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THE ROLE OF P-SELECTIN IN DEVELOPMENT AND PROGRESSION OF CHRONIC KIDNEY DISEASE

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РОЛЬ Р-СЕЛЕКТИНА В ФОРМИРОВАНИИ И ПРОГРЕССИРОВАНИИ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК

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SURUNKALI BUYRAK KASALLIGI SHAKLLANISHI VA RIVOJLANISHIDA P-SELECTINNING ROLI

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Проанализирована литература, посвященная изучению клинико-диагностического и прогностического значения эндотелиальной дисфункции у больных с хронической болезнью почек (ХБП). Р-селектин, принадлежащий к семейству молекул адгезии – селектинов, является одним из маркеров эндотелиальной дисфункции, участвующим в процессах развития воспаления и гемостаза, инициирующим тромбообразование. Роль Р-селектина изучена при остром коронарном синдроме. Несмотря на то, что изучению эндотелиальной дисфункции и состояния гемостаза при болезнях почек уделяется очень большое внимание, роль Р-селектина в формировании и прогрессировании ХБП изучена мало, что доказывает необходимость проведения дальнейших исследований.

Ключевые слова: *хроническая болезнь почек, эндотелиальная дисфункция, Р-селектин.*

Maqolada surunkali buyrak kasalligi (SBK) bo'lgan bemorlarda endotelial disfunktsiyaning (ED) klinik diagnostikasi va prognostik ahamiyati to'g'risidagi adabiyotlarning sharhi keltirilgan. Adgezion molekulalari oilasiga tegishli bo'lgan P-selektin endothelial disfunksiya markerlaridan biri, u tromb hosil bo'lishiga yetaklovchi yallig'lanish va gemostazni rivojlanishida ishtirok etadi. O'tkir koronar sindromda P-selectinning roli o'rganilgan. ED va buyrak kasalliklarida gemostaz holatini o'rganishga katta e'tibor qaratilayotganiga qaramay, SBK ning shakllanishi va rivojlanishidagi P-selektsionning ahamiyati juda kam o'rganilgan, bu keyingi tadqiqotlar zarurligini isbotlaydi.

Kalit so'zlar: *surunkali buyrak kasalligi, endotelial disfunktsiya, P-selectin.*

Currently, when studying the mechanisms of progression of chronic kidney disease (CKD), a large impact is given to impaired vascular endothelial function locally in the kidney and in the systemic blood stream. The degree of expression of endothelial dysfunction (ED) is associated with a progressive decline in kidney function and the development of sclerosis, being a predictor of an unfavorable prognosis of CKD. With long-term exposure to damaging factors (hypoxia, toxins, immune complexes, inflammation mediators, hemodynamic overload, etc.) there is activation and damage to endothelial cells, leading subsequently to pathological response even to the usual stimuli in the form of vasoconstriction, thrombosis amplification of cellular proliferation, hypercoagulation with intravascular deposition of fibrinogen, microhemorheology violations [1,6].

In the last decade, scientific information on endothelium as an actively functioning and complex metabolic system has expanded significantly. To date, it has been established that vascular endothelium is an active endocrine system of humoral regulation of hemovascular homeostasis, which takes part in modulating vascular tone, regulating the transport of dissolved substances into the vascular wall, as well as in the growth and differentiation of endotheliocytes, the formation of extracellular matrix, activation chemotactic, inflammatory and reparative processes in response to local damage. In addition, the endothelium determines the balance of profibrinolytic and prothrombogenic blood activity. Endothelial vascular lining regulates local processes of hemostasis, proliferation, blood cell migration to the vascular wall and vascular tone. Violations are found in almost all cardiovascular diseases, atherosclerosis, hypertension, diabetes, CKD, sepsis, tumors, erectile dysfunction [5,11]. Risk factors for endothelial damage include hypercholesterolemia, hyperhomocytheemia, elevated levels of cytokines (IL-1, TNF-γ, IL-8) [2,5].

One of the current trends in modern endotheliology is the study of the mechanisms of functional heterogeneity of the endothelium, which, as it turned out, is not only genetically determined. The formation of the endothelial phenotype is influenced by hemodynamic factors, as well as organ function and the interaction of endotheliocytes with other cells.

The state of endothelium can be assessed determining substances synthesized in it. By the speed of formation of various factors in the endothelium (which are largely due to their structure), as well as the predominant direction of secretion of these substances (intracellular or noncellular), substances of endothelial origin can be divided into the following groups: factors that are constantly formed in the endothelium and are released from cells in a basolateral direction or in the

blood (NO, prostacyclin); factors accumulating in and out of the endothelium during stimulation (Willebrand factor, P-selectin, plasminogen tissue activator); factors, the synthesis of which in normal conditions practically does not occur, but increases dramatically with the activation of endothelium (endothelin-1, molecules of intercellular adhesion (ICAM-1) and vasculoendothelial growth factor (VCAM-1), E-selectin, PAI-1); factors synthesized and accumulated in the endothelium (t-PA) or are endothelium membrane proteins (receptors) (thrombomodulin, C protein receptor) [2,3,6,11].

Selectins play the key role in the development of inflammatory response, as they provide the initial stages of the process of adhesion of white blood cells to the endothelial vessels in the places of inflammation. Selectins mediate recruitment, primary fixation, skating (rolling) and white blood cell adhesion to the sites of inflammation. Selectins belong to the family of adhesive proteins, which are known to play the key role in the recruitment of white blood cells in activated endothelials and in platelets [8,9,13].

P-selectin (P-selectin; GMP-140 – granule membrane protein-140) is an adhesive molecule that promotes the interaction of activated endothelial cells or plates with white blood cells (Johnston G.I., 1990). P-selectin (platelet selectin) is a member of the selectins family of adhesive glycoproteins and is found in the Weibel-Palade bodies of endothelial cells and in the alpha-pellets of platelets. It quickly mobilizes in the plasma membrane after stimulation of the vasoactive glycoproteins substances, such as histamine and thrombin [4,11,12].

The selectins family includes E-selectin and L-selectin. The cluster encoding these selectins is localized on 1 human chromosome in the position of 1q21-g24 [7,10]. P-selectin gene is more than 50 kb in length and consists of 17 exons. P-selectin provides rapid adhesion of neutrophils and monocytes to activated vascular endothelium in the early phase of inflammation, as well as white blood cells to activated platelets. Because of P-selectin, circulating tumor cells, carrying carbohydrate ligands to it, can make contact with the endothelial lining of the vessel, as well as with activated platelets in the initial stage of their aggregation (the latter is important in vascular wall invasion) [7,11].

P-selectin is also involved in the transmission of the activating signal inside the white blood cells, which leads to activation on their surface (32-integrins). Activation of integrins leads to stabilization of white blood cells on the surface of the endothelium that is necessary for subsequent transmigration of white blood cells to inflammation zones [14]. Along with the membrane form, there is a soluble form of P-selectkin, which is normally present in the blood plasma. In platelets and endothelial cells was found a special mRNA of P-selectin, which does not contain an exon, encoding transmembrane domain, but there are eszones of the cytoplasmic site [13].

P-selectin is a platelet activation marker [6, 11]. Selectins mediate functions unique to blood vessels – the adhesion of leukocytes to the vessel wall with the formation of labile adhesions to the wall, which allow leukocytes to slide in the direction of flow. Damage to the endothelium, an “unstable” atherosclerotic plaque and subsequent platelet activation initiates thrombosis in the coronary vessels and the development of acute coronary syndrome [9,11,13,15].

The activation of endothelium and platelets in the zone of damage to the vascular wall is accompanied by the release of various biologically active compounds from them. In response to acute inflammatory mediators such as histamine or thrombin, P-selectin is rapidly transferred to the plasma membrane and acts as a receptor, by which leukocytes bind to activated platelets and endothelium. P-selectin-mediated adhesion is directed to cell-cell adhesion through molecular binding and is most likely very important in the development of inflammation and hemostasis [15].

It is known that platelet stimulation is manifested by the expression of pro-inflammatory markers on their membrane, such as P-selectin and CD40L. By means of P-selectin and its leukocyte ligand PSGL-1, platelets form platelet leukocyte aggregates [14].

A.D. Michelson et al. [11] found that after acute coronary syndrome, the number of circulating monocyte-platelet coaggregates is a more indicative marker of platelet activation than the determination of P-selectin expression on their surface.

Analysis of the studied scientific and medical literature and state registration materials showed that the need for knowledge of the pathogenetic mechanisms of the development and progression of chronic kidney disease (CKD) is currently in doubt. The studies on the role of P-selectin in the formation and progression of CKD are practically absent in the literature, which proves the need for further research.

Conclusion

Patients suffering from CKD have a significant range of metabolic disorders affecting protein, carbohydrate, lipid and water-salt metabolism, as well as impaired regulation of the hemostasis system, which is given great attention to kidney diseases. It should be noted that coagulation changes occur even before the formation of CKD itself. The mechanisms of hemostasis impairment and the ways in which hemostasis components are involved in the progression of renal pathology are still not clear. This requires further studies of hemostasiological phenomena in CKD. In this regard, the study of red blood cells is of particular interest, especially since there is evidence in which red blood cells in uremic patients exhibit increased procoagulant activity. Clarification of the role of these mechanisms at different stages of the course of CKD (exacerbation and remission) is important both from a scientific point of view and in practical terms.

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The article provides a literature review on clinical-diagnostic and prognostic significance of endothelial dysfunction (ED) in patients with chronic kidney disease (CKD). P-selectin, belonging to the family of adhesion molecules – selectines, is one of ED markers, involved in the development of inflammation and hemostasis, initiating thrombosis. The role of P-selectin is studied in acute coronary syndrome. Despite of a lot of studies on ED and the state of hemostasis in kidney diseases, the role of P-selectin in the formation and progression of CKD is poorly studied, which proves the need for further researches.

Key words: *chronic kidney disease, endothelial dysfunction, P-selectin.*