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Markers of kidney injury, lipid metabolism, and carbonyl stress in patients with type 1 diabetes and different levels of albuminuria

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ABSTRACT

The **aim** of this work was to study the levels of podocalyxin and β-2-microglobulin and parameters of lipid metabolism and carbonyl stress in type 1 diabetes mellitus (T1DM) patients with different levels of albuminuria.

Materials and methods. 56 men of reproductive age with T1DM were divided into two groups: 24 patients with stage A1 albuminuria (group A1) and 32 patients with stage A2 albuminuria (group A2). The control group consisted of 28 healthy men. The levels of renal function markers, lipid metabolism parameters, and methylglyoxal were assessed using enzyme immunoassay and spectrophotometric and fluorometric methods.

Results. Higher values for total cholesterol, triacylglycerol, and very-low-density lipoprotein medians in both groups A1 and A2 were found. In these groups, increased podocalyxin and methylglyoxal medians were revealed. Correlation analysis in the group A1 showed the presence of a relationship between the glomerular filtration rate (GFR) and creatinine. In the group A2, correlations between the generally accepted parameters of kidney injury (the albumin / creatinine ratio and GFR) and the duration of the disease and between GFR and the creatinine and methylglyoxal levels in the blood were identified. The podocalyxin level in this group correlated with the β2-microglobulin and methylglyoxal levels and lipid metabolism parameters. The level of β2-microglobulin correlated with the lipid metabolism parameters.

Conclusion. Regardless of the level of albuminuria, men with T1DM had significantly increased levels of podocalyxin, lipid metabolism parameters, and methylglyoxal, as well as strong relationships between these parameters. The data of this study can be used for development of potential strategies for prevention and early treatment of diabetic nephropathy.

Keywords: type 1 diabetes mellitus, men, albuminuria, podocalyxin, β-2-microglobulin, carbonyl stress, lipids

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All participants signed an informed consent to take part in the study. The study was approved by the local Ethics Committee at the Scientific Center for Family Health and Human Reproduction Problems (Protocol No. 8.2 of 02.11.2018).

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Маркеры почечного повреждения, липидного обмена и карбонильного стресса у пациентов с сахарным диабетом I типа и разным уровнем альбуминурии

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РЕЗЮМЕ

Цель – изучение уровня подокаликсина, β-2-микроглобулина, показателей липидного обмена и карбонильного стресса у пациентов с сахарным диабетом (СД) I типа и разным уровнем альбуминурии.

Материалы и методы. Проведено обследование 56 мужчин репродуктивного возраста с СД I типа, разделенных на две группы: 24 пациента с альбуминурией стадии А1 (группа А1) и 32 – с альбуминурией стадии А2 (группа А2). Контрольную группу составили 28 здоровых мужчин. Оценивался уровень почечных маркеров, компонентов липидного обмена и метилглиоксаля (МГ) с использованием иммуноферментных, спектрофотометрических и флюорометрических методов.

Результаты. Установлены более высокие значения медиан общего холестерина, триацилглицеридов и липопротеидов очень низкой плотности в обеих группах с СД I типа. В данных группах отмечались также повышенные значения медианы подокаликсина и основного показателя карбонильного стресса – МГ. Проведенный корреляционный анализ в группе А1 показал наличие зависимости уровня скорости клубочковой фильтрации (СКФ) и креатинина. В группе А2 отмечались связи общепринятых показателей почечного повреждения (соотношения альбумин/креатинин и СКФ) с длительностью заболевания, показателя СКФ с уровнем креатинина и МГ. Уровень подокаликсина в данной группе коррелировал с уровнем β2-микроглобулина, МГ, показателей липидного обмена; β2-микроглобулин имел взаимосвязи с параметрами липидного обмена.

Заключение. У мужчин с СД I типа вне зависимости от уровня альбуминурии отмечаются значительно более высокий уровень подокаликсина, увеличенные показатели липидного обмена и МГ, а также наличие тесных взаимосвязей между этими параметрами, что может быть использовано для разработки потенциальных стратегий профилактики и ранней терапии диабетической нефропатии.

Ключевые слова: сахарный диабет I типа, мужчины, альбуминурия, подокаликсин, β-2-микроглобулин, карбонильный стресс, липиды

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Diabetes mellitus (DM) is considered a pressing problem due to the development of numerous complications. Diabetic nephropathy (DN) occupies a prominent place among the DM complications due to early disability and mortality [1, 2]. The incidence of DN among patients with type 1 diabetes mellitus (T1DM) is 20.1% [3]. DN is a complex lesion of the arteries, arterioles, glomeruli, and tubules of the kidneys, often leading to the development of diffuse or nodular glomerulosclerosis and, subsequently, to chronic renal failure [4].

Multiple factors contribute to the DN development, including metabolic (hyperglycemia, hyperlipidemia) and hemodynamic factors [2, 4]. Poor glycemic control and hereditary predisposition contribute to the progression of DN[1]. Hyperglycemia can adversely affect renal structures through a number of factors, such as activation of the sorbitol pathway of glucose metabolism, increased synthesis of diacylglycerol, accumulation of non-enzymatic glycation products of proteins and lipids in tissues, etc. [5, 6]. It is commonly accepted to differentiate several stages in DN development; however, it was established that changes in kidney tissues in patients with diabetes occur already when excretion of albumin in the urine is normal [7]. For this reason, it becomes especially important to clarify the mechanisms that contribute to early changes in renal structures in DM patients. Currently, the main groups of new potential renal markers have been identified: tubular markers, markers of podocyte damage, growth factors, immune and inflammatory factors, and products of extracellular matrix metabolism, that allow to predict the development of DN with high specificity and sensitivity [8].

Carbonyl stress is a condition that is accompanied by an increase in the content of carbonyl compounds, such as aldehydes, ketones, carboxylic acids, carbohydrates, etc. Most of the compounds of such nature are aldehydes: malondialdehyde, 4-hydroxynonenal, glyoxal, methylglyoxal, acrylic aldehyde, etc. [9]. Most aldehyde synthesis reactions involve free radicals or free radical oxidation products, which determines a close causal relationship between carbonyl and oxidative stress [10]. Currently, it has been shown that carbonyl compounds can accumulate in the body for a long period of time in DM, which together with additional pathogenetic mechanisms leads to serious dysregulations in the kidneys [11, 12].

Despite the available research data, there is still insufficient knowledge about the relationship between various factors of kidney injury and carbonyl stress parameters in the T1DM development. Therefore, the aim of this study was to investigate the levels of podocalyxin, β-2-microglobulin, and lipid metabolism and carbonyl stress parameters in T1DM patients with different levels of albuminuria.

MATERIALS AND METHODS

The data of 56 T1DM patients of young reproductive age (average age 30.25 ± 8.51 years) with a poor glycemic profile were used. According to the latest classification, this group was divided into 2 subgroups: patients with stage A1 albuminuria (group A1) (n = 24, average age 29.38 ± 9.78 years) and patients with stage A2 albuminuria (group A2) (n = 32, average age 30.88 ± 7.54 years) [13]. According to the disease duration, glycated hemoglobin level (HbA1c), and glycemic profile, the mean values in these groups did not differ from each other ($p > 0.05$).

The examination of patients included a comprehensive assessment of clinical and laboratory data. The glycemic profile (fasting blood glucose, postprandial glucose 2 hours after a meal) was assessed. The concentration of glycated hemoglobin (HbA1c) was determined by ion-exchange high-performance liquid chromatography, using a D-10 analyzer (Bio-Rad, USA). The following diagnostic methods were used to assess early kidney injury: glomerular filtration rate (GFR), albumin content, urinary albumin / creatinine ratio. The albumin content and the albumin / creatinine ratio in the urine were determined on the SYNCHRON CX9 PRO biochemical analyzer (Beckman Coulter, USA) using the immunoturbidimetric assay. GFR was calculated according to CKD – EPI equation (ml / min / 1.73 m^2).

The research materials were serum and urine. The level of podocalyxin in the urine was determined by enzyme immunoassay using the Podocalyxin ELISA Kit (USA). The level of β-2-microglobulin in the urine was determined using the Beta-2-microglobulin kit (BioChemMack, Russian Federation). The content of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and triacylglycerols (TG) in the blood serum was determined using the

Bio Systems commercial kits (Spain). Measurements were carried out on the SYNCHRON CX9 PRO biochemical analyzer (Beckman Coulter, USA). The level of very-low-density lipoprotein (VLDL) cholesterol was calculated using the following formula: VLDL = TG / 2.2; and low-density lipoprotein (LDL) cholesterol = TC – (HDL + VLDL). The content of methylglyoxal, a carbonyl stress parameter in the blood serum, was determined using the Human Methylglyoxal ELISA Kit (USA). Enzyme immunoassay was performed on the MultiSkan ELX808 microplate reader (Biotek, USA).

This study was carried out using the equipment of the Center for the Development of Progressive Personalized Health Technologies at Scientific Center for Family Health and Human Reproduction Problems (Irkutsk).

Statistica 8.0 package (StatSoft Inc., USA) was used for statistical processing of the obtained results. At the first stage, the normality of distribution was determined by the visual – graphic method and the Kolmogorov – Smirnov test with the correction using the Lilliefors and Shapiro – Wilk tests). The equality of generalized variance was checked using Fisher's exact test (F-test). Further, due to the difference between the sample and the normal distribution, the nonparametric Mann – Whitney test was used. The results were presented as the median and the interquartile range of $Me[Q_1–Q_3]$. The Spearman's rank correlation coefficient was used for correlation analysis. The differences were considered statistically significant at $p = 0.05$.

RESULTS

The analysis of serum lipid content in T1DM patients in the groups with different levels of albuminuria is presented in Table 1.

Table 1

Serum lipid content in T1DM patients with different levels of albuminuria, *Me* [Q_1–Q_3]

Parameter, mmol / l	Control group	Group A1	Group A2
TC	4.21 [3.74–4.58]	4.6 [4.15–5.18]*	4.65 [4.15–5.5]*
TG	0.66 [0.47–0.93]	1 [0.8–1.55]*	1.2 [0.8–1.8]*
HDL cholesterol	1.28 [1.00–1.4]	1.39 [1.1–1.5]	1.3 [1–1.7]
LDL cholesterol	2.47 [2.22–2.99]	2.44 [1.96–2.86]	2.37 [1.98–2.9]
VLDL cholesterol	0.3 [0.21–0.42]	0.46 [0.36–0.71]*	0.55 [0.36–0.82]*

* Here and in Table 2, statistically significant differences with the control group ($p < 0.05$).

According to the results, group A1 had higher median values of TC ($p = 0.005$), TG ($p = 0.007$), and VLDL cholesterol ($p = 0.007$) compared with the controls (Table 1). Group A2 also differed from the control values in higher TC ($p = 0.001$), TG ($p = 0.022$), and VLDL cholesterol ($p = 0.022$). No statistically significant differences ($p > 0.05$) were identified in the other parameters in the study groups (Table 1).

Urinary excretion levels of kidney injury markers were measured in groups A1 and A2 (Figure). Higher levels of podocalyxin were found in group A1 ($p = 0.003$) and group A2 ($p = 0.004$) compared with the control group. No significant differences were found concerning β2-microglobulin ($p > 0.05$).

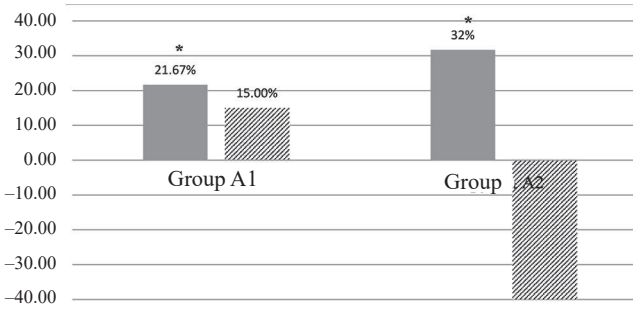

Figure. Urinary excretion levels of podocalyxin and β-microglobulin in patients with T1DM and different levels of albuminuria, %. * Statistically significant differences with the control group ($p < 0.05$). The control values are taken as 0%

Table 2 shows the results of assessing the concentration of serum methylglyoxal, a key carbonyl stress parameter, in patients with T1DM. It was found that higher median methylglyoxal values ($p = 0.031$) in group A1 were noted compared with the control. In group A2, similar differences were found ($p < 0.001$) compared with the control.

Table 2

Serum methylglyoxal concentration in patients with T1DM and different levels of albuminuria, *Me*[Q_1–Q_3]

Control group	Group A1	Group A2
2.14 [1.02–3.67]	3.24 [2.6–3.51]*	3.46 [2.9–4.21]*

The correlation analysis conducted in group A1 showed a single relationship between GFR and creatinine ($r = –0.79$; $p = 0.0001$). Group A2 was characterized by correlations between the duration of the disease and albumin / creatinine ratio ($r = 0.47$;

$p = 0.018$) and between GFR and blood creatinine level ($r = –0.44$; $p = 0.027$) and methylglyoxal level ($r = 0.64$; $p = 0.043$). Podocalyxin levels in this group correlated with the levels of another renal marker, β2-microglobulin ($r = 0.47$; $p = 0.018$), and with the methylglyoxal level ($r = 0.52$; $p = 0.008$). In addition, podocalyxin showed correlations with lipid metabolism parameters: TC ($r = 0.42$; $p = 0.036$), TG ($r = 0.41$; $p = 0.04$), VLDL cholesterol ($r = 0.41$; $p = 0.04$). β2-microglobulin had correlations with TC ($r = 0.52$; $p = 0.007$), TG ($r = 0.42$; $p = 0.035$), and VLDL cholesterol ($r = 0.42$; $p = 0.035$). In group A2, there were also multiple correlations of lipid metabolism parameters among themselves and with other parameters: TC – TG ($r = 0.62$; $p = 0.001$), TC – VLDL cholesterol ($r = 0.62$; $p= 0.001$), TG – VLDL cholesterol ($r = –0.6$; $p = 0.002$), LDL cholesterol – VLDL cholesterol ($r = –0.6$; $p = 0.002$), HDL cholesterol – creatinine ($r = –0.43$; $p = 0.032$).

DISCUSSION

Assessment of the serum lipid content in the groups showed a slight increase in TC, TG, and VLDL cholesterol in groups A1 and A2. Currently, hyperlipidemia is considered as a separate serious factor in DN progression due to the direct relationship of complex lipid disorders with the formation of glomerulosclerosis [4, 14]. In our study, there were no significant changes in the lipid content in both groups, although a definite trend was observed. Hyperlipidemia has recently been considered as a separate nephrotoxic factor, with a clear parallel drawn between the processes of glomerulosclerosis and vascular atherosclerosis [15]. It was found that oxidized LDL, growth factors, and cytokines increase synthesis of mesangial matrix components, accelerating glomerular sclerosis, which contributes to the progression of DN [4].

The analysis of the urinary excretion levels of podocalyxin and β-microglobulin in the study groups showed significant changes only for podocalyxin. We noted that its urinary excretion was elevated in both groups relative to the control, with higher excretion in group A2. Podocalyxin is a specific protein expressed on the surface of podocytes [16]. Experimental studies on models of DN formation showed that podocyte damage plays a crucial role in filtration barrier permeability disorders and glomerulosclerosis development, with significant podocyte desquamation into the urinary space [17].

Currently, the link between the number of podocytes in the urine and kidney diseases, such as nephropathy, systemic nephritis, focal segmental glomerulosclerosis, etc., has been convincingly proven [18]. This parameter reflects damage to the juxtaglomerular apparatus of the kidneys, with increased podocyte excretion in the urine [19]. Several studies showed that podocyturia develops in 74% of patients with normal albuminuria and in 54% of patients with microalbuminuria, with the same frequency in types 1 and 2 diabetes [20]. These data indicate that podocytes in DM are damaged much earlier than filtration barrier permeability disorders occur, i.e. in stage A2 albuminuria [21]. Thus, our data confirm previous studies on the increase in this parameter in patients with DN [19, 20].

Another parameter, β-microglobulin, showed no significant changes in both groups. This parameter characterizes damage to the renal tubules, and, thus, it can be stated that no pronounced changes of this kind were detected in the patients.

Methylglyoxal, a key carbonyl stress parameter, was elevated in T1DM patients of both groups. Methylglyoxal is a carbonyl compound, a precursor of glycotoxins formed by the non-enzymatic browning reaction [10, 12, 22]. Thus, under the conditions of chronic hyperglycemia, there is a significant increase in the intracellular glucose content, and pathological pathways of its metabolic transformation are activated along with insufficient utilization [6]. These processes, together with oxidative stress reactions, lead to the formation of stable Amadori products from reversible unstable Schiff bases. During the reactions, Amadori products are converted into fluorescent proteins, glycotoxins, and so-called advanced glycation end products (AGEs).

The latter were found to accumulate, slowly degrade, and persist for a long time in the vascular bed, even with further stabilization of glucose levels – a mechanism of metabolic memory [12, 23]. AGEs are involved in cross-linking of long-lived proteins, which contributes to arterial wall stiffening [23]. Their role was shown in the mitochondrial protein modification, impaired mitochondrial function, and overproduction of free radicals [10]. In this regard, methylglyoxal is considered as an important biomarker of diabetic complications due to

its close connection with glycation processes, β-cell dysfunction, and insulin resistance [24]. The amount of AGEs was found to be directly proportional to the level of blood glucose, and even a moderate increase in blood glucose leads to an increase in AGEs.

Methylglyoxal is also considered to be the most reactive among AGEs due to its direct involvement in disrupting insulin secretion and function, as well as in signal transduction processes. There is evidence that the intrinsic AGE receptor, RAGE, present on the cell surface, may serve as an important therapeutic target in DM patients with chronic kidney disease, and its blockade leads to a delay in the progression of vascular complications [22]. Thus, less functional damage to renal structures was observed in mice with AGE receptor knockout [23]. It was also found that increased AGE levels are closely associated with various structural and functional changes characteristic of DN, in particular with GFR. [12, 22]. Mitochondrial AGE formation is also thought to be an irreversible phenomenon underlying the metabolic memory mechanism through formation of reactive oxygen species, which in turn may contribute to the development of damaging effects in mitochondrial DNA and inhibition of the respiratory chain [24, 25].

Therefore, increased methylglyoxal concentrations in the blood of T1DM patients with microalbuminuria may indicate DM development, whereas under the conditions of stage A2 albuminuria, they may indicate a potential role of carbonyl stress in DN development. The correlation analysis in the group of patients with microalbuminuria revealed a regular relationship between GFR and creatinine. Under the conditions of stage A2 albuminuria, there were correlations between the generally accepted parameters of kidney injury (albumin / creatinine ratio and GFR) and the duration of the disease. Podocalyxin showed a close relationship with methylglyoxal, which may indicate a significant contribution of glycotoxins to the mechanisms of kidney injury during the development of albuminuria.

This fact was also confirmed by the revealed relationship of methylglyoxal with GFR. Although no changes in the mean values of β-microglobulin were detected in group A2, this parameter correlated with podocalyxin, which demonstrates the similarity of their damaging effects in different parts of the juxtaglomerular apparatus of the kidneys. The similarity of podocalyxin and β-microglobulin correlations with the lipid content (TC, TG, and VLDL cholesterol), which may be due to the significant contribution of these components to the DN progression, is of great interest.

CONCLUSION

It can be stated that men with T1DM have an increase in podocalyxin, which indicates damage to the juxtaglomerular apparatus of the kidneys. The development of carbonyl stress is also recorded. These disorders also apply to stage A1 albuminuria, when pronounced changes in the functioning of renal structures have not yet occurred. This confirms the suggestion that even in early stages of the disease there are conditions for the activation of adverse factors and progression of diabetic complications. This can be used to develop potential strategies for prevention and therapy of DN.

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Darenskaya M.A. – conception and design, statistical processing of the results, drafting and editing of the manuscript. Chugunova E.V. – examination of patients, collection and processing of clinical and laboratory data, analysis of statistical data, drafting of the manuscript. Kolesnikov S.I. – conception and design, analysis of the results, drafting and final editing of the manuscript. Grebenkina L.A. – collection and processing of clinical and laboratory data. Semyonova N.V. – analysis of results, collection and processing of clinical and laboratory data. Nikitina O.A. – collection and processing of clinical and laboratory data. Kolesnikova L.I. – conception and design, analysis of the results, drafting and final editing of the manuscript. All the authors made a significant contribution to the research and preparation of the manuscript, read and approved the final version of the manuscript before publication.

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