ORIGINAL ARTICLE

CONTENTS

Study of the relationship between the level of pro-inflammatory cytokines and β2-microglobulin with indicators of changes in the functional status of the kidneys in diabetic nepropathy to determine the degrees of chronic renal failure

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ABSTRACT

Aim: The purpose of this study is to analyze the correlations of pro-inflammatory cytokines and β2-microglobulin with indicators of changes in the functional state of kidneys in patients with diabetic nephropathy, to determine different degrees of chronic renal failure.

Materials and Methods: 80 patients with type 1 and type 2 diabetes, complicated by diabetic nephropathy, at different levels of the functional state of the kidneys were examined.

Results: It has been shown that the level of tumor necrosis factor α (TNFα) in the blood of patients with diabetic nephropathy (DN) is increased already with sufficient kidney function, decreases with chronic renal failure (CRF) of the I degree and reaches maximum values with CRF of the II and III degrees. which indicates the degree of progression of fibroplastic and sclerotic processes in the kidneys with DN. The level of interleukin-1α (IL-1α) in the blood of patients with DN begins to decrease with sufficient kidney function, increases with CRF of the II degree, but remains below the values of the control group and is minimal in patients with CRF of the III degree, which reflects a decrease in the intensity of the acute-phase inflammatory process in the development of CRF.

Conclusions: The development and progression of CRF is accompanied by an increase in the excretion of β2-microglobulin in the urine in parallel with changes in the cytokine profile in the blood.

KEY WORDS: proinflammatory cytokines, chronic renal failure, diabetic nephropathy, ketosteril

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INTRODUCTION

Diabetic nephropathy (DN) remains one of the urgent problems of modern medicine. It develops in 36-48% of patients with diabetes mellitus (DM) type 1 and in 18-26% of patients with diabetes mellitus type 2, has a prolonged natural evolution, which leads to the irreversible development of proteinuria and kidney failure [1,2].

Recent renal registries suggest that 27% to 34% of all cases of terminal chronic renal failure are associated with diabetic nephropathy. In the USA and Europe, every third patient who needs hemodialysis has diabetes [1,3].

The pathogenesis of diabetic nephropathy is the subject of numerous scientific studies around the world. The key chain in the development of this severe complication of diabetes is long-term persistent hyperglycemia, which causes endothelial dysfunction, local hemodynamic disturbances, and the development of glomerular hyperfiltration [4]. Recently, there has been increasing interest in the role of cytokines in the progression of DN, especially the so-called pro-inflammatory cytokines, which activate the metabolism of connective tissue, stimulate the proliferation of fibroblasts, epithelial cells, and the mesangial matrix, and are included as mediators in each link of immunoinflammatory processes [4,5].

Among pro-inflammatory cytokines, the most attention is paid to tumor necrosis factor-α (TNFα) and interleukin-1α (IL-1α), which are secreted by monocytes/macrophages, endotheliocytes and coordinate a complex cascade of local immunoinflammatory reactions that lead to the development of glomerulosclerosis [6,7]. The value of IL-1α and TNFα as diagnostic and prognostic markers of kidney damage at different stages of DN, the possibility of cytokine/anticytokine therapy is studied [8,9]. Also, it remains relevant to determine the excretion of β_2-microglobulin with urine

for the timely diagnosis of tubulointerstitial lesions in patients with DN, an increase in the level of this protein in the plasma may indicate early violations of the filtering function of the kidneys, which is characteristic of this disease [7].

All this indicates the need to deepen scientific research on the importance of pro-inflammatory cytokines in the development and course of DN, the possibility of correcting changes in the cytokine system, which should delay the development of kidney damage in diabetes, and prolong the pre-dialysis period of chronic renal failure [10-12].

AIM

The purpose of this work is to study the relationship between the level of pro-inflammatory cytokines and β_2-microglobulin with indicators of changes in the functional state of the kidneys in patients with diabetic nephropathy, to determine different degrees of chronic renal failure.

MATERIALS AND METHODS

To conduct research, the necessary sample volume was determined to obtain the best result during a random survey, according to the formula:

$$n = \frac{t^2 \cdot \omega \cdot (1 - \omega)}{\Delta_\omega^2},$$

where t is a standardized value at a given level of reliability α = 0.95; ω – the number of patients with confirmed chronic renal failure, %; – marginal sampling error of 5%.

A representative volume of the sample was determined, which was 67-95 people.

In the study, the sample included 80 patients with type 1 and type 2 diabetes, complicated by diabetic nephropathy with varying degrees of kidney function. There are 43 men and 37 women among the patients. At the time of anamnesis collection, the age of the subjects was in the range from 20 to 75 years. Patients with an unspecified diagnosis and with the disease for less than 5 years did not participate in the study. The duration of the disease in patients with type 1 DM was 12.9±3.1 years, and in type 2 DM – 13.2±3.7 years.

The study was conducted over 11 months.

Diabetic nephropathy patients were divided into 4 groups depending on the functional state of the kidneys: 20 patients were diagnosed with sufficient kidney function (group I), 18 patiens had CRF I degree (II group), at 23 patients – CRF II degree (III group) and at 19 patients – CRF III degree (IV group). The basis for the distribution of patients with renal failure according to the degrees of CRF is the classification according to the order of the Ministry of Health of Ukraine №05/462 dated 09/30/2003 "Degrees of chronic renal failure depending on the rate of glomerular filtration and plasma creatinine concentration", and the determination of the stage of diabetic nephropathy was made according to the classification of C.E. Mogensen.

The control group consisted of 10 conditionally healthy persons, 6 men and 4 women, whose average age was 42.7±5.8 years.

The diagnosis was established on the basis of a thorough clinical (interrogation of the patient for complaints, study of the medical and life anamnesis, physical data) and laboratory (daily proteinuria, creatinine and urea content in the blood, glomerular filtration rate, tubular reabsorption) examination of patients with diabetic nephropathy of various degrees functional state of kidneys [2,13].

All patients underwent clinical and laboratory examinations, which included: clinical blood analysis, clinical urine analysis, biochemical blood analysis. The content of pro-inflammatory cytokines (TNFα and IL-1α) in the blood and the excretion of β_2-microglobulin in the urine were studied by enzyme-linked immunosorbent assay (ELISA). Determination of "free" human interleukin-1α in blood serum by the CytElisa – IL-1α method (a sandwich ELISA method that measures "free" forms of the human cytokine interleukin-1α). Determination of "free" human TNFα in blood serum by the CytElisa – TNFα method (a sandwich ELISA method that measures "free" forms of the human cytokine tumor necrosis factor (TNFα)) [14,15].

The study of excretion of β_2-microglobulin with urine was carried out in order to assess the degree of damage to tubulo-interstitial structures in diabetic nephropathy Quantitative determination of β_2-microglobulin in urine by the ELISA method [14,15].

Findings were statistically processed with help of SPSS 19 program product (IBM, USA). Correlation analysis with use of the Spearman coefficient (r) and the Chaddock scale was made for assessing relationships between indices.

RESULTS

The first group of investigated patients with DN with sufficient kidney function (CRF 0 degree) consisted of 20 patients aged 36 to 72 years. The duration of DM in this group averaged 12.3±1.74 years; blood pressure was on average: systolic blood pressure (SBP) – 143±18.3 mm Hg. and diastolic blood pressure (DBP) – 86.5±14.3 mm Hg. The average daily proteinuria was 1.3±0.38 g/

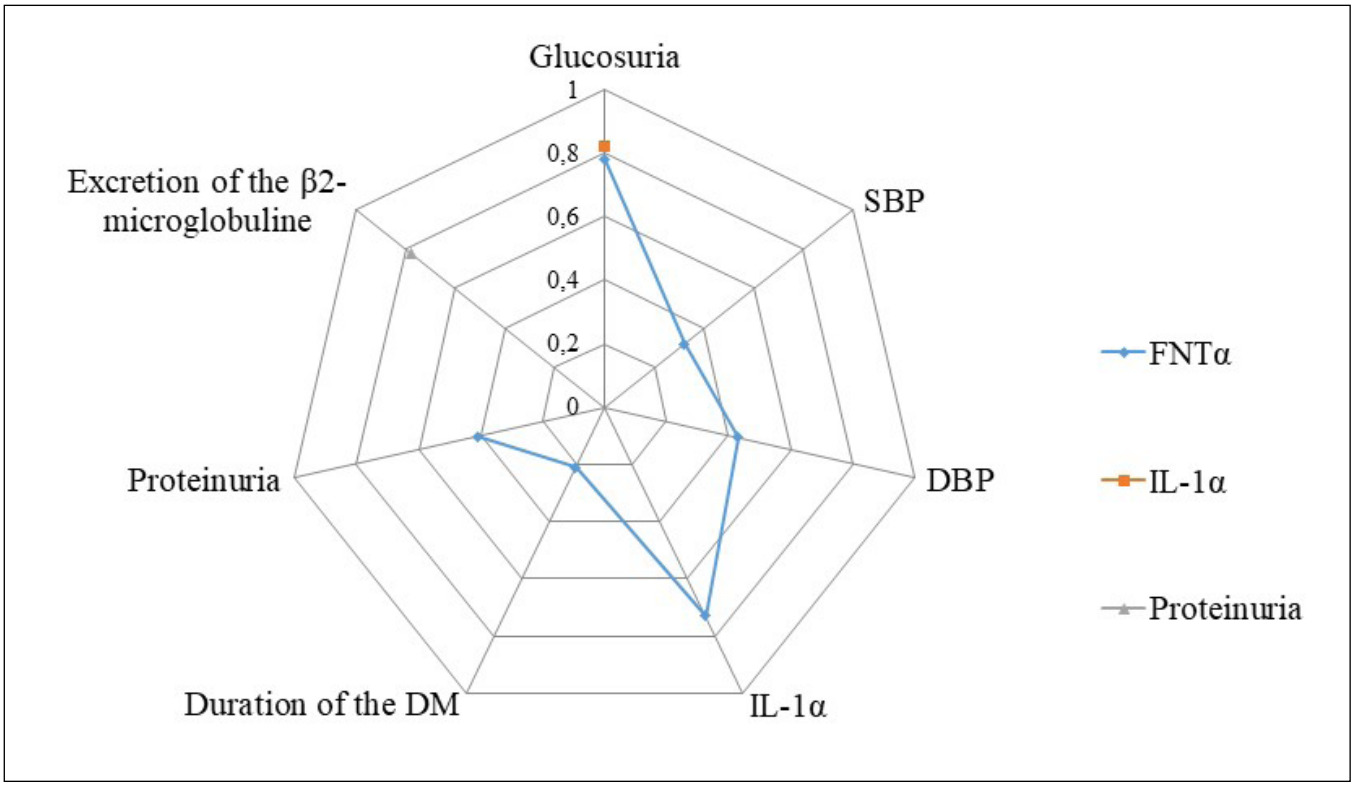

Fig. 1. Significant correlations in the group with sufficient renal function.

day. The content of creatinine in blood serum was on average 89.1±3.76 μmol/l and urea in blood serum was 6.4±0.43 mmol/l. The glomerular filtration rate (GFR) averaged 81.05±6.07 ml/min. and tubular reabsorption (R urine) – 92.5±1.75%.

Excretion of β_2-microglobulin with urine with sufficient kidney function was increased compared to the control group and averaged 0.15±0.04 pg/ml ($p<0.05$).

The content of IL-1α in the blood ranged from 0 to 7.1 pg/ml, on average 5.01±0.38 pg/ml, which is lower compared to the control group ($p<0.05$); the content of TNFα in the blood ranged from 4 to 76 pg/ml, on average 17.38±4.35 pg/ml and was significantly increased compared to the control group ($p<0.05$).

In patients of this group, a direct strong correlation between IL-1α and glucosuria was found ($r=0.82$, $p<0.05$), which confirms the importance of glucose toxicity in the development of immunoinflammatory processes in the kidneys. In addition, there is a direct strong correlation between urinary β_2-microglobulin excretion and daily proteinuria ($r=0.78$, $p<0.05$). This testifies to the fact that proteinuria is one of the most important factors of tubulointerstitial damage, which is established even with sufficient nitrogen excretory function of the kidneys.

A direct strong correlation relationship between TNFα and glucosuria ($r=0.78$, $p<0.05$), a weak correlation relationship between TNFα and SBP ($r=0.32$, $p<0.05$) and moderate – between TNFα and DBP ($r=0.43$, $p<0.05$), direct strong correlation between TNFα and IL-1α ($r=0.73$, $p<0.05$), weak correlation between TNFα and duration of diabetes ($r=0.21$, $p<0.05$) and moderate – between TNFα and proteinuria ($r=0.41$, $p<0.05$). The results of the detected correlations in the first group are presented in Fig. 1.

The decrease in the IL-1α content in the blood of DN patients with sufficient kidney function is explained by the long-term effect of hyperglycemia on immunocytes and endotheliocytes, which leads to the development of a cascade of pathological processes, resulting in the depression of the immune system. One of the main sources of IL-1α is endotheliocytes, which are also affected in diabetes. Endotheliocytes are insulin-independent, in conditions of hyperglycemia, glucose enters them without obstacles and causes a violation of their function. Endothelial dysfunction leads to a decrease in the production of IL-1α and its level in the blood.

It is known that IL-1α reduces the number of receptors for TNFα. A decrease in the content of IL-1α and an increase in the content of TNFα in the blood of patients with DN even with sufficient nitrogen-excreting function of the kidneys is evidence of the development of fibroplastic, sclerosing processes and a decrease in the severity of acute-phase inflammatory reactions even at this stage of the disease.

The second group of studied patients with DN with

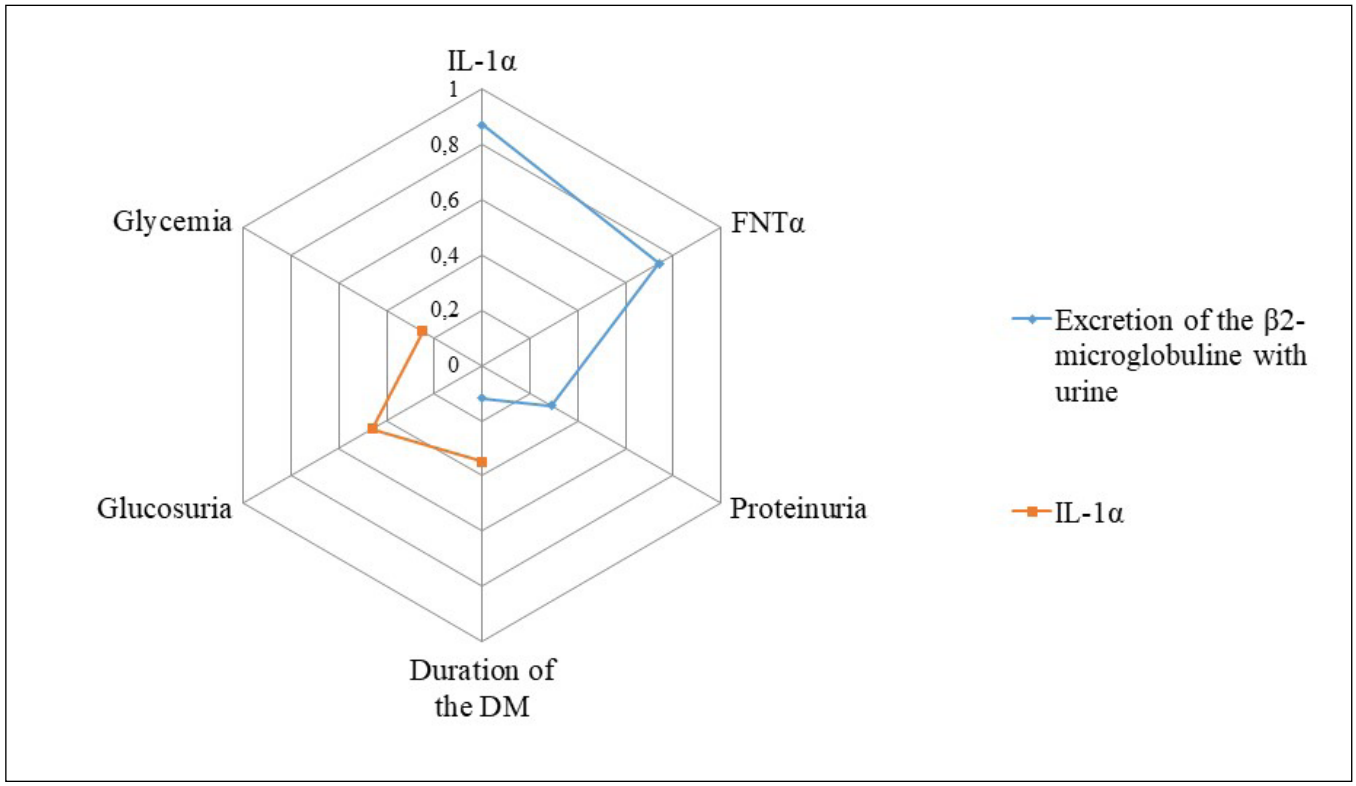

Fig. 2. Significant correlations in the group with CRF of I degree.

CRF I degree consisted of 18 patients aged 26 to 72 years. The duration of diabetes in this group averaged 13.7±2.63 years; blood pressure was on average: SBP – 162±11.4 mm Hg. and DBP – 98±6.6 mm Hg; Daily proteinuria – 2.3±0.52 g/day. The levels of azotemic indicators were: creatinine in blood serum – 163±7.4 μmol/l and urea in blood serum – 11.03±0.69 mmol/l. GFR was 61.6±3.0 ml/min. and R urine – 93±0.18%.

Excretion of β_2-microglobulin with urine in this group was on average 0.43±0.12 pg/ml ($p<0.05$), i.e. it was increased compared to the control group and the indicators of group I ($p<0.05$).

The level of pro-inflammatory cytokines in the patients of the second group was: the content of IL-1α in the blood – on average 3.78±0.47 pg/ml, which is significantly lower compared to the control group ($p<0.05$); the content of TNFα in the blood was on average 9.33±1.65 pg/ml, that is, it significantly exceeded this indicator in the control group ($p<0.05$), but decreased compared to the first group.

Direct strong correlations were revealed between IL-1α and urinary β_2-microglobulin excretion ($r=0.87$, $p<0.05$), between TNFα and urinary β_2-microglobulin excretion ($r=0.74$, $p<0.05$). This may be evidence that the level of pro-inflammatory cytokines in the blood reflects the severity of damage to tubulointerstitial structures and can be used as a marker of immuno-inflammatory processes in the kidneys in DN.

Weak correlations were also found between urinary β_2-microglobulin excretion and proteinuria ($r=0.29$, $p<0.05$), and between urinary β_2-microglobulin excretion and the duration of diabetes ($r=0.12$, $p<0.05$). Direct correlations were also found between the following indicators: moderate – between IL-1α and duration of diabetes ($r=0.35$, $p<0.05$), moderate – between IL-1α and glucosuria ($r=0.46$, $p<0.05$), weak – between IL-1α and glycemia ($r=0.25$, $p<0.05$), which emphasizes the importance of hyperglycemia for the development of immunoinflammatory processes in the kidneys. The results of the detected correlations in the second group are presented in Fig. 2.

In the second group of patients (CKD I degree) a decrease in the content of TNFα in the blood was found in comparison with the patients of the first group, although it remained significantly increased in comparison with the control group. It is possible that this dynamics of the level of TNFα during the development of CKD I degree is a compensatory reaction in accordance with the existence in new conditions (increased creatinine and urea content, blood pressure) and the preservation of protective mechanisms aimed at reducing the rate of kidney sclerosing in diabetic nephropathy.

The third group of investigated patients with DN with CRF II degree consisted of 23 patients aged 21 to 69 years. The duration of diabetes in this group av-

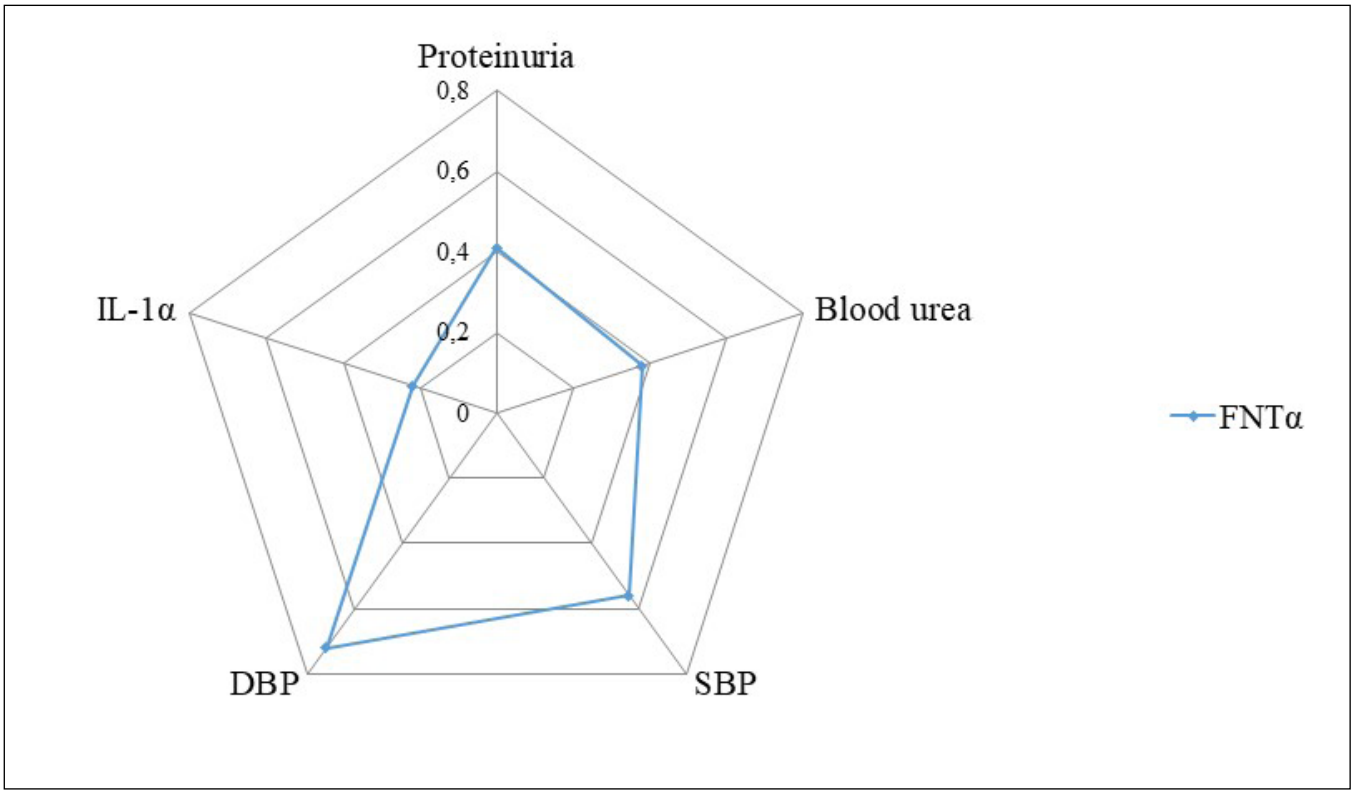

Fig. 3. Significant correlations in the group with CRF of II degree.

eraged 14.1±2.82 years; average blood pressure was: SBP – 168.5±15.6 mm Hg. and DBP – 97±11.2 mm Hg; daily proteinuria – 2.8±0.29 g/day; creatinine content in blood serum – 281.3±16.4 μmol/l, urea in blood serum – 14.3±0.81 mmol/l. GFR was 36.5±3.27 ml/min. and R urine – 93.2±1.23%.

Excretion of β_2-microglobulin with urine is significantly increased in this group: M±m was 1.17±0.07 pg/ml; $p<0.05$ in comparison with the control group, as well as patients of I and II groups.

The content of IL-1α in the blood ranged from 5 to 6.8 pg/ml, on average it was 4.51±0.53 pg/ml, which is significantly lower than the indicator of the control group ($p<0.05$). The increase in the level of IL-1α in the third group, in contrast to the second, reflects an increase in the activity of the immunoinflammatory process in response to the progressive damage of endotheliocytes with increasing intoxication in patients of the III group.

The content of TNFα in the blood of patients of this group increases significantly again and varies from 5 to 116 pg/ml, on average it is 24.65±6.73 pg/ml, which is the highest value among all the studied groups. This allows us to state that the activity of sclerosing processes is maximal in patients with DN with CRF II degree. Such an increase in the level of TNFα is also facilitated by a decrease in the clearance of this cytokine when kidney function deteriorates. Perhaps this also leads to a relative increase in the level of IL-1α in the blood and activation of immunoinflammatory processes in the kidneys.

In this group, a significant increase in correlations between TNFα and other indicators was noted: with proteinuria ($r=0.41$, $p<0.05$), with blood urea ($r=0.38$, $p<0.05$), with SBP ($r=0.56$, $p<0.05$) and with DBP ($r=0.72$, $p<0.05$). The relationship between TNFα and IL-1α at this stage of CRF is significantly weaker ($r=0.22$, $p<0.05$) than in patients of the previous groups. The results of the detected correlations in the third group are presented in Fig. 3.

Based on this, it can be concluded that CRF II degree in patients with DN is the stage of the highest activity of pro-inflammatory cytokines, especially TNFα, which leads to the fatal development of sclerotic changes in the kidneys, the progression of glomerulosclerosis.

The fourth group of investigated patients with DN with CRF III degree consisted of 19 patients aged from 31 to 69 years. The average duration of diabetes in this group was 17.6±2.64 years. Blood pressure was: SBP – 178±20.5 mm Hg. and DBP – 102±6.6 mm Hg. Daily proteinuria was the largest among all groups and averaged 3.2±0.49 g/day. The levels of azotemic parameters were as follows: creatinine in blood serum – 676.2±33.18 μmol/l, urea in blood serum – 22.82±1.36 mmol/l. GFR was 28.6±3.57 ml/min., R urine – 83.14±2.08%. The results of the detected correlations in the fourth group are presented in Fig. 4.

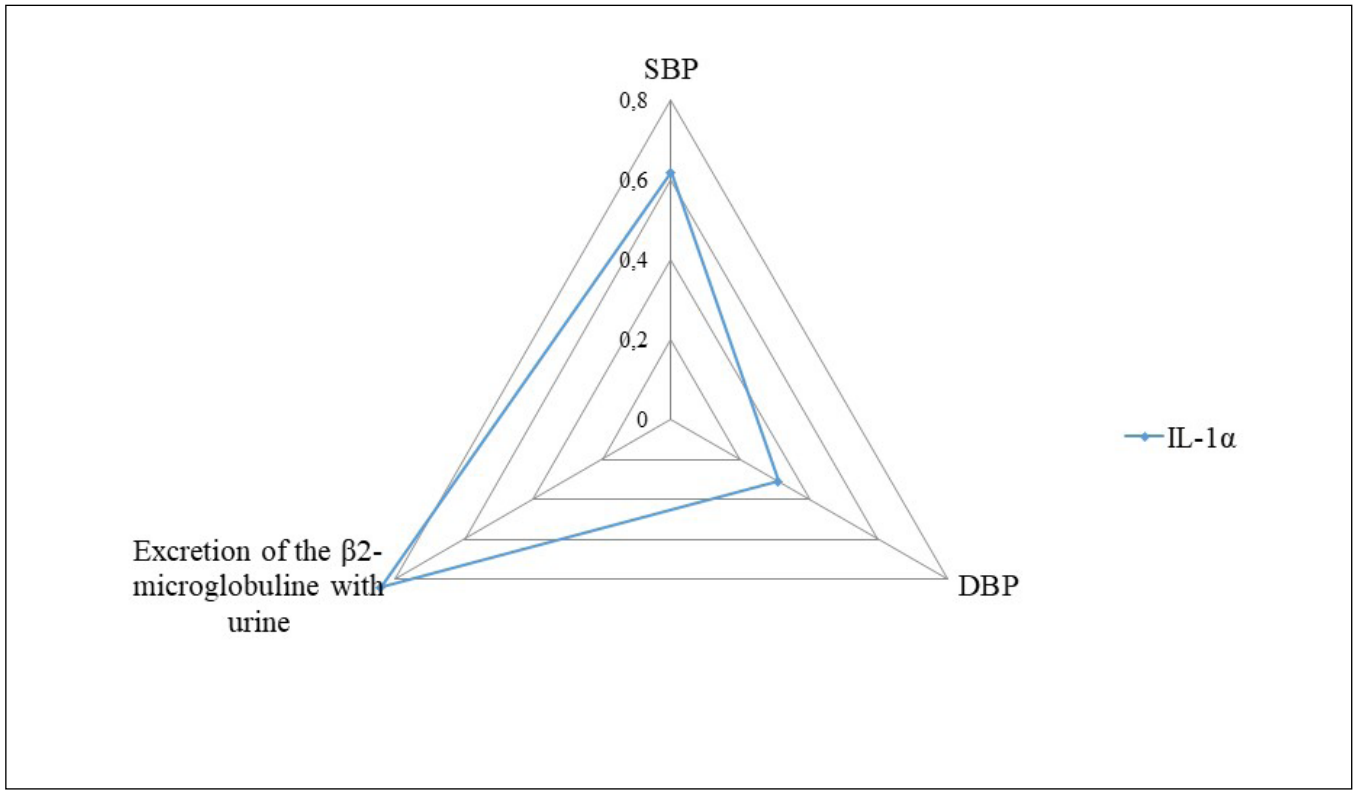

Fig. 4. Significant correlations in the group with CRF of III degree.

With CRF III degree, excretion of β_2-microglobulin with urine reaches the highest values and is on average 3.34±1.63 pg/ml. The content of IL-1α in the blood ranged from 0 to 6.4 pg/ml, with an average of 2.73±0.7 pg/ml and was minimal among all examined groups. In our opinion, this is a sign that the processes of acute inflammation in the kidneys are significantly reduced in CRF III degree and are the least pronounced among all groups of studied patients. The TNFα content in the blood remains at a high level and ranges from 4 to 104 pg/ml, with an average of 20.66±5.25 pg/ml. This indicates the high activity of sclerosing processes in the kidneys, which is the reason for their shrinkage. A certain contribution to maintaining a high level of TNFα is also made by a progressive decrease in the excretory function of the kidneys, as well as an increase in the production of this cytokine by cardiomyocytes.

With CRF III degree, the correlations that were in the previous three groups disappear – between the content of IL-1α in the blood and the duration of diabetes, glucosuria, proteinuria, but direct positive correlations appear between the content of IL-1α in the blood and SBP ($r=0.62$, $p<0.05$), between IL-1α content in the blood and DBP ($r=0.31$, $p<0.05$), as well as between urinary β_2-microglobulin excretion and IL content -1α in blood ($r=0.84$, $p<0.05$). This indicates that patients with DN develop deep damage to the protective mechanisms of cellular immunity as a result of prolonged exposure to hyperglycemia, oxidant stress, hemodynamic damage, and metabolic disorders [13,14].

The results of the study of the content of pro-inflammatory cytokines (TNFα and IL-1α) in the blood and the excretion of β_2-microglobulin in the urine in patients with DN, depending on the degree of CRF, are shown in Fig. 5.

Interleukin-1α is the main mediator of local inflammatory reactions and cellular antigen-specific immune response. The level of this cytokine decreases with the progression of CRF due to endothelial dysfunction, which develops under the destructive influence of hyperglycemia and other factors of disease progression (arterial hypertension, proteinuria, intoxication). This is accompanied by a decrease in the intensity of acute inflammatory reactions in the kidneys.

The level of TNFα increases with the progression of CRF, which leads to the development of sclerosing processes in the kidneys. It is known that this cytokine is produced by macrophages and lymphocytes. Increased expression of TNFα is at the basis of the pathogenesis of autoimmune lesions, induces the expression of tissue procoagulant factors, activation of lysosomal factors, proteases, formation of free radicals and reactive oxygen species.

A decrease in IL-1α content in the blood is accompanied by an increase in the density of fibroblast growth factor receptors on target cells. It is also worth

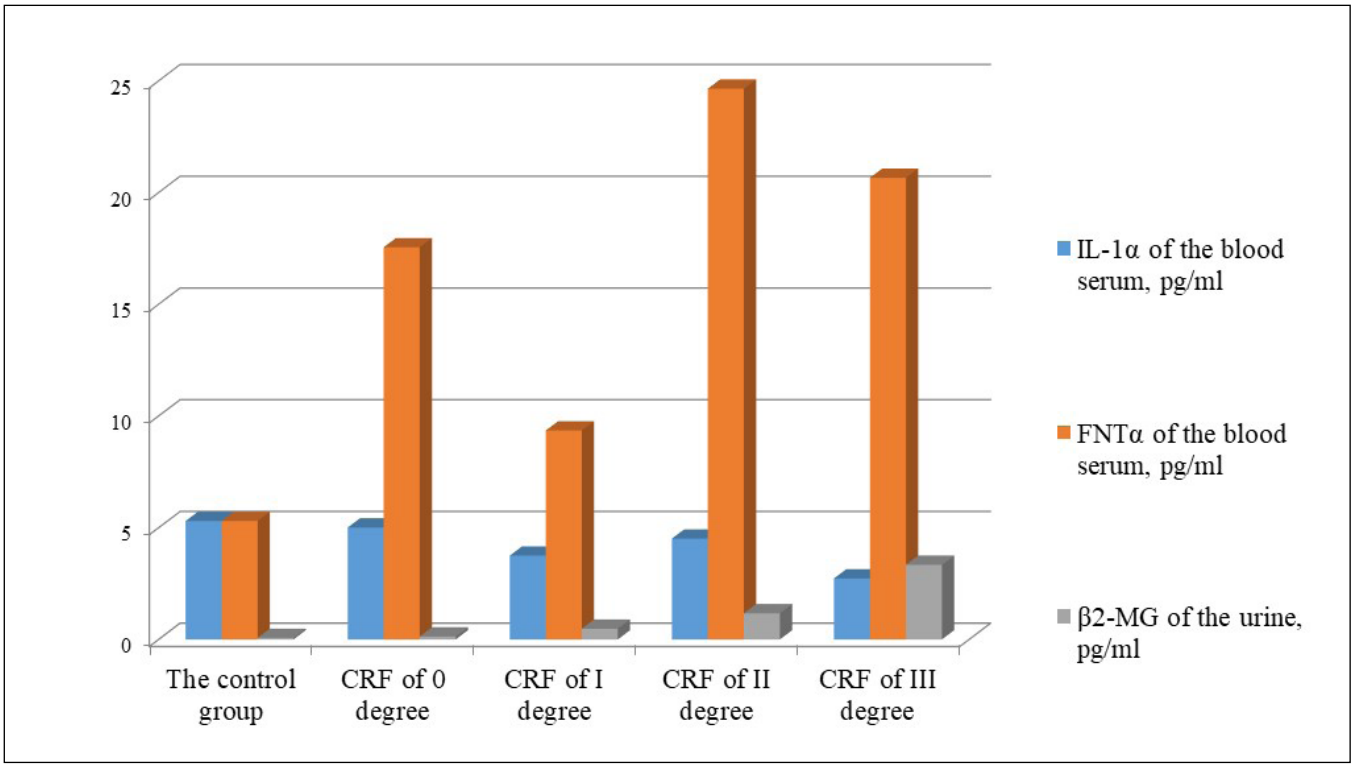

Fig. 5. The content of pro-inflammatory cytokines in the blood and the excretion of β2-microglobulin in the urine in patients with DN at different stages of CRF.

considering the myocardial theory of TNFα synthesis: unequivocal evidence of the production of this cytokine by cardiomyocytes in response to pressure and volume overload has been obtained.

DISCUSSION

Pro-inflammatory cytokines activate the metabolism of connective tissue, stimulate the proliferation of fibroblasts and epithelial cells, regulate the development of an adequate response to the introduction of the pathogen, its localization and removal, and the restoration of the affected tissue structure. The role of pro-inflammatory cytokines in the development and progression of diabetic nephropathy is almost unexplored. The study of pro-inflammatory cytokines in diabetic nephropathy can be useful for deepening the knowledge of the mechanisms of pathogenesis, developing criteria for its progression and prognosis, as well as for developing new approaches to the treatment of this common and dangerous complication of diabetes.

The mechanisms of the damaging effect of hyperglycemia on the structural components of the kidneys are associated with a violation of renal hemodynamics – the development of hyperfiltration, intraglomerular hypertension and hyperperfusion. Under the influence of these factors, the permeability of the basal membrane of the glomerular capillaries increases, the level of protein in the urine, which is the main cause of the spread and sclerosis of the mesangial matrix, dystrophy of the tubular epithelium. [16,17].

The presented studies proved the presence of positive correlations between the content of TNFα in the blood and the level of blood pressure. According to the literature [2,4], the synthesis of TNFα can increase with dyslipidemia, activation of the local renin-angiotensin-aldosterone system (RAAS) and other factors characteristic of chronic renal failure. This cytokine acts as a mediator that controls the proliferation of mesangial cells and the synthesis of the extracellular matrix, thereby potentially contributing to the progression of chronic renal failure and, as a result, contributes to the progression of poisoning and the accumulation of toxins, increasing pressure. in blood vessels, loss of fluid-electrolyte balance, i.e. a violation of the balance of fluid, sodium, potassium and other electrolytes in the body, which can lead to serious complications, a decrease in the number of erythrocytes, which can lead to the development of anemia and a loss of oxygen transfer efficiency, etc. [5, 7].

The presence of correlations between the main factors of the progression of well-controlled diabetes (duration of diabetes, level of proteinuria, blood pressure) and the level of pro-inflammatory cytokines allows us to use the determination of IL-1α and TNFα levels in the blood as potential markers of the progression of diabetic nephropathy. High levels of IL-1α and TNFα in the blood may indicate active inflammatory process-

es, endothelial dysfunction, and damage to kidney cells that contribute to the progression of diabetic nephropathy. This makes them potential markers for the prevention and monitoring of this complication in patients with diabetes. An increase in the level of TNFα and a decrease in the level of IL-1α in the blood can be criteria for an unfavorable prognosis of the course of this disease.

The results of our research indicate that damage to the tubules precedes a violation of the nitrogen-excreting function of the kidneys in DN with chronic renal failure. It is possible that renal interstitial fibrosis is the basis of the progression of kidney damage in diabetic nephropathy.

The mechanisms of action of these cytokines and their interaction with other factors of disease progression require further studies to understand their exact role in the pathogenesis of diabetic nephropathy. Additional research may open new opportunities for treatment and, more importantly, prevention of this serious complication of diabetes.

CONCLUSIONS

Thus, in the work, a study of the relationship between the level of pro-inflammatory cytokines (TNFα and IL-1α) and β_2-microglobulin with indicators of changes in the functional state of the kidneys in patients with diabetic nephropathy, which allows determining different degrees of chronic renal failure. All correlations presented in the work (medium and strong) were significant ($p \leq 0.05$).

It has been proven that changes in the profile of pro-inflammatory cytokines: a decrease in the content of IL-1α and an increase in the content of TNFα in blood serum are markers of the progression of chronic renal failure in patients with diabetic nephropathy. It has been shown that the excretion of β_2-microglobulin with urine increases even with sufficient kidney function, increases in parallel with changes in the cytokine profile during the development and progression of CRF, which indicates early damage to tubulointerstitial structures in patients with DN and confirms the value of urinary β_2-microglobulin excretion as an indicator of progression fibroplastic processes in the tubulointerstitium of the kidneys.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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