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Оценка показателей воспаления и апоптоза тромбоцитов у пациентов с ожирением при проведении различных видов антикоагулянтной профилактики венозных тромбоэмболических осложнений на фоне COVID-19

А. Б. Агапов[1, 2] ✉, Р. Е. Калинин[1], Н. Д. Мжаванадзе[1], В. О. Поваров[1], А. А. Никифоров[1], Д. А. Максаев[1, 3], А. А. Чобанян[3], И. А. Сучков[1]

[1] Рязанский государственный медицинский университет имени академика И. П. Павлова, Рязань, Российская Федерация;
[2] Областная клиническая больница, Рязань, Российская Федерация;
[3] Городская клиническая больница скорой медицинской помощи, Рязань, Российская Федерация

АННОТАЦИЯ

Актуальность. Наличие гиподинамии, гиповентиляции, а также хронического воспаления у пациентов с ожирением усугубляет их состояние при различных заболеваниях. Указанные особенности стали важными с приходом пандемии COVID-19, при которой воспаление и коагулопатия, обусловленная активацией тромбоцитов, тесно связаны между собой.

Цель. Изучить содержание лабораторных показателей воспаления и апоптоза тромбоцитов у пациентов с ожирением при использовании различных видов антикоагулянтной профилактики венозных тромбоэмболических осложнений на фоне COVID-19.

Материалы и методы. В исследование включено 370 пациентов с COVID-19. В зависимости от наличия или отсутствия ожирения и варианта парентерального антикоагулянта пациенты в нашем исследовании разделены на группы: группа 1 — без ожирения + низкомолекулярный гепарин (НМГ) (n = 114), группа 2 — без ожирения + нефракционированный гепарин (НФГ) (n = 58), группа 3 — наличие ожирения + НМГ (n = 76), группа 4 — наличие ожирения + НФГ (n = 66). Проведен анализ частоты развития венозных тромбоэмболических осложнений (ВТЭО), кровотечений, общих маркеров острой фазы воспаления, специфических маркеров апоптоза тромбоцитов (фосфатидилсерина и кальретикулина).

Результаты. В конце стационарного лечения отмечено снижение уровня ферритина у пациентов как с ожирением, так и без него, получавших НМГ. Концентрация кальретикулина оказалась выше у пациентов, принимавших НМГ (1 и 3 группы). Уровень фосфатидилсерина имел высокие показатели у пациентов, получавших НМГ, только при наличии ожирения. Высокая частота развития тромбоэмболии легочных артерий (ТЭЛА) без источника была у пациентов, принимавших НФГ, в сравнении с НМГ (13,6% случаев против 2,6% случаев соответственно, p = 0,029) и ТЭЛА с источником в нижних конечностях (9,1% случаев против 0% случаев соответственно, p = 0,018). При использовании НМГ наблюдалась меньшая частота развития кровотечений в сравнении с применением НФГ (5,3% случаев против 16,7% случаев соответственно, p = 0,056).

Заключение. Уровень фосфатидилсерина и кальретикулина у пациентов с ожирением выше у пациентов получавших НМГ. При этом у пациентов данной группы имеет место низкая частота развития ВТЭО и геморрагических осложнений в сравнении с группой пациентов, принимавших НФГ.

Ключевые слова: *венозные тромботические осложнения; ожирение; апоптоз тромбоцитов; фосфатидилсерин; кальретикулин*

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ЭКО•ВЕКТОР

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Evaluation of Inflammation and Platelet Apoptosis Parameters in Obese Patients in Various Types of Anticoagulant Prophylaxis of Venous Thromboembolic Complications in Context of COVID-19

Andrey B. Agapov[1, 2]✉, Roman E. Kalinin[1], Nina D. Mzhavanadze[1], Vladislav O. Povarov[1], Aleksandr A. Nikiforov[1], Denis A. Maksayev[1, 3], Artyom A. Chobanyan[3], Igor' A. Suchkov[1]

[1] Ryazan State Medical University, Ryazan, Russian Federation;
[2] Ryazan Regional Clinical Hospital, Ryazan, Russian Federation;
[3] City Clinical Emergency Hospital, Ryazan, Russian Federation

ABSTRACT

INTRODUCTION: The physical inactivity, hypoventilation, as well as chronic inflammation in obese patients aggravates their condition in various diseases. These features have become important with the advent of the COVID-19 pandemic, in which inflammation and platelet-activated coagulopathy are closely linked.

AIM: To study laboratory parameters of inflammation and platelet apoptosis in obese patients using various types of anticoagulant prophylaxis of venous thromboembolic complications with the underlying COVID-19.

MATERIALS AND METHODS: The study included 370 patients with COVID-19. Depending on the presence or absence of obesity and the type of parenteral anticoagulant, patients in our study were divided into groups: group 1 — non-obese + low molecular weight heparin (LMWH) (n = 114), group 2 — non-obese + unfractionated heparin (UFH) (n = 58), group 3 — obesity + LMWH (n = 76), group 4 — obesity + UFH (n = 66). The incidence of venous thromboembolic complications (VTEC), bleeding, general markers of the acute phase of inflammation, and specific markers of platelet apoptosis (phosphatidylserine and calreticulin) have been analyzed.

RESULTS: At the end of hospital treatment, a decrease in ferritin levels was noted in patients both with and without obesity receiving LMWH. The concentration of calreticulin was higher in patients taking LMWH (groups 1 and 3). Phosphatidylserine levels were high in patients receiving LMWH only if they were obese. In patients taking UFH compared to LMWH, a high incidence of pulmonary embolism (PE) without a source (13.6% of cases versus 2.6%, respectively, p = 0.029) and PE with a source in the lower extremities (9.1% of cases versus 0%, respectively, p = 0.018) was found. When using LMWH, a lower incidence of bleeding was observed compared to using UFH (5.3% of cases versus 16.7%, respectively, p = 0.056).

CONCLUSION: The levels of phosphatidylserine and calreticulin are higher in obese patients receiving LMWH. At the same time, patients in this group have a low incidence of VTEC and hemorrhagic complications compared to the group of patients taking UFH.

Keywords: *venous thrombotic complications; obesity; platelet apoptosis; phosphatidylserine; calreticulin*

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ECO•VECTOR

LIST OF ABBREVIATIONS

ACT — anticoagulant therapy
AF — atrial fibrillation
ALT — alanine aminotransferase
ALV — artificial lung ventilation
aPTT— activated partial thromboplastin time
AST — aspartate aminotransferase
CAD — coronary artery disease
CKD — chronic kidney disease
COVID-19 — infection caused by new coronavirus SARS-CoV-2
CRP — C-reactive protein
CT — computed tomography
CVD — chronic venous disorder
DM — diabetes mellitus
DOAC — direct oral anticoagulants
DVT — deep vein thrombosis
EH — essential hypertension
ESR — erythrocyte sedimentation rate
GU — gastric ulcer
INR — international normalized ratio
ICU — intensive care unit
LMWH — low molecular weight heparin
NILV — non-invasive lung ventilation
OALLA — obliterating atherosclerosis of lower limb arteries
PCR — polymerase chain reaction
PCT — procalcitonin
PE — pulmonary embolism
PICS — post-infarction cardiosclerosis
PT — prothrombin time
SARS-CoV-2 — Severe acute respiratory syndrome-related coronavirus 2
VTEC — venous thromboembolic complications
UDS — ultrasound duplex scanning
UFH — unfractionated heparin

INTRODUCTION

According to the literature, venous thromboembolic complications (VTEC) annually affect 10 million people worldwide [1]. The incidence of deep vein thrombosis (DVT) of lower extremities is from 45 to 117 cases per 100 thousand population, and of isolated pulmonary embolism (PE) from 29 to 78 cases per 100 thousand population annually [2]. Historically, the main risk factors for development of VTEC are considered to be immobilization, trauma, surgical intervention, oncology, hormonal therapy, coagulation disorders and obesity [3]. In modern literature, division of VTEC risk factors into major and minor, transient (temporary) and persistent, can be encountered [4]. One common risk factor for VTEC is obesity. Effective anticoagulant therapy (ACT) in real clinical practice is limited by incomplete understanding of the main prothrombotic mechanisms and uncertainty about risks, benefits and dosing of anticoagulants drugs [5]. Two main mechanisms most responsible for obesity-induced thrombosis, are chronic inflammation and disorder in fibrinolysis [6]. A consequence of chronic thrombotic state is activation of prothrombotic signaling pathways in vascular cells. Stimulation of vascular endothelium, platelets and other circulating vascular cells by proinflammatory cytokines leads to up regulation of procoagulant factors and adhesion molecules, down regulation of anticoagulant regulatory proteins, increased production of thrombin and enhanced activation of platelets [7].

Obese patients characteristically have hypoventilation syndrome, high risk of respiratory distress syndrome, hypodynamia, which are also risk factors for VTEC. The specified peculiarities of obese patients became the key ones with advent of COVID-19 pandemic, in which SARS-CoV-2 (Severe acute respiratory syndrome-related coronavirus 2) virus penetrates endothelial cells and leads to endotheliitis, apoptosis, activation of platelets and coagulation factors [8].

In this pathological process, two important roles in coagulation are played by apoptosis participants: calreticulin and phosphatidylserine [9]. Calreticulin is a protein which can ‘oppose thrombosis’ in the mechanism of blood coagulation [10]. Phosphatidylserine is a phospholipid that can increase in the amount in activation of platelets, which leads to production of thrombin and to hypercoagulation [11]. Considering that one key mechanism of thrombosis in obesity and COVID-19 is activation of platelets, an important trend is investigation of markers of platelet apoptosis and a possibility of application of anticoagulant therapy (ACT) in this population of patients.

The **aim** of this study to the content of specific markers of platelet apoptosis (phosphatidylserine and calreticulin) in blood of obese patients using parenteral anticoagulants.

MATERIALS AND METHODS

A prospective observational study was conducted from July 2021 to January 2022, which included 370 patients with COVID 19, 135 men and 235 women. The mean age of patients was 61.1 (23–93) years. The work was carried out in accordance with the plan of the Department of Cardiovascular, X-Ray Endovascular Surgery and Radiation Diagnostics and was approved by the Local Ethics Committee of the Ryazan State Medical University (Protocol No. 3 of October 11, 2020). The

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study is registered on the ClinicalTrials.gov platform (NCT05143567 of December 3, 2020). All procedures performed in this study comply with the ethical standards of Declaration of Helsinki of 1975 and its subsequent amendments or with comparable ethical standards. All study participants signed voluntary informed consent.

Inclusion criteria: patients with COVID-19 aged 18 to 75 years with the diagnosis confirmed by laboratory PCR test and chest CT data. Exclusion criteria from the study: age below 18 years, pregnancy or lactation period, presence of baseline thrombocytopenia, contraindications for use of ACT, extremely severe or agonizing patients on admission.

In accordance with the recommendations of the Ministry of Health of the Russian Federation 'Prevention, diagnosis and treatment of a new coronavirus infection', all patients with COVID-19 were prescribed parenteral anticoagulants in a preventive dose [12]. Upon discharge from the hospital, patients were recommended intake of direct oral anticoagulants (DOAC). In our prospective study, the types of ACT are presented as follows: LMWH was prescribed to 172 (46.5%) patients, UFH was used in 142 (38.4%) patients, and 56 (15.1%) patients took DOAC. Patients taking oral anticoagulants were not considered in this analysis because they were taking them continuously for cardiovascular comorbidities, joint replacement, were not obese, and had mild form of COVID-19, which, according to recommendations, allowed continuation of VTEC prophylaxis with oral anticoagulants in tableted form [12]. Therefore, this study will consider 314 people receiving only parenteral anticoagulants.

In the treatment for COVID-19, if VTEC was identified, which was the endpoint of the study, a therapeutic dose of ACT was prescribed. At the beginning of hospital treatment, increased dose of ACT was used in patients with obesity. Among 370 patients, 151 (40.8%) had obesity (BMI = 34.7 (32.4–38.4) kg/m^2, 219 (59.2%) patients had no obesity (BMI = 24.8 (18.2–25.0) kg/m^2; p = 0.007). According to the temporary methodical recommendations 'Prevention, diagnosis and treatment of a new coronavirus infection', in patients with obesity, increase in the prophylactic dose of parenteral anticoagulant by 50% should be considered [12]. Therefore, in our study, patients with no obesity were prescribed subcutaneous UFH at a dose 5 000 Un 2–3 times a day, and LMWH 40 mg once a day, while patients with obesity were prescribed subcutaneous UFH at a dose 7 500 Un 3 times a day, and LMWH at a dose 1 mg/kg two times a day. Patients in our study were divided into groups: group 1 — no obesity + LMWH (n = 114), group 2 — no obesity + UFH (n = 58), group 3 — obesity + LMWH (n = 76), group 4 — obesity + UFH (n = 66).

The endpoint of the study was verified cases of VTEC: DVT of the lower extremities, PE with or without source at autopsy. Safety of use of anticoagulants was evaluated by identifying cases of significant and major bleeding according to criteria established by the committee of the International Society on Thrombosis and Haemostasis in 2005 [13].

Venous blood for laboratory analysis was collected upon admission to the hospital and upon stabilization of the condition at the end of treatment. In laboratory analyses, the markers of acute phase of inflammation were evaluated: leukocytes, C-reactive protein (CRP), ferritin, coagulation parameters and clinical blood analysis. The concentration of phosphatidylserine and calreticulin was measured in the blood serum using a human ELISA kit (Cloud-Clone Corporation China).

Statistical analysis of the clinical study was performed using IBM SPSS Statistics 26. Analysis of qualitative parameters was performed using Pearson and Fisher $\chi 2$ criteria. Quantitative parameters were assessed using Kolmogorov–Smirnov criterion ($p > 0.05$). Due to the non-normal distribution of parameters, the mean values were presented as median (Me) and interquartile range (Q_1–Q_3), and the analysis was performed using Wilcoxon, Mann–Whitney, and Kruskal–Wallis criteria ($p < 0.05$).

RESULTS

The groups of patients included in the study were comparable in age (p = 0.331) and the volume of viral lung damage according to CT data (p = 0.067) (Table 1). In the groups with obesity, there were more women than men (p = 0.001). The difference between groups by these parameters did not affect the study results. Among the comorbidities, obese patients, as opposed to non-obese ones, more often had hypertension (p = 0.032), post-infarction cardiosclerosis (p = 0.022), type 2 diabetes mellitus (p = 0.032), chronic kidney disease (p = 0.001), chronic venous disorders (p = 0.012) and a history of VTEC (p = 0.013).

During treatment, some patients showed a negative dynamics, namely, increase in temperature, decrease in saturation, increase in the area of viral lung lesion on CT scan of the lungs. Patients had to be transferred from the ward to the intensive care unit (ICU). Among patients transferred to ICU, there were more obese than non-obese patents (p = 0.01) (Figure 1). Of attention is the fact that obese patients receiving LMWH, were more often transferred to NILV (p = 0.005), and for patients receiving UFH, ALV was more often used (p < 0.001). In our study, transfer of the patient to ALV was accompanied by a 100% fatal outcome. According to our data, higher mortality was observed in obese patients receiving UFH, than in those receiving LMWH (p < 0.001).

Table 1. Clinical and Anamnestic Characteristics of Patients at the Time of inclusion in the Study

Parameter	Non-obese patients n = 171		Obese patients n = 142		p
	Group 1, LMWH n = 113	Group 2, UFH n = 58	Group 3, LMWH n = 76	Group 4, UFH n = 66	
Age, Me (Q_1–Q_3), years	63 (53–71)	61.5 (49–70)	63.5 (58–69)	61 (52–67)	0.331
Gender: male, n (%) female, n (%)	 58 (50.9) 56 (49.1)	 22 (37.9) 36 (62.1)	 27 (35.5) 49 (64.5)	 13 (19.7) 53 (80.3)	 0.001
BMI, Me (Q_1–Q_3)	24.9 (20.9–25.3)	23.7 (19.8–24.8)	34.4 (32.1–38.4)	35.9 (32.7–38.3)	0.048
CT-0, n (%) CT-1, n (%) CT-2, n (%) CT-3, n (%) CT-4, n (%)	8 (7.0) 30 (26.3) 48 (42.1) 23 (20.2) 5 (4.4)	0 (0) 14 (24.1) 27 (46.6) 13 (22.4) 4 (6.9)	3 (3.9) 13 (17.1) 33 (43.4) 22 (28.9) 5 (6.6)	0 (0) 9 (13.6) 26 (39.4) 24 (36.4) 7 (10.6)	0.067
Comorbid diseases					
CAD, n (%)	27 (23.7)	12 (20.7)	21 (27.6)	14 (21.2)	0.761
PICS, n (%)	7 (6.1)	2 (3.4)	9 (12)	7 (10.6)	0.022
AF, n (%)	18 (15.8)	9 (15.5)	12 (15.8)	8 (12.1)	0.911
EH, n (%)	84 (73.7)	41 (70.7)	67 (88.2)	55 (83.3)	0.032
ACVA, n (%)	11 (9.6)	2 (3.4)	2 (2.6)	0 (0)	0.017
BA, n (%)	2 (1.8)	2 (3.4)	4 (5.3)	7 (10.6)	0.058
COPD, n (%)	10 (8.8)	0 (0)	5 (6.6)	2 (3)	0.08
GU, n (%)	10 (8.8)	8 (13.8)	1 (1.3)	5 (7.6)	0.054
DM, n (%)	17 (14.9)	16 (28.1)	42 (55.2)	27 (40.9)	0.032
CKD, n (%)	19 (16.7)	5 (8.6)	20 (26.3)	2 (3)	0.001
OALLA, n (%)	8 (7.0)	3 (5.2)	1 (1.3)	0 (0)	0.061
CVD, n (%)	5 (4.4)	6 (10.3)	11 (14.5)	13 (19.7)	0.012
VTEC, n (%)	2 (1.8)	4 (6.9)	2 (2.6)	8 (12.1)	0.013
Oncology, n (%)	12 (10.6)	5 (8.6)	10 (13.2)	4 (6.1)	0.539

Notes: LMWH — low molecular weight heparin; UFH — unfractionated heparin; BMI — body mass index; CT — computed tomography; CAD — coronary artery disease; PICS — post-infarction cardiosclerosis; AF — atrial fibrillation; EH — essential hypertension; ACVA — acute cardiovascular accident; BA — bronchial asthma; COPD — chronic obstructive pulmonary disease; GU — gastric ulcer; DM — diabetes mellitus; CKD — chronic kidney disease; OALLA — obliterating atherosclerosis of lower limb arteries; CVD — chronic vein disorder; VTEC — venous thromboembolic complication; p — statistical difference

The groups were also comparable in general laboratory parameters, inflammation markers (CRP and ferritin), and platelet apoptosis markers (Table 2). Statistically reliable differences were observed in blood glucose level, which was higher in obese patients. Differences were also obtained in fibrinogen concentration and prothrombin time, which were higher in patients receiving LMWH.

At the end of treatment for coronavirus infection, differences appeared in the laboratory parameters in the study groups (Table 2). In particular, decrease in blood glucose level, in concentration of fibrinogen and ferritin was found in patients receiving LMWH, with and without obesity. Concentration of calreticulin was higher in patients receiving LMWH, with and without obesity. In an intergroup comparison, the level of phosphatidylserine was higher in patients receiving LMWH only in the presence of obesity.

The analysis of incidence of thrombotic complications showed a comparable VTEC incidence in patients without obesity (groups 1 and 2) (Figure 2). According to our data, in obese patients, PE with a source in the lower extremities developed only in patients receiving UFH (9.1% of cases ($p = 0.004$)), with the absence of this complication in patients receiving LMWH ($p = 0.004$). Upon that, patients of group 4 with obesity receiving UFH, had a high incidence of isolated PE without a source in the lower extremities (13.6% of cases), whereas in patients of group 3 with obesity receiving LMWH, this complication developed in 2.6% of cases ($p = 0.004$). When evaluating the incidence of major and minor bleedings, a high frequency of this complication was noted in patients receiving UFH, both obese and non-obese ($p < 0.001$).

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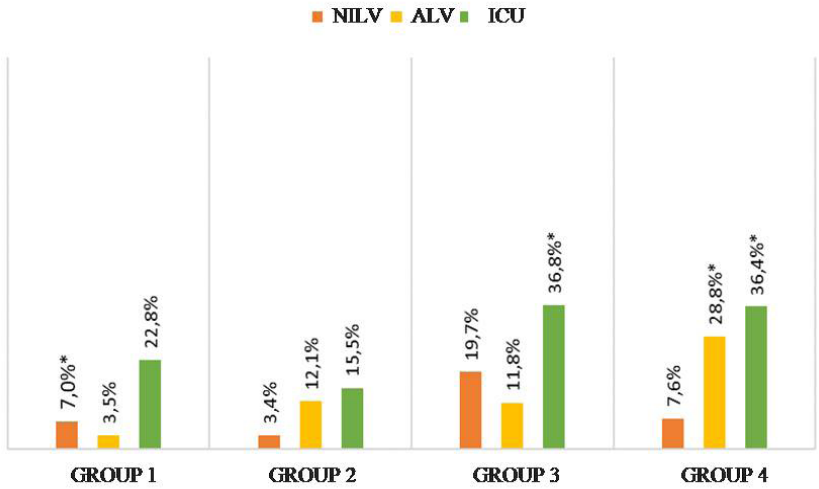

Fig. 1. Frequency of hospitalization in the intensive care unit and use of non-invasive and artificial ventilation.
Notes: Notes: ICU — intensive care unit; NILV — non-invasive lung ventilation; ALV — artificial lung ventilation; * — $p < 0.05$.

Table 2. Data of Laboratory Tests in Study Groups upon Admission, Me (Q_1–Q_3)

Parameter	Non-obese patients n = 171		Obese patients n = 142		p
	Group 1, LMWH n = 113	Group 2, UFH n = 58	Group 1, LMWH n = 76	Group 2, UFH n = 66	
Erythrocytes, $\times10^{12}$/l	4.7 (4.4–5)	4.8 (4.3–5.1)	4.8 (4.5–5.2)	4.7 (4.3–4.9)	0.17
Hemoglobin, g/l	135 (122–144)	141 (132–150)	137 (125–145)	135 (123–145)	0.044
Leukocytes, $\times10^{9}$/l	6.11 (4.3–9.2)	6.65 (5.2–7.8)	6.87 (5.4–9.2)	7.05 (4.8–9.8)	0.555
Platelets, $\times10^{9}$/l	179 (142–262)	199 (173–281)	197 (145–260)	188 (151–239)	0.168
ESR, mm/h	23 (11–31)	25.5 (10–35.5)	23.5 (15–35)	13 (8–31)	0.211
Glucose, mmol/l	6.44 (5.55–7.67)	57 (4.1–10.23)	7.5 (6.22–13.26)	7.4 (5.55–9.65)	0.005
CRP, mg/l	53.3 (21.8–90.2)	69.4 (36.6–114)	58.6 (25–139.8)	89.1 (41.4–146)	0.011
Ferritin, μg/l	628 (212–419)	884 (713–920)	641 (175–614.5)	749 (414–956)	0.358
aPTT, s	33.2 (26.3–36.7)	32.7 (27.7–36.9)	35.7 (25.9–36.8)	35 (29–40.8)	0.49
PT, s	13.3 (12.1–14.4)	12.1 (11–13.1)	13.1 (12.3–14.2)	12.7 (11.6–13.5)	$p < 0.001$ $p_{1–2} = 0.002$ $p_{1–3} = 1$ $p_{1–4} = 0.001$ $p_{2–3} = 0.004$ $p_{2–4} = 1$ $p_{3–4} = 0.003$
Fibrinogen, g/l	6.1 (5.2–6.6)	4.5 (3.5–5.5)	6.4 (5.9–7.1)	4.5 (3.2–5.7)	$p < 0.001$ $p_{1–2} = 0.001$ $p_{1–3} = 1$ $p_{1–4} = 0.004$ $p_{2–3} = 0.002$ $p_{2–4} = 1$ $p_{3–4} = 0.001$
INR	1.13 (1.03–1.24)	1.05 (0.97–1.1)	1.1 (1.04–1.19)	1,08 (1–1.16)	0.002
D-dimer, ng/ml	0.48 (0.36–0.57)	0.53 (0.32–0.92)	0.52 (0.4–0.81)	0.7 (0.39–1.12)	0.108
Calreticulin, pg/ml	5.03 (2.22–8.6)	3.85 (1.88–4.74)	4.82 (2.82–7.7)	4.18 (2.24–5.87)	0.204
Phosphatidylserine, pg/ml	64.75 (42.65–89.73)	66.2 (43.4–86.4)	63.15 (41.2–83.1)	62.6 (44.1–97.8)	0.654

Notes: LMWH — low molecular weight heparin, UFH — unfractionated heparin, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, aPTT — activated partial thromboplastin time, PT — prothrombin time, INR — international normalized ratio

Table 3. Laboratory Parameters in Study Groups at the End of Hospital Treatment, Me (Q_1–Q_3)

Parameter	Non-obese patients n = 171		Obese patients n = 142		p
	Group 1, LMWH n = 113	Group 2, UFH n = 58	Group 1, LMWH n = 76	Group 2, UFH n = 66	
Erythrocytes, $\times10^{12}$/l	4.51 (4.1–4.93)	4.5 (4.2–4.72)	4.52 (4.07–4.84)	4.4 (4–4.8)	p = 0.731
Hemoglobin, g/l	128 (118–137)	133 (123–144)	127 (111–133)	126.5 (119–139)	p = 0.105
Leukocytes, $\times10^{9}$/l	10.1 (8.4–12.7)	10.8 (9.32–13.7)	10.39 (8.24–12.9)	10.2 (7.91–13)	p = 0.603
Platelets, $\times10^{9}$/l	228 (176–319)	289 (176–338)	206 (172–280)	220.5 (184–293)	p = 0.19
ESR, mm/h	14 (6–19)	8 (1–20)	18 (11–25)	13 (2–26)	p = 0.071
Glucose, mmol/l	5.7 (4.9–7.3)	9.1 (6.6–14.57)	6.5 (4.8–9.6)	9.5 (7.8–13.7)	p < 0.001
CRP, mg/l	6.2 (1.4–13.9)	7.85 (4–18.9)	8 (2.5–18)	7.6 (4.5–11)	p = 0.456
Ferritin, μg/l	372.5 (347.5–445.5)	877.8 (512–988)	367 (265–523)	676 (502.2–923)	p = 0.001 p_{1-2} = 0.013 p_{1-3} = 1 p_{1-4} = 0.065 p_{2-3} = 0.01 p_{2-4} = 1 p_{3-4} = 0.054
aPTT, s	31.4 (25.9–36.8)	29.7 (25.7–37.5)	34.9 (30.5–36.8)	29.4 (25–36.9)	p = 0.422
PT, s	12 (11–13)	11.65 (10.75–12.7)	12.1 (11.2–12.8)	11.6 (10.9–12.2)	p = 0.36
Fibrinogen, g/l	3.31 (2.8–4.7)	2.39 (1.94–3.44)	3.4 (2.6–5.03)	2.5 (1.8–3.43)	p < 0.001 p_{1-2} = 0.001 p_{1-3} = 1 p_{1-4} = 0.002 p_{2-3} = 0.003 p_{2-4} = 1 p_{3-4} = 0.004
INR	1 (0.94–1.1)	1.01 (0.93–1.15)	1.02 (0.96–1.08)	0.98 (0.93–1.05)	p = 0.323
D-dimer, ng/ml	0.4 (0.34–0.46)	0.56 (0.24–0.83)	0.42 (0.4–0.54)	0.48 (0.31–0.97)	p = 0.363
Calreticulin, pg/ml	4.93 (2.65–11)	2.44 (0.94–3.7)	6.4 (3.39–15.24)	3.11 (1.87–4.7)	p < 0.001 p_{1-2} = 0.001 p_{1-3} = 1 p_{1-4} = 0.066 p_{2-3} < 0.001 p_{2-4} = 1 p_{3-4} = 0.009
Phosphatidylserine, pg/ml	74.6 (53.2–112)	61.4 (43.2–117.15)	81.95 (62.2–107.6)	54.4 (43.2–89.2)	p = 0.036 p_{1-2} = 1 p_{1-3} = 1 p_{1-4} = 0.25 p_{2-3} = 0.312 p_{2-4} = 1 p_{3-4} = 0.046

Notes: LMWH — low molecular weight heparin, UFH — unfractionated heparin, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, aPTT — activated partial thromboplastin time, PT — prothrombin time, INR — international normalized ratio

Thus, the conducted study established different dynamics of specific apoptosis markers calreticulin and phosphatidylserine in patients with and without obesity, with the underlying prophylaxis of VTEC using different parenteral anticoagulants.

DISCUSSION

Before COVID-19, obesity directly represented a pandemic which led to a high risk of developing type 2 diabetes mellitus and death from cardiovascular

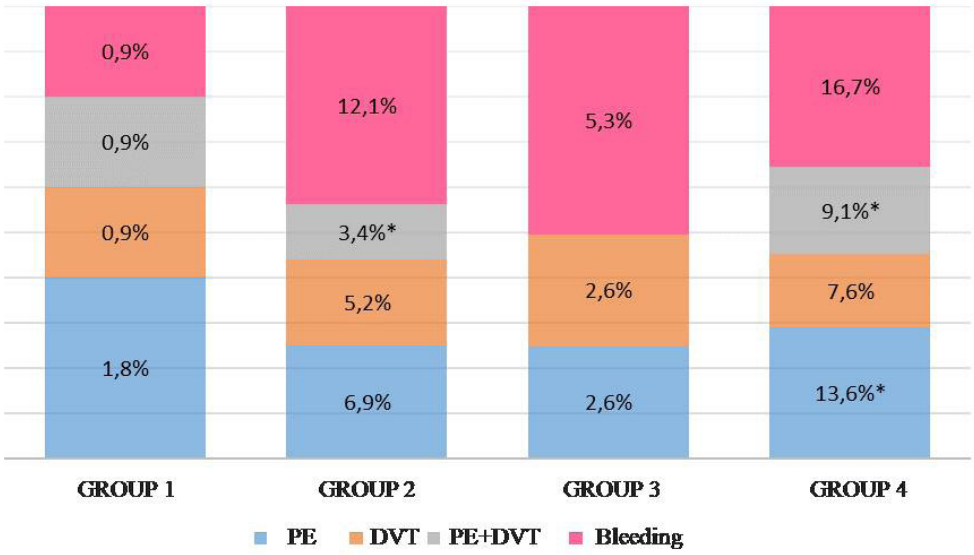

Fig. 2. Incidence of venous thrombotic complications and bleeding in examined patients.
Notes: PE — pulmonary embolism; DVT — deep vein thrombosis; * — $p < 0.05$.

diseases [14]. With the advent of COVID-19, obesity entered the triad of concomitant diseases, along with diabetes mellitus and cardiovascular diseases, which were noted in patients with a severe course of a new coronavirus infection [15]. This is also confirmed by our observation where obesity often came in company with type 2 diabetes mellitus, postinfarction cardiosclerosis, essential hypertension, chronic vein disorders and history of VTEC. Literature data show that in treatment of patients with severe COVID-19, ALV was used 7 times more often in patients with obesity compared to non-obese patients [16]. In our study, mechanical ventilation was more often used in patients with obesity, and in the intergroup comparison in this population, a high frequency of using forced lung ventilation was noted in patients receiving NFH ($p_{3-4} = 0.011$). Thus, the presence of obesity is a particular adverse predictive factor in patients with COVID-19, which is conditioned by a pronounced respiratory failure due to hypoventilation on the one hand, and systemic inflammation, resulting from exposure to virus, on the other.

A feature of COVID-19 is the development of VTEC, which occurs against the background systemic inflammatory process leading to the release of large amounts of cytokines, chemokines, inhibitors and activators of apoptosis [17]. Adipose tissue is a source of proinflammatory cytokines synthesized by adipocytes, which leads to supporting a chronic latent inflammatory process in an organism. Obesity leads to hypertrophy of adipocytes and dysregulation of prothrombotic adipokines (leptin and resistin) and is an independent risk factor for VTEC. E. K. Broni, et al. found association of high plasma resistin levels with a higher risk of VTEC in the human population [18]. P. F. Bodary, et al. in an experimental study on animals found that mice with leptin deficiency are protected from arterial thrombosis [19]. The prothrombotic effect of leptin is mediated by the activation of leptin receptors in platelets and endothelial cells, which promotes the synthesis of thromboxane and activation of fibrinogen receptor aIIbβ3, which leads to increased platelet aggregation [20]. One way or another, the inflammatory process in COVID-19, enhanced by the presence of obesity, leads to up regulation of procoagulant factors, increased platelet activation and apoptosis of blood cells [21].

The study of laboratory parameters of platelet apoptosis and inflammation in obese patients with COVID-19 is a relevant area and can characterize previously known parenteral anticoagulants in new conditions of use. When platelets are activated, the level of phosphatidylserine, which has a powerful procoagulant potential, increases. Studies have shown that phosphatidylserine can be a potential participant in inflammation and coagulation disorders in patients with COVID-19 [22]. Phosphatidylserine can be exposed on the surface of platelets during the coagulation process, contributing to the explosive production of thrombin, which promotes hypercoagulation [23]. Calreticulin

is recognized as a protein with anticoagulant activity, possessing other functions. It is involved in the regulation of cell proliferation, phagocytosis, apoptosis, as well as of adaptive and innate immune responses. It is due to these functions that increased expression of calreticulin is observed in tissues subjected to severe cellular stress, just as in the subcutaneous adipose tissue and liver of obese patients, in which calreticulin is found in high concentrations [24]. In our study, at the beginning of therapy, the presence or absence of obesity did not show a reliable statistical difference in specific apoptosis markers phosphatidylserine and calreticulin in the study groups. However, according to the study by V. Antoniotti, et al., the level of calreticulin was slightly higher in children with obesity than without it [25]. The concentration of inflammatory parameters in the blood plasma at the beginning of therapy was naturally high in all patients in our study, and in particular in obese patients.

At the end of therapy, a decrease in ferritin concentration was observed in patients with and without obesity receiving LMWH. Calreticulin level was higher in patients of groups 1 and 3 receiving LMWH, both with and without obesity, and phosphatidylserine level was higher only in patients with obesity receiving LMWH (group 3). Thus, by the end of therapy with LMWH, obese patients had high level of platelet apoptosis markers than patients taking UFH.

When analyzing thrombotic complications, a low incidence of isolated pulmonary thromboembolism and PE with a source in the lower extremities was observed in obese patients taking LMWH than in those taking UFH. Given the above properties of phosphatidylserine, the low incidence of VTEC at its high concentration in patients of our study who received LMWH is a dissonance. However, it should be noted that LMWHs have properties of endothelial cell protection and binding of inflammatory cytokines, upon this, longer half-life compared to UFH ensures a low potential for inducing bleeding [26]. According to our data, obese patients taking LMWH had a low incidence of bleeding compared to those taking UFH (5.3% of cases versus 16.7%, respectively, $p_{3-4} = 0.056$). The reason for the high frequency of bleeding in patients receiving UFH may lie in the fact that the lack of phosphatidylserine on the surface of activated platelets will inevitably lead to a decrease in thrombin production, which will make it impossible to complete the hemostasis process and will cause hypocoagulation.

CONCLUSION

Thus, the concentration of specific markers of platelet apoptosis in blood is significantly higher in patients with obesity receiving low molecular weight heparin compared to patients receiving unfractionated heparin. Upon that, in patients of this group, a low incidence of thromboembolic complications and bleeding was observed compared to the group of patients taking unfractionated heparin. In light of the recent progress in understanding the basic mechanisms and regulatory factors responsible for obesity-related thrombosis, there is hope that new molecular targets for antithrombotic therapy will appear. Considering the central role of chronic inflammation in increase in the risk of obesity-induced thrombosis, the potential of the effect of low molecular weight heparin on pro-inflammatory pathways is an important area of research.

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ОБ АВТОРАХ

***Агапов Андрей Борисович**, к.м.н.;
ORCID: https://orcid.org/0000-0003-0178-1649;
eLibrary SPIN: 2344-5966; e-mail: agapchik2008@yandex.ru

Калинин Роман Евгеньевич, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-0817-9573;
eLibrary SPIN: 5009-2318; e-mail: kalinin-re@yandex.ru

Мжаванадзе Нина Джансуговна, д.м.н., доцент;
ORCID: https://orcid.org/0000-0001-5437-1112;
eLibrary SPIN: 7757-8854; e-mail: nina_mzhavanadze@mail.ru

Поваров Владислав Олегович, к.м.н.;
ORCID: https://orcid.org/0000-0001-8810-9518;
eLibrary SPIN: 2873-1391; e-mail: ecko65@mail.ru

Никифоров Александр Алексеевич, к.м.н., доцент;
ORCID: https://orcid.org/0000-0003-0866-9705;
eLibrary SPIN: 8366-5282; e-mail: alnik003@yandex.ru

Максаев Денис Алексеевич, к.м.н.;
ORCID: https://orcid.org/0000-0003-3299-8832;
eLibrary SPIN: 9962-2923; e-mail: denma1804@yandex.ru

Чобанян Артем Александрович, к.м.н.;
ORCID: https://orcid.org/0000-0002-8129-5976;
eLibrary SPIN: 4639-9650; e-mail: artaleksandrovich@gmail.com

Сучков Игорь Александрович, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-1292-5452;
eLibrary SPIN: 6473-8662; e-mail: suchkov_med@mail.ru

AUTHORS' INFO

***Andrey B. Agapov**, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-0178-1649;
eLibrary SPIN: 2344-5966; e-mail: agapchik2008@yandex.ru

Roman E. Kalinin, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-0817-9573;
eLibrary SPIN: 5009-2318; e-mail: kalinin-re@yandex.ru

Nina D. Mzhavanadze, MD, Dr. Sci. (Med.), Associate Professor;
ORCID: https://orcid.org/0000-0001-5437-1112;
eLibrary SPIN: 7757-8854; e-mail: nina_mzhavanadze@mail.ru

Vladislav O. Povarov, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0001-8810-9518;
eLibrary SPIN: 2873-1391; e-mail: ecko65@mail.ru

Aleksandr A. Nikiforov, MD, Cand. Sci. (Med.), Associate Professor;
ORCID: https://orcid.org/0000-0003-0866-9705;
eLibrary SPIN: 8366-5282; e-mail: alnik003@yandex.ru

Denis A. Maksayev, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-3299-8832;
eLibrary SPIN: 9962-2923; e-mail: denma1804@yandex.ru

Artyom A. Chobanyan, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0002-8129-5976;
eLibrary SPIN: 4639-9650; e-mail: artaleksandrovich@gmail.com

Igor' A. Suchkov, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-1292-5452;
eLibrary SPIN: 6473-8662; e-mail: suchkov_med@mail.ru

* Автор, ответственный за переписку / Corresponding author