Оригінальні дослідження

DOI: 10.31793/1680-1466.2024.29-4.310

Lipid profile and levels of C-reactive protein and interleukin-6 in diabetic patients in the late post-COVID period

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Abstract. Diabetes mellitus (DM) and cardiovascular diseases (CVDs) are factors that, on the one hand, complicate the course of COVID-19 (COronaVIrus Disease 2019), and on the other hand, provoke further complications of these diseases. **Aim.** The aim of the study was to determine the level of apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), lipids, C-reactive protein (CRP) and interleukin-6 (IL-6) in the blood of 122 patients with DM and COVID-19 2-3 years after the disease. **Material and methods.** ApoA1, ApoB, CRP, IL-6, low-density lipoproteins (LDL), high-density lipoproteins (HDL) and triglycerides (TG) were measured using ELISA kits (Elabscience, USA). **Results.** Determination of the impact of COVID-19 on the level of ApoA1 and ApoB in the blood plasma of patients with DM 2-3 years after the disease showed that only the level of ApoB changed significantly. At the same time, the ApoB/ApoA1 ratio, which indicates the risk of CVDs, increased from 0.361 to 0.404. Gender differences in blood plasma levels of ApoA1 and ApoB in patients with DM and COVID-19 were noted for ApoA1, and the level of ApoA1 varied depending on the type of DM. The study of apolipoproteins content dependence on the body mass index and the level of glycated hemoglobin (HbA1c) showed a decrease in the ApoA1 and an increase in the ApoB concentration in people with a body mass index over 30 kg/m² and with HbA1c concentration of more than 7%. Determination of COVID-19 effect on the lipid profile in blood plasma of patients with DM 2-3 years after the disease showed that the levels of LDL and TG significantly increased, and the level of HDL decreased. At the same time, there was no difference between the mild and severe course of COVID-19. **Conclusion.** There is a significant weakening of the body's response to the amplitude of changes in the lipids and, especially, apolipoproteins concentration in the blood of patients who contracted COVID-19 2-3 years ago compared to the acute disease.

Keywords: COVID-19, diabetes mellitus, cardiovascular diseases, apolipoprotein A1, apolipoprotein B, C-reactive protein, interleukin-6.

DM and CVDs are factors that, on the one hand, complicate the course of COVID-19, and on the other – provoke further complications of these diseases [1-3]. More than 200 symptoms of the disease have been described, which are united by the term «long covid», including DM, CVDs and hyperlipidemia [4, 5]. Levels of ApoA1, ApoB, HDL cholesterol, LDL cholesterol, and oxidized LDL (oxLDL) in plasma are associated with the risk of CVDs [6, 7]. In addition to the potential cardioprotective function, HDL and ApoA1 – the main apolipoproteins of HDL – are also characterized by antidiabetic properties [6, 8]. It has been established that the ApoB/ApoA1 ratio is associated with type 2 DM and is proposed as a new biomarker for predicting the risk of CVDs [9]. Lipid profile (LDL, HDL, TG) is also associated with the risk of DM and CVD developing. A meta-analysis shows that a decrease in ApoA1 level and an increase in ApoB level and the ApoB/A1 ratio are risk factors for the first ischemic stroke [10]. Previously, we noted significant changes in the amount of ApoA1, ApoB, oxLDL, as well as in the ApoB/A1 ratio in the blood of patients during COVID-19 [11-13].

CRP and IL-6 are important indicators of inflammation in DM and initiators of the severe course of COVID-19 [14-16].

The aim of the study was to determine the dynamic of ApoA1, ApoB, lipids, CRP and IL-6 levels in the blood of patients with DM who contracted COVID-19, 2-3 years after the acute illness.

Material and methods

The research was conducted in the Department of Diabetology and the Department of Fundamental and Applied Problems of Endocrinology of the SI «V.P. Komisarenko Institute of Endocrinology and Metabolism of NAMS of Ukraine». The research protocol was approved by the Ethics Committee of the Institute. All patients signed informed consent for the use of biomaterials for further diagnostic and scientific research. In the process of carrying out the research, the principles of bioethics were followed: the main provisions of the Council of Europe Convention on Human Rights and Biomedicine dated 04.04.1997, Good Clinical Practice from 1996, the Helsinki Declaration of the World Medical Association on the ethical principles of scientific research of medical research with human participation (1964-2000) and order of the Ministry of Health of Ukraine No. 281 dated November 1, 2000.

Blood was obtained by standard venipuncture and stored in EDTA tubes. Plasma was separated by centrifugation within 1 hour after blood sampling. Samples were stored at -20 °C until use. ApoA1, ApoB, CRP, IL-6, LDL, HDL and TG were determined using enzyme-linked immunosorbent assay kits (Elabscience, USA). Measurements were performed at an optical wavelength of 450 nm on a Stat Fax 3200 (Awareness Technology, USA) immunoenzymatic tablet analyzer. HbA1c was determined using the One HbA1c FS kit (DiaSys Diagnostic Systems GmbH, Germany). Measurements were performed at an optical wavelength of 660 nm.

Statistical analysis of data was performed using Origin 7.0 software. Study results are presented as M±SE. Student's *t*-test, non-parametric methods and correlation analysis were used to compare groups of data. Values were considered significant at $p \leqslant 0.05$.

Results and discussion

Management of DM and comorbidities followed American Diabetes Association/European Association for the Study of Diabetes guidelines for patients at high cardiovascular risk was similar in all groups. COVID-19 occurrence in patients was determined by the PCR method. The severity degree ascertainment of COVID-19, as well as its treatment, was performed in accordance with the protocol «Providing medical assistance in the treatment of the coronavirus disease COVID-19», approved by the order of the Ministry of Health of Ukraine No. 762 from April 2, 2020.

The examined group consisted of 122 patients (57 men and 65 women) with type 1 DM (n=31) and type 2 (n=91) DM with various comorbid pathologies. DM was diagnosed according to the criteria of the American Diabetes Association, updated in 2021. Diagnosis and treatment of comorbid diseases were carried out according to protocols approved by the Ministry of Health of Ukraine. The control group included healthy individuals who have not confirmed COVID-19.

The patients of the research groups were representative in terms of age, sex, DM duration and the state of carbohydrate metabolism compensation. The average age of the patients was 61.4 years (30-72 years).

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The group with a severe course of COVID-19 (n=19) included patients who used oxygen during treatment or were ill 2 or more times. The same number of patients was in the group with mild COVID-19. The patients had COVID-19 in 2020-2022.

The average body mass index of the patients was excessive and amounted to 28.58±0.54 kg/m². The average HbA1c content of the patients was 9.43±0.20%, which indicates the presence of DM.

Determination of ApoA1, ApoB, CRR and IL-6 in blood plasma of patients with DM and COVID-19

Hydrophobic lipids do not dissolve in blood plasma and to deliver them to tissues they are packaged in lipoproteins with cholesterol esters, TGs in the core and phospholipids, free cholesterol and apolipoproteins on the surface. ApoA1, the main protein component of HDL, is a polypeptide of 243 amino acids with a molecular weight of 28 kDa [17].

The hydrophobic core of LDL consists of approximately 170 TGs, 1.500 cholesterol esters, a hydrophilic shell consisting of 700 phospholipid molecules, about 500 unesterified cholesterol molecules, and one large copy of ApoB with a molecular weight of 500 kDa [18]. ApoB is the main apolipoprotein and is a carrier for the following lipids: chylomicrons, very low-density lipoproteins, intermediate-density lipoproteins, and lipoproteins (a). ApoB is not contained in HDL, the latter are restored to lipoproteins from ApoA [19].

We measured the levels of ApoA1, ApoB, which are associated with DM and its cardiovascular complications, as well as CRP and IL-6, as markers of inflammation in DM and COVID-19.

The study of COVID-19 impact on ApoA1 and ApoB levels in the blood plasma of patients with DM 2-3 years after the disease showed that only the level of ApoB significantly increased (**Table 1**). The ApoB/ApoA1 ratio, which indicates the risk of CVDs, increased from 0.361 to 0.404, remaining within the normal range. These indicators are in sharp contrast with the results of ApoA1 and ApoB determination in the blood of patients with COVID-19, when the level of ApoB exceeded its amount in healthy individuals by 2.3 times, and in patients with DM by more than 2 times. The level of ApoA1 in the blood of patients with COVID-19 was more than 7 times lower than that of controls, and compared to patients with DM, it was 4.7 times lower [11-13]. In the blood of some patients with COVID-19 the level of ApoA1 decreased almost to zero values – 0.09 g/L. The ApoB/ApoA1 ratio increased to 9.041, which indicated an extremely high risk of CVDs [11].

Table 1. Impact of COVID-19 on the level of ApoA1, ApoB, IL-6 and CRP in the blood plasma of patients with DM

Indicators	DM (n=60)	DM after COVID-19 (n=38)
ApoA1, g/L	2.22±0.05	2.17±0.05
ApoB, g/L	0.80±0.02	0.88±0.02*
IL-6, pg/mL	5.58±0.42	6.62±0.39
CRP, mg/L	3.51±0.19	3.91±0.44

*Note. * – differences between two groups are significant, p<0.05.*

Gender differences were noted for ApoA1, IL-6 and CRP (**Table 2**). No changes were observed for ApoB.

Table 2. Gender differences in the levels of ApoA1/B, IL-6 and CRP in blood plasma of patients with DM and COVID-19

Indicators	Men (n=57)	Woman (n=65)
ApoA1, g/L	1.92±0.04	2.24±0.05*
ApoB, g/L	0.84±0.02	0.82±0.02
IL-6, pg/mL	5.41±0.40	4.51±0.18*
CRP, mg/L	3.05±0.11	3.93±0.20*

*Note. * – differences between two groups by gender are significant, p<0.05.*

Indicators of ApoA1, ApoB and CRP were worse in T2DM than in T1DM (**Table 3**). The level of IL-6 did not change.

Table 3. Levels of ApoA1, ApoB, IL-6 and CRP in blood plasma of patients depending on the type of DM

Indicators	T1DM (n=31)	T2DM (n=91)
ApoA1, g/L	2.31±0.05	1.97±0.04*
ApoB, g/L	0.77±0.02	0.86±0.02*
IL-6, pg/mL	4.969±0.19	4.538±0.27
CRP, mg/L	2.45±0.06	3.56±0.12*

*Note. * - differences between two groups by type of DM are significant, p<0.05.*

Since the duration of DM is important for the course of both COVID-19 and T2DM, the

dependence of ApoA1, ApoB, IL-6, and CRP on this indicator was determined. Significant changes were noted only for ApoB (**Table 4**).

Table 4. Differences in the levels of ApoA1/ApoB, IL-6 and CRP in the blood plasma of patients with DM and COVID-19 depending on DM duration

DM duration	<15 years (n=91)	≥15 years (n=31)
ApoA1, g/L	2.13±0.05	1.99±0.04
ApoB, g/L	0.81±0.02	0.88±0.02*
IL-6, pg/mL	5.06±0.35	5.53±0.31
CRP, mg/L	4.43±0.35	4.18±0.25

Note. *– differences between two groups by DM duration are significant, p<0.05.

In addition, the correlation between the indicators of ApoA1/CRP (-0.21766, p=0.02501) and ApoB/CRP (0.2254, p=0.02018) was confirmed.

IL-6 and CRP were the strongest predictors of severity in hospitalized patients with COVID-19 [14]. Elevated CRP in combination with elevated serum lactate and a high lactate/albumin ratio may assist clinicians in identifying patients with COVID-19 who are at risk for mechanical ventilation and death during hospitalization [15]. High levels of IL-6 have been detected in several highly pathogenic coronavirus-infected diseases, such as severe acute respiratory syndrome in 2002, Middle East respiratory syndrome in 2012, and COVID-19, and the IL-6 pathway has been shown to be pivotal in the pathogenesis of hyperinflammatory state [16]. It can be seen that the body's response to these indicators is significantly weakened (Tables 1, 3, 4).

Determination of lipid metabolism parameters in the blood plasma of patients with DM and COVID-19.

Determination of COVID-19 impact on the lipid profile in the blood plasma of patients with DM 2-3 years after the disease showed that the levels of LDL and TGs increased, and the level of HDL decreased (**Fig. 1 a-c**). At the same time, there was no significant difference between the mild and severe course of COVID-19.

Recent evidence suggests that, by regulating cellular cholesterol homeostasis, HDL and ApoA1 may also regulate inflammatory responses in endothelial cells and other cell types activated by proinflammatory stimuli in the arterial intima

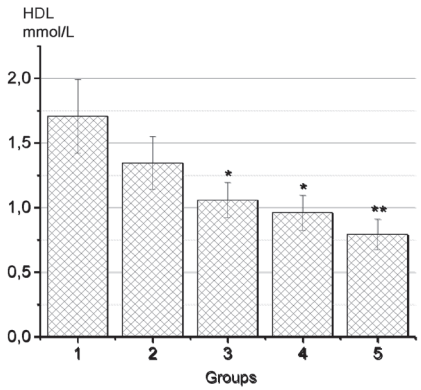

Fig. 1a. HDL amount in the blood plasma of patients depending on the severity of COVID-19 course.

*Note. 1 – control, 2 – DM, 3 – newly diagnosed DM, 4 – DM+mild COVID-19, 5 – DM+severe COVID-19. * – differences from control are significant, p<0.05; ** – p<0.01.*

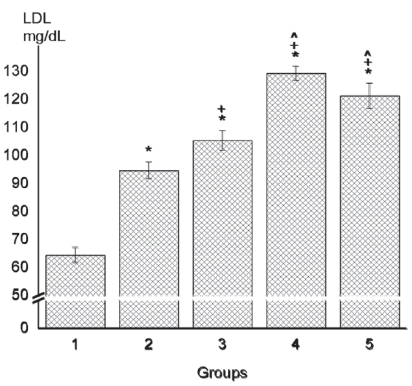

Fig. 1b. LDL amount in the blood plasma of patients depending on the severity of COVID-19 course.

*Note. 1 – control, 2 – DM, 3 – newly diagnosed DM, 4 – DM + mild COVID-19, 5 – DM + severe COVID-19. * – differences from control are significant, P < 0.01; + – deviations from group 2 (DM) are significant, p<0.05; ^ - deviations from group 3 are significant, p<0.05*

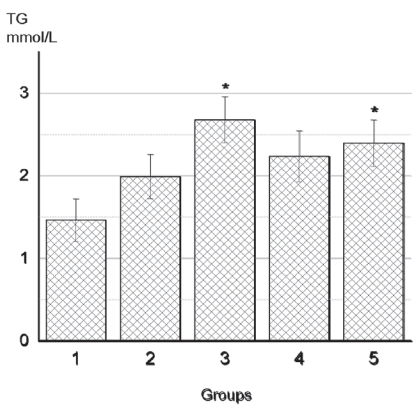

Fig. 1c. TG amount in blood plasma of patients with DM and COVID-19.

*Note. 1 – control, 2 – DM, 3 – newly diagnosed DM, 4 – DM + mild COVID-19, 5 – DM + severe COVID-19. * - differences from control are significant, p<0.05; For group 4 – p=0.1*

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[20]. It was established that the increased level of HDL and ApoA1 in plasma is associated with a reduced risk of developing CVDs. In addition to their potential cardioprotective function, HDL and ApoA1 are also characterized by antidiabetic properties. Elevated plasma HDL and ApoA1 improve glycemic control in patients with type 2 DM due to increased pancreatic β-cell function and increased insulin sensitivity. Therefore, treatment that increases HDL levels may be beneficial in CVDs associated with DM and COVID-19 [21]. ApoA1 also stimulates glucose uptake *in vivo* in skeletal and cardiac muscles [8].

LDL amount in the blood plasma of patients with DM and COVID-19 increases significantly, which is also consistent with our data on the increase in the amount of ApoB in acute COVID-19 [11]. It should be noted that LDL amount in the blood plasma of patients in the group with newly diagnosed type 2 DM is higher compared to group 2 (Fig. 1b).

Under oxidative stress conditions, LDL oxidation occurs in the process of lipid peroxidation, with the participation of phospholipid molecules. In pathological conditions, plasma lipoproteins containing ApoB penetrate through the damaged endothelium into the subendothelial intima of vessels, being oxidized by ROS (reactive oxygen species). Thus, LDL is modified to oxLDL, which contribute to the formation and progression of atherosclerotic plaque through several mechanisms, including the induction of endothelial cell activation and dysfunction, the formation of foam cells by macrophages, and the migration and proliferation of smooth muscle cells [7, 22].

The level of TGs significantly increased in the blood of patients with newly diagnosed DM and in patients with DM who experienced severe COVID-19 (Fig. 1c). No significant changes were observed in patients of groups 2 and 4, but an upward trend can be noted.

According to other authors, lipid profiles were significantly affected by COVID-19 with decreased levels of total cholesterol, HDL cholesterol, LDL cholesterol, and increased TGs concentrations compared to control subjects. The amount of ApoA1 in the plasma of patients decreased by 55% compared to controls [17, 23, 24]. In patients with COVID-19, hypolipidemia was observed, which was positively correlated with the severity of the disease [25]. On the other hand, one of the symptoms of «long covid» is hyperlipidemia [1-3]. According to our data, the quantity of LDL (Fig. 1b) and ApoB [11-13] significantly increased.

Conclusions

Thus, we note a significant weakening of the body's response to the amplitude of changes in the concentration of lipids and, especially, apolipoproteins in patients who fell ill with COVID-19 2-3 years ago compared to the acute disease.

Determination of COVID-19 effect on the lipid profile in the blood plasma of DM patients 2-3 years after the disease showed that the levels of LDL and TGs increased, and the level of HDL decreased.

There was no difference between mild and severe course of COVID-19.

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Abbreviations

ApoA1 – apolipoprotein A1
ApoB – apolipoprotein B
CRP – C-reactive protein
CVDs – cardiovascular diseases
DM – diabetes mellitus
HDL – high-density lipoproteins
IL-6 – interleukin-6
LDL – low-density lipoproteins
oxLDL – oxidized low-density lipoproteins
TG – triglycerides

Ліпідний профіль і рівні С-реактивного білка та інтерлейкіну-6 у хворих на цукровий діабет у пізньому постковідному періоді

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Резюме. Цукровий діабет (ЦД) і серцево-судинні захворювання (ССЗ) є факторами, які, з одного боку, ускладнюють перебіг коронавірусної інфекції 2019 року (COronaVIrus Disease 2019, COVID-19), а з іншого – провокують подальші ускладнення цих захворювань. **Мета.** Дослідити рівень аполіпротеїну А1 (АроА1), аполіпротеїну В (АроВ), ліпідів, С-реактивного білка (C-reactive Protein, CRP) та інтерлейкіну-6 (IL-6) у крові 122 хворих на ЦД і COVID-19 через 2-3 роки після захворювання. **Матеріал і методи.** АроА1, АроВ, CRP, IL-6, ліпопротеїни низької щільності (Low Density Lipoproteins, LDL), ліпопротеїни високої щільності (High Density Lipoproteins, HDL) та тригліцериди (TG) визначали за допомогою наборів для імуноферментного аналізу (ELISA) фірми («Elabscience», США). **Результати.** Визначення впливу COVID-19 на рівні АроА1 та АроВ, у плазмі крові хворих на ЦД через 2-3 роки після захворювання показало, що вірогідно змінювався тільки рівень АроВ. Разом із тим співвідношення АроВ/АроА1, яке свідчить про ризик ССЗ, зростало з 0,361 до 0,404. Гендерні відмінності рівнів АроА1 та АроВ у плазмі крові хворих на ЦД та COVID-19 були відмічені для АроА1, також рівень АроА1 змінювався залежно від типу ЦД. Вивчення залежності вмісту аполіпопротеїнів від індексу маси тіла (IMT) та рівня глікованого гемоглобіну (HbA1c) показало зниження вмісту АроА1 і зростання концентрації АроВ в осіб з IMT понад 30 кг/м^2 та з концентрацією HbA1c більше 7%. Визначення впливу COVID-19 на ліпідний профіль у плазмі крові хворих на ЦД через 2-3 роки після захворювання показало, що LDL та TG зростали, а рівень HDL знижувався. При цьому не відмічалося різниці між легким і важким перебігом COVID-19. **Висновок.** Спостерігається значне ослаблення реакції організму щодо амплітуди змін концентрації ліпідів та, особливо, аполіпопротеїнів у крові пацієнтів, які перехворіли на COVID-19 2-3 роки тому порівняно з гострим захворюванням.

Ключові слова: COVID-19, цукровий діабет, серцево-судинні захворювання, аполіпопротеїн А1, аполіпопротеїн В, С-реактивний білок, інтерлейкін-6.

For citation: Tronko MD, Kovzun OI, Sokolova LK, Pushkarev VM, Levchuk NI, Popova VV, Het'man NV, Pushkarev VV. Lipid profile and levels of C-reactive protein and interleukin-6 in diabetic patients in the late post-covid period. Endokrynologia. 2024;29(4):310-316. DOI: 10.31793/1680-1466.2024.29-4.310.

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Personal contribution: Pushkarev V.V., Levchuk N.I. – setting up experiments, writing, design and translation; Sokolova L.K., Pushkarev V.M., Kovzun O.I., Popova V.V., Het'man N.V. – analysis of literature sources, writing, design, editing text and translation; Tronko M.D. – idea of work and consultation when editing an article.

Funding: with the support of National Research Foundation of Ukraine, grant 2021.01_0213.

Declaration of ethics: the authors have declared no conflicts of interest or financial obligations.

Article: received November 11, 2024; revised November 21, 2024; accepted November 26, 2024; published December 30, 2024.

Для цитування: Тронько МД, Ковзун ОІ, Соколова ЛК, Пушкарьов ВМ, Левчук НІ, Попова ВВ, Гетьман НВ, Пушкарьов ВВ. Ліпідний профіль та рівні С-реактивного білка та інтерлейкіну-6 у хворих на цукровий діабет у пізньому постковідному періоді. Ендокринологія. 2024;29(4):310-316. DOI: 10.31793/1680-1466.2024.29-4.310.

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Особистий внесок: Пушкарьов В.В., Левчук Н.І. – постановка експериментів, написання, дизайн та переклад; Соколова Л.К., Пушкарьов В.М., Ковзун О.І., Попова В.В., Гетьман Н.В. – аналіз літературних джерел, написання, оформлення, редагування тексту та переклад; Тронько М.Д. – ідея роботи та консультації при редагуванні статті.

Фінансування: за підтримки гранту Національного фонду досліджень України, грант 2021.01_0213.

Декларація з етики: автори задекларували відсутність конфлікту інтересів і фінансових забов'язань.

Стаття: надійшла до редакції 11.11.2024 р.; перероблена 21.11.2024 р.; прийнята до друку 26.11.2024 р.; надрукована 30.12.2024 р.