OXIDATIVE PROTEIN DESTRUCTION PRODUCTS AS MARKERS OF CHRONIC KIDNEY DISEASE PROGRESSION IN 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] Patrice Lumumba Peoples' Friendship University of Russia, Moscow, Russia

Chronic kidney disease (CKD) represents one of the most common complications of type 1 diabetes mellitus (T1D). Oxidative stress (OS) can be considered as a key link of pathogenesis of CKD associated with T1D, therefore, identification of the redox status markers is important for prevention of the development and progression of this disorder. The study aimed to assess the substances generated during oxidative destruction of proteins and their correlation with glomerular filtration rate (GFR) in patients with T1D and stage 1–3 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). Healthy participants were matched to the index group by age and gender: 42.9% were males, 57.1% were females, the average age was 30.6 ± 4.2 years; body mass index, systolic and diastolic blood pressure, lipid profile were within normal. It has been found that patients with T1D and stage 1–3 CKD demonstrate plasma accumulation of early and delayed neutral and base products of oxidative protein modification (OPM): spontaneous 157% based on median, metal-induced 143% based on median relative to healthy individuals. We have revealed a decrease in overall antioxidant status (OAS) of plasma in 51% of patients with T1D and stage 3 CKD compared to patients with T1D without CKD. Estimated GFR, the integral indicator of renal function, decreases with increasing plasma levels of OPM products, decreasing OAS. The data obtained allow us to consider plasma levels of OPM products, OAS as affordable and informative methods to assess progression of early stage CKD in patients with T1D.

Keywords: type 1 diabetes mellitus, stage 1–3 chronic kidney disease progression, oxidative protein destruction

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

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ПРОДУКТЫ ОКИСЛИТЕЛЬНОЙ ДЕСТРУКЦИИ БЕЛКОВ КАК МАРКЕРЫ ПРОГРЕССИРОВАНИЯ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК ПРИ САХАРНОМ ДИАБЕТЕ

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, Челябинск, Россия

[2] Челябинская областная клиническая больница, Челябинск, Россия

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

Одно из наиболее частых осложнений сахарного диабета 1-го типа (СД1) — это хроническая болезнь почек (ХБП). Окислительный стресс (ОС) можно рассматривать как ключевое звено в патогенезе ХБП при СД1, в связи с чем востребовано выявление маркеров редокс-статуса для предотвращения развития и прогрессирования этого заболевания. Целью исследования было провести анализ веществ, образующихся при окислительном повреждении белков, и их связь со скоростью клубочковой фильтрации (СКФ) у пациентов с СД1 при ХБП 1–3 стадий. 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). Здоровые участники сопоставимы по возрасту и полу с основной группой: мужчин 42,9%, женщин 57,1%, средний возраст 30,6 ± 4,2 лет, показатели индекса массы тела, систолического и диастолического артериального давления, липидограммы в пределах нормальных значений. Выявлено, что у больных с СД1 и ХБП 1–3-й стадий в плазме накапливаются ранние и поздние нейтрального и основного характера продукты окислительной модификации белков (ОМБ) в спонтанном режиме по медиане 157%, в металл-индуцированном режиме по медиане 143% в сравнении со здоровыми. Отмечено снижение общего антиоксидантного статуса (ОАС) плазмы на 51% у пациентов с СД1 и ХБП 3-й стадии в сравнении с пациентами СД1 без ХБП. Интегральный показатель функции почек — расчетная СКФ — снижается по мере увеличения продуктов ОМБ в плазме, снижения ОАС. Полученные данные позволяют рассматривать содержание в плазме продуктов ОМБ, ОАС как доступные и информативные методы оценки прогрессирования начальных стадий ХБП у больных с СД1.

Ключевые слова: сахарный диабет 1-го типа, прогрессирование хронической болезни почек 1–3-й стадий, окислительная деструкция белков

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 черновика рукописи; А. А. Федосов — анализ литературы, интерпретация данных, подготовка черновика рукописи.

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

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Diabetes mellitus (DM) and chronic kidney disease (CKD) are significant medical and social challenges faced by the global community. According to the International Diabetes Federation, in 2021, there were 537 million people with DM registered in the world, which is 6% of the global population [1]. As of January 1, 2023, the number of DM patients in Russia was 4.9 million (3.31% of the population), and 277.1 thousand of them (5.58%) suffered from type 1 DM (T1DM). The trend for T1DM prevalence is upward: in 2010, there were 146 cases registered per 100 thousand population, and in 2022, the figure was 191, which gives an annual growth of 2–3% [2]. Diabetic nephropathy is the most common complication: 40% of T1DM patients have it, and the probability of diagnosing this condition after 8–10 years with T1DM is 50%, growing to 75% after 15–20 years [3]. The risks of developing CKD in T1DM increase significantly as the target parameters of carbohydrate metabolism grow (HbA1c above 7%) [4, 5]. The prevalence of CKD among T1DM patients reaches 25–75%; the disease remains the main microvascular complication [7, 8]. Globally, the prevalence of CKD is 10–18%, and in Russia it is about 11% [9]. It is assumed that by 2040, CKD will become one of the main reasons for the shortening of life expectancy [10]. In high-income states, dialysis and kidney transplantation consume 2–3% of the overall healthcare budget, and the share of patients receiving such treatment is less than 0.03% of the country's population [11].

In 2022, one of the topics discussed at the KDIGO conference was the importance of establishing the risk factors associated with CKD development and progression, since the impact of the disease on the health of the population is growing, and there are obvious gaps in this subject matter [12]. Early diagnosing of CKD and the introduction of modern treatment methods can significantly reduce the need for renal replacement therapy in the late stages of the disease. The progression of CKD in T1DM patients causes death in over 70% of patients within five years; in addition, CKD affects the cost of diabetes treatment [13]. Deliberate interferences at the early stages of CKD in T1DM patients help prevent deterioration of kidney function and improve treatment outcomes, which necessitates regular screenings for CKD [14]. Understanding the molecular and cellular mechanisms contributing to the progression of CKD in DM patients is a key factor for the development of effective diagnostic and therapeutic strategies [8, 15]. An important aspect thereof is the spectrophotometric assessment of the plasma total antioxidant capacity (TAC) that enables oxidative stress (OS) monitoring.

The purpose of the study was to analyze substances resulting from the oxidative degradation of proteins, and to determine their connection to the glomerular filtration rate (GFR) in T1DM patients with stage 1–3 CKD.

METHODS

The study was conducted at the Chelyabinsk Regional Clinical Hospital under the South Ural State Medical University of the Ministry of Health of the Russian Federation. Criteria for inclusion in the study: informed consent, T1DM diagnosed over 3 months as per the clinical recommendations of the Russian National Medical Research Center for Endocrinology [16]. Exclusion criteria: the age of men- over 60 years old, postmenopausal age for women; estimated glomerular filtration rate (eGFR) ≤ ≤ 29 ml/min/1.73 m^2; diagnosed T2DM, pheochromocytoma, primary hyperparathyriosis, Itsenko–Cushing's disease, acromegaly, hypothyroidism, thyrotoxicosis; diagnosed hypertension before the onset of T1DM; severe concomitant diseases of the liver, lungs, tuberculosis, rheumatological, autoimmune and oncological diseases; inflammatory kidney diseases, congenital kidney abnormalities; active inflammatory processes; intake of glucocorticoids and cytostatics, vitamin D preparations, phosphatebinders; pregnancy; non-standard body size; paraplegia and quadriplegia; acute renal injury; transplanted kidney.

Group 1 included healthy people comparable in age and gender to the treatment group (n = 14), group 2 consisted of T1DM patients without CKD (n = 30), group 3 was comprised of T1DM patients with CKD (n = 129), subdivided by stages [17] (stage 1, subgroup 3.1, n = 60; stage 2, subgroup 3.2, n = 38; stage 3, subgroup 3.3, n = 31). eGFR was assessed using the CKD-EPI equation that reveals serum creatinine according to standard methods, the equipment was Cobas Integra 400 analyzers (Roche, Switzerland),using kinetic colorimetric method. The protein oxidative modification (POM) was analyzed by spectrophotometry [18], the reaction with 2,4-dinitrophenylhydrazine [19]. TAC was measured using the B-7501 Total Antioxidant Capacity test system (Vector-Best, Russia). The result was expressed in mmol/L. In the heptane and isopropanol phases of the lipid extract, we measured the optical density at wavelengths of 220 nm (shows content of isolated double bonds), 232 nm (shows content of diene conjugates, DC), 278 nm (shows content of ketodienes and conjugated trienes, KCT), 400 nm (shows content of Schiff bases, SB). The relative content of lipid peroxidation products (LPP) was expressed in units of oxidation indices (UOI): E232/E220 (DC), E278/E220 (KCT) and E400/E220 (SB). Blood plasma POM products were determined by the reaction of carbonyl derivatives of proteins with 2,4-dinitrophenylhydrazine in spontaneous and metal-dependent Fenton reaction (metal-catalyzed oxidation, MCO), with spectrophotometric registration of aldehyde 2,4-dinitrophenylhydrazine (ADNPH) and ceton 2,4-dinitrophenylhydrazine (CDNPH) in the ultraviolet (uv) and visible light (vs) parts of the spectrum with the calculation of the reserve and adaptive potential. The result was expressed in units of optical density per 1 mg of protein (cu/mg). For statistical processing of the data, we used Microsoft Office Excel (Microsoft Corporation, USA) and IBM SPSS Statistics v. 23 (SPSS: IBM Company, USA). Quantitative data were presented as a median (Me) with interquartile intervals (Q_1; Q_3), the values of the lower (25) and upper (75) quartiles, respectively. Nonparametric Kruskal–Wallis and Mann–Whitney tests were used for intergroup comparison of quantitative data. Spearman's rank correlation coefficient allowed determining the interrelationships of the indicators, and the Chaddock scale was used to assess the strength of the connection (weak — from 0.1 to 0.3, moderate — from 0.3 to 0.5, noticeable — from 0.5 to 0.7, high — from 0.7 to 0.9, very high — from 0.9 to 1.0). The differences were considered statistically significant at $p < 0.05$.

RESULTS

Initially, we established eGFR in the groups (Table 1). This assessment revealed the indicator to be 17% higher in group 1 than in group 2 (be median), which is a significant difference; in subgroup 3.1, the value was 10% lower, in subgroup 3.2 — 28% lower, and in subgroup 3.3 — 62% lower. In addition, eGFR was significantly lower in subgroups 3.1, 3.2, 3.3 compared to group 2. eGFR values in patients of subgroup 3.2 significantly differed from those registered in subgroup 3.1, and in patients of subgroup 3.3 they were significantly differed from the values in subgroups 3.1 and 3.2. In T1DM patients, including those with CKD, the changes of the content of blood plasma POM

Table 1. Estimated glomerular filtration rate in T1DM patients with CKD, ml/min/1.73 m^2 (Iu [Q_1; Q_3])

Group 1 (n = 14)	Group 2 (n = 30)	Group 3 (DM+CKD)			p-value, with $p < 0,05$
		Subgroup 3.1 (n = 60)	Subgroup 3.2 (n = 38)	Subgroup 3.3 (n = 31)	
105.000 [91.000; 118.000]	123.000 [120.000; 134.000]	94.000 [92.000; 126.000]	76.000 [67.000; 78.000]	40.000 [31.000; 58.000]	$p_{1-2} < 0.001$ $p_{1-3.1} < 0.001$ $p_{1-3.2} < 0.001$ $p_{1-3.3} < 0.001$ $p_{2-3.1} = 0.016$ $p_{2-3.2} < 0.001$ $p_{2-3.3} < 0.001$ $p_{3.1-3.2} < 0.001$ $p_{3.1-3.3} < 0.001$ $p_{3.2-3.3} < 0.001$

products were the following; specifically, in group 2, the total concentration of such products was elevated, contributed to by both early- and late-stage neutral and basic products. A proportional increase in the content of POM products in spontaneous and metal-induced modes did not lead to significant changes in the reserve and adaptive potential. Accordingly, blood plasma TAC in group 2 was decreasing (Table 2).

The most pronounced changes were recorded in group 2. In subgroups 3.1, 3.2, 3.3, the total concentration of blood plasma POM products increased with early- and late-stage products, neutral and basic types, both in the spontaneous and metal-induced modes.The most significant growth of concentration of the products was observed in subgroup 3.3, both in spontaneous mode (median157% compared with group 1) and in metal-induced mode (median 143% compared with group 1). In subgroup 3.3, the total number of POM products, both early- and late-stage, significantly differed from the values registered in group 2 and subgroup 3.1. Group 3.1 was also found to have a diminished reserve and adaptive potential in plasma. In addition, TAC in blood plasma in group 3 also decreased: by 19% in subgroup 3.1, by 39% in subgroup 3.2, and by 51% in subgroup 3.3.

To assess the relationship between the changes in OS parameters and renal function — eGFR in group 3 patients — we conducted a correlation analysis (Table 3).

In group 2, we registered a significant direct correlation with the overall antioxidant level. A strong inversed correlation was observed with the total amount of blood plasma POM products, late-stage POM products in the spontaneous mode, the total volume of POM products, as well as neutral POM products in the metal-induced test; a very strong inversed correlation was established for the content of neutral and basic POM products in the spontaneous test, as well as basic POM products in the metal-induced test. In subgroup 3.1, we found inversed correlation with the content of late-stage POM products, and a direct correlation with the reserve adaptive potential and TAC. In subgroup 3.2, the correlation with TAC was also direct, but it turned out to be inversed for the plasma levels of late-stage POM products. In subgroup 3.3, we established an inversed correlation with various POM products, both early- and late-stage, as well as with neutral products. In subgroup 3.3, a strong inversed correlation was observed with the amount of early and late-stage POM products. Ultimately, the number of correlations between eGFR and the plasma redox status increases from group 2 to subgroup 3.3, which confirms the growing importance of these correlations, group 2 (8 in total, including 1 notable, 4 strong, and 3 very strong) to subgroup 3.1 (10 in total, including 4 notable, 1 strong, 5 very strong), to subgroup 3.2 (10 in total, including 1 notable, 3 strong, 6 very strong), and, maximizing, to subgroup 3.3 (11 in total, including 4 notable, 5 strong, 2 very strong).

DISCUSSION

Analysis of the level of eGFR showed that it increased in group 2. From 10 to 67% of the respective patients had higher eGFR and hyperfiltration, with the maximum values up to 162 ml/min/1.73 m^2. Various pathogenetic factors can cause this situation, including compensatory hypertrophy and hyperfunction of the kidneys against the background of chronic hyperglycemia, and the impact of inflammatory cytokines, growth factors, local angiotensin II, imbalanced vasoactive substances regulating blood flow at the levels of pre- and postglomerular arterioles.

Altered reabsorption of sodium, glucose, and hydrogen ions in the proximal tubules of nephrons are important factors, too [20–22]. Currently, intraclubular hyperfiltration is considered one of the key mechanisms triggering the onset and progression of diabetic nephropathy [23, 24].

Elevated levels of POM products and deteriorating TAC in T1DM patients, including those stages 1–3 CKD, point to the impact of OS in this group. Oxidative stress is one of the main pathogenetic forces influencing the development of CKD in DM patients. It appears with excessive amounts of active oxygen forms and nitrogen derivatives in the background, and weakening antioxidant protection [25]. The key processes contributing to the formation of active forms include activation of various NADPH oxidase isoforms (NOX1-NOX5, DUOX1 and DUOX2) in the immune system cells, as well as various forms of NO synthase (NOS) and other enzymes. In DM patients, blood sugar levels are rising constantly, and the immune cells and the related processes are activated, which translates into formation of excessive amounts of glycated compounds that trigger intracellular signaling pathways such as phosphoinositide-3-kinase and nuclear factor kappa B, which, in turn, aggravate the inflammatory processes. As a result, vascular walls and metabolic shunts are damaged, and the DM becomes exacerbated, since chronic inflammation is an important factor contributing to complications, such as diabetic nephropathy.

The growing level of glycated compounds in the blood contributes to the accumulation of toxic metabolites, which also exacerbates OS and damages cells and tissues. Moreover, activation of the nuclear factor kappa B boosts production of pro-inflammatory cytokines such as TNFa and IL6. These molecules play a key role in the development of DM complications, intensifying pain, impairing organ functions, and causing other systemic disorders.

To minimize the risks, it is important to control blood glucose level, since it affects the metabolic state and also suffocates the inflammatory processes, which eventually translates into slower development of DM complications [26].

It was previously noted that DM boosts the activity of NADPH oxidase isoenzymes, especially NOX4 and NOX5, while the activity of antioxidant enzymes slows down; these effects are associated with hyperglycemia. Activating NADPH

Table 2. Blood plasma POM and TAC indicators, T1DM patients with CKD (Me [Q_1; Q_3])

Indicators	Group 1	Group 2 (n = 30)	Group 3			p-value, with $p < 0,05$
			Subgroup 3.1 (n = 60)	Subgroup 3.2 (n = 38)	Subgroup 3.3 (n = 31)	
S POM cu/mg of protein	5.956 [5.286; 7.744]	8.443 [7.330; 14.752]	8.561 [5.762; 14.639]	9.500 [8.307; 16.915]	15.319 [13.323; 33.675]	p_{1-2} = 0.002 $p_{1-3.1}$ = 0.044 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.009 $p_{3.1-3.3}$ = 0.001 $p_{3.2-3.3}$ = 0.012
S ADNPH, cu/mg protein	5.735 [5.088; 7.361]	8.069 [7.016; 14.003]	8.205 [5.483; 14.078]	9.124 [7.967; 16.124]	13.755 [12.626; 31.956]	p_{1-2} = 0.002 $p_{1-3.1}$ = 0.044 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.012 $p_{3.1-3.3}$ = 0.002 $p_{3.2-3.3}$ = 0.016
S KDNPH, cu/mg protein	0.220 [0.198; 0.296]	0.374 [0.314; 0.749]	0.431 [0.297; 0.561]	0.465 [0.372; 0.741]	1.031 [0.564; 1.649]	p_{1-2} = 0.001 $p_{1-3.1}$ < 0.001 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.003 $p_{3.1-3.3}$ = 0.001 $p_{3.2-3.3}$ = 0.002
S uv, cu/mg protein	5.862 [5.199; 7.574]	8.291 [7.187; 14.423]	8.396 [5.656; 14.393]	9.346 [8.162; 16.537]	15.064 [12.994; 32.893]	p_{1-2} = 0.002 $p_{1-3.1}$ = 0.044 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.008 $p_{3.1-3.3}$ = 0.001 $p_{3.2-3.3}$ = 0.012
S vl, cu/mg protein	0.087 [0.082; 0.122]	0.152 [0.143; 0.329]	0.167 [0.106; 0.246]	0.243 [0.146; 0.378]	0.388 [0.298; 0.782]	p_{1-2} < 0.001 $p_{1-3.1}$ = 0.009 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.002 $p_{3.1-3.3}$ = 0.001 $p_{3.2-3.3}$ = 0.009
S POM, metal-induced mode, cu/mg protein	9.660 [9.240; 12.865]	14.303 [11.269; 24.749]	14.225 [12.550; 21.752]	15.155 [13.222; 28.696]	23.498 [18.848; 57.269]	p_{1-2} < 0.001 $p_{1-3.1}$ = 0.002 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.002 $p_{3.1-3.3}$ = 0.050 $p_{3.2-3.3}$ = 0.009
S ADNPH, metal-induced mode cu/mg of protein	8.481 [8.235; 11.308]	12.435 [10.002; 21.855]	12.503 [11.029; 19.443]	13.087 [11.243; 24.884]	20.323 [16.572; 49.375]	p_{1-2} = 0.001 $p_{1-3.1}$ = 0.002 $p_{1-3.2}$ = 0.001 $p_{1-3.3}$ < 0.000 $p_{2-3.3}$ = 0.002 $p_{3.1-3.3}$ = 0.007 $p_{3.2-3.3}$ = 0.009
S KDNPH, metal-induced mode, cu/mg protein	1.034 [0.974; 1.556]	1.868 [1.267; 3.414]	1.722 [1.507; 2.309]	2.090 [1.592; 3.812]	3.175 [2.049; 7.895]	p_{1-2} = 0.001 $p_{1-3.1}$ = 0.001 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.002 $p_{3.1-3.3}$ = 0.044
S uv, metal-induced mode, cu/mg protein	8.740 [8.441; 11.618]	12.803 [10.252; 22.393]	12.788 [11.328; 19.872]	13.556 [11.708; 25.301]	21.012 [16.878; 51.153]	p_{1-2} = 0.001 $p_{1-3.1}$ = 0.002 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.002 $p_{3.1-3.3}$ = 0.040 $p_{3.2-3.3}$ = 0.044
S vl, metal-induced mode, cu/mg protein	0.803 [0.788; 1.247]	1.500 [1.017; 2.668]	1.440 [1.222; 1.883]	1.599 [1.154; 3.395]	2.486 [1.687; 6.116]	p_{1-2} < 0.001 $p_{1-3.1}$ = 0.002 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.3}$ = 0.002 $p_{3.1-3.3}$ = 0.044
RAP, %	39.715 [36.706; 44.284]	37.413 [34.960; 42.280]	36.030 [35.385; 37.722]	37.454 [33.686; 41.064]	41.199 [35.385; 44.320]	$p_{1-3.1}$ = 0.021
TAC, mmol/L	1.800 [1.610; 1.960]	1.610 [1.470; 1.680]	1.145 [0.980; 1.670]	1.100 [0.780; 1.410]	0.890 [0.800; 1.100]	p_{1-2} = 0.021 $p_{1-3.1}$ = 0.004 $p_{1-3.2}$ < 0.001 $p_{1-3.3}$ < 0.001 $p_{2-3.2}$ = 0.004 $p_{2-3.3}$ = 0.002 $p_{3.1-3.3}$ = 0.019

Note: the table gives total (S) POM products content values, spontaneous and metal-induced modes; ADNPH — aldehyde-dinitrophenylhydrozone; KDNPH — ketone-dinitrophenylhydrozone; S uv — the level of carbonyl derivatives measured in the UV spectrum; S vl — the level of carbonyl derivatives measured in the visible light spectrum; RAP — reserve adaptive potential.

Table 3. Correlation between eGFR (ml/min/1.73 m²) and POM, LPP, and TAC, T1DM patients with CKD

Indicators	Group 2 (n = 30)	Group 3		
		Subgroup 3.1 (n = 60)	Subgroup 3.2 (n = 38)	Subgroup 3.3 (n = 31)
S POM, cu/mg protein	R = –0.75 p = 0.002	R = –0.99 p < 0.001	R = –0.99 p < 0.001	R = –0.67 p = 0.008
S ADNPH, cu/mg protein	R = –0.52 p = 0.057	R = –0.98 p < 0.001	R = –0.99 p < 0.001	R = –0.67 p = 0.008
S KDNPH, cu/mg protein	R = –0.83 p < 0.001	R = –0.62 p = 0.018	R = –0.74 p = 0.002	R = –0.63 p = 0.016
S uv, cu/mg protein	R = –0.91 p < 0.001	R = –0.98 p < 0.001	R = –0.99 p < 0.001	R = –0.60 p = 0.023
S vl, cu/mg protein	R = –0.91 p < 0.001	R = –0.97 p < 0.001	R = –0.68 p = 0.007	R = –0.91 p < 0.001
S POM, metal-induced mode, cu/mg protein	R = –0.83 p < 0.001	R = –0.62 p = 0.018	R = –0.97 p < 0.001	R = –0.77 p < 0.001
S ADNPH, metal-induced mode, cu/mg protein	R = –0.46 p = 0.102	R = –0.62 p = 0.018	R = –0.97 p < 0.001	R = –0.76 p < 0.001
S KDNPH, metal-induced mode, cu/mg protein	R = –0.53 p = 0.050	R = –0.58 p = 0.028	R = –0.84 p < 0.001	R = –0.72 p = 0.004
S uv, metal-induced mode, cu/mg protein	R = –0.89 p < 0.001	R = –0.62 p = 0.018	R = –0.97 p < 0.001	R = –0.76 p < 0.001
S vl, metal-induced mode, cu/mg protein	R = –0.92 p < 0.001	R = –0.52 p = 0.055	R = –0.89 p < 0.001	R = –0.76 p < 0.001
RAP, %	R = –0.04 p = 0.903	R = 0.75 p = 0.002	R = –0.21 p = 0.462	R = –0.22 p = 0.458
TAC, mmol/L	R = 0.68 p = 0.007	R = 0.93 p < 0.000	R = 0.58 p = 0.030	R = 0.98 p < 0.000

Note: the table gives the Spearman's rank correlation coefficient (R) values; the statistically significant connections are highlighted in bold (p < 0.05).

oxidase, angiotensin II plays a key role in the development of OS associated with diabetic nephropathy. Mitochondrial dysfunction with increased activity of complex-I and increased production of reactive oxygen species (ROS) also contribute to the onset and aggravation of diabetic nephropathy, but not as significantly as NADPH oxidase [15, 27, 28].

Oxidative stress and mitochondrial dysfunction mutually reinforce each other in the pathogenesis of the disease. Against the background of hyperglycemia, the activity of cytochrome P450, especially CYP4A, grows, which boosts the synthesis of the NADPH oxidase activator, 20-hydroxyeicosatetraenoic acid. In preclinical studies, it was established that a drip in the expression of Nrf2 has a significant impact on the overall level of antioxidant activity in patients with T1DM and signs of CKD [15]. The positive effect of various antioxidants confirms the weight of OS in the pathogenesis of renal pathology [26, 30]. High levels of ROS and nitrogen damage cellular structures and DNA, causing endothelial dysfunction, inflammation, and fibrosis [24, 31]. The need to assess the progression of CKD and the associated risks substantiates the search for specific biomarkers enabling diabetic nephropathy diagnosing and monitoring.

Given that OS is a significant factor in the development of renal failure in DM cases, clinicians seek to tally the excessive amounts of reactive species of oxygen and nitrogen, as well as their metabolites, through laboratory tests of biological fluids. Both of the said species decompose quickly, so their detection is complicated, which adds to the importance of methods designed for identification of the products of oxidative damage, such as lipids, proteins, and nucleic acids [15].

The known markers of OS are malonic dialdehyde, thiobarbituric acid, and glycation end products, as well as 4-hydroxynonenal and 8-deoxyguanosine. Gaging the levels of endogenous intoxication in T1DM patients at various stages of albuminuria can help identify early biomarkers of primary kidney damage [24, 32]. The levels of conjugated dienes, ketodienes, and trienes, as well as medium-molecular peptides, can be increased as early as at the A1 stage of CKD 1–3.

In recent years, researchers have grown more interested in studying OS and its role in the pathogenesis of various diseases, including CKD. In this work, we observed pronounced changes in the concentration of POM products in T1DM patients without CKD. This is consistent with the data reported by other authors, who also note that OS may be a significant factor contributing to the progression of diabetic nephropathy [33]. In T1DM patients with stages 1–3 CKD, we registered growth of the total blood plasma POM products concentration, which was detected in both spontaneous and metal-induced tests, in line with the reports emphasizing the role of OS in boosting the progression of CKD [34]. The most significant increase in the concentration of POM products was identified in T1DM patients with stage 3 CKD, which may indicate more pronounced disorders in the antioxidant system and a higher level of OS in this group. Other researchers received similar results [35]. In addition, it was found that patients at later stages of CKD exhibit significantly elevated levels of OS markers compared with patients at early stages of the disease, which underscores the need to monitor OS as a potential prognostic marker enabling assessment of the severity of the disease and the risk of CKD progression. Given that OS can add to the damage of cells and tissues, its monitoring can be an important tool in clinical practice that allows timely identification of patients at risk [35, 36].

We have also found that the reserve and adaptive potential of blood plasma was significantly reduced in the stage 1 CKD subgroup. This fact confirms that even at the early stages of the disease, plasma's functional state changes, which may indicate the need for more careful monitoring and early intervention seeking to prevent the progression of the disease. In addition, the analysis of plasma TAC level in patients at various stages of CKD showed a significant decrease thereof:

in the stage 1 CKD subgroup, it dropped by 19%, in the stage 2 CKD subgroup — by 39%, and in the stage 3 CKD subgroup — by 51%. These data emphasize the importance of assessing the antioxidant status of CKD patients, since a decreasing TAC may signal growth of the OS level and overall health deterioration. It is important to remember that early diagnosing and adequate treatment can significantly affect the quality of life of such patients and the respective prognoses. According to our data, T1DM patients without CKD have a significant direct correlation with the overall level of antioxidants. This may mean that in these cases, antioxidants play an important role in protecting cells from OS, which is common against the background of DM. There are studies that stress the critical importance of maintaining high levels of antioxidants in the matter of prevention of DM-related complications [33]. The strong inversed connection with the total amount of blood plasma POM products, especially late-stage, is another described phenomenon. This may indicate that an increase in the level of oxidative products is associated with a deterioration of the antioxidant status. According to some data, OS can hamper antioxidant activity [37], which is consistent with our observations. We have also registered different correlation patterns in T1DM patients at different stages of CKD. In T1DM and stage 1 CKD cases, the correlation with late-stage POM products was inversed, that with reserve adaptive potential and antioxidant status — direct. This may point to the persisting possibility of adaptation of the antioxidant system at the early stages of CKD. In T1DM and stage 2 CKD cases, the correlation with antioxidant status was direct, that with late-stage POM products — inversed. This may mean that as the disease progresses, the antioxidant system begins to weaken. In T1DM and stage 3 CKD cases, the correlation with both early- and late-stage POM products was inversed. The strong inversed correlation with the amount of early- and late-stage POM products may indicate a significant deterioration in the OS and antioxidant response at this stage. It was previously shown that the progression of CKD is associated with a growing OS and diminishing antioxidant activity [38], which is consistent with our data on the correlation between the stages of CKD and the levels of oxidative products. Other authors also confirm that patients with DM and CKD have a significantly lower antioxidant status, which is associated with a deteriorating kidney function and a growing level of oxidative markers [39].

A comprehensive study of these indicators in T1DM patients with early stages 1–3 CKD, as well as correlation analysis, allow considering them as promising biomarkers of OS in the context of progressive diabetic nephropathy [40, 41].

CONCLUSIONS

This study has shown that T1DM patients with early CKD have growing blood plasma levels of primary and secondary LPP products (in heptane and isopropanol lipid extract), as well as early- and late-stage neutral and basic POM products in spontaneous and metal-induced modes, and the plasma TAC decreases. In T1DM cases with concomitant early-stage CKD, the severity of OS progresses, maximizing at stage 3. Dropping GFR, an integral indicator of kidney function, in T1DM patients with early-stage CKD is accompanied by a growing amount of products of LPP (secondary products in isopropanol extract of lipids, early- and late-stage neutral and basic POM products in spontaneous and metal-induced modes) and POM. In parallel, we observed a decreasing blood plasma TAC. The resulting data suggest that blood plasma POM products and TAC can be easily measured and informative indicators of progression of CKD at initial stages in T1DM patients. Studying the respective interaction may help design new anti-inflammatory strategies that can slow the progression of CKD. The development of algorithms for predicting the risk of CKD based on early OS markers will be an important step towards successful prevention. The results of this study expand the knowledge about the impact of OS on CKD in T1DM cases. They also refine the current understanding of the role of OS in the pathogenesis of CKD in T1DM patients and support further research, modernization of diagnostic and prognostic criteria, and improvement of preventive and therapeutic measures for such patients.

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