PHTHISIOLOGY

LEVELS OF MARKERS OF COAGULATION AND FIBRINOLYSIS SYSTEMS IN PATIENTS WITH PULMONARY TUBERCULOSIS WITH CONCOMITANT DIABETES MELLITUS AFTER COVID-19

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ABSTRACT

Background. *It is known that COVID-19 can be followed by a shift in the hemostatic system towards hypercoagulation, which is more pronounced in the presence of diabetes mellitus (DM). Tuberculosis process is often accompanied with hypercoagulation syndrome. Of great interest is the study of the state of hemostatic systems in patients with pulmonary tuberculosis (TB) with concomitant DM who have had COVID-19.*
The aim. *To study the relationship between the state of the hemostatic and fibrinolysis systems and moderate and severe COVID-19 in patients with pulmonary tuberculosis and diabetes mellitus.*
Methods. *Thirty two patients with TB and DM were divided into two groups. Group 1 included 16 patients with TB and DM who have previously had COVID-19 (TB-DM-COVID). Group 2 included 16 patients with TB and DM who did not have COVID-19 (TB-DM).*
Results. *It was found that TB-DM-COVID patients were more likely to develop a hypercoagulable shift compared to TB-DM patients. This was evidenced by a more frequent shortening of such indicator as activated partial thromboplastin time (43.7 % and 25.0 % of cases, respectively; $\chi^2 = 7.22$; $p = 0.01$), an increase in fibrinogen levels (43.7 % and 25.0 %, respectively; $\chi^2 = 7.22$; $p = 0.01$) and D-dimer (43.7 % and 18.7 %, respectively; $\chi^2 = 14.74$; $p = 0.0001$). These changes were closely associated with the systemic inflammatory response, as strong and positive correlations were found between fibrinogen and C-reactive protein levels ($r = 0.420$; $p = 0.01$), and erythrocyte sedimentation rate ($r = 0.433$; $p = 0.01$) in TB-DM-COVID patients.*
Conclusion. *In patients with pulmonary tuberculosis and diabetes mellitus after moderate and severe COVID-19, compared to patients who have not had COVID-19, a hypercoagulable shift associated with the development of more pronounced systemic inflammation develops more often.*

Key words: *pulmonary tuberculosis, diabetes mellitus, COVID-19, hemostasis, fibrinolysis, systemic inflammation*

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УРОВЕНЬ МАРКЕРОВ СИСТЕМ СВЁРТЫВАНИЯ И ФИБРИНОЛИЗА У БОЛЬНЫХ ТУБЕРКУЛЁЗОМ ЛЁГКИХ С СОПУТСТВУЮЩИМ САХАРНЫМ ДИАБЕТОМ ПОСЛЕ ПЕРЕНЕСЁННОЙ COVID-19

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РЕЗЮМЕ

Обоснование. *Известно, что при COVID-19 в системе гемостаза наблюдается сдвиг в сторону гиперкоагуляции, который носит более выраженный характер при наличии сахарного диабета (СД). Спутником туберкулёзного процесса часто является гиперкоагуляционный синдром. Большой интерес представляет изучение состояния систем гемостаза у больных туберкулёзом лёгких (ТБ) с сопутствующим СД, перенёсших COVID-19.*

Цель исследования. *Изучить взаимосвязь между состоянием систем гемостаза и фибринолиза и перенесённого COVID-19 средней и тяжёлой степени у больных туберкулёзом лёгких и сахарным диабетом.*

Методы. *32 больных ТБ и СД были разделены на две группы. В первую группу вошли 16 больных ТБ и СД, которые ранее перенесли COVID-19 (ТБ-СД-COVID). Вторая группа включала 16 больных ТБ и СД, которые не перенесли COVID-19 (ТБ-СД).*

Результаты. *Было обнаружено, что у больных ТБ-СД-COVID чаще развивался гиперкоагуляционный сдвиг по сравнению с больными ТБ-СД. Об этом свидетельствовало более частое укорочение такого показателя, как активированное частичное тромбопластиновое время (соответственно 43,7 % и 25,0 % случаев; $\chi^2 = 7,22$; $p = 0,01$), повышение уровня фибриногена (соответственно 43,7 % и 25,0 %; $\chi^2 = 7,22$; $p = 0,01$) и D-димера (соответственно 43,7 % и 18,7 %; $\chi^2 = 14,74$; $p = 0,0001$). Эти изменения были тесно связаны с системным воспалительным ответом, поскольку были обнаружены тесные и позитивные корреляциионные связи между уровнем фибриногена и уровнем С-реактивного белка ($r = 0,420$; $p = 0,01$), а также скоростью оседания эритроцитов ($r = 0,433$; $p = 0,01$) у больных ТБ-СД-COVID.*

Заключение. *У больных ТБ и СД, перенёсших COVID-19 средней и тяжёлой степени, по сравнению с больными, не перенёсшими COVID-19, чаще развивается гиперкоагуляционный сдвиг, связанный с развитием более выраженного системного воспаления*

Ключевые слова: *туберкулёз лёгких, сахарный диабет, COVID-19, гемостаз, фибринолиз, системное воспаление*

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INTRODUCTION

Currently, despite improvements in a number of epidemiological indicators for tuberculosis (TB) both globally and in the Russian Federation, the situation remains alarming. According to the global report of the World Health Organization (WHO), 10.6 million people fell ill with tuberculosis in 2022 [1]. In the Russian Federation, the incidence of tuberculosis in 2022 was 31.11 cases per 100,000 population (45,377 cases) [2]. There are several reasons for the tense situation, including the consequences of the recent coronavirus infection COVID-19 outbreak, which had a significant impact on the implementation of anti-tuberculosis measures [3, 4], as well as the significant spread of diabetes mellitus (DM), which, according to the WHO global report on tuberculosis, is one of the five main factors creating the risk of developing tuberculosis [1, 5, 6]. According to literature data, diabetes mellitus has been diagnosed in more than 15 % of the population (1.5 million people) of tuberculosis patients worldwide [7–9].

Today, the clinical burden of COVID-19 has significantly decreased [10]. Despite this, the infection consequences remain significant worldwide [11]. A certain amount of information has accumulated in the literature indicating the COVID-19 impact on the clinical, radiological and laboratory parameters of the tuberculosis process [12, 13]. It is known that with COVID-19, a hypercoagulable shift in the hemostasis system is observed, which is accompanied by intravascular blood coagulation (IVBC), and these changes are closely related to the systemic inflammatory response [14, 15]. There is also evidence that the tuberculosis development in patients with diabetes is accompanied by a hypercoagulable shift [16]. In these conditions, the study of the state of the coagulation and fibrinolytic systems in TB patients with concomitant diabetes mellitus who have a COVID-19 history is of great interest.

THE AIM OF THE STUDY

To study the relationship between the state of the hemostasis and fibrinolysis systems and the COVID-19 history in patients with pulmonary tuberculosis and concomitant diabetes mellitus.

METHODS

A prospective cohort study was performed. Thirty two patients with pulmonary TB and diabetes mellitus were divided into two groups. The first group included 16 patients with pulmonary TB and concomitant diabetes mellitus, who had a history of COVID-19 infection (TB-DM-COVID). The second group included 16 patients with pulmonary TB and concomitant diabetes mellitus who had not had COVID-19 (TB-DM). The time from recovery from COVID-19 to admission to the tuberculosis hospital in patients included in the study was up to 6 months. All patients had moderate to severe COVID-19 before admission to the clinic.

The study included: patients aged 18 to 60 years with pulmonary tuberculosis and a history of type 1 and type 2 diabetes mellitus, as well as confirmed infection caused by COVID-19, moderate or severe in accordance with the temporary guidelines of the Ministry of Health of the Russian Federation [17], as well as patients aged 18 to 60 years with pulmonary tuberculosis, a history of type 1 and type 2 diabetes mellitus, who have not had COVID-19.

The study excluded patients with HIV infection, chronic diseases in the decompensation stage, malignant neoplasms, alcoholism, drug addiction, and pregnancy.

There were 56.3 % men and 43.7 % women in each group. The patients' age ranged from 18 to 60 years (median 45.5 years). Newly diagnosed and previously treated pulmonary TB occurred in equal proportions in both groups (50.0 % and 50.0 %, respectively). The incidence of patients with different forms of pulmonary tuberculosis in both groups also did not differ statistically significantly. Patients with tuberculomas were more common (37.6 % in each group), while focal pulmonary tuberculosis was less common (25.0 % in each group). The incidence of patients with infiltrative tuberculosis was 18.7 %, and with cirrhotic tuberculosis was also 18.7 % (in each group).

In the TB-CD-COVID group, lung decay and bacterial excretion were observed in 43.8 % of patients, in the TB-CD group – in 31.3 % of patients ($p > 0.05$). Preserved drug sensitivity of Mycobacterium tuberculosis (MBT) to anti-tuberculosis drugs was observed in 56.3 % of cases in the TB-CD-COVID group and in 43.8 % in the TB-CD group. Patients excreting MBT with multiple and extensive drug resistance were observed in both groups in 31.3 % of cases.

Type 1 diabetes was detected in 11 (68.7 %) patients in the TB-DM-COVID group and in 8 (50.0 %) patients in the TB-DM group ($p > 0.05$). Type 2 diabetes was detected in 31.3 % of patients in the TB-DM-COVID group and in 8 (50.0 %) patients in the TB-DM group ($p > 0.05$). Complications of diabetes were diagnosed in the form of retinopathy (in 25.0 % of the TB-DM-COVID patients, in 18.7 % of the TB-DM group; $p > 0.05$), polyneuropathy (in 7 (43.7 %) and 6 (37.5 %) patients, respectively; $p > 0.05$), nephropathy (in 5 (31.5 %) and 4 (25.0 %) patients, respectively; $p > 0.05$), encephalopathy (in 1 (6.2 %) and 1 (6.2 %) patient, respectively; $p > 0.05$). The incidence of comorbidities in the compared groups also did not differ statistically significantly. Hypertension was observed in 4 (25.0 %) patients in the TB-DM-COVID group, and in 5 (31.2 %) patients in the TB-DM group ($p > 0.05$); cardiovascular diseases – in 4 (25.0 %) and 3 (18.7 %) patients, respectively ($p > 0.05$); viral hepatitis – in 2 (12.5 %) and 2 (12.5 %) patients, respectively ($p > 0.05$); obesity – in 2 (12.5 %) and 2 (12.5 %) patients, respectively ($p > 0.05$); chronic obstructive pulmonary disease – in 1 (6.2 %) and 1 (6.2 %) patient, respectively ($p > 0.05$).

As can be seen from the presented data, the compared groups in this study did not differ statistically significantly in terms of demographic indicators, clinical and radiological signs, as well as laboratory characteristics of the course of the tuberculosis process and diabetes.

A detailed examination of patients included in the study was conducted at the clinic of the Central Scientific Institute of Tuberculosis using clinical, radiological and laboratory methods.

To assess the plasma hemostasis system state, changes in the parameters of activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time (PT) and fibrinogen (F) were studied. The anticoagulation system state was assessed by the level of antithrombin III (AT III). The fibrinolytic system activity was judged by the content of D-dimer in the blood plasma. Along with this, some parameters of the clinical blood test were assessed, which indicate changes in the platelet link of the hemostasis system: the platelet count (PLT), the thrombocrit index (TI) and the values of the relative platelet distribution width (PDW). Of the markers of the systemic inflammatory response, the content of acute phase proteins (C-reactive protein (CRP) and F) in the blood serum was determined, and, in addition, the erythrocyte sedimentation rate (ESR) was studied.

Laboratory tests were conducted upon admission of patients to the clinic of the Central Scientific Institute of Tuberculosis before the start of anti-tuberculosis chemotherapy. To determine the reference values of the above laboratory tests, serum and plasma tests were performed in 47 healthy volunteers.

The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki ("Ethical Principles for Conducting Medical Research Involving Human Subjects"). The local Ethics Committee of the Central Scientific Institute of Tuberculosis approved this study (Protocol No. 1 dated January 18, 2021). Voluntary informed consent to participate in the study was obtained from all patients in written form.

The patient database was created using MS Excel (Microsoft Corp., USA) and SPSS Statistics, version 27 (IBM Corp., USA). The Kolmogorov – Smirnov criteria were used to assess the distribution of values. The frequency (in %) with which certain values of qualitative features occurred in the sample was used to describe qualitative data. Quantitative data were described using the median (Me) and percentiles (Q1 and Q3). The hypothesis about the equality of sample means was tested using the Mann – Whitney criterion. The Pearson's χ^2 criterion was used to assess the statistical significance of differences in the frequency of features of the compared samples depending on their size. Differences were considered statistically significant at $p < 0.05$.

THE RESULTS OF THE STUDY

The analysis of the occurrence frequency of various deviations in the parameters of the coagulation and fibrinolysis systems in patients with pulmonary tuberculosis, with concomitant diabetes mellitus, who have had COVID-19, is presented in Table 1.

As can be seen from the data provided, the APTT indicator was shortened in 43.7 % of cases in the TB-DM-COVID-19 group of patients, and in 25.0 % of cases in patients with pulmonary tuberculosis with concomitant diabetes mellitus who had not had COVID-19 ($\chi^2_{1-2} = 7.22$; $p = 0.01$). APTT shortening is one of the indicators of the hypercoagulable shift presence. PT shortening, which also indicated the hypercoagulable shift presence, was observed with the same frequency in the compared groups (25.0 % and 25.0 %, respectively; $p > 0.05$). A decrease in the AT III level, which is one of the indicators of the hypercoagulation presence, was observed only in the group of patients with pulmonary TB with concomitant diabetes mellitus who had COVID-19 (18.7 %). In the group of patients who did not have COVID-19, no such cases were detected. An increase in the F content, which is also one of the markers of the hypercoagulable shift presence, was more often detected in the group of patients with TB-DM-COVID compared to patients with TB-DM (43.7 % and 25.0 %, respectively; $\chi^2 = 7.22$; $p = 0.01$). There were no changes in the TB indicator in both groups of patients. An increase in the D-dimer level, which, on the one hand, is an indicator of the intravascular blood coagulation presence, and on the other hand, a marker of the fibrinolytic system activity, was more often observed in the group of patients with TB-DM-COVID (43.7 %). In the group of patients with TB-DM, such a shift was noted in 18.7 % of cases ($\chi^2 = 14.74$; $p = 0.0001$). There were no statistically significant changes in the PLT, TI, and PDW indicators.

The levels of coagulation and fibrinolysis system parameters in patients with pulmonary TB with concomitant diabetes mellitus who have and have not had COVID-19 infection are presented in Table 2.

As can be seen from the data provided, in the group of patients with pulmonary tuberculosis with concomitant diabetes mellitus who had COVID-19, an APTT indicator shortening was observed compared to healthy volunteers.

The PT was shortened in both groups of patients compared to healthy controls, indicating the hypercoagulation syndrome presence.

The AT III level in all study groups did not statistically differ significantly from that in healthy volunteers.

The F content in the group of patients with pulmonary TB with concomitant diabetes mellitus who had COVID-19 was statistically significantly higher compared to both healthy individuals and the group of patients with TB-DM.

The median value of the TT indicator in all compared groups did not statistically differ significantly from that in healthy individuals.

Compared with healthy volunteers, the D-dimer content was higher in the TB-DM-COVID and TB-DM groups. However, no significant differences were found between the groups.

TABLE 1

FREQUENCY OF CHANGES IN MARKERS OF COAGULATION AND FIBRINOLYSIS SYSTEMS IN PATIENTS WITH PULMONARY TUBERCULOSIS WITH CONCOMITANT DIABETES MELLITUS WHO HAVE AND HAVE NOT HAD COVID-19 (%)

Indicators	TB-DM patients who had COVID-19 infection (n = 16)						TB-DM patients who have not had COVID-19 infection (n = 16)					
	norm		decrease		increase		norm		decrease		increase	
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
		1		2		3		4		5		6
APTT	6	37.5	7	43.75	3	18.75	10	62.5	4	25.0	2	12.5
Prothrombin time	12	75.0	4	25.0	–	–	12	75.0	4	25.0	–	–
Antithrombin III	10	62.5	3	18.75	3	18.75	13	81.25	–	–	3	18.75
Fibrinogen	7	43.75	2	12.5	7	43.75	10	62.5	2	12.5	4	25.0
Thrombin time	16	100.0	–	–	–	–	16	100.0	–	–	–	–
D-dimer	10	62.5	–	–	6	37.5	13	81.25	–	–	3	18.75
Platelets	13	81.25	1	6.25	2	12.5	15	93.75	1	6.25	–	–
Thrombocrit	16	100.0	–	–	–	–	16	100.0	–	–	–	–
Platelet volume distribution width	16	100.0	–	–	–	–	16	100.0	–	–	–	–

TABLE 2

LEVEL OF MARKERS OF COAGULATION AND FIBRINOLYSIS SYSTEMS IN PATIENTS WITH PULMONARY TUBERCULOSIS WITH CONCOMITANT DIABETES MELLITUS WHO HAVE AND HAVE NOT HAD COVID-19, ME (Q1; Q3)

Indicators	Healthy volunteers	TB-DM patients who had COVID-19 infection (n = 16)	TB-DM patients who have not had COVID-19 infection (n = 16)
	1	2	3
APTT	36.5 (34.5; 37.7)	33.5 (31.25; 34.4) $p_{1-2} < 0,05$	36 (32.25; 37.75)
Prothrombin time	14.0 (12.0; 16.0)	11.5 (10.6; 12.0) $p_{1-2} < 0.05$	11.2 (10.8; 11.6) $p_{1-3} < 0.02$
Antithrombin III	100 (91.7; 108.7)	102 (96; 114)	109 (103.7; 114.7)
Fibrinogen	3.10 (2.71; 3.20)	3.82 (3.21; 5.39) $p_{1-2} < 0.05$	2.88 (2.65; 3.2)
Thrombin time	20 (17.2; 22.0)	18 (17; 19)	18 (17; 19)
D-dimer	0.25 (0.19; 0.40)	0.5 (0.19; 1.31) $p_{1-2} < 0,01$	0.43 (0.24; 0.50) $p_{1-3} < 0.05$
Platelets	250.0 (220.0; 290.0)	243 (197.5; 299.7)	220 (192; 282.7)
Thrombocrit	0.19 (0.14; 0.25)	0.20 (0.17; 0.26)	0.17 (0.16; 0.20)
Platelet volume distribution width	14 (11.3; 15.2)	12.2 (11.1; 12.9)	11.3 (9.6; 12.3)

TABLE 3

LEVEL OF C-REACTIVE PROTEIN AND ERYTHROCYTE SEDIMENTATION RATE IN PATIENTS WITH PULMONARY TUBERCULOSIS WITH CONCOMITANT DIABETES MELLITUS, WHO HAVE AND HAVE NOT HAD COVID-19, ME (Q1; Q3)

Indicators	Healthy volunteers	TB-DM patients who had COVID-19 infection (*n* = 16)	TB-DM patients who have not had COVID-19 infection (*n* = 16)
	1	2	3
CRP	1.5 (1.0; 2.0)	12.6 (7.0; 22.5) $p_{1-2} < 0.01$	3 (2.0; 7.0) $p_{2-3} < 0.02$
ESR	15.0 (8.5; 24.5)	38 (30.7; 88.7) $p_{1-2} < 0.01$	7 (2.5; 36.2)

The groups of patients also did not differ from healthy ones in terms of platelet count and thrombocrit. In both groups of patients examined, the PDW indicator was lower compared to healthy ones, but there were no statistically significant differences between the groups.

The differences in the level of markers of the coagulation and fibrinolysis systems in patients with pulmonary tuberculosis with diabetes types 1 and 2 in the group of those who had COVID-19 were statistically insignificant. This was probably due to the absence of statistically significant differences in the incidence of diabetes complications in these groups.

Considering that changes in the hemostasis and fibrinolysis systems are components of the systemic inflammatory response, we studied changes in the level of CRP and ESR.

It was found that an increase in the CRP level in the group of patients with TB-DM-COVID was observed in the overwhelming majority of cases (87.5 %), and in the group of patients with TB-DM – in 31.2 % of cases ($\chi^2 = 64.82$; $p = 0.00001$).

A statistically significant increase in the ESR index was observed more often in the group of TB-DM-COVID patients compared to TB-DM patients (75.0 % and 31.2 %, respectively; $\chi^2_{1-2} = 38.86$; $p = 0.00001$).

Analysis of the study results of the CRP and ESR levels showed that their values were statistically significantly higher in the group of patients with pulmonary TB with concomitant diabetes who had COVID-19 (table 3).

Correlation analysis showed that fibrinogen levels closely and positively correlated with CRP levels (r = 0.420; $p = 0.01$) and ESR (r = 0.433; $p = 0.01$) in patients with pulmonary tuberculosis and concomitant diabetes who had COVID-19.

CONCLUSION

An analysis of the occurrence frequency of various deviations and the median of the coagulation and fibrinolysis systems indicators showed that patients with pulmonary tuberculosis with concomitant diabetes mellitus who had moderate and severe COVID-19 more often develop a hypercoagulable shift compared to patients who have not had COVID-19. This was evidenced by a frequent shortening of the APTT indicator, a decrease in the level of AT III, an increase in the level of fibrinogen and D-dimer. At the same time, the hypercoagulable shift in the group of patients who had COVID-19 was more pronounced, which was documented by statistically significantly high fibrinogen values. These changes were probably associated with damage to the vascular system after COVID-19. The above-described changes in the hemostasis and fibrinolysis system were closely associated with the systemic inflammatory response, which was observed more frequently and was more pronounced in the group of patients with pulmonary tuberculosis and concomitant diabetes mellitus and who had COVID-19. This is confirmed by the statistically significant frequent and more pronounced increase in the level of CRP, fibrinogen and ESR in these patients.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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