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THE COURSE OF COVID-19 INFECTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

The purpose of the study — to study the features of the clinical course of COVID-19 in the presence of diabetes mellitus (DM), as well as possible causes of their mutual aggravation.

Materials and methods. The study included 64 patients with COVID-19, including 32 with diabetes (the main group) and 32 without diabetes (the control group). During the hospitalization, the dynamics of clinical, glycemic, coagulation parameters, markers of systemic inflammation, kidney and liver dysfunction were monitored and compared.

Results. Viral pneumonia was more severe among patients with DM, as indicated by an increase in the proportion of people with extensive (>50%) lung damage (2.2 times, p=0.05), an increased likelihood of death, and a longer duration of oxygen saturation disorders (p=0.0004). When COVID-19 and diabetes are combined, hyperglycemia is stable, with no pronounced variability, C-reactive protein (p=0.028), creatinine (p=0.035) and fibrinogen (p=0.013) increase to a greater extent and manifestations of hypercoagulation persist longer, including slower normalization of antithrombin III (p=0.012), fibrinogen (p=0.037) and D-dimer (p=0.035).

Conclusion. The presence of concomitant diabetes in COVID-19 is associated with a greater severity and prevalence of pneumonia, a persistent decrease in oxygen supply, high hyperglycemia, acceleration of renal dysfunction, systemic inflammatory disorders and hypercoagulation.

Keywords: COVID-19; SARS-CoV-2; hyperglycemia; hypercoagulation; systemic inflammation.

Introduction

Introduction

Epidemiological studies conducted during the COVID-19 pandemic prove the powerful negative impact of comorbid pathology on the severity and outcomes of SARS-CoV-2 virus infection [1-15]. Concomitant diseases that are common among COVID-19 patients and are associated with the maximum number of complications (according to the experience of those regions of the world that were first affected by the pandemic) include cardiovascular diseases, especially arterial hypertension (AH), and diabetes mellitus (DM) [9-15]. Thus, according to the observations of Chinese scientists, the majority of deaths were noted among patients with comorbid pathology, including hypertension (53.8%), DM (42.3%), heart disease (19.2%) and strokes (15.4%) [6]. In Italy, the most severe patients who needed treatment in the intensive care unit often had

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hypertension (49%), other cardiovascular diseases (21%), and diabetes (17%) [7]; the incidence of DM among those who died infected with SARS CoV-2 was 35.5% [8]. In the United States, 10.9% of patients with COVID-19 had diabetes, and 32% of those in need of treatment in the intensive care unit [9]. Obesity, which is often found in DM, makes a certain contribution to the deterioration of the prognosis [7].

The data obtained allow us to speak with confidence about the significant contribution of diabetes to the development of severe forms and deaths in COVID-19. If we take into account that diabetes is often associated with other risk factors for adverse outcomes of this disease, including hypertension and other cardiovascular diseases, obesity and old age, it becomes obvious that such patients require special approaches when determining the prognosis and choosing therapy. For the successful treatment of patients with COVID-19 on the background of diabetes, it is necessary to uncover the mechanisms mediating the more severe course of the combined pathology, without which the correct choice of pathogenetic therapy is impossible. It is also important to identify predictors of adverse outcomes in patients with a combination of COVID-19 and diabetes in order to choose the optimal management strategy for such patients in a timely manner. The presence of obesity in many patients with diabetes contributes to the maintenance of systemic inflammation: excess adipose tissue, on the one hand, additionally stimulates it due to increased production of proinflammatory cytokines, adipokines and chemokines, and, on the other, is associated with vitamin D deficiency, which, among other things, is an immunomodulator and inhibits excessive production of inflammatory mediators (both mechanisms can increase the severity of COVID-19) [11].

Another potential intersection point of pathogenetic pathways in diabetes and COVID-19 is the association with the expression of angiotensin converting enzyme 2 (ACE 2). Specific mechanisms leading to the aggravation of RAAS disorders in combination with COVID-19 and diabetes may be related: 1) with a decrease in the ratio of ACE 2/ACE in the lungs in the late stages of diabetes [18], which in the context of COVID-19 does not exclude a unidirectional negative effect on the angiotensin balance; 2) with the effect of ACE 2 expression on pancreatic β-cells on their function, which suggests the possibility of hyperglycemia and diabetes induction against the background of COVID-19 [3,17]; 3) with the aggravation of endothelial dysfunction with direct exposure of the virus to ACE 2 on the surface of endothelial cells [19]; 4) with the frequent association of diabetes with hypertension and, as a result, with the use of RAAS inhibitors [7]. Liver dysfunction [23,24], coagulation [2], and endothelial dysfunction [19] are considered as other possible aggravating factors for COVID-19 in the presence of diabetes.

Further study of the ways of mutual aggravation of COVID-19 and diabetes can be of great scientific and practical importance for predicting complications and prescribing timely and adequate pathogenetic therapy to this large cohort of patients.

Materials and methods

An open comparative study was conducted on those hospitalized at the temporary hospital for the treatment of coronavirus infection in Pavilions 3 and 4 of Uzexpomarkaz under the leadership of the Central Military Clinical Hospital of the Ministry of Defense.(In accordance with the decision of the meeting of the Special Commission of the Republic of Uzbekistan March 3, 2021), during

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which 64 patients with COVID-19 were observed, of which 32 had concomitant diabetes (the main observation group). The main criteria for inclusion in the study for all patients: 1) a positive laboratory test for SARS-CoV-2 (based on a smear from the nasopharynx and oropharynx); 2) signs of viral pneumonia according to computed tomography (CT) results.

Criteria for inclusion in the main group: 1) type 2 diabetes (DM2), which was diagnosed taking into account the medical history, as well as glycemic indices that exceeded the target values in most patients; or 2) newly diagnosed diabetes (diagnosed based on an increase in blood sugar levels at the time of hospitalization).

The control group (COVID-19 without diabetes) was formed according to the "case–control" principle: after the inclusion of a DM patient in the main group, the control group in turn included a hospitalized patient without DM of the same sex and belonging to the same age group.

As a result, the control and main groups were comparable in gender (31.2% for 10 men), age (56.1±13.8 and 60.4±12.0 years) and body mass index (31.8±5.5 and 33.7±6.9, respectively; $p>0.05$ for all indicators). Hypertension was most often detected among concomitant diseases, and its prevalence was significantly lower in the control group compared to the main group — 10 (31.2%) and 20 (62.5%) patients, respectively, $p=0.012$. In addition, there was a tendency to a higher frequency of Ischemic heart disease (IHD) detection among patients with DM — 3 (9.4%) and 8 (25.0%), $p=0.09$.

In the main follow—up group, there were 19 patients with newly diagnosed DM (59.4%), and 13 patients with previously diagnosed DM 2 (40.6%). In individuals with a history of diabetes, the duration of the disease was 3.7±5.9 years, most were diagnosed with diabetic polyneuropathy before hospitalization (12 out of 13 people); in the subgroup of patients with newly diagnosed diabetes, there were no individuals with manifestations of microangiopathies. The severity of pneumonia and the probability of death in all patients were assessed by the nature and volume (percentage) of damage to lung tissue — according to CT, oxygen saturation (SpO2) — by pulse oximetry. Hematological and biochemical data and C-reactive protein (CRP) were studied using standard methods over time. Aspartate and alanine aminotransferase (AST and ALT) were determined by Reitman–Frenkel, hemostasis parameters (D-dimer, international normalized ratio (INR), antithrombin III activity (AT III), prothrombin time (PTT), activated partial thromboplastin time (APTT)) — by coagulometry using the ACL Elite Pro analyzer (Instrumentation Laboratory, USA). The Statistica 8.0 and MedCalc software packages were used for statistical processing of the results. To compare qualitative data, the criteria of $\chi 2$ and Fisher, and to determine predictors of adverse outcomes, univariate and multifactorial regression analysis were used in a logistic regression model. When describing the samples, the average value ± standard deviation (M±σ) was used. The differences were considered significant at $p<0.05$.

Results and discussion

The main indicators characterizing the severity of COVID-19 and its outcomes in both observation groups are presented in Table 1.

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Table 1 Features of the course of COVID-19 in the presence and absence of diabetes mellitus

Indicator	The control group (n=32)	Main group (n=32)	P
Severity of pneumonia and risk of death, % (M±σ)	4,5±1,6	6,0±3,6	0,043
CT (computed tomography) scan on admission, abs. number/% percentage of lung damage:			
up to 50	26/81,2	19/59,4	0,050
more than 50	6/18,8	13/40,6	-
Respiratory rate upon admission, M±σ	19,0±1,5	21,0±4,1	0,005
Number of days before normalization SpO2, M±σ	4,1±3,8	9,8±6,8	0,0004
Unfavorable outcome, abs. number/ %:			
admission to the ICU (Intensive care unit)	3/9,4	6/18,8	0,24
fatal outcome	3/9,4	6/18,8	0,24
	1/3,1	1/3,1	-

Viral pneumonia was more severe among patients with concomitant diabetes, as indicated by a large proportion of patients with extensive (>50%) involvement of lung tissue in the pathological process according to CT results (2.2 times, p=0.050). Severe pneumonia in DM was associated with more pronounced symptoms of respiratory failure, including an increase in the number of respiratory movements upon admission (respiratory rate, p=0.005), and a persistent decrease in oxygen saturation.

Another area of research was the study of the metabolic status and laboratory characteristics of COVID-19 patients without and with diabetes, as well as their possible relationship with the severity of the disease and adverse outcomes (Table 2).

Table 2 **Indicators of metabolic, biochemical and coagulation status of COVID-19 patients with and without diabetes mellitus (M±σ)**

Indicator	The control group (n=32)	Main group (n=32)	P
Glycemia upon admission, mmol/l	4,8±0,8	9,1±2,9	0,00001
Creatinine, mmol/L:			
upon admission	85,9±25,4	98,4±32,7	0,23
3-5 days	98,6±25,6	113,6±33,4	0,035
upon discharge	96,2±19,1	95,2±27,9	0,56
D-dimer, ng/ml:			
upon admission	824,2±1291,8	986,4±1690,7	0,89
Day 2-	618,0±1020,4	421,6±632,5	0,81
	663,8±1215,3	615,4±987,5	0,92

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day 3-5th day at discharge	59,1±111,2	31,2±106,9	0,22
Fibrinogen, g/l: upon admission , 3-5 days upon dischargee	 5,5±1,6 4,4±0,9 3,9±0,9	 6,0±1,8 5,2±1,2 4,0±1,5	 0,22 0,013 0,73
APTT, c: upon admission , 3-5 days upon discharge	 30,1±6,1 33,7±7,1 37,0±17,4	 34,9±26,8 40,6±24,8 36,9±16,1	 0,91 0,77 0,55
INR: upon admission , 3-5 days upon discharge	 1,1 ±0,1 1,1±0,1 1,1±0,3	 1,1±0,3 1,1±0,4 1,1±0,3	 0,51 0,52 0,92
CRP, mg/l: on admission , day 3-5, day 7-10 on discharge	 41,6±37,3 51,1±61,2 53,5±57,3 7,3±9,9	 91,3±90,0 97,1±87,3 60,1±65,5 10,3±16,7	 0,028 0,015 0,86 0,50

The glycemic level in the main group was expected to exceed similar control values ($p<0.00001$), and hyperglycemia with concomitant diabetes was stable, especially at the beginning of the inpatient treatment phase, despite the intensification of hypoglycemic therapy. The development and aggravation of glycemia in SARS-CoV-2 is facilitated by the specific effect of infection on carbohydrate metabolism in the form of: 1) the use of the virus as a functional APF2 receptor, which is expressed in the liver and pancreas, among other things, turning them into a potential target and thereby increasing hyperglycemia [13, 14]; 2) activation of the transcription factor of proinflammatory cytokine genes — interferon-regulating factor-5 during a cytokine storm and its binding to uridine diphosphate-N-acetylglucosamine formed during glucose metabolism, which stimulates its production by a feedback mechanism [22]; 3) increased glucose formation due to virus damage to deoxyhemoglobin—glycated hemoglobin [11,15]. Another factor significantly influencing the course of SARS-CoV-2 infection was the functional state of the kidneys. At the same time, its characteristic feature in both observation groups was a slight decrease in renal function on the 3rd-5th day of treatment, followed by recovery by the time of discharge. As can be seen from Table 2, these changes are more noticeable against the background of diabetes, which was confirmed by significantly higher creatinine values compared with the control after 3-5 days of therapy. Taking into account the possibility of liver damage due to SARS-CoV-2 infection and insufficient therapy, the level of liver transaminase was monitored over time, which, like creatinine, showed an increase by the 3rd-5th day of hospitalization, followed by a decrease (for ALT, $p=0.017$ (see Table. 2), while the differences between the main and control groups were not statistically significant. One of the recognized common links in the pathogenesis of COVID-19 and diabetes is systemic inflammation, the markers of which play the role of predictors of the severe course of both diseases [18, 25]. According to our data, in both follow-up groups, the average CRP level was significantly increased throughout hospitalization,

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including the moment of discharge from the hospital, which confirms the typicality and significance of inflammatory changes in the pathogenesis of COVID-19 (see Table 2). In addition, a single-factor analysis in the combined cohort of patients identified CRP as statistically significant the endpoint predictor. At the same time, the combined pathology was characterized by greater activity and relatively persistent inflammation. Thus, the level of CRP in the main observation group was statistically significantly higher than in the control group both at admission (p=0.028) and 3-5 days after hospitalization (p=0.015). Initially, Erythrocyte sedimentation rate (ESR) was equally increased in both observation groups (p=0.22), but decreased more slowly in the presence of diabetes, which is why it significantly exceeded the control values (p=0.048) and the upper limit of the norm at discharge. Coagulopathies with hypercoagulation phenomena and a high risk of venous, arterial and microvascular thrombosis are considered to be another central pathogenetic factor in the development of complications in COVID-19 [2].

According to our data, hypercoagulation and high thrombogenic activity are characteristic of the entire cohort of SARS-CoV-2 infected people (see Table 2). In both observation groups, the average levels of D-dimer and fibrinogen significantly exceeded the norm, at least at the beginning of the hospital period, and the achieved APTT lengthening was less than expected. When comparing blood clotting parameters, significant differences between the main and control groups were noted, clearly indicating a greater severity and stability of coagulopathies in patients with concomitant diabetes. Thus, in DM, normalization of AT III (p=0.012), fibrinogen (p=0.037) and D-dimer (p=0.035) did not occur statistically significantly longer, there was a high degree of hyperfibrinogenemia (especially on day 3-5, p=0.013), and PTV decreased in dynamics (p=0.019). and there was no increase in APTT (p=0.23).

The data obtained confirm the role of coagulopathies in the pathogenesis and clinical picture of SARS-CoV-2 infection, their particular severity and duration with concomitant diabetes.

Conclusion:

The conducted research allowed us to draw the following conclusions:

1. The presence of concomitant diabetes mellitus in COVID-19 is associated with a greater severity and prevalence of pneumonia, a persistent decrease in oxygen supply, a high need for modern immunosuppressive, immunoactive and combined antiviral agents, as well as high doses of anticoagulants, which together leads to a significant prolongation of the hospital period.
2. High hyperglycemia in patients with SARS-CoV-2 infection and diabetes mellitus is associated with a decrease in O2 saturation, greater severity of respiratory failure and severe pneumonia.
3. Patients with COVID-19 are characterized by impaired renal and hepatic functions, which can worsen in the first days after hospitalization and the start of active therapy; at the same time, creatinine and AST levels are correlated with the risk of adverse disease outcomes. In diabetes mellitus, these disorders can accelerate, especially in the form of a larger initial increase in creatinine levels.
4. COVID-19 causes severe and persistent systemic inflammatory disorders that decrease but do not disappear by the end of the hospital period. The presence of diabetes mellitus and CVD in people infected with SARS-CoV-2 contributes to an additional increase in the degree and duration

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of manifestations of systemic inflammation. An increase in the level of CRP is a predictor of the severe course of COVID-19.

5. Patients with COVID-19 are characterized by the development of hypercoagulation, which is accompanied by a pronounced and steady increase in the content of D-dimer and fibrinogen in the blood. The severity of coagulopathies and the timing of normalization of the main coagulogram parameters were significantly increased against the background of concomitant diabetes mellitus and CVD. The level of fibrinogen is an independent predictor of adverse outcomes for the general population of SARS-CoV-2 patients and especially in diabetes mellitus.

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