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INFLAMMATORY MARKERS IN PATIENTS WITH DECOMPENSATED TYPE 2 DIABETES MELLITUS AND ACUTE CORONAVIRUS INFECTION

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Type 2 diabetes mellitus (T2DM) was found to be one of the main comorbidities in patients with COVID-19. However, there is a lack of studies regarding the relationship between glycated hemoglobin (HbA1c) levels, inflammatory markers, elevated body mass index (BMI) and disease severity in patients with T2DM and COVID-19.

The aim of the study was to analyze inflammatory markers in patients with decompensated type 2 diabetes mellitus who were hospitalized with acute coronavirus infection.

Materials and Methods. A retrospective study of 103 hospitalized patients was conducted from March 2020 to March 2024. Medical records of patients with acute SARS-CoV-2 infection and a confirmed history of T2DM were thoroughly reviewed. The study included 54 women (52.43%) and 49 men (47.57%). To study the inflammatory markers, two groups of patients were formed based on the main target indicator of glycemic control HbA1c. Group A (HbA1c < 7.0%) included 33 patients (32.04%), while Group B (HbA1c ≥ 7.0%) included 70 patients (67.96%).

Results and discussion. Blood glucose levels were significantly higher in the group of patients with poorly controlled diabetes compared to the group with well-controlled diabetes – 10.8 [8.55–14.4] vs. 7.0 [5.9–9.3] ($p < 0.001$). In Group A, the median HbA1c level was significantly lower than in Group B, which is expected: 6.27 [6.08–6.63] vs. 8.55 [7.79–10.1] ($p < 0.001$). Patients with poorly controlled diabetes showed significantly higher C-reactive protein levels 95.1 [60.5–174] vs. 61.4 [14.7–138] ($p = 0,021$), more pronounced among women; neutrophilia 9.69 [6.48–14.5] vs. 6.1 [3.56–10.3] ($p = 0,005$); neutrophil-to-lymphocyte ratio 5.74 [3.17–9.97] vs. 4.22 [1.94–9.11] ($p = 0,163$). A direct correlation was observed between inflammatory markers interleukin-6 and ferritin in patients with poorly controlled diabetes and elevated HbA1c levels.

Conclusions. In patients with poorly controlled diabetes, significantly higher levels of C-RP and pronounced neutrophilia were observed. A direct correlation was found between inflammatory markers IL-6 and ferritin and elevated HbA1c levels in the group of patients with poorly controlled diabetes, confirming the link between chronic hyperglycemia and systemic inflammation.

Keywords: type 2 diabetes mellitus, coronavirus infection, COVID-19, inflammatory markers, glycemic control.

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ПОКАЗНИКИ ЗАПАЛЬНОГО ПРОЦЕСУ В ПАЦІЄНТІВ З ДЕКОМПЕНСОВАНИМ ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ НА ТЛІ ГОСТРОЇ КОРОНАВІРУСНОЇ ІНФЕКЦІЇ

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Мета дослідження – проаналізувати маркери запального процесу в пацієнтів з декомпенсованим цукровим діабетом 2-го типу, госпіталізованих із гострою коронавірусною інфекцією.

Проведено ретроспективне дослідження 103 пацієнтів, госпіталізованих у відділення лікарні з гострою інфекцією SARS-CoV-2 та цукровим діабетом 2-го типу.

У групі пацієнтів із цукровим діабетом 2-го типу і поганим глікемічним контролем переважали пацієнти з високим індексом маси тіла (56,31%, $p > 0,05$), виявлено значно вищі рівні глікованого гемоглобіну, С-реактивного білку, нейтрофільозу. Встановлено статистично значущу пряму кореляцію між маркерами запалення інтерлейкіну-6 та феритину та високими рівнями глікованого гемоглобіну.

Ключові слова: цукровий діабет 2-го типу, коронавірусна інфекція, COVID-19, маркери запалення, глікемічний контроль.

Introduction

Diabetes mellitus is currently recognized as a noncommunicable pandemic of the 21st century and is considered one of the most important and rapidly growing medical and social problems in many countries. According to estimates of the International Diabetes Federation, which brings together more than 250 national diabetes associations in 158 countries and territories, 588.7 million adults aged 20–79 years were living with diabetes in 2024 [1]. The total number of adults with diabetes is projected to reach 852.5 million by 2050, affecting 1 in 8 individuals [1].

According to the Ministry of Health of Ukraine, 531,200 cases of diabetes mellitus were diagnosed in 2023, and 1,111,575 prescriptions for insulin preparations were issued [2]. Patients with diabetes, especially in the absence of treatment, are at increased risk of complications that lead to disability. These include diabetic retinopathy, renal failure, limb amputations, polyneuropathies, cardiovascular complications, and others [3; 4].

The 2019 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) changed the epidemiology of noncommunicable diseases. Type 2 diabetes mellitus (T2DM), which researchers consider a systemic chronic inflammatory disease, has been reported as one of the major comorbidities among patients with COVID-19 [5]. It has been shown that patients with a history of diabetes had an increased risk of severe COVID-19, a higher likelihood of developing complications, admission to intensive care units, and mortality. Patients with diabetes and prolonged hyperglycemia are at risk of developing chronic complications with varying rates of progression, especially those who are overweight or obese, conditions diagnosed in 80% of patients with diabetes [6]. Patients with diabetes have nearly a threefold higher mortality rate and a twofold greater risk of severe COVID-19-related outcomes [7]. However, the characteristics of the clinical course, glycemic and metabolic profiles in patients with T2DM infected with SARS-CoV-2 and having different body mass indices remain insufficiently elucidated. There is also a lack of studies investigating the relationship between glycated hemoglobin levels, inflammatory markers, and elevated body mass index (BMI). The impact of blood glucose control on the overall condition of the patient, the extent of medical interventions, and prognosis remains an open question [7].

The aim of this study was to analyze markers of the inflammatory response in patients with decompensated T2DM hospitalized with acute coronavirus infection.

Materials and Methods

A retrospective cohort study was conducted using data from outpatient records and medical histories of patients hospitalized at the Medical House Odrex, Odesa, during the COVID-19 pandemic period (March 2020 to March 2024). A total of 103 medical records of patients hospitalized with acute SARS-CoV-2 infection and a documented history of T2DM were selected for detailed review. Confirmation of COVID-19 diagnosis was performed using polymerase chain reaction (PCR) testing (positive SARS-CoV-2 result in a respiratory specimen). The study included 54 women (52.43%) and 49 men (47.57%). To investigate inflammatory markers, patients were divided into two groups according to the primary target indicator of glycemic control, glycated hemoglobin (HbA1c). Group A with HbA1c < 7.0% included 33 patients (32.04%), whereas Group B with HbA1c ≥ 7.0% included 70 patients (67.96%). HbA1c levels were measured on the day of patient admission.

The inclusion criteria were age over 18 years, acute COVID-19 infection, and a history of T2DM (the diagnosis had been established according to the criteria of the American Diabetes Association, 2023, and the clinical guideline “Diabetes Mellitus”, Ministry of Health of Ukraine, 2024). Patients younger than 18 years, those not infected with SARS-CoV-2, patients with malignant neoplasms, chronic progressive liver diseases, primary or secondary immunodeficiencies, and those with type 1 diabetes mellitus were excluded.

The following parameters were analyzed: age, sex, BMI, duration of diabetes, and presence of comorbidities. The results of common blood count and biochemical markers were evaluated, including glucose, glycated hemoglobin (HbA1c), C-reactive protein (C-RP), D-dimer, ferritin, interleukin-6 (IL-6), and the neutrophil-to-lymphocyte ratio (NLR). The NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count. Glycemic levels were determined repeatedly for each patient: before admission to the respiratory department or intensive care unit; during hospitalization; and at the time of discharge.

The study was conducted in accordance with the principles of the World Medical Association Code of Ethics (Declaration of Helsinki) and was approved by the Bioethics Commission of Odesa National Medical University (Protocol No. 18 dated December 6, 2023). Written informed consent was obtained from all patients for all laboratory examinations described in this study. All measures were taken to ensure patient anonymity throughout the study.

Statistical analysis of the obtained data was performed using Microsoft Excel and Jamovi software version 2.3.28.0. Data normality was assessed using the Shapiro–Wilk test. Categorical variables were presented as frequencies (percentages) and compared using the χ^2 test or Fisher’s exact test. Continuous variables with normal distribution were presented as mean ± standard deviation (M ± SD). Variables with non-normal distribution were presented as medians and interquartile ranges. Normally distributed variables were analyzed using Student’s t-test, whereas non-normally distributed variables were analyzed using the Mann–Whitney U test. Differences were considered statistically significant at $p < 0.05$. Spearman’s correlation analysis (r) was used to assess relationships between variables.

Research results and their discussion

A total of 103 patients hospitalized with a diagnosis of coronavirus infection (COVID-19) and a history of T2DM were studied, including 54 women (52.43%) and 49 men (47.57%). All patients were divided according to HbA1c levels into Group A – 33 patients (32.04%) (15 women and

18 men) and Group B – 70 patients (67.96%) (39 women and 31 men) (Table 1). The reason for hospitalization was severe COVID-19 with pulmonary involvement and respiratory failure. The main symptoms in both groups were fever (66.33%), cough (92.07%), fatigue (57.42%), and dyspnea (52.47%).

The mean age in Group A was slightly higher than in Group B: 69.77 ± 9.96 and 66.11 ± 11.86, respectively; however, this difference was not statistically significant (p = 0.137). The female-to-male ratio between the compared groups was 52.43% and 47.57% (χ^2 = 1.13, p = 0.288). Thus, demographic parameters did not have a significant impact on the obtained results.

The mean BMI did not differ significantly between the study groups: Group A – 30.0 ± 5.37 and Group B – 31.27 ± 6.53 (p = 0.312). Patients with well-controlled diabetes (Group A) and overweight/obesity had lower mean BMI values compared to patients with poorly controlled diabetes (Group B) (p = 0.286). However, in Group B, the proportion of patients with normal body weight was 11.65% (23.63 ± 1.29), while the proportion of patients with BMI 25.0 was 56.31% (32.84 ± 6.05). The predominance of patients with higher BMI in the poorly controlled diabetes group, as well as the metabolic characteristics of such patients, may have contributed to an increased inflammatory response in the context of COVID-19. Notably, there were more patients with normal body weight in the poorly controlled diabetes group compared to the well-controlled diabetes group, and this difference was statistically significant (p = 0.025).

The mean duration of hospitalization from disease onset in Groups A and B was 6.77 ± 2.94 versus 6.56 ± 3.23 days. Prior to hospitalization, patients received COVID-19-related therapy, including oral symptomatic treatment (100%), antibacterial therapy (48%), antiviral therapy (17.8%), and hormonal therapy (20.8%) for 1–3 days.

Regarding the duration of T2DM, it was nearly identical between the groups: 11.5 ± 5.0 and 12.2 ± 3.4 years (p = 0.32); therefore, this parameter was unlikely to have a significant influence on differences in laboratory findings between the groups.

The most frequently recorded comorbidities in both groups were arterial hypertension (79.61%), ischemic heart disease (44.66%), and atherosclerosis (24.27%). However, no statistically significant differences in comorbidities between groups or in sex distribution were observed: arterial hypertension (χ^2 = 0.416, p = 0.519), ischemic heart disease (χ^2 = 1.73, p = 0.188), atherosclerosis (χ^2 = 0.072, p = 0.789).

The analysis of HbA1c levels between the two groups revealed the following. In Group A, the median HbA1c level was significantly lower than in Group B, which was expected: 6.27 [6.08–6.63] versus 8.55 [7.79–10.1] (Table 2). No significant differences in HbA1c levels between men and women were observed in either group: 6.46 [6.2–6.75] in men versus 6.23 [5.88–6.37] in women

Table 1

General characteristics of patients with well-controlled (Group A) and decompensated diabetes (Group B)

Parameter	Group A (HbA1c < 7.0%) n = 33		p	Group B (HbA1c ≥ 7.0%) n = 70		p
	men = 18	women = 15		men = 31	women = 39	
Age (years)	69.77 ± 9.96		–	66.11 ± 11.86		0.137
BMI, kg/m^2:	30.00 ± 5.37		–	31.27 ± 6.53		0.312
	28.34 ± 4.09*	31.94 ± 5.83*	0.027*	29.14 ± 4.13	32.88 ± 7.63	0.085
– up to 24.9	5.83%		–	11.65%		0.025*
	21.92 ± 1.9*		–	23.63 ± 1.29*		
– over 25.0	26.21%		–	56.31%		0.286
	31.55 ± 4.3		–	32.84 ± 6.05		
Duration of diabetes (years)	11.5 ± 5.0		–	12.2 ± 3.4		0.32
	10.63 ± 4.2	11.7 ± 6.7	0.617	11.4 ± 2.72	12.8 ± 4.1	0.732
Hypertension	13/72.22%	11/73.33%	1.0	27/87.1%	31/79.49%	0.529
Ischemic heart disease:	9/50.0%	7/46.67%	0.204	13/41.94%	17/43.59%	1.0
– stable angina	1/11.1%	5/71.4%	–	2/15.4%	7/41.2%	–
– unstable angina	0	0	–	1/7.7%	0	–
– cardiosclerosis	8/88.9%	2/28.6%	–	9/69.2%	9/52.9%	
– silent IHD	0	0	–	0	1/5.9%	–
– chronic IHD	0	0	–	1/7.7%	0	–
Atherosclerosis:	6/33.33%	5/33.3	1.0	7/22.58%	7/17.95%	1.0
– coronary arteries	0	1/20.0%	–	2/28.6%	2/28.6%	–
– cerebral arteries	3/50.0%	2/40.0%	–	1/14.3%	4/57.1%	–
– aorta	0	0		1/14.3%	0	
– peripheral arteries	1/16.7%	0	–	1/14.3%	0	–
– generalized	2/33.3%	2/40.0%	–	2/28.6%	1/14.3%	–

Note: Variables are presented as M ± SD – mean value ± standard deviation. Differences were considered statistically significant at *p < 0.05. Abbreviations: HbA1c – glycated hemoglobin; IHD – ischemic heart disease; BMI – body mass index.

Table 2

Values of glycemic control parameters, inflammatory markers, and D-dimer levels in patients with well-controlled (Group A) and decompensated (Group B) diabetes who had COVID-19

Parameter	Group A (HbA1c < 7.0%), n = 33		p	Group B (HbA1c ≥ 7.0%) n = 70		p
	men = 18	women = 15		men = 31	women = 39	
HbA1c, %	6.27 [6.08–6.63]*		–	8.55 [7.79–10.1]*		< 0.001*
	6.46 [6.2–6.75]*	6.23 [5.88–6.37]*	< 0.001*	8.46 [7.83–10.2]**	8.67 [7.7–9.96]**	< 0.001**
Blood glucose, mmol/L	7.0 [5.9–9.3]*		–	10.8 [8.55–14.4]*		< 0.001*
	7.8 [5.85–9.68]	6.9 [6.4–8.5]	0.868	10.4 [8.55–14.1]	11.4 [8.57–14.4]	0.335
C-RP, mg/L	61.4 [14.7–138]*		–	95.1 [60.5–174]*		0.021*
	115 [41.8–160]	25.4 [6.87–80.5]*	< 0.008	114 [70–176]	79.6 [39.1–172]*	< 0.003*
Ferritin, ng/mL	575 [286–926]		–	442 [255–1012]		0.908
	535 [270–875]	575 [331–992]	0.367	619 [344–1074]	414 [200–894]	0.094
IL-6, pg/mL	47.7 [20.2–95.5]		–	38.7 [15.6–92.2]		0.367
	91.3 [63.5–138]*	20.6 [11.1–36.7]*	0.003*	32.7 [16.9–114]	42 [15.6–86.1]	0.632
NLR	4.22 [1.94–9.11]		–	5.74 [3.17–9.97]		0.163
	6.34 [2.63–11.4]	2.82 [1.78–4.22]	0.062	8.65 [5.26–13.3]*	4.11 [2.48–7.4]*	0.002*
D-dimer, μg/mL	0.96 [0.645–2.81]		–	0.86 [0.44–2.18]		0.817
	0.95 [0.795–2.63]	0.96 [0.58–2.21]	0.284	1.5 [0.523–2.58]	0.81 [0.43–1.46]	0.063
Neut, 10^9/L	6.1 [3.56–10.3]*		–	9.69 [6.48–14.5]*		0.005*
	6.15 [4.24–12.1]*	3.7 [3.05–9.7]**	0.018*	9.87 [8.53–15]*	9.58 [5.62–13.1]**	0.027**
Lym, 10^9/L	1.58 [1.14–1.92]		–	1.6 [1.14–2.2]		0.474
	1.47 [1.04–1.85]	1.76 [1.31–1.97]	0.111	1.27 [0.96–1.76]*	1.97 [1.48–2.56]*	0.002*

Note. Variables are presented as Me [Q1–Q3] (median and interquartile range). Differences were considered statistically significant at $p < 0.05$. Abbreviations: HbA1c – glycated hemoglobin; C-RP – C-reactive protein; IL-6 – interleukin-6; NLR – neutrophil-to-lymphocyte ratio; Neut – neutrophils; Lym – lymphocytes.

(Group A), and 8.46 [7.83–10.2] in men versus 8.67 [7.7–9.96] in women (Group B), respectively.

Regarding the relationship between HbA1c levels and BMI, no statistically significant correlation was found either between Groups A and B ($r = 0.068$, $p = 0.249$) or between men and women within Groups A and B ($r = 0.018$, $p = 0.461$ and $r = 0.056$, $p = 0.324$, respectively).

The study demonstrated that blood glucose levels were significantly higher in the group of patients with poorly controlled diabetes compared to those with well-controlled diabetes, as expected: 10.8 [8.55–14.4] versus 7.0 [5.9–9.3] ($p < 0.001$). However, the difference in glucose levels by sex within Groups A and B was not statistically significant ($p = 0.868$ and $p = 0.335$, respectively). A statistically significant difference in glucose levels was observed between men in Group B and men in Group A: 10.4 [8.55–14.1] versus 7.8 [5.85–9.68] ($p < 0.004$), respectively. Similarly, glucose levels in women of Group B were significantly higher than in women of Group A: 11.4 [8.57–14.4] versus 6.9 [6.4–8.5] ($p < 0.001$). At hospitalization, blood glucose levels exceeded reference values in 72.22% of men and 84.62% of women in Group A, and in 96.77% of men and 92.31% of women in Group B.

We analyzed indicators of the intensity of the inflammatory response in patients of both groups. C-reactive protein (C-RP) levels significantly exceeded reference values in all men of Groups A and B and in 94.23% of women in both groups. As shown in Table 2, C-RP levels in Group B patients were significantly higher than in Group A: 95.1 [60.5–174] versus 61.4 [14.7–138] ($p = 0.021$). It should be noted that in Group A, C-RP levels in men were significantly higher than in women: 115 [41.8–160] versus 25.4 [6.87–80.5] ($p < 0.008$), indicating a more pronounced systemic inflammatory response in men with controlled diabetes. Comparison of C-RP levels revealed a significant increase in women of Group B compared with Group A: 79.6 [39.1–172] versus 25.4 [6.87–80.5] ($p < 0.003$). No difference was found between men ($p = 0.576$).

In one study [8], patients with poorly controlled T2DM demonstrated significantly higher mean C-RP levels (93.4 mg/L versus 78.6 mg/L, $p = 0.002$). Significantly higher C-RP levels were shown in patients with T2DM compared to those without diabetes: 6.85 [4.10–9.78] versus 2.50 [1.90–3.70], $p < 0.001$. A marked increase in C-RP with worsening glycemic status has also been described in patients without COVID-19 infection [9]. Other authors demonstrated a significant positive correlation between C-RP levels (155.75 ± 73.95) and HbA1c (7.5 ± 3.23) in patients with T2DM without COVID-19 ($r = 0.761$, $p < 0.001$) [10].

In this study, serum ferritin levels significantly exceeded reference values in both men and women across both groups. However, no statistically significant differences were found either between the groups or between sexes: 575 [286–926] versus 442 [255–1012] ($p = 0.908$). This finding differs from the results reported by other authors, who demonstrated significantly higher ferritin levels in patients with poorly controlled diabetes compared with those with

well-controlled diabetes (524.7 μg/L versus 449.2 μg/L, p = 0.01) [8]. Comparison of mean ferritin levels between women in both groups (p = 0.751) and between men in both groups (p = 0.234) also revealed no statistically significant differences. In other studies, ferritin levels were significantly higher in patients with T2DM than in patients without diabetes and without SARS-CoV-2 infection: 73.30 [66.25–117.75] versus 65.50 [49.00–78.00], p < 0.001. Ferritin concentrations in patients with T2DM increased significantly with rising HbA1c levels and worsening glycemic status (p < 0.01) [9].

A significant positive correlation was observed between HbA1c levels (7.5 ± 3.23) and serum ferritin concentrations (6005.2 ± 2639.83) (r = 0.853, p < 0.001) [10]. According to the authors, these findings indicate a relationship between inflammatory processes and glycemic status in patients with T2DM. Although our results did not demonstrate higher ferritin levels in the poorly controlled diabetes group compared with the well-controlled diabetes group, this may be explained by the limited sample size, which could have affected the statistical power of the analysis.

Serum levels of the proinflammatory cytokine IL-6 significantly exceeded reference values in both Groups A and B: 47.7 [20.2–95.5] and 38.7 [15.6–92.2], respectively, p = 0.367. Significantly higher IL-6 levels were observed in men of Group A: 91.3 [63.5–138] versus women 20.6 [11.1–36.7] (p = 0.003). No statistically significant differences in IL-6 levels between men (p = 0.098) and women (p = 0.095) of both study groups were found, although IL-6 levels were markedly elevated in both groups. The absence of a statistically significant difference in IL-6 levels between groups does not exclude its clinical relevance. IL-6 is considered a key proinflammatory cytokine promoting activation of T- and B-lymphocytes. Studies have shown higher IL-6 levels in non-surviving COVID-19 patients, and it is considered a prognostic marker of disease severity and mortality [11]. Elevated IL-6 levels have been shown to correlate with ischemic heart disease (r = 0.229, p = 0.048) and obesity (r = 0.309, p = 0.007), but no association with diabetes was found [12]. The role of IL-6 in glucose metabolism disorders and autoimmune diabetes has been demonstrated, given its involvement in insulin resistance and β-cell dysfunction. In one study, IL-6 levels were significantly increased in patients with diabetes, particularly in those with acute COVID-19 [13]. Elevated IL-6 levels indicate increased inflammatory activity and are associated with worse renal function in diabetic patients [14].

Regarding D-dimer levels, although values in both groups exceeded reference ranges, no statistically significant difference was found between Group A and Group B: 0.96 [0.645–2.81] versus 0.86 [0.44–2.18] (p = 0.908), respectively. However, in men with poorly controlled diabetes, mean D-dimer levels were significantly higher than in men with well-controlled diabetes: 1.5 [0.523–2.58] versus 0.96 [0.58–2.21]. Plasma D-dimer is an important marker of coagulation system activation and a significant indicator for diagnosing vascular complications in patients with diabetes. Persistent hyperglycemia may lead to endothelial dysfunction with inflammation, thereby promoting thrombus formation [15]. The most common cause of increased D-dimer levels is considered to be viremia combined with cytokine storm syndrome, accompanied by uncontrolled elevation of proinflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF-α), which overloads the coagulation system [16]. It has been reported that significantly higher D-dimer levels were observed in patients with diabetes (1.68 μg/mL), with levels above 0.50 μg/mL detected in 80.1% of hospitalized patients, and such elevated values present in 96% of patients with fatal outcomes. In addition, a significant association between elevated D-dimer levels, diabetes, and advanced age has been identified [5].

An increased absolute neutrophil count was observed in 61.11% of men and 46.15% of women in Group A, and in 90.32% of men and 69.23% of women in Group B. Neutrophilia was more frequently observed in Group B than in Group A (78.58% versus 54.83%) and more often in men than in women (79.59% versus 63.46%). In all patients of Group A, the mean absolute neutrophil count was 6.1 [3.56–10.3], which was statistically lower than in Group B: 9.69 [6.48–14.5], p = 0.005. In men, and especially in women with poorly controlled diabetes, absolute neutrophil counts were significantly higher compared with patients in the well-controlled group. Lymphopenia was detected in 44.44% of men and 7.69% of women in Group A. In Group B, lymphopenia was observed in 51.61% of men and 17.94% of women. Lymphopenia was more frequent in Group B than in Group A (32.6% versus 29.03%) and occurred more often in men than in women in both groups, being more pronounced in men. The mean absolute lymphocyte count did not differ significantly between Groups A and B: 1.58 [1.14–1.92] versus 1.6 [1.14–2.2], respectively (p = 0.474). A higher mean absolute lymphocyte count was observed in women than in men in the poorly controlled diabetes group: 1.97 [1.48–2.56] versus 1.27 [0.96–1.76] (p = 0.002). Lymphopenia in patients with diabetes and COVID-19 was also observed in other studies [8], being more pronounced in patients with poorly controlled diabetes. Severe COVID-19 cases with fatal outcomes were characterized by high viral load and reduced adaptive immune response. In another study in patients with T2DM without COVID-19 infection, absolute lymphopenia was also detected [17], possibly indicating immunodeficiency that may predispose to SARS-CoV-2 infection. An increased absolute neutrophil count without a left shift was observed in patients with T2DM, and was more pronounced in those with overweight or obesity [17]. Increased leukocyte levels due to neutrophils and monocytes are characteristic not only of the pathogenesis of T2DM but are also associated with the additional effect of excess body weight or obesity, resulting in synergistic amplification of their impact on the organism [17]. A higher rate of neutrophilia in diabetic patients with COVID-19 was reported by Zhu L. et al. [7], although Zhang J. et al. did not find such differences [18].

We analyzed NLR between the study groups. This marker of systemic inflammation, which is considered a

prognostic indicator of COVID-19 severity, was higher in the poorly controlled diabetes group (5.74 [3.17–9.97] versus 4.22 [1.94–9.11], p = 0.163). At the same time, this index was almost two times higher in men than in women in the poorly controlled diabetes group: 8.65 [5.26–13.3] versus 4.11 [2.48–7.4], p = 0.002 (Table 2).

The relationship between the NLR index and HbA1c levels in patients of Groups A and B was also investigated (Table 3).

In 65.05% of hospitalized patients, the NLR index exceeded reference values, with 71.64% of these cases occurring in patients with poorly controlled diabetes. Patients with HbA1c ≥ 7.0% more frequently demonstrated an elevated NLR index (> 3.53). According to chi-square test, no statistically significant association was found between HbA1c levels (HbA1c < 7.0% and HbA1c ≥ 7.0%) and NLR ($\chi^2 = 1.05$, $p > 0.05$). Additionally, correlation analysis revealed a weak positive correlation between HbA1c levels and the NLR index (r = 0.102, p = 0.306). Although the obtained results did not reach statistical significance, possibly due to sample characteristics, they indicate that patients with poorly controlled diabetes and, consequently, higher HbA1c levels tend to have higher NLR values.

Other studies have demonstrated a direct correlation between NLR and glycemic control, showing elevated NLR levels associated with increased HbA1c and poorly controlled diabetes [19]. Significantly higher NLR values were reported in patients with poorly controlled diabetes and COVID-19 (7.2 versus 5.7, p < 0.001) [8]. Elevated NLR levels correlated with higher HbA1c and poor glycemic control have also been demonstrated by Varma S. et al. [20]. According to these authors, all patients with T2DM and elevated NLR should be evaluated for diabetic complications (renal, ocular, cardiovascular). HbA1c reflects the severity of hyperglycemia; however, glycemic control alone does not allow precise assessment of inflammatory processes and diabetic complications. In patients with COVID-19, elevated NLR alone was identified as an independent risk factor for severe disease (OR 2.648, 95% CI 1.566–4.479, p < 0.001) [21], which may be used for early stratification of patients at high risk of severe outcomes.

We investigated the correlation between mean inflammatory markers and HbA1c levels across all patients in Groups A and B (Table 4).

The association between HbA1c levels and the frequency and mean values of C-RP, IL-6, ferritin, and D-dimer was assessed, and a statistically significant positive correlation between the two parameters was identified, indicating a higher IL-6 levels (r = 0.317, p = 0.012) and ferritin levels (r = 0.270, p = 0.02) in patients with poorly controlled diabetes and higher HbA1c levels. A high HbA1c level associated with higher IL-6 and ferritin levels demonstrates that poor glycemic control in patients with T2DM in the setting of coronavirus disease is accompanied by activation of inflammatory processes.

Table 3

Relationship between neutrophil-to-lymphocyte ratio and glycated hemoglobin in patients with well-controlled (Group A) and decompensated diabetes (Group B)

Indicator NLR	HbA1c		Total, *n*
	< 7.0%, *n*	≥ 7.0%, *n*	
0.78–3.53	14	22	36
> 3.53	19	48	67
Total	33	70	103

Note: $\chi^2 = 1.05$, $p > 0.05$. Abbreviations: HbA1c – glycated hemoglobin; NLR – neutrophil-to-lymphocyte ratio.

Table 4

Relationship between inflammatory markers and glycated hemoglobin levels in patients with well-controlled (Group A) and decompensated diabetes (Group B)

Indicators	Group A (HbA1c < 7.0%), n = 33	Correlation coefficient, r	Group B (HbA1c ≥ 7.0%), n = 70	Correlation coefficient, r
C-RP, mg/L	61.4 [14.7–138]	r = –0.020 p = 0.542	95.1 [60.5–174]	r = 0.075 p = 0.271
D-dimer, μg/mL	0.96 [0.645–2.81]	r = –0.101 p = 0.622	0.86 [0.44–2.18]	r = 0.056 p = 0.655
IL-6, pg/mL	47.7 [20.2–95.5]	r = –0.155 p = 0.270	38.7 [15.6–92.2]*	r = 0.317 p = 0.012*
Ferritin, ng/mL	575 [286–926]	r = 0.17 p = 0.220	442 [255–1012]*	r = 0.270 p = 0.02*

Note: HbA1c – glycated hemoglobin; C-RP – C-reactive protein; IL-6 – interleukin-6.

Conclusions

Patients with poorly controlled diabetes demonstrated significantly higher C-RP levels and more pronounced neutrophilia. A positive correlation was found between inflammatory markers (IL-6 and ferritin) and high HbA1c levels in the group of patients with poorly controlled diabetes, confirming the association between chronic hyperglycemia and systemic inflammation.

Poor glycemic control in patients with T2DM is associated with a more pronounced inflammatory response and higher levels of inflammatory markers in the setting of acute coronavirus infection, emphasizing the need for intensive blood glucose control and monitoring in such patients.

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