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Endothelial Dysfunction in Patients with Type 2 Diabetes Mellitus who have had COVID-19

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ABSTRACT

From the very first report of mass mortality among diabetic patients infected with COVID-19 infection, emphasis was placed on the severity of damage to the respiratory system in the form of acute respiratory distress syndrome in adults. The unifying factor in the pathogenesis of such a fatal change was the development of dysfunction of the endothelial system (DES), which leads not only to systemic inflammatory damage to the vascular endothelium but also to its consequences in the form of increased blood clotting and a decrease in fibrinolysis processes. The changes that occur in the body of patients after COVID-19 do not disappear completely. First of all, this should be noted about patients with chronic morbid backgrounds, such as, for example, type 2 diabetes mellitus (T2DM). In our study, endothelial function conditions were evaluated in 92 patients who have T2DM. Three cohorts of patients were organized. Indicators characterizing the state of DES were examined in blood obtained by puncture from a peripheral vein. The results obtained showed that the determination of indicators of vascular endothelial damage in the blood unequivocally allows for characterizing the development of this pathology. The studied indicators can be very useful in the case of diagnosing both the DES itself and the degree of development of irreversible changes in the tissues of the affected limb.

Keywords: *type 2 diabetes mellitus, COVID-19, endothelial dysfunction*

INTRODUCTION

The evolution of the physiological system of the body is determined by the presence of a reliable hemostasis system, thanks to which, from the first seconds of injury, a mechanism aimed at stopping bleeding as soon as possible is launched. Damage to the inner lining of the vessel provokes the formation of a thrombus (thrombosis). In the process of restoring damage in the intimate membrane of blood vessels, under normal conditions, the body launches the opposite mechanism, which dissolves the formed clots - fibrinolysis. Even if there is no traumatic injury to the inner lining of the vessels, the ongoing process of thrombogenesis can be fully recognized as

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a pathological shift on the part of the hemostatic system [1, 2].

With a severe form of COVID-19 infection, the above process can occur even if the inner lining of the vessels is not damaged. Patients with severe COVID-19 infection develop a high risk of vascular thrombosis, both venous and arterial [3].

When there was a global COVID-19 pandemic, most doctors focused on changes in blood clotting markers in patients with negative disease dynamics. These indicators were also important in assessing the results of treatment [4].

A review of the literature indicates an increase in thrombosis among patients with type 2 diabetes mellitus (T2DM), which was noted in all patients with this disease in COVID-19. At the same time, as many doctors describe, such disorders were the causes of death of patients [5, 6].

The development of endothelial system disorders in patients with T2DM is the basis for the formation of complications in diabetic foot syndrome (DFS). This, in turn, against the background of infection with a covid infection, can worsen the already damaged inner lining of the vessels. This leads to another new problem associated with COVID-19 infection in patients with T2DM, which worsens the course of the underlying disease with the progression of complications [7, 8]. Particular attention should be paid to complications of T2DM that occur with an enhanced necrobiotic process, such as purulent-necrotic lesions of DFS [9, 10]. In this regard, the assessment of the state of the vascular ES in patients with T2DM will make it possible to develop methods for objective assessment of both the severity of the development of purulent-necrotic complications and to predict the effectiveness of therapy.

Necrobiotic changes in the development of DFS have an approximate pathomorphological form, even with various types of complications of T2DM. The most dangerous is the neuro-ischemic form of the pathology, in which the degree of development of irreversible changes depends on both the innervation system and the microcirculation system. However, in the microcirculatory process, a large role is also assigned to damage to the inner lining of blood vessels. Thus, a vicious circle of pathological processes is formed, which aggravates the already incurable pathology.

MATERIALS

A total of 92 patients with T2DM who were treated at the Surgical Infection Center for the period from 2021 to 2024 were examined. All patients were divided into three groups: I – control, which consisted of 20 patients with T2DM; II – comparative, which consisted of 35 patients with T2DM complicated by DFS who had no history of COVID-19; III - main consisted of 37 patients with T2DM complicated by neuroischemic DFS with a history of COVID-19. All main group patients suffered a COVID-19 infection and appropriate treatment for this in a specialized hospital for 15 days or more.

METHODOLOGY

Study Inclusion Criteria

Patients came to our clinic on their own or were transferred from a specialized infectious diseases clinic only if the contagious phase of the disease was excluded. In any case, we checked patients by conducting PCR tests.

In the presence of septic complications of diabetic foot syndrome, we operated on patients on an emergency basis. In the presence of pronounced limb ischemia with severe pain, we also performed hip amputation.

Definition of the endothelial system

To assess the ES status, we evaluated in the blood: asymmetric dimethylarginine (μmol/L), endothelin-1 (f/μmol/L), von Willebrand factor (IU/dL), thrombomodulin (ng/mL), endothelial growth factor (pg/mL), vasogibin-1 (pg/mL), vascular cell (ng/mL) and intercellular adhesion molecules (ng/mL), as well as C-reactive protein (mg/L) and homocysteine (μmol/L). All these parameters were determined in the blood serum by the enzyme-linked immunosorbent method using the ELISA-HUMAN analyzer (Germany).

To obtain reference values, blood samples were examined from 20 people recognized by the medical commission as absolutely healthy at the time of receipt of the analysis.

Statistical research

Statistical data processing was performed on a personal computer using Statistica 10.0 (StatSoft Inc., USA). Quantitative indicators are described in the form of their average value (M). Standard error (m), qualitative indicators in the form of their fractions (%). Statistically significant differences were less than <0.05.

RESULTS

The mean serum asymmetric dimethylarginine significantly increased in patients with T2DM ($p<0.05$). With the reference value of this parameter at the level of

0.58±0.11 μmol/L, it increased to 1.05±0.04 μmol/L ($p<0.05$) in the control group of patients, to 3.48±0.55 μmol/L ($p<0.05$), and to 3.77±0.11 μmol/L ($p<0.05$) in the patients of the study group. That is, this value directly testified to the specificity of participation in inflammatory and necrobiotic processes. At the same time, in patients with DFS, the studied data reflected a violent reaction in increasing this parameter by 6 ($p<0.001$) and 6.5 ($p<0.001$) times, respectively, compared to the reference indicator.

The reaction in the change in the concentration of endothelin-1 in the blood sample, in comparison with the previous indicator, was more pronounced and was characterized by a significant change already in the presence of T2DM (control group). At the level of the reference value of endothelin-1 in the blood sample of 0.11±0.01 f/μmol/L, in the patients of the control group it reached 27.43±2.11 f/μmol/L ($p<0.05$), in the patients of the comparative group – up to 67.03±7.12 f/μmol/L ($p<0.05$), and in the patients of the main group – up to 126.53±11.12 f/μmol/L ($p<0.05$). In general, there was a significant increase in the concentration of this substrate, which in patients with T2DM exceeded the reference values by 9.5 times ($p<0.001$). In the context of the development of DFS, the increase in the value of endothelin-1 in blood samples was more pronounced and exceeded the reference values starting from 249.4 times and higher ($p<0.0001$).

The mean level of reference values of von Willebrand factor in blood samples of healthy people ranged from 80.1 IU/dL to 125.5 IU/dL, which corresponded to the physiological parameters of the normal value of this indicator (110.6±22.6 IU/dL). The mean level of thrombomodulin in healthy individuals ranged from 0.1 to 0.3 ng/ml (0.18±0.02 ng/ml).

In patients with T2DM, there was an increase in the values of both von Willebrand factor (from 142.0±11.4 IU/dL in the control group and to 148.4±12.7 IU/dL in the comparison group) and thrombomodulin (from 1.41±0.12 ng/ml in the control group and to 1.92±0.11 ng/ml in the comparison group; $p<0.05$), in blood samples, reaching its maximum value in the patients of the study group (up to 224.2±13.1 IU/dL and up to 3.59±0.1 ng/ml, respectively; $p<0,001$).

The reference values of endothelial growth factor averaged 109.65±21.8 pg/mL, and vasogibin-1 - 0.13±0.03 pg/mL.

In patients with T2DM, the blood level of endothelial growth factor decreased to 64.23±5.21 pg/ml, i.e. 1.7 times compared to the reference values ($p<0.05$), while the level of vasogibin-1 increased to 0.26±0.04 pg/ml, that is, 2 times compared to the reference values ($p<0.05$). This trend of changes continued in patients of the comparative and study groups. Thus, the level of endothelial growth factor in the patients of the comparative group decreased to 45.88±7.12 pg/ml ($p<0.05$), and in the patients of the study group – to 33.83±6.41 pg/ml ($p<0.05$).

Accordingly, the level of vasogibin-1 increased to 0.75±0.12 pg/ml ($p<0.001$) in comparative patients and to 1.83±0.21 pg/ml ($p<0.001$) in patients of the study groups.

At the level of reference values of vascular cell and intercellular adhesion molecules at the level of 3.86±0.23 ng/ml and 5.20±0.25 ng/ml, respectively, in patients with T2DM, we found an increase in it in blood to 4.33±0.65 ng/ml and 5.88±0.32 ng/ml.

In the patients of the comparative group, the continued increase in values was more pronounced about vascular intercellular adhesion molecules at 7.57±0.43 ng/ml, while about vascular cell adhesion molecules, the increase was only up to 5.98±0.33 ng/ml. In the patients of the study group, these changes were significantly pronounced and reached the level of 9.55±0.72 ng/ml and 10.31±0.78 ng/ml ($p<0.05$).

In general, the nature of changes in vascular adhesion molecules in patients with T2DM after COVID-19 infection changes significantly, which may indicate its prognostic significance.

The mean level of C-reactive protein in patients with T2DM was equal to 23.1±6.23 mg/L, and the average level of homocysteine was 9.47±2.17 μmol/L. In both cases, these values exceeded the reference values, which were equal to 3.05±0.97 mg/L and 4.05±1.02 μmol/L, respectively.

The level of C-reactive protein in patients with T2DM increased to 8.88±1.16 mg/L ($p<0.05$) in the control group, to 25.95±2.32 mg/L ($p<0.01$) in the patients of the comparative groups, and to 48.98±5.16 mg/L ($p<0.0001$) in the patients of the study group. In contrast to these changes, the level of homocysteine in the blood of patients of the control and comparative groups did not have a significant difference and was equal to 15.03±2.53 μmol/l and 15.55±2.03 μmol/l, respectively. However, in the patients of the study group, its level was much higher (34.43±4.11 μmol/l), which also increased the reliability of the detected changes ($p<0.01$).

DISCUSSION

As our studies have shown, patients with T2DM develop ES disorders. This was especially revealed by us in patients with DFS, in whom, apparently, this pathologi-

cal process aggravated the course of the underlying disease. In case of a previous COVID-19 infection, the severity of endothelial disorders is more visible, changing by an order of magnitude more reliably.

Concerning endothelin-1, it should be noted that the formation of this peptide is directly related to the ischemic process [11, 12]. Endothelin-1 can also serve as one of the significant markers of endothelial dysfunction (ED) in pathological conditions associated with the development of ischemic and necrobiotic processes. Moreover, this peptide can also be considered as a predictor of the severity and outcome of the above pathological conditions.

Determining the levels of von Willebrand factor and thrombomodulin enables the identification of thromboresistance disorders in the vascular wall in ED. As noted by M.I. Costache et al., when these disorders occur, the remodelling mechanism of the vascular bed starts to activate. This process can be crucial in adapting to conditions like circulatory problems, hypoxia, and chronic tissue damage [13].

Among these components, a certain cytokine, vascular endothelial growth factor, should be singled out. It can also regulate the permeability of the vascular wall [14].

Vasogibin-1 can also have the same property. According to H. Miyashita et al., is synthesized in vascular endothelial cells due to the activity of endothelial growth factor [15].

C-reactive protein is one of the main proteins of the acute phase, which is considered a generally recognized non-specific marker of inflammatory processes. This is important both in the diagnosis of the generalization of the inflammatory process and in the prognostic assessment of the degree of its progression.

CONCLUSION

Determination of the concentration of substances in the blood that damage endothelial cells unequivocally characterizes the development of ED in patients with T2DM who have had a COVID-19 infection. The parameters studied by us may reflect the specific functional side of the endothelium and, accordingly, reflect the stage of development of irreversible complications of DFS. At the same time, they can also be very useful in the case of diagnosing both ED and the degree of assessment of the treatment of the purulent-necrotic process in patients with DFS, which may be based on diabetic angiopathy and the consequences of a previous COVID-19 infection, aggravating the above pathological process.

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COVID-19 BILAN KASALLANGAN VA 2-TUR QANDLI DIABETGA CHALINGAN BEMORLARDA ENDOTELIAL DISFUNKTSIYA

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Annotatsiya

COVID-19 infeksiyasi bilan kasallangan qandli diabetli bemorlar orasida ommaviy o‘lim holatlari qayd etilgan dastlabki xabarlardanoq, asosiy e’tibor kattalarda o‘tkir respirator distress-sindrom ko‘rinishida namoyon bo‘ladigan nafas tizimi zararlanishining og‘irligiga qaratilgan edi. Bunday o‘lim bilan yakunlanuvchi o‘zgarishlar patogenezida birlashtiruvchi omil sifatida endotelial tizim disfunktsiyasining rivojlanishi qayd etilgan bo‘lib, u nafaqat tomir endoteliyining tizimli yallig‘lanishli shikastlanishiga, balki qon ivuvchanligining oshishi va fibrinoliz jarayonlarining pasayishi kabi oqibatlarga ham olib keladi.

COVID-19dan keyin bemor organizmida yuzaga keladigan o‘zgarishlar to‘liq yo‘qolib ketmaydi. Bu, ayniqsa, 2-tur qandli diabet kabi surunkali og‘ir fon kasalliklariga ega bo‘lgan bemorlarda yaqqol namoyon bo‘ladi. Tadqiqotimizda 2-tur qandli diabetga chalingan 92 nafar bemorda endotelial funksiyaning holati baholandi. Uchta bemor guruhi shakllantirildi. Endotelial tizim holatini tavsiflovchi ko‘rsatkichlar periferik vena punksiyasi orqali olingan qon namunalarida tekshirildi. Olingan natijalar tomir endoteliyasi shikastlanishi ko‘rsatkichlarini aniqlash ushbu patologiya rivojlanishini aniq tavsiflash imkonini berishini ko‘rsatdi. O‘rganilgan ko‘rsatkichlar nafaqat endotelial disfunktsiyani, balki zararlangan to‘qimalarda qaytmas o‘zgarishlar darajasini aniqlashda ham muhim diagnostik ahamiyatga ega bo‘lishi mumkin.

Kalit so‘zlar: 2-tur qandli diabet, COVID-19, endotelial disfunktsiya

ЭНДОТЕЛИАЛЬНАЯ ДИСФУНКЦИЯ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА, ПЕРЕНЁСШИХ COVID-19

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Аннотация

С самых первых сообщений о массовой летальности среди больных сахарным диабетом, инфицированных COVID-19, акцент был сделан на тяжесть поражения дыхательной системы в виде острого респираторного дистресс-синдрома у взрослых. Объединяющим фактором в патогенезе подобных фатальных изменений стало развитие дисфункции эндотелиальной системы, приводящей не только к системному воспалительному повреждению сосудистого эндотелия, но и к таким последствиям, как повышение свёртываемости крови и снижение процессов фибринолиза. Изменения, возникающие в организме пациентов после перенесённого COVID-19, не исчезают полностью. В наибольшей степени это характерно для пациентов с хроническим отягощённым фоном, в частности с сахарным диабетом 2 типа.

В настоящем исследовании была оценена функциональная состоятельность эндотелиальной системы у 92 больных сахарным диабетом 2 типа. Были сформированы три когорты пациентов. Показатели, характеризующие состояние эндотелиальной системы, исследовались в крови, полученной при пункции периферической вены. Полученные результаты показали, что определение маркёров повреждения сосудистого эндотелия в крови позволяет достоверно характеризовать развитие данной патологии. Изученные показатели могут быть полезны как для диагностики эндотелиальной дисфункции, так и для оценки степени формирования необратимых изменений в тканях поражённой конечности.

Ключевые слова: сахарный диабет 2 типа, COVID-19, эндотелиальная дисфункция