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The Role of ICAM-1 Expression in Renal Tissue in the Progression of Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Diabetic nephropathy is the main microvascular complication of diabetes mellitus (DM). Intercellular adhesion molecule 1 (ICAM-1) plays a critical role in the development of morphological changes in renal tissue in patients with type 2 (T2DM) diabetes mellitus. The work is devoted to studying the role of ICAM-1 (CD54) expression in renal tissue in the development and progression of morphological changes in diabetic kidney disease (DKD) in patients with T2DM.

Objective: The examination was carried out in 50 patients with T2DM (mean age 66.58±3.27 years). There were 35 women, 14 men. The duration of disease in patients with diabetes was 17.70 ± 0.35 years. The duration of DKD from the moment of detection of microalbuminuria to the morphological examination of the renal tissue and diagnosis was 1.65±0.34 years.

Methods: All patients underwent light and immunofluorescence microscopy of kidney tissue biopsies. Morphological changes in tissue were assessed according to the latest international classification of diabetic nephropathy, developed in 2010. CD54 (ICAM-1) expression was determined using monoclonal antibodies labeled FITC (anti-human CD54 Antibody) (USA).

Results: According to light microscopy, class IIa (mild mesangial expansion) was detected in 12 patients, class IIb (severe mesangial expansion) in 14 patients, class III (Kimmelstiel-Wilson lesions) in 19 patients and in 5 patients – class IV (advanced diabetic glomerulosclerosis). It has been shown that there is a regression model between the expression of ICAM-1 in the glomerular endothelium with the development of expansion of the mesangial matrix, thickening of the basement membrane and arteriolar hyalinosis. Expression in peritubular capillaries is associated with the development of tubulointerstitial fibrosis and progression of diabetic kidney disease in patients with T2DM.

Conclusions: Based on the data obtained, it was suggested that the study of ICAM-1 expression in kidney tissue can be used as a biomarker for the progression of kidney disease in patients with T2DM.

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Introduction

According to the International Diabetes Federation (IDF), in 2021, approximately 536.6 million (10.5%) people suffered from Diabetes Mellitus (DM) worldwide; by 2045, this number will increase by 100-250 million people and will be about 783. 2 million (12.2%) [1,2]. In 2016, of the 23 million adults in the United States, 90.9% were diagnosed with T2DM and only 5.8% were diagnosed with type 1 (T1DM) diabetes mellitus [3]. Due to the rising incidence of Diabetes Mellitus, DKD is now the leading cause of end-stage renal disease (ESRD) worldwide. Patients with diabetes are almost twice as likely to develop chronic kidney disease (CKD) as people without diabetes. The odds ratio for developing CKD ranges from 1.3 to 4.6 depending on the region of the world, and this risk is exacerbated by the presence of hypertension. The percentage of patients who develop CKD as a result of diabetes is unclear. This is due to the presence of other factors that contribute to renal dysfunction, including hypertension, dyslipidemia, obesity, cerebrovascular disease, acute kidney injury (AKI), arteriolonephrosclerosis, renal ischemia, and nephron loss associated with aging. Consequently, it is rarely possible to accurately define "diabetic kidney disease" (DKD) or

"diabetic nephropathy" (DN) in epidemiology or clinical practice in patients with T2DM [4].

The prevalence of CKD among people with diabetes varies greatly between countries. The development of T2DM, unlike T1DM, often goes unnoticed, and therefore the prevalence and incidence are underestimated. The prevalence of type 2 diabetes is highest in North America, the Caribbean, the Western Pacific, and the Middle East and North Africa and lowest in sub-Saharan Africa. The increase in the prevalence of diabetes is driven by T2DM and is projected to increase by 61.2% (95% UI 56.2-68.1), from 5.9% (5.5-6.3) in 2021 to 9.5% (9.0-9.9) in 2050, affecting more than 1.27 billion (1.19-1.35) people. This varies by region, from 82.7% (76.8-90.5) in North Africa to 30.3% (27.3-33.0) in the high-income region of the Middle East. Age-adjusted prevalence of T2DM will increase by more than 70% in six regions: North Africa and the Middle East (82.7%; 76.8-90.5), eastern Asia (80.1%; 72.1-89.2), central sub-Saharan Africa (79.9%; 72.4-89.9), southern sub-Saharan Africa (74.7%; 67.9-83.7), central Latin America (74.7%; 68.5-80.2), and Australia (71.9%; 63.6-81.8). The age-standardized T2DM prevalence is projected to increase by more than 100% in 11 countries in three regions: seven countries (Oman, United Arab Emirates, Syria, Iran, Libya, Sudan, and Saudi Arabia) in north Africa and the Middle East, two countries (Kenya and Tanzania) in eastern sub-Saharan Africa, and two countries (Zimbabwe and Botswana) in southern sub-Saharan Africa. Those at highest risk for developing end-stage renal disease due to DKD include middle-aged African Americans, Native Americans, and Hispanics [5-7]. According to data published by Alicic R.Z. et al. the incidence of T2DM is about 40% [8]. DM poses enormous problems to public health and health care delivery systems worldwide. In 2021, WHO launched the Global Compact on Diabetes to improve care for and work closely with people with diabetes. An indicator of the state of the healthcare system in different countries is the treatment of diabetes, reducing premature mortality from diabetes and other non-communicable diseases by a third by 2030 [9].

DN is one of the main microvascular complications of DM, characterized by structural and functional changes. The morphological changes observed in the kidneys with DN affect almost all nephron structures: the glycocalyx and glomerular endothelial cells, the glomerular basement membrane (GBM), podocytes and slit diaphragm, the mesangial matrix, the renal interstitium and renal tubules [10]. Morphological damage to renal tissue in T1DM and T2DM is identical, although there is a point of view that the heterogeneity of type 2 diabetes plays an additional role [11]. The earliest signs of DN are thickening of the glomerular basement membrane (GBM), soft mesangial expansion, and arteriolar hyalinosis. Mesangiolysis and mesangial damage finally lead to marked mesangial expansion, the formation of Kimmelstiel–Wilson nodules, hyalinosis of afferent and efferent arterioles, and severe thickening of the GBM. Glomerular lesions occur together with specific vascular lesions, including arteriolar hyalinosis, as a result of the accumulation of hyaline material, a product of exudation of plasma proteins, in both the structure of afferent and efferent arterioles [12]. Patients with T2DM often have a shorter period between diagnosis and the development of morphological damage to the renal tissue. This is likely due to the insidious and asymptomatic onset of T2DM [11].

In contrast, the history of kidney disease is often different. This discrepancy is mainly due to the shorter interval between diagnosis and overt renal damage in T2DM, which was initially simplistically explained by the insidious and asymptomatic onset of T2DM. This disease is increasingly being described in young patients with T2DM, where genetic background may play an important role.

As a result of chronic hyperglycemia, pathogenic changes in the vascular wall develop, and the frequency of micro- and macrovascular complications associated with morbidity and mortality among patients with diabetes increases. However, the exact mechanism of vascular complications is currently not completely clear [13]. Teodoro J.S., et al. in their work showed that oxidative stress is the result of hyperglycemia, and the production and secretion of pro-inflammatory cytokines by adipose tissue leads to the development of inflammation and endothelial dysfunction [14]. It is endothelial dysfunction that plays a key role in triggering the development of inflammatory mechanisms that are associated with vascular complications in patients with T2DM. Activation of the endothelium due to increased release of cytokines and expression of adhesion molecules promotes platelet activation and their adhesion to the activated endothelium [15]. The main cell adhesion molecules involved in the development of microvascular complications are intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and selectins (E-selectin, L-selectin and P-selectin) [16].

ICAM-1 is a transmembrane glycoprotein of the immunoglobulin superfamily and is characterized by five distinct immunoglobulin-like domains, a transmembrane domain and a cytoplasmic tail, and is expressed in endothelial cells and leukocytes. This transmembrane protein plays a critical role in stabilizing cell-cell interactions and promoting endothelial transmigration of leukocytes [15]. Stimulation of increased ICAM-1 expression occurs in response to several types of stimuli, including pro-inflammatory cytokines, oxidative stress, activation of protein kinase C and advanced glycation end products (AGEs), hemodynamic changes [17,18].

Currently, kidney biopsy is still the gold standard for diagnosing diabetes complicated by renal disease, especially important when patients with type 2 diabetes develop atypical symptoms (for example, absence of diabetic retinopathy, short duration of diabetes, microscopic hematuria, subnephrotic range proteinuria, lower levels of glycated hemoglobin and fasting blood glucose) [19]. Xue Tong et al. in their work concludes that kidney biopsy is of great importance for personalized treatment of patients with T2DM [20].

Dong ZY et al. suggested that patients with type 2 diabetes complicated by renal disease should actively undergo renal biopsy for five reasons: 1). high importance of correct DKD diagnosis; 2). limitations in making a diagnosis of DKD; 3).the need for a biopsy-confirmed pathological diagnosis; 4). Indications for kidney biopsy; 5). Safety of kidney biopsy [21]. There is still no uniform standard for performing a kidney biopsy procedure throughout the world. Each country, each region, and each nephrologist's practice has its own criteria for performing a kidney biopsy. As a result, there is a wide variety of reports in the literature regarding the prevalence of DKD. Moreover, even if renal biopsy is strongly recommended by the treating nephrologist based on clinical factors, patient compliance is also a factor, resulting in large variability in the outcome. There is no consensus on the safety of kidney biopsy for kidney disease. There is a limited number of published studies worldwide on the development of standardized criteria for performing kidney biopsy in patients with DM [20].

The Aim of the Study

Research the role of ICAM-1 (CD54) expression in the glomerular endothelium and peritubular capillaries in patients with T2DM with different morphological classes of DN and to assess their influence on the development and progression of histological changes in renal tissue.

Material and Methods

The study included 50 patients suffering from T2DM complicated by the development of diabetic nephropathy. The average age of the patients was 66.58±3.27 years. There were 35 women, 14 men. The duration of disease in patients with diabetes was 17.70 ± 0.35 years. The duration of DN from the moment of detection of microalbuminuria to the morphological examination of the renal tissue and diagnosis was 1.65 ± 0.34 years. At the time of the examination, all patients were receiving complex antihypertensive therapy (including ACE inhibitors or angiotensin II receptor blockers), arterial hypertension was compensated at the level of systolic blood pressure = 142.936 ± 2.312 mm Hg (95% CI: 138.511 - 147.468) and diastolic blood pressure = 80.021±1.018 mmHg (95% CI: 78.043 - 82.063). It should be noted that all patients had stage 2 Chronic Kidney Disease (GFR CKD-EPI = 69.445 ± 4.684 ml/min (95% CI: 60.097 - 78.540), without severe creatinemia (serum creatinine level 106.400 ± 7.521 μmol/l (95 % CI: 93.260 - 122.612) and albuminuria level A2 (1143.020 ± 316.012 mg/day (95% CI: 597.304 - 1789.044). The clinical research carried out in compliance with the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2013) and the Protocol of Council of Europe Convention on human rights and biomedicine 1999 and articles 20, 22, 23 of the Act "On the basics of healthcare for the Russian Federation citizens" dated November 21, 2011 Fed. Statute №323-FZ (May 26, 2021 edition). The clinical study was conducted in accordance with a procedure approved by the local ethical committee under LLC "Center of Dialysis of St. Petersburg" FRESENIUS MEDICAL CARE. All study participants had signed voluntary informed consent.

The indication for a puncture biopsy of the kidney was an increase in the level of albuminuria in the absence of diabetic retinopathy. All patients underwent light and immunofluorescence microscopy of renal tissue biopsies obtained by intravita percutaneous kidney biopsies. Biopsies were performed by nephrologists under ultrasound guidance. The biopsy contained at least 10 glomeruli, excluding incomplete glomeruli at the biopsy margin, as recommended [22].

Standard biopsy staining for light microscopy was performed using hematoxylin and eosin, periodic acid-Schiff stain (PAS), Masson's trichrome, and periodic acid-methenamine silver stain. Morphological changes in tissue were assessed in accordance with the latest international classification of diabetic nephropathy developed by the Scientific Committee of the Pathology Society, USA [23]. In 2006 in San Diego and in September 2008 in Leiden, the Research Committee of the Society of Renal Pathology discussed the creation of a classification of DN, which was adopted and published in 2010. According to the accepted classification, four classes of DN are identified.

Class I: Thickening of the glomerular basement membrane. In the absence of mesangial expansion, Kimmelstiel–Wilson lesion, and global glomerulosclerosis of more than 50% of the glomeruli, the biopsy is classified as class I. GBM thickness averages thicker than 430 nm in men and thicker than 395 nm in women. These extreme levels are described as "prediabetic" lesions: in patients with proteinuria and isolated thickening of the GBM, but without overt diabetes. This group includes cases that were called "normal or near normal DN" [23].

Class II: Mesangial expansion, mild (IIa) or severe (IIb). Mesangial expansion is defined as an increase in extracellular material in the mesangium such that the width of the intercellular space exceeds two mesangial cell nuclei in at least two lobes of the glomerulus. The difference between mild and severe mesangial expansion is based on whether the mesangial expansion is smaller or larger than the average capillary lumen area. If there is moderate mesangial expansion in more than 25% of the total mesangium, the biopsy is classified as IIa. If there is significant mesangial expansion in more than 25% of the total mesangium, the biopsy is classified as IIb.

Class III: Nodular sclerosis (Kimmelstiel-Wilson lesions). The presence of one Kimmelstiel–Wilson lesion in the biopsy specimen and no more than 50% total glomerulosclerosis is classified as class III. Kimmelstiel–Wilson lesions appear in T1DM and T2DM as focal, lobular, round-oval mesangial lesions with an acellular hyaline/matrix core surrounded peripherally by sparse crescent-shaped mesangial nuclei [25]. In the initial stage of development of nodular sclerotic lesions in DN, two important processes occur: lytic changes in the mesangial region, called mesangiolysis, and detachment of endothelial cells from the GBM. Dissociation of endothelial cells disrupts connections between the mesangial region and the GBM, which precedes Kimmelstiel–Wilson lesions, which consist of an accumulation of mesangial matrix with collagen fibrils, small lipid particles, and cellular debris. A fully developed Kimmelstiel–Wilson lesion destroys the normal structure of the glomerular tuft with a decrease in the number of mesangial cells, especially in the central region. The nodules are distributed in a horseshoe-shaped area corresponding to the peripheral or intralobular mesangium. The formation of Kimmelstiel–Wilson lesions is considered transitional from an early or moderate stage to disease progression [26].

Class IV: progressive diabetic glomerulosclerosis. Class IV implies a progressive course of DN with more than 50% of cases of total glomerulosclerosis, with clinical or pathological evidence that sclerosis is associated with DN. Glomerulosclerosis in DN is the endpoint of multifactorial mechanisms that lead to excessive accumulation of extracellular matrix proteins such as collagen types I, III and IV, and fibronectin in the mesangial space, ultimately leading to glomerulosclerosis [27].

Light microscopy of kidney biopsy tissue was assessed using the following indicators: the presence of global and segmental glomerular sclerosis; cellularity of the glomerulus; severity of expansion of the mesangial matrix (less than and more than 25%); GBM thickening; Kimmelstiel–Wilson nodules; availability of capsule drops; periglomerular sclerosis; sclerotic changes in the interstitium; the presence and severity of mononuclear inflammatory infiltrates in the interstitium; the presence of protein masses in the lumens of the tubules; atrophy and dystrophy of the epithelium of the urinary tubules (thickness of the apical edge and height of the epithelium of the tubules); hyalinosis of afferent and efferent arterioles.

The severity of morphological changes was assessed using a semi-quantitative method in points (0–3). Global and segmental glomerular sclerosis was assessed as the percentage of globally and segmentally sclerotic glomeruli from the total number of glomeruli in the nephrobiopsy section. Interstitial fibrosis and

tubular atrophy (IFTA) was assessed as a percentage of the total interstitial and tubular area affected. Score 0 - absence of IFTA in the biopsy; score 1 - IFTA less than 25%; score 2 - 25%, but less than 50% of biopsies have IFTA; score 3 - IFTA at least 50% [28]. Mononuclear infiltration (IM), afferent and efferent hyalinosis (AH) were also scored (0–2 and 0–2, respectively) according to the criteria of the international classification of DN [23].

According to light microscopy, class IIa (mild mesangial expansion) was detected in 12 patients, class IIb (severe mesangial expansion) in 14 patients, class III (nodular Kimmelstiel-Wilson lesions) in 19 patients, class IV in 5 patients (advanced diabetic glomerulosclerosis). Based on the results of light microscopy, no evidence of glomerulonephritis was obtained in any patient.

In all patients, the expression of ICAM-1 (CD54) was determined using monoclonal antibodies labeled with FITc (FITC anti-human CD54 Antibody, clone HCD54 Cat#322720, Biolegend, USA). The intensity of expression in points (0–4) , the nature and location of CD54 expression in the glomerular endothelium and in peritubular capillaries were assessed [29].

Statistical Analysis

Statistical treatment of acquired data was conducted by means of a software package IBM SPSS Statistics, 26 version (Armonk, NY: IBM Corp.). Group results are presented in form of mean arithmetic M ± Standard Error. Statistical comparison of data between patient groups was carried out using nonparametric Mann–Whitney U. Differences in continuous variables were assessed using the independent sample Student's t test and were considered significant if $p \leq 0.05$. Parametric (Pearson's method) and non-parametric (Spearman's criterion method, Kendall's tau (τ) method) were used for statistical processing. To verify compliance with condition of independence of observations we conducted linear regression analysis (with computation of coefficient of determination (R Square) and criterion of Durban-Watson) and dispersion analysis (ANOVA Analysis of Variance) with computation of criterion of Fisher (F) for verification of model significance. Standardized rate ß with 95% confidence intervals was calculated. Critical significance level of difference of indicators was taken to be equal 0.05.

Results

Expression of ICAM-1 (CD54) in the renal tissue of patients with T2DM was detected in the area of glomerular endothelium and periglomerular capillaries. The results obtained are presented in Table 1.

Table 1: Intensity of ICAM-1 expression in glomerular capillary endothelium and peritubular capillaries in patients with type 2 diabetes with DN

Expression area	Intensity of ICAM-1 expression
Glomerular endothelium	1,297 ± 0,163 Me=1,101 (95% CI: 0,978 - 1,617)
Peritubular capillaries	1,276± 0,1458 Me=1,036 (95% CI: 0,978 - 1,553)

Pronounced expression of ICAM-1 was detected in both glomerular endothelium and peritubular capillaries. ICAM-1 expression was not detected in the mesangial cell region or tubules.

Table 2 shows the severity of ICAM-1 expression in renal tissue depending on the class of DN (Table 2).

Table 2: Intensity of ICAM-1 expression in kidney tissue depending on the class of DN

Expression area	IIa class (n = 12) (1)	IIb class (n = 14) (2)	III class (n = 19) (3)	IV class (n = 5) (4)	P
ICAM-1 expression in glomerular endothelium					
Glomerular endothelium	1,500 ±0,372 Me=1,269 (95% CI: 0,800 – 2,200)	1,142 ± 0,261 Me=1,027 (95% CI: 0,642 – 1,642)	1,000 ± 0,208 Me=0,942 (95% CI: 0,613 – 1,421)	0,500± 0,227 Me= 0,797 (95% CI: 0,083 – 1,000)	P1,2=0,05 P1,3=0,01 P1,4=0,001 P2,3=0,08 P2,4=0,04 P3,4=0,05
ICAM-1 expression in peritubular capillaries					
Peritubular capillaries	1,400±0,380 Me=1,264 (95% CI: 0,700 - 2,100)	1,285 ±0,238 Me=0,913 (95% CI:0,857 – 1,785)	1,157 ±0,221 Me=1,014 (95% CI: 0,736 – 1,613)	0,750±0,207 Me=0,753 (95% CI: 0,333 – 1,166)	P1,2=0,07 P1,3=0,06 P1,4=0,001 P2,3=0,07 P2,4=0,05 P3,4=0,06

The results show that the intensity of ICAM-1 expression decreases as morphological changes progress. The maximum intensity of expression was detected in the class IIa group and was assessed mainly as 3 points; in the class IIb group, the expression intensity was assessed as 2 and 3 points; in the class III group, expression was assessed as 2 points; in the class IV group - 1 point. This was observed both in the region of the glomerular endothelium and peritubular capillaries.

During a correlation analysis of the relationship between ICAM-1 expression in renal tissue and morphological changes separately in each group, the following results were obtained: ICAM-1 expression in the glomerular endothelium is associated with the development of thickening of the basement membrane in patients with class IIa DN ($\tau = 0.753$ $p = 0.014$; $r=0.823$ $p=0.003$; $R=0.815$ $p=0.004$). No other correlations were identified. Next, a correlation analysis was carried out on the effect of ICAM-1 expression in renal tissue on morphological changes in the general group of T2DM patients with DN. The data obtained are presented in Table 3.

Table 3: Correlation of ICAM-1 expression in renal tissue with morphological changes in DN in the general group of patients

Morphological changes	Correlations		
	Kendall(τ)	Spearman (r)	Pearson (R)
ICAM-1 expression in glomerular endothelium			
Mesangial matrix expansion	τ= -0,339 p=0,011	r= -0,373 p=0,010	R = -0,398 p=0,006
ICAM-1 expression in peritubular capillaries			
Periglomerular sclerosis	τ=0,281 p=0,038	r=0,310 p=0,036	-

The table data shows that the expression of ICAM-1 in the glomerular endothelium inversely affects the development of expansion of the mesangial matrix, and expansion in the peritubular capillaries contributes to the development of periglomerular sclerosis. No other correlations with the influence of ICAM-1 expression in the general group of patients were identified. In order to identify the prognostic significance of ICAM-1 expression in the development of morphological changes in renal tissue and the progression of the stage of DN, we conducted a regression analysis with the calculation of coefficients of determination R2 (R Square) and analysis of variance (ANOVA Analysis of Variance) using the F test with a 95% confidence interval . The obtained values, indicating the significance of the regression models, are presented below (Table 4).

Table 4: Regression models of the significance of ICAM-1 expression in the glomerular endothelium in the general group of DN patients

Morphological changes	Coefficient of determination (R2)	Standardized coefficient (ß)	Fisher test (F)	P
ICAM-1 expression in glomerular endothelium				
Mesangial matrix expansion	0,532	β=0,732	53,059	0,000
Basement membrane thickening	0,520	β=0,720	49,919	0,000
Arteriole hyalinosis	0,445	β=0,670	38,644	0,000
ICAM-1 expression in peritubular capillaries				
Interstitial sclerosis	0,457	β=0,685	40,646	0,000
Atrophy of tubular epithelium	0,548	β=0,740	55,603	0,000

The table data shows that increased of ICAM-1 expression in the glomerular endothelium is associated with the severity of mesangial matrix expansion, basement membrane thickening and arteriolar hyalinosis. Also, we can talk about the presence of a regression model between increased of ICAM-1 expression in peritubular capillaries and the development of interstitial sclerosis with atrophy of tubular epithelium. The totality of these data fits into the obtained regression model of the intensity of ICAM-1 expression in the glomerular endothelium and the progression of the stage of DN in the general group of patients: R2= 0,430 β=0,620 F= 36,420 p=0,000.

Discussion

The literature contains numerous research data on the role of adhesion molecules and selectins in the development of DN in patients with DM [30]. Infiltration of leukocytes into the site of inflammation occurs through adhesion to endothelial cells and transmigration from the lumen of blood vessels. Adhesion molecules are expressed on the surface of cells and mediate intercellular binding and attachment of the cell to the matrix. Expressed on leukocytes and endothelial cells, adhesion molecules promote the adhesion of leukocytes to vascular endothelial cells. Further, leukocyte adhesion to the endothelium is mediated by intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [31].

Published works devoted to the study of integrin expression in tissue are mainly presented on experimental animals. In an experiment, ICAM-1-deficient (ICAM-1 (-/-)) mice and ICAM-1 (+/+) mice were induced to develop diabetic nephropathy. ICAM-1 expression has been shown to be increased in the glomeruli of diabetic ICAM-1(+/+) mice [32]. The results of the work showed that glomerular infiltration of macrophages was lower in diabetic ICAM-1(-/-) mice compared with that of ICAM-1(+/+) mice. Maximum expression of ICAM-1 in peritubular capillaries and tubular epithelial cells was detected in ICAM-1+/+ mice. The authors of the work concluded that ICAM-1 plays an important role in interstitial infiltration by macrophages and the development of interstitial fibrosis32. In experimental conditions on rats with diabetes, expression of ICAM-1 in glomerular endothelial cells and participation in the development of DN was shown [33].

The first study of ICAM-1 expression in biopsy tissue from five normal kidneys and 47 kidney biopsies with different morphological diseases (rapidly progressive glomerulonephritis, mesangioproliferative glomerulonephritis, IgA nephropathy, Henoch-Schönlein purpura, lupus nephritis and focal segmental glomerulosclerosis) was published in 1991 [34]. The authors of the work showed that ICAM-1 expression was detected on 59% of infiltrating mononuclear cells in all forms of glomerulonephritis. In 1993, J A Bruijn and N J Dinklo published the results of an immunohistochemical analysis of ICAM-1 expression in healthy volunteers and patients with different forms of chronic glomerulonephritis. Increased expression of ICAM-1 was detected only on the endothelium of interstitial arterioles and venules of affected kidneys; expression was absent or weakly expressed in peritubular and interstitial capillaries. The authors of the work were the first to demonstrate the expression of ICAM-1 in

different morphological forms of glomerulonephritis and showed the role of ICAM-1 in the pathogenesis of immune-mediated glomerulonephritis [35].

Fuggle S.V. et al. published the results of a study of the expression of adhesion molecules in renal tissue and showed a high correlation between the number of infiltrating leukocytes and the amount of expression of endothelial cell adhesion molecules ICAM-1, VCAM-1 and E-selectin in renal pre-transplant biopsies (n = 20) and renal transplant biopsies (n = 42) [36]. There were differences in endothelial expression of ICAM-1 and VCAM-1 in the proximal tubule between pre- and post-transplant biopsies. After transplantation, tubular induction of ICAM-1 and VCAM-1 expression was detected. The authors of the work suggested that the induction of the expression of adhesion molecules is associated with focal leukocyte infiltration.

In vivo studies in a rat model of nephrotoxic nephritis treated with interleukin-1 receptor antagonist also demonstrated that interstitial ICAM-1 expression is closely associated with interstitial leukocyte infiltration and tubulointerstitial damage. At the same time, glomerular expression of adhesion molecules does not play an important role in the development of tubulointerstitial damage [37]. The authors suggested that tubular expression of ICAM-1 and VCAM-1 may simply be a by-product of extensive leukocyte infiltration.

Roy-Chaudhury Prabir et al. conducted a study of the expression of integrins and selectins in 119 renal tissue biopsies from patients with different morphological variants of glomerulonephritis. There was a strong positive Spearman correlation between the degree of histological damage (tubular atrophy and interstitial fibrosis) and ICAM-1 expression (0.61, $P < 0.0001$). In the groups of patients with moderate and severe tubulointerstitial damage, the Spearman correlation between ICAM-1 expression in peritubular capillaries and in infiltrating lesions was significantly higher ($P < 0.0001$). This correlation was independent of the morphological diagnosis [38]. In our work, correlation analysis showed a connection between the expression of ICAM-1 in peritubular capillaries and the development of tubulointerstitial sclerosis in patients with T2DM (τ=0.281 p=0.038; and r=0.310 p=0.036; respectively). The linear regression method was used to show the influence of ICAM-1 expression in peritubular capillaries on the development of tubular epithelial atrophy ($p = 0.000$) and tubulointerstitial sclerosis ($p = 0.000$). Expression of ICAM-1 in the glomerular endothelium had no effect on the development of tubulointerstitial sclerosis, which is confirmed by the obtained unreliable data from regression analysis: R2 = 0,029 F = 1,322 β = 0,171 p = 0,256. Roy-Chaudhury Prabir et al. did not reveal a significant correlation between glomerular expression of ICAM-1 with tubulointerstitial damage and glomerular macrophage infiltration. In patients with T2DM in our study, there were also no associations between the expression of ICAM-1 in the glomerular endothelium and peritubular capillaries with cellular infiltration (R2 =0,053 β=0,231 F = 2,539 p = 0,118; and R2 =0.028 β=-0,169 F =1,316 p = 0,257; respectively). These data confirmed the data published by other researchers.

The results published by Roy-Chaudhury Prabir et al. suggest that there is a common pathway for tubulointerstitial injury, regardless of the primary diagnosis, and that the expression of adhesion molecules within the tubulointerstitium may be an important mechanism in its pathogenesis. This study supported the hypothesis that, regardless of the severity of the initial tissue damage, there may be a common mechanism responsible for the progression of renal dysfunction [38]..

Our analysis of biopsy tissue from patients with type 2 diabetes using regression analysis confirmed the hypothesis of Roy-Chaudhury Prabir et al. on the role of integrin expression in peritubular capillaries on the development of tubulointerstitial fibrosis. We were also able to show that there is a regression model between the expression of ICAM-1 in the glomerular endothelium with the development of mesangial matrix expansion ($p = 0.000$), basement membrane thickening ($p = 0.000$) and arteriolar hyalinosis ($p = 0.000$). Based on the data obtained, we demonstrated a statistically significant model of the influence of ICAM-1 expression on the development of morphological changes in renal tissue, confirming the hypothesis put forward by Roy-Chaudhury Prabir et al. about the mechanism of tubulointerstitial damage. This is also confirmed by the association between the expression of ICAM-1 in renal tissue and the progression of the stage of diabetic kidney damage in patients with T2DM (p=0.000). Glomerular and interstitial tissue lesions, being independent factors, contribute to decreased renal function in patients with type 2 diabetes. However, published studies have shown that the severity of chronic interstitial and glomerular lesions is closely related [39,40].

Conclusion

A study of biopsy kidney tissue from patients with T2DM complicated by DN demonstrated the role of ICAM-1 expression in the development of histological changes in renal tissue with the formation of tubulointerstitial fibrosis. Studying the intensity of ICAM-1 expression in kidney tissue can be used as a biomarker of the progression of kidney disease in patients with T2DM. In the future, it is planned to study the expression of other adhesion molecules and their role in the morphological changes of renal tissue in DN.

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Authors' contribution

Conception and research design: Ryabova T. S, Rakityanskaya I. A.
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Data analysis and interpretation: Rakityanskaya I. A, Ryabova T. S; lab research – Rakityanskaya I. A
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Editing – Ryabova T. S
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All the authors have made substantial contribution to this study and approved final script version.

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