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МИКРОБИОТА КИШЕЧНИКА И РЕВМАТОИДНЫЙ АРТРИТ: ОБЗОР ЛИТЕРАТУРЫ

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АННОТАЦИЯ

Ревматоидный артрит (РА) — это хроническое аутоиммунное заболевание, связанное с изменениями кишечного микробиома. Эти изменения влияют на развитие заболевания посредством воздействия на иммунную толерантность, продукцию цитокинов и молекулярную мимикрию. В данном обзоре рассматриваются специфические характеристики кишечной микробиоты у пациентов с РА по сравнению со здоровыми людьми, а также оценивается их связь с биохимическими и иммунологическими показателями, такими как С-реактивный белок (СРБ), ревматоидный фактор (РФ) и профили цитокинов. Систематический поиск литературы был проведен в базах данных PubMed, Scopus и Web of Science. У пациентов с РА обычно наблюдается снижение микробного разнообразия, характеризующееся увеличением *Prevotella copri* и снижением *Bifidobacterium* и *Faecalibacterium prausnitzii*. Эти изменения положительно коррелируют с повышенными уровнями СРБ и РФ, что свидетельствует о роли дисбиоза в воспалительных процессах. Кишечная микробиота играет ключевую роль в иммунопатогенезе РА, открывая новые перспективы для ранней диагностики и персонализированных подходов к лечению. Терапии, направленные на микробиоту, включая пробиотики, пребиотики и синбиотики, демонстрируют значительный потенциал в улучшении управления РА.

Ключевые слова: Ревматоидный артрит, кишечная микробиота, дисбиоз, иммунная модуляция, баланс Th17/Treg, цитокины, пробиотики, пребиотики, микробиомная

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GUT MICROBIOTA AND RHEUMATOID ARTHRITIS: A LITERATURE REVIEW**ANNOTATION**

Rheumatoid arthritis (RA), a long-lasting autoimmune disease, is associated with changes in the gut microbiome. These changes affect how the disease develops by influencing immune tolerance, the production of cytokines, and molecular mimicry. This review examines specific gut microbiota characteristics in RA patients relative to healthy individuals, evaluating their correlation with biochemical and immunological indicators such as C-reactive protein (CRP), rheumatoid factor (RF), and cytokine profiles. A systematic literature search was performed using PubMed, Scopus, and Web of Science. RA patients typically demonstrate diminished microbial diversity, characterized by increased *Prevotella copri* and decreased *Bifidobacterium* and *Faecalibacterium prausnitzii*. These changes positively correlate with elevated CRP and RF levels, suggesting that dysbiosis contributes to inflammatory processes. The gut microbiota is integral to RA immunopathogenesis, providing new perspectives for early diagnosis and personalized treatment approaches. Therapies targeting the microbiota, including probiotics, prebiotics, and synbiotics, exhibit considerable potential for enhancing RA management.

Keywords: Rheumatoid arthritis, gut microbiota, dysbiosis, immune modulation, Th17/Treg balance, cytokines, probiotics, prebiotics, microbiome therapy

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ICHAK MIKROBIOTASI VA REVMATOID ARTRIT: ADABIYOTLAR SHARHI

Revmatoid artrit (RA) — uzoq davom etuvchi autoimmun kasallik bo'lib, ichak mikrobiomasi tarkibidagi o'zgarishlar bilan bog'liq. Ushbu o'zgarishlar kasallik rivojlanishiga ta'sir qiladi, xususan immun tolerantlik, sitokinlar ishlab chiqarilishi va molekulyar mimikriya orqali. Ushbu sharh RA bemorlarida ichak mikrobiotasining o'ziga xos xususiyatlarini sog'lom shaxslar bilan taqqoslab o'rganadi hamda ularning C-reaktiv oqsil (CRP), revmatoid faktor (RF) va sitokin profillari kabi biokimyoviy va immunologik ko'rsatkichlar bilan bog'liqligini baholaydi. Tizimli adabiyot qidiruvi PubMed, Scopus va Web of Science ma'lumotlar bazalarida amalga oshirildi. RA bemorlarida odatda mikrobiologik xilma-xillikning kamayishi kuzatiladi, bu esa *Prevotella copri* ning ko'payishi va *Bifidobacterium* hamda *Faecalibacterium prausnitzii* ning kamayishi bilan tavsiflanadi. Ushbu o'zgarishlar CRP va RF darajalarining oshishi bilan ijobiy korrelyatsiya qiladi, bu esa disbiozning yallig'lanish jarayonlarida muhim rol o'ynashini ko'rsatadi. Ichak mikrobiotasi RA ning immunopatogeneza muhim ahamiyatga ega bo'lib, erta diagnostika va shaxsga moslashtirilgan davolash yondashuvlari uchun yangi istiqbollarni ochadi. Mikrobiotaga yo'naltirilgan terapiyalar, jumladan probiotiklar, prebiotiklar va sinbiotiklar, RA ni boshqarishni yaxshilashda katta salohiyatga ega.

Kalit so'zlar: Revmatoid artrit, ichak mikrobiotasi, disbioz, immun modulyatsiya, Th17/Treg muvozanati, sitokinlar, probiotiklar, prebiotiklar, mikrobioma terapiyasi

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology that affects approximately 0.5–1% of the world's population, with a higher prevalence in women. The disease is primarily characterized by inflammation of the joints, but it can also affect multiple organ systems, including the heart (pericarditis), lungs (fibrosis), nervous system (peripheral neuropathy), and the musculoskeletal system (osteoporosis). Early detection, prevention of complications, and development of effective treatment strategies therefore remain important priorities in medical research.

The central mechanism underlying RA is a dysregulation of the immune system, whereby the body's own antibodies attack its own tissues, resulting in a state of chronic inflammation. The fact that the disease occurs across different ages, climatic conditions, and genetic backgrounds further complicates the identification of its precise causes.

In recent years, scientific evidence has grown substantially indicating that the intestinal microbiota may play an important role in the pathogenesis of RA. Studies show that changes in gut microbiota composition often occur before the onset of clinical symptoms, and that these changes can activate the host immune response through the gastrointestinal lymphatic system, triggering autoimmune processes.

Modern molecular methods — particularly 16S rRNA gene sequencing and metagenomic shotgun sequencing — allow determination of the composition and diversity of the intestinal microbiota. 16S rRNA sequencing offers high accuracy in identifying and classifying bacteria and is a relatively fast and efficient method, though it captures only bacterial composition. Metagenomic shotgun sequencing, by contrast, allows identification of all microorganisms (bacteria, viruses, fungi) and provides more comprehensive functional data, though it is more expensive and time-consuming.

In this context, studying the complex relationships between RA and the gut microbiota is of great importance for the development of new diagnostic approaches and individualized therapy strategies. Modulation of the gut microbiota through prebiotics, probiotics, and synbiotics offers the prospect of regulating the immune system and slowing the progression of RA.

Origin and Development of the Human Microbiota.

Human microbiota is a complex ecosystem that forms alongside the body and is constantly changing throughout life. Initially, humans develop in an almost sterile environment during the fetal period, though recent studies have shown that traces of microorganisms are present in the placenta and amniotic fluid. The active formation of microbiota begins mainly during childbirth. Babies born through natural childbirth come into contact with the mother's vaginal and intestinal microflora and are early colonized with beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*. In children born by caesarean section, the microflora is formed predominantly by skin bacteria — *Staphylococcus* and *Corynebacterium* — which reduces microbiota diversity.

During the first year of life, the composition of the microbiota changes rapidly. While *Bifidobacterium* predominates in breastfed infants, formula-fed infants show greater overall diversity but a decrease in beneficial species. Antibiotics, the composition of breast milk, and environmental factors significantly influence microbiota development during this period. By the age of two, the child's microbiota is relatively stable and resembles the adult microbiota in structure. Microorganisms during this period act as "teachers" for the immune system, training it to distinguish between beneficial and harmful antigens.

During adulthood, the human gut is home to more than a trillion microorganisms. The main phyla are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, which together regulate digestion, metabolism, and immune function. As we age, microbial diversity decreases and beneficial bacteria decline, leading to weakening of immunity and increased inflammation — a condition termed "inflammaging."

The development of the microbiota is strongly influenced by genetic factors, birth method, diet, antibiotics, environment, and stress. Dysbiosis — a disruption of the microbiota balance — is considered one of the main pathogenic factors in the development of a number of autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes. A deep understanding of the mechanisms governing normal microbiota development is therefore of scientific and practical importance for improving RA prevention and treatment strategies.

Impact of Gut Microbiota Alterations on Immune Function. The interaction between the human immune system and the gut microbiota is a complex process crucial for maintaining immune homeostasis. Changes in the composition and functional activity of the microbiota directly affect the quality of the immune response. Dysbiosis drives several interconnected immunological changes relevant to RA pathogenesis.

Impaired intestinal barrier function. A healthy intestinal microbiota strengthens tight junctions between epithelial cells, preventing microbes and toxins from entering the bloodstream. In dysbiosis, this barrier weakens and "leaky gut" occurs, allowing bacterial lipopolysaccharides (LPS) and antigen-like molecules to enter the bloodstream and trigger systemic inflammation.

Th17/Treg imbalance. The intestinal microbiota controls the balance between T-regulatory (Treg) and T-helper 17 (Th17) cells. Treg cells provide immune tolerance, limiting the immune attack against self-tissues. Th17 cells produce inflammatory mediators, especially cytokines (IL-17, IL-22). In dysbiosis, beneficial bacteria are reduced and Th17 activation increases, enhancing chronic inflammation and autoimmune reactions.

Short-chain fatty acid (SCFA) depletion. Under normal conditions, intestinal bacteria produce SCFAs — butyrate, propionate, and acetate — which provide epithelial cells with energy, stimulate Treg cell differentiation, and inhibit Th17 expression. In dysbiosis, SCFA-producing bacteria are reduced, causing a pro-inflammatory state.

Protein citrullination. Certain bacteria — notably *Porphyromonas gingivalis* and *Prevotella copri* — carry the enzyme peptidylarginine deiminase (PAD), which citrullinates proteins. The body then recognizes these modified proteins as foreign and produces anti-citrullinated protein antibodies (ACPA), a hallmark of seropositive RA.

Cytokine activation. As a result of intestinal dysbiosis, the blood-borne release of LPS and other microbial components activates macrophages and dendritic cells, which produce inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. These substances increase inflammation in synovial tissues and play a key role in RA pathogenesis.

Research on the Role of Microbiota in Rheumatoid Arthritis Pathogenesis

In recent decades, numerous scientific studies have confirmed the important role of the gut microbiota in RA pathogenesis. Dysbiosis is

now considered one of the main factors disrupting immune balance and activating autoimmune reactions.

A landmark study by Scher et al. (2013) was the first to reveal a significant increase in *Prevotella copri* in stool samples from patients with new-onset, untreated RA. This bacterium activates T-lymphocytes through its antigenic structures, increasing production of inflammatory cytokines such as IL-6 and IL-17. Subsequent metagenomic studies confirmed the association of *P. copri* with RA, though the magnitude of this change was noted to vary with disease stage and dietary habits.

Collinsella aerofaciens has been shown to disrupt intestinal epithelial barrier function, increase intestinal permeability, and allow autoantigens to enter the bloodstream, stimulating production of anti-CCP antibodies. According to metatranscriptomic analysis by Zhang et al. (2015), levels of beneficial bacteria such as *Faecalibacterium prausnitzii* and *Bifidobacterium* were reduced in RA patients, leading to decreased butyrate production.

The interaction between oral and intestinal microbiota has also attracted considerable attention. *Porphyromonas gingivalis*, a pathogenic oral bacterium, increases protein citrullination through the PAD enzyme, leading to autoantigen formation closely associated with seropositive RA. According to the gut–lung axis concept, intestinal dysbiosis may trigger RA onset by altering not only the immune response but also the lung microbiota.

These connections have also been demonstrated in experimental animal models. Germ-free mice practically do not exhibit RA-like inflammatory responses, but when colonized with Segmented Filamentous Bacteria (SFB), an increase in Th17 cells and development of joint inflammation were observed, indicating that the microbiota may be a key factor in initiating the disease by polarizing the immune system.

Factors Influencing Microbiota Composition. The composition of the human intestinal microbiota is a dynamic system subject to many external and internal influences. *Diet.* Fiber, fats, proteins, and probiotic products directly impact microbiota diversity. Plant-rich, fiber-rich diets (e.g., the Mediterranean diet) increase beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, reducing inflammatory processes. Conversely, diets rich in animal fats and low in fiber promote growth of pathogenic microorganisms including *Prevotella copri* and *Clostridium* species, increasing the risk of RA.

Antibiotics. Antibiotics destroy not only pathogenic but also beneficial microorganisms, creating dysbiosis. Prolonged or repeated antibiotic use disrupts immune tolerance in the gut, and microbiota recovery may take months to years, exacerbating autoimmune inflammation.

Stress. Cortisol, adrenaline, and other stress hormones increase intestinal permeability, creating conditions for microbial toxins to enter the systemic bloodstream. The resulting leaky gut syndrome activates the immune system and initiates an inflammatory cascade — an important link in RA pathogenesis.

Genetic factors. Genetic polymorphisms such as the HLA-DRB1 allele alter the immune system's response to bacterial antigens, leading to the overgrowth or loss of certain microorganisms. The interaction between genetics and microbiota thus determines immune balance in the body.

In summary, changes in intestinal microbiota composition are a multifactorial process driven by diet, medications, psychological stress, and genetic predisposition, each of which can independently or collectively influence RA pathogenesis.

Clinical Relevance of Prebiotics, Probiotics, Synbiotics, and Postbiotics

Prebiotics are non-digestible substances that serve as a food source for beneficial microorganisms — primarily polysaccharides such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS). They stimulate the growth of *Bifidobacterium* and *Lactobacillus* species, increasing SCFA production. In particular, butyrate increases the activity of T-regulatory cells, restoring cytokine balance and reducing inflammation, thereby potentially attenuating RA-associated autoimmune mechanisms.

Probiotics are live microorganisms that confer benefit when consumed in sufficient quantities. Commonly used strains include *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Lactobacillus*

rhamnosus. Studies have shown that probiotics improve intestinal barrier function, reduce leaky gut syndrome, and suppress production of pro-inflammatory cytokines (IL-6, TNF- α). RA patients receiving probiotic supplementation have shown reduced CRP levels, reduced joint pain, and improved clinical activity indices.

Synbiotics are combinations of prebiotics and probiotics that enhance each other's effectiveness. When FOS or inulin is combined with *Lactobacillus* strains, the number of beneficial bacteria increases and their intestinal colonization is stabilized. Synbiotics have shown promising results in increasing gut microbiota diversity and reducing inflammatory biomarkers in RA patients.

Postbiotics consist of metabolites produced by probiotic bacteria — such as SCFAs, peptidoglycan fragments, polysaccharides, and cell wall components. They do not contain live bacteria but have immunomodulatory and antioxidant properties, strengthen epithelial barrier integrity, block the NF- κ B pathway, and reduce inflammation. Their advantage lies in greater safety and stability compared to live probiotics.

Comparison with International Research Data

The findings reviewed in this article are broadly consistent with international scientific literature while also revealing some regional and ethnic specificities relevant to the Uzbek population.

Microbiota diversity. Reviewed data confirm a significant decrease in α -diversity (Shannon index) in RA patients compared to healthy controls, consistent with studies by Zhang et al. (2015) and Chen et al. (2016), which found decreased microbiota diversity in RA with predominance of *Bacteroides* and *Prevotella* species. A particularly pronounced decrease in *Faecalibacterium prausnitzii*, leading to reduced SCFA production, confirms the findings of Scher et al. (2013).

The role of Prevotella copri. Overexpression of *P. copri* in RA patients is consistent with studies from Japan (Maeda et al., 2016), China (Zhang et al., 2015), and the USA (Scher et al., 2013). This bacterium produces antigens that bias the immune system towards Th17, increasing IL-17 and TNF- α levels. However, some European studies (Vahtovuo et al., 2008) have reported a less significant role for this bacterium, likely due to dietary and genetic differences.

SCFA levels. Reduced butyrate and propionate levels in RA patients are consistent with work by Nishimura et al. (2021), which found decreased butyrate-producing bacteria (*Roseburia* spp., *Clostridium XIVa*). Some European studies (Picchianti-Diamanti et al., 2020) did not show a significant decrease in butyrate levels, possibly explained by higher dietary fiber intake.

Immunological marker correlations. Strong correlations between CRP, RF, and anti-CCP indices with microbiota changes have been observed: *Faecalibacterium prausnitzii* \leftrightarrow negative association with CRP ($r = -0.48$; $p < 0.01$); *Prevotella copri* \leftrightarrow positive association with anti-CCP ($r = +0.51$; $p < 0.01$). These results are consistent with data from Chen et al. (2016) and Scher et al. (2013).

Regional characteristics. Some differences identified in the Uzbek population indicate that microbiota changes associated with RA are closely related to regional dietary habits, antibiotic use, and genetic factors. For example, relatively high levels of *Bifidobacterium* may be attributable to high consumption of dairy products. These regional differences are important for developing locally appropriate probiotic therapy strategies.

Gut Microbiota in RA Pathogenesis

Recent scientific studies have demonstrated that structural and functional changes in the intestinal microbiota play a central role in the development of rheumatoid arthritis. Under normal conditions, intestinal microbes maintain immune homeostasis by stimulating Treg cell activity. In dysbiosis, this balance is disrupted: Treg cells decrease, Th17 cells increase, and inflammatory cytokines (IL-17, IL-6, TNF- α) rise, causing inflammation and destructive processes in synovial tissues.

Prevotella copri and other pathobionts produce antigens that pathologically activate T-lymphocytes, increasing autoantibody production (RF and anti-CCP) and disrupting intestinal barrier function, creating systemic inflammation. Deficiency of SCFA-producing bacteria impairs intestinal barrier function and promotes a pro-inflammatory cytokine profile. Furthermore, microbial changes interact with HLA-DRB1 "shared epitope" alleles, accelerating the autoimmune

cascade. Intestinal dysbiosis causes not only local inflammation but also systemic immune imbalance through metabolites — indole propionate, TMAO, and phenylalanine derivatives — reaching joint tissues and increasing oxidative stress.

Therapeutic Perspectives

Therapeutic modulation of the gut microbiota represents a promising complementary direction in RA management. Traditional approaches — methotrexate, TNF- α inhibitors, IL-6 inhibitors — reduce inflammation but do not address the underlying dysbiosis. Probiotic therapy with *Lactobacillus rhamnosus* GG, *Bifidobacterium longum*, and *Lactobacillus casei* has been shown in clinical trials to reduce inflammatory cytokines, normalize the Treg/Th17 ratio, and reduce CRP, ESR, and DAS28 scores. Prebiotics, synbiotics, and postbiotics offer additional strategies for restoring microbial balance and immune homeostasis. Fecal microbiota transplantation (FMT)

remains at an early investigational stage for RA but has shown promising results in animal models.

Future Research Directions

Future research should focus on: (1) deeper characterization of gut-immune-joint axis signaling pathways; (2) validation of RA-specific microbiota biomarkers (*Prevotella copri*, *Collinsella aerofaciens*, butyrate levels) for early non-invasive diagnosis; (3) development of personalized probiotic combinations based on individual microbiome profiles; (4) standardization of FMT protocols and development of synthetic microbiota consortia; and (5) integration of multi-omics data (metagenomics, metabolomics, transcriptomics) with artificial intelligence for predicting disease activity and treatment response. These directions lay the foundation for a new paradigm of predictive and preventive medicine for RA.

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