

Level of oxidized low-density lipoproteins in the blood of diabetic patients after COVID-19

V.M. Pushkarev¹,
L.K. Sokolova¹,
N.I. Levchuk¹,
V.V. Pushkarev¹,
A.M. Sokolova²,
I.G. Markovych³,
M.D. Tronko¹

¹State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine»

²Shupyk National Healthcare University of Ukraine

³National Academy of Medical Sciences of Ukraine

Abstract. COVID-19 infection (COronaVirus Disease 2019) is associated with dyslipidemia and cardiovascular complications. It has been proven that a high content of low-density lipoproteins (LDL) and, especially, oxidized LDL (oxLDL) causes cholesterol accumulation in blood vessel walls and significantly increases the risk of atherosclerosis and other cardiovascular diseases (CVD). **Aim.** The aim of the work was to determine oxLDL content in the blood of 82 patients with diabetes mellitus (DM), who had a coronavirus infection between 2020 and 2022. **Material and methods.** Blood was obtained by standard venipuncture and stored in EDTA tubes. Plasma was separated by centrifugation for 10 min after blood collection. Samples were stored at -80 °C until use. OxLDL was determined using enzyme-linked immunosorbent assay kits (Elabscience, USA). **Results.** It was shown that oxLDL level in the blood of patients with type 2 DM (T2DM) and, especially, patients who had recovered from COVID-19, was significantly higher than in the blood of healthy people. There is also a significant difference between patients with mild and severe forms of COVID-19. In the absence of treatment with hypoglycemic drugs in patients who had recovered from COVID-19, the level of oxLDL increases significantly, especially in the absence of insulin treatment. The effect of treatment was more pronounced in patients with COVID-19, and when treated with inhibitors of sodium-dependent glucose cotransporter type 2 (SGLT2i), the level of oxLDL decreased almost to control values. Therefore, oxLDL levels remain elevated in diabetic patients who have recovered from COVID-19, although lower than in the acute disease. **Conclusions.** OxLDL levels in the blood of diabetic patients who have recovered from COVID-19 remain elevated, although lower than in the acute form of the disease. Treatment with hypoglycemic drugs may be a promising strategy to reduce oxLDL levels, and therefore the risk of atherosclerosis, in individuals who have recovered from COVID-19. OxLDL levels may be an important marker of post-COVID syndrome.

Keywords: oxidized low-density lipoproteins, COVID-19, diabetes mellitus, obesity, cardiovascular disease.

DM, obesity, and CVD are factors that complicate the course of COVID-19, and the latter provokes further complications of these diseases [1, 2, 3]. Currently, more than 200 symptoms of the disease have been described, including DM, CVD, and

dyslipidemia, which are combined under the term «post-COVID syndrome» or «long COVID» [4, 5].

It is known that elevated levels of LDL, apolipoprotein B (ApoB), and especially oxLDL in blood plasma are associated with an increased risk

of developing CVD and, primarily, atherosclerosis. Under conditions of oxidative stress, which is happening in obesity and T2DM, LDL oxidation occurs in the process of lipid peroxidation, mainly with the participation of phospholipid molecules. Aldehydes produced during lipid peroxidation modify ApoB100, the protein part of LDL, forming Schiff bases with lysine residues of ApoB. In this way, an oxLDL is formed. In pathological conditions, plasma lipoproteins containing ApoB penetrate through the damaged endothelium into the subendothelial intima of the vessels, being oxidized by reactive oxygen species. Thus, LDL is modified to oxLDL [6, 7].

Atherosclerosis is a chronic inflammatory response to cholesterol deposition in the arteries. LDL, especially oxLDL, play a crucial role in the onset and development of atherosclerosis by inducing endothelial cell dysfunction, recruiting monocytes/macrophages, and promoting chronic inflammation. Macrophages engulf oxLDL, forming foam cells that release pro-inflammatory cytokines and enhance local inflammation [8-10].

The aim was to investigate the level of oxLDL in the blood of diabetic patients who had COVID-19 in 2020-2022, with the probable formation of post-COVID syndrome.

Material and methods

The study was conducted in the Department of Diabetology and Department of Fundamental and Applied Problems of Endocrinology of the State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine». The study protocol was approved by the Institutional Ethics Committee. All patients signed informed consent for the use of their biomaterials for further diagnostic and scientific research.

Blood was obtained by standard venipuncture and stored in EDTA tubes. Plasma was separated by centrifugation for 10 min after blood collection. Samples were stored at -80°C until use. The amount of oxLDL was determined using enzyme immunoassay kits (Elabscience, USA). Measurements were performed at an optical wavelength of 450 nm on a Stat Fax 3200 enzyme immunoassay plate analyzer (Awareness Technology, USA).

Statistical analysis and presentation of the obtained data were performed using Origin 2019b

software. The results of the study are presented as $M \pm SE$. Student's t-test was used to compare data groups. P values ≤ 0.05 were considered as significant.

Results and discussion

The studies used blood plasma from 82 patients with DM. The blood of healthy people ($n=7$) without chronic diseases, representative in age, served as controls. The patients group included 46 female and 36 male with the average age of 61.4 years (range, 30-72). The average body mass index (BMI) of the patients was excessive and was 28.58 ± 0.537 kg/m². The average Hb1Ac content of the patients was 9.43 ± 0.196 %, which indicates decompensation of DM. The group included 24 patients with type 1 diabetes (T1DM) and 58 – with T2DM.

It was found that the level of oxLDL is more than 2 times higher in patients with COVID-19 (Fig. 1, col. 3) compared to control values. In patients with DM, the amount of oxLDL is also significantly higher than the control level. In patients with DM after COVID-19, the content of oxLDL in the blood is higher than in patients with DM (Fig. 1, col. 2 and 3), although the amplitude of changes is much lower than in acute COVID-19, where the level of oxLDL exceeded the control values by 3.8 times, and the indicator of patients with DM – by 2.6 times [11]. There is also a significant difference between patients with mild and severe forms of COVID-19 (Fig. 1, col. 4 and 5). No difference was observed between vaccinated and unvaccinated patients (Fig. 1, col. 6 and 7). Thus, the amount of oxLDL in the blood of patients with DM who have had COVID-19 remains high, which indicates an increased risk of atherogenesis.

There is no significant difference between the levels of oxLDL in the blood of patients with different types of DM, but the amplitude of the increase in its amount in type 2 DM is significantly higher than in type 1 DM (Table 1, groups 4 and 5). An increase in the duration of DM, body weight over 30 kg/m² and COVID-19 disease leads to an increase in the amount of oxLDL in the blood, and therefore the risk of atherosclerosis.

Studies have shown that estrogen has a protective effect against oxidative stress, which could potentially explain the lower oxLDL levels in premenopausal women compared with men. However, as women enter menopause and ovarian production

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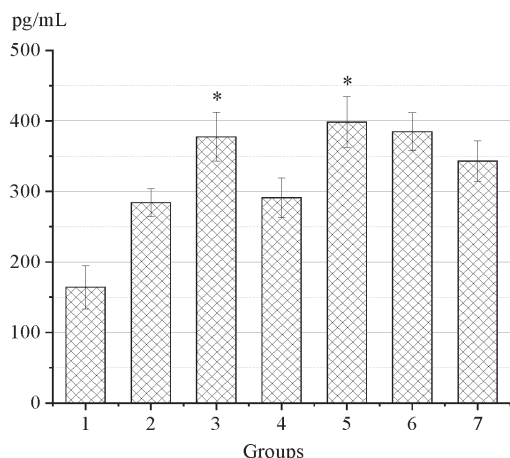


Fig. 1. 1. Plasma oxLDL levels in patients with DM who recovered from COVID-19 in 2020-2022 (M±SE).

Note. 1 – control (n=7); 2 – patients with DM (n=50); 3 – patients with DM after COVID-19 (n=32); 4 – patients with DM after mild COVID-19 (n=24); 5 – patients with DM after severe COVID-19 (n=8); 6 – unvaccinated patients with DM and/or COVID-19 (n=41); 7 – vaccinated patients with DM and/or COVID-19 (n=41); differences between the control (1) and other groups are significant ($p \leq 0.05$); * – significant differences from the previous groups, $p \leq 0.05$.

Table 1. The amount of oxLDL (pg/mL) in blood plasma depending on the type and duration of DM, BMI, Hb1Ac concentration and gender

N	Groups	n	M±SE
1	Control	7	164.13±30.7
2	T1DM	24	279.56±12.05
3	T2DM	58	321.93±31.66
4	T1DM + COVID-19	11	352.84±48.02 ²
5	T2DM + COVID-19	20	451.48±63.82 ³
6	Duration of DM <15	27	270.99±19.94
7	Duration of DM >15	17	352.59±47.35 ⁶
8	Duration of DM <15 + COVID-19	11	411.38±41.89 ⁶
9	Duration of DM >15 COVID-19	14	419.05±62.95
10	BMI <30 kg/m ²	28	296.13±34.99
11	BMI >30 kg/m ²	17	396.75±45.32 ¹⁰
12	BMI <30 kg/m ² + COVID-19	16	370.62±47.56 ¹⁰
13	BMI >30 kg/m ² + COVID-19	11	400.12±10.38
14	Hb1Ac <7,5%	20	309.72±33.03
15	Hb1Ac >7,5%	25	346.53±41.24
16	Hb1Ac <7,5% + COVID-19	9	402.98±50.47 ¹⁴
17	Hb1Ac >7,5% + COVID-19	10	418.65±70.66
18	Women	46	274.41±38.45
19	Men	36	283.71±37.29
20	Women + COVID-19	16	353.90±53.61
21	Men + COVID-19	8	377.73±49.58

Note. All values are significantly different from control, $p \leq 0.05$; subscripts indicate significant differences relative to the respective group, $p \leq 0.05$.

of 17-beta-estradiol decreases, their oxLDL levels tend to increase, contributing to the reduction of the cardiovascular protective benefits [12]. This may be why we did not observe gender differences in oxLDL levels.

The amount of oxLDL in blood plasma was also determined at different levels of left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR) and albuminuria (AU) in the norm and with pathological changes (Table 2). The table 2 shows that with disorders of these indicators, the level of oxLDL is higher (group 2 vs. groups 4, 9 and 12). There is also a higher response to the amount of oxLDL to COVID-19 at eGFR <60 (group 7 vs. 3 and 5).

Table 2. The amount of oxLDL (pg/mL) in blood plasma at different LVEF (%), eGFR (ml/min/1.73 m²) and AU (mg/day)

N	Groups	n	M±SE
1	Control	7	164.13±30.7
2	DM	50	284.05±19.93
3	DM + COVID-19+	32	377.36±34.63 ²
4	eGFR <60	17	424.82±62.57 ²
5	eGFR >60	54	348.93±51.46
6	eGFR <60 + COVID-19	7	511.29±69.52
7	eGFR >60 + COVID-19	19	517.92±63.76 ^{3,5}
8	AU <30	17	279.85±41.45
9	AU 30-300	27	385.27±48.52 ^{2,8}
10	AU <30 + COVID-19	11	387.44±46.68 ⁹
11	AU 30-300 + COVID-19	13	364.89±57.24
12	LVEF <40	3	327.69±9.20 ²
13	LVEF 40-50	21	274.77±15.87 ¹²
14	LVEF >50	21	237.82±23.49 ¹²
15	LVEF <40 + COVID-19	-	-
16	LVEF 40-50 + COVID-19	15	422.50±35.71 ¹³
17	LVEF >50 + COVID-19	8	389.97±37.24 ¹⁴

Note. Group 2 – average value across the entire group of patients with DM without COVID-19; all values are significantly different from the control, $p \leq 0.05$; superscripts indicate significant differences relative to the corresponding group, $p \leq 0.05$.

It is known that high levels of oxLDL in circulating immune complexes were associated with an increased probability of abnormal AU developing, and also contribute to the development of retinopathy in people with T1DM [13, 14].

The study of the treatment effect of patients with glucose-lowering drugs (GLD) in the blood concentration of oxLDL showed that insulin, metform-

in and SGLT2i drugs effectively (close to control values) reduce the amount of oxLDL in the blood of patients who have had COVID-19 (Table 3, groups 6, 10 and 14). In the absence of treatment with these GLD, the level of lipoproteins exceeded its average amount, which was observed in patients with DM (Table 3, group 2 vs. groups 3, 7, 11). It is also noteworthy that in the absence of GLD treatment in patients who have had COVID-19, the level of oxLDL increases significantly, especially in the absence of insulin treatment (Table 3, groups 5, 9, 13). Interestingly, the effect of treatment was more pronounced in patients with COVID-19 (Table 3, groups 6, 10, 14).

Table 3. OxLDL levels in plasma of patients with DM and after COVID-19 depending on drug treatment with insulin, metformin and SGLT2i

N	Groups	n	M±SE	%
1	Control	7	164.13±30.77	100.00
2	DM	50	284.05±19.93	173.06
3	Insulin -	38	370.62±35.04	227.20
4	Insulin +	44	248.02±34.69	152.04
5	Insulin -, COVID-19+	7	591.89±50.15	362.83
6	Insulin +, COVID-19+	18	203.85±23.90	124.96
7	Metformin -	37	363.27±43.24	222.69
8	Metformin +	45	341.50±43.39	209.34
9	Metformin - COVID-19 +	13	415,18±49.07	254.51
10	Metformin + COVID-19 +	12	242.83±23.63	148.85
11	SGLT2i -	71	385.97±41.16	236.60
12	SGLT2i +	11	288.83±41.23	177.06
13	SGLT2i - COVID-19 +	17	459.47±40.70	281.66
14	SGLT2i + COVID-19 +	6	198.10±24.58	121.44

Note. Group 2 – averaged data for diabetic patients with and without GLD treatment; group 3 – diabetic patients with combined treatment, but without insulin, as well as groups 7 and 11 – patients with DM with combined treatment, but without the use of metformin or SGLT2i; all values, except for groups 6 and 14, are significantly different from the control, $p \leq 0.05$; superscripts indicate significant differences relative to the corresponding group, $p \leq 0.05$.

Therefore, GLD treatment in the post-COVID period can significantly improve the atherogenic lipid profile of diabetic patients.

Determination of oxLDL concentration in blood plasma depending on the age of patients showed an increase in its level with age, both in the group with DM and in patients with DM who had COVID-19,

along with a significant decrease in the amount of oxLDL in the oldest age group (75-90 years), compared to group 61-75 years (Fig. 2).

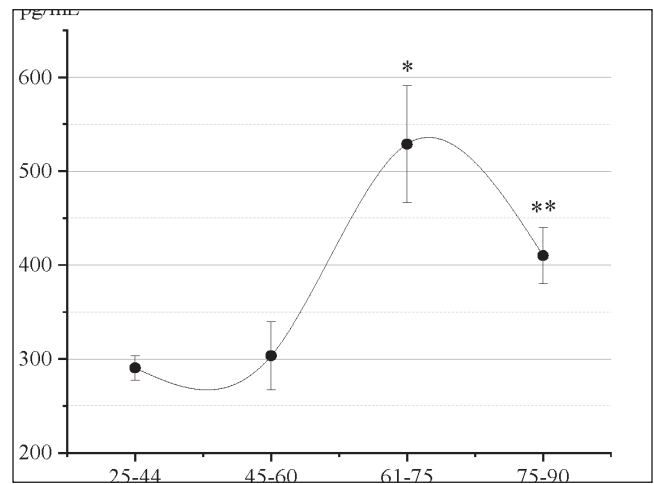


Fig. 2. OxLDL concentration in blood plasma depending on the age of patients.

Note. * – significant differences from the groups 25-44 and 45-60 years, $p \leq 0.05$; ** – significant differences from the group 61-75 years, $p \leq 0.05$.

It has been proven that high levels of LDL and, especially, oxLDL cause cholesterol accumulation on the walls of blood vessels and significantly increase the risk of atherosclerosis and other CVDs [9, 10]. OxLDL exert their harmful effect through the lectin-like oxLDL receptor 1 [12].

Dyslipidemia associated with SARS-CoV-2 has been confirmed repeatedly. However, some authors have found that serum total cholesterol, HDL- and LDL-cholesterol levels were lower in COVID-19 patients compared to the healthy ones [8, 15]. We have shown that, in both acute COVID-19 and post-COVID, only ApoA1 and HDL levels are decreased, while oxLDL, LDL, and ApoB levels are significantly increased [11, 16], suggesting an increased risk of CVD.

OxLDL contribute to the formation of foam cells, endothelial activation and the initiation of inflammatory cascades in the vascular wall. High levels of oxLDL are associated with the progression of atherosclerosis, especially in patients with metabolic disorders. In patients with DM, increased free radical formation and impaired antioxidant defense are observed, which contributes to an increase in oxLDL levels even without an additional trigger. DM is an independent factor in increasing oxLDL. COVID-19 causes excessive oxidative and inflam-

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matory stress, SARS-CoV-2 infection activates the production of pro-inflammatory cytokines (IL-6, IL-17, TNF- α) [16, 17] and increases the level of reactive oxygen species, which leads to a significant increase in oxLDL levels in the acute phase of infection. In patients with DM, this effect is even more pronounced. After COVID-19, oxLDL levels remain elevated. Cohort study [18] shows that even 3-6 months after recovery, oxLDL levels in patients with DM remain higher than in uninfected individuals. This may be a consequence of long-term metabolic imbalance and residual inflammation. Our data suggest that oxLDL levels may be one of the markers of post-COVID syndrome.

OxLDL is a key pathogenetic factor in the development of cardiovascular pathology. Also oxLDL is a proatherogenic and prooxidant factor that plays a central role in the progression of endothelial dysfunction, the formation of atherosclerotic plaques and chronic inflammation. These processes are the basis for the development of ischemic heart disease – one of the leading causes of heart failure. OxLDL directly damages the myocardium, contributing to cardiomyocyte dysfunction through the activation of Toll-like receptors 4, the accumulation of free radicals in the myocardium, impaired mitochondrial respiration in cardiomyocytes, the activation of apoptosis and fibrosis. It is known that elevated levels of oxLDL are associated with a more severe course of heart failure. Clinical studies shown that patients with heart failure have higher oxLDL levels compared to controls. OxLDL levels correlate with NYHA symptom severity, decreased LV ejection fraction, and NT-proBNP levels, and oxLDL is a predictor of LV remodeling after myocardial infarction. Monitoring this parameter, especially after COVID-19, may have clinical significance for the prevention of cardiovascular events in patients with DM [18].

Conclusions

1. The level of oxidized low-density lipoproteins in the blood of diabetic patients who have recovered from COVID-19 remains high, although lower than in the acute illness.

2. Treatment with hypoglycemic drugs may be a promising strategy to reduce oxidized LDL levels in individuals who have recovered from COVID-19, and therefore the risk of atherosclerosis.

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Abbreviations

- ApoB** – apolipoprotein B
AU – albuminuria
BMI – body mass index
CVD – cardiovascular diseases
DM – diabetes mellitus
eGFR – estimated glomerular filtration rate
GLD – glucose-lowering drugs
Hb1Ac – glycated hemoglobin
LDL – low-density lipoproteins
LVEF – left ventricular ejection fraction
oxLDL – oxidized low-density lipoproteins
SGLT2i – sodium-dependent glucose cotransporter type 2 inhibitors
T1DM – type 1 diabetes mellitus
T2DM – type 2 diabetes mellitus

Рівень окислених ліпопротеїнів низької густини в крові хворих на діабет після COVID-19

**В.М. Пушкарьов¹, Л.К. Соколова¹, Н.І. Левчук¹,
 В.В. Пушкарьов¹, А.М. Соколова², І.Г. Маркович³,
 М.Д. Тронько¹**

¹ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України»

²Національний університет охорони здоров'я України ім. П.Л. Шупика

³Національна академія медичних наук України

Резюме. Інфекція COVID-19 (COroNaVirus Disease 2019) пов'язана з дисліпідемією та серцево-судинними ускладненнями. Доведено, що високий вміст ліпопротеїнів низької густини (LDL) та, особливо, окислених LDL (oxLDL) спричиняє накопичення холестерину на стінках судин і значно збільшує ризик атеросклерозу та інших серцево-судинних захворювань (ССЗ). **Мета.** Метою роботи було визначення вмісту oxLDL у крові 82 хворих на цукровий діабет (ЦД), які в період із 2020 по 2022 р. перенесли коронавірусну інфекцію. **Матеріал і методи.** Кров отримували шляхом стандартної венепункції та зберігали в пробірках з ЕДТА. Плазму відділяли центрифугуванням протягом 10 хвилин після забору крові. Зразки зберігали при температурі -80 °C до використання. OxLDL визначали за допомогою наборів для імуноферментного аналізу (Elabscience, США). **Результати.** Показано, що рівень oxLDL у крові хворих на цукровий діабет 2-го типу і, особливо, пацієнтів, що перехворіли COVID-19 був значно вищим, ніж у крові здорових людей. Існує також достовірна різниця між пацієнтами з легкою і важкою формами COVID-19. За відсутності лікування цукрознижувальними препаратами (ЦЗП) у пацієнтів, що

перехворіли COVID-19, рівень oxLDL значно зростає, особливо за відсутності лікування інсуліном. Ефект лікування був більш виражений саме у хворих на COVID-19, а при лікуванні інгібіторами натрійзалежного котранспортера глюкози 2-го типу (iN3KTF-2) рівень oxLDL знижувався майже до контрольних значень. Отже, концентрація oxLDL залишається високою у крові хворих на ЦД, які перехворіли COVID-19, хоча і нижчою ніж при гострому захворюванні. **Висновки.** Рівень oxLDL у крові пацієнтів із діабетом, які одужали від COVID-19, залишається високим, хоча й нижчим, ніж при гострій формі захворювання. Лікування ЦЗП може бути перспективною стратегією щодо зниження рівня oxLDL, а отже і ризику атеросклерозу, в осіб, що перехворіли COVID-19. Рівень oxLDL може бути одним із важливих маркерів пост-ковідного синдрому.

Ключові слова: окислені ліпопротеїни низької густини, COVID-19, цукровий діабет, ожиріння, серцево-судинні захворювання.

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Correspondence address: Pushkarev Volodymyr Mykhaylovych; pushkarev.vm@gmail.com; SI «V.P. Komisarenko Institute of Endocrinology and Metabolism of the NAMS of Ukraine», 69, Vyshgorodska st., Kyiv 04114, Ukraine.

Information about the authors: Pushkarev Volodymyr Mykhaylovych, Dr. Sci. (Biology), Senior Scientist, Chief Researcher of the Fundamental and Applied Problems of Endocrinology Department, ORCID: 0000-0003-0347-7771; Sokolova Liubov Kostyantynivna, Dr. Sci. (Medicine), Senior Research Fellow, Head of the Diabetology Department, ORCID: 0000-0003-0011-0106; Levchuk Nataliia Ivanivna, Cand. Sci. (Biology), Senior Scientist, Leading Research Fellow of the Department of Fundamental and Applied Problems of Endocrinology, ORCID: 0000-0003-0482-5176; Pushkarev Viktor Volodymyrovych, Cand. Sci. (Biology), Senior Research Fellow of the Department of Fundamental and Applied Problems of Endocrinology, ORCID: 0000-0001-5940-5510; Sokolova Anastasiia Maksymivna - Shupyk National Healthcare University of Ukraine, PhD student of the Endocrinology Department, ORCID 0009-0006-5334-7333. Markovych Iryna Grigoryvna, Dr. Sci. (Medicine), Senior Scientist, Senior Research Fellow Scientific coordination management National Academy of Medical Sciences of Ukraine, ORCID: 0000-0002-0688-4746; Tronko Mykola Dmytrovych, Dr. Sci. (Medicine), Cor. Member of the NAS of Ukraine, Acad. of the NAMS of Ukraine, Head of the Department of Fundamental and Applied Problems of Endocrinology, Director of the Institute, ORCID: 0000-0001-7421-0981.

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Адреса для листування: Пушкар'єв Володимир Михайлович; pushkarev.vm@gmail.com; ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України», вул. Вишгородська, 69, Київ 04114, Україна.

Відомості про авторів: Пушкар'єв Володимир Михайлович – д-р біол. наук, старш. наук. співроб., головний науковий співробітник відділу фундаментальних та прикладних проблем ендокринології, ORCID: 0000-0003-0347-7771; Соколова Любов Костянтинівна, д-рка мед. наук, старш. наук. співроб., завідувачка відділу діабетології, ORCID: 0000-0003-0011-0106; Левчук Наталія Іванівна – канд. біол. наук, старш. наук. співроб., провідна наукова співробітниця відділу фундаментальних та прикладних проблем ендокринології, ORCID: 0000-0003-0482-5176; Пушкар'єв Віктор Володимирович, канд. біол. наук, старш. наук. співроб. відділу фундаментальних та прикладних проблем ендокринології, ORCID: 0000-0001-5940-5510; Соколова Анастасія Максимівна –

Національний університет охорони здоров'я України ім. П.Л. Шупика, аспірант кафедри ендокринології, ORCID 0009-0006-5334-7333; Маркович Ірина Григорівна – д-рка мед. наук, старш. наук. співроб., старша наукова співробітниця науково-координаційного управління Національної академії медичних наук України, ORCID: 0000-0002-0688-4746; Тронько Микола Дмитрович – д-р. мед. наук, чл.-кор. НАН України, акад. НАМН України, завідувач відділу фундаментальних та прикладних проблем ендокринології, директор Інституту, ORCID: 0000-0001-7421-0981.

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