ORIGINAL ARTICLE

ROLE OF PROINFLAMMATORY CYTOKINES IN PATHOGENESIS OF ARTHROPATHIES IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

The aim: Of our work was to study the level of proinflammatory cytokines in patients with diabetic arthropathy and to investigate their possible effect on the development of this complication.

Materials and methods: 118 patients were examined, which were divided into groups by type of diabetes, the presence and severity of diabetic arthropathy. The content of IL-1, TNF-α, IL-6 and receptors to S IL-6-R in serum was determined by immunoassay.

Results: In patients with diabetic arthropathy, levels of TNF-α (with type 1 diabetes 44.5%, type 2 diabetes 42.9%) and IL-6 (with type 1 diabetes 52.1%, with diabetes 2 types by 64.4%) significantly increased. There is a direct correlation between the severity of joint damage and the level of TNF-α and IL-6. For IL -1, receptors for S IL-6-R have not been detected.

Conclusions: The chances of detecting arthropathy with type 1 diabetes with increasing TNF levels increase by 1.7 times, with an increase in IL-6 by 1.5 times. For type 2 diabetes, it is 1.8 and 1.3 times, respectively. Thus, TNF-α and IL-6 may be markers of the presence and progression of arthropathy in patients with diabetes mellitus

KEY WORDS: diabetes mellitus, diabetic arthropathy, joints, chondrocytes, cytokines

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INTRODUCTION

Diabetes (DM) is still one of the most important medical and social problems of the present since diabetes-related morbidity and disability rates are continuously increasing and incidence of its severe and complicated forms is also growing with every coming year. To date, in Ukraine there have been registered more than 1 million patients with DM. However, experts believe that this reflects just the tip of the iceberg; the real number of such patients exceeds 3-4 million people. Since the number of patients with diabetes doubles every 10-15 years, we can talk about the global epidemic of this disease [1]. With the increase in the life expectancy of patients with DM, the new, extremely important issue comes to the forefront and is connected with the growing severity of late complications of the disease that involve practically all organs and systems. Not exception is the damage to the osteoarticular system in patients with DM, the prevalence of which, according to various authors, is from 10 to 77.8% [2,3,4], with the involvement of joints in 58% of patients with type 1 DM and 24% of patients with type 2 DM. However, development, clinical picture and diagnosis of diabetic arthropathies require a comprehensive investigation since it has turned out that only fragmentary studies dedicated to these issues are available today.

Damage to the joints in patients with DM is associated with the occurrence of degenerative-dystrophic changes in the juxta-articular structures, vessels and bone tissues [5]. DM contributes to the development of the biochemical preconditions for the formation of a clinical picture of joint damage [6].

The only energy substrate for chondrocytes with an anaerobic metabolism is glucose, the content of which in chondrocytes is much lower than in synovial fluid and plasma. Delivery of glucose to chondrocytes is carried out by transport proteins GLUT1 and GLUT3 without participation of insulin [7].

Insufficient supply of glucose to chondrocytes, including those with diabetes, leads to a decrease in the intensity of synthetic processes and primary degeneration of cartilage tissue. At the same time, chronic hyperglycemia with type 2 DM inevitably leads to an increase in glucose concentration in synovial fluid, ligaments and joint capsules, which causes osteoarthrosis in type 2 DM through activation of the polyol pathway of glucose metabolism and non-enzymatic glycation of proteins. [8.9]. The formation of end-products of glycation (AGEs), in turn, stimulates chondrocytes and synoviocytes to produce prodegenerative (destructive) and pro-inflammatory mediators and alter the quality of subchondral bone tissue [10]. Neurotoxicity of hyperglycemia leads to neuromuscular insufficiency, which also aggravates joint damage, resulting in destabilization of the joint and worsening of degenerative-dystrophic changes in it [11].

Diabetic arthropathy is characterized by synovial

inflammation that occurs with increased expression of proinflammatory mediators and accelerated catabolism of the matrix of articular cartilage. Synovitis activates sensory nerve fibers as well as causes pain and neurogenic inflammation [12,13]. That is, the imbalance of cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1, 6, 17) plays a crucial role in the development of a chronic inflammatory disease. Simultaneously, chondrocytes express receptors for IL-1, which increase their sensitivity to this cytokine [14]. The function of IL-1 is its effects on plasminogen, which promote the transformation of the latter into an active plasmin, which, in turn, translates inactive pro-metal proteases into an active form, enhancing the degradation of the extracellular matrix. The catabolic effect of IL-1 manifests itself in its ability to stimulate chondrocytes and synoviocytes to release nitrogen oxide (NO) that damages the extracellular matrix. In addition, NO activates IL-1 and affects apoptosis of chondrocytes by reducing the concentration of an IL-1 receptor antagonist. IL-1β enhances calcium excretion and activates osteoblasts, which leads to a decrease in the intensity of bone formation. IL-1β causes reduced concentrations of osteocalcin, thus promoting the destruction of the subchondral bone [15,16]. Moreover, hyperexpression of the enzyme cyclooxygenase-2, which induces the synthesis of prostaglandins involved in the development of inflammation, is observed. There is good reason to believe that proinflammatory cytokines can be produced by chondrocytes or cells of surrounding tissues, even in the absence of explicit inflammation, while the DM itself initiates increased activity of these cytokines [17]. Thus, expression of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) was observed in the subchondral bone, cartilage and synovial membrane of joints without clinical signs of inflammation. It is known that TNF-α has receptors on chondrocytes, it activates inflammation and tissue damage in joint diseases, stimulates the synthesis of prostaglandins, platelet activation factor, superoxide radicals, metalloproteinases, induces the synthesis of other proinflammatory cytokines (IL-1, -6, -8 and etc.). TNF-α stimulates proliferation of fibroblasts and inhibits the synthesis of collagen and proteoglycans. The described mechanisms of the effect of TNF-α on the components of homeostasis and inflammation of the musculoskeletal system may support degenerative and inflammatory processes in the joints [15,17]. The elderly with obesity and pain in the knee joints had decreased soluble TNF-α receptor while trying to reduce their body weight [18].

IL-6 was high in patients with joint pathology associated with diabetes mellitus, especially in those with obesity. It was found that IL-6 affects resorption of bone tissue, release of matrix metalloproteases, inhibits the synthesis of proteoglycans and collagen by chondrocytes [18].

Thus, proinflammatory cytokines impair the homeostasis of the extracellular matrix of the articular cartilage as well as contribute to the increased levels of superoxide radicals, the synthesis of metalloproteinases and the decreased synthesis of their inhibitors, which ultimately leads to the degeneration of cartilage and the development of inflammatory and degenerative processes of joints in association with diabetes mellitus. In the pathogenesis of joint damage, a wide range of inflammatory mediators is involved, the effect of which extends not only to cartilage, but also to the synovial membrane, subchondral bone, ligament apparatus and results in the development of synovitis, periostitis, tendinitis.

THE AIM

The aim of our study was to investigate the level of TNF-alpha, IL-1 alpha, IL-6 and receptors for S IL-6-R in patients with diabetic arthropathy and their possible effects on the development of this complication.

MATERIALS AND METHODS

The study was attended by 118 patients (39 men and 79 women) who were undergoing medical treatment at the State Institution "V. P. Komisarenko Institute of Endocrinology and Metabolism" of NAMSU. Of these, 61 patients were diagnosed with type 1 DM (23 men and 38 women), and 57 patients had type 2 DM (16 men and 41 women). Women were predominant in both groups ($p<0.05$), but gender differences between groups with diabetes mellitus were insignificant ($\chi 2 = 1.2$; $p = 0.26$). The mean age of patients and their body mass index (BMI) are significantly lower than in the group of patients with type 2 DM ($p <0.001$). In this sample, the mean BMI in the group of patients with type 2 DM is 23.0% higher ($t = 13.2$; $p = 0.001$) than in the group of patients with type 1 DM. DM duration is 19.0% higher ($t = 2.3$; $p = 0.023$) in the group of patients with type 1 DM. Gender differences in the observed values were not detected ($p> 0.3$).

Arthropathy was noted in 90 (77.2%) patients, and in 28 (22.8%) patients with DM, this complication was absent. The presence and degree of severity of diabetic arthropathy was evaluated using the Rosenbloom method [19]. Nephropathy was graded according to C. F. Mogenson classification (1992) and retinopathy – according to E. Kohner, M. Porta classification. The content of glucose in the blood was determined by glucose oxidase method. Normal values were considered from 3.3 to 5.5 mmol/l. The degree of compensation of carbohydrate metabolism of the examined patients was assessed by the level of glycosylated hemoglobin (HbA1c), which was determined by calorimetric method with thiobarbituric acid. Compensation for DM was recorded at HbA1c level up to 7%. The research also included traditional clinical tests (biochemical blood test, complete blood count, urinalysis, determination of daily proteinuria, K, Ca total and ionized glycemic profile). The function of the kidneys was evaluated by GFR using the CKD-EPI formula. The content of IL-6, TNF-α, IL-1 and S IL-6-R receptors in serum was determined by the enzyme-linked immunosorbent assay (ELISA) using a set of reagents from Diaclone company (France) and Stat fax 3200 (USA) – ELISA microwell plate reader.

The statistical processing of the findings was carried out

Table I. Comparison of mean values of laboratory parameters in patients with type 1 DM and type 2 DM (t-test)

Parameters	Type 1 DM			Type 2 DM			t	p
	X	m	σ	X	m	σ		
HbA1c,%	8,40	0,20	1,59	8,24	0,15	1,15	0,6	0,531
Fasting glucose, mmol/l	9,89	0,51	3,98	8,03	0,28	2,11	3,2	0,002
Blood glucose after a meal mmol/l	11,44	0,59	4,62	10,39	0,41	3,06	1,5	0,149
Cholesterol, mmol/l	5,46	0,16	1,24	5,85	0,23	1,72	1,4	0,169
Creatinine, mkmol/l	93,56	3,69	28,85	97,56	3,81	28,75	0,8	0,452
GFR, ml/min	107,57	6,57	51,31	90,62	5,43	40,98	2,0	0,049
Proteinuria, g/l	0,08	0,02	0,13	0,15	0,03	0,25	2,0	0,047
Calcium, mmol/l	2,29	0,07	0,56	2,16	0,03	0,25	1,6	0,115
Kalium, mmol/l	4,45	0,06	0,37	4,41	0,05	0,31	0,5	0,644
Total protein,g/l	69,25	0,82	6,42	69,58	0,60	4,54	0,3	0,749

Table II. Mean values of cytokines at the distribution of the patients according to the type of DM and gender (two-factor dispersion analysis)

Groups	TNF, pg/ml				IL-6 ,pg/ml				IL – alpha, pg/ml				S IL - 6-R, pg/ml			
	N	X	σ	m	N	X	σ	m	N	X	σ	m	N	X	σ	m
Type 1 DM	60	20,2	12,4	1,6	60	23,8	19,7	2,5	20	12,0	3,3	0,7	20	323,7	68,9	15,4
Men	23	19,7	10,2	2,1	23	26,0	18,4	3,8	6	11,6	2,8	1,1	6	344,5	89,4	36,5
Women	37	20,5	13,7	2,3	37	22,5	20,5	3,4	14	12,2	3,6	1,0	14	314,8	59,8	16,0
Type 2 DM	55	24,5	17,4	2,3	55	28,6	25,2	3,4	18	11,3	3,0	0,7	18	358,7	64,4	15,2
Men	16	23,9	23,0	5,8	16	27,3	30,2	7,5	5	10,3	1,8	0,8	5	373,6	79,4	35,5
Women	39	24,7	14,9	2,4	39	29,2	23,2	3,7	13	11,7	3,3	0,9	13	353,0	60,4	16,8
F	0,00				0,36				0,11				0,04			
P	1,00				0,549				0,747				0,852			

using the methods of variation statistics of the standard package for statistical calculations Statistica 5.0 Microsoft OfficeExel 2003. The study presents statistical variables of the mean values (denoted as M) and the mean square deviation (SD), the standard error of the average value (m). To compare mean absolute values, the t-criterion of Student was used in the various study groups. The difference in the findings was considered statistically significant with the value of the index $p \leq 0.05$. Correlation, dispersion, single-factor and multiple regression analysis, as well as discriminant statistics were used for data analysis.

RESULTS

In the group of patients with type 1 DM, arthropathy was detected in 75.4 ± 5.5% of patients, in the group of patients with type 2 DM – in 77.2 ± 5.6% (t = 0.23; p> 0.1). This sample did not confirm the assumption that women with type 2DM have higher chances of developing arthropathy than men (OR = 2.91; CI = 0.80-10.68; p = 0.106). In type 1 DM, the chances of developing arthropathy in men and women are also equal (OR = 1.14; CI = 0.34-3.75; p = 0.833). In the group of patients with type 1 DM, kidney damage was detected in 72.9% (n = 35) of patients and with type 2 DM – in 74.5% (n = 38) of patients. Arthropathy was diagnosed in 66,7% (n = 22) of patients with type 1 DM and kidney damage and in 81,6% (n = 31) of patients with type 2 DM and kidney damage. The relationship between the factors of kidney damage and the development of arthropathy has been confirmed only for patients with type 2 DM. The chances for the development of arthropathy in patients with type 2 DM and renal impairment are 5.2 times higher than in patients without this complication (OR = 5.17; CI = 1.32-20.22; p = 0.018). For patients with type 1 DM, the chances are equal (OR = 0.31; CI = 0.06-1.61; p = 0.163).

In the group of patients with type 2 DM, fasting glucose levels and GFR in the blood are significantly lower than in the group of patients with type 1 DM (Table I). The level of protein in urine is higher in the group of patients with type 2 DM. According to other laboratory parameters, no statistical differences were detected.

Comparison of mean values of laboratory parameters in patients with and without arthropathy and in patients with different types of DM showed an increase in the level of GFR in patients with type 1 DM and arthropathy (t = 2.2; p = 0.034). In patients with type 1 DM without arthropathy, the GFR rate is 88.73 ± 7.96 ml / min, with arthropathy – 113.72 ± 8.15 ml / min. The corresponding rates in the group of patients with type 2 DM are 95.63 ± 9.11 and 89.15 ± 6.53 ml / min. Other indicators of statistical difference are

not defined. An increase in the level of GFR may indicate a compensatory reaction of the kidneys in the initial stages of nephropathy, and as it is known, arthropathy is an advanced complication of DM, and more often develops in patients with DM complicated by other conditions.

A two-factor dispersion analysis with the factors "DM" and "gender" did not reveal any differences in the average levels of cytokines (Table II). Logistic regression analysis found out that in diabetes mellitus and the presence of arthropathy, the levels of tumor necrosis and interleukin-6 are significantly higher than in the absence of arthropathy. Logistic regression models with a dependent variable of TNF and the presence / absence of arthropathy as an independent variable are statistically significant both for the group of patients with type 1 DM ($\chi2 = 27.2$; $p < 0.001$) and for the group of patients with type 2 DM ($\chi2 = 26.8$; $p < 0.001$). The sensitivity of the model for a group of patients with type 1 DM was 53.3%, specificity – 93.0%. The corresponding rates for the group of patients with type 2 DM were 76.9% and 90.5%. With an increase in the level of TNF in type 1 DM, the chances for the detection of arthropathy rise 1.7 times (OR = 1.70; CI 1.19-2.44), in type 2 DM – 1.8 times (OR = 1.78; CI 1.21-1.2.61).

Logistic regression models with dependent variable IL-6 and the presence / absence of arthropathy as an independent variable are also statistically reliable for the group of patients with type 1 DM ($\chi2 = 23.2$; $p < 0.001$) and for the group of patients with type 2 DM ($\chi2 = 29.6$; $p < 0.001$). The sensitivity of the model for the group of patients with type 1 DM was 70.0%, specificity – 90.6%. The corresponding rates for the group of patients with type 2 DM were 92.3% and 86.2%. With an increase in the level of IL-6 in type 1 DM, the chances for the detection of arthropathy rise 1.5 times (OR = 1.47; CI 1.08-1.98), in type 2 DM – 1.3 times (OR = 1.34; CI 1.03-1.74).

Reliable logistic regression models with IL-1 IL-6R as independent variables and the presence / absence of arthropathy as an independent variable could not be obtained ($p > 0.2$).

Differences in the average level of TNF were determined depending on the stage of arthropathy ($F = 37.3$; $p < 0.001$). In patients with type 1 DM, the average level of TNF in the presence of arthropathy is 44.5% higher than in its absence ($t = 5.2$; $p < 0.001$). For type 2 DM, this value is 42.9% ($t = 7.2$; $p < 0.001$). In the case of type 1 DM, there were identified some differences in the mean values of TNF in patients without arthropathy and with the 1st stage ($t = 3.1$; $p < 0.01$), and with the 2nd and 3rd stages ($t = 2.4$; $p < 0.05$). No significant differences were found between the levels of TNF at the 1st and 2nd stages ($t = 1.7$; $p = 0.10$). In the case of type 2 DM, there were established some differences in the mean values of TNF in patients with the 1st and 2nd stages ($t = 3.6$; $p < 0.01$) and with the 2nd and 3rd stages ($t = 4.4$; $p < 0.001$). No significant differences were found between the levels of TNF in the absence of arthropathy and the 1st stage ($t = 0.96$; $p = 0.36$).

There were determined some differences in the average level of IL-6 depending on the stage of arthropathy ($F = 28.2$; $p < 0.001$). In patients with type 1 DM, the average level of IL-6 in the presence of arthropathy is 52.1% higher than in its absence ($t = 5.6$; $p < 0.001$). For type 2 DM, this value is 64.4% ($t = 7.3$; $p < 0.001$). In type 1 DM, there were detected some differences in the mean values of IL-6 in patients without arthropathy and with the 1st stage ($t = 3.4$; $p < 0.05$) and with the 1st and 3rd stages ($t = 2.8$; $p < 0.05$). No significant differences were found between the levels of IL-6 at the 1st and 2nd, as well as the 2nd and 3rd stages ($t = 1.8$; $p = 0.07$ and $t = 1.9$; $p = 0.08$). In type 2 DM, there were detected some differences in the mean values of IL-6 in patients without arthropathy and with the 1st stage ($t = 2.6$; $p < 0.05$), with the 1st and 2nd stages ($t = 3.9$; $p < 0.01$) and with the 2nd and 3rd stages ($t = 3.4$; $p < 0.01$). For IL-1 and IL-6 R, differences in mean values at different stages of arthropathy were not detected ($p > 0.4$).

DISCUSSION

Thus, the development of joint damage in patients with diabetes of both types is accompanied by increased levels of pro-inflammatory cytokines. IL-6, TNF-α were the most sensitive for patients with diabetes with joint lesions. Our results are confirmed in many studies, because these cytokines are most often mentioned as inducers of nonspecific inflammation and stimulators of the synthesis of other interleukins, which promote cartilage catabolism through the synthesis of metalloproteases, induction of oxidative stress and apoptosis of chondrocytes [15, 20]. Although it is known that the main trigger of joint degradation in patients with diabetes is hyperglycemia [12]. And in our study, the vast majority of patients were in a state of decompensation (HbA1c level exceeded 8%). Local increase in glucose concentration leads to changes in cartilage tissue due to increased end products of increased glycosylation (AGEs), which, in turn, stimulates chondrocytes and synoviocytes to produce prodegenerative (destructive) and proinflammatory mediators [21]. The level of pro-inflammatory cytokines is a reflection of nonspecific inflammation. A probable increase in IL – 6, TNF-α was found in patients with type 1 and type 2 diabetes with arthropathies. In patients with type 1 diabetes, the average level of IL-6 in the presence of arthropathy is 52.1% higher than in its absence, in patients with type 2 diabetes – by 64.4%. In the analysis of this indicator, depending on the stage of arthropathy, a probable increase in IL-6 with each stage of the disease in patients with diabetes of both types with arthropathy. In the examined patients with type 1 diabetes, the average level of TNF-α in the presence of arthropathy is higher by 44.5% than in its absence, in type 2 diabetes – by 42.9%. TNF-α has receptors on chondrocytes, is an activator of inflammation and tissue damage in OA, stimulates the synthesis of prostaglandins, platelet activating factor, superoxide radicals, metalloproteinases, induces the synthesis of other proinflammatory cytokines (IL-1, -6, -8 and others). TNF-α stimulates the proliferation of fibroblasts and inhibits the synthesis of collagen and proteoglycans. The biological action of TNF-α as an inflammatory cytokine depends on

its concentration in tissues. At high concentrations, which we obtained in our study, TNF-α acts as a mediator of cartilage and bone damage and the development of systemic inflammatory reactions [16,22].

In our work, reliable logit regression models with IL-1 and IL-6R as independent variables and the presence / absence of arthropathy as an independent variable could not be obtained. Although, it is believed that the increase in IL-1 is the most characteristic of osteoarthritis [15, 20, 21, 22]. But almost all work concerned IL-β. It is known that IL 1 is one of the pathogenetically significant cytokines in OA. IL 1 itself increases the transcription of genes that control destructive processes in cartilage and the production of proinflammatory prostaglandins. As a result – suppression of chondrocyte production by type 2 collagen and aggrecans. In addition, the level of IL-α reflects to a greater extent the lesions of the large supporting joints of the lower extremities (hip, knee) [23]. Because, in our study, the vast majority of affected joints affected the upper extremities, this may be due to the lack of probable IL-α changes in patients with arthropathy. Thus, the most informative markers among cytokines, according to our studies and IL-6, TNF-α.

CONCLUSIONS

1. It has been established that women and men with type 1 and type 2 DM have similar chances for the development of arthropathy.
2. In patients with type 1 DM and arthropathy, an increase in the level of GFR was noted. It may indicate a compensatory reaction of the kidneys in the initial stages of nephropathy, and as it is known that arthropathy is an advanced complication of DM, and more often develops in patients with DM complicated by other conditions. Although the chances of developing arthropathy for patients with type 1 DM and renal impairment were equal (OR = 0.31; CI = 0.06-1.61; p = 0.163), the chances for the development of arthropathy in patients with type 2 DM and renal impairment were 5.2 times higher than in patients without this complication (OR = 5.17; CI = 1.32-20.22; p = 0.018).
3. In patients with type 1 DM, the average level of TNF in the presence of arthropathy is 44.5% higher than in its absence (t = 5.2; p <0.001). For type 2 DM, this value is 42.9% (t = 7.2; p <0.001). With an increase in the level of TNF in type 1 DM, the chances for the detection of arthropathy rise 1.7 times (OR = 1.70; CI 1.19-2.44), in type 2 DM – 1.8 times (OR = 1.78; CI 1.21-1.2.61).
4. In patients with type 1 DM, the average level of IL-6 in the presence of arthropathy is 52.1% higher than in its absence (t = 5.6; p <0.001). For type 2 DM, this value is 64.4% (t = 7.3; p <0.001). With an increase in the level of IL-6 in type 1 DM, the chances for the detection of arthropathy rise 1.5 times (OR = 1.47; CI 1.08-1.98), in type 2 DM – 1.3 times (OR = 1.34; CI 1.03-1.74).
5. For IL-1 and IL-6 R, differences in mean values at different stages of arthropathy were not detected (p> 0.4).
6. As a result, the main proinflammatory cytokines, namely, TNF-alpha and IL-6, which may serve as markers of the presence and progression of arthropathy in patients with diabetes mellitus, can be identified.

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The Authors declare no conflict of interest.

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