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Prognostic markers for the COVID-19 outcomes and its complications in patients with diabetes mellitus

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Summary

Background. The prognosis of the development of complications of COVID-19 in patients with diabetes mellitus is of great practical interest.

Aim: to reveal prognostic markers for the COVID-19 outcomes and its complications in patients with diabetes mellitus

Material and methods: We analyzed data of 113 patients with type 2 diabetes who applied for hospitalization at the clinic of the Republican Specialized Scientific-and-Practical Centre of Endocrinology from March 2020 to December 2020. All patients were divided into 3 groups: the first group consisted of 31 patients who had a coronavirus infection within 1-3 days after hospitalization; the second group consisted of patients with documented COVID-19 - 52 people; and the third group consisted of 30 people without a history of coronavirus infection with a negative test for neutralizing antibodies to the SARS-CoV-2 virus.

Results: Fasting glycemia and postprandial glycemia were significantly higher in the group of people with acute COVID-19 in relation to persons who had not had a coronavirus infection, as well as in relation to persons who had a history of COVID-19, while significant differences in the level of glycated hemoglobin between groups was not observed, which can be explained by an acute inflammatory process in the 1st group of patients. the acute period of coronavirus infection is characterized by an increase in fasting and postprandial glycemia, the absence of leukocytosis, an increase in the level of ALT, GGT, C-reactive protein, fibrinogen, APTT, D-dimer, von Willebrand factor, ferritin, and interleukin 6. The post-COVID period in patients with type 2 diabetes is characterized by an increase in the level of AST, the perisistance of high levels of GGT, fibrinogen, D-dimer, von Willebrant factor, ferritin, procalcitonin and interleukin 6.

Conclusion: persistence of markers of inflammation after COVID-19 shows the necessity of thorough follow up of diabetes patients after recovery after COVID-19.

Key words: diabetes mellitus, COVID-19, prognosis of outcomes

Background

The prognosis of the development of complications of COVID-19 in patients with diabetes mellitus is of great practical interest. First of all, the role of uncontrolled glycemia in increasing the risk of a severe course of coronavirus infection and adverse outcomes is seen. However, a number of studies that aimed to

evaluate the effectiveness of a number of hypoglycemic drugs in the development of complications of COVID-19 and its adverse outcomes did not show the role of hyperglycemia. On the contrary, in groups of patients with better outcomes and prognosis of viral infection, the average level of glycemia or glycated hemoglobin could be higher than in groups with poor prognosis [1-4].

Accordingly, it is necessary to search for factors and markers that would help predict the course of coronavirus infection, regardless of the level of glycemic control.

The next question that needs to be studied concerns the effect of various classes of hypoglycemic drugs on the outcomes of COVID-19 in DM. The fundamental issue of canceling or continuing therapy with various groups of antidiabetic drugs, depending on the severity of COVID-19, remains unresolved [5].

Since the beginning of the COVID-19 pandemic, recommendations for hypoglycemic therapy have been limited to the abolition of tablet drugs - metformin due to the risk of developing lactic acidosis, iSGLT2 due to the risk of euglycemic ketoacidosis. However, in practice, the use of none of the hypoglycemic drugs was associated with a worsening of the course of COVID-19.

Studies that aimed to analyze the impact of hypoglycemic therapy that preceded COVID-19 on the outcome of a viral infection have been conducted since the beginning of the pandemic [5,6].

According to the outcomes of the Korean studies, there was no significant difference depending on oral hypoglycemic drugs and their combination with insulin (except for hypertension, myocardial infarction, kidney disease, antiviral drugs and antipyretics) [7].

Another group of Korean scientists also found no relationship between drug therapy (insulin, PSM, metformin, DPP4 iSGLT2 or RAAS inhibitors) and disease severity or death in patients with diabetes and COVID-19. The authors used multivariate logistic regression adjusted for age, gender, and comorbidities. At the same time, 235 patients with DM were studied [8].

The first prospective study of coronavirus and diabetes outcomes (CORONADO), which followed 1317 patients with COVID-19 and diabetes mellitus, found no effect of hypoglycemic therapy on outcomes (tracheal intubation and death - primary outcome, death on day 7 - secondary outcome). In an unadjusted analysis, the authors showed a lower incidence of deaths among patients who took metformin before hospitalization (OR 0.59; 95% CI 0.42-0.84), but no significant difference in outcomes was obtained when conducting a multivariate analysis [9].

COVID-19 often leads to hypercoagulability, which significantly worsens the prognosis and increases mortality. Extensive thrombosis of the micro- and macrovascular bed is the basis of heterogeneous manifestations observed in COVID-19. Currently, the search for the main mechanisms of thrombosis is underway [10].

It has been documented that microthrombi form during COVID-19 infections in almost every organ. A manifestation of coagulopathy are sharply elevated levels of D-dimer and fibrin breakdown products. Activation of innate immunity may be the key reason for increased expression of the tissue factor initiating the enzyme of the external coagulation pathway. Complement activation and direct infection of the

endothelium with a virus can be other factors that stimulate thrombus formation. As a result of the coagulopathic response, the corresponding clinical manifestations characteristic of each target organ are observed: ranging from pulmonary embolism, myocardial infarction and cerebral stroke to complications such as renal failure, avascular necrosis, acute limb ischemia, cavernous sinus thrombosis, aortic thrombosis and thrombosis ovarian vein. Inflammation and thrombosis are not mutually exclusive and are often mutually aggravating pathogenetic factors in severe manifestations of COVID-19.

COVID-19 can also cause cardiovascular pathologies such as cardiomyopathy and disruption of the conduction system of the heart. Studies suggest direct damage to the heart muscle in some patients. Generally, infective myocarditis is the most common cardiac complication of COVID-19. High expression of ACE 2 receptors in the lungs and heart may increase the risk of myocardial injury in patients with COVID-19. Tachyarrhythmia is also a common cardiovascular complication in patients with COVID-19 [11].

In early reports of COVID-19 cases, up to 40% of hospitalized patients had cardiovascular or cerebrovascular disease. The largest cohort study to date, conducted in Wuhan, China, in 138 hospitalized patients with 2019 coronavirus-infected pneumonia, notes that acute heart failure, shock, and arrhythmias were present in 7.2%, 8.7%, and 16.7% of patients, respectively [12].

Today, the question remains whether the risk of cardiovascular diseases remains in the future after the resolution of the coronavirus infection. Thus, a 10-year study by Colombian authors notes the therapeutic use of corticosteroids and impaired lipid metabolism for a long time as the main reason for the increased risk of cardiovascular complications. And it is likely that cases of infection resulting from outbreaks of respiratory viruses will have similar adverse outcomes.

Material and methods

We analyzed data of 113 patients with type 2 diabetes who applied for hospitalization at the clinic of the Republican Specialized Scientific-and-Practical Centre of Endocrinology from March 2020 to December 2020. All patients were divided into 3 groups: the first group consisted of 31 patients who had a coronavirus infection within 1-3 days after hospitalization; the second group consisted of patients with documented COVID-19 - 52 people; and the third group consisted of 30 people without a history of coronavirus infection with a negative test for neutralizing antibodies to the SARS-CoV-2 virus. Data analyzed included anamnesis vitae and morbis, anamnesis of COVID-19 infection and its clinical manifestation. Laboratory findings were performed at the central laboratory using standardized analyzers.

Statistical analysis was performed on the personal computer using methods of variation statistics with $p<0.05$ for statistically significant difference between groups.

Study results and discussion

The general characteristics of the studied groups are presented in Table 1.

Table 1.

General characteristics of the studied groups of patients with type 2 diabetes who applied for hospitalization to the RSNPMCCE clinic

Characteristics	Group of patients			P between groups		
	1: acute COVID-19	2: post COVID-19	3: no COVID -19	1 and 2	1 and 3	2 and 3
n	31	52	30			
Men (n, %)	18 (58%)	15 (29%)	15 (50%)			
Age, years, M±m	58.19±1.47	58.31±1.10*	53.97± 1.76	0.948	0.948	0.039
Diabetes duration, years	8.39±1.31	8.58±0.98	6.03±1.23	0.908	0.194	0.109
BMI, kg/m^2	30.76±0.95	30.15±0.87	30.36± 1.08	0.637	0.782	0.880
Systolic blood pressure, mm Hg	129.19±3.01	128.79±2.16	126.67 ±2.46	0.914	0.519	0.519
Diastolic blood pressure, mm Hg	82.58±1.60	82.85±1.38	83.0±1.28	0.899	0.838	0.937

† at $p<0.05$ in relation to the group of patients with post COVID-19
* at $p<0.05$ in relation to the group of patients who did not have COVID-19

In the group of patients in whom COVID-19 was diagnosed within 1-3 days after admission to the RSPPMCE clinic (group 1), 58% were men, among patients of the 2nd group (with a history of COVID-19), there were fewer men - 29%, in the group of people without COVID-19 (group 3), the number of women and men was the same.

The average age of the examined was higher in the 2nd group, there was no significant difference in age between groups 1 and 2.

All three groups did not differ significantly in the duration of DM – the average duration of DM ranged from 6.03±1.23 years in the 3rd group to 8.58±0.98 years in the 2nd group.

There were no statistical differences between the groups regarding body mass index and blood pressure.

Indicators of glycemic control of patients of the examined groups are shown in Table 2.

Table 2.

Glycemic control of the studied groups of patients with type 2 diabetes admitted to the clinic of the RSSPMCE

Index	Group of patients			P between groups		
	1: acute COVID-19	2: post COVID-19	1: acute COVID-19	2: post COVID-19	1: acute COVID-19	2 и 3
n	31	52	30			
Fasting glycemia, mmol/L	12.87±0.77†*	9.81±1.04	8.85±0.65	0.020	0.0002	0.436
Postprandial glycemia, mmol/L	15.12±0.49†*	10.39±0.48	10.57±0.69	<0.0001	<0.0001	0.831
HbA1c, %	9.02±0.34	8.97±0.27	7.97±0.46	0.909	0.071	0.064

† at p<0.05 in relation to the group of patients with post COVID-19
* at p<0.05 in relation to the group of patients who did not have COVID-19

Fasting glycemia and postprandial glycemia were significantly higher in the group of people with acute COVID-19 in relation to persons who had not had a coronavirus infection, as well as in relation to persons who had a history of COVID-19, while significant differences in the level of glycated hemoglobin between groups was not observed, which can be explained by an acute inflammatory process in the 1st group of patients.

Indicators of haemogram, blood biochemistry, coagulogram, inflammatory markers of patients of the examined groups are shown in Table 3.

Table 3.

Haemogram, blood biochemistry, coagulogram, inflammatory markers of the studied groups of patients with type 2 diabetes

Index	Group of patients			P between groups		
	1: acute COVID-19	2: post COVID-19	3: нет COVID-19	1: acute COVID-19	2: post COVID-19	2 и 3
n	31	52	30			
Leucocytes, $*10^9$/L	5.88±0.34†*	7.77±0.33*	6.82±0.24	0.0001	0.028	0.022
ALT, U/L	49.77±8.1	31.96±4.56	27.28±	0.061	0.014	0.419

	7*		3.54			
AST, U/L	43.97±12.62	24.98±2.53*	18.77±1.07	0.144	0.051	0.026
GGT, U/L	80.13±15.56*	72.0±8.58*	45.53±6.03	0.649	0.042	0.014
CRP, U/L	21.69±4.72*	11.43±3.25	5.2±1.76	0.077	0.002	0.096
Fibrinogen, g/L	5.46±0.42†*	3.91±0.17*	2.92±0.16	0.001	<0.001	<0.0001
APTT	25.83±0.88*	24.69±0.65	23.67±0.51	0.301	0.038	0.221
D-dimer	1.36±0.22†*	0.62±0.11*	0.30±0.05	0.003	<0.001	0.009
Willebrand factor	149.65±11.01*	140.31±8.37*	117.57±5.29	0.501	0.011	0.024
PTI	97.35±4.29*	104.83±2.00	109.57±2.24	0.118	0.014	0.118
Ferritin	414.36±67.01*	338.25±59.69*	120.76±10.56	0.399	<0.001	0.0006
Procalcitonin	0.17±0.06	0.10±0.01*	0.07±0.01	0.253	0.106	0.037
IL 6	57.35±11.32†*	29.20±3.26*	3.59±0.48	0.019	<0.001	<0.0001
Vitamin D3	17.24±1.76	18.44±2.26	20.66±2.81	0.676	0.307	0.539

† at p<0.05 in relation to the group of patients with post COVID-19
* at p<0.05 in relation to the group of patients who did not have COVID-19

The group of patients in the acute period of COVID-19 was characterized by a statistically lower level of leukocytes in the blood, compared with patients who did not have a coronavirus infection, although the average level of leukocytes corresponded to normal values.

The ALT level was higher in group 1 compared to the group of people who did not have a coronavirus infection, while the AST level was significantly higher among patients in the post-COVID period. Attention is drawn to the increase in the level of GGT in the acute period of a viral infection (80.13±15.56 U/l), which persists in the post-COVID period (72.0±8.58 U/l) compared with persons who have not undergone COVID-19 (45.53±6.03 U/L, p=0.042 and 0.014, respectively).

Of the inflammatory markers, the CRP index was significantly higher in the group of people with acute coronavirus infection (21.69±4.72 U/l), and remained elevated in the post-COVID period, however, in this group of patients (group 2) there was a significant difference with group 3 was not observed.

Fibrinogen was also significantly higher in the acute period of COVID-19 (5.46±0.42 g/l) and remained elevated in the post-COVID period (3.91±0.17) compared with group 3 patients (2.92±0 .16, p=0.001 and <0.001, respectively).

The level of interleukin 6 was significantly higher in the acute period of COVID-19 (57.35±11.32) and remained elevated in the post-COVID period (29.20±3.26) compared with patients of group 3 (3.59±0, 48, p=0.019 and <0.001, respectively). The same is valid for blood ferritin: in the acute period, the ferritin level was 414.36 ± 67.01, in patients in the post-COVID period, the ferritin level remained high and amounted to 338.25 ± 59.69 compared with people who did not have coronavirus infection (120.76±10.56, p<0.001 and p=0.0006, respectively).

In coagulogram, attention is drawn to the increase in APTT in the acute period of COVID-19 with a simultaneous increase in the level of D-dimer (1.36±0.22, p<0.001), as well as the von Willebrand factor (149.65±11.01, p =0.011) and a decrease in the level of PTI (97.35±4.29, p=0.014) compared to people who did not have coronavirus infection, which indicates the development of coagulopathy, while an increase in the level of D-dimer (0.62±0, 11, p=0.009) and the von Willebrant factor (140.31±8.37, p=0.024) is also preserved in the group of people in the post-COVID period.

It should be noted that in all groups of the examined, the level of vitamin D3 was low, but there was no significant difference between the groups.

Of patients with acute coronavirus infection, 13 (42%) were admitted to hospitals specializing in COVID-19. For comparison, among patients who applied to the clinic in the post-COVID period, 22 patients (42%) received inpatient treatment in COVID-specialized clinics for the period of acute viral infection.

Conclusion

Thus, the acute period of coronavirus infection is characterized by an increase in fasting and postprandial glycemia, the absence of leukocytosis, an increase in the level of ALT, GGT, C-reactive protein, fibrinogen, APTT, D-dimer, von Willebrand factor, ferritin, and interleukin 6. Our data correspond to literature data [7-9].

The post-COVID period in patients with type 2 diabetes is characterized by an increase in the level of AST, the perisistance of high levels of GGT, fibrinogen, D-dimer, von Willebrant factor, ferritin, procalcitonin and interleukin 6.

Persistence of markers of inflammation after COVID-19 shows the necessity of thorough follow up of diabetes patients after recovery after COVID-19.

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