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Study of the role of proinflammatory cytokines in the progression of diabetic nephropathy

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Abstract. In the progression of diabetic nephropathy (DN), great importance is attached to immune factors, in particular, the cytokine system, which is a universal polymorphic regulatory network of mediators that control the proliferation and differentiation of cellular elements in hematopoietic, immune and other homeostatic systems. The role of proinflammatory cytokines in the development and progression of DN is almost unexplored, so the authors studied the role of proinflammatory cytokines in DN at different degrees of the functional state of the kidneys. Results of the presented studies indicate that pro-inflammatory cytokines play an important role in the progression of DN, contribute to the development of sclerotic processes in the kidneys. Indicators of IL-1α and TNF-α levels can be used as markers of progression of DN and criteria for the prognosis of this common and dangerous disease. The study of cytokines in DN can be useful for deepening knowledge of the mechanisms of pathogenesis, the development of criteria for its progression and prognosis, as well as to develop new approaches to the treatment of this common and dangerous complication of diabetes mellitus.

Key words: diabetic nephropathy, diabetes mellitus, cytokine system, mechanisms of pathogenesis, chronic renal failure.

Introduction

Diabetic nephropathy (DN) remains one of the most actual problems of modern nephrology, endocrinology, despite the large number of studies on the pathogenesis, mechanisms of progression, diagnosis and treatment of this complication of diabetes mellitus (DM), which is characterized by rapid progression and short-term development. In industrialized countries, the incidence of DM is on average 6–9% of the total population. Maintenance of sustainable compensation for DM is possible through intensive insulin therapy [1, 2].

DN develops, usually 10–15 years after the onset of DM and too quickly leads to the development of chronic renal failure (CRF). Global statistics show that 21.7% to 32.4% of all cases of terminal CRF are associated with DN [3].

In present day it is known that the trigger for the complex pathogenesis of DN is prolonged hyperglycemia, which has a toxic effect on the capillary endothelium, glomerular basement membrane, promotes hyperfiltration and intraglomerular hypertension, leading to progressive proteinuria and CRF [3–5]. In the progression of DN, great importance is attached to immune factors, in particular, the cytokine system, which is a universal polymorphic regulatory network of mediators that control the processes of proliferation and differentiation of cellular elements in hematopoietic, immune and other homeostatic systems [6].

Proinflammatory cytokines activate connective tissue metabolism, stimulate the proliferation of fibroblasts and epithelial cells, regulate the development of an adequate response to the embodiment of the pathogen, its localization and removal, restoration of the affected tissue structure. The role of proinflammatory cytokines in the development and progression of DN is almost unexplored [7].

The study of cytokines in DN can be useful for deepening knowledge of the mechanisms of pathogenesis, the development of criteria for its progression and prognosis, as well as to develop new approaches to the treatment of this common and dangerous complication of DM.

With the aim of optimize the diagnosis and treatment of DN, the authors studied the role of proinflammatory cytokines in DN at different degrees of the functional state of the kidneys.

Materials and methods

We examined 80 patients with type 1 and type 2 DM complicated by DN with varying degrees of renal function, 36 men and 44 women aged 21 to 71 years; the average age of patients was 48.7±12.8 years. 40 patients had type 1 DM and 40 patients had type 2 DM. The duration of the disease in patients with type 1 DM was 16.9±4.4 years and in type 2 DM 12.2±6.9 years, in on average — 14.9±6.5 years.

Depending on the functional state of the kidneys, patients with DN were divided into 4 groups: at 20 patients sufficient renal function (group I) was ascertained, at 20 patients — CRF of the I degree (group II), at 20 patients — CRF of the II degree (group III) and at 20 patients — CRF of the III degree (group IV). The basis for the distribution of patients with DN by degrees of CRF is the classification of degrees of CRF according to the order of the Ministry of Health of Ukraine № 45/540 from 25.08.2015.

The content of proinflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1α) in the blood, quantification of β_2-microglobulin (β_2-MG) and microalbumin in urine were studied by enzyme-linked immunosorbent assay (ELISA).

Results

The severity of tubulointerstitial changes in type 2 DM is greater than in type 1 DM. This is associated with ischemic kidney disease due to renal arteriosclerosis. It is renal ischemia in patients with type 2 DM that leads to kidney shrinkage, which distinguishes the «terminal» kidney of a patient with type 2 DM from the «terminal» kidney of normal size in type 1 DM [8, 9].

With the aim of assess the degree of damage to the tubulointerstitial structures in DN, we conducted a study of excretion of β_2-MG in the urine (Table 1).

Already in patients with sufficient renal function, this figure was almost doubled compared with the control group (M±m=0.13±0.04 pg/ml). Urinary excretion of β_2-MG increases with the progression of CRF and reaches a maximum in CRF of the III degree (M±m=3.34±1.63 pg/ml).

Results of studies indicate that the defeat of the tubules is preceded by impaired nitrogen function of the kidneys in DN with CRF. It is possible that renal interstitial fibrosis is the basis for the progression of kidney damage in DN.

The development of sclerosing of renal tissue occurs directly under the influence of the cytokine cascade and, above all, TNF-α. In chronic immune inflammation, the glomeruli are infiltrated by monocytes, which penetrate the mesangium in the form of activated macrophages, come into contact with mesangial cells and extracellular matrix, which contains a large number of major fibroblast growth factor and transforming fibroblasts growth factor β.

Under the influence of TNF-α, mesangial cells of the glomeruli produce a large number of reactive oxygen radicals, superoxide, oxidative stress develops, which supports chronic inflammation [10, 11].

Results of the content of TNF-α in the blood of patients with DN depending on the degree of CRF are given in Table 2.

Researches that were conduct shown that the level of TNF-α in the blood of patients with DN significantly increases in patients of the first group with adequate renal function (M±m=17.55±4.45 pg/ml; p<0.05). The highest level of TNF-α is reached in patients with CRF of the II degree (M±m=24.65±6.73 pg/ml) and at CRF of the II degree (M±m=20.66±5.25 pg/ml) that testifies about the role of this cytokine in the development of sclerosing processes in the kidneys.

Interestingly, in stage I of CRF, the level of TNF-α decreases in comparison with the first group of patients (with sufficient renal function), but remains elevated in comparison with the control group (p<0.05). It is possible that at the initial stage of CRF development, in response to a decrease in GFR, accumulation of creatinine, urea, medium molecules, compensatory mechanisms are activated that reduce the production of TNF-α. With the progression of CRF, these mechanisms are depleted, and the level of TNF-α in the blood increases again.

The level of TNF-α increases with the progression of CRF, which leads to the development of sclerosing processes in the kidneys. Increased TNF-α expression underlies the pathogenesis of autoimmune lesions, inducing the expression of tissue procoagulant factors, activation of lysosomal factors, proteases, the formation of free radicals and reactive oxygen species [10, 12].

It is important to emphasize that in patients with CRF of the I degree, the level of TNF-α in the blood is significantly reduced, but remains significantly elevated compared with the control group. This may be due to the inclusion in the early stages of CRF of compensatory mechanisms that reduce the production of TNF-α by macrophages/monocytes. We found the same phase fluctuations with respect to the level of IL-1α in the blood.

It is known that IL-1α reduces the number of receptors for TNF-α. Reducing the level of IL-1α and increasing the content of TNF-α in the blood of patients with DN already with sufficient nitrogen-releasing function of the kidneys is evidence of fibroplastic, sclerosing processes and reducing the severity of acute inflammatory reactions at this stage of the disease.

Evidence for TNF-α production by cardiomyocytes in response to blood pressure overload, blood volume, and the effect of β-adrenergic activity on myocardial production of this cytokine has been obtained. In the studied patients, the level of blood pressure increases with the progression of CRF in parallel with the increase in the content of TNF-α in the blood: in type 1 DM — in patients of the first group SBP averages 145.0±22.0 mm Hg., DBP — 88.5±12.5 mm Hg., in the second group — SBP (157.0±16.4 mm Hg.) and DBP (96.0±5.6 mm Hg.), in the third group — SBP (162.5±16.4 mm Hg.) and DBP (101.0±11.2 mm Hg.), in the fourth group — SBP (176.0±20 mm Hg.) and DBP (96.0±9.6 mm Hg.), respectively; with type 2 DM, blood pressure is higher than type 1 DM and is in the first group — SBP (154.0±22.0 mm Hg.) and DBP (85.0±7.0 mm Hg.). In the second group — SBP (178.0±26.0 mm Hg.) and DBP (103.0±11.6 mm Hg.), in the third group — SBP (187.0±19,6 mm Hg.) and DBP (103.0±11.0 mm Hg.), in the fourth group — SBP (185.5±9.6 mm Hg.) and DBP (100.5±6.7 mm Hg.), respectively.

Table 1 Excretion of β2-MG in the urine of patients with DN depending on the degree of CRF

Indicator	Degrees of the CRF				
	Control group, n=10 M±m	CRF-0 n=20 M±m	CRF-I n=20 M±m	CRF-II n=20 M±m	CRF-III n=20 M±m
β_2-MG in the urine, pg/ml	0.07* ±0.02	0.13* ±0.04	0.48* ±0.12	1.17* ±0.07	3.34* ±1.63

*p<0.05 compared to the control group.

Table 2 The indicators of TNF-α in the blood of patients with DN depending on the degree of CRF

Indicator	Degrees of the CRF				
	Control group, n=10 M±m	CRF-0 n=20 M±m	CRF-I n=20 M±m	CRF-II n=20 M±m	CRF-III n=20 M±m
TNF-α in the blood, pg/ml	5.30* ±2.02	17.55* ±4.45	9.35* ±1.64	24.65** ±6.73	20.66** ±5.25

*p<0.05 compared to the control group, **p<0.001 compared to the control group.

Table 3 The content of IL-1a in the blood of patients with DN depending on the degree of CRF

Indicator	Degrees of the CRF				
	Control group, n=10 M±m	CRF-0 n=20 M±m	CRF-I n=20 M±m	CRF-II n=20 M±m	CRF-III n=20 M±m
IL-1α in the blood, pg/ml	5.30* ±0.22	5.01* ±0.41	3.75* ±0.57	4.51* ±0.53	2.73* ±0.70

*p<0.05 compared to the control group.

In patients with DN with CRF revealed a decrease in the content of IL-1α in the blood. This indicator in all examined patients averaged 4.0±0.55 pg/ml, which is significantly lower than the level of IL-1α in the blood in the control group (p<0,05) (Table 3).

The level of IL-1α in the blood decreases already in DN in patients with sufficient renal function (M±m=5.01±0.41 pg/ml; p<0.05). In the second group of patients with CRF of the I degree it makes 3.75±0.57 pg/ml, at CRF of the II degree of 4.51±0.53 pg/ml and at CRF of the III degree this indicator is the lowest among all groups of studied patients (M±m=5.01±0.41 pg/ml).

Prolonged maintenance in the blood of patients with CRF of the I–II degrees interleukin-1α at a relatively high level leads to a violation of hemodynamic parameters, increased intravascular circulation, which deepens the pattern of lesions in the kidney tissue.

Significant decrease in the content of IL-1α in the blood of patients with CRF of the III degree may be due to profound disorders in the functioning of the T-cell immune system, the development of systemic autoimmune reactions as a result of the combined action of long-standing hyperglycemia, hemodynamic trauma, ischemia and metabolic disorders characterize the development of DN and CRF.

The decrease in the content of IL-1α in the blood of patients with DN with sufficient renal function is due to the long-term effect of hyperglycemia on immunocytes and endothelial cells, which leads to the development of a cascade of pathological processes, resulting in depression of the immune system.

One of the main sources of IL-1α is endothelial cells, which are affected by DM. Endotheliocytes are non-insulin dependent,

in conditions of hyperglycemia glucose enters them without hindrance 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 [13, 14].

Reducing the content of IL-1α in the blood increases the density of receptors for fibroblast growth factor on target cells. In turn, fibroblasts, which have receptors for growth factor, are highly sensitive to its action, which leads to their active proliferation and rapid progression of sclerotic processes. The number of fibroblasts increases significantly, the ability to synthesize collagen types I, III, V increases 4–5 times. All this causes a deterioration in the excretory function of the kidneys and the rapid progression of CRF. Reducing the content of IL-1α in the blood in CRF on the one hand reduces the activity of the acute phase of inflammation in the kidneys, and on the other — promotes the activity of sclerosing processes, potentiates the action of TNF-α [15].

The synergistic effect of TNF-α and IL-1α is particularly pronounced on fibroblasts. Decreased levels of IL-1α with the progression of CRF also undergoes phase fluctuations: in patients with CRF of the II degree (group 3) there was a significant increase in this indicator compared with patients in group 2. Such phase changes were observed in relation to TNF-α in patients of group 2. It is probable that in the first stages of CRF development (I and II degrees) the body still retains compensatory capabilities that respond to intoxication, acidosis, electrolyte shifts by modulating effects on cytokines (increase in IL-1α and decrease in TNF-α).

Conclusions

Thus, results of our studies suggest that proinflammatory cytokines (IL-1α and TNF-α) play an important role in the progression of DN, contribute to the development of sclerosing processes in the kidneys.

Indicators of IL-1α and TNF-α levels can be used as markers of progression of DN and criteria for the prognosis of this common and dangerous disease.

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Вивчення ролі прозапальних цитокінів у прогресуванні діабетичної нефропатії

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Анотація. У прогресуванні діабетичної нефропатії (ДН) велике значення надається імунним факторам, зокрема системі цитокінів, яка є універсальною поліморфною регуляторною мережею медіаторів, що контролюють проліферацію та диференціацію клітинних елементів у кровотворній, імунній та інших гомеостатичних системах. Роль прозапальних цитокінів у розвитку та прогресуванні ДН майже не вивчена, тому автори вивчали роль прозапальних цитокінів у ДН при різних ступенях функціонального стану нирок. Результати представлених досліджень свідчать, що прозапальні цитокіни відіграють важливу роль у прогресуванні ДН, зумовлюють розвиток склеротичних процесів у нирках. Показники рівнів інтерлейкіну-1α та фактора некрозу пухлини-α можуть бути використані як маркери прогресування ДН та критерії прогнозу цього поширеного та небезпечного захворювання. Вивчення цитокінів при ДН може бути корисним для поглиблення знань про механізми патогенезу, розробки критеріїв її прогресування та прогнозу, а також для розробки нових підходів до лікування цього поширеного та небезпечного ускладнення цукрового діабету.

Ключові слова: діабетична нефропатія, цукровий діабет, цитокінова система, механізми патогенезу, хронічна ниркова недостатність.

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