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ABSTRACT

Research Objective: The work is devoted to studying the role of the expression of P-selectin (CD62P) and E-selectin (CD62E) in the glomerular capillary endothelium and peritubular capillaries and their role in the development and progression of morphological changes in renal tissue during diabetic nephropathy in patients with type 2 diabetes mellitus.

Material and Methods: The examination was carried out in 50 patients with type 2 diabetes mellitus (average age 66.58±3.27 years). All patients underwent light and immunofluo-rescence microscopy of renal tissue biopsies obtained by intravita percutaneous kidney biopsies. Morphological changes in tissue were assessed in accordance with the latest international classification of diabetic nephropathy, developed in 2010. According to light microscopy, class IIa (mild mesangial expansion) was identified in 12 patients, class IIb (severe mesangial expansion) was identified in 14 patients. , in 19 patients – class III (nodular Kimmelstiel-Wilson lesions) and in 5 patients – class IV (advanced diabetic glomerulosclerosis).

Keywords: type 2 diabetes mellitus, diabetic nephropathy, P-selectin (CD62P), E-selectin (CD- 62E), kidney tissue biopsy, microvascular complications.

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ABSTRACT

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The expression of P- and E-selectin was determined using monoclonal antibodies labeled with FITC (anti-human CD62P (P-Selectin) Antibody and anti-human CD62E (E-Selectin) Antibody) (USA). The intensity of expression in points (0–4), the nature and location of selectin expression in the glomerular endothelium and in peritubular capillaries were assessed.

Results. Analysis using linear and exponential regression was performed to identify the prognostic significance of CD62P and CD62E expression in the progression of tissue morphological changes during the development of DN. The resulting models demonstrated the role of selectin expression in the development of mesangial matrix expansion, the formation of nodular Kimmelstiel–Wilson lesions, arteriolar hyalinosis, and tubulointerstitial lesions.

Conclusion: Based on the data obtained, it can be assumed that the cell adhesion molecules P- and E-selectins are a predictor of the development of microvascular complications in DN. Expression of CD62P and CD62E in glomerular capillary endothelium influences the progression of DN.

Keywords: type 2 diabetes mellitus, diabetic nephropathy, P-selectin (CD62P), E-selectin (CD-62E), kidney tissue biopsy, microvascular complications.

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(T2DM)

Diabetic kidney disease (DKD) is a severe complication of diabetes mellitus, which is currently one of the leading causes of chronic kidney disease (CKD) and end-stage renal failure (ESRD) worldwide [1, 2]. Globally, diabetes mellitus (DM) affects more than 8% of the planet's population (about 350 million people).

Moreover, the International Diabetes Federation (IDF) estimates that the prevalence of diabetes will increase to 642 million people by 2040 [3, 4, 5]. More than 40% of people with diabetes develop kidney disease.

DKD is one of the main microvascular complications of diabetes, which is characterized by structural and functional changes. The morphological changes observed in kidneys with DN affect almost all nephron structures: the glycocalyx and glomerular endothelial cells, the glomerular basement membrane, podocytes and slit diaphragm, the mesangial matrix, the renal interstitium and renal tubules [6]. The earliest signs of DN are thickening of the glomerular basement membrane (GBM), soft mesangial expansion, and arteriolar hyalinosis. Mesangiolysis and severe mesangial damage ultimately lead to severe mesangial expansion, formation of nodular Kimmelstiel-Wilson lesions, hyalinosis of afferent and efferent arterioles, and marked 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, which usually occurs in the structure of both afferent and efferent arterioles [7, 8, 9]. A major contribution to the development of segmental sclerosis of the glomeruli is made by the detachment of podocytes from the GBM; as a result, the outflow from the glomeruli is disrupted and the so-called atubular glomeruli develop, which are characteristic of DN.

Recently, it has been shown that renal tubular damage is not only secondary to glomerular damage, but is itself a contributing factor to the development of DKD in patients with or without proteinuria [10, 11]. Various mechanisms are involved in the primary damage to proximal tubules in very early stages of DKD, including hypoxia, mitochondrial dysfunction, activation of innate immune mechanisms and autophagy [11].

The inflammatory response in the tubules leads to the development of nonspecific tubulointerstitial changes, including tubular atrophy, accumulation of activated myofibroblasts, collagen, inflammatory cells, and loss of capillary architecture [12]. Morphological damage to renal tissue in types 1 and 2 diabetes is identical, although there is a point of view that the heterogeneity of type 2 diabetes plays an additional role [13].

Chronic inflammation plays an important role in the development of DKD. In 1991, A. Bohle et al. [14] for the first time conducted a study of kidney biopsies from 488 patients with diabetic glomerulosclerosis of varying severity and revealed the presence of monocytes, macrophages, T cells and fibroblasts in the kidney tissue associated with tubulointerstitial changes in DKD. The authors suggested that diabetic nephropathy develops not only due to hyperperfusion lesions, but also due to nonspecific tubulointerstitial changes. Patients with type 2 diabetes develop systemic inflammation, including the production of a wide variety of chemokines that promote inflammation in the microenvironment, thereby expanding and increasing renal damage. As a result of inflammation, the renal tissue is infiltrated by monocytes and lymphocytes, which produce proinflammatory cytokines (IL-6, IL-8, IL-10, TNF-α), chemokines (CCL2/C-C motif ligand 2), adhesion molecules (ICAM-1 and VCAM-1, P-selectin, E-selectin) and oxygen-free radicals, which further enhances the inflammatory response with the development of cell damage and the development of fibrosis [15, 16].

There is evidence of the key role of activated platelets in the development of inflammation, coagulation disorders and tissue fibrosis, resulting in the development and progression of DKD [17, 18]. In inflammatory diseases, an increase in the expression of adhesion molecules is observed, which is considered an indicator of endothelial damage. In patients with T2DM, platelets are characterized by increased expression of adhesion molecules, which is an indicator of endothelial damage and leukocyte activation [19]. Adhesion molecules are divided into four categories: integrins, selectins, adhesion molecules that are part of the immunoglobulin superfamily, and cadherins [20]. The selectin family consists of three molecules called P-, E-, and L-selectins. P- and E-selectins play an important role in the mechanisms of pathogenesis of the development

of DN. P-selectin (CD62P) is a membrane glycoprotein with a high degree of glycosylation, deposited in specific granules localized in α-granules of platelets and in endothelial cells in the membrane of the Weibel-Palade body [18, 21].

When platelets are stimulated, P-selectin is rapidly redistributed from α-granules to the platelet surface [22]. E-selectin (CD62e), a membrane glycoprotein, is produced in large quantities and is expressed only on activated endothelium, promoting the adhesion of monocytes and neutrophils to the endothelium [23].

The purpose of the research was to study the role of the expression of P- and E-selectins (CD62p and CD62e) in the glomerular capillary endothelium and peritubular capillaries in patients with different morphological classes of DN and to evaluate their influence on the development and progression of histological changes in renal tissue.

I. PARENTS AND METHOD

The study included 50 patients with type 2 diabetes mellitus (DM), 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.

The material for histological examination was obtained through intravita percutaneous kidney biopsies and was subsequently examined by light and immunofluorescence microscopy. 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 [24].

Light microscopy of kidney biopsy tissue was assessed using the following indicators.

1. The presence of global and segmental glomerular sclerosis;
2. Cellularity of the glomerulus;
3. Severity of expansion of the mesangial matrix (less than and more than 25%);
4. GBM thickening;
5. Kimmelstiel–Wilson nodules;
6. Presence of hyaline caps;
7. Periglomerular sclerosis;
8. Sclerotic changes in the interstitium;
9. The presence and severity of mononuclear inflammatory infiltrates in the interstitium;
10. The presence of protein masses in the lumens of the tubules;
11. Atrophy and dystrophy of the epithelium of the urinary tubules (thickness of the apical edge and height of the epithelium of the tubules);
12. 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 scored (0–3) as a percentage of the total interstitial and tubular area in the biopsy specimen. 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 [24].

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).

In addition to light microscopy, the expression of CD62P (P-selectin) and CD62E (E-selectin) in the glomerular endothelium and peritubular capillaries was determined in all patients using monoclonal antibodies labeled Fitc (FITC anti-human CD62P (P-Selectin) Antibody, clone AK4 Cat#304904 and FITC anti-human CD62E (E-Selectin) Antibody, clone HCD62E Cat# 322606, Biolegend (USA)). The intensity of expression was assessed in points (0–4) [25], the

nature and location of the expression of CD62P and CD62E in the glomerular endothelium and in peritubular capillaries.

II. STATISTICAL ANALYSIS

Statistical processing of the obtained data was carried out using the IBM SPSS Statistics software package, version 26 (Armonk, NY: IBM Corp.). Group results are presented as the arithmetic mean ± standard error (M ± Standard Error).

Statistical comparison of data between groups of patients was carried out using the nonparametric Mann–Whitney U test. Differences in continuous variables were assessed using the independent sample Student's t test and were considered significant if $p \leq 0.05$.

For statistical processing, parametric (Pearson's method) and non-parametric (Spearman's method, Kendall's tau (τ) method) were used. To verify compliance with the condition of independence of observations, linear regression analysis was carried out (with the calculation of the coefficient of determination (R Square) and the Durban–Watson test) and analysis of variance (ANOVA Analisis of Variance) with the calculation of the Fisher test (F) to test the significance of the model. The standardized ß coefficient with 95% confidence intervals was calculated. The critical level of significance for the difference in indicators was taken equal to 0.05.

III. RESULT

Analysis of the expression of P- and E-selectins in renal tissue showed that expression is present in the area of glomerular endothelium and periglomerular capillaries. The results are presented in Table 1.

Table 1: Intensity of expression of CD62p and CD62e in the glomerular endothelium and peritubular capillaries in patients with type 2 diabetes with DN

Expression area	Expression intensity CD62P	Expression intensity CD62E	P
Glomerular endothelium	1,63±0,47 (95% CI:0,95 – 2,72)	0,64 ±0.13 (95% CI: 0,36 – 0,91)	0,001
Peritubular capillaries	1,17±0,13 (95% CI: 0,91 – 1,42)	0,95±0,18 (95% CI:0,61 – 1,29)	0,001

The table data shows that the expression of CD62P in both zones is significantly more pronounced. Next, the expression of CD62P and CD62E in renal tissue was analyzed depending on the class of DN (Table 2, 3)

Table 2: Intensity of CD62P expression in the glomerular endothelium and peritubular capillaries in groups of patients with different classes 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
Expression of CD62P in glomerular endothelium					
Glomerular endothelium	3,500±2,088 (95% CI: -1,224 - 8,224)	1,500± 0,291 (95% CI: 0,869 – 2,130)	1,000±0,253 (95% CI: 0,467 – 1,532)	0,000	P1,2=0,04 P1,3=0,001 P1,4 =0,0001 P2,3 =0,04 P2.4 =0,0001 P3,4=0,0001
Expression of CD62P in peritubular capillaries					
Peritubular capillaries	1,600±0,266 (95% CI: 0,996 - 2,203)	1,214±0,280 (95% CI: 0,607 – 1,821)	0,842±0,191 (95% CI: 0,440 – 1,244)	0,297±0,109 (95% CI: 0,106 – 0,531)	P1,2 =0,05 P1,3 =0,001 P1,4=0,001 P2,3=0,05 P2,4=0,001 P3,4=0,05

Table 3: Intensity of CD62E expression in the glomerular endothelium and peritubular capillaries in groups of patients with different classes 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
Expression of CD62E in glomerular endothelium					
Glomerular endothelium	0,900±0,349 (95% CI: 0,200– 1,600)	0,428±0,226 (95% CI: 0,063 -0,920)	0,421±0.183 (95% CI: 0,157 – 0,736)	0,000	P1,2=0,001 P1,3 =0,001 P1,4=0,0001 P2,3=0,07 P2,4=0,0001 P3,4=0,0001
Expression of CD62E in peritubular capillaries					
Peritubular capillaries	1,400±0,452 (95% CI: 0,600 - 2,203)	0,785±0,309 (95% CI: 0,2143 – 1,498)	0,684±0,212 (95% CI: 0,315 – 1,157)	0,195±0.088 (95% CI: 0,042 – 0,383)	P1,2=0,001 P1,3=0,001 P1,4=0,0001 P2,3=0,08 P2,4=0,004 P3,4=0,002

From the presented data it is clear that the expression of selectins in renal tissue depends on the morphological class of DN.

Next, a correlation analysis of the relationship between the expression of selectins in renal tissue and morphological changes in the general group of patients was carried out. The obtained data are presented in Table 4.

Table 4: Correlations between the expression of CD62P and CD62E in the glomerular endothelium with morphological changes in the general group of patients with DN

Morphological changes	Correlations		
	Kendall (τ)	Spearman (r)	Pearson (R)
Expression of CD62P in glomerular endothelium			
Glomerular basement membrane thickening	τ=-0,289 p=0,029	r=-0,319 p=0,029	R=-0,357 =0,014
Kimmelstiel–Wilson nodules	τ=-0,289 p=0,26	r=-0,325 p=0,025	R =-0,326 p= 0,025
Hyalinosis of arterioles	τ= -0,316 p=0,015	r = -0,378 p=0,009	R =-0,340 p=0,019
Expression of CD62E in glomerular endothelium			
Kimmelstiel–Wilson nodules	τ= - 0,289 p=0,026	r= -0,325 p=0,026	R = - 0,300 p=0,040
Hyalinosis of arterioles	τ= - 0,298 p=0,026	r= - 0,355 p=0,014	R = - 0,324 p=0,026

To identify the prognostic significance of the expression of CD62p and CD62e and their role in the progression of morphological changes in renal tissue during the development of DN, linear regression analysis was carried out with the calculation of determination coefficients R2 (R Square) and analysis of variance (ANOVA Analysis of Variance) using the F test with 95% confidence interval. The obtained values, indicating the significance of the regression models, are presented below (Table 5, 6).

Table 5: Regression models of the significance of CD62P and CD62E expression in the glomerular endothelium in the general group of patients with DN

Selectin expansion zone	Coefficient of determination (R^2)	Fisher criterion (F)	p
Expression of CD62P in glomerular endothelium			
Expansion of the mesangial matrix	0,317	21,317	0,000
Hyalinosis of arterioles	0,213	12,476	0.001

	-	-	-
Glomerular basement membrane thickening	0,255	15,708	0.000
Expression of CD62E in glomerular endothelium			
Expansion of the mesangial matrix	0,206	11,926	0,001
Kimmelstiel–Wilson nodules	0,125	6,556	0,014
Glomerular basement membrane thickening	0,216	13,926	0,001
Hyalinosis of arterioles	0,206	13,202	0.001

Table 6: Regression models of the significance of CD62P and CD62E expression in the peritubular capillaries in the general group of patients with DN

Selectin expansion zone	Coefficient of determination (R^2)	Fisher criterion (F)	p
Expression of CD62P in peritubular capillaries			
Atrophy of the tubular epithelium	0,558	6,632	0.013
Interstitial sclerosis	0,549	54,732	0,0001
Expression of CD62E in peritubular capillaries			
Atrophy of the tubular epithelium	0,356	25,462	0,0001
Interstitial sclerosis	0,338	22,932	0,0001

From the data presented in the table it is clear that the expression of CD62P and CD62E has a pronounced effect on the development and progression of morphological changes in the renal tissue in patients with DN. Next, we analyzed the influence of the expression of CD62P and CD62E on the progression of the stage of DN in the general group of patients (Table 7).

Table 7: Regression models of the significance of CD62P and CD62E expression in the glomerular endothelium on the progression of the stage of DN in the general group of patients

Glomerular capillary endothelium	Coefficient of determination (R^2)	Fisher criterion (F)	p
Expression of CD62P	0,216	12,684	0,001
Expression of CD62E	0,204	11,779	0,001

IV. DISCUSSION

In the pathogenesis of glomerular diseases, platelets play an active role through mechanisms involved in the development of the inflammatory process. Numerous studies have shown increased platelet activation in patients with diabetes (2With increased platelet hyperreactivity in patients with diabetes, proteins are released from α-granules, dense granules and lysosomal granules, which act as pro-inflammatory mediators, pro-fibrotic mediators, growth factors and vasoactive mediators that contribute to the pathophysiological mechanisms of DN development [26, 18]. Proinflammatory mediators increase the expression of adhesion molecules on the endothelium and initiate the migration of leukocytes to the site of inflammation. The migration of leukocytes from blood to tissues involves several stages: coagulation, adhesion, diapedesis, and chemotaxis (27). The earliest and necessary event is coagulation, which initiates leukocyte extravasation and inflammation. Blood coagulation is mediated by a family of adhesion molecules, including various ligand/receptor molecules that promote intercellular and intercellular-ECM adhesion [28]. Selectins include endothelial E-selectin, platelet P-selectin and leukocyte L-selectin [29].

Selectins are involved in the constitutive return of leukocytes and in chronic and acute inflammatory processes [23]. E- and P-selectins are expressed by endothelial cells. P-selectin is the main

mediator of platelet and leukocyte aggregation. When P-selectin interacts with P-selectin glycoprotein ligand-1 (PSGL-I), which is expressed on the membrane of monocytes and neutrophils, adhesion of platelets and endothelial cells to leukocytes occurs [2]. PSGL-1 has high affinity for P-selectin. E-selectin is produced upon pro-inflammatory stimulation and is considered important for leukocyte transport [30, 31]. Gotoh R. et al. showed in their work that E-selectin regulates adventitial inflammation through leukocyte adhesion and promotes the process of intimal hyperplasia [32].

The most comprehensive and one of the first studies of the expression of P- and E-selectins in renal tissue from T2DM patients with DN was published by Roy-Chaudhury Prabir et al. in 1996. The study was conducted on 119 biopsy blocks of kidneys taken from patients with different morphological diagnoses. The expression of P- and E-selectins on extraglomerular vascular endothelium was assessed. The authors showed that the expression of adhesion molecules in the tubulointerstitium is associated with interstitial fibrosis and tubular atrophy and may contribute to the progression of kidney disease (E-selectin (0.71, P <0.0001) and P-selectin (0.72, P <0 ,0001)). Spearman's correlation was found regardless of the morphological form of the primary diagnosis, but was clearly associated with histological damage. Expressions of E-selectin (P < 0.0001) and P-selectin (P < 0.0001) were dramatically increased in extraglomerular capillaries. The authors of the work showed that there is a common pathway of tubulointerstitial damage, regardless of the primary diagnosis, and the expression of adhesion molecules within the tubulointerstitium may be an important mechanism in the pathogenesis of DN [33].

In our study, regression analysis showed that the expression of CD62P and CD62E contribute to the development of interstitial sclerosis and atrophy of the tubular epithelium. This confirms previously published data on morphological changes in diabetic nephropathy [33]. Also, the mechanism of tubulointerstitial damage and progression of DN is confirmed by our regression model of the relationship between the expression of CD62P and CD62E with the progression of the stage of DN in the general group of patients.

Taken together, these data support the hypothesis of Roy-Chaudhury Prabir et al. about the unified mechanism of tubulointerstitial damage and the significant role of the expression of CD62P and CD62E molecules in its development.

The literature contains data on a comparative analysis of the intensity of selectin expression in DN, lupus nephritis, membranous proliferative glomerulonephritis and IgA nephropathy [34].

There is also evidence of increased serum levels of E-selectin and P-selectin in patients with diabetes [35, 36]. Several cross-sectional studies have assessed the expression of cell adhesion molecules in blood [37] and renal tissue [38] and identified them as markers of endothelial dysfunction associated with the incidence of various microvascular complications of diabetes. In our study, the expression of P- and E-selectins was detected in the glomerular endothelium and in the peritubular capillaries of the renal tissue of patients. Regression analysis showed the influence of CD62P expression on the development of expansion of the mesangial matrix, arteriolar hyalinosis, and basement membrane thickening. CD62E expression promotes the development of mesangial matrix expansion, Kimmelstiel–Wilson nodules, arteriolar hyalinosis, and basement membrane thickening. Our data confirm and agree with data published by other authors.

It is known from the literature that in the early stages of DN, matrix expansion is formed due to the expansion of glycoproteins, collagen I, collagen III, collagen IV (α1 and α2 chains), collagen V, collagen VI, laminin, fibronectin and small leucine-rich (SLR) proteoglycans and other structural components. That is, expansion of the mesangial matrix is the result of metabolic disturbances caused by chronic hyperglycemia, which leads to an imbalance between the synthesis of extracellular matrix (ECM) glycoproteins and their degradation [39, 40, 41].

An inverse relationship was shown between the relative volume of the mesangium and the surface

filtration density of peripheral capillaries, as well as an inverse relationship between the surface filtration density and the density of the endothelial-mesangial border (r=-0.86 p=0.0005 – correlation of the percentage of total mesangium and peripheral S/V surface of capillaries) [42]. This mechanism can probably explain the regression models we obtained.

V. CONCLUSION

A study of biopsy tissue from patients with DN demonstrated the role of the expression of P- and E-selectins in the development of histological changes in renal tissue. P-selectin plays a greater role in the development of expansion of the mesangial matrix and the formation of Kimmelstiel–Wilson nodules with arteriolar hyalinosis. Both selectins play a role in the development of tubulointerstitial lesions.

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 – Rakityanskaya I. A., Ryabova T. S.;
material gathering and processing – Ryabova T. S.. Rakityanskaya I. A.,
data analysis and interpretation – Rakityanskaya I. A., Ryabova T. S.;
lab research – Rakityanskaya I. A.;
statistical processing of data – Ryabova T. S., Rakityanskaya I. A.;
script composition – Ryabova T. S., Rakityanskaya I. A.,
editing – Ryabova T. S.;
research supervision – Rakityanskaya I.A.;
text writing and editing – Rakityanskaya I. A., Ryabova T. S.;
responsibility for integrity of all article's parts – Rakityanskaya I.A.;
Script further revision for important intellectual content – Rakityanskaya I. A., Ryabova T. S.,
All the authors have made substantial contribution to this study and approved final script version.

REFERENCES

1. Lim A. Diabetic nephropathy–complications and treatment. Int. J. Nephrol. Renov. Dis. 2014; 7: 361–381. doi: 10.2147/IJNRD.S40 172.
2. Rustiasari U. J., Roelofs J. J.. The Role of Platelets in Diabetic Kidney Disease. Int J Mol Sci. 2022; Aug; 23(15): 8270. doi: 10.3390/ijms23158270.
3. Gheith O., Farouk N., Nampoory N., A Halim M., Al-Otaibi T. Diabetic kidney disease: World wide difference of prevalence and risk factors. J. Nephropharmacol. 2015;5:49–56. doi: 10.4103/1110-9165.197379.
4. Alicic R. Z., Rooney M. T., Tuttle K. R. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin. J. Am. Soc. Nephrol. 2017;12:2032–2045. doi: 10.2215/CJN.11491116.
5. Ameh O. I., Okpechi I. G., Agyemang C., Kengne A. P. Global, regional, and ethic differences in diabetic nephropathy. In: Roelofs J. J. T. H., Vogt L., editors. Diabetic Nephropathy: Pathophysiology and Clinical Aspects. 1st ed. Springers; Cham, Switzerland: 2019; 33–44.
6. Ilyas Z. Chaiban, A. Krikorian. Novel insights into the pathophysiology and clinical aspects of diabetic nephropathy. Reviews in Endocrine & Metabolic Disorders. 2017; -18: (1): 21–28. doi: 10.1007/s11154-017-9422-3.
7. Najafian B. Alpers C.E. Pathology of kidney in diabetes. In: Roelofs J.J.T.H., Vogt L., editors. Diabetic Nephropathy: Pathophysiology and Clinical Aspects. 1st ed. Springers; Cham, Switzerland. 2019; 113–140. doi: 10.1002/cphy.c100049.
8. Reidy K. Kang H. M., Hostetter T., Susztak K. Molecular mechanisms of diabetic kidney disease. J. Clin. Investig. 2014;124:2333–2340. doi: 10.1172/JCI72271.
9. Kanwar Y. S. Sun L., Xie P., Liu F.-Y., Chen S. Glimpse of Various Pathogenetic Mechanisms of Diabetic Nephropathy. Annu. Rev. Pathol. Mech. Dis. 2011; 6: 395–423. doi: 10.1146/annurev.pathol.4.110807.092150.

10. Chang J., Yan J., Li X., Liu N., Zheng R., Zhong Y. Update on the Mechanisms of Tubular Cell Injury in Diabetic Kidney Disease. Front Med (Lausanne). 2021; Mar 30; 8: 661076. doi: 10.3389/fmed.2021.661076.
11. Qi R., Yang C. Renal tubular epithelial cells: the neglected mediator of tubulointerstitial fibrosis after injury. Cell Death Dis. 2018; Nov 13: 9(11): 1126. doi: 10.1038/s41419-018-1157-x.
12. Gilbert R. E. Proximal Tubulopathy: Prime Mover and Key Therapeutic Target in Diabetic Kidney Disease. Diabetes. 2017; Apr: 66(4): 791-800. doi: 10.2337/db16-0796.
13. Liu H., Feng J., Tang L. Early renal structural changes and potential biomarkers in diabetic nephropathy. Front Physiol. 2022; Nov 8:13:1020443. doi: 10.3389/fphys.2022.1020443.
14. Bohle A., Wehrmann M., Bogenschütz O., Batz C., Müller C. A., Müller G. A. The pathogenesis of chronic renal failure in diabetic nephropathy. Investigation of 488 cases of diabetic glomerulosclerosis. Pathol Res Pract. 1991; Mar; 187(2-3): 251-9. doi:10.1016 s0344-0338(11)80780-6.
15. Wolf G., Neilson E. G. Molecular mechanisms of tubulointerstitial hypertrophy and hyperplasia. Kidney Int. 1991; Mar; 39(3): 401-20. doi: 10.1038/ki.1991.52.
16. Yiu W.H., Lin M., Tang S.C. Toll-like receptor activation: from renal inflammation to fibrosis. Kidney Int Suppl. (2011). 2014; Nov; 4(1): 20-25. doi: 10.1038/kisup.2014.5.
17. Sobel B. E., Schneider D. J. Platelet function, coagulopathy, and impaired fibrinolysis in diabetes. Cardiol Clin. 2004; Nov; 22(4): 511-26. doi: 10.1016/j.ccl.2004.06.009.
18. Kaur R., Kaur M., Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018; Aug; 31:17(1):121. doi: 10.1186/s12933-018-0763-3.
19. Avei E., Uzeli S. The role of adhesion molecules and cytokines in patients with diabetic nephropathy. Biomed. Res. 2016; 343–S348.
20. Abbas A. K., Lichtman A. H. Maturation, activation and regulation of lymphocytes. Cellular and molecular immunology. WB Saunders (5th edn). 2003; 127-241.
21. Kubisz P., Stančiaková L., Staško J., Galajda P., Mokáň M. Endothelial and platelet markers in diabetes mellitus type 2. World J Diabetes. 2015; Apr 15; 6(3): 423-31. doi: 10.4239/wjd.v6.i3.423.
22. Omoto S., Nomura S., Shouzu A., Hayakawa T., Shimizu H., Miyake Y., Yonemoto T., Nishikawa M., Fukuhara S., Inada M. Significance of Platelet-Derived Microparticles and Activated Platelets in Diabetic Nephropathy. Nephron Exp. Nephrol. 1999; 81:271–277. doi: 10.1159/000045292.
23. Fries J. W. U., Williams A. J., Atkins R. C., Newman W., Lipscomb M. F., Collins T. Expression of VCAM-1 and E-selectin in an in vivo model of endothelial activation. Am J Pathol. 1993; 143: 725±737.
24. Tervaert T. W. Mooyaart A. L., Amann K. et al. Pathologic classification of diabetic nephropathy. J. Am. Soc. Nephrol. 2010; Vol.21; 4:556–563. doi: 10.1681/ASN.2010010010.
25. Floege J., Burns M. W., Alpers C. E. Glomerular cell proliferation and PDGF expression precede glomerulosclerosis in the remnant kidney model. Kidney Int. 1992; 41: 297-309. DOI: 10.1038/ki.1992.42.
26. Sonmez O., Sonmez M. Role of platelets in immune system and inflammation. Porto Biomed. J. 2017; 2: 311–314. doi: 10.1016/j.pbj.2017.05.005.
27. Carlos T. M., Harlan J. M. Leukocyte–endothelial adhesion molecules. Blood. 1994; 84: 2068–2101.
28. Elangbam C. S., Qualls C. W., Dahlgren R. R. Cell Adhesion Molecules--Update. Vet Pathol. 1997; 34:61–73. doi: 10.1177/030098589703400113.
29. Ley K. The role of selectins in inflammation and disease. Trends Mol Med. 2003; 9:263–268.
30. Friedman G., Jankowski S., Shahla M. Administration of an antibody to E-selectin in patients with septic shock. Crit Care Med. 1996; 24: 229–233.

31. Singbartl K., Ley K. Protection from ischemia–reperfusion induced severe acute renal failure by blocking E-selectin. Crit Care Med. 2000; 28: 2507–2514.
32. Gotoh R., Suzuki J., Kosuge H. E-selectin blockade decreases adventitial inflammation and attenuates intimal hyperplasia in rat carotid arteries after balloon injury. Arterioscler Thromb Vasc Biol. 2004; 24: 2063–2068.
33. Roy-Chaudhury Prabir, Wu B. R., King G., Campbell M., Macleod A. M., Haites N. E., Simpson J. G., Power D.A. Adhesion molecule interactions in human glomerulonephritis: Importance of the tubulointerstitium. Kidney International 1996; VoL 49:127—134.
34. Hirata K., Shikata K., Matsuda M., Akiyama K., Sugimoto H., Kushiro M., Makino H.. Increased expression of selectins in kidneys of patients with diabetic nephropathy. Diabetologia 1998; 41: 185±192.
35. Denton M. D., Marsden P. A., Luscinskas F. W., Brenner B. M., Brady H. R. Cytokine-induced phagocyte adhesion to human mesangial cells: Role of CD11/CD18 integrins and ICAM-1. Am J Physiol. 1991; F1071—F1079.
36. Blum A. Levels of adhesion molecules in peripheral blood correlat with stages of diabetic retinopathy and may serve as biomarkers for microvascular complications/ A. Blum, N. Pastukh, D. Socea, H. Jabaly // Cytokine. – 2018. -106. – p. 76–9. doi: 10.1016/j.cyto.2017.10.014.
37. Eschen O. Soluble cellular adhesion molecules in patients with diabetes mellitus / O. Eschen, J.H. Christensen, E.B. Schmidt // Endocrinologist – 2006. – 16. – p. 303–7. doi: 10.1097/01.ten.0000249139.45366.36.
38. Kelley V. R., Diaz G.C., JEvNikar A. M., Singer G. O.: Renal tubular epithelial and T cell interactions in autoimmune renal disease. Kidney int. 1993; 43(Supp 39):108—115.
39. Mason R. M., Wahab N. A. Extracellular matrix metabolism in diabetic nephropathy. J. Am. Soc. Nephrol. 2003; 14(5): 1358–1373.
40. Kolset S. O., Reinholt F. P., Jenssen T. Diabetic nephropathy and extracellular matrix. J. Histochem. Cytochem. 2012; 60(12): 976–986.
41. Chun Hu, Lin Sun, Li Xiao, Yachun Han, Xiao Fu, Xiaofen Xiong, Xiaoxuan Xu, Yinghong Liu, Shikun Yang, Fuyou Liu, Yashpal S Kanwar. Insights into the mechanisms involved in the expression and regulation of extracellular matrix proteins in diabetic nephropathy. Curr Med Chem. 2015; 22(24): 2858–2870.doi: 10.2174/0929867322666150625095407.
42. Falk R. J., Scheinman J. I, Mauer S. M., Michael A.F. Polyantigenic expansion of basement membrane constituents in diabetic nephropathy. diabetes. 1983; May: 32; Suppl 2:34-9. doi: 10.2337/diab.32.2.s34.