ORIGINAL STUDY

Сравнительная характеристика параметров липидного спектра и маркеров сосудистого воспаления в группах пациентов со стабильной стенокардией при наличии и отсутствии сахарного диабета 2 типа

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Обоснование. *Несмотря на интенсивные исследования атеросклероза, ассоциированного с сахарным диабетом (СД), механизмы тесной взаимосвязи между диабетом и ишемической болезнью сердца (ИБС) пока полностью не обозначены, вследствие этого интенсивно продолжаются поиск и изучение других причин, в частности, процессов сосудистого воспаления, ускоряющих и усугубляющих развитие атеросклеротического поражения сосудов и их осложнений, что определяет актуальность изучаемой нами проблемы.*

Цель. *Провести сравнительный анализ и выявить особенности параметров липидного спектра и маркеров сосудистой воспалительной реакции у пациентов с ИБС, стабильной стенокардией без и в сочетании с СД 2 типа (СД2).*

Методы. *Обследовано 169 пациентов (60,3±9,8 лет) с ИБС, стабильной стенокардией напряжения. Пациенты распределены: 1-я группа – больные ИБС (n=123), 2-я группа – ИБС с СД2 (n=46). Исследованы параметры липидного профиля, маркеры сосудистой воспалительной реакции, маркеры эндотелиальной дисфункции. Исследование биохимических параметров проводилось в группах пациентов до проведения коронароангиографии (КАГ).*

Результаты. *В обеих группах пациентов выявлено превышение референсных значений атерогенных параметров липидного профиля (ОХС, ЛПНП, ЛПОНП, ТГ). Зарегистрировано достоверное превышение уровня маркеров сосудистого воспаления (вч-СРБ, гомоцистеина, ИЛ-1β) и превышение нормативных значений ФНО-α, ММР-9, эндотелина-1 в группе пациентов с ИБС и СД2, что свидетельствует о наличии более выраженного процесса сосудистой воспалительной реакции в данной группе больных.*

Заключение. *Системный характер сосудистой воспалительной реакции более выражен у пациентов с ИБС и СД2 по сравнению с пациентами без диабета, что свидетельствует о наличии повышенного потенциала в развитии нежелательных сосудистых осложнений.*

Ключевые слова: *сахарный диабет 2 типа; ишемическая болезнь сердца; липидный профиль; маркеры воспаления*

Comparative characteristics of lipid spectrum parameters and markers of vascular inflammation in patients with stable angina with presence and absence of type 2 diabetes mellitus

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Backgraund. *Despite intensive study of atherosclerosis in diabetes, the mechanisms of the close relationship between diabetes and coronary artery disease have not been studied fully. The search and study of other factors continue, in particular the processes of inflammatory vascular reactions, which accelerate and enhance the development of atherosclerotic vascular lesions and their complications, that determines the urgency of the problem of the study.*

Aims. *To compare features of lipid profile and inflammatory markers in patients with coronary artery disease (CAD), stable angina and patients with and without diabetes mellitus of type 2 (DM) .*

Materials and methods. *A total of 169 patients were examined. Group 1 included 123 patients with CAD without DM. Group 2 consisted of 46 patients with CAD and DM. The study of biochemical parameters was carried out in the Group 1and 2 prior to the coronary angiography.*

Results. *In both groups of patients, the excess of the reference values of atherogenic parameters of the lipid profile (TC, LDL, VLDLP, TG) was revealed. A significant increase in the level of markers of vascular inflammation (hs-CRP, homocysteine, IL-1β) and exceeding of the normative values of TNF-α, MMP-9, endothelin-1 in the group of patients with coronary artery disease and diabetes mellitus was registered, that indicates a more pronounced process of vascular inflammatory reactions in this group of patients*

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Conclusions. *The systemic nature of the vascular inflammatory response is more pronounced in patients with CAD associated with type 2 diabetes than in patients without diabetes, that indicates an increased potential in the development of unwanted vascular complications.*
Keywords: *diabetes mellitus; coronary disease; lipids; inflammation*

Most countries report a dramatic increase in the incidence of diabetes mellitus (DM), as DM is one of the most common non-infectious diseases. According to the recent data, the overall number of diabetic patients in the world has more than doubled over the last 10 years. By the end of 2014, numbers reached 387 million. As of 1st January 2015, a total of 4.1 million of patients with DM were registered by the Russian State Register of Diabetic Patients with 3.7 million having type 2 DM (T2DM) [1]. Furthermore, the results of epidemiological studies, carried out by the Endocrinological Research Centre between 2002 and 2010, suggest that the true prevalence of the disease is 3–4 times higher than the official numbers and reaches 9–10 million, accounting for 7% of the adult population. By 2030, the number of DM patients is expected to increase to reach 438.7 million, with approximately 7.7% of the adult population affected by the disease [2, 3]. DM and its complication pose a major threat to global public health [4].

Patients with T2DM are at 2–4 times greater risk for coronary artery disease (CAD) compared to individuals without hyperglycemia. DM increased the risk of cardiovascular complications by 4–6 fold, which account for more than 75% of all hospitalisations and 80% of all deaths of patients with DM [2]. Several large studies (including the Framingham study (1979), the multiple risk factor intervention trial (MRFIT, 1993), the multinational monitoring of trends and determinants of cardiovascular disease (MONICA), and the thrombolysis in myocardial infarction (TIMI, 1997–2006)) demonstrated the following findings: DM increased the risk of CAD by 66% in men and 203% in women; DM is an established coronary risk factor independent of the level of cholesterol, smoking and blood pressure; and five-year mortality after myocardial infarction (MI), as well as the mortality associated with unstable angina and non-ST-elevation MI, is twice as high in diabetic patients as in non-diabetic patients. According to the pathomorphological and angiographic data for CAD, individuals with DM are characterised by more severe, diffuse and distal lesions in the coronary arteries (three-vascular lesions, multi-segmental lesions in a single artery). Moreover, atherosclerosis in T2DM patients is often multifocal and affects other arteries, in addition to the coronary arteries. [2, 5].

Despite the intensive study of the DM-associated atherosclerosis, the mechanisms of interaction between diabetes and CAD remain largely unknown. Researchers continue to investigate other factors that can possibly accelerate and exacerbate atherosclerotic lesions and their complications [2, 6]. Circulating inflammatory factors and procoagulants play an important role in the pathogenesis of vascular damage in atherosclerosis and the impact of chronic inflammation is under actively investigation. DM is strongly associated with the increased levels of subclinical inflammation markers. It is well known that diabetic patients with CAD have higher concentrations of markers, such as C-reactive protein (CRP), cytokines, fibrinogen and peripheral blood leukocytes than non-diabetic patients with CAD [6, 7]. During the last decades, insulin resistance (IR) is considered an important risk factor of atherosclerosis. Arteriosclerosis and IR are believed to have similar pathogenic mechanisms, primarily associated with two main pro-inflammatory cytokines: tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) [9]. In addition to the generally accepted and widely used laboratory markers, such as CRP, homocysteine, endothelin-1 and cytokines, increasing attention is being paid to the new biochemical mediators of inflammation, including matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), molecules of the CD40 ligand/CD40-signalling pathway, and other factors that have a prominent role in the initiation of early atherosclerotic changes, their progression, and the development of acute thrombotic complications [10]. Elevated levels of inflammatory markers and markers of endothelial dysfunction increase the risk of acute atherothrombotic events, especially after percutaneous coronary intervention both in diabetic and non-diabetic patients with CAD [1]. The degree of systemic inflammation should be considered as a main marker of the processes promoting vessel wall lesions and destructive changes in the atherosclerotic plaques in patients with CAD and DM.

Aim

The present study was undertaken to identify specific features of the lipid profile and vascular inflammatory markers in patients with CAD and stable angina with the presence of T2DM.

Materials and methods

We examined 169 patients (both males and females) aged 60.3 ± 9.8 years with CAD and stable exertional angina. Patients were divided into two groups: the first group included participants with CAD (n=123), while the second one included participants with CAD and T2DM (n=46). Laboratory testing was performed in both groups upon admission to the hospital prior to coronary angiography (CAG).

The study protocol was approved by the Ethic Committees of the Tyumen Cardiology Research Center and the Tomsk National Research Medical Center of the

Russian Academy of Sciences, Tomsk, Russia (protocol No. 12 dated 15.10.2014). All patients gave signed informed consent for participation in the study.

The exclusion criteria were as follows: acute coronary syndrome developed within the last 30 days, acute disorders of cerebral circulation developed within the last 6 months, type 1 DM (T1DM), functional class (FC) IV chronic heart failure (CHF) (based upon NYHA guidelines), cancer and mental disorders.

The diagnostics of CAD and concomitant diseases was conducted in accordance with recommendations of the European Society of Cardiology (ESC), Russian Society of Cardiology (RSC) and European Association for the Study of Diabetes (EASD). It included the following diagnostic procedures: clinical examination, laboratory and instrumental assessment of the coronary circulation (selective CAG).

CAG was performed using the femoral route based upon the standard method developed by M. Judkins (1967) using the angiographic complexes 'Diagnost ARC A', 'Polydiagnost C', 'IntegrisAllura' (Phillips, Netherlands). We evaluated the number of affected coronary arteries (CA) and the maximum percentage of stenosis.

Blood samples were collected into VACUETTE® tubes (Japan) after overnight fasting. The tubes were centrifuged for 15 min at 2,500 rpm using a Sigma centrifuge (Germany). Serum was aliquoted and then frozen at–700C. Prior to testing, the frozen aliquots were thoroughly mixed.

The parameters of lipid metabolism were evaluated using the automatic biochemical analyser COBAS INTEGRA® 400 plus (Roche, Switzerland). The serum triglycerides (TG) and total cholesterol (TC) levels were measured using an enzymatic-colorimetric method. The levels of high-density lipoproteins (HDL) and low-density lipoproteins (LDL) were assessed using the direct enzymatic-colorimetric method. The levels of apolipoproteins A-I (Apo A-I), apolipoproteins B (Apo-B), and lipoproteins a (LP(a)) were analysed using the immunoturbidimetric method using kits and control materials provided by Roche Diagnostics GmbH (Roche, Germany).

The following inflammatory markers were evaluated: high-sensitivity CRP (hs-CRP, reference interval 0–3.0 mg/L) measured using immunoturbidimetric method with the 'C-reactive proteins' kit (BioSystem, Spain) using the semi-automatic open type analyser Clima MC-15 (Spain); interleukin-1 beta (IL-1β, reference interval 0–5.0 pg/mL), IL-6, interleukin-8 (IL-8), TNF-α, reference interval 0–8.11 pg/mL measured by sandwich ELISA, homocysteine (HYC, reference intervals 5.0–15.0 μmol/L) measured by solid-phase competitive chemiluminescent enzyme immunoassay with diagnostic kits. IL-1β, IL-6, IL-8, TNF-α, homocysteine were analysed using the Immulite 1000 Immunology Analyser (Siemens Diagnostics, USA). Soluble CD40 and its ligand (sCD40 L) were measured by sandwich ELISA with Human sCD40L Elisa kits using the BenderMedSystems Analyser (BenderMedSystems, Austria). CD40 receptor and matrix metalloproteinase-9 (MMP-9, reference intervals 20.3–77.2 ng/mL) were measured using the Bender Med Systems Bioscience company, Austria, and tissue inhibitor of metalloproteinase-1 (TIMP-1, reference intervals 92–116 ng/mL) was measured with a TIMP-1 Human ELISA Kit (Invitrogen, USA) using the Personal LAB™ Automatic ELISA analyser (Italy).

Glucose metabolism was estimated using the levels of glucose and glycated haemoglobin (HbAlc). Blood glucose was measured by an enzymatic hexokinase method using the automatic biochemical analyser COBAS INTEGRA® 400 plus (Roche, Switzerland). Glycated haemoglobin was measured by the chromatographic method using the Biorad D10 chemistry analyser (Biorad, USA).

The following parameters were calculated: very-low-density lipoprotein (VLDL) cholesterol: VLDL = TG/2.2; atherogenic index (AI) = (TC–HDL)/HDL; atherogenic coefficient (AC) = Apo-B/ Apo A-I.

We assessed markers of endothelial activation: the level of nitrites (reference intervals 3.77 ± 0.87 nmol/L) measured using the Human HUMALYZER 2000 Chemistry Analyser (Human, Germany, 1995) and the level of endothelin (1-21) (reference intervals 0.2–0.7 fmol/L) using the semi-automated enzyme immunoassay analyser Dynatech (Germany, 1989).

Blood specimens were collected from a peripheral vein upon admission to the hospital (prior to CAG).

Statistical data analysis was performed using the software package Statistica (SPSS Inc, ver 11.5). Normal distribution of data was checked using the Komogorov-Smirnov normality test. We used the Student's t-test to compare normally distributed continuous variables, and the Mann–Whitney U-test to compare non-normally distributed categorical and continuous variables. Comparison of paired variables was carried out using the Wilcoxon test for paired samples. We calculated means with standard deviations (M ± SD) for $p<0.05$. The Pearson's and Spearman's rank correlation coefficients were calculated to assess the correlation between normally and non-normally distributed data, respectively.

Results and discussion

Clinical and epidemiological characteristics of the patients included in the study are presented in Table 1.

There was no significant difference between the groups in age, gender, MI in anamnesis (62.6% and 65.2% for males; 37.4% and 34.8% for females), individual risk factors (smoking), presence and duration of concomitant diseases, including dyslipidemia, arterial hypertension (AH), CAD, and T2DM. Most of the patients in both groups had II FC exertional angina (68.3% and 58.7%) and stage I obesity (52.8% and 45.7%). We observed significant differences in the degree of AH and FC of the heart failure (based upon NYHA guidelines) between the groups, with the number of patients with 3rd degree AH and III FC CHF significantly higher in the group with DM ($p<0.001$). The proportion of patients with significant stenosis (vessel lumen narrowed

Table 1

Clinical and epidemiological characteristics of diabetic and non-diabetic patients with CAD (M ± SD)

Parameter	Patients with CAD (n = 123)	Patients with CAD and T2DM (n = 46)	p
Age	61.7±9.02	59.7±9.89	0.577
Male Female	43 (35%) 80 (65%)	20 (43.5%) 26 (56.5%)	0.308
Non-smokers Smokers	90 (73.2%) 33 (26.8%)	38 (82.6%) 8 (17.4%)	0.203
Duration of DM	7.5±4.20	6.5±5.13	0.617
Duration of CAD	12.7±9.70	8.6±6.25	0.148
Presence of AH Duration of AH	110 (89.4%) 11.7±5.12	44 (95.7%) 9.8±6.13	0.206 0.167
Degree of AH: 1 2 3	 1 (12.2%) 26 (23.6%) 69 (62.7%)	 0 3 (6.8%) 41 (93.2%)	0.001
FC of exertional angina: 1 2 3	 15 (12.2%) 84 (68.3%) 24 (19.5%)	 2 (4.3%) 27 (58.73%) 17 (37.0%)	0.054
FC of CHF: 1 2 3	 12 (9.8%) 97 (78.9%) 14 (11.4%)	 1 (2.2%) 28 (60.9%) 17 (37.0%)	0.001
BMI	35.9±3.91	33.0±4.76	0.114
Dyslipidemia no yes	 15(12.2%) 108(87.8%)	 2 (4.3%) 44 (95.7%)	0.131
Percentage of stenosis of the CA: Less than 50% 50–74% 75% and greater	 41 (33.3%) 50 (40.7%) 32 (26.0%)	 23 (50.0%) 4 (8.7%) 19 (41.3%)	0.032

Note: n–number of patients, %–number of patients in percent, p–significance of differences, DM–diabetes mellitus, CAD–coronary artery disease, AH–arterial hypertension, FC–functional class, CHF–chronic heart failure, BMI–body mass index, CA–coronary arteries

greater than 50%) was 66.7% and 50.0% in the first and second groups, respectively. Severe (> 75%) stenosis was more frequently observed in patients with T2DM (41.2%) than in non-diabetic patients (26.0%).

Patients in both groups were comparable in terms of their outpatient treatment, such as beta-blockers (63.6% and 86.4%), diuretics (72.7% and 59.1%), statins (27.3% and 31.8%), antiplatelet agents (45.5% and 72.7%), angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) (62.45% and 54.5%; 36.4% and 22.7%, respectively), calcium antagonists (45.5% and 27.3%, $p < 0.05$). The majority of patients with T2DM (99.4%) received hypoglycaemic drugs.

Baseline biochemical parameters of the patients included in the study are presented in Table 2.

Both diabetic and non-diabetic patients demonstrated increased levels of atherogenic lipid markers (LDL, TG, and VLDL), although these parameters did not vary significantly between the groups ($p > 0.05$). The level of TC was significantly higher in the diabetic group ($p = 0.028$), whereas the LP (a) level was higher in the CAD-only group ($p = 0.015$).

It is well known that T2DM is associated with specific quantitative and qualitative changes in the lipid profile that further increase its atherogenic potential. Non-enzymatic glycosylation of Apo proteins leads to an impaired clearance and accumulation of LDL particles. These changes are considered some of the main reasons for rapid development of atherosclerosis in T2DM [11].

Increased levels of VLDL were observed equally in both groups. Twenty patients (45.3%) with T2DM had HDL lower than 1.0 mmol/L, and 41 patients (89.1%) had hypertriglyceridemia (with TG greater than 1.75 mmol/L). Diabetic patients tended to have higher values of LDL than patients with CAD only (3.01 ± 0.80 mmol/L vs 2.91 ± 1.01 mmol/L).

The presence of a direct medium strength correlation ($r = 0.4–0.5$) between the level of glycated haemoglobin and the markers of atherogenic dyslipidemia (including TC ($p = 0.02$), VLDL ($p = 0.04$), AI ($p = 0.01$), Apo-B ($p = 0.01$), and TG ($p = 0.003$)) among the patients with T2DM is associated with diabetic dyslipidemia. Diabetic dyslipidemia is a specific variant of atherogenic dyslipidemia contributing to the development of atherosclerosis regardless of TC and VLDL levels. It carries the same risks of CAD development as isolated moderate hypercholesterolemia [12]

The mean value of LP (a) in the first and second group was borderline and comprised 30.51 ± 27.05 and 20.61 ± 19.95 mg/dL, respectively. LP (a) shares the same structural features with plasminogen, and it can be considered as a competitive antagonist of plasminogen that is able to increase the risk of thrombosis of the coronary arteries. Some retrospective studies suggest that increased levels of Lp (a) are associated with the progression of atherosclerotic plaques in the coronary arteries without stenosis [13, 14].

Chronic subclinical inflammation is a component of the insulin resistance syndrome, and cytokines are considered as predictors of vascular complications of T2DM [9].

The CAD+T2DM patients had increased production of markers of systemic and local inflammation, including hs-CRP ($p = 0.007$), homocysteine ($p = 0.001$), and TNF-α ($p = 0.056$). The levels of IL-6 and IL-8 in this group were mostly within normal levels, although they were slightly higher compared to the first group.

Patients with T2DM demonstrated significantly increased levels of IL-1β compared to non-diabetic patients ($p=0.002$). IL-1β is the main factor that mediates development of local inflammation and the acute-phase response in an organism. According to the currently available data, impaired coronary blood flow combined with myocardial ischaemia leads to an increase IL-1β levels. Several reports suggest that no activation of IL-1β in both stable and unstable angina. Some authors suppose that initiation of smouldering inflammation associated with increased levels of hs-CRP leads to IR, and the inflammation is induced by the pro-inflammatory cytokines, particularly IL-6 and IL-1β [15–18].

Increased level of homocysteine in plasma is currently considered a significant risk factor of atherosclerotic

Table 2

Baseline biochemical parameters of diabetic and non-diabetic patients with CAD (M±SD)

Parameter	Patients with CAD (n = 123)	Patients with CAD and T2DM (n = 46)	p
Lipid profile			
TC. mmol/L	4.93±1.22	5.43±1.12	0.028
HDL. mmol/L	1.12±0.26	1.10±0.22	0.170
LDL. mmol/L	2.91±1.01	3.01±0.80	0.603
TG. mmol/L	2.02±0.83	2.23±1.15	0.549
VLDL. mmol/L	0.76±0.29	0.83±0.315	0.215
AI	3.70±1.19	4.11±1.53	0.081
LP(a). mg/dL	30.51±27.05	20.61±19.95	0.015
Apo A-I. mg/dL	149.01±24.85	153.42±27.16	0.322
Apo-B. mg/dL	86.52±21.89	91.73±22.17	0.173
Markers of inflammation			
hs-CRP. mg/L	3.01±1.19	3.52±1.21	0.007
TNF-α. pg/mL	9.81±3.21	10.83±3.61	0.056
HYC. μmol/l	12.34±5.61	15.73±6.33	0.001
IL-1β. pg/mL	4.41±1.27	5.25±1.65	0.002
IL-6. pg/mL	3.73±2.58	4.34±3.37	0.357
IL-8. pg/mL	16.22±12.96	19.84±16.37	0.166
CD 40. ng/mL	90.44±36.18	92.05±40.85	0.623
sCD40L. ng/mL	3.51±1.01	3.54±1.16	0.873
TIMP-1. ng/mL	90.22±17.24	90.16±15.09	0.967
MMP-9. ng/mL	95.93±31.02	92.64±31.10	0.878
Markers of endothelial dysfunction			
Endothelin-1. fmol/L	1.02±0.414	0.90±0.477	0.114
Nitrites. nmol/L	3.02±1.24	2.94±1.30	0.599
Glucose metabolism			
Blood glucose. mmol/L	5.4±0.79	7.6±1.98	0.000
HbA1c. %	5.5±0.50	7.1±1.00	0.000

Note: n–number of patients, p–significance of differences. TC–total cholesterol, HDL–high-density lipoproteins, LDL–low-density lipoproteins, TG–triglycerides, VLDL–very low-density lipoproteins, AI–atherogenic index, LP(a)–lipoproteins a, Apo A-I–apolipoproteins A-I, Apo-B–apolipoproteins B, hs-CRP–high-sensitivity C-reactive protein, TNF-α–tumour necrosis factor-alpha, HYC–homocysteine, IL-1β–interleukin-1 beta, IL-6–interleukin-6, IL-8–interleukin-8, TIMP-1–tissue inhibitor of metalloproteinase-1, MMP-9–matrix metalloproteinase-9, HbA1c–glycated haemoglobin.

vascular lesions. Homocysteine contributes to oxidative stress through its auto-oxidation and formation of free radicals that damage the vascular endothelium, inducing subsequent development of endothelial dysfunction. Endothelial dysfunction, in turn, triggers a cascade of enzymatic reactions that ultimately lead to an increased production of TC and oxidation of LDL, which stimulates atherogenesis [19, 20]. More than 80 clinical and epidemiological studies confirmed that hyperhomocysteinemia (HHC) is one of the most important independent risk factors for early and rapid progression of atherosclerosis and arterial thrombosis. The results of clinical trials suggest that HHC and the associated oxidative stress foster the development of IR and beta cell dysfunction, facilitating the progression of DM [21]. Furthermore, Fonseca et al. demonstrated that increased levels of homocysteine can be caused by hyperinsulinemia after insulin injections, which can potentially contribute to the establishment of a vicious circle in insulin-dependent DM in a study on rats.

Using the method of binary logistic regression, we found that a 1 mmol/L rise in the level of homocysteine increases the risk of T2DM by 1.1 times among patients from the first group (Odds ratio (OR) = 1.115; 95% confidence interval (CI) 1.011–1.229; p = 0.03). For elevated hs-CRP (over 3 mg/L), an increase of its concentration by 1 mg/L increases the risk of T2DM by 3.8 times (OR = 3.819; 95% CI 1.551–9.404; p = 0.004).

Participants in both groups demonstrated increased levels of the local inflammatory marker MMP-9 and reduced levels of TIMP-1 (without significant differences between the groups). Our findings correlate with the results of the other experimental studies and clinical trials, showing that a reduction in the activity of anti-inflammatory mediators is associated with increased levels of pro-inflammatory cytokines and proteases in patients with T2DM. However, some studies provide evidence of reduced production of pro-inflammatory cytokines in DM complicated by macroangiopathy [22].

Within our study, we observed no significant differences in the level of the markers of systemic inflammation (CD40, sCD40L) between the groups

The sCD40L belongs to a family of TNF-α receptors and its main biological role is interacting with CD40. Activated platelets are believed to be the main source of sCD40L in the blood. Upon entering the bloodstream, sCD40L may increase the thrombogenic potential of blood, particularly by stimulating the expression of the tissue factor in cells which have it. The number of studies on this marker is limited, with most studies being experimental with very few clinical trials [10].

We should still mention that the prognostic value of the markers currently used for the assessment of endothelial activation remains poorly understood. HHC in patients with T2DM can exacerbate endothelial dysfunction, promote the development of atherosclerotic lesions, cause oxidative stress, reduce thromboresistance, and increase platelet aggregation and their adhesion capacity. Both experimental studies and clinical trials provided multiple evidences of endothelial dysfunction in T2DM patients. Hyperglycemia activates protein kinase C in endothelial cells, which can potentially induce increased production of vasoconstrictor prostaglandins, endothelin-1, and angiotensin-converting enzyme that may have both direct and indirect effects on the vasomotor reactivity [20].

Within our study, we observed no significant differences in the level of endothelin (1-21) and nitrites between the groups. However, both diabetic and non-diabetic patients had increased levels of endothelin-1.

We have identified the following direct medium strength correlations in patients with CAD and T2DM: hs-CRP with TC (p = 0.004) and Apo-B (p = 0.02); IL-1β with TC (p = 0.01), TG (p = 0.04), and AI (p = 0.01); endothelin-1 with

hs-CRP (p = 0.02), TNF-α (p = 0.01), MMP-9 (p = 0.05); CD 40 with TG (p = 0.03). Our findings are consistent with the theory of atherosclerosis, which considers it as a disease that combines inflammation and thrombosis. We observed a correlation between the duration of T2DM and body mass index (BMI) (p = 0.002), as well as the level of homocysteine (p = 0.02). HHC greater than 15 μmol/L was more frequent in patients with T2DM than in non-diabetic individuals, and it was strongly associated with the level of glycemia (p = 0.04, r = 0.40). We revealed direct medium strength (r = 0.4) correlations between the duration of smoking and the levels of TG (p = 0.03) and LDL (p = 0.03); hs-CRP and homocysteine (p = 0.028) and IL-6 (p = 0.031) among patients with CAD only group.

The results of the correlation analysis confirmed the presence of strong correlation between the lipid profile parameters and vascular inflammatory markers in both groups. This may determine their role in the initiation of atherosclerotic changes, as well as in the destruction of existing atherosclerotic plaques.

Conclusion

Our results suggest that patients with CAD, stable angina, and T2DM have significantly higher levels of vascular inflammatory markers (hs-CRP, homocysteine, and IL-1β) compared to non-diabetic patients with CAD, despite equally elevated levels of atherogenic lipid markers and endothelial dysfunction registered in these groups. For the chronic hyperglycemia observed in patients with CAD and DM, the degree of systemic inflammation should be considered as the most important risk factor for vascular complications, including destabilisation of the atherosclerotic plaque and the development of atherothrombosis.

Additional information

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Conflict of interest

The authors declare no conflict of interest related to current manuscript.

Authors contribution

Petelina T.I.—development of a research concept and study design, data analysis, and drafting the manuscript; Musikhina N.A.—data analysis, drafting the manuscript; Gapon L.I.—development of a research concept, drafting the manuscript; Emeneva I.V.—data collection, drafting the manuscript; Gorbatenko E.A.—statistical data analysis.

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