THE IMPACT OF DIABETES MELLITUS ON THE SEVERITY OF CORONAVIRUS INFECTION: ANALYSIS OF INFLAMMATION MARKERS IN COVID-19 PATIENTS

Abstract. It has been established that the most severe course of COVID-19 is observed in individuals with chronic diseases, including those with diabetes mellitus. There are reports in the literature of cases of hyperglycemia first registered against the background of coronavirus infection. Aims. To determine the frequency of previously diagnosed and newly diagnosed diabetes mellitus in patients infected with COVID-19. To assess the relationship between the level of glycated hemoglobin (HbA1c) and markers of inflammatory process and the severity of infectious disease. Methods. Data collection included medical history, laboratory and instrumental studies. Depending on the presence of diabetes mellitus in the medical history, patients were divided into 2 groups: without previously diagnosed diabetes; with diabetes mellitus in the medical history (group D). Patients without diabetes in the medical history were subdivided into subgroups according to the level of HbA1c: with HbA1c ≤6.0% (group A), HbA1c >6.0% and <6.5% (group B), with HbA1c ≥6.5% (group C). In addition, all patients were assessed for inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6)). Results. Associations between the level of glycated hemoglobin (HbA1c) and markers of inflammatory process were studied.
Individuals without diabetes were divided into subgroups according to the level of HbA1c. Inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6)) were also evaluated. Regardless of the presence of confirmed diabetes mellitus, a significant positive correlation was noted between the level of HbA1c and inflammatory markers ESR, CRP, IL-6. **Conclusion.** An analysis of carbohydrate metabolism indicators in 40 individuals who contracted a new coronavirus infection revealed that diabetes mellitus was present in 75% of cases. In 10% of patients, carbohydrate metabolism indicators were normal. In the remaining 10% and 5% who did not have diabetes mellitus in the medical history, the interpretation of carbohydrate metabolism was complicated due to discrepancies between glycemia and HbA1c. A significant positive correlation was noted between the level of HbA1c and inflammatory markers (ESR, CRP, IL-6).

**Keywords:** SARS-CoV-2; diabetes mellitus, hyperglycemia, glycated hemoglobin HbA1c.
were infected with COVID-19. To estimate the correlation between the level of glycated hemoglobin (HbA1c) and markers of the inflammatory process and the severity of the infection.

**Methods.** Zdizniyvali sbir dannykh anamnesu, laboratorno-instrumentalnymi doslidzhennymy. Zalezhno vid naivnosti of CД in anamnesi patients were divided into 2 groups: without previously established CД; with CД in the anamnesis (group D). Patients without CД in the anamnesis were divided into subgroups: with HbA1c ≤6,0% (group A), HbA1c>6,0% i <6,5% (group B), with HbA1c ≥6,5% (group C). In addition, all patients were evaluated for markers of inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6)).

**Results.** Studying the correlations between the level of glycated hemoglobin (HbA1c) and markers of the inflammatory process. Individuals without diabetes were divided into subgroups according to the level of HbA1c. Also evaluated the markers of inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein, interleukin-6 (IL-6)). Independently of the presence of confirmed CД, there was a significant positive correlation between the level of HbA1c and markers of inflammation (ESR, CRP, IL-6).

**Conclusion.** Under the study of 40 individuals infected with the new coronavirus infection, it was established that CД in the anamnesis was found in 75% of cases. In 10% of cases, the markers of carbohydrate metabolism were normal. In 10%, and 5% of cases that had no CД in the anamnesis, the interpretation of the state of carbohydrate metabolism was complicated due to the similarity of the data of glycemia and HbA1c. There was a significant positive correlation between the level of HbA1c and markers of inflammation (ESR, CRP, IL-6).

**Keywords:** SARS-CoV-2, diabetes, hyperglycemia, glycated hemoglobin HbA1c.

**Problem formulation.** The pandemic of the novel coronavirus infection, which began in December 2019 and rapidly spread worldwide, causing the most severe global health crisis in history [1]. According to the European Centre for Disease Prevention and Control, by early October 2020, there were over 32 million cases worldwide and approximately 1 million fatalities [2].

The emergence of three new pathogenic species of coronavirus in the 21st century raises serious questions. These RNA viruses include β-coronaviruses of the Coronaviridae family, among which particular attention has been drawn to the causative agent of Middle East Respiratory Syndrome (MERS) - MERS-CoV, and the source of Severe Acute Respiratory Syndrome (SARS) - SARS-CoV [3-6].

The primary target of the virus is the alveolar type 2 (AT2) cells of the lungs, which is why the most common clinical manifestation of the new variant of coronavirus infection is bilateral pneumonia. Acute respiratory distress syndrome (ARDS) develops in 3-4% of patients. The leading theory explaining the characteristics of the disease's clinical presentation is the high affinity of the coronavirus S glycoproteins to angiotensin-converting enzyme 2 (ACE2) type 2 receptors [7]. It has been established that the most severe course of COVID-19 is observed in individuals with chronic diseases, including those with diabetes mellitus (DM).
Analysis of recent research and publications. Diabetes mellitus ranks among the leading comorbidities. In one study of 41 hospitalized patients in Wuhan, China, 20% had DM [8], and in another study of 191 patients, DM was present in 19% [9]. Among 122,653 laboratory-confirmed diagnoses of coronavirus infection in the United States, 10.9% were accompanied by DM [10]. In diabetes mellitus, not only does the expression of the ACE2 receptor increase (in many tissues), but also its binding to the virus, which may explain the more severe course of coronavirus infection [11]. Meanwhile, there are data in the literature showing cases of hyperglycemia, first registered in the context of coronavirus infection[12, 13]. Such cases may correspond to the following situations: newly diagnosed diabetes mellitus (previously undiagnosed), where plasma glucose levels meet the criteria for diabetes and remain so after discharge from the hospital; first-time COVID-induced diabetes, the nature of which is not yet understood[12, 13]; stress-induced hyperglycemia (SIH), which may normalize after resolving the acute situation [14, 15]. Additional determination of HbA1c in this case allows differentiation between SIH and previously undiagnosed diabetes [14-16].

Aim. To determine the frequency of previously diagnosed and newly diagnosed diabetes mellitus (DM) in patients who have been infected with COVID-19. To evaluate the relationship between the level of glycated hemoglobin (HbA1c) and markers of inflammatory processes and the severity of infectious disease.

Presentation of the main material. The study included patients who were infected with COVID-19. Depending on the presence of diabetes mellitus (DM) in the medical history, patients were divided into 2 groups: without previously diagnosed DM; with DM in the medical history (Group D). Patients without DM in the medical history were further subdivided based on HbA1c levels into subgroups: HbA1c ≤6.0% (Group A), HbA1c >6.0% and <6.5% (Group B), HbA1c ≥6.5% (Group C). Additionally, markers of inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6)) were evaluated in all patients.

All results were analyzed based on serum blood test results. HbA1c was determined using high-performance liquid chromatography. HbA1c values were interpreted as follows: ≤6.0% considered normal, >6.0% but <6.5% considered as high risk for diabetes mellitus (DM), ≥6.5% considered as DM [17].

Biochemical blood analysis was conducted using an automated biochemical analyzer with standard methods and manufacturer's reagents. Reference intervals for biochemical blood parameters were as follows: glucose: 3.1-6.1 mmol/L, ALT - 0.0-55.0 U/L, AST - 5.0-34.0 U/L, creatinine - 50-98 μmol/L, potassium - 3.5-5.1 mmol/L, sodium - 136-145 mmol/L, lactate dehydrogenase - 125-220 U/L, albumin - 34-48 g/L [18].

The estimated average glucose (eAG) was calculated based on the HbA1c level using the formula: eAG (mmol/L) = 1.5944 × HbA1c (%) – 2.594.

Stress-induced hyperglycemia (SIH) is the value by which the estimated glucose exceeds the average daily glycemia calculated based on the HbA1c level. SIH was calculated using the formula: eAG - eAG(FPG). A SIH level >4.0 mmol/L is considered unfavorable [19].
Markers of inflammation: erythrocyte sedimentation rate (ESR) was determined using a hematological automated analyzer. Reference range: 0-10 mm/hr. C-reactive protein (CRP), ferritin, IL-6 were measured using an automated immunoassay analyzer. Reference ranges: CRP - 0.1-5 mg/L, IL-6 - 10 pg/mL, ferritin - 30-300 ng/mL.

The study group consisted of samples from 40 patients. The corresponding group was divided into two groups:

1. Group of patients with a history of diabetes (DM):
   Analysis of 30 individuals: 29 with type 2 diabetes mellitus (T2DM) and 1 with type 1 diabetes mellitus (T1DM). The duration of DM ranged from 5 to 23 years.

2. Group of patients without a history of diabetes (non-DM):
   This group was further divided into 3 subgroups based on HbA1c levels:
   - Group A: HbA1c ≤6.0% (n=4).
   - Group B: HbA1c >6.0% but <6.5% (n=4).
   - Group C: HbA1c ≥6.5% (n=2) (table 1).

Table 1.

| Characteristics of carbohydrate metabolism indicators in patients with COVID-19 |
|----------------------------------|---------------------|---------------------|
| group of analyses of individuals without a history of diabetes mellitus (DM) | Group A | Group B | Group C |
| 10(25%)                          | 1 | 2 | 3 |
| HbA1c ≤6,0%                     | n=4 (10%) | HbA1c >6,0 та <6,5% | HbA1c ≥6,5% |
| FPG <7,0 mmol/L                 | RGP <11,1 mmol/L | FPG <7,0 mmol/L | FPG ≥7,0 mmol/L |
| n=4(10%)                        | n=3 (7,5%) | n=1 (7,5%) | n=1 (2,5%) |
| FPG ≥7,0 mmol/L                 | RGP ≥11,1 mmol/L | FPG ≥7,0 mmol/L | RGP ≥11,1 mmol/L |
| n=1 (2,5%)                      | n=1 (2,5%) | n=1 (2,5%) |

Group of analyses of individuals with a history of diabetes mellitus 30(75%)
(group D): -.

The results of the study of individuals without a history of diabetes mellitus. Group A with HbA1c level ≤6.0% (n=4). In all patients of this group, the FPG and RGP indices did not exceed the values corresponding to the diagnostic criteria for diabetes mellitus (Table 1). Thus, in 10% of all hospitalized patients with carbohydrate metabolism disorders, diabetes mellitus was not detected. The median HbA1c was 5.8% (Table 2).
Group B with borderline HbA1c levels >6.0% and <6.5% (n=4). In all patients of this group, except for one individual, the FPG and RGP indices did not exceed values corresponding to the diagnostic criteria for diabetes mellitus. However, considering the borderline level of HbA1c, which may indicate a high risk of diabetes mellitus, we could not definitively classify the carbohydrate metabolism status in these patients. The median HbA1c was 6.3% (Table 2).

Group C with HbA1c ≥6.5% (n=2). In one patient of this group, simultaneous elevation of either FPG ≥7.0 mmol/L or RGP ≥11 mmol/L was observed, which combined with the "diabetic" level of HbA1c allowed for the diagnosis of "newly detected" type 2 diabetes mellitus. In the second patient of this group, despite the "diabetic" level of HbA1c, the FPG and RGP indices did not exceed values corresponding to the diagnostic criteria for diabetes mellitus, which did not allow for a definitive classification of the carbohydrate metabolism status. The median HbA1c was 6.7% (Table 2).

Patients in group C (HbA1c ≥6.5% and without a history of diabetes mellitus) comprised the most severe cohort among all examined individuals.

Compared to patients in group A (without diabetes mellitus with HbA1c ≤6.0%), patients in group C had significantly lower levels of hemoglobin in the complete blood count (141 g/L and 132 g/L), higher levels of CRP (54.5 mg/L and 92.5 mg/L), ESR (32 mm/hour and 47.5 mm/hour), IL-6 (10.2 pg/mL and 44.9 pg/mL).

### Table 2.

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Group of analyses of individuals without a history of diabetes mellitus</th>
<th>Group of analyses of individuals with a history of diabetes mellitus</th>
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<tbody>
<tr>
<td></td>
<td>HbA1c ≤6,0% (n=4 (10%)) Group A</td>
<td>HbA1c &gt;6,0 and &lt;6,5% (n=4(10%)) Group B</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5,8</td>
<td>6,3</td>
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<tr>
<td>Hemoglobin, g/L</td>
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<td>130</td>
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<tr>
<td>FPG, mmol/L</td>
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<td>RGP, mmol/L</td>
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<tr>
<td>SIH, mmol/L</td>
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<td></td>
<td></td>
<td>HbA1c ≥6,5% (n=2 (5%)) Group C</td>
</tr>
<tr>
<td>HbA1c, %</td>
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<td>8,3</td>
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<tr>
<td>Hemoglobin, g/L</td>
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<tr>
<td>FPG, mmol/L</td>
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<td>RGP, mmol/L</td>
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<td>MDPG, mmol/L</td>
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<tr>
<td>SIH, mmol/L</td>
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<td>0,36</td>
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</tbody>
</table>

Compared to patients in group A (HbA1c ≤6.0%), patients in group D (with a history of diabetes mellitus) had lower levels of hemoglobin and higher levels of
ESR (p = 0.045). However, for other indicators, the level of differences was practically absent (Table 2).

When comparing the obtained results of the analysis of individuals in group C (HbA1c ≥6.5% without a history of diabetes) and individuals in group D (with a history of diabetes), it was determined that these groups are similar in terms of the level of inflammatory markers (IL-6, CRP, ESR). Despite the absence of diabetes in the medical history and lower glycemic and HbA1c levels (Table 2), this group is at a higher risk.

The most favorable results of the analysis were observed in group A, individuals with normoglycemia and HbA1c ≤6.0%.

Distinguishing cases of previously undiagnosed diabetes from newly diagnosed or stress-induced hyperglycemia (SIH) is allowed by the level of HbA1c. In our study, no cases of severe SIH were found. Thus, in patients without diabetes in the medical history (groups A, B, and C), the maximum SIH values did not exceed 1.64 mmol/L, and in patients with diabetes (group D), they were no more than 2.1 mmol/L. Clinically and prognostically significant is considered to be a glycemic increase in response to stress of 4.4 mmol/L or more, which increases the likelihood of severe course and fatal outcome in critically ill patients with diabetes [14].

It is noted that the new coronavirus infection is also associated with a high frequency of developing stress-induced hyperglycemia (SIH).

An unexpected finding of our study was the discovery of high HbA1c levels in individuals without a history of diabetes and without accompanying hyperglycemia: in 10% of patients, HbA1c >6.0% and <6.5%, and in 5% of patients, HbA1c was ≥6.5% (see Table 1).

The question of the decrease in CRP levels in patients who have had COVID-19 requires separate discussion.

Our study had several limitations, primarily due to the small sample size, which does not allow for drawing population-wide conclusions fully. Additionally, the verification of all diagnoses, sample collection, and analysis were not performed by us independently as a result of the study.

Conclusions. Upon analyzing the parameters of carbohydrate metabolism in 40 individuals who contracted the new coronavirus infection, it was found that diabetes mellitus (DM) in the medical history was present in 75% of cases. In 10% of patients, carbohydrate metabolism indicators were normal. In the remaining 10%, who had no DM in their medical history, the interpretation of carbohydrate metabolism was complicated due to discrepancies between glycemia and HbA1c data.

There was a significant positive correlation noted between the level of HbA1c and inflammatory markers (ESR, CRP, IL-6). Elevated HbA1c levels with normal glycemic parameters require further analysis.
Blood glucose measurements were performed in all patients only upon admission and once in a fasting state. It is possible that more frequent glycemic control would have allowed for the detection of stress hyperglycemia in this group.

References:


Анотація:


