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TYPE 2 DIABETES AND ITS IMPACT ON THE IMMUNE SYSTEM

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Abstract

INTRODUCTION: *Type 2 Diabetes (T2D) is a majorhealth problem worldwide. This metabolic disease is indicated by high blood glucose levels due to insufficient insulin production by the pancreas. An inflammatory response occurs as a result of the immune response to high blood glucose levels as well as the presence of inflammatory mediators produced by adipocytes and macrophages in fat tissue. This low and chronic inflammation damages the pancreatic beta cells and leads to insufficient insulin production, which results in hyperglycemia. Hyperglycemia in diabetes is thought to cause dysfunction of the immune response, which fails to control the spread of invading pathogens in diabetic subjects. Therefore, diabetic subjects are known to more susceptible to infections. The increased prevalence of T2D will increase the incidence of infectious diseases and related comorbidities.*

Key words

Type 2 diabetes, immune status, infection, hyperglycemia

ATERIALS AND METHODS

148 patients with DM2 who were treated in the endocrinology department of the Tver Regional Clinical Hospital (56 men and 92 women; average age 55.0±0.75 years) were examined. 77.5% of the examined patients were diagnosed with moderate DM2, and 84.5% of the patients had arterial hypertension (AH) according to their medical history. The average duration of DM2 was 10.8±0.77 years. Most patients had late complications of DM: 100% had polyneuropathy, 74.5% of the examined patients were diagnosed with microangiopathy (initial manifestations) and 21.5% with macroangiopathy. In 74.5% of patients, DM was decompensated (the average fasting glycemia level was 8.4±0.31 mmol/l; HbA1c was 10.8±0.40%). All patients had a normal body temperature, were examined by an otorhinolaryngologist, dentist, dermatologist to exclude foci of chronic infection and acute microbial inflammatory diseases.The process of intravascular ARO was

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studied using a standard technique. Capillary blood was taken from the examined patients, a drop was applied to a slide and a smear was made. Blood samples were fixed in a Nikiforov mixture, stained according to the Romanovsky–Gimza method, after which they were well washed with distilled water and dried in air. Autoresets (AR) were counted in stained smears by immersion microscopy in absolute quantity (109/l) and as a percentage per 100 leukocytes. The AP was taken to be a cellular association formed by a neutrophil or monocyte with three or more erythrocytes tightly adjacent to their surface.The state of humoral immunity

was assessed by the level of immunoglobulins (Ig A, G, M) in blood serum, determined by turbodimetric analysis. The normal values were: for Ig A – 0.9–2.5 g/l; Ig G – 8.0–18.0 g/l; Ig M – 0.6–2.8 g/l. The innate link of humoral immunity, as well as the activity of the inflammatory process, were determined by C-reactive protein (CRP) in blood serum. For this purpose, the principle of two-site enzyme immunoassay was used. The values of CRP from 0 to 5 mg/l were taken as the norm. The cellular link of innate immunity or the activity of oxygen-dependent microbiocidicity of neutrophils was evaluated by the nitro-blue tetrazolium reduction test (NST test). The spontaneous HCT test characterized the initial state of this indicator, and the induced one characterized the potential ability of neutrophils to activate their cellular function in response to a microbial stimulus. The normal values were considered: for the spontaneous HCT test - % of HCT positive cells – 10-15%, the neutrophil activation index (IAN) – 0.1–0.15 units; for the induced HCT test, 40-80% and 0.5–1.5 units respectively.The control group for the study of ARO consisted of 63 practically healthy people (49 men and 14 women; average age 47.3±2.31 years).Statistical processing and analysis of the research materials were carried out using statistical packages of the Statistica 6.0, 2003 program. Depending on the normality of the distribution of the results obtained, the methods of parametric (Student's criterion) and nonparametric (Mann-Whitney criterion) statistics were used. The presence of the relationship and its orientation were established by conducting a correlation analysis using Spearman's criterion (r).Informed consent of patients for examination is available. The study was conducted on the basis of the endocrinological department of the Tver Regional Clinical Hospital. Upon hospitalization, a written agreement was concluded with the patients on their consent to all necessary examinations and treatment, which are carried out in the hospital. This contract is pasted into the medical history. Additional studies were conducted only with the consent of the patients.

2.INSULIN RESISTANCE AND HYPERGLYCEMIA

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Increased blood glucose levels after eating induce insulin production and secretion by islet β cells into the blood. The binding of insulin and insulin receptors in cell membranes induces glucose transporter translocation to the cell membrane and increases glucose uptake by the cells, resulting in decreased glucose levels in the blood. Failure of the pancreas to produce sufficient insulin, improper insulin action, or both, results in hyperglycemia. This is associated with damage and failure of various organs and tissues in the long term.Elevated levels of tumor necrosis factor (TNF)-α in adipose tissue of obese mice were shown to be associated with insulin resistance in those mice. Furthermore, interleukin (IL)-6, C-reactive protein, plasminogen activator inhibitor, and other inflammation mediators were elevated in the plasma of obese mice. TNF-α, free fatty acids, diacylglyceride, ceramide, reactive oxygen species (ROS), hypoxia activate Iκβα kinase β (IKKβ), and c-Jun N-terminal kinase I (JNK1) in adipose tissue and the liver induce insulin receptor substrate (IRS-1) inhibition (Fig. 1). Moreover, TNF-α also leads to insulin resistance via inhibition of peroxisome proliferator-activated receptor-gamma function. Insulin binds with its receptor, resulting in tyrosine phosphorylation at IRS-1 and -2. Insulin signaling inhibition occurs due to serine phosphorylation of IRS substrates by IKKβ and JNK1, which are the mediators for stress and inflammatory responses. Furthermore, JNK1 and IKKβ induce the transcriptional activation of various genes related to inflammatory response, resulting in insulin resistance. In addition, the influx of free fatty acids and glucose during obesity also activates JNK1 and IKKβ signaling pathways.Activated IKKβ phosphorylates Iκβα, promotes ubiquitination and degradation of Iκβα in proteasome, and results in NFκβ translocation into the nucleus to induce transcription of various genes involved in inflammation and other immune responses. IKKβ also inhibits insulin signaling pathways via phosphorylation of IRS-1 serine residues in adipocytes . JNK activation induced by TNF-α inhibits insulin signaling by phosphorylation of IRS-1. In addition, insulin signaling inhibition can be produced via the janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. Tyrosine phosphorylation of STAT by JAK kinases induces dimerization and translocation of STAT to the nucleus and results in IRS-1 phosphorylation at Ser636 and Ser307. This inhibition of insulin signaling eventually impairs the Glut-4 translocation to cell membranes and leads to hyperglycemia.

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RESULTS AND DISCUSSION

In the study of intravascular ARO in patients with DM2, the average number of sockets registered in peripheral blood was 31.5±1.08% with 0.75±0.11% in healthy individuals ($p<0.001$). AR, formed by neutrophils (22.1±0.79% in patients and 0.61±0.01% in healthy ones) and monocytes (6.8±0.35% and 0.14±0.03%, respectively) prevailed in all examined patients. However, in patients with DM2, unlike healthy individuals, eosinophilic (0.6±0.11%), basophilic (1.4±0.18%) and platelet (0.6±0.07%) AR were also found.Activation of intravascular ARO in patients with DM2 is obviously associated with changes in the membranes of blood cells [4, 5], increasing the level of their adhesion, which cannot be different for the implementation of their biological functions, including immune against neutrophils and monocytes.When assessing the factors determining the intensity of the ARO process, it was noted that with an increase in the duration of DM2 in the peripheral blood of the examined patients, an increase in the number of AR was recorded (from 22.3±0.66% with a duration of DM2 less than 5 years to 39.7±1.06% with a duration of more than 10 years; $p<0.001$; $r=0.9$; $p<0.001$).Note: p is the statistical significance of the differences between groups 1 and 2; n is the number of people surveyed in the group.The relationship between ARO and the presence and level of blood pressure (BP) in patients with DM2 was also revealed. Thus, tables 1 and 2 show the number of AR registered in the peripheral blood of patients with DM2, depending on the presence and level of systolic and diastolic blood pressure.From the data shown in the tables, it can be seen that with an increase in systolic blood pressure compared to normal, the number of sockets in patients increased by 37% ($p<0.01$; $r=0.32$; $p<0.05$), and with an increase in diastolic blood pressure – by 23% ($p<0.001$; $r=0.93$; $p<0.05$).As a result of the study, no relationship was established between ARO and the severity of diabetes and metabolic disorders. Thus, with fasting glycemia <6.5 mmol/l, the amount of AR was 32.4 ± 1.93% and with glycemia >6.5 mmol/l – 30.8 ± 1.17%. The ARO process and treatment did not affect (the number of AR 32.8 ± 1.39% with insulin therapy and 28.3 ± 1.16% with hypoglycemic tablet drugs), as well as the presence of late complications.In half of the examined (55%), the values of immunoglobulins in the blood exceeded the norm. At the same time, in 37.5% of cases, several classes of immunoglobulins were elevated simultaneously, mainly a combination of Ig A and G, in 31.2% there was an increase in Ig G, in 18.8% - Ig A and in 12.5% of cases – Ig M. The majority of patients (90%) with DM2 had elevated CRP levels (18.5 [10.8;33.1] mg/l). In more

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than half of the examined patients (70%), the spontaneous NST test was changed (in 34% of cases it was increased and in 36% it was reduced), while the induced NST test in most patients (86%) was normal.The study of the relationship of humoral immunity indicators with various clinical and laboratory manifestations of diabetes showed that the most pronounced association of immunoglobulin levels was noted with late onset of DM2 and metabolic disorders. In the presence of microangiopathies, the level of Ig A (2.4±0.17 g/l versus 3.6±0.36 g/l in the absence of microangiopathies; $p<0.01$) and Ig G (17.6±0.61 g/l and 19.8±0.87 g/l respectively; $p<0.05$) decreased in patients. The higher the fasting glycemia level in patients, the lower the Ig A values were (3.6±0.37 g/l with glycemia <6.5 mmol/l and 2.5±0.17 g/l with glycemia >6.5 mmol/l; $p<0.01$).The level of CRP in the blood of patients with DM2 varied in depending on various factors. The highest values of CRP protein were obtained in patients with DM duration of more than 5 years (22.7 [12.5;36.3] mg/l versus 11.2 [8.3;14.1] mg/l with DM duration of less than 5 years; $p<0.05$); presence of grade 2 and 3 hypertension (20.3 [11.2;36.3] mg/l versus 10.6 [5.3;18.5] mg/l with grade 0-1 hypertension; $p<0.05$); in patients with macroangiopathies (25.7 [18.1;33.1] mg/l versus 12.6 [8.2;23.2] mg/l in the absence of macroangiopathies; $p<0.05$),), as well as in hypertriglyceridemia (25.8 [15.8;36.3] mg/l versus 14.3 [8.8;22.3] mg/l in triglyceridemia <2.2 mmol/l; $p<0.05$).The relationship between various clinical and laboratory manifestations of DM and the indicators of the HCT test was revealed. Thus, contrary to the expected increase in the spontaneous HCT test, based on increased values of CRP in later stages of DM2 in combination with grade 2-3 hypertension, the following results were obtained.

CONCLUSION

1. In healthy individuals, a minimal number of AR is recorded in the peripheral blood, and in patients with DM2 with hypertension, an intensive ARO process is noted (mainly due to neutrophils and monocytes), which increases with longer duration of DM, as well as with an increase in both systolic and diastolic blood pressure.

2. In most cases, patients with DM2 have dysimmunoglobulinemia, impaired functional activity of neutrophils (decrease), and increased CRP, which is recommended to be used to assess the severity of diabetes and predict the progression of complications.

3. The above-mentioned changes in immunological parameters and acute phase protein are aggravated with a longer duration of the disease, in the presence of hypertension, severe diabetes, micro- and macroangiopathies, as well as with pronounced hyperglycemia and hypertriglyceridemia.

4. A better understanding of how immune dysfunctions occur during hyperglycemia can lead to novel treatments and preventions for infectious diseases and T2D comorbidities, thus improving the outcome of infectious disease treatment in T2D patients.

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