Review

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The significance of microcirculation disorders and changes in blood rheological characteristics for the development of inflammatory bowel diseases

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ABSTRACT. The review provides an analysis of literature data on changes in the blood microcirculation system at inflammatory bowel diseases and their impact on the development of general disorders in the body. It explores the consequences of damage to the inner lining of blood vessels (endothelium) and the slowdown in capillary blood flow. These processes are being studied because the hemostasis system and blood fluidity (haemorheology) ensure normal blood supply to tissues, and when these systems are disrupted, perfusion is severely impaired. An analysis of scientific data allows us to draw a clear conclusion: disruptions in microcirculation and a decrease in blood fluidity, primarily due to increased clumping of red blood cells and a loss of their flexibility, play a crucial role in the development of inflammatory bowel diseases. These abnormalities create a vicious cycle: the worse the blood supply to tissues, the more pronounced the tissue ischemia is, and the more severe the inflammation is. This combination causes the disease to worsen.

KEYWORDS: *inflammatory bowel disease, IBD, viscosity, inflammation, red blood cells, blood supply*

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Обзор

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Значение расстройств микроциркуляции и изменений реологических характеристик крови для развития воспалительных заболеваний кишечника

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РЕЗЮМЕ. В обзоре представлен анализ данных литературы об изменениях в системе микроциркуляции крови при воспалительных заболеваниях кишечника и их влиянии на развитие общих нарушений в организме. Разобрано, чем может обернуться травма внутренней выстилки сосудов (эндотелия) и изменение скорости капиллярного кровотока на более медленное. Эти процессы исследуются, поскольку система гемостаза и текучесть крови (гемореология) обеспечивают нормальное кровоснабжение тканей, а при их расстройстве перфузия серьезно нарушается. Анализ научных данных позволяет сделать однозначный вывод: сбои в микроциркуляции и ухудшение текучести крови, в первую очередь из-за повышенного слипания красных клеток крови и потери ими гибкости, играют решающую роль в развитии воспалительных заболеваний кишечника. Эти нарушения провоцируют порочный круг: чем хуже кровоснабжение тканей, тем более выражена тканевая ишемия и тем сильнее в них протекает воспаление. Это в совокупности провоцирует обострение болезни.

КЛЮЧЕВЫЕ СЛОВА: *воспалительные заболевания кишечника, ВЗК, вязкость, воспаление, красные клетки крови, кровоснабжение*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), represent a serious medical and social problem in modern gastroenterology. The relevance of this group of diseases is multifactorial: their etiology remains unclear, the incidence among the working-age population continues to rise, and the course of the disease becomes chronic and recurrent. The main risk factors include complications that pose a life-threatening risk to the patient. The situation is further exacerbated by the lack of curative treatments and the need for expensive, long-term therapy. Patients' quality of life is significantly reduced as a result [1].

Currently, there is a trend toward the disease affecting younger age groups — 20% of all newly diagnosed cases of IBD occur in children under 6 years of age, and among adolescents, the peak incidence is between 15 and 29 years of age [2]. Data from various regions of Russia confirm the global trend of an increasing number of these diseases in children.

The significance of Crohn's disease and ulcerative colitis in pediatric practice cannot be overstated. These conditions strike children during their most active period of growth and development, a time when the body's need for proteins, fats, and carbohydrates — as well as micronutrients and macronutrients — is heightened. As a result, there is a decrease in appetite, as well as impaired absorption and metabolism in general; in the long term, such disruptions in intestinal absorption inhibit growth, weight gain, and skeletal mineralization. This leads to delayed puberty, an imbalance in the child's psycho-emotional state, and, consequently, reduced social adaptation [3].

THE ROLE OF MICROCIRCULATORY ALTERATIONS IN THE DEVELOPMENT OF INFLAMMATORY BOWEL DISEASE

Despite extensive research, the exact causes of IBD remain unclear. According to current understanding, the disease develops due to a combination of genetic predisposition and environmental factors, leading to a disruption in the regulation of the immune response to the intestinal microbiota and a loss of control over the inflammatory reaction in the intestinal mucosa [4, 5].

An important link in the pathogenesis is damage to the epithelial barrier, increased permeability, and the development of endogenous intoxication. These processes have a variety of negative effects on cellular structures and contribute to the maintenance of metabolic disturbances in IBD [6–8].

Although the pathogenesis of IBD has been studied in considerable detail, there is still no unified concept explaining the mechanisms of development and progression of UC and CD. Improving therapeutic efficacy is directly linked to an in-depth investigation of currently emerging individual pathogenetic pathways [8]. One such insufficiently studied aspect is the role of microcirculatory disorders.

Chronic inflammation in IBD is a complex process involving both immune and non-immune cells, including components of the microcirculatory bed. The inflammatory process in the intestine differs fundamentally from that in other organs. First, UC and CD are characterized by the phenomenon of leukocyte hyperadhesion to the vascular endothelium against a background of microvascular dysfunction [9]. Second, microcirculatory alterations maintain chronic inflammation through reduced tissue perfusion, development of ischemia, activation of the coagulation system, and angiogenesis leading to structural tissue remodeling [10–12].

Structural changes include remodeling and proliferation of endothelial cells in capillaries and venules, which contributes to the persistence of inflammation in the gastrointestinal tract [13]. Experimental and clinical observations have demonstrated an increased reticular structure of microvessels, as well as an increase in their diameter and density in patients with IBD [14, 15].

The severity of endothelial dysfunction correlates with disease severity and activity in both adults and children [16–19]. Microvascular disturbances are also associated with increased oxidative stress and represent a specific feature of intestinal involvement in IBD [20].

Perfusion studies demonstrate a reduction in small intestinal blood flow in CD, depending on the degree of inflammation [21]. In children with UC, changes in capillary blood flow velocity in the duodenum have been identified, which are not associated with inflammatory markers or disease activity [22]. The most pronounced reductions in

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blood volume and flow are observed in CD when inflammation is combined with fibrosis [23]. In the active phase of IBD, a significant deterioration in microcirculatory function is observed compared with remission [24]. Even in UC remission, an imbalance in mucosal blood supply persists, and incomplete restoration correlates with local ischemia [25].

Experimental data confirm that a decrease in capillary blood flow occurs already in the early stages of colitis. Impaired microcirculation precedes chronic histological changes and contributes to functional disturbances during disease progression, whereas its improvement is associated with stabilization of intestinal permeability [26].

THE EFFECT OF BLOOD RHEOLOGICAL PARAMETERS ON MICROCIRCULATION FUNCTION

The functioning of the microcirculatory system largely depends on the rheological parameters of blood, with erythrocytes serving as a universal model for studying the state of cytoplasmic membranes and cellular metabolism [27]. The study of erythrocyte membrane characteristics and their functional properties in IBD is of fundamental importance for understanding the pathogenesis of these diseases.

As the most numerous blood cells, red blood cells play a key role in microcirculation, ensuring oxygen delivery to tissues and responding to changes in its local concentration [28]. They determine the rheological properties of blood in the microvascular bed due to their ability to aggregate and deform [29].

The process of erythrocyte aggregation is actively studied in both clinical and basic research [30–33]. A continuous dynamic "aggregation–disaggregation" process occurs in the blood, with disaggregation normally prevailing over aggregation. When blood flow velocity decreases, erythrocytes form linear aggregates, which are disrupted when shear rate increases [34]. Optimal aggregation is of great importance for the microcirculatory bed, as it regulates venous resistance and maintains the necessary hydrostatic pressure in capillaries [35].

The aggregation process is influenced both by plasma properties and by characteristics of the erythrocytes themselves. Albumin, immunoglobulins, prostaglandins, and other components possess pro-aggregatory activity [36, 38], with fibrinogen recognized as the most potent stimulator of aggregation [37]. The formation of "rouleaux" occurs with the participation of plasma proteins that create molecular "bridges" between cells [39–41]. According to the alternative "depletion layer" theory, aggregation is driven by an osmotic gradient [41]. The contradictions between existing theories indicate that the mechanisms of aggregation remain insufficiently studied [40].

Important determinants of aggregability include biochemical, geometric, and biomechanical properties of erythrocytes, including sialic acid content, membrane phospholipid composition, and cell shape [42–44]. Altered erythrocytes (e.g., echinocytes) can form particularly strong aggregates.

In pathological conditions, a syndrome of increased blood viscosity is observed, characterized by the formation of stable "clump-like" aggregates that persist even at high shear rates. Erythrocyte hyperaggregation is recorded in type 1 and type 2 diabetes mellitus, cardiovascular, oncological, and inflammatory diseases [44–47], leading to a reduction in the density of functioning capillaries, an increase in vascular resistance [48], and impaired tissue perfusion [49].

Of particular concern are pathologically strong aggregates that cannot pass through narrow capillaries, resulting in blood flow shunting and the formation of "plasma" capillaries devoid of erythrocytes [50, 51].

The second key rheological parameter is erythrocyte deformability, i.e., the ability of red blood cells to change shape under flow conditions [52, 53]. Deformability is of fundamental importance for gas exchange, as it enhances intracellular oxygen convection [54]. A reduction in deformability by as little as 10% significantly impairs tissue oxygenation [55].

Deformational properties are determined by the viscoelastic characteristics of the membrane, intracellular viscosity, and the surface-to-volume ratio of the cell [56]. Impaired deformability may be caused by activation of lipid peroxidation, changes in hemoglobin concentration, or adenosine triphosphate deficiency.

Thus, the rheological properties of blood, determined by erythrocyte aggregability and deformability, play a decisive role in ensuring adequate tissue perfusion, gas exchange, and metabolism.

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THE SIGNIFICANCE OF RHEOLOGICAL ABNORMALITIES IN INFLAMMATORY BOWEL DISEASES

Studies on the rheological properties of erythrocytes in inflammatory bowel disease remain limited. Existing data indicate increased erythrocyte aggregation in both active and inactive forms of CD in adult patients, accompanied by an increase in fibrinogen concentration during the active phase of the disease. A correlation has been established between rheological parameters and markers of systemic inflammation, allowing erythrocyte aggregation to be considered a nonspecific indicator of inflammatory activity in IBD [57].

A significant finding in 2009 was the discovery of increased strength of erythrocyte aggregates in IBD patients, correlating with disease activity, fibrinogen levels, and erythrocyte sedimentation rate [58]. At the same time, studies using dextran did not reveal differences in erythrocyte aggregative properties between patients and healthy individuals, indicating the preservation of the main cellular aggregation mechanisms in IBD. These findings suggest the presence of similar rheological disturbances in the intestinal microcirculation system, which, in combination with endothelial dysfunction, may lead to tissue hypoxia, intestinal wall damage, and compensatory angiogenesis.

Disorders of rheological properties in IBD are not limited to changes in aggregation. Experimental and clinical studies confirm a persistent reduction in erythrocyte deformability in both active and inactive forms of IBD, with the most pronounced changes during exacerbation [59].

An additional factor aggravating rheological disturbances in IBD is an increase in plasma viscosity, particularly pronounced in active CD. This parameter shows a close correlation with major markers of inflammatory activity [60]. The combination of these abnormalities such as increased plasma viscosity, enhanced erythrocyte aggregation, and reduced erythrocyte deformability leads to a significant deterioration in blood rheological properties, impaired tissue perfusion, and progression of intestinal inflammation.

CONCLUSION

Analysis of scientific data suggests that disturbances in microcirculation and blood rheological properties play a significant role in the mechanisms underlying the development of inflammatory bowel disease. Of key importance in this context are changes in erythrocyte aggregability and deformability. The resulting impairments of capillary blood flow initiate a vicious cycle of pathological processes: the development of ischemia and tissue hypoxia leads to the exacerbation of the inflammatory response, which in turn promotes disease progression.

Thus, disturbances in blood rheology and microcirculation create a pathological basis for the persistence of the inflammatory process in IBD, forming a self-sustaining mechanism of disease development.

ADDITIONAL INFORMATION

Authors' contribution. E.N. Fedulova — the concept and design of the study; A.N. Popovicheva, V.A. Tsarev — literature selection, writing and editing of the text.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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