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The Role and Significance of Complement C3 Factor in the Clinical Course of Diabetic Polyneuropathies

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Abstract Nowadays, one of the urgent problems not only in the field of neurology, but also in the entire field of medicine is diabetes mellitus (DM). Because the complications of this disease bring patients to a state of disability, deeply disrupt the quality of life of patients, and cause socio-economic problems.

Keywords Diabetes, Diabetic polyneuropathy, Complement, Blood plasma, Dysregulation

1. Introduction

The International Diabetes Federation estimates that 425 million people worldwide have diabetes [20], making it the largest global epidemic of the 21st century [24]. 115 million people in China, 73 million in India, and 30 million in the United States have diabetes [26]. In Uzbekistan, in 2015, 170,000 patients with diabetes were registered, and to date, more than 230,000 patients have been registered and monitored. We see that the number of people with diabetes has increased by almost 60,000 in the last 3 years. According to analysis, this figure may exceed 550 million by 2030.

2. The Main Results and Findings

Diabetic polyneuropathy (DP) is diagnosed in one out of three patients with diabetes and is manifested by a number of negative consequences: neuropathic pain, limitation of daily movement activity, occurrence of trophic disorders and its infectious complications, sleep and mood disorders, quality of life decline Diabetic polyneuropathies are the most common of these complications, which manifest themselves in patients with motor, sensory and vegetative pathologies, as well as increase the disability status of patients and stabilize economic problems.

Due to microvascular disorders, the pathogenesis of which is often unclear in QD, complications such as retinopathy, nephropathy and neuropathy also develop, causing serious changes in human health. Patients suffering from diabetes mellitus should not only monitor the concentration of glucose and glycated hemoglobin in the blood, but also perform regular screening with the help of markers that allow to predict the risk of developing microvascular diseases, to understand parallel and separate independent mechanisms [25,19].

Currently, there are several types of classification of diabetic polyneuropathies, including the classification approved at the San Antonio conference proposed by the American Academy of Neurology in 1998 [4,11], Levin O.S. in 2006. [5,8,10] and in 2007 Galstyan G.R. Classifications proposed by [1,2] are used.

Later, there is increasing interest in the study of complement factors in the process of demyelination in neuropathies. The complement system is considered a key component of innate immunity and plays an important role in inflammation and defense of the body against common pathogens. Activation of the complement system is observed in many metabolic disorders and inflammatory diseases of nerve fibers, including diabetic neuropathies.

The complement system is a part of the immune system that protects the body against bacteria and other pathogens in a non-specific manner. The complement system is a collection of membrane-bound proteins that circulate in the blood of humans and animals and participate in tissue damage in autoimmune and other pathological processes, as well as in the protection of the body from infectious diseases [3,7,14].

In recent years, the biological and other functions of complements have been studied, such as: phagocytosis, activation of the release of biologically active substances (histamine, serotonin, bradykinin) from fat cells, increase in cell membrane permeability, decrease in blood-vessel tone, positive chemotaxis, opsonization, etc.

Components of the complement system make up about 4% of plasma proteins. They are synthesized by hepatocytes, macrophages and neutrophils, and most of them are β-globulins [7]. The complement system is an effector of innate and acquired immunity. It is composed of more than 30 cell membrane and plasma proteins, synthesized mainly

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in hepatocytes and partly in peripheral nerves [6,9], usually circulating as inactive proproteins.

According to the nomenclature adopted by WHO, the complement system is denoted by the symbol S, and its individual components are denoted by the symbols S1, S2, S3, S4, S5, S6, S7, S8, S9.

Complement C3 is the most centrally activated component of the complement system in the development of diabetes complications [16,21]. High concentrations of complement C3 are associated with insulin resistance, obesity, dyslipidemia, and diabetes [16,22]. Currently, there is some evidence that complement C3 may play an important role in the development of microvascular diseases [12]. C3d and C5b-9 have been found in the endoneurial microvessels of patients with diabetic neuropathy, and C3 complement overload has been identified in diabetic neuropathies [23]. To date, the increase in the concentration of complement C3 in the plasma of patients, which is associated with a higher risk of developing diabetic microvascular complications, has been little studied. Deposition of immunoglobulins and complement C3 in nerve fibers in diabetic polyneuropathies was first described by Graham and Johnson [15]. Pathological changes in the walls of capillaries, arterioles and venules of nerves lead to the development of early structural abnormalities and decreased perfusion, resulting in ischemic damage to nerve fibers [13]. In diabetes, complement C3 provides a key link between inflammation and thrombosis. Complement C3 interacts with fibrin and causes long-term fibrinolysis in the blood of patients with type 2 diabetes, and as a result of fibrinolysis, neuropathies develop [17,18].

A deep analysis of the scientific literature shows that there is very little information on the role and importance of the complement C3 factor in the clinical course of diabetic polyneuropathies. In this context, we found it necessary to study the dysregulation of C3 complement activation in the occurrence and development of diabetic polyneuropathies.

3. The Purpose of Scientific Work

To study the role and importance of dysregulation of activation of complement component C3 in blood plasma of patients with diabetic polyneuropathy, and to develop early diagnostic criteria.

4. Research Material and Its Methods

In our research work, we collected the main contingent of patients from the endocrinology department of the multidisciplinary clinic of the Tashkent Medical Academy and the neuroendocrinology department of the Republican Specialized Endocrinology Scientific and Practical Medical Center. During the study, we studied blood plasma samples of 88 patients (men, women) with type 2 diabetes and diabetic neuropathy. We divided the collected patients into 2 groups. The first group consisted of 74 patients with diabetic polyneuropathy (34 men and 40 women), and the second group - the control group - 14 patients (8 men and 6 women) with diabetes, but without diabetic polyneuropathy, and at least one year before the beginning of the research patients who did not suffer from acute infectious or other serious diseases a month ago were selected and their blood plasmas were examined. The total mean age and the total mean duration of the disease were calculated for the patients in the main group and the control group. All patients underwent clinical and neurological examinations. Quality of life levels of patients were assessed based on the EQ 5D-3L questionnaire. Also, blood biochemical analyzes were carried out in patients - determination of blood glucose index and lipid spectrum, as well as blood immuno-enzyme analysis (IFA). In order to determine the activation dysregulation of the complement component C3, blood samples were collected from the patient's vein at 9:00 a.m. on an empty stomach in special vacuum tubes with lithium heparin and immediately placed in a refrigerator. The tubes were centrifuged at 3000 g/min for 10 minutes and blood plasma was separated. The isolated plasma samples were stored in a freezer at -30℃. The results of clinical-neurological and biochemical examinations were compared with the results of electromyographic examination. Statistical methods were used.

5. Research Results

We found it necessary to study the gender characteristics of diabetic polyneuropathies in the first stages of research. Diabetic polyneuropathies were found in 40 women (54.2%) and 34 cases (45.8%) in men. The average age of patients in the general group was 55.9±5.6 years, and in the control group it was 52.9±6.4 years. The average age of patients in the main group was 53.6±4.7 years in men and 57.8±6.1 years in women. It was found that the duration of the disease was 10.0±5.7 years in the main group, 9.9±3.8 years in women and 10.6±4.3 years in men, and 2.0±0.8 in the control group. The average weight of patients in the general group was 80.2±11.2 kg, 74.3±13.6 kg in men and 87.2±12.1 kg in women, and 54.3±96 in the control group. The blood glucose level of patients in the main group was 11.3±4.1 mmol/l, 11.7±5.2 mmol/l in men and 11.1±3.9 mmol/l in women, and 11.7 in the control group. ±4.2. The amount of blood glucose in men and women in the main group, as well as in patients in the control group, did not differ significantly, $r \geq 0.05$. When glycated hemoglobin content was compared, the difference between patients in the main and control groups was significant, 11.3±2.1 and 7.4±2.1, $r \leq 0.05$. A significant difference was also observed between men and women in the main group, 8.6±2.2 and 14.2±3.1. When comparing the amount of triglycerides in the blood, the main group of patients was 4.7±2.9 and 2.1±1.8, $r \leq 0.05$. These indicators differed in women and men, 3.4±1.8 and 5.4±2.8, $r \leq 0.05$. The amount of total cholesterol was 7.1±2.6 in the main

group and 2.1±0.5 in the control group, a reliable difference was observed, r≤0.05. 5.9±1.2 and 8.2±2.5 in men and women, the difference is reliable. Very low density lipoprotein was 3.28±1.6 in patients in the main group and 1.08±0.7 in the control group, r≤0.05. 4.1±1.1 and 2.8±0.9 in men and women, the difference is reliable. When the amount of glucose in urine is compared, it is 1.43±0.9 in the main group and 0.9±0.2 in the control group, the difference is reliable. The difference was reliably shown in both men and women. Total cholesterol is normally 0-5.2 mmol/l, triglycerides are normally 0-1.71 mmol/l, very low density lipoproteins in men: 2.25-4.82 mmol/l; in women: 1.92-4.51 mmol/l. The obtained results are shown in Table 1.

The obtained results show that higher obesity in women compared to men, and the duration of the disease is observed relatively more, is the impetus for the development of diabetic polyneuropathies. The analysis of laboratory parameters in the blood shows that the amount of glucose is not a risk factor, but glycated hemoglobin, total cholesterol, very low density lipoproteins and the amount of glucose in the urine can trigger the development of polyneuropathies.

The analysis of electroneuromyography (ENMG) parameters showed that in 27 men and 29 women in the main group, we found a decrease in the speed of conduction along the sensory nerve fibers. In the remaining 5 men and 8 women, motor nerve fibers were damaged, and in 2 men and 3 women, sensorimotor disorders were observed, Table 2. In diabetic polyneuropathy, it was found that sensory polyneuropathies were more common than motor and sensorimotor polyneuropathies, and this was consistent with laboratory results.

At the next stage of our study, we analyzed the level of complement factor S3 in the blood serum of patients in the main and control groups. In the main group, i.e. patients suffering from diabetic polyneuropathy, the level of factor S3 in blood serum was 15.3±3.2 ng/ml, and in the blood serum of patients in the control group it was 2.8±1.8 ng/ml. It was found that patients in the main group increased almost 5.5 times compared to the control group. Complement factor S3 is a factor that enhances demyelination, and the obtained results are explained by this. Although diabetic polyneuropathy is not considered a demyelinating neuropathy, Schwann cells are targeted by chronic hyperglycemia. Therefore, patients with severe forms of diabetic polyneuropathy have signs of demyelination. Given the strong interactions between axons and Schwann cells, Schwann cell damage can result in several changes in the axon. When the body is in a healthy state, complement components are inactive in the plasma. When pathogenic microbes, bacteria and viruses enter the body, the components become active. They are activated in the process of multistep activation reactions.

Table 1. Indicators of patients and laboratory test results in the main and control groups

Indicators	Main group	Including		Control
		Men	Women	
Average age of patients, years	55,9±5,6	53,6±4,7	57,8±6,1	52,9±6,4
Disease duration, years	10,0±5,7	9,9±3,8	10,6±4,3	2,0±0,8
Average weight of patients, kg	80,2±11,2	74,3±13,6	87,2±12,1	54,3±96
Blood glucose level, mmol/l	11,3±4,1	11,7±5,2	11,1±3,9	11,7±4,2
Glycated hemoglobin, %	11,3±2,1	8,6±2,2	14,2±3,1	7,4±2,1
Triglycerides, mmol/l	4,7±2,9	3,4±1,8	5,4±2,8	2,1±1,8
Total cholesterol, mmol/l	7,1±2,6	5,9±1,2	8,2±2,5	2,1±0,5
Very low density lipoprotein, mmol/l	3,28±1,6	4,1±1,1	2,8±0,9	1,08±0,7
Urine glucose in mmol/day	1,43±0,9	1,1±0,8	1,8±0,7	0,9±0,2

Table 2. Results of electroneuromyographic examination of the main group (n=74)

Nerves	Sensor DPN		Motor DPN		Sensorimotor DPN	
	Male, n =27	woman, n =29	Male, n =5	woman, n =8	Male, n =2	woman, n =3
Sensory nerve fibers						
n. plantaris lateralis	9	10	–	–	1	–
n. plantaris medialis	10	10	–	–	–	–
n. suralis	8	9	–	–	–	1
Motor nerve fibers						
n. tibialis	–	–	2	3	1	–
n. peroneus	–	–	3	5	–	2

Note: DPN is diabetic polyneuropathy.

At the next stage, we analyzed complement factor S3 in blood serum of patients with diabetic polyneuropathy according to the duration of diabetes. Because the development of diabetic polyneuropathy depends on the periods of the disease and the amount of glycated hemoglobin. Duration of diabetes.

The change of factor S3 in the blood serum of patients aged 1-5 years is 4.5±2.8 ng/l, and the blood serum of patients with a disease duration of 6-10 years is 7.8±3.3 ng/l and the disease duration is 11 and more the level of blood serum in patients with high blood pressure was 21.7±4.6 ng/l, and in the control group it was 2.8±1.8 ng/ml. Compared to the control group, it was observed that the complement factor S3, which increases the level of demyelination, was higher as the duration of the disease increased, which means that it has a correct correlation.

The development of diabetic polyneuropathy does not always depend on the period of diabetes, it may depend on the amount of glycated hemoglobin. Therefore, in the next step of our study, we compared the degree of change in complement factor S3 with glycated hemoglobin levels. In patients with glycated hemoglobin up to 10%, the amount of complement S3 factor in blood serum was 5.4 ng/l±3.9, and in patients with glycated hemoglobin above 10%, it was 19.0±5.7 levels. The degree of change in the amount of complement factor was also compared with the level of glucose in the blood of the patients. The obtained results show that the complement S3 factor does not always have a proportional relationship with the amount of glucose in the blood.

6. Conclusions

1. The development of diabetic polyneuropathies has a gender characteristic, it develops faster in women than in men. The average age, weight and duration of the disease of the patient are of great importance.
2. Glycated hemoglobin in the blood, total cholesterol, very low density lipoproteins and glucose in the urine can affect the development of diabetic polyneuropathies as risk factors.
3. Complement factor S3 is considered to be a factor that enhances demyelination, and its increase in blood serum can be considered as a non-specific marker of the development of diabetic polyneuropathy.

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