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CLINICAL AND GENETIC FEATURES OF THE COURSE OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AGAINST THE BACKGROUND OF CARDIOVASCULAR DISEASES WHO UNDERWENT COVID -19

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ABSTRACT

During the COVID-19 pandemic, many large studies have confirmed a direct relationship between the severity of an infectious disease and a history of diabetes mellitus. Diabetes, hypertension, and especially cardiovascular disease are important risk factors for the severity and mortality of people infected with COVID-19. The severe course of covid-19 in patients with diabetes mellitus on the background of cardiovascular pathology is associated with the development of endothelial dysfunction, which served to start our own research in this direction and to establish a connection between the course of type 2 diabetes mellitus and the role of the C3872T polymorphism of the CRP gene in this pathological process .

Purpose and objectives of the study

Study of the role of the C3872T polymorphism of the C RP gene in the development of endothelial dysfunction in patients with type 2 diabetes mellitus who underwent covid-19.

Methods and materials

The object of the study was DNA isolated from the venous blood of 105 patients, of which 75 patients with type 2 diabetes with CVD who underwent covid-19, 30 patients with type 2 diabetes without CVD who did not survive covid-19, and 104 healthy donors who made up the control group.

Results and discussion

To study the frequency of C3872T polymorphism of the CRP gene in the development of endothelial dysfunction in patients with type 2 DM, we conducted a genetic study that showed that unfavorable genotypic C3872T variants of the CRP gene were significantly more common among patients with type 2 diabetes with cardiovascular pathology who underwent covid-19. compared to the control sample. When considering the frequency of distribution of genotypes, it was found that in the group of patients **with** type 2 diabetes with CVD who underwent covid-19 **the heterozygous** C /T genotype was determined in 38.6% (n -29) of patients, and in the group of patients with type 2 diabetes without CVD who did not survive covid-19 in 40% (n -12).

Conclusions

Thus, a significant association of unfavorable genotypes for the development of endothelial dysfunction in patients with type 2 diabetes with CVD was found to lead to an increase in severe course and adverse outcomes in patients infected with covid-19.

INTRODUCTION

Epidemiological studies conducted during the COVID-19 pandemic prove a powerful negative impact of comorbid pathology on the severity and outcomes of SARS-CoV-2 viral infection [1–15]. Comorbidities that are common among patients with COVID-19 and are associated with the maximum number of complications (according to the experience of those regions of the world that were the first to be 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 observed among patients with comorbid pathology, including hypertension (53.8%), diabetes (42.3%), heart disease (19.2%) and strokes (15.4%) [6]. A meta-analysis of 8 studies involving almost 50 thousand patients with COVID-19 showed that diabetes mellitus (DM) ranks second among the most common comorbidities after coronary artery disease and arterial hypertension. In Italy, the most critically ill patients requiring treatment in the intensive care unit often had hypertension (49%), other cardiovascular diseases (21%), and diabetes (17%) [7]; The incidence of DM among deceased infected with SARS CoV-2 was 35.5% [8]. In the United States, among patients with COVID-19, diabetes was detected in 10.9% of cases, and among those requiring treatment in the intensive care unit, in 32% of cases [9]. A certain contribution to the deterioration of the prognosis is made by obesity, which is often found in DM [7]. The presence of obesity in many patients with DM contributes to the maintenance of systemic inflammation: an excess of adipose tissue, on the one hand, additionally stimulates it due to increased production of pro-inflammatory cytokines, adipokines , and chemokines , and, on the other hand, is associated with vitamin D deficiency, which is also an immunomodulator and inhibits excessive production of inflammatory mediators (both mechanisms may increase the severity of COVID-19) [11].

The obtained data allow us to speak with confidence about the significant contribution of DM to the development of severe forms and deaths in COVID-19. If we take into account that DM is often associated with other risk factors for adverse outcomes of this disease, including hypertension and other cardiovascular diseases, obesity and advanced age, it becomes obvious that such patients require special approaches in determining the prognosis and choosing therapy. Coagulopathy [2] and endothelial dysfunction [19] are considered as other possible aggravating factors for COVID-19 in the presence of DM .

The severe course of covid-19 in patients with diabetes mellitus against the background of cardiovascular pathologies is associated with the development of endothelial dysfunction , which served to start our own research in this area.

MATERIALS AND METHODS

This study involved 105 patients with type 2 diabetes with CVD who had covid-19 (n - 75) and patients with type 2 diabetes without CVD who did not have covid-19 (n - 30), aged 45 to 65 years, who were on a stationary treatment at the clinics of the Tashkent Medical Academy in 2021-2022. (main observation group). The main criteria for inclusion in the study for all patients: 1) laboratory test for SARS-CoV-2 (nasopharyngeal and oropharyngeal swab); 2) signs of viral pneumonia according to the results of CT and associated cardiovascular diseases.

The control group included conditionally healthy unrelated persons (n - 104) of Uzbek nationality.

Molecular genetic methods included four stages : 1st stage - collection of biological material from a patient; 2nd stage - isolation of lymphocytic DNA; 3rd stage - carrying out a standard polymerase chain reaction (PCR) and 4th stage - electrophoresis and visualization of the obtained results of a standard PCR. With the help of molecular genetic methods , detection of C RP gene polymorphism (C3872T).

The selection of the nucleotide sequence for the detection of polymorphisms of the C RP gene (C3872T) is carried out using a special program " Oligo v.6.31 " (USA). Primers for PCR are synthesized by prior order in a specialized enterprise and are synthesized at LLC NPF " Litekh " (Moscow) research , Australia).

For accounting and processing of research material, all data are entered in Excel format . To analyze the existing deviation in the frequency of variants of the genotypes of the C RP gene (C3872T) in accordance with the Hardy- Weinberg law (RHV), we carried out the analysis of genetic data using the GenePop program

Additionally, to determine endothelial dysfunction in patients, C-reactive protein (CRP) was determined by Reitman -Frenkel, hemostasis indicators (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 analyzer Pro (Instrumentation Laboratory , USA). The statistical processing of the results was carried out using the Statistica 8.0 and MedCalc software packages . When describing the samples, the mean value ± standard deviation (M±σ) was used. Differences were considered significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Table 1 Distribution frequency of alleles and genotypes of C 3872 T polymorphism in the CRP gene in groups of patients and controls

Num	Group	Allele frequency				Frequency distribution of genotypes					
		C		T		C/C		C/T		T/T	
		n	%	n	%	n	%	n	%	n	%
1	Main group (n=105)	137	65.24	73	34.76	48	45.71	41	39.05	16	15.24
2	Patients with type 2 diabetes with cardiovascular pathology who had covid-19 (n=75)	93	62	57	38	32	42.67	29	38.67	14	18.67
3	Patients with type 2 diabetes without cardiovascular pathology who had covid-19 (n=30)	44	73.33	16	26.67	16	53.33	12	40	2	6.67
4	Control group (n=104)	160	76.92	48	23.08	64	61.54	32	30.77	8	7,69

To study the frequency of C3872T polymorphism of the CRP gene in the development of endothelial dysfunction in patients with type 2 DM, we conducted a genetic study that showed that unfavorable genotypic C3872T variants of the CRP gene were significantly more common among patients with type 2 diabetes with cardiovascular pathology who underwent covid-19. compared to the control sample. When considering the frequency of distribution of genotypes, it was found that in the group of patients **with** type 2 diabetes with CVD who underwent covid-19 **the heterozygous** C /T genotype was determined in 38.6% (n -29) of patients, and in the group of patients with type 2 diabetes without CVD who did not survive covid-19 in 40% (n -12). An analysis of the distribution frequency of the C3872T genotypes of the C RP gene showed that the mutant T / T genotype was more common in the group **with** patients with type 2 diabetes and CVD who underwent covid-19 in 18.6% (n -14) of patients compared with the group with type 2 diabetes without CVD who did not survive covid-19 in 6.6% (n -2) of patients.

Table 2 Indicators of the coagulation status of patients with COVID-19 in the presence of diabetes mellitus with CVD (M±σ)

Index	**Control group (n=104)**	**Main group (n=75)**	**Main group (n=30)**	**R**
D- dimer , ng /ml: after				
2 months	663.8±1215.3	615.4±987.5	415.4±787.5	0.92
5 months	59.1±111.2	31.2±106.9	21.2± 96.4	0.22
Fibrinogen, g /l: after				
2 months	4.4±0.9	5.2±1.2	4.2±1.1	0.013
5 months	3.9±0.9	4.0±1.5	3.0±1.2	0.73
CRP, mg/l: after				
2 months	53.5±57.3	60.1±65.5	50.1±55.2	0.86
5 months	7.3±9.9	10.3±16.7	9.3±14.5	0.50
APTT, after				
2 months	33.7±7.1	40.6±24.8	38.6±21.6	0.77
5 months	37.0±17.4	36.9±16.1	31.7±14.1	0.55
INR: after				
2 months	1.1±0.1	1.1±0.4	1.0±0.3	0.52
5 months	1.1±0.3	1.1±0.3	1.0±0.3	0.92

One of the recognized common links in the pathogenesis of COVID-19 and DM is systemic inflammation, markers of which play the role of predictors of the severe course of both diseases [18, 19]. According to our data, in both groups of observation, the average level of CRP was significantly increased for 5 months, 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, in a univariate analysis in a pooled cohort of patients, CRP was identified as a statistically significant predictor of the endpoint. At the same time, the combined pathology was characterized by greater activity and a relatively persistent nature of inflammation. Thus, the level of CRP in the main observation group was statistically

significantly higher than in the control group during and 5 months (p=0.028). Another central pathogenetic factor in the development of complications in COVID-19 is coagulopathy that occurs with hypercoagulation and a high risk of venous, arterial, and microvascular thrombosis [2].

According to our data, hypercoagulability and high thrombogenic activity are characteristic of the entire cohort of those infected with SARS-CoV-2 (see Table 2). In both observation groups, the average levels of D- dimer and fibrinogen significantly exceeded the norm, at least for 5 months, and the APTT prolongation achieved in dynamics was less than expected. In a comparative assessment of blood coagulation parameters, significant differences between the main and control groups drew attention, unambiguously indicating a greater severity and stability of coagulopathy in patients with type 2 diabetes with cardiovascular pathology who had covid-19 . Thus, with DM, there was no statistically significant normalization of AT III (p = 0.012), fibrinogen (p = 0.037) and D- dimer (p = 0.035) for a longer time, a greater degree of hyperfibrinogenemia was noted (especially before 2 months, p = 0.013) and no elongation of APTT was detected (p=0.23).

CONCLUSION

The study made it possible to draw the following conclusions:

1. A significant association of unfavorable genotypes for the development of endothelial dysfunction in patients with type 2 diabetes with CVD was found to lead to an increase in severe course and adverse outcomes in patients infected with covid-19.
2. A pronounced association of the C3872T polymorphism of the C RP gene with the risk of developing cardiovascular complications after post-sleeping covid-19 in the Uzbek population has been established.
3. With COVID-19, severe and persistent systemic inflammatory disorders occur, which decrease, but do not disappear until 5 months after suffering COVID-19. The presence of diabetes mellitus and CVD after SARS-CoV-2 contributes to an additional increase in the degree and duration of manifestations of systemic inflammation. An increase in CRP levels is a predictor of severe COVID-19.
4. Patients with COVID-19 are characterized by the development of hypercoagulability , which is accompanied by a pronounced and steady increase in the content of D- dimer and fibrinogen in the blood. The severity of coagulopathy and the timing of normalization of the main indicators of the coagulogram 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 population of patients with past COVID-19 in general, and especially in diabetes mellitus.

REFERENCES

1. Angelidi A.M., Belanger M.J., Mantzoros C.S. COVID-19 and diabetes mellitus: what we know, how our patients should be treated now, and what should happen next. Metabolism 2020; 107: 154245, https://doi.org/10.1016/j
2. Abou-Ismail M.Y., Diamond A., Kapoor S., Arafah Y., Nayak L. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. Thromb Res 2020; 194: 101–115, https://doi.org/10.1016/j.thromres.2020.06.029.

3. Yang J.K., Lin S.S., Ji X.J., Guo L.M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010; 47(3): 193–199,https://doi.org/10.1007/s00592-009-0109-44.
4. Center for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). U.S. Department of Health & Human Services; 2020. URL: https://www.cdc.gov/ coronavirus/2019-ncov/hcp/clinical-guidance-managementpatients.html.
5. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 — United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 382–386, https://doi.org/10.15585/mmwr.mm6913e2.
6. Deng S.Q., Peng H.J. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J Clin Med 2020; 9(2): 575, https://doi.org/10.3390/jcm9020575.
7. Diaz J.H. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Trav Med 2020; 27(3):taaa041,https://doi.org/10.1093/jtm/taaa041.
8. Fadini G.P., Morieri M.L., Longato E., Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest 2020; 43(6):867–869,https://doi.org/10.1007/s40618-020-01236-2.
9. Guan W.J., Liang W.H., Zhao Y., Liang H.R., Chen Z.S., Li Y.M., Liu X.Q., Chen R.C., Tang C.L., Wang T., Ou C.Q., Li L., Chen P.Y., Sang L., Wang W., Li J.F., Li C.C., Ou L.M., China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55(5): 2000547, https://doi.org/10.1183/13993003.00547-2020.
10. Grasselli G., Zangrillo A., Zanella A., Antonelli M., Cabrini L., Castelli A., Cereda D., Coluccello A., Foti G., Fumagalli R., Iotti G., Latronico N., Lorini L., Merler S., Natalini G., Piatti A., Ranieri M.V., Scandroglio A.M., Storti E., Cecconi M., Pesenti A.; COVID-19 Lombardy ICU Network; Nailescu A., Corona A., Zangrillo A., Protti A., Albertin A., Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020; 323(16): 1574–1581, https://doi.org/10.1001/ jama.2020.5394.
11. Liu W., Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv 2020; https://doi.org/10.26434/chemrxiv.11938173.v7.
12 . Maffetone P.B., Laursen P.B. The perfect storm: coronavirus (COVID-19) pandemic meets overfat pandemic. Front Public Health 2020; 8: 135, https://doi.org/10.3389/ fpubh.2020.00135.
13. 31. Muniyappa R., Gubbi S. The COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab 2020; 318(5): E736–E741, https://doi.org/10.1152/ajpendo.00124.2020.
14. Maddaloni E., Buzzetti R. COVID-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev 2020; e33213321 , https://doi.org/10.1002/dmrr.3321 . [PMC free article] [PubMed]

15. Onder G., Rezza G., Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020; https://doi.org/10.1001/population.2020.4683. [PMC free article] [PubMed]
16. Puig -Domingo M, Marazuela M, Giustina A. COPD and endocrine diseases. A statement from the European Society of Endocrinology. Endocrine 2020 ;68 (1):2–5; [PMC free article] [PubMed]
17. Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ Characterization of ACE and ACE2 expression within different organs of the NOD mouse. Int J Mol Sci2017 ;18 (3):563; [PMC free article] [PubMed]
18. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, Deftereos S, Tousoulis D. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol 2019; 14(1): 50– 59, https://doi.org/10.15420/ecr.2018.33.1. [PMC free article] [PubMed]
19. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395(10234):1417–1418, https://doi.org/10.1016/S0140-6736(20)30937-5.25.Diaz JH