INDICATORS OF BLOOD LEUKOCYTE COMPOSITION, VNL INFLAMMATORY INDEX AND SUBPOPULATION STATE OF BLOOD LYMPHOCYTES IN PATIENTS WITH NEWLY DIAGNOSED TYPE 2 DIABETES WITH DIFFERENT BODY MASS INDEX IN THE POST-COVID PERIOD

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Abstract. Today, there is a dramatic global increase in the incidence of diabetes mellitus (DM), one of the most common diseases worldwide and non-infectious pandemic. It has been established that the annual growth of this disease is in a geometric progression. Over the past 25 years, the number of people diagnosed with DM worldwide increased more than 4 times, reaching 589 million people aged 20-79, according to the data of International Diabetes Federation.

According to expert forecasts, this number will increase to 643 million by 2030 and to 783 million by 2045. Approximately 90% of all patients suffering from this disease are patients with type 2 diabetes (T2D). A similar progressive increase in the incidence of DM is observed in Ukraine too. The coronavirus pandemic has had a global impact on human health worldwide, including the endocrine system, causing significant disruptions due to an unprecedented increase in mortality and morbidity. The data obtained confirm that the onset of T2D in post-COVID period is characterized with significant impairments in innate and adaptive immunity, necessitating immediate study and a thorough fundamental understanding of the general pathophysiology and clinical and immunological patterns of post-COVID pathogenesis in patients with onset of T2D with different body mass index (BMI), which potentially determines the choice of therapeutic strategy in this category of patients.

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Despite the large volume of publications devoted to the combination of COVID-19 and T2D, these studies were mainly performed in patients with T2D with different disease durations. At the same time, published data on the leukocyte composition, the VNL inflammatory index (the ratio of the absolute number of neutrophils to the absolute number of lymphocytes), and the subpopulation composition of lymphocytes in the peripheral blood (PB) in patients with the debut of T2D in the post-COVID period are extremely limited and contradictory. Blood subpopulation composition indicators are currently among the key characteristics of immune function. These parameters are particularly important in patients with newly diagnosed T2D in the post-COVID period. However, data on leukocyte composition, VNL parameters, and lymphocyte immunophenotype in patients with newly diagnosed T2D with different BMI in the post-COVID period are extremely limited and debatable. Information on the relationship between systemic inflammatory markers and BMI parameters in patients with newly diagnosed T2D in the post-COVID period is virtually nonexistent. Thus, **the objective** of the study was to investigate the total leukocyte count, the leukocyte composition of the PB, the VNL inflammation index, and determine the lymphocyte immunophenotype (CD3+T, CD4+T, CD8+T, CD20+, and CD56+ cells) in the blood of patients with newly diagnosed T2D with different BMI on the background of a history of COVID. **Materials and methods.** The study included 98 patients with onset of T2D within 3 months of COVID-19, with varying BMI, and 94 patients with onset of T2D with varying BMI and disease manifestation in the pre-pandemic period. The comparison groups consisted of 93 normoglycemic individuals with varying BMI after COVID-19 and 88 normoglycemic individuals with varying BMI and without COVID-19 in anamnesis. **Results.** It was established that for patients with the debut of T2D and different BMI in post-COVID, compared to patients with newly diagnosed T2D and different BMI in the pre-COVID period, significant leukocytosis (an increase in the total number of leukocytes by almost 1.5 times, $p < 0.001$), neutrophilosis (an increase in the absolute number of neutrophils by almost 2.0 times, $p<0.001$), monocytosis (an increase in the absolute number of monocytes by almost 2.0 times, $p < 0.001$), lymphopenia (a decrease in the relative number of lymphocytes by almost 2.0 times, $p<0.001$) and an increase in the VNL inflammatory index by more than 2.0 times in patients with the debut of T2D after coronavirus disease were likely characteristic. Similar changes in the leukocyte composition, which were found in patients with the debut of T2D and different BMI in the post-COVID period, but less significant, were also observed in normoglycemic individuals with different BMI in the post-COVID period and were completely absent in normoglycemic people with different BMI in the pre-COVID period, which indicates the key importance of the changed post-COVID state of immunity in the pathogenesis of the debut of T2D in patients with different BMI after a previous coronavirus disease. For patients with T2D in the post-COVID period, a decrease in the absolute number of all lymphocyte subpopulations is likely characteristic compared to patients in the pre-COVID period and groups of normoglycemic individuals in the pre-COVID and post-COVID periods. When distributing patients depending on BMI into 4 subgroups: 1) 25.5 kg / m^2; 2) 25.9-29.9 kg / m^2; 3) 30.0-34.9 kg / m^2; 4) > 35.0 kg/m^2– a progressive decrease in CD3+ T-, CD4+ T-, D8+ T-, CD20+- and CD56+-cells was revealed compared to patients with newly diagnosed T2D in the pre-COVID period, in whom, on the contrary, a progressive increase in all lymphocyte subpopulations was noted. A similar increase in the absolute number of CD4+ T cells depending on BMI was also noted in normoglycemic individuals, but it was less pronounced. **Conclusion.** Changes in the leukocyte composition and lymphocyte subset composition in patients with the debut of T2D depend not only on the BMI value, but are also due to the systemic inflammatory state of post-COVID-19 background, which exacerbates the chronic low-grade inflammation that forms the pathogenetic basis of DM2 debut. For patients with newly diagnosed T2D in the post-COVID period, a decrease in the content of all lymphocyte subpopulations in the peripheral blood is characteristic, which is most pronounced with concomitant obesity, which indicates the immunosuppressive effect of coronavirus disease on the immune system in patients with the debut of T2D and different BMI in the post-COVID period. The changes we have identified in the leukocyte and subpopulation content in patients with the debut of DM2 with different BMI in the post-COVID period explain the bidirectional relationship between DM2 and coronavirus disease and determine the strategic choice of further pathogenetic therapy for this category of patients.

Key words: type 2 diabetes, coronavirus disease, immunity, blood subpopulation composition, VNL inflammatory index, immunophenotype of blood lymphocytes.

Показники лейкоцитарного складу крові, індексу запалення внл та субпопуляційного стану лімфоцитів крові у хворих з вперше виявленним цукровим діабетом 2 типу з різним індексом маси тіла в постковідний період

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Резюме. **Вступ.** Наразі відбувається глобальне драматичне збільшення захворюваності на ЦД, яке є однією з найпоширеніших нозологій в усьому світі та набуло характеру неінфекційної пандемії. Встановлено, що щорічне зростання цього захворювання відбувається у геометричній прогресії. Так, за останні 25 років кількість хворих на діабет у світі збільшилася більш ніж у 4 рази і становить нині 589 млн, віком 20-79 років, згідно з даними Міжнародної федерації діабету.

За прогнозами експертів, ця кількість зросте до 643 млн до 2030 року і до 783 млн до 2045 року. Приблизно 90 % всіх пацієнтів, які страждають на це захворювання складають хворі на ЦД2. Аналогічне прогресивне зростання захворюваності на ЦД спостерігають і в Україні. Пандемія коронавірусної хвороби глобально вплинула на здоров'я людей в усьому світі, в тому числі і на ендокринну систему, спричиняючи значний руйнівний вплив через безпрецедентне підвищення смертності та захворюваності. Отримані дані підтверджують, що при дебюті ЦД2 в постковідний період мають місце значні порушення вродженого та адаптивного імунітету, що диктує необхідність невідкладного вивчення і глибинного фундаментального розуміння загальної патофізіології та клініко-імунологічних закономірностей постковідного патогенезу у хворих з дебютами ЦД2 та різним ІМТ, що потенційно визначає вибір терапевтичної стратегії у цієї категорії хворих. Незважаючи на великий обсяг публікацій, присвячених поєднанню COVID-19 і ЦД2, ці дослідження переважно були виконані у хворих на ЦД2 з різними термінами захворювання. В той же час дані публікацій, щодо лейкоцитарного складу, індексу запалення ВНЛ (відношення абсолютної кількості нейтрофілів до абсолютної кількості лімфоцитів), субпопуляційного складу лімфоцитів в периферичній крові (ПК) у хворих з дебютом ЦД2 в постковідному періоді вкрай обмежені та суперечливі. Показники субпопуляційного складу крові на наразі є одними із ключових характеристик функції імунітету. Особливе значення ці параметри мають у хворих на вперше виявлений цукровий діабет 2 типу (ЦД2) в постковідному періоді. Проте дані досліджень щодо лейкоцитарного складу, показників ВНЛ та стану імунофенотипу лімфоцитів у хворих на вперше виявлений ЦД2 з різним індексом маси тіла (ІМТ) в постковідному періоді вкрай малочисельні та дискутабельні. Майже відсутня інформація про взаємозв`язок між системними маркерами запалення та показниками ІМТ у хворих із вперше виявленим ЦД2 в постковідному періоді. Таким чином, **метою** роботи стало дослідження загальної кількості лейкоцитів, лейкоцитарного складу ПК, індексу запалення ВНЛ, визначення показників імунофенотипу лімфоцитів (CD3+Т-, CD4+Т-,CD8+Т-,CD20+-і CD56+-клітин) крові у хворих з вперше виявленим ЦД2 і різним ІМТ на тлі перенесеного ковіду.

Матеріали та методи. До дослідження були залучені 98 хворих з дебютом ЦД2, що відбувся протягом 3 місяців після перенесеного ковіду, з різним ІМТ та 94 хворих з дебютом ЦД2 та різним ІМТ з маніфестацією захворювання в передпандемічний період. Групи порівняння склали 93 нормоглікемічних людей після перенесеного коронавірусного захворювання з різним ІМТ та 88 нормоглікемічних з різним ІМТ без ковіду в анамнезі.

Результати. Встановлено, що для хворих з дебютом ЦД2 з різним ІМТ в постковіді порівняно з хворими з вперше виявленим ЦД2 з різним ІМТ в передковіді характерні вірогідні значний лейкоцитоз (підвищення загальної кількості лейкоцитів майже в 1,5 рази, $p<0,001$), нейтрофільоз (підвищення абсолютної кількості нейтрофілів майже в 2 рази, $p<0,001$), моноцитоз (підвищення абсолютної кількості моноцитів майже в 2 рази, $p<0,001$), лімфоцитопенія (зменшення відносної кількості лімфоцитів майже в 2 рази, $p<0,001$) та підвищення індексу запалення ВНЛ більше ніж в 2 рази ($p<0,001$), що свідчить про сумарне підвищення рівня системного запалення у хворих з дебютами ЦД2 після перенесеного коронавірусного захворювання. Подібні зміни лейкоцитарного складу, що були виявлені у хворих з дебютом ЦД2 з різним ІМТ в постковіді, але менш значущі, спостерігали і в нормоглікемічних людей з різним ІМТ в постковіді та були зовсім відсутні у нормоглікемічних з різним ІМТ в передковідному періоді, що свідчить про ключове значення зміненого постковідного стану імунітету

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в патогенезі дебюту ЦД2 у хворих з різним ІМТ після перенесеного коронавірусного захворювання. Для хворих на ЦД2 в постковідному періоді характерне вірогідне зниження абсолютної кількості всіх субпопуляцій лімфоцитів порівняно з хворими в доковідному періоді та групами нормоглікемічних людей в доковідному та постковідному періодах. При розподілі хворих залежно від ІМТ на 4 підгрупи: 1)25,5 кг/м^2; 2) 25,9–29,9 кг/м^2; 3) 30,0–34,9 кг/м^2; 4) > 35,0 кг/м^2 — виявлено прогресуюче зниження CD3+ Т-, CD4+ Т-, D8+ Т-, CD20+- і CD56+-клітин порівняно з хворими на вперше виявлений ЦД2 в доковідному періоді, в яких відзначалося, навпаки, прогресуюче збільшення всіх субпопуляцій лімфоцитів. Подібне підвищення абсолютного числа CD4+ Т-клітин залежно від ІМТ відзначали також і в нормоглікемічних людей, але було менш вираженим. Для хворих на ЦД2 в постковідному періоді характерне вірогідне зниження абсолютної кількості всіх субпопуляцій лімфоцитів порівняно з хворими в доковідному періоді та групами нормоглікемічних людей в доковідному та постковідному періодах. Подібне підвищення абсолютного числа CD4+ Т-клітин залежно від ІМТ відзначалось також і в нормоглікемічних людей, але воно було менш вираженим. **Висновки.** Зміни в лейкоцитарному та субпопуляційному складі лімфоцитів у хворих з дебютом ЦД2 залежать не тільки від значень ІМТ, але й зумовлені системним запальним станом постковідного тла, що підсилює хронічне запалення низького ступеня, яке становить патогенетичний базис дебюту ЦД2. Для пацієнтів з вперше виявленим ЦД2 в постковідному періоді характерне зниження вмісту в периферичній крові всіх субпопуляцій лімфоцитів, яке максимально виражене при супутньому ожирінні, що свідчить про імуносупресивний вплив коронавірусного захворювання на стан імунної системи у хворих з дебютом ЦД2 з різним ІМТ в постковідному періоді. Виявлені нами зміни в лейкоцитарному та в субпопуляційному вмісті у хворих з дебютом ЦД2 з різним ІМТ в постковідному періоді пояснюють двосторонній зв'язок між ЦД2 і коронавірусним захворюванням та обумовлюють стратегічний вибір подальшої патогенетичної терапії цієї категорії хворих.

Ключові слова: діабет 2 типу, коронавірусна хвороба, імунітет, лейкоцитарний склад крові, ВНЛ індекс, імунофенотип лімфоцитів крові.

It is currently generally accepted that type 2 diabetes mellitus (T2D) is a disease that is based on systemic low-intensity chronic inflammation and is characterized by the presence of characteristic inflammatory biomarkers of inflammation (leukocytosis, monocytosis, neutrophilosis, increased VNL inflammatory index, increased levels of C-reactive protein and pro-inflammatory cytokines) [1, 2, 3, 4]. According to modern concepts, one of the key pathophysiological mechanisms of coronavirus disease 2019 (COVID-19) is immune system dysfunction both during the development of the disease and in the post-COVID period. However, the role of the immune system in the pathogenesis of T2D in the post-COVID period is currently almost unstudied. In particular, data on the subpopulation composition and relative and absolute number of blood lymphocytes in patients with newly diagnosed T2D in the post-COVID period are sporadic and debatable [5]. A number of studies have already established that in patients with newly diagnosed T2D in the pre-COVID period, an increase in lymphocyte subpopulations in the PB was noted [6, 7, 8]. Also, many studies have reliably established that there is a direct correlation between the increase in the number of blood lymphocyte subpopulations and the BMI level in patients with newly diagnosed T2D who developed the disease in the pre-pandemic period [9]. In patients with the debut of T2D, which occurred already in the post-COVID period, the situation, according to research, is the opposite. A number of recent studies have found that the number of peripheral blood lymphocyte subpopulations in patients with newly diagnosed T2D in the post-COVID period is reduced [10, 11]. Thus, the number of CD4+ and CD8+ T-lymphocytes in patients with newly diagnosed T2D in the post-COVID period is lower than in patients without DM after a coronavirus disease [12]. Currently, data on the immunophenotype of lymphocytes in the peripheral blood of patients with newly diagnosed T2D in the post-COVID period are few and ambiguous. The question of the impact of COVID on the subpopulation composition of blood lymphocytes in patients with newly diagnosed T2D and different BMI is also open.

For studying immunophenotype of lymphocytes (CD3+ T-, CD4+ T-, CD8+ T-, CD20+, and CD56+ cells) in blood of patients with newly diagnosed T2D and different BMI in the post-COVID period, 98 patients with newly diagnosed T2D who had recovered from COVID-19 and varied in BMI, and 94 patients with onset T2D and varied in BMI with disease manifestation in the pre-pandemic period were included in the invastigation. The groups were equally distributed by gender and had no history of cardiovascular, oncological, or other systemic diseases. The comparison groups consisted of 93 normoglycemic individuals with varied BMI after COVID-19 and 88 normoglycemic individuals without a confirmed history of COVID-19, recruited in the pre-COVID period. These indi-

viduals were normoglycemic healthy individuals with varied BMI. Based on BMI, the groups of patients with onset T2DM and the normoglycemic individuals were divided into four subgroups, each with a different BMI. The group of patients with the onset of T2D in the pre-COVID period: 1) with normal BMI (<25.0 kg/m^2) — 25 patients; 2) BMI from 25.0 to 29.9 kg/m^2 — 23 patients; 3) BMI from 30 to 34.9 kg/m^2 — 25 patients; 4) BMI above 35.0 kg/m^2 — 21 patients. The group of patients with the onset of T2D after COVID-19: 1) with normal BMI (<25.0 kg/m^2) — 22 patients; 2) BMI from 25.0 to 29.9 kg/m^2 — 27 patients; 3) BMI from 30 to 34.9 kg/m^2 — 26 patients; 4) BMI above 35.0 kg/m^2 — 23 patients. A group of normoglycemic people with different BMI after coronavirus disease: 1) with normal BMI (<25.0 kg/m^2) — 23 people; 2) BMI from 25.0 to 29.9 kg/m^2 — 25 people; 3) BMI from 30 to 34.9 kg/m^2 — 24 people; 4) BMI above 35.0 kg/m^2 — 21 people. A group of normoglycemic people with different BMI without a confirmed history of coronavirus disease, that is, recruited in the pre-COVID period: 1) with normal BMI (<25.0 kg/m^2) — 21 people; 2) BMI from 25.0 to 29.9 kg/m^2 — 24 people; 3) BMI from 30 to 34.9 kg/m^2 — 23 people; 4) BMI over 35.0 kg/m^2 — 20 people.

The body mass index was defined as the ratio of body weight in kg to the square of the height in meters. According to the generally accepted international classification, BMI values between 18 and 24.9 kg/m^2 are defined as normal, from 25.0 to 29.9 kg/m^2 — overweight, 30.0-34.9 kg/m^2 — grade 1 obesity, 35 — 39.9 kg/m^2 — grade 3 obesity. The diagnosis of T2D was established according to the recommendations of the American Diabetes Association [13]. The level of glycosylated hemoglobin, cholesterol, lipoproteins and triglycerides were determined fasting by a biochemical method with the HummaStar 600 automatic analyzer (Germany). Systolic and diastolic blood pressure — on an automatic tonometer UA778 (Japan), according to the recommendations of the American Heart Association.

The total number of leukocytes in the PB was determined using a hematological analyzer, and the leukocyte composition was determined both using the analyzer and in blood smears stained according to Pappenheim using cacodylate buffer (Ph 6.85) per 200 identifiable cells.

The content of lymphocytes of various immunological phenotypes (CD3+T-, CD4+T-, CD8+T-, CD20+T-, and CD56+T-cells) was determined by flow cytometry using a FACStar Plus Becton Dickenson laser cytofluorimeter (USA) and a panel of "BectonDickinson" (USA) and "Dakopat" (Denmark). For this purpose, mononuclear cells from heparinized PB were isolated by differential centrifugation in a Ficoll-Urostat density gradient (Sweden) with subsequent incubation in plastic dishes for 1 hour in a CO2 incubator to eliminate monocytes. The purified lymphocyte fraction was treated with specific monoclonal antibodies labeled with fluorescein isothiocyanate or phycoerythrin. Statistical processing of the obtained data was carried out using the variation statistics method by the standard statistical calculation package in the LibreOffice Calc program.

The results of the general clinical and clinical laboratory studies of patients with the onset of T2D and different BMI against the background of a previous coronavirus disease and patients with newly diagnosed T2D and different BMI before COVID-19 and comparison groups consisting of a group of normoglycemic people after COVID-19 with different BMI after a previous coronavirus disease, that is, recruited in the pre-pandemic period, are presented in Table 1.

Table 1

Clinical and laboratory parameters of the total number of patients with newly diagnosed T2D with different BMI in pre- and post-COVID period and healthy normoglycemic people with different BMI in pre-and post-COVID

Clinical and laboratory parameters	Normoglycemic people with different BMI n=181		P1	Patients with the debut of T2D with different BMI n=192		P2	P3	P4
	After COVID n=93	Without COVID n=88		After COVID n=98	Without COVID n=94			
Age. years	52 (42-71)	51 (40-67)	>0.05	54 (44-73)	53 (41-72)	>0.05	>0.05	>0.05
BMI. kg/m^2	24.93±0.58	24.13±0.12	>0.05	30.89±0.16	30.43±0.27	>0.05	<0.05	<0.05
HbA1c. %	5.34±0.07	5.23±0.06	>0.05	8.2±0.06	7.89±0.03	>0.05	<0.05	<0.05
SBP. mmHg	128.34±2.73	127.54±1.67	>0.05	148.16±2.85	145.43±1.12	>0.05	<0.05	<0.05
Cholesterol. mmol/l	4.90 (4.50 -5.20)	4.40 (4.00 -4.90)	>0.05	5.68 (4.10-5.72)	5.30 (4.79 5.80)	>0.05	<0.05	<0.05
Triglycerides. mmol/l	1.30 (1.10 -2.26)	1.15 (1.10-2.26)	>0.05	2.34 (1.14-3.30)	2.16 (1.12-3.30)	>0.05	<0.05	<0.05
Low-density lipoproteins. mmol/l	2.4 (0.7 — 3.0)	2.95 (0.90 — 3.0)	>0.05	3.12 (0.84-3.32)	3.09 (0.86-3.40)	>0.05	<0.05	<0.05
High-density lipoproteins. mmol/l	1.45 (1.30 — 1.60)	1.80 (1.68-1.95)	>0.05	1.12 (0.84-1.55)	1.34 (0.85-1.57)	>0.05	<0.05	<0.05

Notes: P1 — between groups of normoglycemic people in post-COVID and pre-COVID periods;
P2 — between patients with the debut of T2D in post-covid and pre-covid periods;
P3 — between normoglycemic individuals and patients with the debut of T2D in post- COVID period;
P4 — between normoglycemic individuals and patients with the debut of T2D in the pre-COVID period.

The results of the examination of patients with newly diagnosed T2D presented in Table 1 indicate a probable increase in BMI, glycosylated hemoglobin levels, some lipid profile parameters, and systolic blood pressure compared to healthy normoglycemic individuals. The results of the examination of groups of patients with the onset of T2D in the pre- and post-COVID periods and the examination of groups of normoglycemic individuals in the post- and pre-COVID periods did not differ significantly for any of the parameters examined. Conversely, differences in the parameters examined between groups of patients with newly diagnosed T2D with different BMI in the pre- and post-COVID periods and healthy normoglycemic individuals with different BMI in the pre- and post-COVID periods were probable.

When studying the leukocyte composition (Table 2), it was found that in patients with newly diagnosed T2D in the pre-COVID period, statistically significant leukocytosis was detected compared to the group of normoglycemic people in the pre-COVID period, which is consistent with the data of other authors [14].

The results of the study of patients with the onset of T2D in the post-COVID period compared to normoglycemic individuals with different BMI, who were examined in the post-COVID period, revealed a significant increase in the total leukocyte count, which is also consistent with the results of some studies [15]. The greatest increase in leukocyte count was observed in the group of patients with the onset of T2D in the post-COVID period compared to the group of patients with newly diagnosed T2D in the pre-COVID period, which is consistent with the data of other authors [16]. As can be seen from Table 2, leukocytosis in the two groups of patients with the debut of T2D compared to that in the two groups of normoglycemic individuals was due to a significant increase in the number of neutrophils. The neutrophilosis level in patients with the debut of T2D in the pre- and post-COVID periods indicates an increase in the number of neutrophils in the post-COVID period, both relative and absolute. Thus, the study results established that the debut of T2D with different BMI in the post-COVID period is characterized by significant, reliable neutrophilosis. Similar changes were observed in monocytes in patients of two groups with the debut of T2D compared with those in two groups of normoglycemic individuals. Monocytosis was due, as shown in Table 2, to a significant increase in the number of monocytes in both the post- and pre-COVID periods. An increase in monocytes was also detected in normoglycemic individuals during similar periods. When studying the level of monocytosis between the groups of patients with the debut of T2D in the post- and pre-COVID periods, an increase in the number of monocytes was found in the post-COVID period. When studying the level of lymphocytes in two groups of patients with the debut of T2D compared with those in the two groups of normoglycemic individuals, a significant decrease in the number of lymphocytes was found, as shown in Table 2. However, the maximum decrease in the lymphocyte count was determined in patients with the debut of T2D in the post-COVID

Table 2

The total number of leukocytes, leukocyte composition and NLR index in patients with newly diagnosed T2D with different BMI in pre- and post-COVID periods and healthy normoglycemic people with different BMI in pre- and post-COVID patients (M±m)

Leukocyte composition	Normoglycemic people with different BMI n=181		P1	Patients with T2D debute with different BMI n=192		P2	P3	P4
	After COVID n=93	Without COVID n=88		After COVID n=98	Without COVID n=94			
Leukocytes. 10^9/l	8.36±0.13	6.16±0.27	<0.001	10.16±0.34	7.32±0.16*	<0	<0.05	<0.001
Neutrophils. %	66.33±1.02	58.37±1.12	<0.001	70.82±0.79	62.44±1.35	<0.001	<0.001	<0.05
Neutrophils. 10^9/l	5.54±0.17	3.56±0.16	<0.001	7.20±0.12	4.20±0.16	<0.001	<0.05	<0.001
Eosinophils. %	1.06±0.13	2.01±0.25	<0.001	1.46±0.16	1.75±0.12	<0.001	<0.001	>0.05
Eosinophils. 10^9/l	0.34±0.01	0.18±0.01	<0.001	0.15±0.03	0.17±0.01	<0.001	<0.001	>0.05
Basophils. %	0.18±0.05	0.29±0.03	<0.05	0.32±0.09	0.43±0.09	<0.05	<0.05	<0.05
Basophils. 10^9/l	0.01±0.00	0.02±0.01	>0.05	0.03±0.01	0.03±0.01	>0.05	<0.05	<0.05
Monocytes. %	9.27±0.18	7.36±0.39	<0.001	10.70±0.28	9.26±0.21	<0.001	<0.001	<0.001
Monocytes. 10^9/l	0.77±0.03	0.45±0.05	<0.001	1.06±0.02	0.68±0.02	<0.001	<0.001	<0.001
Lymphocytes.%	21.89±1.17	31.09±1.13	<0.001	16.70±0.64	26.78±0.63	<0.001	<0.001	<0.001
Lymphocytes. 10^9/l	1.83±0.03	1.92±0.09	>0.05	1.69±0.08	1.94±0.06	<0.05	<0.05	<0.05

Notes: P1 — between groups of normoglycemic people in post- and pre-COVID periods; P2 — between patients with the debut of T2D in post- and pre-COVID periods; P3 — between normoglycemic individuals and patients with the debut of T2D in post-COVID period; P4 — between normoglycemic individuals and patients with the debut of T2D in the pre-COVID period.

period compared to the group of patients with the debut of T2D in the pre-COVID period. Thus, the results of the study established that the debut of T2D with different BMI in the post-COVID period is accompanied by significant lymphocytopenia, which is due to the immunosuppressive effect of both the onset of T2D and newly diagnosed T2D, in contrast to patients with the debut of T2D with different BMI in the pre-COVID period, in which lymphocytopenia is due only to the presence of low-grade inflammation, which is a key feature of the onset of T2D in the pre-COVID period. The results of the study also established that the onset of T2D with different BMI in the post-COVID period is associated with a significant increase in the VNL index, which is a marker of the maximum increase in the level of systemic inflammation in patients with the onset of T2D against the background of post-COVID, which is also consistent with the results of publications of other authors [16].

Our data obtained during a flow cytometric study of the immunophenotype of blood lymphocytes (CD3+ T-, CD4+ T-, CD8+ T-, CD20+-, and CD56+-cells) revealed that a significant decrease in most subsets of these cells is characteristic of the group of patients with newly diagnosed T2D in the post-COVID period. This is similar to the group of patients diagnosed with T2D in the pre-COVID period and, accordingly, the groups of normoglycemic individuals in the pre-COVID and post-COVID periods, which is currently included in the concept of the pathogenetic development of T2D in the post-COVID period, in which the most vulnerable is the chain of innate immunity, which is most damaged at the debut of T2D against the background of a previous coronavirus disease (Table 3).

The data obtained in this study are consistent with the results of studies on this issue by other authors [17, 18, 19]. When dividing the entire examined cohort of patients with newly diagnosed T2D both in the pre-COVID and post-COVID periods into four subgroups depending on BMI: < 25.0 kg/m^2, 25.0–29.9 kg/m^2, 30–34.9 kg/m^2, 35 kg/m^2 of the CD3+T, CD4+T, CD8+T, and CD56+T lymphocyte subpopulations. The studies conducted, as shown in Table 4, demonstrated that in patients with the onset of T2D and different BMI in the pre-COVID period, the levels of all studied T-lymphocyte subpopulations were sharply increased. The greatest changes in subpopulation composition were observed in patients with onset of T2D and a BMI greater than 35 kg/m^2. In patients with newly diagnosed T2D and varying BMI, the post-COVID period showed a completely opposite relationship: the levels of all studied T-lymphocyte subpopulations were sharply reduced, compared to normoglycemic individuals in both the post-COVID and pre-COVID periods, as well as in patients in the pre-COVID period. The degree of this reduction likely correlated with the progressive increase in BMI (Table 4).

Discussion Thus, the conducted studies have established that for patients with the debut of T2D and different BMI in post-COVID period, compared to patients with newly diagnosed T2D and different BMI in pre-COVID period, are characteristic probable significant leukocytosis (an increase in the total number of leukocytes by almost 1.5 times, $p < 0.001$), neutrophilosis (an increase in the absolute number of neutrophils by almost 2.0 times, $p < 0.001$), monocytosis (an increase in the absolute number of monocytes by almost

Table 3

Relative and absolute number of lymphocytes of different immunophenotypes in patients with newly diagnosed DM2 with different BMI in the post-COVID and pre-COVID periods and healthy normoglycemic people with different BMI after COVID and without previous coronavirus disease (M±m)

Immunopheno-type of CD lymphocytes	Normoglyce-mic people in the pre-COVID period	Patients with T2D in the pre-COVID period	P4	Normoglyce-mic people in the post-COVID period	Patients with T2D in the post-COVID period	P3	P1	P2
1. CD3+T-cells (%)	56.91±0.41	58.69±0.57	<0.05	55.12±0.21	54.02±0.16	<0.05	<0.05	<0.05
2. CD3+T-cells (10^9/l)	1.07±0.01	1.13±0.03	<0.05	1.01±0.02	0.86±0.03	<0.05	>0.05	<0.05
3. CD4+T-cells (%)	36.49±0.41	39.94±0.58	<0.05	35.27±0.31	31.37±0.18	<0.05	<0.05	<0.05
4. CD4+T-cells (10^9/l)	0.69±0.01	0.88±0.02	<0.05	0.64±0.01	0.59±0.03	<0.05	<0.05	<0.05
5. CD8+T-cells (%)	22.08±0.41	23.79±0.53	<0.05	21.03±0.12	19.31±0.53	<0.05	<0.05	<0.05
6. CD8+T-cells (10^9/l)	0.41±0.03	0.48±0.02	<0.05	0.39±0.01	0.36±0.01	<0.05	<0.05	<0.05
7. CD20+T-cells (%)	10.51±0.25	11.55±0.23	<0.05	9.12±0.21	8.15±0.31	<0.05	<0.05	<0.05
8. CD20+T-cells (10^9/l)	0.20±0.02	0.22±0.01	>0.05	0.18±0.01	0.15±0.01	<0.05	>0.05	<0.05
9. CD56+T-cells (%)	10.21±0.21	11.34±0.28	<0.05	9.10±0.13	8.02±0.10	<0.05	<0.05	<0.05
10. CD56+T-cells (10^9/l)	0.20±0.03	0.25±0.01	<0.05	0.17±0.01	0.14±0.01	<0.05	<0.05	<0.05

Notes: P1 — between groups of normoglycemic people in the post-Covid and pre-Covid periods; P2 — between patients with the debut of DM2 in the post-Covid and pre-Covid periods; P3 — between normoglycemic people and patients with the debut of DM2 in the post-Covid period; P4 — between normoglycemic people and patients with the debut of DM2 in the pre-Covid period.

Table 4

Relative (%) and absolute (109/l) number of lymphocytes of different immunophenotypes (CD) in the PB of patients with newly diagnosed T2D depending on BMI in the pre- and post-COVID periods

CD	BMI in patients with newly diagnosed type 2 mellitus							
	pre-Covid				post-Covid			
	<25.0 kg/m²	25.0–29.9 kg/m²	25.0–29.9 kg/m²	Over 35.0 kg/m²	<25.0 kg/m²	25.0–29.9 kg/m²	30.0–34..9 kg/m²	Over 35.0 kg/m²
1.	56.99±0.34	57.97±0.42*	58.94±0.54#	60.88±0.35g	55.01±0.12a	54.03±0.01**b	53.07±0.16##c	52.13±0.27ggd
2.	1.06±0.01	1.12±0.01	1.15±0.01#	1.30±0.05g	1.00±0.03a	0.91±0.01**b	0.84±0.02##c	0.73±0.03ggd
3.	36.37±0.15	37.52±0.12*	42.61±0.13#	43.27±0.16g	35.15±0.14a	34.05±0.25**b	29.12±0.15##c	27.17±0.12ggd
4.	0.73±0.03	0.82±0.01*	0.94±0.02#	1.07±0.01g	0.67±0.01a	0.61±0.03**b	0.57±0.01##c	0.51±0.02ggd
5.	23.01±0.12	23.42±0.10*	24.16±0.15#	24.57±0.13g	21.04±0.15a	20.01±0.21**b	19.06±0.10##c	17.16±0.15ggd
6.	0.44±0.01	0.46±0.01*	0.49±0.01#	0.54±0.02g	0.41±0.01a	0.38±0.01**b	0.34±0.01##c	0.31±0.01ggd
7.	10.03±0.15	11.01±0.21*	12.04±0.54#	13.03±0.19g	9.78 ±0.10a	8.71±0.32**b	7.63±0.31##c	6.46±0.13ggd
8.	0.22±0.01	0.21±0.03	0.20±0.02	0.26±0.04g	0.17±0.02a	0.15±0.01b	0.14±0.01c	0.13±0.03d
9.	10.25±0.25	10.98±0.12*	11.41±0.13#	12.63±0.27g	9.01±0.12a	8.51±0.27**b	7.99±0.10##c	6.58±0.12ggd
10.	0.23±0.01	0.24±0.01*	0.27±0.01#	0.31±0.02g	0.19±0.01a	0.16±0.01**b	0.13±0.01##c	0.10±0.01ggd

Notes: * — P1 < 0.05 — between patients with the debut of T2D with BMI < 24.9 kg/m² and patients with the debut of T2D with BMI ≥ 25.0 kg/m² to ≤ 29.9 kg/m² in the pre-COVID period; # — P2 < 0.05 — between patients with the debut of T2D with BMI 25.0 kg/m² — ≤ 29.9 kg/m² and patients with the debut of T2D with BMI 30.0 kg/m² to ≤ 34.9 kg/m² in the pre-COVID period; g — P3 < 0.05 — between patients with the debut of T2D with BMI 30.0 kg/m² — ≤ 34.9 kg/m² and patients with the debut of T2D with BMI ≥ 35.0 kg/m² in the pre-COVID period; ** — P4 < 0.05 — between patients with the debut of T2D with BMI<24.9 kg/m² and patients with the debut of T2D with BMI ≥ 25.0 kg/m² to ≤29.9 kg/m² in post-COVID period; ## — P5 < 0.05 — between patients with the debut of T2D and BMI from 25.0 kg/m² — ≤29.9 kg/m² and patients with the debut of T2D with BMI30.0 kg/m² to ≤.34.9 kg/m² in post-COVID period; gg — P6 < 0.05– between patients with the debut of T2D and BMI 30.0 kg/m² — ≤.34.9 kg/m² and patients with the debut of T2D and BMI — ≥ 35.0 kg/m² in post-COVID period; a — P7 < 0.05 — between patients with the debut of T2D and BMI<24.9 kg/m² in pre-COVID period and patients with the debut of T2D with BMI<24.9 kg/m² in pre-COVID period; b — P8 < 0.05 — between patients with the debut of T2D with BMI from 25.0 kg/m² — ≤29.9 kg/m² in post-COVID period and patients with the debut of T2D with BMI from 25.0 kg/m² — ≤29.9 kg/m² post-COVID period; c — P9 < 0.05 — between patients with the debut of T2D with BMI 30.0 kg/m² — ≤.34.9 kg/m² in post-COVID period and patients with the debut of T2D with BMI 30.0 kg/m² — ≤.34.9 kg/m² in pre-COVID period; d- P10 < 0.05– between patients with the debut of T2D with BMI >35 kg/m² in post-COVID period and patients with the debut of T2D with BMI >35 kg/m² in pre-COVID period.

2.0 times, p < 0.001). lymphopenia (a decrease in the relative number of lymphocytes by almost 2.0 times., p < 0.001), and an increase in the VNL inflammatory index by more than 2.0 times (p < 0.001), which indicates a total increase in the level of systemic inflammation in patients with the debut of type T2D after coronavirus disease. The results of the study demonstrate that at the debut of T2D in the pre-COVID period, an increase in almost all lymphocyte subsets is detected, with the exception of CD20+. The obtained results are consistent with both our previous data and the data of other authors, who also found elevated rates of leukocytosis, neutrophilosis, monocytosis and an increase in the VNL inflammatory index, which together are markers of low-gradient systemic inflammation [20, 21]. In contrast, according to our study, in a cohort of patients with newly diagnosed T2D with different BMI in the post-COVID period, a progressive decrease in all lymphocyte subsets was observed against the background of sharply increased indicators of leukocytosis, neutrophilosis, monocytosis, the VNL inflammatory index, and lymphocytopenia. Thus, our data may explain the extremely high level of inflammation combined with a decrease in the lymphocyte immunophenotype in patients with the debut of T2M with different BMI in the post-COVID period. These processes may be explained by the fact that in patients with the debut of T2D in the post-COVID period, there is a layering of inflammatory on existing systemic low-grade inflammation, accompanied by an immunosuppressive state inherent to the disease, as shown by our data [22, 23] and data from other authors [24, 25]. It is this combination of hyperinflammation and immunosuppression that may explain the more complicated course of COVID, observed specifically in patients with T2D [26]. Our findings fully support the current concept that newly diagnosed T2D with different BMI is a disease based on low-grade inflammation, which underlies both T2D and overweight/obesity. In patients with the debut of T2D with different BMI in the post-COVID period, there

is a layering of inflammatory processes in combination with immunosuppression, which leads to an increase in the imbalance between pro-inflammatory and anti-inflammatory T-lymphocyte subpopulations, which leads to a further increase in the pathologically impaired immune status, in particular, CD4+ T-cells, which causes a more severe clinical course of the disease and increases the risk of developing comorbid complications.

Conclusions

Changes in leukocyte composition, namely the level of leukocytosis, neutrophilosis, monocytosis, lymphocytopenia, and the VNL index in patients with debut of T2D, depend not only on BMI but are also due to the systemic inflammatory state of the post-COVID-19 background, which enhances low-grade chronic inflammation, which is the pathogenetic basis for the onset of type 2 diabetes. Patients with newly diagnosed T2D in the post-COVID-19 period are characterized by a decrease in the content of most lymphocyte subsets in the peripheral blood, which is most pronounced in patients with concomitant obesity. This indicates the immunosuppressive effect of coronavirus disease on the immune system in patients with debut of T2D with various BMI in the post-COVID-19 period. Thus, based on an analysis of the results of our own research and literature data, we can conclude that changes in the immunological phenotype detected in patients with the debut of T2D and various BMI in the pre-COVID period are due to the combination of T2D and overweight/obesity, and in patients with newly diagnosed T2D in the post-COVID period, this classic combination is also accompanied by an immunosuppressive state of cellular immunity [27]. Taking this into account, today, the choice of the most effective drugs for the treatment of patients with the onset of T2D with different BMI in the post-COVID period, as demonstrated by the data of our study, should be considered those that, in addition to the hypoglycemic effect, also have a powerful immunomodulatory effect on the state of the immunophenotype of blood lymphocytes in patients with newly diagnosed T2D with different BMI in the post-COVID period against the background of post-COVID.

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