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Original Research

Changes in Indicators of Biochemical Homeostasis in Patients With Moderate SARS-CoV-2

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Abstract

This article demonstrates changes in biochemical homeostasis in patients with moderate SARS-CoV-2 and type 2 diabetes mellitus (T2DM) or hyperglycemia identified for the first time. The results of the study were estimated according to the indicators of a biochemical blood test in the acute phase and the convalescent phase of the SARS-CoV-2. The most significant deviations of homeostasis were observed in patients with T2DM. The development and worsening of hyperglycemia were due to the specific effect of the virus on carbohydrate metabolism mediated via ACE2 receptors located in hepatocytes and pancreatic cells. The development of hyperglycemia in SARS-CoV-2 patients was not associated with the use of drugs with hyperglycemic effects in particular glucocorticoids. The obtained data indicate the blood coagulation system's activation and the severity of this activation depended on the severity of SARS-CoV-2 and somatic complications.

Conclusion: Further examination is recommended to fully comprehend the complex association between SMU, AP, and WB. The study highlights the need for guidance and supervision from parents, teachers, and authority figures to prevent undesirable effects on students' WB and AP. Researchers may suggest models such as emotional intelligence to increase self-awareness, self-management, empathy, and communication. Appropriate policies and models are urgently needed to prevent serious issues related with SMU among students.

Keywords: SARS-CoV-2, ACE2, biochemical homeostasis, type 2 diabetes mellitus, hemostasis, pharmacotherapy.

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Introduction

The International Committee on Taxonomy of Viruses declared SARS-CoV-2 to be the name of a new virus on 11 February 2020 [1]. The disease caused by SARS-CoV-2 is more commonly called COVID-19. The development of severe bilateral pneumonia and acute respiratory distress syndrome are the most visible manifestations of it [2].

Unlike diseases caused by influenza viruses that predominantly affect the respiratory system, SARS-CoV is characterized by a defeat of the whole organism [3]. The severity of SARS-CoV-2 is largely determined by the presence of concomitant diseases, one of which is diabetes mellitus (T2DM). Disorder of carbohydrate metabolism is currently one of the most common pathologies among the global population. According to WHO, the frequency of T2DM amounts to 463 million adults [4].

The lethality of SARS-CoV-2 in patients with disorders of carbohydrate metabolism increases by two to four times [5]. Therefore, the study of the pathophysiological foundations of the aggravation of the course of the disease against the background of metabolic disorders is important.

Purpose

To explore pathophysiological mechanisms of biochemical homeostasis in SARS-CoV-2 patients with decompensation of type 2 diabetes mellitus (T2DM) and hyperglycemia identified for the first time.

Materials and methods

A retrospective analysis of 62 case reports of patients between 40 and 70 years with medium to severe SARS-CoV-2, complicated by community-acquired bilateral polysegmental pneumonia. Patients were separated according to the anamnesis and the results of blood biochemical analysis into three groups: 1st group (n=14): control group (CG), patients without disorders of carbohydrate metabolism; 2nd group (n=18): main group 1 (MG1), with manifested type 2 T2DM; 3rd group (n=30): main group 3 (MG3), with transient hyperglycemia. The study was performed based on the results obtained in the Voronezh State Clinical Hospital no.2 named after K.F. Fedyaevskiy. The results of the study were estimated according to the indicators of a biochemical blood test in the acute phase and the convalescent phase of the SARS-CoV-2.

The levels of glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, urea, and amylase were analyzed. Coagulation parameters such as thrombin time, prothrombin index (PTI), fibrinogen, and hematocrit were also investigated.

Results

It should be noted that all patients from all studied groups had moderate to severe clinical pictures of SARS-CoV-2. All patients were treated according to the clinical guidelines of the Ministry of Health of the Russian Federation.

However, in CG all indicators of blood biochemical analysis were within the normal

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range, however the glucose levels were at the high end of the normal range. Glucose level amounted to 5,05± 0.4 mM/L on average.

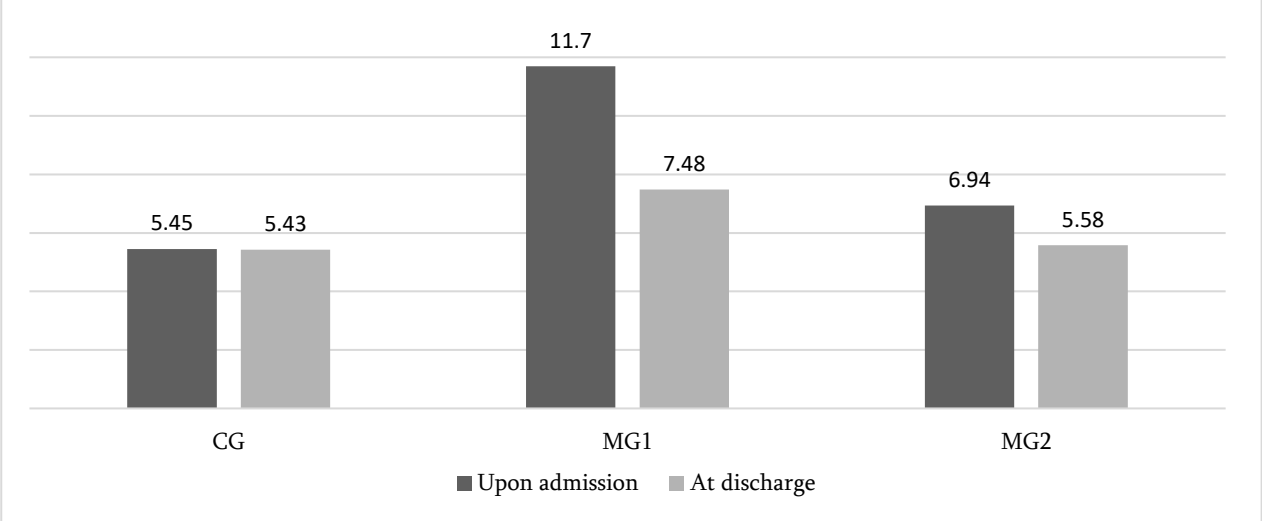

Figure 1. Blood glucose levels in patients with SARS-CoV-2 upon admission and at discharge.

The average level of glucose in MG2 was 6.94 mM/L at the time of admission to the hospital. It did not return to the normal range by the time of discharge from the hospital and amounted to 5.6 mM/L. ALT and AST levels amounted to 67.2 IU/l and 57.4 IU/l respectively. Other indicators were not elevated in MG2.

Table 1. Parameters of biochemical blood test in patients with SARS-CoV-2 and carbohydrate metabolism disorders.

Indicator	Group of patients		
	CG	MG1	MG2
ALT (IU/l)	33.8	71.9	67.2
AST (IU/l)	31.4	62.5	57.5
Creatinine (μM/L)	75.2	85.1	68.4
Urea (mM/L)	5.6	8.24	7.16
Amylase (IU/l)	116.4	140	131.9
Total protein (g/L)	66.4	66.6	66.5
Total bilirubin (μM/L)	11.9	15.4	11.3

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The greatest deviations of homeostasis were observed in patients with T2DM who constantly received antidiabetic drugs. The average level of glucose in MG1 amounted to 11.69 mM/L (but not less than 9 mM/L) at the time of admission to the hospital. Hyperglycemia in MG1 was sustainable. Pharmacotherapy of T2DM was changed in all patients from MG1 – they were transferred to injectable insulin with an increase of dose by 25%. Despite the increased dosage of insulin in MG1, normalization of glucose levels could not be reached. The average level of glucose upon discharge from the hospital amounted to 7.48 mM/L. ALT and AST levels increased by 84% and 90% respectively. The average level of ALT in these patients amounted to 71.9 IU/l, of AST- 62.5 IU/l. Some indicators of biochemical blood tests were within upper normal values: bilirubin 15.,4 μM/L, creatinine 85.4 μM/L, urea 8.24 mM/L. Levels of amylase (140 IU/l) and total protein (66.6 g/L) were normal. The level of urea was 1.5-2 times higher than normal in 50% of patients in MG1.

According to the research of the majority of authors, changes in the hemostatic system are one of the leading pathogenetic mechanisms in COVID-19 disease. However significant changes in coagulation indicators are detected in more severe forms of the disease [6]. A correlation between the severity of carbohydrate metabolism disorders and coagulogram variation was found in our study. The average PTI level was increased in MG1 and amounted to 103.3±2.5. In CG and MG2 PTI level was within upper normal values (100.5). Fibrinogen level was increased in all groups of patients. The greatest deviation of fibrinogen was observed in MG2 (5.5). The average level of fibrinogen was 4.1 and 4.3 in MG1 and CG respectively.

Table 2. Indicators of coagulogram in patients with SARS-CoV-2 and carbohydrate metabolism disorders.

Indicator	Group of patients		
	CG	MG1	MG2
Thrombin time	17.9	17.6	17.8
Fibrinogen	4.3	5.5	4.1
PTI	100.6	103.4	100.4
Hematocrit	46	43.1	41.6

Since reference values of hematocrit are different for men and women, patients were separated by gender to assess changes in hematocrit level. The greatest increase of hematocrit was observed in women from CG (48.3). Hematocrit level was slightly increased in women from MG1 (42.7). This

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parameter was within the upper normal value in women from MG2 and amounted to 40,9. Hematocrit level was within the normal range in men of all groups.

Discussion

It is known that COVID-19 causes multisystem disorders. The main element of pathogenesis is virus penetration into the cells with the involvement of functional receptor angiotensin-converting enzyme 2 (ACE2) [7]. Our study revealed that several internal organs were damaged even in patients with medium (CT2) severity of SARS-CoV-2. Both first identified hyperglycemia and decompensation of manifested T2DM type 2 indicate that pancreatic function was impaired. However, normal amylase level in the blood of patients of all groups suggests that pancreatic failure is of a functional but not a morphological nature. The development and worsening of hyperglycemia were due to the specific effect of the virus on carbohydrate metabolism: ACE2 receptors are located in hepatocytes and pancreatic cells [8]. It means that these organs are targets for SARS-CoV-2. During hyperglycemia, glycosylation of receptors occurs, which significantly increases their affinity for the virus [9, 10]. Penetration of SARS-CoV-2 into pancreatic cells may worsen beta-cell damage, causing insulin resistance [11].

Many researchers associate the development of hyperglycemia in SARS-CoV-2 patients with the use of drugs with hyperglycemic effects in particular glucocorticoids [12]. However, the increase in glucose level in our investigation was detected at the time of hospitalization before the application of glucocorticoids. It should be noted that the increased insulin dose did not manage to normalize the glucose level. Patients with manifested T2DM were discharged with an unachieved target level of glucose because the further increase of the amount of insulin was unadvisable on the background of SARS-CoV-2 pharmacotherapy. Thus, the development of hyperglycemia in patients with moderate COVID-19 is associated with the pathogenetic effects of the disease.

A significant increase in the transaminase levels indicates cytolysis syndrome both in hepatocytes and cardiomyocytes [13]. Meanwhile, liver damage is considered to be concomitant by the majority of researchers [14]. It should be noted that in this sample of patients' failure of hepatic protein synthesis was not observed. It may be explained by the severity of the disease [15]. The systemic inflammatory reaction caused by SARS-CoV-2 is a major cause of liver damage. Another mechanism of liver damage is a cytokine storm [16]. It is known that the level of acute phase proteins increases in patients with COVID-19, and an imbalance in innate and acquired immunity occurs. This imbalance is expressed as excessive activation of cytokine synthesis by macrophages and neutrophils [17].

Hypoxia associated with viral pneumonia leads to the development of ischemic liver injury [18]. Oxygen reduction causes the accumulation of lipids, which can cause necrosis of hepatocytes. Moreover, after the mitochondrial damage cells accumulate reactive oxygen species that enhance the

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production of pro-inflammatory cytokines [19].

Hyperglycemia is stimulated by the feedback mechanism by the activation of the gene transcription factor of the interferon regulatory factor-5 during the period of the cytokine storm and its binding with Uridine diphosphate N-acetylglucosamine which is formed during the metabolism of glucose [20].

Moderate COVID-19 in patients without concomitant somatic diseases does not cause renal functional disorders. We can assume that moderate COVID-19 in patients with type 2 T2DM leads to initial renal dysfunction [21]. It is confirmed by the fact that there was a significant increase in urea levels in 50% of patients from MG1.

The obtained data on the blood coagulation system's activation correspond to the literature [22, 23, 24]. The degree of severity of this activation depends on the severity of COVID-19 and somatic complications [25].

Conclusions

The results of the study demonstrated changes in biochemical homeostasis in patients with moderate SARS-CoV-2 and type 2 diabetes mellitus (T2DM) or hyperglycemia identified for the first time. Careful study of concomitant diseases in patients is required for better identifying etiopathogenetic factors of the clinical picture of SARS-CoV-2. However, there is no doubt that pathologic premorbid changes in cell membranes are morphological preconditions for a more severe course of SARS-CoV-2 in patients with manifested T2DM of any type. The development and worsening of hyperglycemia were due to the specific effect of the virus on carbohydrate metabolism: ACE2 receptors are located in hepatocytes and pancreatic cells. The development of hyperglycemia in SARS-CoV-2 patients was not associated with the use of drugs with hyperglycemic effects in particular glucocorticoids. The obtained data indicate the blood coagulation system's activation and the severity of this activation depended on the severity of COVID-19 and somatic complications.

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ბიოქიმიური ჰომეოსტაზის მაჩვენებლების ცვლილება საშუალო სიმძიმის SARS-COV-2-ით დაავადებულ პაციენტებში

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აბსტრაქტი

სტატიაში მოცემულია მეორე ტიპის შაქრიანი დიაბეტის ან პირველად გამოვლენილი ჰეპერგლიკემიის ფონზე, თანდართული SARS-COV-2-ის საშუალო სიმძიმით მიმდინარე პაციენტებში, ბიოქიმიური ჰომეოსტაზის მაჩვენებლების ცვლილება. კვლევის შედეგები მოიცავს პაციენტების სისხლის ბიოქიმიური მაჩვენებლების გამოვლენას SARS-COV-2-ის, როგორც მწვავე ისე გამოჯანმრთელების ფაზებში. ბიოქიმიური ჰომეოსტაზის მეტად მნიშვნელოვანი გადახრები აღინიშნა მეორე ტიპის შაქრიანი დიაბეტის შემთხვევაში, რაც კავშირშია ჰეპატოციტებსა და კუჭქვეშა ჯირკვლის უჯრედებში არსებულ ACE2-რეცეპტორებზე. SARS-CoV-2-ით დაავადებულ პაციენტებში ჰიპერგლიკემია არ იყო გამოწვეული პრეპარატებით, მაგალითად, გლუკოკორტიკოიდებით.

მოცემული შედეგები ადასტურებს სისხლის შემდედებელი სისტემის აქტივაციას, რაზეც არის დამოკიდებული SARS-CoV-2-ის მძიმე მიმდინარეობა და მისგან გამოწვეული სომატური გართულებები.

საკვანძო სიტყვები: SARS-CoV-2, ACE2, ბიოქიმიური ჰომეოსტაზი, შაქრიანი დიაბეტის მე-2 ტიპი, ჰემოსტაზი, ფარმაკოთერაპია.

References

1. Bilichenko TN. 2020. Epidemiology of Coronavirus Disease 2019 (COVID-19). Academy of Medicine and Sports 1(2): 14-20. doi:10.15829/2712-7567-2020-2-15

2. Starshinova AA., Kushnareva EA., Malkova AM., Dovgalyuk IF., Kudlay DA. 2020. New Coronaviral Infection: Features of Clinical Course, Capabilities of Diagnostics, Treatment and Prevention in Adults and Children. Current Pediatrics.; 19 (2): 123–131. doi: 10.15690/vsp.v19i2.2105

3. Osman M, Klopfenstein T, Belfeki N, Gendrin V, Zayet S. 2021. A Comparative Systematic Review of COVID-19 and

Influenza. Viruses. Mar 10;13(3): 452. doi: 10.3390/v13030452.

4. Najafipour H, Farjami M, Sanjari M, Amirzadeh R, Shadkam Farokhi M, Mirzazadeh A. 2021. Prevalence and Incidence Rate of Diabetes, Pre-diabetes, Uncontrolled Diabetes, and Their Predictors in the Adult Population in Southeastern Iran: Findings From KERCADR Study. Front Public Health. 1(9) :611652. doi: 10.3389/fpubh.2021.611652.

5. Shestakova M.V., Mokrysheva N.G., Dedov I.I. 2020. Course and Treatment of Diabetes Mellitus in the Context of COVID-19. Diabetes mellitus. 23(2): 132-139. doi.org/10.14341/DM12418

6. Luo HC, You CY, Lu SW, Fu YQ. 2021. Characteristics of Coagulation Alteration in Patients With COVID-19. Ann Hematol. 100(1): 45-52. doi: 10.1007/s00277-020-04305-x.

7. Nersisyan SA., Shkurnikov MY., Osipyants AI., Vechorko VI. 2020. Role of ACE2/TMPRSS2 Genes Regulation by Intestinal Microrna Isoforms in the COVID-19 Pathogenesis. Bulletin of RSMU 2: 17-20. doi: 10.24075/brsmu.2020.024

8. Shirbhate E, Pandey J, Patel VK, Kamal M, Jawaid T, Gorain B, Kesharwani P, Rajak H. 2021. Understanding the Role of ACE-2 Receptor in Pathogenesis of COVID-19 Disease: a Potential Approach for Therapeutic Intervention. Pharmacol Rep. 73(6): 1539-1550. doi: 10.1007/s43440-021-00303-6.

9. Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiong M, Deng A, Zhang Y., Zheng L, Huang K. 202. Clinical Characteristics and Outcomes of Patients with Diabetes and COVID-19 in Association with Glucose--Lowering Medication. Diabetes Care 43(7): 1399–1407, https://doi.org/10.2337/dc20–0660.

10. Fang L, Karakiulakis G, Roth M. 2020. Are Patients with Hypertension and Diabetes Mellitus at Increased Risk for COVID-19 Infection? Lancet Respir Med 8(4): e21. https://doi.org/10.1016/S2213–2600(20)30116–8

11. Carlsson PO, Berne C, Jansson L. 1998. Angiotensin II and the Endocrine Pancreas: Effects on Islet Blood Flow and Insulin Secretion In Rats. Diabetologia. 41(2):127-133.

12. Alimov AV, Khaydarova FA, Alieva AV, Alimova NU, Sadikova AS, Talenova AS, Tojieva IM. 2017. Hyperglycemia on the Background of Treatment Of COVID-19-Associated Pneumonia Using Glucocorticoids. Juvenis scientia. 27 (2):5-11. https://doi.org/10.32415/jscientia_2021_7_2_5-11

13. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. 2020. COVID-19: Abnormal Liver Function Tests. J Hepatol. 73(3): 566-574. doi: 10.1016/j.jhep.2020.04.006.

14. Fierro NA. 2020. COVID-19 and the Liver: What Do We Know After Six Months of the Pandemic? Ann Hepatol. 19(6): 590-591. doi: 10.1016/j.aohep.2020.09.001.

15. Wong YJ, Tan M, Zheng Q, Li JW, Kumar R, Fock KM, Teo EK, Ang TL. 2020. A Systematic Review and Meta-Analysis of the COVID-19 Associated Liver Injury. Ann

Hepatol. 19(6): 627-634. doi: 10.1016/j.aohep.2020.08.064.

16. Zhang C, Shi L, Wang FS. 2020. Liver Injury in COVID-19: Management and Challenges. Lancet Gastroenterol Hepatol. 5(5): 428-430. doi: 10.1016/S2468-1253(20)30057-1.

17. Pinchuk TV, Orlova NV, Suranova TG, Bonkalo TI. 2020. Mechanisms of liver damage in COVID-19. Medical alphabet. 1(19): 39-46. doi: 10.33667/2078-5631-2020-19-39-46

18. Bertolini A, van de Peppel IP, Bodewes FAJA, Moshage H, Fantin A, Farinati F, Fiorotto R, Jonker JW, Strazzabosco M, Verkade HJ, Peserico G. 2020. Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis. Hepatology. 72(5): 1864-1872. doi: 10.1002/hep.31480.

19. Zhang XJ, Cheng X, Yan ZZ, Fang J, Wang X, Wang W, Liu ZY, Shen LJ, Zhang P, Wang PX, Liao R, Ji YX, Wang JY, Tian S, Zhu XY, Zhang Y, Tian RF, Wang L, Ma XL, Huang Z, She ZG, Li H. 2018. An ALOX12–12- HETE-GPR 31 Signaling Axis is a Key Mediator of Hepatic Ischemia-Reperfusion Injury. Nat Med. 24: 73–83. doi:10.1038/nm.4451.

20. Wang D., Hu B., Hu C., Zhu F., Liu X., Zhang J., Wang B., Xiang H., Cheng Z., Xiong Y., Zhao Y., Li Y., Wang X., Peng Z. 2020. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 323(11): 1061–1069. doi: 10.1001/jama.2020.1585.

21. Abdulaziz Al-Muhanna F, Ibraham Ali Albakr W, Subbarayalu AV, Cyrus C, Ahmed Aljenaidi H, Ali Alayoobi L, Al-Muhanna O. 2022. Impact of COVID-19 on Kidney of Diabetic Patients. Medicina (Kaunas). 58(5): 644. doi: 10.3390/medicina58050644.

22. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. 2020. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 382(18): 1708–20.

23. Godier A, Clausse D, Meslin S, Bazine M, Lang E, Huche F, Cholley B, Hamada SR. 2021. Major Bleeding Complications in Critically Ill Patients with COVID-19 Pneumonia. J Thromb Thrombolysis. 9: 1–4.

24. Di Minno MND, Calcaterra I, Lupoli R, Storino A, Spedicato GA, Maniscalco M, Di Minno A, Ambrosino P. 2020. Hemostatic Changes in Patients with COVID-19: a Meta-Analysis with Meta-Regressions. J Clin Med. 9(7): 2244.

25. Teimury, A., Khameneh, M.T. & Khaledi, E.M. 2022. Major Coagulation Disorders and Parameters In COVID-19 Patients. Eur J Med Res 27: 25. doi: 10.1186/s40001-022-00655-6.