DYNAMIC CHANGES OF INFLAMMATORY MARKERS IN THE EARLY STAGES OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

Osikov MV[1,2], Efros LA[1,2], Zhuravleva LYu[1,2] ✉, Fedosov AA[3]

[1] South Ural State Medical University, Chelyabinsk, Russia

[2] Chelyabinsk Regional Clinical Hospital, Chelyabinsk, Russia

[3] Peoples' Friendship University of Russia, Moscow, Russia

Diabetes mellitus (DM) is one of the major factors contributing to the development and aggravation of chronic kidney disease (CKD). The accurate and convenient markers for early detection, estimation of progression, and adequate control of CKD therapy in individuals with DM are limited to glomerular filtration rate (GFR) and albuminuria. Given the role of chronic inflammation in the pathogenesis of DM and CKD, the study aimed to assess indicators of inflammation and the correlation of those with GFR in patients with type 1 DM (T1D) and early stage CKD. The study involved healthy individuals (n = 14), patients with T1D showing no signs of CKD (n = 30), as well as patients with T1D and stage 1 CKD (n = 60), stage 2 CKD (n = 38), and stage 3 CKD (n = 31). GFR was calculated using the formula CKD-EPI (eGFR); serum levels of IL1β and TNFα, C-reactive protein (CRP), and ceruloplasmin (CP) were determined by enzyme immunoassay; the neutrophil-to-lymphocyte index and the leukocyte intoxication index (LII) were calculated. It has been found that serum concentrations of IL1β, TNFα, CRP, and CP are elevated; LII and the neutrophil-to-lymphocyte index are increased. The inflammation and acute phase response severity progresses and reaches its maximum in stage 3b CKD, when the serum concentration of IL1β is increased 2.4-fold (p = 0.042), TNFα concentration by 34% (p = 0.005), CRP concentration 33-fold (p < 0.000), CP concentration by 73% (p = 0.008), LII 8.4-fold (p < 0.000), neutrophil-to-lymphocyte index 5-fold (p = 0.013). The integral kidney function indicator, eGFR, decreases with increasing serum levels of the above indicators. Thus, IL1β, TNFα, CRP, CP, LII, and the neutrophil-to-lymphocyte index can be considered as affordable and informative indicators for estimation of inflammation, the levels of which increase with progression of early stage CKD in patients with T1D.

Keywords: type I diabetes mellitus, chronic kidney disease, progression, C-reactive protein, ceruloplasmin, IL1β, TNFα, neutrophils

Author contribution: Osikov MV, Efros LA — study planning, developing the study concept and design, literature review, data interpretation, manuscript draft writing; Zhuravleva LYu — data acquisition, statistical processing, and interpretation, manuscript writing; Fedosov AA — literature review, data interpretation, manuscript writing.

Compliance with ethical standards: the study was approved by the Ethics Committee of the South Ural State Medical University (protocol No. 5 dated 10 June 2024) and conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

✉ **Correspondence should be addressed:** Lyudmila Yu. Zhuravleva
Vorovsky, 70 (Medgorodok), korp. 8, 454048, Chelyabinsk, Russia; milana_1610@mai.ru

Received: 24.10.2024 **Accepted:** 25.11.2024 **Published online:** 21.12.2024

DOI: 10.24075/brsmu.2024.060

ДИНАМИКА МАРКЕРОВ ВОСПАЛЕНИЯ НА НАЧАЛЬНЫХ СТАДИЯХ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК ПРИ САХАРНОМ ДИАБЕТЕ 1-ГО ТИПА

М. В. Осиков[1,2], Л. А. Эфрос[1,2], Л. Ю. Журавлева[1,2] ✉, А. А. Федосов[3]

[1] Южно-Уральский государственный медицинский университет Министерства здравоохранения Российской Федерации, Челябинск, Россия

[2] Челябинская областная клиническая больница, Челябинск, Россия

[3] Российский университет дружбы народов имени Патриса Лумумбы, Москва, Россия

Сахарный диабет (СД) — один из основных факторов, способствующих развитию и усугублению хронической болезни почек (ХБП). Точные и удобные маркеры для раннего выявления, оценки прогрессирования и надлежащего контроля терапии ХБП у лиц с СД ограничены показателями скорости клубочковой фильтрации (СКФ) и альбуминурией. В связи с ролью хронического воспаления в патогенезе СД и ХБП целью работы было изучить показатели воспалительного процесса и их взаимосвязь с СКФ у больных СД 1-го типа (СД1) при ранних стадиях ХБП. В исследовании участвовали здоровые люди (n = 14), больные СД1 без признаков ХБП (n = 30), а также больные СД1 с 1-й стадией ХБП (n = 60), 2-й стадией ХБП (n = 38) и 3-й стадией ХБП (n = 31). СКФ рассчитывали по формуле CKD-EPI (рСКФ), в сыворотке иммуноферментным методом определяли концентрацию IL1β и TNFα, С-реактивного белка (С-РБ), а также концентрацию церулоплазмина (ЦП), рассчитывали индекс нейтрофилы/лимфоциты, лейкоцитарный индекс интоксикации (ЛИИ). Установлено, что в сыворотке повышается концентрация IL1β, TNFα, С-РБ и ЦП, увеличивается ЛИИ, индекс нейтрофилы/лимфоциты. Выраженность воспалительного процесса и острофазового ответа прогрессирует и максимальна при 3б стадии ХБП, когда концентрация в сыворотке IL1β увеличивается в 2,4 раза (p = 0,042), TNFα — на 34% (p = 0,005), С-РБ — в 33 раза (p < 0,000), ЦП — на 73% (p = 0,008), ЛИИ — в 8,4 раза (p < 0,000), индекс нейтрофилы/лимфоциты — в 5 раз (p = 0,013). Интегральный показатель функции почек рСКФ снижается по мере увеличения содержания в сыворотке вышеперечисленных показателей. Таким образом IL1β, TNFα, С-РБ, ЦП, ЛИИ и индекс нейтрофилы/лимфоциты можно считать доступными и информативными показателями оценки воспалительного процесса, возрастающими по мере прогрессирования начальных стадий ХБП у больных СД1.

Ключевые слова: сахарный диабет 1-го типа, хроническая болезнь почек, прогрессирование, С-реактивный белок, церулоплазмин, IL1β, TNFα, нейтрофилы

Вклад авторов: М. В. Осиков, Л. А. Эфрос — планирование исследования, разработка концепции и дизайна исследования, анализ литературы, интерпретация данных, подготовка черновика рукописи; Л. Ю. Журавлева — сбор данных, статистическая обработка, интерпретация данных, подготовка рукописи; А. А. Федосов — анализ литературы, интерпретация данных, подготовка рукописи.

Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБОУ ВО ЮУГМУ Минздрава России (протокол № 5 от 10 июня 2024 г.); проведено в соответствии со стандартами надлежащей клинической практики и принципами Хельсинкской декларации.

✉ **Для корреспонденции:** Людмила Юрьевна Журавлева
ул. Воровского, 70 (Медгородок), корпус 8, 454048, г. Челябинск, Россия; milana_1610@mai.ru

Статья получена: 24.10.2024 **Статья принята к печати:** 25.11.2024 **Опубликована онлайн:** 21.12.2024

DOI: 10.24075/vrgmu.2024.060

Diabetes mellitus (DM) is one of the main causes of premature death from chronic non-communicable disorders; it accounts for about 1.5 million deaths annually. In 2023, the total number of patients with DM in Russia was 4.9 million or 3.31% of the population, among them 277.1 thousand had type 1 DM (T1D). Despite advances in diagnosis and treatment, the increase in the prevalence of T1D by about 2–3% a year is observed; in 2022, the prevalence was 191 cases per 100,000 population [1].

The majority of patients with T1D are in their prime work years (30–39 years); the average age of death from T1D is 53.2 years. Diabetic nephropathy is a common microvascular complication of DM, it occurs on average in 40% of affected individuals, and the rate of diabetic nephropathy associated with T1D is 50% after 10 years and 75% after 20 years [2]. According to the United Nations, chronic kidney disease (CKD) requires special attention and represents one of the indicators of progress in achieving global goals of reducing premature mortality from non-communicable diseases by 2030 [1, 3]. The importance of risk factor detection aimed at CKD progression prevention is emphasized considering the growing influence of CKD on public health [4]. It has been proven that targeted interventions in early-stage CKD associated with T1D effectively prevent kidney failure progression and improve treatment outcomes in patients; regular CKD screening represents the basic principle of the DM patient management [5]. To date, pathogenesis of CKD associated with DM is poorly understood, it includes such mechanisms, as endothelial dysfunction, chronic inflammation and thrombosis, mitochondrial dysfunction and oxidative stress, histone hypermethylation, DNA methylation, atherogenic dyslipidemia and arterial hypertension, etc. Understanding synergetic cellular molecular mechanisms underlying DM and CKD is crucial for assessment of the DM-associated CKD progression and development of effective diagnostic and therapeutic approaches [3, 6].

Inflammation is a standard disease process underlying many disorders and syndromes, including DM and CKD. Special attention is paid to low-grade chronic systemic inflammation and its markers: pro-inflammatory cytokines (interleukin 1β (IL1β) and tumor necrosis factor α (TNFα), IL6, etc.), acute phase reactant (highly sensitive C-reactive protein (CRP), serum amyloid A, ceruloplasmin (CP), etc.) [7, 8]. Chronic inflammation is considered as a key factor of pathogenesis of macrovascular and microvascular DM complications, including CKD [9]. At the same time, in clinical settings, calculation of the white blood cell differential (increased immature neutrophils) and its derivatives (leukocyte intoxication index (LII), neutrophil-to-lymphocyte index) remains the most affordable method to assess severity of inflammatory and acute phase response, which is very informative in terms of predicting the long-term survival, mortality, as well as ranking the factors contributing to cardiovascular disorders [10]. Most information about the relationship between inflammatory markers in blood and diabetic nephropathy worsening was acquired from patients suffering from T2D, which was due to its high prevalence.

The study aimed to assess indicators of inflammation and their correlation with the glomerular filtration rate in patients with T1D and early stage chronic kidney disease.

METHODS

The study was conducted at the Chelyabinsk Regional Clinical Hospital. The study involved females aged 18–54, males aged 18–60. Inclusion criteria: 1) having T1D for more than 6 months in accordance with the national clinical guidelines [11]; 2) informed consent to participation in the study. Exclusion criteria: 1) age over 60; 2) eGFR ≤ 29 mL/min/1.73 m^2; 2) T2D or other endocrine disorder; 3) severe concomitant diseases of the liver, lung, tuberculosis, rheumatic diseases, autoimmune kidney diseases, postmenopausal osteoporosis, cancer; 4) taking glucocorticoids, cytostatics, vitamin D products, phosphate binders; 5) patients with inflammatory diseases affecting kidneys and other organs and systems. Group 1 is represented by clinically healthy individuals matched by age and sex to the index group (n =14): 42.9% males, 57.1% females, average age 30.6 ± 4.2 years, body mass index, systolic and diastolic blood pressure, lipid profile within normal. Group 2 includes patients with T1D showing no signs of CKD (n = 30). Group 3 is represented by patients with T1D showing signs of CKD (n = 129), including stage 1 CKD (group 3.1; n = 60), stage 2 CKD (group 3.2; n = 38), stage 3a CKD (group 3.3; n = 21), stage 3b CKD (group 3.3; n = 10). CKD was staged in accordance with the national clinical guidelines [12]. At admission, the patients had compensated (n = 12; 7.5%), subcompensated, and decompensated T1D; compensation was achieved against the background of therapy in hospital settings; the inflammatory markers were collected before discharge (n = 147; 92.5%). Clinical characteristics of the groups of patients with T1D having and not having CKD are provided in Table 1.

Analysis of the results showed that the group of patients with CKD showed significantly lower eGFR compared to patients with no CKD (p = 0.037). In patients with CKD, the diabetes duration was 13 years, while in the group of patients with no CKD this indicator was significantly lower (p = 0.000). We revealed significant differences in the average glycated hemoglobin levels in patients having and not having CKD (9.8% and 8.1%, respectively). The average systolic and diastolic blood pressure was higher in the group of patients with CKD (p = 0.000); higher total cholesterol levels were reported for the group of patients with CKD (p = 0.035).

Analysis of the results showed that the DM duration was longer in patients with stage 1 CKD compared to patients with no CKD (p < 0.001). The average systolic blood pressure turned out to be significantly higher in the group of patients with stage 1 CKD (p = 0.001). Patients with T1D and stage 2 CKD had lower eGFR compared to patients with no CKD (p = 0.000). The diabetes duration was longer in patients with stage 2 CKD (p = 0.000). Patients with stage 2 CKD had significantly higher average glycated hemoglobin (p = 0.012) and average total cholesterol (p = 0.007) levels. The average systolic and diastolic blood pressure in the group with stage 2 CKD turned out to be significantly higher compared to the group with no CKD (p = 0.001 and p < 0.001). Significant differences were revealed when comparing the groups of patients with stage 3 CKD and no CKD. The average age was higher in the group of patients with stage 3 CKD (p = 0.015). Longer diabetes duration was reported for patients with stage 3 CKD (p = 0.001). The average systolic and diastolic blood pressure turned out to be higher in the group of patients with stage 3 CKD (p < 0.001), the glycated hemoglobin levels were higher in patients with stage 3 CKD (p = 0.010). The results of comparative analysis of the group of patients with stage 2 CKD and the group of patients with stage 3 CKD showed a significant decrease in glomerular filtration rate (p < 0.001).

Albuminuria indicators, as CKD markers, are provided in Table 2.

It was found that patients with stage 1 CKD more often had stage A1 albuminuria (p = 0.031), while patients with stage 3a and 3b stage CKD more often had stage A3 albuminuria (p = 0.022).

Table 1. Clinical characteristics and comparative analysis of the groups of patients with T1D having and not having CKD (n = 159)

Indicator		Group with CKD (n = 129)	Group without CKD (n = 30)	p
Sex, abs. (%)	Males	47 (36.4)	12 (40.0)	0.834
	Females	82 (63.6)	18 (60.0)	
Age, years, Me [Q_1; Q_3]		32.0 [25.0; 40.0]	26.0 [22.0; 30.0]	0.001*
Body mass index, kg/m^2, Me [Q_1; Q_3]		23.7 [21.0; 26.0]	22.7 [20.0; 24.3]	0.163
Systolic blood pressure, mm Hg, Me [Q_1; Q_3]		150.0 [110.0; 160.0]	110.0 [100.0; 110.0]	0.000*
Diastolic blood pressure, mm Hg, Me [Q_1; Q_3]		90.0 [70.0; 90.0]	70.0 [60.0; 70.0]	0.000*
Glomerular filtration rate, mL/min/1.73 m^2, Me [Q_1; Q_3]		87 [62.0; 111.0]	121.0 [96.0; 124.0]	0.000*
Diabetes duration, years, Me [Q_1; Q_3]		13 [8.0; 20.0]	4.0 [2.0; 8.0]	0.000*
Glycated hemoglobin, %, Me [Q_1; Q_3]		9.8 [8.5; 11.6]	8.1 [7.6; 8.8]	0.000*
Total cholesterol, mmol/L, Me [Q_1; Q_3]		5.2 [4.2-6.3]	4.5 [4.1; 5.5]	0.035*
Triglycerides, mmol/L, Me [Q_1; Q_3]		1.3 [0.8; 1.8]	1.1 [0.8; 1.6]	0.388
LDL cholesterol, mmol/L, Me [Q_1; Q_3]		3.0 [2.2; 4.0]	2.9 [2.1; 3.5]	0.34
LDL cholesterol, mmol/L, Me [Q_1; Q_3]		0.58 [0.35; 0.76]	0.57 [0.40; 0.69]	0.631

Note: * — significant intergroup differences ($p < 0.05$). Categorical indicators were compared using the Pearson's chi-squared test (χ^2), Mann–Whitney U test was used in other cases.

To calculate GFR using the formula CKD-EPI (eGFR), we determined serum creatinine concentrations by the kinetic colorimetric method using the Cobas Integra 400 analyzer (Switzerland) [2]. Total white blood cell counts were determined using the CoulterLH 500 hematology analyzer (BeckmanCoulter; USA), while the white blood cell differential was determined by microscopy of the Romanowsky–Giemsa-stained blood smears involving enumeration of 200 cells. The leukocyte intoxication index (LII) was calculated using the following formula:

$$\frac{4 \times \text{myelocytes} + 3 \times \text{immature} + 2 \times \text{band} + \text{segmented neutrophils} \times (\text{plasma cells} + 1)}{\text{lymphocytes} + \text{monocytes} \times (\text{eosinophils} + 1)}$$ [13].

Moreover, we determined the ratio of the quantities of all neutrophil and lymphocyte populations in blood (neutrophils/lymphocytes). Serum IL1β and TNFα concentrations were determined using the Personal LAB automated ELISA testing platform (Adaltis Italia; Italy) and the Vector-Best test systems (Novosibirsk); the results were expressed in pg/mL. Serum concentrations of the highly sensitive CRP were determined using the ChemWell 2910 automated ELISA testing system (Awareness Technology; USA) and the Vector-Best test system (Novosibirsk); the results were expressed in IU/L. Serum concentrations of ceruloplasmin (CP) were determined using the SF-56 spectrophotometer (LOMO-Spectrum; Russia) by the modified method by Revin based on p-phenylenediamine oxidation; the results were expressed in mg/L [14]. The results obtained were processed using the IBM SPSS Statistics v. 23 software package (SPSS: An IBM Company; USA). The quantitative indicator distribution in the group of patients with stage 1 CKD was tested for normality using the Kolmogorov–Smirnov test, while in the groups with stage 2, 3a and 3b CKD, as well as in healthy individuals and patients with no CKD, the Shapiro–Wilk test was used for this purpose. The data are presented as Me (Q_1; Q_3), where Me is the median, Q_1 and Q_3 are the lower (25) and upper (75) quartiles, respectively. Verification of statistical hypotheses in the groups was performed using the Mann–Whitney U test. Spearman's rank correlation coefficient (R) was used to reveal correlations between the studied parameters, and the Chaddock scale was used to estimate the correlation strength.

RESULTS

The eGFR values for the studied groups of patients are provided in Table 3. It has been found that eGFR significantly increases in the group of patients with T1D showing no signs of CKD (group 2) compared to the group of healthy individuals and naturally decreases in the group of patients with CKD (group 3). Furthermore, the increase in group 2 is 17% based on the median relative to the values of the group of healthy individuals, while there is a decrease by 10% in group 3.1 (stage 1 CKD), by 28% in group 3.2 (stage 1 CKD), by 46% in group 3.3 (stage

Table 2. Albuminuria indicators in patients with T1D and CKD, abs. (%)

Albuminuria stage	Group 3				p
	Stage 1 CKD (3.1)	Stage 2 CKD (3.2)	Stage 3*a* CKD (3.3)	Stage 3*b* CKD (3.4)	
A1	24 (40.0)	13 (34.2)	6 (28.6)	0	0.031*
A2	17 (28.3)	12 (31.6)	4 (19.0)	4 (40.0)	0.649
A3	19 (31.7)	13 (34.2)	11 (52.4)	6 (60.0)	0.022*

Note: * — significant intergroup differences ($p < 0.05$). Categorical indicators were compared using the Pearson's chi-squared test (χ^2).

Table 3. eGFR (mL/min/1.73 m²) in patients with T1D and CKD, Me [Q_1; Q_3]

Healthy (group 1)	No CKD (group 2)	Group 3				*p*-values with $p < 0.05$
		Stage 1 CKD (group 3.1)	Stage 2 CKD (group 3.2)	Stage 3*a* CKD (group 3.3)	Stage 3*b* CKD (group 3.4)	
105.000 [91.000; 118.000]	123.000 [120.000; 134.000]	94.000 [92.000; 126.000]	76.000 [67.000; 78.000]	56.000 [50.000; 58.000]	37.000 [31.000; 40.000]	$p_{1-2} < 0.001$ $p_{1-3.1} < 0.001$ $p_{1-3.2} < 0.001$ $p_{1-3.3} < 0.001$ $p_{1-3.4} < 0.001$ $p_{2-3.1} = 0.016$ $p_{2-3.2} < 0.001$ $p_{2-3.3} < 0.001$ $p_{2-3.4} < 0.001$ $p_{3.1-3.2} < 0.001$ $p_{3.1-3.3} < 0.001$ $p_{3.1-3.4} < 0.001$ $p_{3.2-3.3} < 0.001$ $p_{3.2-3.4} < 0.001$ $p_{3.3-3.4} < 0.001$

Note: Mann–Whitney *U* test was used to compare the values.

3a CKD), by 65% in group 3.4 (stage 3b CKD). Moreover, eGFR is significantly decreased in groups 3.1, 3.2, 3.3, 3.4 compared to group 2. The eGFR values of the groups 3.1, 3.2, 3.3, and 3.4 match the criteria of stage 1, stage 2, stage 3a, stage 3b CKD, respectively [12]. The eGFR value of patients with stage 2 CKD is significantly different from the values of the group of patients with stage 1 CKD, the value of patients with stage 3a CKD is significantly different from the values of the group of patients with stage 1 and 2 CKD, the value of patients with stage 3b CKD is significantly different from the values of the groups of patients with stage 1, 2, and 3a CKD.

The results of assessing inflammation severity in patients with T1D and CKD are provided in Table 4. First of all, the changes in serum concentrations of pro-inflammatory cytokines should be noted. Thus, the IL1β concentration in the group of patients with T1D showing no signs of CKD significantly increased (by 31% based on the median) relative to the values of the group of healthy individuals; in the group of patients with T1D and CKD, the IL1β concentration progressively increased from stage 1 to stage 3b: by 40% based on the median relative to the group of healthy individuals in group 3.1, by 91% in group 3.2, 1.8-fold in group 3.3, and 2.4-fold in group 3.4. We revealed significant changes in serum concentrations of IL1β in patients with stage 2, 3a, and 3b CKD compared to the group of patients with T1D showing no signs of CKD and the group of patients with stage 1 CKD, as well as in individuals with stage 3a CKD compared to those with stage 2 CKD, stage 3b CKD compared to those with stage 2 and 3a CKD. Serum concentrations of TNFα were not significantly different from those of the group of healthy individuals, patients with T1D showing no signs of CKD, and patients with T1D and stage 1 and 2 CKD; in patients with T1D and stage 3a and 3b CKD, these increased by 34% based on the median. We revealed changes in serum concentrations of TNFα in patients with stage 2, 3a, and 3b CKD compared to patients with T1D showing no signs of CKD and the group of patients with stage 1 CKD, as well as in patients with stage 3b CKD compared to those with stage 2 CKD.

The severity of the acute phase response associated with T1D, including combined with CKD, was associated with the changes in the content of white blood cell populations in peripheral blood, which, in particular, was reflected in the LII and neutrophil-to-lymphocyte index changes. Thus, LII significantly increased in the groups of patients with T1D and stage 2, 3a, and 3b CKD (2.3-fold, 7.8-fold, and 8.4-fold based on the median, respectively) relative to the values of the group of healthy individuals. Moreover, LII significantly increased in the groups of patients with T1D and stage 2, 3a, and 3b CKD relative to patients with T1D showing no signs of CKD and stage 1 CKD. In patients with T1D and stage 3a and 3b CKD, LII increased relative to the group with stage 2 CKD. More prominent changes in the population spectrum of white blood cells were reported when assessing the neutrophil-to-lymphocyte index. In patients with T1D and CKD, the index significantly increased relative to the group of healthy individuals: by 22% based on the median in group 3.1, by 81% in group 3.2, 2.3-fold in group 3.3, 5-fold in group 3.4. We noted a significant increase in the neutrophil-to-lymphocyte index in patients with T1D and stage 1, 2, 3a, and 3b CKD relative to the group of patients with T1D showing no signs of CKD, as well as in patients with T1D and stage 3a and 3b CKD relative to the group of patients with T1D and stage 1 and 2 CKD; in patients with T1D and 3b stage relative to patients with 3a stage CKD. We noted the increase in the IL1β and TNFα levels with CKD progression in patients with T1D, but within normal range, which requires continuous monitoring of these indicators.

In the next phase we assessed serum concentrations of the acute phase reactants, CRP and CP (Table 5). Elevated CRP concentrations were found in patients with T1D showing no signs of CKD, as well as in patients with T1D and stage 1, 2, 3a, 3b CKD relative to the group of healthy individuals: 2.7-fold, 3.5-fold, 5.1-fold, 9.9-fold, 33-fold based on the median, respectively. In all groups of patients showing signs of CKD, serum CRP levels were increased relative to the group of patients with T1D showing no signs of CKD; in the groups with T1D and stage 3a and 3b CKD relative to those with T1D and stage 1, 2 CKD, in the group with T1D and stage 3b CKD relative to the group with T1D and stage 3a CKD. We revealed elevated serum concentrations of CP in patients with T1D showing no signs of CKD, as well as in patients with T1D and stage 1, 2, 3a, 3b CKD relative to the group of healthy individuals: by 31%, 16%, 24%, 41%, and 73% based on the median, respectively. Serum CP levels were increased in the groups with T1D and stage 3a and 3b CKD relative to the group of patients with T1D showing no signs of CKD, as well as with T1D and stage 1 CKD; in the group with T1D and stage 3a CKD relative to the group with T1D and stage 2 CKD; in the group with T1D and stage 3b CKD relative to the group with T1D and stage 3a CKD. The increase in CP levels with increasing CKD stage was reported, due to which the dynamic monitoring of this marker is necessary.

We performed analysis of the correlation between eGRF being one of the key kidney function parameters essential for

Table 4. Inflammatory markers in patients with T1D and CKD, Me [Q_1; Q_3]

Indicators	Healthy (group 1)	No CKD (group 2)	Group 3				*p*-values with $p < 0.05$
			Stage 1 CKD (3.1)	Stage 2 CKD (3.2)	Stage 3*a* CKD (3.3)	Stage 3*b* CKD (3.4)	
IL1β, pg/mL	1.724 [1.553; 2.931]	2.226 [1.410; 2.941]	2.405 [1.930; 3.600]	3.276 [2.590; 6.650]	4.879 [2.241; 7.379]	5.824 [4.793; 8.031]	$p_{1-2} = 0.021$ $p_{1-3.1} = 0.009$ $p_{1-3.2} = 0.003$ $p_{1-3.3} = 0.003$ $p_{1-3.4} = 0.029$ $p_{2-3.2} = 0.006$ $p_{2-3.3} = 0.046$ $p_{2-3.4} = 0.004$ $p_{3.1-3.2} = 0.044$ $p_{3.1-3.3} = 0.033$ $p_{3.1-3.4} = 0.042$ $p_{3.2-3.3} = 0.001$ $p_{3.2-3.4} = 0.003$ $p_{3.3-3.4} = 0.301$
TNFα, pg/mL	2.264 [1.981; 2.642]	2.170 [1.415; 3.019]	2.264 [1.604; 2.736]	2.443 [2.358; 3.113]	3.019 [2.547; 3.491]	3.019 [2.311; 3.490]	$p_{1-3.3} = 0.001$ $p_{1-3.4} < 0.000$ $p_{2-3.2} = 0.005$ $p_{2-3.3} = 0.047$ $p_{2-3.4} < 0.000$ $p_{3.1-3.2} = 0.044$ $p_{3.1-3.3} = 0.003$ $p_{3.1-3.4} = 0.005$ $p_{3.2-3.4} = 0.003$
LII, AU	0.320 [0.170; 0.690]	0.560 [0.450; 0.750]	0.485 [0.200; 0.800]	1.050 [0.690; 1.350]	2.800 [1.860; 8.700]	3.000 [1.520; 6.400]	$p_{1-3.2} = 0.004$ $p_{1-3.3} < 0.000$ $p_{1-3.4} < 0.000$ $p_{2-3.2} = 0.016$ $p_{2-3.3} < 0.000$ $p_{2-3.4} < 0.000$ $p_{3.1-3.2} = 0.027$ $p_{3.1-3.3} = 0.001$ $p_{3.1-3.4} < 0.000$ $p_{3.2-3.3} = 0.002$ $p_{3.2-3.4} = 0.008$
Neutrophils/ lymphocytes, AU	1.720 [1.020; 1.930]	1.680 [1.200; 2.100]	2.100 [1.530; 5.700]	3.160 [2.800; 3.900]	5.600 [3.200; 5.700]	10.295 [2.390; 12.680]	$p_{1-3.1} = 0.021$ $p_{1-3.2} < 0.000$ $p_{1-3.3} < 0.000$ $p_{1-3.4} < 0.000$ $p_{2-3.1} = 0.001$ $p_{2-3.2} < 0.000$ $p_{2-3.3} = 0.003$ $p_{2-3.4} = 0.001$ $p_{3.1-3.3} = 0.004$ $p_{3.1-3.4} = 0.013$ $p_{3.2-3.3} = 0.001$ $p_{3.2-3.4} = 0.002$ $p_{3.3-3.4} = 0.020$

Note: Mann–Whitney *U* test was used to compare the values.

assessment of CKD progression, CKD staging in accordance with the national and international criteria and the signs of inflammation in patients with T1D and early stage CKD (Table 6). The use of the Chaddock scale in stage 1 CKD revealed a moderate correlation with serum concentrations of TNFα, marked correlation with LII and the neutrophil-to-lymphocyte index, very strong correlation with serum concentrations of IL1β, CRP, and CP; all the correlations were negative. In stage 2 CKD, we revealed a marked correlation with serum concentrations of TNFα, strong correlation with LII and the neutrophil-to-lymphocyte index, very strong correlation with serum concentrations of IL1β, CRP, and CP; all the correlations were negative. In stage 3a CKD, we found a strong correlation with LII and serum CP concentrations, very strong correlation with serum concentrations of IL1β, TNFα, CRP and the neutrophil-to-lymphocyte index. In stage 3b CKD, we revealed a strong correlation with serum concentrations of TNFα, CRP, and CP, very strong correlation with serum concentrations of IL1β, LII and the neutrophil-to-lymphocyte index; the correlation was negative.

DISCUSSION

Assessment of eGFR showed that eGFR was increased in the group of patients with T1D showing no signs of CKD (group 2). Elevated eGFR and hyperfiltration associated with T1D (with the maximum values up to 162 mL/min/1.73 m^2) found in 10–67% of patients are considered to result from compensatory renal hypertrophy and hyperfunction in response to hyperglycemia, effects of pro-inflammatory cytokines and growth factors, local angiotensin (II), imbalance of vasoactive factors regulating pre- and postglomerular blood flow, alteration of reabsorption of sodium, glucose, and H^+ in proximal parts of the nephron [15, 16]. Currently, glomerular hyperfiltration is considered as one of the main mechanisms underlying the emergence and progression of diabetic kidney disease (DKD) [16, 17].

Pathogenesis of the signs of inflammation in the form of increased serum concentrations of IL1β, TNFα, CRP, CP, increased LII and the neutrophil-to-lymphocyte index, found by us in patients with T1D and CKD, is multifactorial [18]. The mechanism underlying formation of phlogogenic potential

Table 5. Markers, acute phase reactants, in patients with T1D and CKD, Me [Q_1; Q_3]

Indicators	Healthy (group 1)	No CKD (group 2)	Group 3				*p*-values with $p < 0.05$
			Stage 1 CKD (3.1)	Stage 2 CKD (3.2)	Stage 3*a* CKD (3.3)	Stage 3*b* CKD (3.4)	
CP, mg/L	172.050 [132.100; 217.000]	225.800 [183.800; 317.000]	200.150 [181.100; 245.000]	214.400 [198.000; 289.300]	242.300 [152.300; 245.000]	297.550 [268.400; 311.000]	$p_{1-2} = 0.014$ $p_{1-3.1} = 0.001$ $p_{1-3.2} = 0.003$ $p_{1-3.3} = 0.004$ $p_{1-3.4} = 0.029$ $p_{2-3.3} = 0.027$ $p_{2-3.4} = 0.001$ $p_{3.1-3.3} = 0.004$ $p_{3.1-3.4} = 0.008$ $p_{3.2-3.3} = 0.004$ $p_{3.2-3.4} = 0.042$ $p_{3.3-3.4} = 0.008$
CRP, IU/L	0.335 [0.280; 1.820]	1.260 [0.140; 2.300]	1.540 [1.000; 3.050]	2.050 [1.450; 3.170]	3.675 [2.800; 4.150]	11.625 [6.010; 15.395]	$p_{1-2} = 0.003$ $p_{1-3.1} = 0.041$ $p_{1-3.2} = 0.020$ $p_{1-3.3} = 0.001$ $p_{1-3.4} < 0.000$ $p_{2-3.1} = 0.021$ $p_{2-3.2} = 0.002$ $p_{2-3.3} = 0.047$ $p_{2-3.4} < 0.000$ $p_{3.1-3.4} < 0.000$ $p_{3.2-3.3} = 0.001$ $p_{3.2-3.4} = 0.001$ $p_{3.3-3.4} = 0.039$

Note: Mann–Whitney U test was used to compare the values.

in DM includes primarily hyperglycemia resulting in protein glycosylation, formation of advanced glycation end products causing tissue damage and immune cell activation, as well as the release of pro-inflammatory cytokines. Secondly, in DM, excess amounts of glucose result in the increased production of reactive oxygen species, oxidative stress, which causes further damage to the kidney cells and provokes inflammation. Thirdly, in diabetic nephropathy, hyperactivation of the renin-angiotensin system is observed that not only contributes to arterial hypertension, but also increases renal inflammation through production of pro-inflammatory cytokines, such as IL6 and TNFα. Finally, local immune response is activated in response to renal cell damage, when lymphocytes, macrophages and other cells enter the kidney tissue, secrete inflammatory mediators, thereby exacerbating kidney damage.

Activation of myeloid lineage in the bone marrow with the increase in proliferation and differentiation of precursor cells, increase in peripheral blood neutrophil (including myelocyte and metamyelocyte) counts occurs in response to the synthesis, secretion, and increase in blood levels of pro-inflammatory mediators, including the reported IL1β, TNFα. We have reported this fact in the form of the increased LII and neutrophil-to-lymphocyte index. Neutrophils represent a white blood cell population that is most common in humans; their degranulation, phagocytosis, generation of reactive oxygen and nitrogen active species, release of extracellular traps initiate and prolong inflammation, take part in the pathogenesis of myocardial ischemia, heart failure, stroke, and other disorders [19]. It is believed that neutrophil counts and functional activity are associated with chronic inflammation, development of micro- and macroalbuminuria associated with DM, while the increase in neutrophil counts in blood is an early marker of the DM-associated renal damage, DKD progression, along with microalbuminuria and eGFR, as well as shows a nonlinear relationship with the risk of death from DKD [10, 20]. According to the data provided by other researchers, the circulating neutrophil counts positively correlate with DKD-associated proteinuria [21].

The neutrophil-to-lymphocyte ratio of blood indicating systemic inflammation is associated with the prevalence of DKD

Table 6. Correlation between eGFR (mL/min/1.73 m^2) and inflammatory markers in patients with T1D and CKD

Indicators	No CKD (group 2)	Group 3			
		Stage 1 CKD (group 3.1)	Stage 2 CKD (group 3.2)	Stage 3*a* CKD (group 3.3)	Stage 3*b* CKD (group 3.4)
IL1β, pg/mL	$R = -0.576$ $p = 0.031$	$R = -0.992$ $p < 0.000$	$R = -0.922$ $p < 0.000$	$R = -0.956$ $p = 0.003$	$R = -0.916$ $p = 0.001$
TNFα, pg/mL	$R = 0.559$ $p = 0.038$	$R = -0.448$ $p = 0.002$	$R = -0.616$ $p = 0.019$	$R = -0.986$ $p < 0.000$	$R = -0.842$ $p = 0.009$
LII, AU	$R = -0.018$ $p = 0.951$	$R = -0.566$ $p < 0.000$	$R = -0.801$ $p < 0.000$	$R = -0.750$ $p = 0.003$	$R = -0.955$ $p < 0.000$
Neutrophils/lymphocytes	$R = -0.054$ $p = 0.854$	$R = -0.698$ $p = 0.045$	$R = -0.769$ $p = 0.028$	$R = -0.957$ $p < 0.000$	$R = -0.902$ $p = 0.035$
CRP, IU/L	$R = 0.581$ $p = 0.030$	$R = -0.951$ $p < 0.000$	$R = -0.911$ $p < 0.000$	$R = -0.945$ $p = 0.009$	$R = -0.849$ $p = 0.008$
CP, mg/L	$R = -0.413$ $p = 0.143$	$R = -0.927$ $p < 0.000$	$R = -0.964$ $p < 0.000$	$R = -0.846$ $p = 0.003$	$R = -0.854$ $p = 0.007$

Note: Spearman's rank correlation coefficients (*R*) are provided.

and cardiovascular disorders, all-cause mortality in DM [22, 23]. The neutrophil-to-lymphocyte index is considered as a reliable measure of the systemic inflammation severity, given the role of neutrophils as nonspecific contributors to inflammation (innate immunity) and lymphocytes as regulators of all inflammatory responses and contributors to adaptive immunity [24]. Positive correlation between the neutrophil-to-lymphocyte index and serum concentrations of IL1β and CRP has been shown [25]. The results of several meta-analyses of clinical trials have shown higher neutrophil-to-lymphocyte index values in patients with diabetic nephropathy compared to patients with DM having no kidney disease, as well as the prospects of using the index for stratification and prediction of the risk of all-cause mortality, cardiovascular mortality [21, 26, 27]. At the same time, CKD also can cause chronic inflammation, worsening damage to organs and tissues and leading to escalation of inflammatory responses [8]. However, all these data are related to the role of neutrophils in patients with T2D. It should be also noted that LII and the neutrophil-to-lymphocyte index have some benefits in terms of affordability, economy and information content compared to other inflammatory markers. According to our data these have shown a strong negative correlation with eGFR in stage 2 CKD and a very strong correlation in stage 3a and 3b CKD.

When blood levels of pro-inflammatory cytokines increase, the synthesis of the inflammation acute phase reactants (APRs) is triggered in hepatocytes, including CRP and CP as members of the first wave (blood levels are increased within the first 6–12 h reaching their maximum after 24 h) and third wave (maximum concentration is achieved within 48–72 h) APRs [28]. APRs are widely used in clinical practice to monitor the course of inflammatory disorders and control treatment. CRP is represented by the native pentameric and monomeric forms showing pleiotropic activity, except for the marker role of inflammation severity and the risk factor of cardiovascular disorders (for highly sensitive CRP fraction) it is directly involved in the pathogenesis of diabetic nephropathy via several mechanisms. The data on the role of CRP in regulation of complement activation via suppression of podocyte autophagy and inhibition of the C3a/C3aR axis signaling are provided, reported in clinical and experimental settings for kidney damage under conditions of DM [29]. Furthermore, in DM, CRP activates the TGFβ/SMAD and κB nuclear factor signaling pathways involved in realization of inflammation in the kidneys and nephrosclerosis associated with diabetic nephropathy via synthesis of IL1β, TNFα, monocyte chemoattractant protein-1, TGFβ1 [27, 30]. The experimental study of streptozotocin-induced DM and the human kidney epithelial cell line has demonstrated CRP involvement in the pathogenesis of diabetic nephropathy via interaction with the FcγRII receptors on the kidney cells, activation of the Wnt/β-catenin, ERK1/2 signaling pathways, and disruption of epithelial-mesenchymal interactions [31]. CRP can cause cell death and progressive renal fibrosis via NF-κB and Smad3-dependent mechanisms [32]. The experimentally induced CRP deficiency inhibits the diabetic nephropathy development [29]. Serum CRP levels are associated with microvascular complications of T2D, including kidney disease [33, 34]. The use of the two-stage regression model in more than 2000 patients with T2D involving assessment of single nucleotide polymorphisms of the CRP gene in the chromosome 1 (1q21–q23) showed a high-level causative relationship between serum CRP levels and the emergence of diabetic nephropathy [35]. Some researchers believe that the serum CRP/albumin index is a more informative independent predictor of the development of diabetic nephropathy associated with T2D [36]. Furthermore, serum CRP levels are associated with the urinary albumin/creatinine ratio in patients with T2D [37].

Ceruloplasmin not only reflects acute and chronic inflammation in the body, but also represents a metalloprotein possessing antioxidant properties due to its ferroxidase activity, and under conditions of oxidative stress it can function as a pro-oxidant taking part in generation of ROCs and oxidated LDL; it is the latter fact that is considered to be related to its pathogenetic role in the development of DM complications. It has been shown that patients with T2D, microalbuminuria, and diabetic nephropathy show the increased elimination of copper as part of CP with urine, which results in the decreased synthesis of Cu, Zn-superoxide dismutase and the development of oxidative stress [38]. Elevated CP levels are reported for T1D and T2D, including under conditions of diabetic nephropathy [39, 40]. In T2D, CP is considered to be a promising sensitive marker involved in the development of oxidative stress, insulin resistance, lipid metabolism disorders associated with this disease [41]. The role of serum CP as an independent prognostic factor of diabetic nephropathy progression in patients with T2D has been defined. We have clearly shown the increase in serum concentrations of CP in patients with CKD under conditions of T1D, progressing from the 16% increase based on the median in stage 1 CKD of the values of the group of healthy individuals to the 73% increase in stage 3b CKD. A strong negative correlation between CP and the CKD stage based on the eGRF values has been proven. Determination of serum CP concentrations is not widely used in clinical practice, however, it can be useful as a marker of diabetic nephropathy in cases of multiple definitions and growth in dynamics, especially when there is no albuminuria.

It is important to note that chronic inflammation in the kidneys results in damage to small blood vessels and glomeruli, proteinuria and decreased renal filtration capacity. Moreover, chronic inflammation is accompanied by activation of fibroblasts and generation of the extracellular matrix products, which causes interstitial fibrosis and loss of renal function. These mechanisms, as well as the mechanisms underlying inflammation initiation in DM and CKD are intertwined, these enhance one another, creating vicious circles, and lead to progression of diabetic nephropathy, loss of renal function, and the need for substitution therapy. Understanding pathophysiology of inflammation associated with diabetic nephropathy opens up prospects for the development of effective methods for the diagnosis and treatment of this severe condition. The issue of the search for sensitive specific diabetic nephropathy markers is relevant for practical medicine in terms of the DM-associated CKD diagnosis, treatment control, and progression [42]. Of primary importance are the currently used clinical biomarkers, such as eGRF, proteinuria, albuminuria, being the most important predictors of progression of kidney diseases, cardiovascular complications, and mortality in patients with diabetic nephropathy [43]. According to the results of the study, serum levels of IL1β, TNFα, CRP and CP, LII, neutrophil-to-lymphocyte index claim to be promising biomarkers of the kidney damage initiation and progression in patients with T1D and early stage CKD.

CONCLUSIONS

Serum concentrations of IL1β, TNFα, CRP and CP, LII, neutrophil-to-lymphocyte index are increased in patients with T1D and early stage CKD. Serum levels of IL1β, neutrophil-to-lymphocyte index, and CRP and CP concentrations are the

most important indicators of inflammatory activity in patients with T1D and early stage CKD. It is reasonable to measure the dynamics of those, if diabetes is compensated and the patient has no active inflammation, starting from stage 1 CKD. The inflammation and acute phase response severity in patients with T1D and early stage CKD progresses to reach its maximum in stage 3b CKD, when the serum IL1β concentration is increased 2.4-fold, TNFα concentration by 34%, CRP concentration 33-fold, CP concentration by 73%, LII 8.4-fold, neutrophil-to-lymphocyte index 5-fold. It has been found that eGRF, the integral renal function indicator, decreases with increasing serum levels of inflammatory markers in patients with T1D and early stage CKD. The maximum number of correlations and correlation strength are reported for stage 3a and 3b CKD in patients with T1D, mainly between eGRF and serum concentrations of IL1β and CRP. The results presented expand the knowledge about the role of inflammation and acute phase response in the pathogenesis of CKD in patients with T1D, create prerequisites for further studies, larger-scale in terms of the number of patients and duration, in various regions of the Russian Federation considering age, sex, constitutional features, concomitant disorders, therapy type, and other factor, as well as for modernization of the diagnostic and prognostic criteria, improvement of preventive and therapeutic measures for patients with T1D and early stage CKD.

References

1. Dedov II, Shestakova MV, Vikulova OK, Zheleznjakova AV, Isakov MA, Sazonova DV, i dr. Saharnyj diabet v Rossijskoj Federacii: dinamika jepidemiologicheskih pokazatelej po dannym Federal'nogo registra saharnogo diabeta za period 2010–2022 gg. Saharnyj diabet. 2023; 26 (2): 104–23. DOI: 10.14341/DM13035. Russian.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022; 102 (5S): S1–S127. DOI: 10.1016/j.kint.2022.06.008.
3. Patidar K, Deng JH, Mitchell CS, Ford Versypt AN. Cross-Domain Text Mining of Pathophysiological Processes Associated with Diabetic Kidney Disease. Int J Mol Sci. 2024; 25(8): 4503. DOI: 10.3390/ijms25084503.
4. Eckardt KU, Delgado C, Heerspink HJL, Pecoits-Filho R, Ricardo AC, Stengel B, et al. Trends and perspectives for improving quality of chronic kidney disease care: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2023; 104 (5): 888–903. DOI: 10.1016/j.kint.2023.05.013.
5. Vyas DA, Eisenstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. N Engl J Med. 2020; 383 (9): 874–82. DOI: 10.1056/NEJMms2004740.
6. Fan X, Yang M, Lang Y, Lu S, Kong Z, Gao Y, et al. Mitochondrial metabolic reprogramming in diabetic kidney disease. Cell Death Dis. 2024; 15: 442. DOI:10.1038/s41419-024-06833-0.
7. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019; 25 (12): 1822–32. DOI: 10.1038/s41591-019-0675-0. PubMed PMID: 31806905.
8. Rayego-Mateos S, Rodrigues-Diez RR, Fernandez-Fernandez B, Mora-Fernández C, Marchant V, Donate-Correa J, et al. Targeting inflammation to treat diabetic kidney disease: The road to 2030. Kidney Int. 2023; 103: 282–96. DOI: 10.1016/j.kint.2022.10.030.
9. Varra FN, Varras M, Varra VK, Theodosis-Nobelos P. Molecular and pathophysiological relationship between obesity and chronic inflammation in the manifestation of metabolic dysfunctions and their inflammation-mediating treatment options (Review). Mol Med Rep. 2024; 29: 95. DOI: 10.3892/mmr.2024.13219.
10. Xie R, Bishai DM, Lui DTW, Lee PCH, Yap DYH. Higher circulating neutrophil counts is associated with increased risk of all-cause mortality and cardiovascular disease in patients with diabetic kidney disease. Biomedicines. 2024; 12(8): 1907. DOI: 10.3390/biomedicines12081907. PubMed PMID: 39200371.
11. Saharnyj diabet 1 tipa u vzroslyh: klinicheskie rekomendacii. Rubrikator klinicheskih rekomendacij [Jelektronnyj resurs]. 2022 [data dostupa: 2024 oktjabr' 21]. Available from: https://cr.minzdrav.gov.ru/recomend/286_2. Russian.
12. Hronicheskaja bolezn' pochek (HBP): klinicheskie rekomendacii. Rubrikator klinicheskih rekomendacij [Jelektronnyj resurs]. 2021 [data dostupa: 2024 oktjabr' 21]. Available from: https://cr.minzdrav.gov.ru/schema/469_2. Russian.
13. Ostrovskij VK, Mashhenko AV, Jangolenko DV i dr. Pokazateli krovi i lejkocitarnogo indeksa intoksikacii v ocenke tjazhesti i opredelenii prognoza pri vospalitel'nyh, gnojnyh i gnojno-destruktivnyh zabolevanijah. Klin. lab. diagnostika. – 2006; 6: 50–3. Russian.
14. Kamyshnikov VS. Kliniko-biohimicheskaja laboratornaja diagnostika. Minsk: Izd-vo «Interpresservis»; 2003. 495 s. Russian.
15. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, Joles JA. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol. 2017; 28 (4): 1023–39. DOI: 10.1681/ASN.2016060666.
16. Kanbay M, Copur S, Guldan M, Ozbek L, Hatipoglu A, Covic A, Mallamaci F, Zoccali C. Proximal tubule hypertrophy and hyperfunction: a novel pathophysiological feature in disease states. Clin Kidney J. 2024; 17 (7): sfae195. DOI: 10.1093/ckj/sfae195.
17. Jin L, Wang X, Liu Y, Xiang Q, Huang R. High levels of blood glycemic indicators are associated with chronic kidney disease prevalence in non-diabetic adults: Cross-sectional data from the national health and nutrition examination survey 2005–2016. J Clin Transl Endocrinol. 2024; 36: 100347. DOI: 10.1016/j.jcte.2024.100347.
18. Rayego-Mateos S, Morgado-Pascual JL, Opazo-Ríos L, Guerrero-Hue M, Garcia-Caballero C, Vazquez-Carballo C, et al. Pathogenic pathways and therapeutic approaches targeting inflammation in diabetic nephropathy. Int J Mol Sci. 2020; 21 (11): 3798. DOI: 10.3390/ijms21113798.
19. Shirakawa K, Sano M. Neutrophils and neutrophil extracellular traps in cardiovascular disease: an overview and potential therapeutic approaches. Biomedicines. 2022; 10: 1850. DOI: 10.3390/biomedicines10081850.
20. Zhang R, Chen J, Xiong Y, Wang L, Huang X, Sun T, et al. Increased neutrophil count Is associated with the development of chronic kidney disease in patients with diabetes. J Diabetes. 2022; 14: 442–54. DOI: 10.1111/1753-0407.13292.
21. Zeng G, Lin Y, Xie P, Lin J, He Y, Wei J. Relationship of the Neutrophil-Lymphocyte Ratio with All-Cause and Cardiovascular Mortality in Patients with Diabetic Kidney Disease: A Prospective Cohort Study of NHANES Study. J Multidiscip Healthc. 2024; 17: 2461–73. DOI: 10.2147/JMDH.S465317. PubMed PMID: 38799017.
22. Wan H, Wang Y, Fang S, Chen Y, Zhang W, Xia F, et al. Associations between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with dabetes: a cross-sectional study. J Diabetes Res. 2020; 2020: 1–9. DOI: 10.1155/2020/6219545
23. Gao JL, Shen J, Yang LP, Liu L, Zhao K, Pan XR, et al. Neutrophil-to-lymphocyte ratio associated with renal function in type 2 diabetic patients. World J Clin Cases. 2024; 12 (14): 2308–15. DOI: 10.12998/wjcc.v12.i14.2308. PubMed PMID: 38765748.
24. Ko HL, Jung J, Lee J, Lim JH, Im DW, Kim YC, et al. Dynamic nature and prognostic value of the neutrophil-to-lymphocyte ratio in critically ill patients with acute kidney injury on continuous renal replacement therapy: A multicenter cohort study. Front Med (Lausanne). 2023; 10: 1162381. DOI: 10.3389/fmed.2023.1162381.
25. Karava V, Kondou A, Dotis J, Taparkou A, Farmaki E, Kollios K, et al. Exploring systemic inflammation in children with chronic kidney disease: correlates of interleukin 6. Pediatr Nephrol. 2024; 39:

1567–76. DOI:10.1007/s00467-023-06234-z.
26. Liu J, Liu X, Li Y, Quan J, Wei S, An S, et al. The association of neutrophil to lymphocyte ratio, mean platelet volume, and platelet distribution width with diabetic retinopathy and nephropathy: a meta-analysis. Biosci Rep. 2018; 38: 2–19. DOI: 10.1042/BSR20180172.
27. Lau LFS, Ng JK, Fung WWS, Chan GCK, Mei-Shan Cheng, Chow KM, et al. Relationship between serial serum neutrophil-lymphocyte ratio, cardiovascular mortality, and all-cause mortality in Chinese peritoneal dialysis patients. Kidney Blood Press Res. 2023; 48 (1): 414–23. DOI: 10.1159/000530554
28. Messias BA, Botelho RV, Saad SS, Mocchetti ER, Turke KC, Waisberg J. Serum C-reactive protein is a useful marker to exclude anastomotic leakage after colorectal surgery. Sci Rep. 2020; 10 (1): 1687. DOI: 10.1038/s41598-020-58780-3.
29. Zhang L, Li W, Gong M, Zhang Z, Xue X, Mao J et al. C-reactive protein inhibits C3a/C3aR-dependent podocyte autophagy in favor of diabetic kidney disease. FASEB J. 2022; 36(6): e22332. DOI: 10.1096/fj.202200198R. PubMed PMID: 35503088.
30. Wang Y, Guo J, Shao B, Chen H, Lan H. The Role of TGF-β1/SMAD in diabetic nephropathy: mechanisms and research development. Sichuan Da Xue Xue Bao Yi Xue Ban. 2023; 54 (6): 1065–73. Chinese. DOI: 10.12182/20231160108. PubMed PMID: 38162063.
31. Zhang L, Shen ZY, Wang K, Li W, Shi JM, Osoro EK, et al. C-reactive protein exacerbates epithelial-mesenchymal transition through Wnt/β-catenin and ERK signaling in streptozocin-induced diabetic nephropathy. FASEB J. 2019; 33 (5): 6551–63. DOI: 10.1096/fj.201801865RR. PubMed PMID: 30794428.
32. Li J, Chen J, Lan HY, Tang Y. Role of C-Reactive protein in Kidney Diseases. Kidney Dis (Basel). 2022; 9 (2): 73–81. DOI: 10.1159/000528693. PubMed PMID: 37065607.
33. Geng T, Zhu K, Lu Q, Wan Z, Chen X, Liu L, et al. Healthy lifestyle behaviors, mediating biomarkers, and risk of microvascular complications among individuals with type 2 diabetes: A cohort study. PLoS Med. 2023; 20 (1): e1004135. DOI: 10.1371/journal.pmed.1004135. PubMed PMID: 36626356.
34. Tang M, Cao H, Wei XH, Zhen Q, Liu F, Wang YF, et al. Association between high-sensitivity C-Reactive protein and Diabetic Kidney Disease in patients with type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2022; 13: 885516. DOI: 10.3389/fendo.2022.885516. PubMed PMID: 35784528.
35. Lin CC, Li CI, Liu CS, Liao LN, Yang CW, Lin CH, et al. Association of high-sensitivity C-reactive protein and diabetic nephropathy in patients with type 2 diabetes: a Mendelian randomization study. BMJ Open Diabetes Res Care. 2023; 11 (1): e003197. DOI: 10.1136/bmjdrc-2022-003197. PubMed PMID: 36828641.
36. Aktas G. Serum C-reactive protein to albumin ratio as a reliable marker of diabetic neuropathy in type 2 diabetes mellitus. Biomol Biomed. 2024; 24 (5): 1380–6. DOI: 10.17305/bb.2024.10426. PubMed PMID: 38635449.
37. Kumari S, Singh B. Assessment of correlation of serum high-sensitive C-Reactive protein, urinary albumin-to-creatinine ratio, and lipid profile in diabetics. J Pharm Bioallied Sci. 2021; 13 (2): S1569–S1572. DOI: 10.4103/jpbs.jpbs_290_21. PubMed PMID: 35018031.
38. Al-Bayati MA, Jamil DA, Al-Aubaidy HA. Cardiovascular effects of copper deficiency on activity of superoxide dismutase in diabetic nephropathy. N Am J Med Sci. 2015; 7(2): 41–6.
39. Lee MJ, Jung CH, Kang YM, Jang JE, Leem J, Park JY, et al. Serum ceruloplasmin level as a predictor for the progression of diabetic nephropathy in korean men with type 2 diabetes mellitus. Diabetes Metab J. 2015; 39 (3): 230–9. DOI: 10.4093/dmj.2015.39.3.230. PubMed PMID: 26124993.
40. de Paula Silva L, de Moraes Rego FG, Picheth G, Müller-Santos M, Alberton D. Prospection of plasma proteins as biomarkers for diabetes mellitus monitoring. J Diabetes Metab Disord. 2021; 20 (1): 611–20. DOI: 10.1007/s40200-021-00788-1. PubMed PMID: 34222081.
41. Wang S, Lu Z, Wang Y, Zhang T, He X. Metalloproteins and apolipoprotein C: candidate plasma biomarkers of T2DM screened by comparative proteomics and lipidomics in ZDF rats. Nutr Metab (Lond). 2020; 17: 66. DOI: 10.1186/s12986-020-00488-2. PubMed PMID: 32817751.
42. Swaminathan SM, Rao IR, Shenoy SV, Prabhu AR, Mohan PB, Rangaswamy D, et al. Novel biomarkers for prognosticating diabetic kidney disease progression. Int Urol Nephrol. 2023; 55 (4): 913–28. DOI: 10.1007/s11255-022-03354-7. PubMed PMID: 36271990.
43. Jung CY, Yoo TH. Pathophysiologic Mechanisms and Potential Biomarkers in Diabetic Kidney Disease. Diabetes Metab J. 2022; 46 (2): 181–97. DOI: 10.4093/dmj.2021.0329.

Литература

1. Дедов И. И., Шестакова М. В., Викулова О. К., Железнякова А. В., Исаков М. А., Сазонова Д. В., и др. Сахарный диабет в Российской Федерации: динамика эпидемиологических показателей по данным Федерального регистра сахарного диабета за период 2010–2022 гг. Сахарный диабет. 2023; 26 (2): 104–23. DOI: 10.14341/DM13035.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022; 102 (5S): S1–S127. DOI: 10.1016/j.kint.2022.06.008.
3. Patidar K, Deng JH, Mitchell CS, Ford Versypt AN. Cross-Domain Text Mining of Pathophysiological Processes Associated with Diabetic Kidney Disease. Int J Mol Sci. 2024; 25(8): 4503. DOI: 10.3390/ijms25084503.
4. Eckardt KU, Delgado C, Heerspink HJL, Pecoits-Filho R, Ricardo AC, Stengel B, et al. Trends and perspectives for improving quality of chronic kidney disease care: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2023; 104 (5): 888–903. DOI: 10.1016/j.kint.2023.05.013.
5. Vyas DA, Eisenstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. N Engl J Med. 2020; 383 (9): 874–82. DOI: 10.1056/NEJMms2004740.
6. Fan X, Yang M, Lang Y, Lu S, Kong Z, Gao Y, et al. Mitochondrial metabolic reprogramming in diabetic kidney disease. Cell Death Dis. 2024; 15: 442. DOI:10.1038/s41419-024-06833-0.
7. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019; 25 (12): 1822–32. DOI: 10.1038/s41591-019-0675-0. PubMed PMID: 31806905.
8. Rayego-Mateos S, Rodrigues-Diez RR, Fernandez-Fernandez B, Mora-Fernández C, Marchant V, Donate-Correa J, et al. Targeting inflammation to treat diabetic kidney disease: The road to 2030. Kidney Int. 2023; 103: 282–96. DOI: 10.1016/j.kint.2022.10.030.
9. Varra FN, Varras M, Varra VK, Theodosis-Nobelos P. Molecular and pathophysiological relationship between obesity and chronic inflammation in the manifestation of metabolic dysfunctions and their inflammation-mediating treatment options (Review). Mol Med Rep. 2024; 29: 95. DOI: 10.3892/mmr.2024.13219.
10. Xie R, Bishai DM, Lui DTW, Lee PCH, Yap DYH. Higher circulating neutrophil counts is associated with increased risk of all-cause mortality and cardiovascular disease in patients with diabetic kidney disease. Biomedicines. 2024; 12(8): 1907. DOI: 10.3390/biomedicines12081907. PubMed PMID: 39200371.
11. Сахарный диабет 1 типа у взрослых: клинические рекомендации. Рубрикатор клинических рекомендаций [Электронный ресурс]. 2022 [дата доступа: 2024 октябрь 21]. Режим доступа: https://cr.minzdrav.gov.ru/recomend/286_2.
12. Хроническая болезнь почек (ХБП): клинические рекомендации. Рубрикатор клинических рекомендаций [Электронный ресурс]. 2021 [дата доступа: 2024 октябрь 21]. Режим доступа: https://cr.minzdrav.gov.ru/schema/469_2.
13. Островский В. К., Мащенко А. В., Янголенко Д. В. и др. Показатели крови и лейкоцитарного индекса интоксикации в оценке тяжести и определении прогноза при воспалительных, гнойных и гнойно-деструктивных заболеваниях. Клин. лаб. диагностика. — 2006; 6: 50–3.
14. Камышников В. С. Клинико-биохимическая лабораторная диагностика. Минск: Изд-во «Интерпрессервис»; 2003. 495 с.

15. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, Joles JA. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol. 2017; 28 (4): 1023–39. DOI: 10.1681/ASN.2016060666.
16. Kanbay M, Copur S, Guldan M, Ozbek L, Hatipoglu A, Covic A, Mallamaci F, Zoccali C. Proximal tubule hypertrophy and hyperfunction: a novel pathophysiological feature in disease states. Clin Kidney J. 2024; 17 (7): sfae195. DOI: 10.1093/ckj/sfae195.
17. Jin L, Wang X, Liu Y, Xiang Q, Huang R. High levels of blood glycemic indicators are associated with chronic kidney disease prevalence in non-diabetic adults: Cross-sectional data from the national health and nutrition examination survey 2005–2016. J Clin Transl Endocrinol. 2024; 36: 100347. DOI: 10.1016/j.jcte.2024.100347.
18. Rayego-Mateos S, Morgado-Pascual JL, Opazo-Ríos L, Guerrero-Hue M, Garcia-Caballero C, Vazquez-Carballo C, et al. Pathogenic pathways and therapeutic approaches targeting inflammation in diabetic nephropathy. Int J Mol Sci. 2020; 21 (11): 3798. DOI: 10.3390/ijms21113798.
19. Shirakawa K, Sano M. Neutrophils and neutrophil extracellular traps in cardiovascular disease: an overview and potential therapeutic approaches. Biomedicines. 2022; 10: 1850. DOI: 10.3390/biomedicines10081850.
20. Zhang R, Chen J, Xiong Y, Wang L, Huang X, Sun T, et al. Increased neutrophil count Is associated with the development of chronic kidney disease in patients with diabetes. J Diabetes. 2022; 14: 442–54. DOI: 10.1111/1753-0407.13292.
21. Zeng G, Lin Y, Xie P, Lin J, He Y, Wei J. Relationship of the Neutrophil-Lymphocyte Ratio with All-Cause and Cardiovascular Mortality in Patients with Diabetic Kidney Disease: A Prospective Cohort Study of NHANES Study. J Multidiscip Healthc. 2024; 17: 2461–73. DOI: 10.2147/JMDH.S465317. PubMed PMID: 38799017.
22. Wan H, Wang Y, Fang S, Chen Y, Zhang W, Xia F, et al. Associations between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with dabetes: a cross-sectional study. J Diabetes Res. 2020; 2020: 1–9. DOI: 10.1155/2020/6219545
23. Gao JL, Shen J, Yang LP, Liu L, Zhao K, Pan XR, et al. Neutrophil-to-lymphocyte ratio associated with renal function in type 2 diabetic patients. World J Clin Cases. 2024; 12 (14): 2308–15. DOI: 10.12998/wjcc.v12.i14.2308. PubMed PMID: 38765748.
24. Ko HL, Jung J, Lee J, Lim JH, Im DW, Kim YC, et al. Dynamic nature and prognostic value of the neutrophil-to-lymphocyte ratio in critically ill patients with acute kidney injury on continuous renal replacement therapy: A multicenter cohort study. Front Med (Lausanne). 2023; 10: 1162381. DOI: 10.3389/fmed.2023.1162381.
25. Karava V, Kondou A, Dotis J, Taparkou A, Farmaki E, Kollios K, et al. Exploring systemic inflammation in children with chronic kidney disease: correlates of interleukin 6. Pediatr Nephrol. 2024; 39: 1567–76. DOI:10.1007/s00467-023-06234-z.
26. Liu J, Liu X, Li Y, Quan J, Wei S, An S, et al. The association of neutrophil to lymphocyte ratio, mean platelet volume, and platelet distribution width with diabetic retinopathy and nephropathy: a meta-analysis. Biosci Rep. 2018; 38: 2–19. DOI: 10.1042/BSR20180172.
27. Lau LFS, Ng JK, Fung WWS, Chan GCK, Mei-Shan Cheng, Chow KM, et al. Relationship between serial serum neutrophil-lymphocyte ratio, cardiovascular mortality, and all-cause mortality in Chinese peritoneal dialysis patients. Kidney Blood Press Res. 2023; 48 (1): 414–23. DOI: 10.1159/000530554
28. Messias BA, Botelho RV, Saad SS, Mocchetti ER, Turke KC, Waisberg J. Serum C-reactive protein is a useful marker to exclude anastomotic leakage after colorectal surgery. Sci Rep. 2020; 10 (1): 1687. DOI: 10.1038/s41598-020-58780-3.
29. Zhang L, Li W, Gong M, Zhang Z, Xue X, Mao J et al. C-reactive protein inhibits C3a/C3aR-dependent podocyte autophagy in favor of diabetic kidney disease. FASEB J. 2022; 36(6): e22332. DOI: 10.1096/fj.202200198R. PubMed PMID: 35503088.
30. Wang Y, Guo J, Shao B, Chen H, Lan H. The Role of TGF-β1/SMAD in diabetic nephropathy: mechanisms and research development. Sichuan Da Xue Xue Bao Yi Xue Ban. 2023; 54 (6): 1065–73. Chinese. DOI: 10.12182/20231160108. PubMed PMID: 38162063.
31. Zhang L, Shen ZY, Wang K, Li W, Shi JM, Osoro EK, et al. C-reactive protein exacerbates epithelial-mesenchymal transition through Wnt/β-catenin and ERK signaling in streptozocin-induced diabetic nephropathy. FASEB J. 2019; 33 (5): 6551–63. DOI: 10.1096/fj.201801865RR. PubMed PMID: 30794428.
32. Li J, Chen J, Lan HY, Tang Y. Role of C-Reactive protein in Kidney Diseases. Kidney Dis (Basel). 2022; 9 (2): 73–81. DOI: 10.1159/000528693. PubMed PMID: 37065607.
33. Geng T, Zhu K, Lu Q, Wan Z, Chen X, Liu L, et al. Healthy lifestyle behaviors, mediating biomarkers, and risk of microvascular complications among individuals with type 2 diabetes: A cohort study. PLoS Med. 2023; 20 (1): e1004135. DOI: 10.1371/journal.pmed.1004135. PubMed PMID: 36626356.
34. Tang M, Cao H, Wei XH, Zhen Q, Liu F, Wang YF, et al. Association between high-sensitivity C-Reactive protein and Diabetic Kidney Disease in patients with type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2022; 13: 885516. DOI: 10.3389/fendo.2022.885516. PubMed PMID: 35784528.
35. Lin CC, Li CI, Liu CS, Liao LN, Yang CW, Lin CH, et al. Association of high-sensitivity C-reactive protein and diabetic nephropathy in patients with type 2 diabetes: a Mendelian randomization study. BMJ Open Diabetes Res Care. 2023; 11 (1): e003197. DOI: 10.1136/bmjdrc-2022-003197. PubMed PMID: 36828641.
36. Aktas G. Serum C-reactive protein to albumin ratio as a reliable marker of diabetic neuropathy in type 2 diabetes mellitus. Biomol Biomed. 2024; 24 (5): 1380–6. DOI: 10.17305/bb.2024.10426. PubMed PMID: 38635449.
37. Kumari S, Singh B. Assessment of correlation of serum high-sensitive C-Reactive protein, urinary albumin-to-creatinine ratio, and lipid profile in diabetics. J Pharm Bioallied Sci. 2021; 13 (2): S1569–S1572. DOI: 10.4103/jpbs.jpbs_290_21. PubMed PMID: 35018031.
38. Al-Bayati MA, Jamil DA, Al-Aubaidy HA. Cardiovascular effects of copper deficiency on activity of superoxide dismutase in diabetic nephropathy. N Am J Med Sci. 2015; 7(2): 41–6.
39. Lee MJ, Jung CH, Kang YM, Jang JE, Leem J, Park JY, et al. Serum ceruloplasmin level as a predictor for the progression of diabetic nephropathy in korean men with type 2 diabetes mellitus. Diabetes Metab J. 2015; 39 (3): 230–9. DOI: 10.4093/dmj.2015.39.3.230. PubMed PMID: 26124993.
40. de Paula Silva L, de Moraes Rego FG, Picheth G, Müller-Santos M, Alberton D. Prospection of plasma proteins as biomarkers for diabetes mellitus monitoring. J Diabetes Metab Disord. 2021; 20 (1): 611–20. DOI: 10.1007/s40200-021-00788-1. PubMed PMID: 34222081.
41. Wang S, Lu Z, Wang Y, Zhang T, He X. Metalloproteins and apolipoprotein C: candidate plasma biomarkers of T2DM screened by comparative proteomics and lipidomics in ZDF rats. Nutr Metab (Lond). 2020; 17: 66. DOI: 10.1186/s12986-020-00488-2. PubMed PMID: 32817751.
42. Swaminathan SM, Rao IR, Shenoy SV, Prabhu AR, Mohan PB, Rangaswamy D, et al. Novel biomarkers for prognosticating diabetic kidney disease progression. Int Urol Nephrol. 2023; 55 (4): 913–28. DOI: 10.1007/s11255-022-03354-7. PubMed PMID: 36271990.
43. Jung CY, Yoo TH. Pathophysiologic Mechanisms and Potential Biomarkers in Diabetic Kidney Disease. Diabetes Metab J. 2022; 46 (2): 181–97. DOI: 10.4093/dmj.2021.0329.