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SOME PATHOBIOCHEMICAL FEATURES OF GLOMERULOPATHIES OF DIABETIC ORIGIN

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Applicant: **Nurana Latifova Fazil**

AUTOREFERAT
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The dissertation work was carried out at the Department of Biological Chemistry of Azerbaijan Medical University.

Scientific leader: doctor of biological sciences, professor
Arif Afandiyev Mustafa

Official opponents: doctor of biological sciences, professor
Ziyaddin Mammadov Mahmud

doctor of biological sciences, professor
Saftar Suleymanov Yusif

Doctor of Philosophy in Biology,
Docent
Shafiddin Hajiyev Mahammad

FD 1.08 Dissertation Council of the Supreme Attestation Commission under the President of the Republic of Azerbaijan operating under the Institute of Physiology named after academician Abdulla Garayev of ANAS

Chairman of the Dissertation Council: doctor of biological sciences, professor
Ulduz Hashimova Fayizi

Scientific Secretary of the Dissertation Council: Doctor of Philosophy in Biology,
Docent
Egana Bayramova Ogtay

Chairman of the scientific seminar: doctor of biological sciences, professor
Adalat Farajov Nurulla

GENERAL CHARACTERISTICS OF THE RESEARCH

The actuality of the theme. Diabetic glomerulopathy (DG) is one of the most common and the clinical complications of long-term diabetes mellitus (DM) with a negative prognosis and is characterized by severe metabolic and physiological disorders [1, 2]. 650-800 people among the world's population of 1 million and 350-400 people in Azerbaijan have been diagnosed with DG disease [1-3]. Late detection of kidney pathology in patients with DM can lead to proteinuria, glomerular filtration rate (GFR), a sharp increase of creatinine and urea in the blood, arterial hypertension, a decrease of the protein in the blood and edema [4]. If DG is not detected early and treated properly, it can lead to chronic kidney disease (CKD). It was found that in 20% of patients with DM, as a result of kidney failure, the kidneys become completely inactive, and patients undergo kidney transplantation or hemodialysis. In developed countries, 20-50% of patients on dialysis consists of especially DM patients[1,3]. The complexity of the pathogenetic mechanisms of DG and CKD in patients with DM put forward the research of immune mechanisms as an actual issue that play a role in the occurrence of metabolic disorders.

Research and application of new and more sensitive biochemical tests in practice that detects the early stages of DG in patients with DM and determines the rate of its progression can allow for timely detection of the disease and the preparation of new effective treatments. Recently, special attention has been paid to the immune mechanisms in the formation and development of DG. In recent years, numerous scientific researches have been carried out on the

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[1] Aghayev, M. Dialysis // Aghayev M., Aliyev S. Oscar, Baku, - 2010. - 414 p.

[2] Ametov, A.S. Diabetes mellitus type 2: problems and solutions M .: GEOTAR-Media, - 2012 .-- 704 p.

[3] KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney int Suppl 2013, No 3 (1), - p. 1-150.

[4] Denisov, I.N., Diabetic nephropathy clinical guidelines / Denisov, I.N., Nadeeva R.A., Sigitova O.N. et al. Moscow - Kazan - Rostov-on-Don, - 2014 .-- 22 p.

study of the role of cytokines and antimicrobial peptides (AMPs) in the pathogenetic mechanisms of DM and DG [5,6,7]. The obtained scientific results are scattered and make it necessary to conduct complex researches. Thus, the study of inflammatory cytokines and AMPs during DG is of great scientific importance in the research of the mechanisms of development of pathology, as well as can create new perspectives in the early diagnosis and treatment of the disease.

The object of the research. The blood samples used in the research case from patients with DM, glomerulopathy of diabetic origin (DG), CKD of the diabetic origin and CKD of chronic glomerulonephritis (CGN).

The main purpose of the research case is to study the role of cytokines and AMPs in the pathobiochemical mechanisms of glomerulopathy of diabetic origin.

The duties of the research:

1. To assess the indicators of carbohydrate interchange in the blood of patients with DM, DG, CKD of the diabetic origin, and CKD of the CGN origin that is not complicated by glomerulopathy;
2. To determine the coagulation of biochemical indicators which assess the functional activity of the kidneys: creatinine, urea and cystatin C in the blood of patients with DM, DG, CKD of the diabetic origin, and CKD of the CGN origin which are not complicated by glomerulopathy included in the research group;
3. To determine the coagulation and informativeness of some cytokines (IL-6, IL-8, IL-10, TNF-α) in the blood of patients with DM, DG, CKD of the diabetic origin, and CKD of the CGN origin which are not complicated by glomerulopathy;

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[5] Mammadhasanov, R.M. Cytokine spectrum of diabetic patients with and without nephropathy / Mammadhasanov, R.M., Babakhanli AN, Valiyeva G.A. // Azerbaijan Medical Journal, - 2014. №1, - p.71-75.

[6] Azizova, G.I. The level of secretion of some endogenous peptides and certain cytokines in diabetes mellitus / Azizova, G.I., Hasanova Sh.I., Niyazova N.K. et al. // Kazan Medical Journal, - 2014. vol. 95, No. 5, - p. 646-649.

[7] Andreeva, A.S. The role of cytokines in the pathogenesis of diabetes mellitus / Andreeva A.S., Khamnueva A.Yu., Shagun O.V. // Siberian medical journal, (Irkutsk), - 2005. №1, - p.5-7.

4. To determine the level of AMPs (calprotectin (CP), cathelicidin and L-FABP) in the blood of patients with DM, DG, CKD of the diabetic origin, and CKD of the CGN origin which are not complicated by glomerulopathy included in the research group;

5. To determine the correlation between carbohydrate interchange, biochemical indicators that assess the functional activity of the kidneys, some cytokines and AMPs in patients with DM, DG, CKD of the diabetic origin, and CKD of the CGN origin which are not complicated by glomerulopathy;

6. To evaluate the diagnostic value and informativeness of carbohydrate interchange, biochemical indicators that assess the functional activity of the kidneys, some cytokines and AMPs in the early diagnosis of DG and CKD in patients with DM included in the research group;

The methods of the research. Biochemical and immunoenzyme analysis methods were used in the research case.

The main provisions of the dissertation defended*:*

1. Inflammatory cytokines (IL-6, IL-8, and TNF-α) and AMPs (KP, cathelicidin, and L-FABP) play an important role and lead to progression of inflammation in the pathogenesis of glomerulopathy and CKD during DM.

2. The determining positive correlation between biochemical indicators reflecting the functional activity of the kidneys with impaired carbohydrate interchange in patients with DM, inflammatory cytokines and AMPs confirms the role of inflammation in the pathogenesis of glomerulopathy in the background of chronic hyperglycemia.

3. According to the results of ROC statistical analysis, Cystatin C, IL-6, IL-8, KP and L-FABP are evaluated as indicators of high diagnostic information and sensitivity in the early detection of glomerulopathy and CKD in patients with DM.

The scientific innovation of the research. DM in the research case and the role of cystatin C, cytokines and AMPs has been examined in the pathogenesis of DG accompanied by glomerular damage to the kidneys, and assessed their pathogenetic and diagnostic value. For the first time in the research case, the functional

indicators of the kidneys, AMPs and cytokines were studied in a complex and comparative manner in patients with DM and its clinical complications: DG and CKD, as well as in CKD patients with glomerulonephritis. For the first time, a positive correlation between the coagulation of cystatin C and creatinine and glycohemoglobin was determined. The research case found that inflammatory cytokines (IL-6, IL-8 and TNF-α) and AMPs (calprotectin, L-FABP) play a major role in the pathogenesis and development of DG in patients with DM.

The practical significance of the research. It is necessary to use the diagnostic role of cytokines and AMPs in the developmental mechanism of DG and CKD during DM. The study of cytokines and AMPs in patients with DM can allow early diagnosis, prognosis, timely prevention and appropriate prophylactic measures for glomerulopathies, including CKD.

Application of scientific research case. The results of the dissertation were applied in the practical activities of the United Hospital of Oil Workers and in the teaching process of the Department of Biochemistry.

Discussion of the dissertation. Dissertation materials were discussed at the following scientific meetings: VI International Symposium Interaction of the nervous and immune systems in health and disease (St. Petersburg, 2017), IV International Medical Congress (Baku-2017), XXIV World International Congress of Allergology and Immunology Immunorehabilitation (Dubai-2017), Scientific-practical conference dedicated to the birthday of national leader H.A.Aliyev (Baku, 2018), Scientific Conference dedicated to the 100th anniversary of the independence of the Republic of Azerbaijan (Baku, 2017), Collection of materials of the International Scientific Conference dedicated to the 85th anniversary of R.A. Askerov (Baku, 2017), ... Materials of the dissertation were discussed at the joint meeting of the Clinical Biochemistry Laboratory and the Department of Biochemistry of the Azerbaijan Medical University (Baku, 2018) (protocol №1).

The organization where the dissertation is performed. The dissertation was carried out at the Department of Biochemistry of

Azerbaijan Medical University.

Printing works. 11 scientific articles and 6 theses on the topic of the dissertation were published.

Size and structure of the dissertation. The dissertation is written on a computer in 151 pages (201,000 characters) in the Azerbaijani language, consists of the introductory part (12,100 characters), literature review (54,600 characters), materials and methods (15,600 characters), results of personal researches (69,000 characters) and their discussion chapters (46,000 characters), results, practical recommendations (3,700 characters) and a reference list. The dissertation is illustrated with 32 tables and 26 graphs. The reference list includes 260 sources, 18 of them are works of Azerbaijani scientists, 79 of Russian scientists and 163 of other foreign scientists.

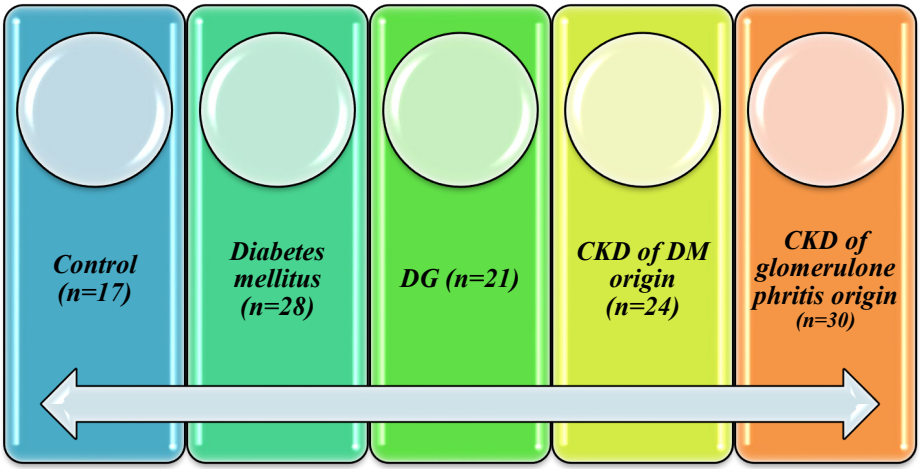
MATERIAL AND METHODS OF RESEARCH

General characteristics of patients. The current research included the materials of 73 patients diagnosed with type II DM by endocrinologists and 30 patients with CKD of the CGN origin from the City Clinical Hospital No. 2 named after M. Afandiyev and the Central Hospital of Oil Workers to the Clinical Biochemical Laboratory of the Azerbaijan Medical University; the control group consists of 17 healthy people. Kidney pathology was not detected in 28 patients with DM included in the research contingent, 21 patients were diagnosed with DG, 24 patients were diagnosed with CKD (terminal stage) of DM origin (graph 1).

Biochemical and immunoenzyme research methods. Coagulation of glucose, glycohemoglobin, creatinine and urea were analyzed by biochemical methods in different clinical groups of practically healthy people and DM patients involved in the research.

Serum glucose taken from the elbow vein on an empty stomach after centrifugation of the blood was determined by “Human” (Germany), urea and creatinine levels were measured using a Lachema (Germany) reagent kit. The amount of glycosylated hemoglobin (HbA1c) is based on the colorimetric determination

method of the colored reaction formed by thiobarbituric acid in erythrocytes.



Graph 1. Characteristics of patients included in the research contingent.

Insulin coagulation was determined by the ELISA immunoenzyme method with the help of the "Mercodia" (Switzerland) reagent kit. Determination of C peptide by "Novo Tec", determination of cytokines (IL-6, IL-8, IL-10 and TNF-α) and coagulation of cystatin C was determined with the help of "Vector-Best" (Russian Federation) reagent kit.

Coagulation of KP and cathelicidin in the blood serum were determined by "Eastbiopharm" (Spain), and L-FABP was determined with the help of the "Diagnosticum" reagent kit by the immunoenzyme method.

The indicators of all numbers obtained during the research were statistically analyzed for the application of variation, discriminant (Pearson), ANOVA, correlation and ROC-analysis methods. The non-parametric U-Wilcoxon (Mann-Whitney) criterion was applied to clarify the obtained statistical results.

All calculations were made in the EXCEL-2010 spreadsheet and SPSS-20 package program, the results are presented in tables and diagrams.

OUTCOMES OF THE RESEARCH

Assessment of the level of carbohydrate interchange, some biochemical indicators reflecting the functional activity of the kidneys, cytokines and antimicrobial peptides in the blood of patients with DM not complicated by glomerulopathy. As a result of the research case, it was found that the coagulation of glucose in the blood of patients with DM not complicated by GP increased statistically significantly by 84.0% ($p<0.001$) compared to the control group and consists of averaged 8.6-0.3 mmol/l (6.1-10.9 mmol / l) (Table 1).

Table 1

Levels of some biochemical indicators reflecting the functional activity of the kidneys in the blood of patients with renal pathologies of DM and CGN origin

Groups	Indicators		
	Creatinine, mkM/l	Urea, mM/l	Cystatin C, mg/l
DM not complicated by GP DM, (n=28)	117,8±7,0 (54-180) p=0,002	8,6±0,4 (5,2-12) p=0,001	1,391±0,091 (0,47-2,3) p<0,001
DG (n=28)	267,6±26,1 (82,1±444,8) p<0,001 p_1<0,001	13,4±1,3 (5,2-24,8) p<0,001 p_1=0,001	1,692±0,169 (0,471-2,962) p<0,001 p_1=0,182
CKD of the DM origin (n=28)	723,9±58,1 (320-1253) p<0,001 p_1<0,001 p_2<0,001	28,3±1,1 (11,5-36) p<0,001 p_1<0,001 p_2<0,001	2,635±0,171 (1,47-3,89) p<0,001 p_1<0,001 p_2<0,001
CKD of the CGN origin, (n=30)	610,3±51,0 (152-1097) p<0,001 p_1<0,001 p_2<0,001 p_3=0,189	19,6±0,6 (12,1-26,8) p<0,001 p_1<0,001 p_2<0,001 p_3<0,001	2,095±0,111 (1,07-3,1) p<0,001 p_1<0,001 p_2=0,051 p_3=0,020
Control, (n=17)	78,6±8,5 (24,6-126,6)	5,3±0,5 (1,8-8,3)	0,856±0,062 (0,434-1,339)

Note: - p - compared to control; p_1 - compared with DM not complicated by GP; p_2 – compared to DG; p_3– compared to the patients with CKD of DM origin.

As can be seen from the table, the coagulation of HbA1c in this group increased by 88.9% (p <0.001) compared to the control group and the average value was 9.3-0.3% (7-13,5%). In this group of patients, the c of insulin increased by 68.5% (p <0.001) compared to the control group, and the average value was determined to be 25.8±1.2 mcg% (12.4 -35.9 mcg%). The coagulation of peptide C tends to increase compared to the control group (698,0±18,4 pmol/ml; 564-897 pmol/ml; p=0,053).

The coagulation of creatinine and urea in this group increased by 49.9% (p = 0.002) and 60.9% (p = 0.001), respectively, compared with the control group, and amounted to 117.8±7.0 μM / l (54-180 μM). / l) and 8.6±0.4 mM / l (5.2-12 mM / l). The coagulation of cystatin C increases statistically significantly compared with the control group, an increase of 62.4% (p <0.001). The coagulation of cystatin C varies in the range of 0.47-2.3 mg / l, and the average coagulation is 1.391±0.091 mg / l.

Studies have shown that the coagulation of IL-6 in the blood serum of patients with type II SD who are not complicated by GP varies at the level of normal limits, as its average concentration is 2.4±0.1 pg / ml (1.2-3, 6 pg / ml: p = 0.664). Although the coagulation of IL-8 in this group increased by 25.9% (p = 0.101) compared to the control group, this difference is not statistically significant, as its average coagulation is 15.6±1.1 pg / ml (8.1- 29 pg / ml). The average coagulation of IL-10 is 12.2±0.9 pg / ml (5.6-19.8 pg / ml). The results show that the coagulation of IL-10 tends to decrease by 9.2% (p = 0.331) compared to the control group. In this group, the coagulation of TNF-α increased 2.3 times (p <0.001) compared to the control group, and the average coagulation consists of 2.03±0.20 pg / ml (0.8-5.4 pg / ml) (Table 2).

Increased concentration of inflammatory cytokines in patients with DM is an important indicator of the activation of inflammatory processes in the body.

In this group, a statistically significant increase (p <0.001) is observed in the coagulation of KP compared to the control group. Its average coagulation is 201.4±10.3 mcg / g (115.4 - 298.6 mcg / g)

(Table 3).

Table 2

Levels of some cytokines in the blood of patients with the kidney pathology of DM and CGN origin

Groups	Indicators			
	IL-6, pg/ml	IL-8, pg/ml	IL-10, pg/ml	TNF-α, pg/ml
DM not complicated by GP (n=28)	2,4±0,1 (1,2-3,6) p=0,664	15,6±1,1 (8,1-29) p=0,101	12,2±0,9 (5,6-19,8) p=0,331	2,03±0,20 (0,8-5,4) p<0,001
DG (n=28)	8,3±0,6 (2,6-14) p<0,001 p_1<0,001	24,1±2,1 (9-38,3) p<0,001 p_1=0,002	9,8±1,0 (2,2-15,3) p=0,056 p_1=0,157	2,19±0,40 (0,5-7,8) p=0,006 p_1=0,564
CKD of the DM origin (n=28)	12,6±1,3 (2,9-22,6) p<0,001 p_1<0,001 p_2=0,030	30,5±2,9 (10,9-62,4) p<0,001 p_1<0,001 p_2=0,139	14,1±1,1 (4,5-24,5) p=0,771 p_1=0,212 p_2=0,008	3,86±0,53 (0,67-9,19) p<0,001 p_1=0,008 p_2=0,011
CKD of the CGN origin (n=30)	13,8±1,2 (5,1-24,7) p<0,001 p_1<0,001 p_2<0,001 p_3=0,465	45,7±4,1 (11,-80,0) p<0,001 p_1<0,001 p_2<0,001 p_3=0,010	12,6±0,8 (5,3-19,9) p=0,263 p_1=0,732 p_2=0,057 p_3=0,261	4,95±0,51 (0,5-9,27) p<0,001 p_1<0,001 p_2<0,001 p_3=0,146
Control (n=17)	2,1±0,2 (0,1-3,1)	12,4±1,2 (4,5-18,7)	13,4±1,7 (0,3-23,5)	0,87-0,14 (0-1,8)

Note: - p - compared to the control group; p_1 - compared with DM not complicated by GP; p_2 – compared to DG; p_3– compared to the patients with CKD of DM origin.

Increased synthesis of KP indicates the activation of inflammatory cytokines. Thus, KP has an immunomodulatory effect by being released during the activation and destruction of neutrophils, as well as during epithelial adhesion of monocytes.

The results show that the coagulation of cathelicidin and L-FABP increased by 42.5% (p = 0.005) and 40.2% (p = 0.001), respectively, compared to the control group. Thus, their average

coagulation constitute to 0.984±0.064 mcg / ml (0.52 -1.8 mcg / ml) and 0.493±0.027 ng / ml (0.2-0.74 ng / ml).

Table 3

Levels of some antimicrobial peptides in the blood of patients with the kidney pathology of DM and CGN

Groups	Indicators		
	KP, ng/ml	Cathelicidin, mcg/ml	L-FABP, ng/ml
DM not complicated by GP, (n=28)	201,4±10,3 (115,4-298,6) p<0,001	0,984±0,064 (0,52-1,8) p=0,005	0,493±0,027 (0,2-0,74) p=0,001
DG (n=28)	217,2±11,2 (113,1-327,1) p<0,001 p_1=0,399	1,082±0,123 (0,27-2,51) p=0,053 p_1=0,987	0,998±0,021 (0,78-1,16) p<0,001 p_1<0,001
CKD of the DM origin, (n=28)	237,8±13,9 (127,3-348,2) p<0,001 p_1=0,075 p_2=0,287	0,885±0,102 (0,17-1,75) p=0,244 p_1=0,378 p_2=0,364	2,152±0,210 (0,44-3,75) p<0,001 p_1<0,001 p_2<0,001
CKD of the CGN origin, (n=30)	329,7±11,3 (237-415) p<0,001 p_1<0,001 p_2<0,001 p_3<0,001	0,715±0,075 (0,2-1,37) p=0,972 p_1=0,014 p_2=0,048 p_3=0,223	4,566±0,238 (2,53-6,79) p<0,001 p_1<0,001 p_2<0,001 p_3<0,001
Control, (n=17)	95,5±2,0 (81,5-106,7)	0,691±0,066 (0,176-1,01)	0,351±0,023 (0,18-0,51)

Note: - p - compared to control; p_1 - compared with DM not complicated by GP; p_2 – compared to DG; p_3– compared to the patients with CKD of DM origin.

Assessment of blood carbohydrate interchange, some indicators reflecting the functional activity of the kidneys, cytokines and antimicrobial peptides in the blood of patients with glomerulopathy of diabetic origin. The research found that the coagulation of glucose and HbA1c in the blood serum of patients with DG increased statistically 2.2 times (p <0.001) and 23.3% (p1 = 0.025), respectively, compared with the control group, the average result makes up 10.3. ± 0.6 mmol / l (6.5-15.5 mmol / l) and 11.5 ±

0.6% (6.7-16.4%).

The coagulation of insulin and peptide C in the blood serum of patients in this group studied increased by 93.8% (p <0.001) and 18.2% (p = 0.002) compared with the control group. Thus, their coagulation is determined as 29.7 ± 1.0 mcg% (11.8-36.4 mcg%) and 753.5 ± 23.4 pmol / l (531-979 pmol / l), respectively.

The results show that the coagulation of creatinine in patients with DG increased by 3.4 times (p <0.001) compared with the control group, and by 2.3 times (p1 <0.001) compared with patients with DM without complications of GP. The average creatinine coagulation in these patients consists of 267.6 ± 26.1 μM / l (82.1-444.8 μM / l). The coagulation of urea increased 2.5 times compared to the control group (p <0.001), 56.1% (p1 = 0.001) compared to patients with DM without complications of GP, the average statistical coagulation comprise to 13.4 ± 1.3 mM / l (5 , 2-24.8 mM / l). In this group, the coagulation of cystatin C increased by 2 times compared to the control group (p <0.001), and by 21.65% (p1 = 0.182) compared to DM patients without complications of GP, consists of 1,692 ± 0.169 ng / ml (0.471- 2,962 ng / ml).

The research case found that the coagulation of IL-6 in the blood serum of patients with DM of DG origin increases 3.9 times (p <0.001) compared with the control group, and 3.5 times (p1 <0.001) compared with patients with DM without complications of GP increases statistically significantly, so the average indicator is 8.3 ± 0.6 pg / ml (2.6-14 pg / ml). IL-6 is one of the most important cytokines in the immune response and inflammatory reactions. In this regard, the increase in the coagulation of IL-6 during DG indicates the progression of chronic infection and inflammatory pathology.

The coagulation of IL-8 in patients with DG increased by 94.3% (p <0.001) compared to the control group, and by 54.3% (p1 = 0.002) compared to patients with DM without complications of GP, reaches 24.1 ± 2.3 pg/ml (p <0.001; 9-38.3 pg / ml). Increased IL-8 coagulation leads to the accumulation of neutrophils, monocytes, eosinophils and T-cells in the area of inflammation.

The coagulation of IL-10 varies mainly within the norm, as its average statistical coagulation consists of 9.8 ± 1.0 pg / ml (2.2-15.3

pg / ml; p1 = 0.157).

The average coagulation of TNF-α in the research group comprise to 2.19 ± 0.40 pg/ml (0.5-7.8 pg/ml). Thus, while the coagulation of this cytokine increased 2.5 times (p=0.006) compared with the control group, it was observed that it does not change significantly compared with the indicators of patients with DM without complications with GP (p1 = 0.564). The effect of TNF-α in patients with DM is multifactorial and is involved in the development of DG through several mechanisms. TNF-α has a direct apoptotic and cytotoxic effect on glomerular cells. It reduces the rate of glomerular filtration by increasing the synthesis of endothelin-1.

According to the results, the coagulation of cathelicidin and KP in the blood serum increased by 56.7% (p = 0.053) and 2.3 times (p <0.001), respectively, compared to the control group makes up 1.082±0.123 μg /ml (0.27-251 mcg/ml) and 217.2 ± 11.2 ng / ml (113.1-327.1 ng / ml).

The results show that the coagulation of L-FABP in this group increased 2.8 times (p<0.001) compared to the control group, and 2.0 times (p1<0.001) compared to patients with DM not complicated by GP, and its coagulation is determined 0.998 ± 0.021 ng. / ml (0.78-1.16 ng/ml).

No significant differences were found in this group compared to patients with DM not complicated by GP due to the coagulation of KP (p1 = 0.399) and cathelicidin (p1 = 0.987).

Assessment of the level of carbohydrate interchange, some indicators reflecting the functional activity of the kidneys, cytokines and antimicrobial peptides in the blood of patients with CKD of DM origin. The average glucose coagulation in this group of patients consists of 11.3 ± 0.6 mmol/l (7.2-17.8 mmol/l) and is 2.4 times higher than the control group (p <0.001) compared with the results of DM patients who do not have GP complications statistically significant increase 31.1% (p1 <0.001). A significant increase in the coagulation of HbA1c is observed in this group, which consists of 2.7 times (p <0.001) compared to the control group. The average coagulation of HbA1c in this group is 13.6 ±

0.7% (8.3-19.1%). The results show that the coagulation of HbA1c increased by 45.2% (p1 <0.001) compared to patients with DM without complications of GP, and by 17.8% (p2 = 0.044) compared with patients with DG. Insulin coagulation increased 2.3 times (p<0.001) compared with the control group, 38.2% (p1<0.001) compared with the results of DM patients not complicated by GP, and 20.1% (p2 = 0.002) compared with patients with DG makes up 35.7 ± 1.7 mcg% (13.9-49.6 mcg%).

In this group, in contrast to other groups, the level of peptide C is observed 52.2% (p <0.001) compared to the control group, 39.0% (p1 <0.001) compared with DM patients without complicated by GP, and 28.8% (p2<0.001) compared to the patients with DG. The average coagulation of C peptide is 970.3 ± 34.7 pmol / l (700-1186 pmol / l).

According to the results of the research, the coagulation of creatinine in the blood serum during CKD of DM origin statistically significant increases 9.2 times (p <0.001) compared to the control group, 6.1 times (p1 <0.001) compared to patients with DM without complications of GP, 2.7 times (p2<0.001) compared to the patients with DG. The average creatinine coagulation in this group is 723.9 ± 58.1 μM / l (320-1253 μM / l).

In this group, the coagulation of urea in the blood serum of all patients increases 5.3 times (p <0.001) compared with the control group, 3.3 times (p1 <0.001) compared with patients with DM without complications of GP, and 2.1 times with the results of patients with DG (p2 <0.001). The average coagulation of urea consists of 28.3 ± 1.1 mM / l (11.5-36 mM / l).

The coagulation of cystatin C is significantly increased in patients with DM origin during CKD, which is 3.1 times higher than in the control group (p <0.001), 1.9 times (p1 <0.001) compared with the corresponding indicators of DM not complicated by GP, 1.6 times (p2 <0.001) compared with the corresponding indicators of patients with DG. The average coagulation of cystatin C is determined to be 2,635 ± 0.171 mg / l (1.47-3.89 mg / l).

The average statistical coagulation of IL-6 in this group consists of 12.6 ± 1.3 pg / ml (2.9-22.6 pg / ml). Its coagulation increases 5.9

times (p <0.001) compared to the control group, 5.4 times (p1 <0.001) compared to DM patients not complicated by GP, and 51.1% (p2 = 0.030) compared to the corresponding indicators of patients with DG. The coagulation of IL-8 increases by 2.5 times (p <0.001) compared to the control group and makes up 30.5 ± 2.9 pg / ml (10.9-62.4 pg / ml). The results show that the coagulation of IL-8 increases 1.9 times (p1 <0.001) compared with patients with DM who do not have GP complications. It is observed that the coagulation of IL-10 in the blood serum during CKD of DM origin changes at the level of the control group. Coagulation of IL-10 and the average coagulation of IL-10 is 14.1 ± 1.1 pg / ml (4.5-24.5 pg / ml; p = 0.771). There is a statistically significant increase in IL-10 coagulation of 43.7% (p2 = 0.008) compared with patients with DG.

The coagulation of TNF-α increases 4.4 times statistically significantly (p<0.001) compared with the control group. This increase consists of 89.8% (p1 = 0.008) in patients with DG who did not have GP complications and 76.5% (p2 = 0.011) in patients with D. Its average coagulation comprise to 3.86 ± 0.53 pg / ml (0.67-9.19 pg / ml).

Determination of KP in the blood has a high interpretation in determining the degree of failure to the kidneys and the intensity of the clinical course of DG, and is used to monitor therapeutic treatment. An increase in the level of KP in the blood is a key indicator of the acute inflammatory process. The coagulation of KP increases statistically significantly by 2.5 times (p <0.001) compared with the control group. Its average coagulation is 237.8 ± 13.9 ng / ml (127.3-348.2 ng / ml). The coagulation of KP varies very little compared to patients with DG (p2 = 0.287).

The average coagulation of cathelicidin in this group consists of 0.885 ± 0.102 mcg / ml (0.17-1.75 mcg / ml). According to the results, the coagulation of cathelicidin increases by 28.2% compared to the control group, and this increase is not statistically significant (p= 0.244). In addition, the coagulation of cathelicidin tends to decrease in patients with DM who do not have GP complications (p2= 0.364).

The coagulation of L-FABP in the blood serum during CKD of

DM origin consists of 2.152 ± 0.210 ng / ml (0.44-3.75 ng / ml) increased by 6.1 times than the control group (p<0.001), 4.4 times than in DM patients without complicated by GP (p1 <0.001), 2.2 times (p2 <0.001) compared with the corresponding indicators of DM patients with DG.

Assessment of the level of carbohydrate interchange, some indicators reflecting the functional activity of the kidneys, cytokines and antimicrobial peptides in the blood of patients with CKD of glomerulonephritis origin. CKD develops on the basis of glomerulonephritis caused by disorders of the kidney tubules and interstitial tissue. There are no significant changes in the serum carbohydrate interchange of patients with CKD of CGN origin compared with the control group. Thus, the average coagulation of glucose, HbA1c, insulin and C-peptide in this group constitute to 5.6 ± 0.1 mmol / l (4.7-6.5 mmol / l), 3.8-5.5% (4.7 ± 0.1%), 16.2 ± 0.5 mcg% (11.5 - 21.6 mcg%) and 538-865 pmol / l (698.2 ± 18.5 pmol / l. l), respectively.

Serious failure of kidneys' function is observed in patients with CKD of CGN origin. In these patients, the creatinine coagulation increased 7.8 times (p <0.001) compared to the control group, and the average coagulation consists of 610.3 ± 51.0 μm/l (152–1097 μm/l). According to the results of a comparative analysis, the coagulation of creatinine increases 2.3 times (p2 <0.001) in patients with DG. There is no statistically significant difference compared to patients with CKD of DM origin (15.7%; p3 = 0.189).

The average urea coagulation in this group makes up 19.6 ± 0.6 mM / l (12.1-26.8 mM / l) and according to statistical calculations, it increases 3.7 times (p <0.001) more accurate than in the control group. It can be seen from the results that the coagulation of urea in this group is 1.5 times (p2 <0.001) higher than in patients with DG. However, the coagulation of urea decreases by 30.7% (p <0.001) compared with patients with CKD of DM origin.

The coagulation of cystatin C during CKD of glomerulonephritis origin is statistically significantly higher than in the control group, respectively, as this increase comprise to 2.4 times (p <0.001). The average coagulation of cystatin C in this group consists of 2.095 ±

0.111 mg / l (1.07 - 3.1 mg / l). The coagulation of cystatin C increased by 23.8% (p2 = 0.051) compared to DG. However, in contrast, it decreased by 20.5% (p3 = 0.020) compared with patients with CKD of DM origin.

The significant increase in the coagulation of inflammatory cytokines is observed as a result of activation of the inflammatory process in patients with CKD of CGN origin. It is clear from the results that the coagulation of IL-6 in this group increased statistically significantly by 6.4 times (p <0.001) compared with the control group, and by 66.1% (p2 = 0.008) compared with patients with DM complicated by DG. The average mathematical coagulation of IL-6 in this group consists of 13.8 ± 1.2 pg / ml (5.1-24.7 pg / ml; p3 = 0.465).

In this research group, the coagulation of IL-8 increases 3.7 times than in the control group (p <0.001), 89.5% (p2 = 0.001) compared with patients with DG, and 50.2% compared with patients with CKD of DM origin (p3 = 0.010). The average coagulation of IL-8 in this group is equal to 45.7 ± 4.1 (11.5-80.0 pg / ml) pg / ml.

It is clear from the results that the level of anti-inflammatory cytokine IL-10 in the blood serum during CKD of CGN origin varies within the normal range (12.6 ± 0.8 pg / ml; 5.3-19.9 pg / ml; p=0.263).

The coagulation of TNF-α in this group increases 5.7 times (p<0.001) compared with the control group, and 2.3 times (p2 = 0.011) compared with patients with DG, the average mathematical indicator is 4.95 ± 0.51 pg /ml (0.5-9.27 pg / ml).

The research case found that the coagulation of AMPs, especially KP, and L-FABP in the blood serum during CKD of CGN origin increases statistically. In this group, the coagulation of KP is 3.5 times higher than in the control group (p <0.001), 51.8% (p2 <0.001) compared with the corresponding indicators of patients with DG, and 38.7% compared with the indicators in patients with CKD of DM origin (p3 <0.001) increased statistically, the average coagulation consists of 329.7 ± 11.3 ng / ml (237-415 ng / ml).

In this group, the coagulation of cathelicidin varies within the control group limits (0.715 ± 0.075 μg / ml; 0.2-1.37 μg / ml;

p=0.972). Calculations show that the coagulation of cathelicidin reduces by 33.9% (p2 = 0.048) compared with patients with DG. There is no significant difference compared with patients with CKD of DM origin (p3 = 0.223).

The research case identifies that L-FABP coagulation increases significantly in the blood serum during CKD of CGN origin. Thus, the coagulation of L-FABP in this group increased statistically 13 times than in the control group (p <0.001), 4.6 times than in patients with DG (p2 <0.001), and 2.1 times than in patients with CKD of DM origin (p3<0.001) and its average makes up 4,566 ± 0.238 ng / ml (2.53-6.79 ng / ml).

Results of the correlation between biochemical indicators and ROC statistical analysis in patients with DM, DG and diabetic origin of non-glomerulopathy. According to the results of statistical analysis, a correlation is revealed between the parameters involved in carbohydrate interchange among the patients included in the research.

A positive correlation dependence is determined between glucose and HbA1c (ρ=0.284, p <0.05), insulin (ρ=0.243, p<0.05) and C peptide (ρ=0.223, p<0.05); C peptide insulin (ρ = 0.369, p <0.01) and HbA1c (ρ = 0.537, p <0.01).

Thus, in these patients, the positive correlation is identified between creatinine and glucose (ρ = 0.283, p<0.05), HbA1c (ρ = 0.440, p <0.01), insulin (ρ = 0.479, p <0.01) and C peptide (ρ = 0.502, p <0.01); glucose and urine (ρ = 0.364, p <0.01), HbA1c (ρ = 0.330, p <0.01), insulin (ρ = 0.526, p <0.001) and C peptide (ρ = 0.498, p <0.001)). This identified dependence indicates that chronic hyperglycemia causes impaired the function of the kidney.

The detection of a positive correlation between cystatin C and HbA1c (ρ = 0.321, p <0.01), insulin (ρ = 0.471, p <0.01), C peptide (ρ = 0.405, p <0.01) and creatinine (ρ = 0.565, p <0.01) proves the diagnostic value of cystatin C along with creatinine.

The correlation between glucose and IL-6 (ρ = 0.325, p <0.05) and IL-8 (ρ = 0.384, p <0.001) shows the effect of chronic hyperglycemia on cytokine synthesis. In addition, a positive correlation is identified between HbA1c and IL-6 (ρ = 0.382, p

<0.001), insulin and IL-6 (ρ = 0.429, p <0.001), IL-8 (ρ = 0.438, p <0.001) and TNF-α (ρ = 0.284, p <0.015); peptide C and IL-6 (ρ = 0.453, p <0.001), IL-8 (ρ = 0.324, p <0.005), and IL-10 (ρ = 0.237, p <0.044). The results demonstrate that cytokines play an important role in the development of insulin resistance. It also proves that glycosylated products in kidney tissue activate the inflammatory process.

A positive correlation is found between glucose interchange and AMPs, so this dependence is shown between L-FABP and HbA1c (ρ = 0.294, p <0.008), insulin (ρ = 0.433, p <0.001), and C peptide (ρ = 0.445, p <0.001).

A correlation dependence is identified between cytokines and biochemical parameters evaluating the function of the kidneys. The correlation between creatine and IL-6 (ρ = 0.676; p <0.001) and IL-8 (ρ = 0.507; p <0.001), urea and IL-6 (ρ = 0.599; p <0.001), IL-8 (ρ = 0.439; p <0.001) and IL-10 (ρ = 0.230; p <0.050), cystatin C and IL-6 (ρ = 0.633; p <0.001), IL-8 (ρ = 0.378; p <0.001) and TNF-α (ρ = 0.315; p <0.007) indicates the importance of cytokines in the inflammatory process in the kidneys.

The correlation connections are found between cytokines in patients with DM and its complications with DG and CKD. There is a positive correlation between IL-8 and IL-6 (ρ = 0.501; p <0.001) and TNF-α (ρ = 0.382; p <0.001). This correlation dependence shows that an increase in the coagulation of IL-6 stimulates the synthesis of IL-8. At the same time, IL-8 also exacerbates inflammation by inducing the synthesis of TNF-α based on a cascade reaction mechanism.

Determining the correlation dependence between AMPs and biochemical parameters assessing the functional activity of the kidneys proves the role of AMPs in the development of inflammatory processes in the kidneys. A correlation is observed between Cystatin C (ρ = 0.247; p <0.035) and KP, creatinine (ρ = 0.723; p <0.001) and L-FABP, urea (ρ = 0.574; p <0.001) and cystatin C (ρ = 0.380; p< 0.001).

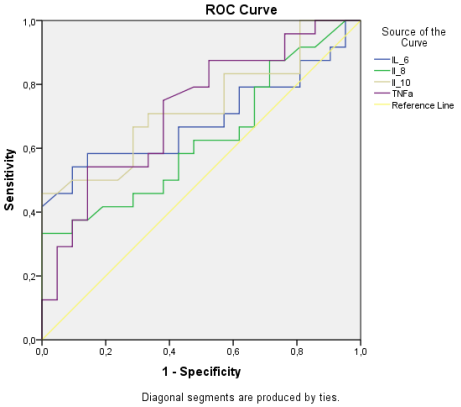
Although no correlation is found between AMPs in these patients, a correlation is observed between changes in AMPs and

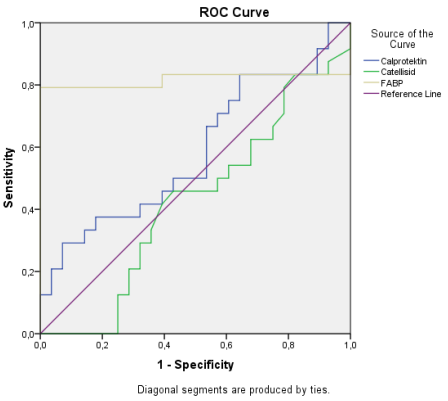
cytokine coagulation. The direct correlation between L-FABP and IL-6 (ρ = 0.706; p <0.001), IL-8 (ρ = 0.473; p <0.001), and TNF-α (ρ = 0.262; p <0.025) shows the great importance of inflammatory cytokines in the synthesis of L-FABP.

In recent years, the ROC (Receiver Operating Characteristic) statistical analysis method has been used to determine the specificity and sensitivity of laboratory tests. It is determined according to the ROC curve that HbA1c (95% EI: 0.663 ± 0.076, p = 0.044), insulin (95% EI: 0.746 ± 0.072: p = 0.002), and C-peptide (95% EI: 0.827 ± 0.057; p <0.001) are tests with high sensitivity and specificity within carbohydrate interchange indicators, but glucose (95% EI: 0.609 ± 0.079, p = 0.180) is not considered a test with high sensitivity and specificity.

According to the ROC statistical calculation method, cystatin C (95% EI: 0.780 ± 0.068; p <0.001), urea (95% EI: 0.950 ± 0.030; p <0.001) and creatinine (95% EI: 0.935 ± 0.034; p<0.001) are tests with high specificity and sensitivity in the diagnosis of the dysfunction of the kidneys in DM patients.

Based on the indicators of the ROC curve, IL-6 (95% EI: 0.689 ± 0.081; p = 0.030), IL-10 (95% EI: 0.730 ± 0.075; p = 0.008) and TNF-α (95% EI: 0.722 ± 0.076; p = 0.011) are identified to possess high sensitivity and specificity tests in the purposes to assess the function of the kidneys. The sensitivity and specificity of IL-8 cytokine (95% EI: 0.629 ± 0.084; p = 0.139) are not statistically significant. (graph 2).





The sphere below the curve

Changes in test results (s)	Sphere	Standard error[a]	P accuracy	95% reliability interval	
				Lower border	Upper border
IL-6	0,689	0,081	0,030	0,530	0,849
Il-8	0,629	0,084	0,139	0,465	0,793
Il-10	0,730	0,075	0,008	0,583	0,878
TNFα	0,722	0,076	0,011	0,573	0,871
KP	0,586	0,081	0,287	0,428	0,745
Cathelicidin	0,425	0,080	0,354	0,268	0,582
L-FABP	0,817	0,076	<0,001	0,667	0,967

Graph 2. ROC curves of cytokines and antimicrobial peptides.

The results of the ROC curves show that L-FABP (95% EI: 0.817 ± 0.076; p <0.001) can be considered a more specific and informative marker in the diagnosis of kidney pathology. Specificity and informativeness of KP (95% EI: 0.586 ± 0.081; p = 0.287) and cathelicidin (95% EI: 0.425 ± 0.080: p = 0.354) are not statistically significant.

In addition, ANOVA test-dispersion analysis has been performed to determine the diagnostic value and informativeness of the tests among the studied biochemical parameters.

According to the results of the ANOVA test, in the differential diagnosis of diseases, glucose is identified greater than 7.5 mmol / l, sensitivity is 95.8 ± 4.1%, factor specificity is 32.1 ± 8.8%, and GDV is 61.5 ± 6, 7% p <0.001; HbA1c is identified greater than 16.5%, sensitivity 29.2 ± 9.3%, factor specificity 100%, GDV 67.3 ± 6.5%, p <0.001; insulin is identified greater than 33.8, sensitivity 62.5 ± 9.9%, factor specificity 89.3 ± 5.8%, GDV 76.9 ± 5.8%, p <0.001; C-peptide is identified greater than 940, sensitivity is 62.5 ± 9.9%, factor specificity is 92.9 ± 4.9%, and GDV is 78.8 ± 5.7%, p <0.001, and in patients with DM can be used in the prediction of kidney pathology.

The results of the ANOVA test, which reflects the functional activity of the kidneys in patients with DM, are identified greater than 25 in urine, sensitivity 79.2 ± 8.2%, factor specificity 100%, and

UDD 88.9 ± 4.7%, p <0.001 ; creatinine is identified greater than 446, sensitivity 79.2 ± 8.3%, factor specificity 100%, GDV 88.9 ± 4.7%, p <0.001; Cystatin C is identified greater than 1.47, sensitivity 100%, factor specificity 47.6 ± 10.9%, and GDV is identified 75.6 ± 6.4%, p <0.001, and these results may be of great practical importance in assessing the functional activity of the kidneys.

According to the results of the ANOVA test, the coagulation of IL-6 is greater than 12.6 pg / ml, the sensitivity is 54.2 ± 10.2%, the specificity of the factor is 90.5 ± 6.4%, and the UDD is 71.1 ± 6. , 8%, p <0.001; the coagulation of IL-8 is greater than 38.9 pg / ml, the sensitivity is 33.3 ± 9.6%, the specificity of the factor is 100%, and the GDV is 64.4 ± 7.1%, p <0.001; IL-10 coagulation is greater than 15.4 pg / ml, sensitivity 45.8 ± 10.2%, factor specificity 100%, GDV 71.1 ± 6.8%, p <0.001; the coagulation of TNF-α is greater than 3.18 pg / ml, the sensitivity is 54.2 ± 10.2%, the specificity of the factor is 85.7 ± 7.6%, and the specific gravity is 68.9 ± 6.9%. p <0.001.

According to the results of the ANOVA test of AMPs in patients with type II DM, the KP was greater than 294 ng / ml, the sensitivity was 29.2 ± 9.3%, the specificity of the factor was 92.9 ± 4.9%, and the GDV was 63, 5 ± 6.7%, p <0.001; catelicidin was greater than 1.01 ng / ml, sensitivity 45.8 ± 10.2%, factor specificity 57.1 ± 9.4%, and GDV 51.9 ± 6.9%, p <0.001; L-FABP was found to be greater than 1.18 pg / ml, sensitivity 79.2 ± 8.3%, factor specificity 100%, and GDV was identified 90.4 ± 4.1%, p <0.001.

Thus, according to the results of the ANOVA test, HbA1c, C-peptide, creatinine, urea, IL-6, IL-8, TNF-α, KP and L-FABP were evaluated as high tests for the detection of kidney pathology in patients with type II DM. The determination of these tests in patients with DM has great importance in the early diagnosis of DG and plays an important role in the prevention of CKD.

CONCLUSIONS

1. Increases in glucose, glycohemoglobin, insulin, and C peptide coagulation during DG 2,2-times (p <0,001); 2,3 times (p<0,001);

93,8% and 18,2%; during CKD of DM origin – 2,4 times ($p < 0,001$); 2,7 times ($p<0,001$); 2,3 times ($p<0,001$) and 52,2% ($p<0,001$) respectively, compared with the control group indicate more severe impairment of carbohydrate interchange in DM patients with kidney pathology [1].

2. Impaired kidney function in patients with DM can lead to the increase of the coagulation of creatinine, urea and cystatin C in the blood of patients with glomerulopathy of diabetic origin, respectively – 2,3 (p1 <0,001); 56,1% ($p_1 <0,001$); 21,6%; in case of CKD of DM origin – 6,1 times ($p_1 <0,001$); 3,3 times ($p_1 <0,001$) and 89,5% ($p_1 <0,001$); in the case of CKD of CGN origin – 5,2 times ($p_1 <0,001$), 2,3 times ($p_1 <0,001$) and 50,6% ($p_1 <0,001$) compared with patients with DM without complications of glomerulopathy [4, 16].

3. The coagulation of cytokines IL-6, IL-8 and TNF-α in glomerulopathy of DM origin increases – 3,5 times, respectively ($p_1 <0,001$); 54,3% ($p_1 <0,001$) and 7,6%; in the case of CKD of DM origin – 5,4 times ($p_1 <0,001$), 94,8% ($p_1 <0,001$) and 89,8% ($p_1 <0,01$); an increase of 5,9 times, 2,9 times and 2.4 times ($p_1 <0,001$) in patients with CKD of GP compared with patients with DM without complications of GP indicates an acceleration of the inflammatory process in chronic kidney disease [2, 4-6, 8, 10, 11, 14, 15].

4. The coagulation of calprotectin and L-FABP antimicrobial peptides in the blood of patients with DM complicated by glomerulopathy was 7,9% and 2 times respectively ($p_1<0,001$); in patients with diabetes mellitus CKD – 18,1% ($p_1 = 0,051$) and 4,4 times ($p_1 <0,001$); an increase of 63,7% ($p_1 <0,001$) and 9,3 times ($p_1 <0,001$) is observed in patients with CKD of CGN origin compared with patients with DM who does not have glomerulopathy [7, 12, 13, 17].

5. The positive correlation is observed between creatinine and glycohemoglobin ($\rho = 0,283$, $p <0,05$), urea and insulin ($\rho = 0,526$, $p <0,01$), cystatin C and creatinine ($\rho = 0,565$, $p <0, 01$), between IL-6 and creatinine ($\rho = 0,676$; $p <0,01$), between urea ($\rho = 0,599$; $p <0,01$) and IL-8 ($\rho = 0,501$; $p <0,001$), between creatine and IL -8 ($\rho = 0,507$; $p <0,01$), creatinine with L-FABP ($\rho = 0,723$; $p <0,001$),

urea (ρ = 0,574; p <0,001), cystatin C (ρ = 0,380; p < 0,001), IL-6 (ρ = 0,706; p <0,001), IL-8 (ρ = 0,473; p <0,001), between IL-8 and TNF-α (ρ = 0,382; p <0,001) [11].

6. According to the ROC curves and the results of the ANOVA test, HbA1c, C-peptide, creatinine, urea, IL-6, IL-8, TNF-α, KP and L-FABP were evaluated as high-value general diagnostic tests in the detection of kidney pathology in patients with type II DM [14].

PRACTICAL RECOMMENDATIONS

1. Determination of cytokines and AMPs levels in patients with type II DM, along with traditional diagnostic methods, is of great scientific importance in the study of the mechanisms of development of ND immune origin, which may allow the application of new methods in the early diagnosis and treatment of CKD in these patients.

2. Co-administration of cystacin C with creatinine and glycohemoglobin can be used as an important indicator in the assessment of kidney function.

3. Determination of IL-6, IL-8, TNF-α and L-FABP in complex examinations of patients with CKD of DG and SD origin can be recommended as tests with high diagnostic value in determining the severity of kidney damage.

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Acronyms

AMP – antimicrobial peptides
ANOVA – Analysis of variance
CKD – chronic kidney disease
DG – diabetic origin glomerulopathy
FABP – fatty acid binding protein
HbA_{1c} – glycohemoglobin
IL – interleukin
CP – calprotectin
CP – chronic pyelonephritis
CG – chronic glomerulonephritis
ROC – receiver operating characteristic
DM – diabetes mellitus
TLR – Toll-like receptors
TNF – tumor necrosis factor
USM – ultrasound
GDV – general diagnostic value
GFR – glomerular filtration rate
M – average indicator
±m – standard error
σ – average square standard error
LL – Lower limit in the range of 95%
UL – Upper limit in the range of 95%
min – minimum
max – maximum

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Electronic versions of the dissertation and autoreferat are posted on the official website (www.physiology.az) of the Institute of Physiology of the Azerbaijan National Academy of Sciences named after academician A.Garayev.

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