ISSN 2518-1432 (Online); ISSN 2227-4782 (Print) https://doi.org/10.21856/j-PEP.2022.1.03

ARTERIAL THROMBOSIS IN PATIENTS WITH TYPE 2 DIABETES AND COVID-19*

S. M. Gramatiuk[1], J. V. Ivanova[2], O. A. Zarudny[2], K. V. Miasoiedov[2]

[1] Ukraine Association of Biobank, Institute of Cellular Biorehabilitation, Kharkiv, Ukraine

[2] State Institution «Zaitsev V.T. Institute of General and Urgent Surgery of the National Academy of Medical Sciences of Ukraine»
gramatyuk@ukrainebiobank.com

Introduction. Acute ischemia of the lower extremities is a common condition with high mortality rate despite progress in surgical methods of treatment and optimization of protocols of management of such patients [1]. Mortality and morbidity in the early postoperative period are largely associated with metabolic disturbances during reperfusion after surgical revascularization.

The available experimental and clinical data indicate that the systemic effects of reperfusion have metabolic, inflammatory and thrombotic components, which are initiated locally in the ischemic limb, and, accordingly, require a multicomponent treatment [2-5].

Coronavirus disease 2019 (COVID-19) caused by coronavirus 2 (SARSCoV-2) is mainly characterized by respiratory symptoms of various degrees of severity. Due to the increase in the number of cases, the close attention of researchers is focused on the study of non-pulmonary manifestations: cardiac, gastrointestinal, skin, renal and neurological manifestations [3–5].

Venous thromboembolism often complicates the course of COVID-19, even in patients receiving therapeutic doses of anticoagulants, often causing death in patients [6–8]. Thus, a series of autopsies have confirmed deep vein thrombosis (DVT) in the majority of patients with COVID-19, and pulmonary embolism (PE) caused death in almost 25% of cases [9]. Arterial thrombosis in coronary arteries [6, 10] and in cerebral arteries [11] has also been reported in COVID-19 patients. Cases of development of mesenteric and aortoiliac thrombosis have been described [12–14].

The aim of the study: to assess the importance of the inflammatory status of the body in patients with type 2 diabetes mellitus and severe COVID-19 as an unfavorable factor for the occurrence of arterial thrombosis of the lower extremities, the course of acute ischemia and the prognosis for ischemic limb.

* The work was carried out in the framework of the clinical trial «Long-term follow-up of subjects with diabetes 2 type treatment with ex vivo gene therapy (AUB001)» ClinicalTrials.gov Identifier: NCT04464213.

The authors assume responsibility for the published work.

The authors guarantee absence of competing interests and their own financial interest when carrying out the research and writing the article.

The manuscript was received by the editorial staff 05.08.2021.

During the period from March to December 2020, the number of patients with acute arterial thrombosis increased, we faced 17 cases of acute arterial thrombosis in patients with confirmed COVID-19. These patients were usually delivered urgently to the Department of Acute Vascular Diseases of the State Institution «V. T. Zaitsev IGUS NAMN of Ukraine» with complaints on pain in the lower extremities, their coldness, pallor of the skin and ulceration. The presence of thrombosis was confirmed by Doppler sonography and CT angiography of the lower extremities. All tested positive for the SARS-CoV-2 virus. Due to the growing number of reports and our own observations of the presence of coagulopathy or vasculopathy [15] in patients with type 2 diabetes and COVID-19, we analyzed cases of arterial thrombosis associated with COVID-19.

MATERIALS AND METHODS

A retrospective cohort study of 35 patients with type 2 diabetes and acute arterial thrombosis of the lower extremities who were treated at the Department of Acute diseases of vessels of the State Institution «V. T. Zaitsev Institute of General and Urgent Surgery of the National Academy of Medical Sciences of Ukraine». All patients were admitted with acute ischemia stages II a – II b, by Rutherford.

The study included patients with type 2 diabetes without a history of intermittent claudication with an ischemia of 6–12 hours, who underwent urgent surgical successful thrombectomy, who met the study criteria and signed an informed consent form. The criterion for the success of revascularization was the restoration of the main arterial blood flow. All studied patients were tested for the SARS-CoV-2 virus, 18 had a negative result (control group), the diagnosis of COVID-19 in 17 patients of the main group was confirmed by a transcriptional polymerase chain reaction (RT-PCR) test from nasopharyngeal samples. The control group included patients with localizations of thrombosis similar to the main group. The diagnosis of acute arterial thrombosis in all patients was established on the basis of angiography or CT angiography.

The average age of patients in the control group was 72.3 years, the main group — 69.8 years. In both groups, the male to female ratio was 1:1. Concomitant diseases in patients of both groups were: hypertension, diabetes mellitus, atrial fibrillation. The initial creatinine level in the control group was (104 ± 18) μmol/L, in the main group (112 ± 22) μmol/L.

In patients of both groups, the levels of K+ and creatinine in blood plasma taken from a peripheral vein before surgery, 12 and 24 hours after restoration of blood flow, were determined. Serum potassium levels were determined ionometrically using ion-selective electrodes. Also, before the operation, 6 hours and 24 hours after the restoration of blood flow, the levels of myoglobin and total creatine phosphokinase in the blood plasma were determined. Total creatine phosphokinase was determined by the kinetic method.

Interleukins IL-1ß, IL-6, IL-8, IL-10, and tumor necrosis factor α (TNF-α) were assessed in peripheral venous blood before surgery and 3, 6, 12, 24 and 48 hours after blood flow restoration. The levels of myoglobin, TNF-α, IL-1ß, IL-2, IL-4, IL-6, IL-8, IL-10 were determined by the enzyme immunoassay on a DENEX Systems Technology analyzer (USA) by kits of reagents for the enzyme immunoassay for the determination of the concentrations of these substances in the blood serum of the company «VEKTOR-BEST» (Ukraine). According to the manufacturer's statement, the minimum detectable concentrations for TNF-α, IL-1ß, IL-6, IL-8, IL-10 are 1 pg/ml, 1 pg/ml, 0.5 pg/ml, 2 pg/ml, 1 pg/ml, respectively, the range of measured concentrations is 0–250 pg/ml, 0–250 pg/ml, 0–300 pg/ml, 0–250 pg/ml, 0–500 pg/ml, respectively. The coefficient of variation of the results of determining content for the mentioned indicators is not more than 8 % anti-ICAM-1 (intercellular adhesion molecule 1).

The number of complications, amputations and postoperative mortality were assessed in the studied patients.

The accumulation, systematization of the initial information and visualization of the results were carried out in Microsoft Office Excel 2007 spreadsheets. Statistical analysis

was carried out using the IBM SPSS Statistics v. 23 program (USA). When comparing the mean values of quantitative data, a two-sample Student's t-test was calculated, which was evaluated by control with critical values. Differences in indicators were considered statistically significant at a significance level of $p < 0.05$.

RESULTS AND THEIR DISCUSSION

Symptoms recorded in patients were classified as signs of limb ischemia (in all studied patients), as well as their combination with respiratory or systemic symptoms (fever, cough, hypoxia, tachypnea, tachycardia, respiratory distress and/or altered mental state) in patients of the main group, while 5 (29.4%) patients were hospitalized in the ICU due to the presence of respiratory failure.

During examination, distal forms of arterial thrombosis were registered in 70.6% of patients in the main and 72.2% of the control group (Table 1).

All patients underwent surgery under spinal anesthesia. They performed open thrombectomies with closure of the arteriotomy wound with a transverse suture or with autovenous patch plastic. Taking into account the

Table 1

The level of the arterial lesion

Level	Group	
	Control group	Main group
Proximal (aorto-illiac segment (%)	5 (27,8 %)	5 (29,4 %)
Distal (popliteal-distal segment) (%)	13 (72,2 %)	12 (70,6 %)
Duration of ischaemia, hours (M ± σ)	7,2 ± 0,6	7,5 ± 0,7

Table 2

Dynamics of cytokine levels in the early postoperative period, pg/ml (M ± σ)

Cytokine	Group	Before surgery	Reperfusion time, hours				
			3 h	6 h	12 h	24 h	48 h
IL-1ß	Main group	17,3 ± 0,5	21,5 ± 1,1*	33,2 ± 1,2*	38,7 ± 1,0*	40,1 ± 1,6*	41,7 ± 1,4*
	Control group	6,2 ± 1,1	6,9 ± 0,8	6,1 ± 0,7	5,5 ± 0,6	6,3 ± 0,9	6,4 ± 0,8
IL-6	Main group	11,2 ± 1,9*	14,9 ± 2,6*	85,3 ± 14,3*	97,6 ± 19,7*	84,9 ± 16,5*	63,7 ± 11,1*
	Control group	9,8 ± 2,1	8,3 ± 1,6	27 ± 6,2	25,3 ± 7,1	30,6 ± 7,8	17 ± 3,2
Il-8	Main group	22,2 ± 1,7	29,7 ± 1,9*	31,3 ± 2,8*	37,3 ± 3,1*	33,6 ± 3,4*	39,4 ± 3,8*
	Control group	14,1 ± 2,0	11,2 ± 1,6	14,1 ± 1,5	15,8 ± 1,9	16,2 ± 1,9	19,8 ± 2,6
IL-10	Main group	5,3 ± 0,5	10,5 ± 0,5	16,9 ± 0,7	18,4 ± 2,2	21,6 ± 4,7	44,2 ± 9,2
	Control group	2,1 ± 0,3	2,4 ± 0,6	2,6 ± 0,8	6,2 ± 1,6	14,5 ± 2,9	29,4 ± 6,4
TNF-α	Main group	25,7 ± 2,0	39,2 ± 2,8	44,3 ± 7,5*	45,4 ± 8,0*	44,8 ± 8,4*	55,1 ± 7,7*
	Control group	16,3 ± 2,2	17,6 ± 1,9	18,9 ± 2,0	16,3 ± 2,5	18,1 ± 3,1	17,4 ± 2,7

Note:
* significant difference between main and control groups ($p < 0,05$).

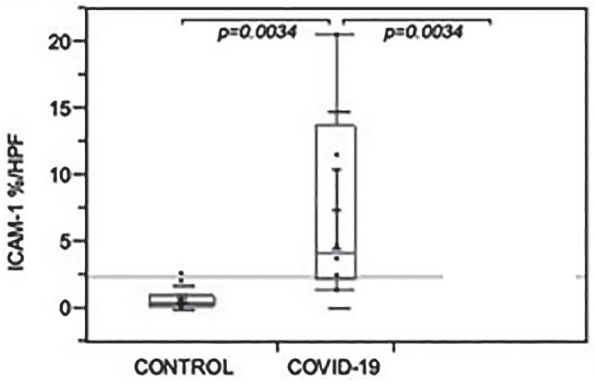

Fig. 1. ICAM-1 levels in the main and control groups.

anticoagulation regimen, fasciotomy on the tibia in patients with proximal thrombosis was performed before intraoperative heparin and thrombectomy.

In the postoperative period, conventional treatment with early stimulation of diuresis with loop diuretics, intravenous infusion of mannitol, sodium bicarbonate, standard infusion and anticoagulant therapy was performed. Therapy of patients in the main group was supplemented by the introduction of antiviral drugs and antibiotics.

The general trend was an increase in IL-10 concentration after 24 h of reperfusion with a further marked increase during the second postoperative day. However, by the end of the second postoperative day, the ratio of anti-inflammatory cytokines to pro-inflammatory in patients of the control group was more favorable.

The concentration of myoglobin in the serum 6 h after surgery was the highest, reaching the highest values in patients of the main group (Table 3). There was a significantly lower concentration of myoglobin in the control group during the first days after the restoration of blood flow. The level of total CPK in the first 24 h after surgery in patients of the control group was also lower than in patients of the main group, although the decrease was not as significant as for myoglobin concentrations.

ICAM-1 levels were significantly higher in the COVID-19 control group than in the control group during the first day after blood flow recovery (Fig. 1).

Activated endothelial cells can express ICAM-1 molecules, which can attract leukocytes (endothelium) and transmit intracellular signals leading to a stable proinflammatory status. The proinflammatory condition can lead to systemic endothelial dysfunction and lead to a loss of its integrity due to the death of endothelial cells. The constant inflammatory signaling of these adhesion molecules will also contribute to later thrombotic events.

The association between endothelial dysfunction and subsequent thrombotic events is already well known in cardiovascular disease and diabetes. Six of our cases had comorbidities such as arterial hypertension, dyslipidemia, diabetes mellitus, and signs of chronic arterial disease. Thus, previous endothelial activation status caused by these comorbidities exacerbated endothelial dysfunction caused by SARS-CoV-2 infection and its inflammatory response, and may have been the cause of the most common fatalities described in these patients.

Programmed cell death resulting from the activation of a protein complex known as inflammasome. Subsequent activation of caspase-1 leads to the release of proinflammatory cytokines and cell fragmentation. It has been suggested that pyroptosis may contribute to endothelial cell death after SARS-CoV-2 infection and may increase the release of proinflammatory cytokines such as IL-1 beta and IL-18. Our results showed higher expression of proinflammatory cytokines in the COVID-19 control group during the first days after blood flow recovery, and this aspect may indicate the

Table 3

Dynamics of CPK and myoglobin levels in the early postoperative period (M ± σ)

Index	Group	Before surgery	After 6 h	After 24 h
Myoglobine, pg/ml	Main group	276 ± 102	1788 ± 584	761 ± 292
	Control group	291 ± 94	568 ± 168	346 ± 96
CPK, U/l	Main group	1364 ± 402	5802 ± 1950	8462 ± 2926
	Control group	1198 ± 378	3980 ± 1268	5026 ± 1540

presence of pyroptosis in capillary-alveolar endothelial cells.

Serum potassium levels at 12 h postoperatively were 5.1 mg/dL in the control group, 5.8 mg/dL in the main group; 6.0 mg/dL in the control group after 24 h, and 6.5 mg in the main group. Creatinine levels at 12 and 24 h postoperatively in patients in the control group were 7.8 mg/dL and 5.4 mg/dL, in patients in the main group — 8.1 mg/dL and 7.3 mg/dL, respectively.

During the hospital stay, signs of different degrees of renal dysfunction in the main group were detected in 13 patients (76.4%), in the control group — in 12 (66.7%). At the same time in the main group signs of mild renal dysfunction (stage I acute kidney damage according to the AKIN classification) were observed in 8 patients (47.1%), symptoms of renal failure — in 5 (29.4%), patients needed intermittent hemodialysis procedures. In the control group, mild renal dysfunction was observed in 10 (55.6%) patients, clinical manifestations of renal failure — in 2 (11.1%).

Recurrences of thrombosis in the early postoperative period occurred in 5 (29.4%) patients of the main group (it should be noted that recurrent thrombosis was localized in the distal arterial bed and developed in patients with the most severe manifestations of COVID-19), which led to amputation. In the control group, recurrent thrombosis led to amputation in 2 (11.1%) cases.

In 7 patients of the main group (41.2%) and 2 patients of the control group (11.1%) in the early postoperative period developed adverse cardiopulmonary events, which in 4 patients of the main group (23.5%) caused death.

Mortality in the main group was 23.5% (4 patients died), in the control group 1 patient died (5.6%). The cause of death of the patient in the control group was progressive multiorgan failure.

Our study is consistent with literature data showing an increase in thromboembolic events in patients with (COVID-19) [16–19, 21]. Our observations show an association between thrombosis of the arteries of the lower extremities and severe acute respiratory manifestations of coronavirus infection, with a feature is the high frequency of localization of thrombosis in the distal arterial bed (70.6% of observations), high (29.4%) recurrence rate, recurrence and a high mortality rate (23.5%) in the early postoperative period [20–22]. A higher mortality rate (40%) was shown by Bellostaet all. [23] in their cohort of patients, however, such differences can be explained by the small number of our observations.

According to the results of Huang et al., the level of IL-1ß, IL-7, IL-8, IL-9, IL-10, G-CSF, GM-CSF, IFN-γ, PDGF, TNF-α and VEGF in blood plasma was higher in patients with severe COVID-19 and mild cases compared with healthy adults [24].

CONCLUSIONS

In conclusion, our results suggest the involvement of endothelial dysfunction and thrombosis in COVID-19 [25–27].

Consistent with this hypothesis, patients with type 2 diabetes and severe COVID-19 have been noted to have significant increase in serum level of inflammatory markers (TNF-α, IL-1ß, IL-6, IL-8, IL-10).

One of the significant factors of endothelial dysfunction as a result of our study was ICAM-1 thereby indicating the occurrence of macrophage activation syndrome.

These thrombotic events can be fatal in patients with type 2 diabetes mellitus, and early diagnosis can help health professionals adjust the anticoagulation regimen and affect endothelial stabilization in high-risk patients, alleviate thrombogenic events, systemic inflammatory response syndrome, and multiorgan failure.

REFERENCES

1. Aghagoli G, Gallo Marin B, Soliman LB, Sellke FW. *J Card Surg* 2020;35(6): 1302-1305.
2. Bhayana R, Som A, Li MD, et al. *Radiology* 2020. https://doi.org/10.1148/radiol.2020201908.
3. Tang K, Wang Y, Zhang H, et al. *Dermatol Ther (Heidelb)* 2020. https://doi.org/10.1111/dth.13528.
4. Puelles VG, Litgehetmann M, Lindenmeyer MT, et al. *N Engl J Med* 2020;383(6): 590-592.
5. Needham EJ, Chou SH, Coles AJ, Menon DK. *Neurocrit Care* 2020;32(3): 667-671.
6. Lodigiani C, Iapichino G, Carenzo L, et al. *Thromb Res* 2020;191: 9-14.
7. Middeldorp S, Coppens M, van Haaps TF, et al. *J Thromb Haemost* 2020;18(8): 1995-2002.
8. Llitjos JF, Leclerc M, Chochois C, et al. *J Thromb Haemost* 2020;18(7): 1743-1746.
9. Wichmann D, Sperhake JP, Litgehetmann M, et al. *Ann Intern Med* 2020;173(4): 268-277.
10. Dominguez-Erquicia P, Dobarro D, Raposeiras-Roubнn S, et al. *Eur Heart J* 2020;41(22): 2132.
11. Hess DC, Eldahshan W, Rutkowski E. *Transl Stroke Res* 2020;11(3): 322-325.
12. Vulliamy P, Jacob S, Davenport RA. *Br J Haematol* 2020;189(6): 1053-1054.
13. de Barry O, Mekki A, Diffre C, et al. *Radiol Case Rep* 2020;15(7): 1054-1057.
14. Beccara L, Pacioni C, Ponton S, et al. *Eur J Case Rep Intern Med* 2020;7(5): 001690.
15. Varga Z, Flammer AJ, Steiger P, et al. *Lancet* 2020; 395(10234): 1417-1418.
16. NYC Health. COVID-19: data. URL: *https://www1.nyc.gov/site/doh/covid/covid-19-data.page.*
17. Laohapensang K, Rerkasem K, Kattipattanapong V. *Eur J Vasc Endovasc Surg* 2004;28(4): 418-420.
18. Mehta RH, Manfredini R, Hassan F, et al. *Circulation* 2002;106(9): 1110-1115.
19. Rosenbaum PR, Rubin DB. *Biometrika* 1983;70(1): 41-55.
20. Golestaneh L, Farzami A, Madu C, et al. *BMC Nephrol* 2019;20(1): 343.
21. Klok FA, Kruip MJHA, van der Meer NJM, et al. *Thromb Res* 2020;191: 145-147.
22. Ouriel K, Greenberg RK, Green RM, et al. *J Vasc Surg* 1999;30(6): 1060-1066.
23. Bellosta R, Luzzani L, Natalini G, et al. *J Vasc Surg* 2020. https://doi.org/10.1016/j.jvs.2020.04.483.
24. Huang C, Wang Y, Li X. *Lancet* 2020 https://doi.org/10.1016/S0140-6736(20)30183-5.
25. Zhou Y, Fu B, Zheng X, et al. *Sci Rev* 2020;7: 998-1002. https://doi.org/10.1093/nsr/nwaa041.
26. Clerkin KJ, Fried JA, Raikhelkar J, et al. *Circulation* 2020;141(20): 1648-1655.
27. Hartnett KP, Kite-Powell A, DeVies J, et al. *Morb Mortal Wkly Rep* 2020;69(23): 699-704.

АРТЕРІАЛЬНИЙ ТРОМБОЗ У ХВОРИХ НА ДІАБЕТ 2 ТИПУ ТА COVID-19

Граматюк С. М.[1], Іванова Ю. В.[2], Зарудний О. О.[2], Мясоєдов К. В.[2]

[1] Українська асоціація Біобанку, Інститут клітинної біореабілітації, м. Харків, Україна

[2] ДУ «Інститут загальної та невідкладної хірургії НАМН України імені Зайцева В. Т.», м. Харків, Україна

gramatyuk@ukrainebiobank.com

Мета дослідження: оцінити важливість запального статусу організму у пацієнтів з цукровим діабетом 2 типу і важкою формою COVID-19 як несприятливого фактора виникнення артеріального тромбозу нижніх кінцівок, перебігу гострої ішемії і прогнозів щодо ішемічної кінцівки.

Матеріали та методи. У дослідження були залучені 35 пацієнтів з діабетом 2 типу без переміжної кульгавості з ішемією 6–12 годин в анамнезі, яким була виконана термінова хірургічна успішна тромбектомія. Всі обстежені пацієнти були протестовані на вірус SARS-CoV-2: у 18 — негативний результат (контрольна група), діагноз COVID-19 у 17 пацієнтів основної групи підтверджений за допомогою транскрипційної полімеразної ланцюгової реакції. Середній вік пацієнтів контрольної групи склав 72,3 року, основної групи — 69,8 року.

Результати. При обстеженні дистальні форми артеріального тромбозу зареєстровані у 70,6 % хворих основної та 72,2 % контрольної групи. Концентрація міоглобіну в сироватці крові через 6 годин після операції була найвищою, досягаючи максимальних значень у пацієнтів основної групи. У перші дні після відновлення кровотоку в контрольній групі була достовірно більш низька концентрація міоглобіну. Рівні ICAM-1 були значно вище в групі COVID-19, ніж у контрольній групі, протягом першого дня після відновлення кровотоку. Зв'язок між ендотеліальної дисфункцією і подальшими тромботичними подіями вже добре відомий при серцево-судинних захворюваннях і діабеті. У шести з обстежених спостерігали кластер супутніх захворювань, таких як артеріальна гіпертензія, дисліпідемія, цукровий діабет і ознаки хронічного захворювання артерій. Таким чином, попередній статус активації ендотелію, обумовлений супутніми захворюваннями, посилив ендотеліальну дисфункцію, викликану інфекцією SARS-CoV-2 та її запальною реакцією, і, скоріше за все, був причиною найбільш частих летальних випадків, описаних у цих пацієнтів. Рецидиви тромбозу в ранньому післяопераційному періоді відбулися у 5 (29,4 %) пацієнтів основної групи, що привело до ампутації. У контрольній групі рецидив тромбозу привів до ампутації в 2 (11,1 %) випадках. У 7 пацієнтів основної групи (41,2 %) і 2 пацієнтів контрольної групи (11,1 %) в ранньому післяопераційному періоді розвинулися несприятливі серцево-легеневі події, які у 4 пацієнтів основної групи (23,5 %) призвели до летального результату.

Висновки. Отримані результати доводять участь ендотеліальної дисфункції і тромбозу в COVID-19. Відповідно до цієї гіпотези у пацієнтів з діабетом 2 типу та важким COVID-19 було відзначено суттєве підвищення рівня запальних маркерів у сироватці крові (TNF-α, IL-1β, IL-6, IL-8, IL-10). Одним із значущих чинників ендотеліальної дисфункції за результатами нашого дослідження був ICAM-1, що вказувало на виникнення синдрому активації макрофагів. Ці тромботичні події можуть бути фатальними у пацієнтів з діабетом 2 типу, і рання діагностика може допомогти медичним працівникам скорегувати режим антикоагулянтної терапії і вплинути на стабілізацію ендотелію у пацієнтів з високим ризиком, полегшити тромбогенні явища, синдром системної запальної відповіді і поліорганну недостатність.

Ключові слова: цукровий діабет 2 типу, COVID-19, артеріальний тромбоз.

ARTERIAL THROMBOSIS IN PATIENTS WITH TYPE 2 DIABETES AND COVID-19

S. M. Gramatiuk [1], J. V. Ivanova [2], O. A. Zarudny [2], K. V. Miasoiedov [2]

[1] Ukraine Association of Biobank, Institute of Cellular Biorehabilitation, Kharkiv, Ukraine

[2] State Institution «V. T. Zaitsev Institute of General and Urgent Surgery of the National Academy of Medical Sciences of Ukraine», Kharkiv, Ukraine

gramatyuk@ukrainebiobank.com

The aim of the study: to assess the importance of the inflammatory status of the body in patients with diabetic 2 type and severe COVID-19 as an unfavorable factor for the occurrence of arterial thrombosis of the lower extremities, the course of acute ischemia and the prognosis for ischemic limb.

Materials and Methods. The study included 35 patients with type 2 diabetes mellitus and acute arterial thrombosis of the lower extremities without a history of intermittent claudication with an ischemia of 6-12 h, who underwent urgent surgical successful thrombectomy. All studied patients were tested for the SARS-CoV-2 virus, 18 had a negative result (control group), the diagnosis of COVID-19 in 17 patients of the main group was confirmed by a transcriptional polymerase chain reaction. The average age of patients in the control group was 72.3 yrs, the main group — 69.8 yrs.

Results. During examination, distal forms of arterial thrombosis were registered in 70.6 % of patients in the main group and 72.2 % in the controls. The concentration of myoglobin in the serum at 6 h after the surgery was the highest, reaching the highest values in patients of the main group. There was a significantly lower concentration of myoglobin in the control group during the first days after the restoration of blood flow. ICAM-1 levels were significantly higher in the COVID-19 group than in the control group during the first day after blood flow recovery

The association between endothelial dysfunction and subsequent thrombotic events is already well known in cardiovascular disease and diabetes. Six of our cases had comorbidities such as arterial hypertension, dyslipidemia, diabetes mellitus, and signs of chronic arterial disease. Thus, previous endothelial activation status caused by these comorbidities exacerbated endothelial dysfunction caused by SARS-CoV-2 infection and its inflammatory response, and may have been the cause of the most common fatalities described in these patients.

Recurrences of thrombosis in the early postoperative period occurred in 5 (29.4 %) patients of the main group, which led to amputation. In the control group, recurrent thrombosis led to amputation in 2 (11.1 %) cases.

In 7 patients of the main group (41.2 %) and 2 patients of the control group (11.1 %) in the early postoperative period developed adverse cardiopulmonary events, which in 4 patients of the main group (23.5 %) caused death.

Conclusions. Our results suggest the involvement of endothelial dysfunction and thrombosis in COVID-19. Consistent with this hypothesis, patients with type 2 diabetes mellitus and severe COVID-19 have been noted to have significant increase in serum level of inflammatory markers (TNF-α, IL-1ß, IL-6, IL-8, IL-10). One of the significant factors of endothelial dysfunction as a result of our study was ICAM-1 thereby indicating the occurrence of macrophage activation syndrome.

These thrombotic events can be fatal in patients with type 2 diabetes, and early diagnosis can help health professionals adjust the anticoagulation regimen and affect endothelial stabilization in high-risk patients, alleviate thrombogenic events, systemic inflammatory response syndrome, and multiorgan failure.

Keywords: type 2 diabetes mellitus, COVID-19, arterial thrombosis.