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METHODS OF HISTOLOGICAL EXAMINATION OF DIABETES MELLITUS IN THE LUNG ENDOTHELIUM

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ANNOTATION

The medical and social significance of diabetes mellitus is determined by the progressive increase in the frequency of the disease, as well as the development of vascular complications that invalidate and reduce the quality of life in patients of working age. It is now recognized that the vascular endothelium is a multifunctional organ. Endothelial cells are metabolically active and possess paracrine, endocrine and autocrine functions necessary to maintain vascular homeostasis under physiological conditions. Endothelial functions include regulation of vascular integrity and permeabllity, angiogenesis, hemostasis. Such complications include microangiopathies, including nephro-, retino- and neuropathies, as well as macroangiopathies, including coronary heart disease and cerebrovascular diseases, for the development of which diabetes mellitus is a proven risk factor. The mechanism of development of angiopathies in diabetes mellitus is multifactorial, but most researchers agree that hyperglycemia, triggering a complex of pathological reactions, including non-enzymatic glycosylation, oxidative stress and inflammation, is a key link in their occurrence and development.
Keywords: diabetes mellitus, endothelial dysfunction development, angiogenic functions

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МЕТОДЫ ГИСТОЛОГИЧЕСКОГО ИССЛЕДОВАНИЯ ЭНДОТЕЛИЯ ЛЕГКИХ ПРИ САХАРНОМ ДИАБЕТЕ

АННОТАЦИЯ

Медико-социальная значимость сахарного диабета определяется ростом заболеваемости, а также развитием сосудистых осложнений, приводящих к снижению качества жизни больных трудоспособного возраста. В настоящее время признано, что эндотелий сосудов является многофункциональным органом. Эндотелиальные клетки метаболически активны и

выполняют паракринные, эндокринные и аутокринные функции, необходимые для поддержания сосудистого гомеостаза в физиологических условиях. Функции эндотелия включают регуляцию целостности и проницаемости сосудов, непосредственно ангиогенез, и управление гемостазом. Доказанным фактором риска для развития таких осложнений как микроангиопатии, включая нефро-, ретино- и невропатии, а также макроангиопатии, включая сердечно-сосудистые и цереброваскулярные заболевания, является сахарный диабет. Механизм развития ангиопатий при сахарном диабете является многокомпентным, но большинство исследователей считают, что основным звеном в их возникновении и развитии является гипергликемия, вызывающая комплекс патологических реакций, включающих неферментативное гликозилирование, окислительный стресс которые в конечным счете приводят к воспалительным процессам непосредственно в стенке сосудов

Ключевые слова: сахарный диабет, развитие эндотелиальной дисфункции, ангионгенные функции

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QANDLI DABETDA O‘PKA ENDOTELIYISINI GISTOLOGIK TEKSHIRISH USULLARI

ANNOTATION

Qandli diabetning tibbiy-ijtimoiy ahamiyati kasallikning tobora ortib borishi, shuningdek, mehnatga layoqatli yoshdagi bemorlarning hayot faoliyatini pasaytirishi va qon tomir asoratlarining rivojlanishi bilan belgilanadi. Hozirgi vaqtda qon tomir endoteliyasi ko'p vazifalarni bajaruvchi a’zo ekanglli aniqlasngan. Endotelial hujayralar metabolik faol bo'lib, flziologik sharoitda qon tomir gomeostazini saqlash uchun zarur bo'lgan parakrin, endokrin va avtokrin funksiyalarga ega. Endoteliy funksiyalariga qon tomirlarining yaxlitligi va o'tkazuvchanligini, angiogenezni, gemostazni tartibga solish kiradi. Bunday asoratlarga mikroangiopatiyalar, shu jumladan nefro-, retino- va neyropatiyalar, shuningdek, makroangiopatiyalar, shu jumladan yurak-qon tomir kasalliklari va serebrovaskulyar kasalliklar kiradi, ularning rivojlanishi uchun qandli diabetni aniqlangan xavf omilidir. Qandli diabetda angiopatiyalarning rivojlanish mexanizmi ko'p faktorli, ammo ko'pchllik tadqiqotchilar patologik reaktsiyalar majmuasini, jumladan fermentativ bo'lmagan glikozillanish, oksidlovchi stress va yallig’lanishni qo'zg’atuvchi giperglikemiya ularning paydo bo'lishi va rivojlanishining asosiy bo'g'ini hisoblanadi.

Kalit so'zlar: qandli diabet, endotelial disfunktsiyaning rivojlanishi, angiogen funsiyalar

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The endothelium is involved in immune responses. It plays a key role in the regulation of vascular tone, inflammatory reactions, control of tissue blood flow, maintenance of rheological properties of blood. Being the main regulator of vascular homeostasis, the endothelium maintains a balance between vasodilation and vasoconstriction, inhibition and stimulation of smooth muscle cell migration and proliferation, fibrinolysis and thrombosis, and also participates in the regulation of platelet adhesion and aggregation. Violation of this regulated equilibrium leads to endothelial dysfunction. Diabetes mellitus is a typical disease in which there is a violation of endothelial function. Therefore, understanding the mechanisms underlying the occurrence and development of endothelial dysfunction in diabetes mellitus is an important direction in the prevention and treatment of vascular complications associated with all forms of diabetes mellitus.

In patients with diabetes mellitus, there is a decrease in the synthesis of major vasodilators, such as nitric oxide (NO) and prostacyclin, as well as an increase in the level of vasoconstrictors, primarily endothelin-1, reflecting the vasomotor function of the endothelium. In diabetes mellitus, there is an increase in the expression of adhesion molecules of the selectin and immunoglobulin family, as well as platelet/endothelial cell adhesion molecule 1 (PECAM-1), thrombogenic biomarkers of the

endothelium — tissue factor (tissue factor, TF), plasminogen activator inhibitor-1 (plasminogen activator inhibitor-1, PAI-1). Hyperglycemia is one of the factors of glycocalyx alteration of endothelial cells, which is accompanied by a violation of the barrier function of the vascular wall [12], and an increase in its adhesive properties, in particular, due to overexpression of vascular adhesion molecules (vascular cell adhesion molecule 1, VCAM-1) on the surface of endotheliocytes, and in the absence of adequate glycemic control — P- and E-selectins.

Under conditions of hyperglycemia, the polyol pathway of glucose oxidation is activated, in which glucose is converted into osmotically active sorbitol and fructose with the help of the enzyme aldose reductase, while a cellular membrane-bound multimolecular enzyme complex (nicotinamide adenine dinucleotide phosphate, NADPH) is consumed, which is of great importance in the functioning of NO synthase (nitric oxide synthases, NOS) and antioxidant systems glutathione and vitamin E. NADPH deficiency causes insufficiency of the antioxidant defense system, activation of free radical oxidation and a decrease in NO synthesis. Under conditions of hyperglycemia, the rate of diffusion of NO to the underlying smooth muscle cells decreases, the availability of L-arginine, the precursor of NO, decreases, free radical destruction of NO increases and inactivation of other vasodilators increases.

Diabetes mellitus (DM) as a concomitant disease in COVID-19 is considered as one of the significant risk factors for the development of adverse outcomes due to a more severe course of infection in conditions of hyperglycemia and other aggravating factors in these patients, such as old age, obesity, high incidence of concomitant pathology (hypertension, cardiovascular diseases. The proportion of DM patients among COVID-19 cases ranges from 16.2% in China to 25% in Russia. At the same time, despite the steady increase in the number of publications devoted to the analysis of various risk factors for severe COVID-19 in DM and its complications, the number of contradictions regarding the management tactics of this category of patients is progressively increasing, which is facilitated by the small volume and heterogeneity of samples in studies, as well as the high speed of information analysis. Thus, verified data on the effect of various classes of hypoglycemic drugs on the outcomes of COVID-19 in DM are currently practically absent. The fundamental issue of canceling or continuing organoprotective therapy with drugs blocking the renin-angiotensin system (RAS), namely angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs), remains unresolved.

An important mechanism of the altering action of hyperglycemia is the activation of the signaling pathway diacylglycerol-protein kinase C. With hyperglycemia, the concentration in cells of the intermediate product of glycolysis dihydroxyacetone phosphate increases, which, being restored to glycerol-3-phosphate, increases the synthesis of diacylglycerol activating protein kinase C. Hyperglycemia-stimulated activation of protein kinase C induces multiple intracellular signaling mechanisms that cause an increase in vascular wall permeability, disruption of endothelium-dependent vascular relaxation and activation of oxidative stress. Protein kinase C stimulates an increase in the production of VEGF, epidermal growth factor and TGF-β, which cause an increase in the angiogenic activity of endotheliocytes, which leads to structural remodeling of the microcirculatory bed. Activation of protein kinase C in smooth muscle cells due to activation of NF-kB inhibits gene expression and suppresses the activity of soluble guanylate cyclase, an enzyme by which NO implements its effects, in particular vasodilation. The literature data of recent years indicate that the control of glycemia in patients with diabetes mellitus reduces the alteration of the vascular wall and prevents the development of clinical signs of angiopathies. At the same time, there is evidence that adequate glycemic control in both type 1 and type 2 diabetes does not completely block the pathogenetic mechanisms of endothelial dysfunction development, but only slows down its progression.

Thus, oxidative stress in diabetes mellitus develops several interrelated pathological processes at once, including activation of NADPH oxidases, mitochondrial dysfunction and structural and functional changes in NOS. The result of oxidative stress is the alteration of endothelial cells and a decrease in NO production, which causes a violation of the vasomotor, barrier, angiogenic functions of the endothelium, as well as its thromboresistance.

Thus, the elimination of the effects of oxidative stress is carried out by a multi-level system of antioxidant protection. Violation of its functioning plays a key role in the occurrence and progression of vascular complications of diabetes mellitus due to the pronounced negative effect of oxidative stress on endothelial cells, causing endothelial dysfunction.

Endothelial function plays an important role in maintaining the body's homeostasis, and today the concept has been formulated according to which endothelial dysfunction is a central link in the pathogenesis of many diseases, including diabetes mellitus. The analysis of the literature shows that the development of endothelial dysfunction in diabetes mellitus consists of several key aspects that can be presented in the form of a diagram. Thus, the presented data make it possible to distinguish among the main factors initiating the alteration of endothelial cells, hyperglycemia and the accumulation of glycation end products. Hyperglycemia, which causes the activation of the polyol and hexosamine pathways, as well as the accumulation of glycolysis products in combination with the receptor and non-receptor effects of the end products of glycation, disrupt the metabolism and functioning of endotheliocyte signaling systems both by changing the activity of enzymes, in particular protein kinase C, endothelial NOS, and by changing the expression of a number of genes, including overexpression of NADPH oxidases, PAI-1, VEGF, inducible NOS, proinflammatory cytokines.

The most significant manifestations of endotheliocyte dysmetabolism in diabetes mellitus shouid be considered oxidative stress and violations of the nitric oxide cycle. Oxidative stress of endotheliocytes in diabetes mellitus is associated with the formation of pathogenetic vicious circles, including mitochondrial dysfunction and monomerization of endothelial NOS, leading to persistent hyperproduction of reactive oxygen species, which, with functional insufficiency of antioxidant systems, provides progressive damage and dysfunction of the endothelium. Therefore, pathogenetic correction of endothelial dysfunction in diabetes mellitus should be aimed not only at ensuring adequate glycemic control, but also at eliminating the phenomena of oxidative stress. In this regard, a system of non-enzyme and enzyme antioxidants can act as a target for targeted therapy and prevention of angiopathies.

The result of oxidative stress of endothelial cells is the inhibition of endothelial NOS, a decrease in the production and bioavailability of NO, which causes a decrease in its ability to effectively exert paracrine dilatatory effects on smooth muscle cells, causing a violation of vasomotor function, and consequently vascular tone and blood pressure. In addition, reduced bioavailability of NO, including changes in paracrine interactions with platelets and leukocytes, as well as overexpression of PAI-1 disrupt endothelial thrombosis, which can cause intravascular microcirculation disorders, which inevitably lead to hypoxia, further exacerbating endothelial dysfunction. Violation of autocrine regulatory effects of NO in combination with overexpression of VEGF and proinflammatory cytokines causes changes in the barrier and angiogenic functions of endotheliocytes, which causes structural remodeling of the vascular bed, leading to the development of angiopathies. Consequently, endothelial dysfunction in diabetes mellitus is manifested by a violation of all the main functions of the endothelium, including barrier, vasomotor, angiogenic and thromboresistance. A number of effective therapeutic strategies currently used to treat patients with diabetic angiopathies are aimed at correcting certain functions of endothelial cells (treatment with vasodilators, antiplatelet agents, anticoagulants; antiangiogenic therapy). To increase the effectiveness of such treatment regimens, further studies of the complex relationships of these disorders in the development of endothelial dysfunction in patients with diabetes mellitus are necessary.

Thus, the pathogenesis of endothelial dysfunction in diabetes mellitus is multicomponent and many of its aspects need to be clarified. Effective prevention and treatment of diabetic angiopathies requires the development of comprehensive pathogenetically based treatment regimens, including adequate glycemic control, suppression of oxidative stress and correction of impaired functions of endothelial cells.

Perhaps it is this mechanism that allows you to protect cells from excessive invasion of coronavirus and provides a protective effect of metformin. However, it is important to note that in all these studies (as in ours), the drug metformin was used in advance, i.e. before the development of