	6.70 [5.63; 8.43]	6.80 [5.90; 8.00]	0.721	5.25 [4.83; 5.68]	5.25 [4.80; 6.08]	0.573

Note. BMI – body mass index, WC – waist circumference, SBP – systolic blood pressure, DBP – diastolic blood pressure, T2DM – type 2 diabetes mellitus, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol.

In all patients, we assessed the levels of adipocytokines (C-peptide, GIP, GLP-1, IL-6, leptin, MCP-1, PP, PYY, TNFa, PAI-1, lipocalin, ghrelin, glucagon, adiponectin, adipsin, resistin, omentin, visfatin) in the subgroups with low (< 4.49) and high (≥ 4.49) TyG index. The GIP level was 1.53 times higher in patients with TyG ≥ 4.49 (34.16 [18.71; 54.98] vs. 22.34 [15.02; 34.77], $p = 0.004$) (Fig. 2).

Next, adipocytokine levels were assessed in the subgroups with low (< 4.49) and high (≥ 4.49) TyG index in patients with unstable and stable atherosclerotic plaques in the CA (Table 2). In patients with TyG < 4.49, the adipsin level was 1.2 times higher in patients with unstable plaques than in patients with stable ones.

In patients with stable plaques and TyG ≥ 4.49, the GIP level was 1.88 times higher than in patients with stable plaques and TyG < 4.49 (42.13 [25.34; 68.95] vs. 22.39 [17.00; 28.60], $p = 0.003$).

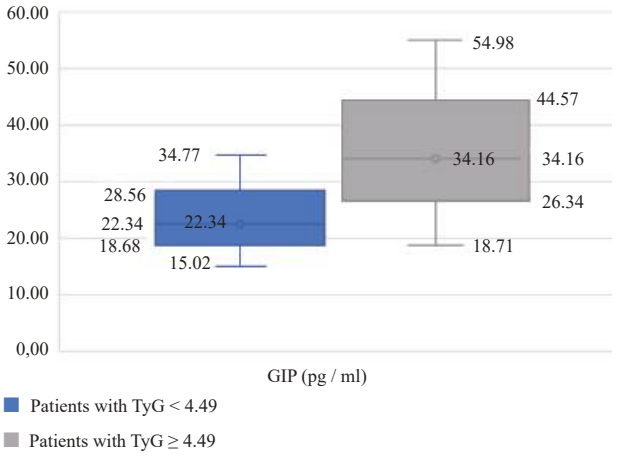

Fig. 2. GIP level (pg / ml) in patients with TyG < 4.49 and TyG ≥ 4.49

In patients with unstable plaques and TyG ≥ 4.49, the PYY level was 1.46 times higher than in patients with unstable plaques and TyG < 4.49 (46.14 [30.49; 70.66] vs. 31.53 [24.71; 43.01], $p = 0.048$).

Table 2

The content of adipocytokines depending on the TyG index and the type of atherosclerotic plaque, *Me* (Q_{25}; Q_{75})

Parameter	Patients with stable plaques and TyG ≥ 4.49, *n* = 28	Patients with unstable plaques, TyG ≥ 4.49 *n* = 15	*p*	Patients with stable plaques, TyG < 4.49 *n* = 30	Patients with unstable plaques, TyG < 4.49 *n* = 24	*p*
C-peptide, ng / ml	1.40 [0.36; 2.43]	1.57 [0.65; 1.90]	0.838	0.76 [0.14; 1.64]	0.83 [0.41; 1.65]	0.403
GIP, pg / ml	42.13 [25.34; 68.95]	26.22 [16.18; 47.27]	0.165	22.39 [17.00; 28.60]	19.55 [12.42; 38.63]	0.824
GLP-1, pg / ml	308.62 [192.49; 742.65]	403.22 [156.31; 671.80]	0.610	275.78 [185.12; 595.60]	432.65 [216.1; 680.38]	0.159
IL-6, pg / ml	5.96 [1.83; 14.48]	7.74 [3.73; 13.35]	0.462	7.14 [2.50; 13.06]	6.55 [1.67; 18.59]	0.709
Leptin, pg /ml	5,764.73 [3,516.42; 8,006.34]	5,874.95 [1,559.14; 12,266.47]	0.894	2,977.39 [869.98; 7,650.03]	4,426.24 [1,105.64; 11,135.62]	0.401
MCP-1, pg / ml	259.25 [154.81; 348.13]	215.00 [182.92; 277.42]	0.610	226.53 [142.34; 334.38]	215.81 [135.90; 325.78]	0.986
PP, pg / ml	87.44 [55.29; 165.58]	87.23 [578.68; 138.54]	0.549	65.34 [36.94; 156.61]	65.35 [39.50; 139.91]	0.914
PYY, pg / ml	46.97 [33.45; 58.99]	46.14 [30.49; 70.66]	0.908	43.01 [25.05; 73.71]	31.53 [24.71; 43.01]	0.105
TNFα, pg / ml	5.52 [3.43; 7.27]	5.66 [4.36; 7.19]	0.593	5.24 [3.11; 7.19]	5.80 [4.75; 6.70]	0.441
PAI-1, ng / ml	30.54 [13.56; 42.04]	20.55 [12.01; 46.98]	0.858	18.19 [13.34; 32.14]	21.04 [15.32; 31.66]	0.354
Lipocalin, ng / ml	551.70 [270.83; 798.91]	386.98 [196.64; 770.38]	0.537	374.40 [173.47; 597.15]	399.19 [204.80; 642.77]	0.932
Ghrelin, pg / ml	17.29 [10.19; 37.55]	13.06 [9.23; 17.29]	0.109	17.29 [9.56; 23.62]	9.23 [9.23; 23.62]	0.288
Glucagon, pg / ml	10.07 [5.89; 23.44]	7.39 [32.68; 28.38]	0.554	10.83 [3.71; 27.04]	7.87 [3.25; 15.28]	0.304
Adiponectin, mcg / ml	32.43 [15.03; 43.15]	13.85 [7.04; 30.45]	0.428	24.27 [13.80; 38.31]	27.91 [15.65; 41.89]	0.608
Adipsin, mcg / ml	9.69 [6.97; 15.96]	9.14 [7.48; 13.10]	0.067	9.39 [5.14; 12.89]	11.13 [10.08; 15.77]	0.032
Resistin, ng / ml	29.02 [13.81; 43.90]	40.76 [22.16; 62.09]	0.650	40.00 [8.95; 63.49]	29.67 [8.08; 67.54]	0.572
Omentin, ng / ml	0.84 [0.65; 1.27]	0.89 [0.73; 1.64]	0.380	1.15 [0.52; 1.38]	0.92 [0.82; 1.38]	0.827
Visfatin, ng / ml	76.84 [17.28; 135.20]	23.86 [17.84; 74.09]	0.320	101.47 [23.86; 127.87]	66.15 [22.60; 113.46]	0.581

Note. GIP – glucose-dependent insulinotropic polypeptide, GLP-1 –glucagon-like peptide-1, IL-6– interleukin-6, MCP-1 – monocyte chemoattractant protein-1, PP – pancreatic polypeptide, PYY – peptide tyrosine – tyrosine, TNFα – tumor necrosis factor alpha, PAI-1 – plasminogen activator inhibitor-1

DISCUSSION

The detection of GIP receptors on the surface of fat cells [10] led to the assumption that GIP participates in fat metabolism [11, 12]. The consumption of foods rich in fats stimulates the release of GIP more strongly than carbohydrates or proteins, and a high-fat diet leads to an increase in the expression of the *GIP* gene and an increase in its concentration in the blood. At the cellular level, activation of the GIP receptor on the adipocyte leads to anabolic effects, including increased glucose uptake into tissues, activation of lipoprotein lipases, and synthesis of free fatty acids.

These data indicate that GIP plays an important role in fat metabolism. The study by E.A. Shestakova showed significantly higher GIP levels in the group of patients with BMI ≥ 35 kg / m^2 compared to those with lower BMI both on an empty stomach and after meals. Similarly, GIP secretion was significantly higher in individuals with insulin resistance (determined by HOMA-IR) compared to individuals without it [13]. In our study, the GIP level was 1.53 times higher in patients with insulin resistance and coronary artery disease according to the TyG index, which was mostly due to its high level in the subgroup of patients with stable plaques.

The study by O.H. Ukkola et al. suggests that a high concentration of PYY in fasting blood serum is independently associated with obesity and insulin resistance [14]. The association of high PYY with high insulin levels was evident among study participants with both type 2 diabetes mellitus and normal glucose levels. Earlier data suggested that different forms of PYY may have different effects on insulin metabolism [15]. Interestingly, low serum PYY levels were associated with insulin resistance in first-degree relatives in patients with type 2 diabetes mellitus [16]. It is yet to be studied whether high insulin levels can affect PYY secretion or secretion of other intestinal peptides that affect PYY concentration. In our study, in patients with unstable plaques and insulin resistance according to the TyG index, the PYY level was 1.46 times higher than

in patients with unstable plaques without insulin resistance.

Adipsin is formed during lipolysis and stimulates appetite [17]. Adipsin levels are reported to be higher in obese people. In addition, overweight people often experience an increase in adipsin levels [18]. T. Ohtsuki et al. showed that patients with coronary artery disease without obesity have higher serum adipsin levels [19]. At the same time, the level of adipsin in the blood of patients with coronary artery disease is significantly and positively associated with the incidence of atherosclerotic plaque with a thin fibrous cap [20]. In the study conducted in patients with TyG < 4.49, the level of adipsin was higher in patients with unstable plaques than in patients with stable ones, which may indicate the association of adipsin with the progression of atherosclerotic foci.

CONCLUSION

Men with coronary artery disease and insulin resistance have higher blood levels of GIP in the general sample and PYY in patients with unstable atherosclerotic plaques. The blood level of adipsin is higher in patients with unstable atherosclerotic plaques and without insulin resistance.

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