REVIEW

Rheumatol. Forum
2022, vol. 8, No. 4, 169–167

ISSN: 2720-3921, e-ISSN: 2720-3913
DOI: 10.5603/RF.2022.0024

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Intestinal dysbiosis and increased intestinal permeability as a potential risk factor for the development and progression of rheumatoid arthritis

ABSTRACT

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases. Factors affecting the development of the disease result from a coincidence of environmental factors, including so-called trigger factors and genetic predisposition which lead to impaired immune tolerance and autoimmune phenomena. The detailed etiopathogenesis of the disease is unclear. Evidence indicates the potential role of the gut microbiome, increased intestinal permeability and disturbed immune response faciliate the development of autoimmune diseases including RA.
The paper is reviewing scientific data on the role of the gut microbiota and increased intestinal permeability in the development and progression of RA. Attention is also focused on factors disrupting the physiological microbial colonization and other factors related to the modern lifestyle in industrialized countries affecting the gut microbiota.
All reported data suggested the role of the gut microbiota in the pathogenesis of RA and further work is necessary to determine whether modulation of the microbiota can serve as a clinical tool to regulate intestinal permeability and influence the development and clinical course of RA.

Rheumatol. Forum 2022, vol. 8, No. 4: 169–177

KEY WORDS: rheumatoid arthritis; microbiome; gut microbiota; dysbiosis; gut permeability; leaky gut

INTRODUCTION

Since the 1960s, there has been an increase in the incidence of autoimmune diseases, allergies and chronic metabolic diseases in industrialized countries. Numerous environmental factors, apart from genetic predisposition are suggested to play an important role in the development of these diseases [1]. It is assumed that changes in the composition and function of the gut microbiome, as well as changes in the permeability of the intestinal barrier, can be involved in altered immunity and contribute to the development of autoimmunity [2].

The paper is reviewing medical literature related to the potential impact of intestinal dysbiosis and increased permeability of the intestinal barrier on the pathogenesis, disease activity and prognosis in patients with rheumatoid arthritis (RA). Finding a trigger factor may be helpful to further research aimed at modulating the gut microbiota and improving the functionality of the gut barrier.

The term microbiome refers to the collection of microbial genomes, their structural elements, metabolites, and signalling molecules, as well as the surrounding environmental conditions, creating a dynamic and interactive micro-ecosystem. Otherwise, the term micro-

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biota pertains to the community of microorganisms, which can include bacteria, fungi, protozoa and others [3]. The gut microbiota is involved in many functions in the body. It can be distinguished by protective, metabolic, trophic and immunological functions. All the above-mentioned functions complement each other, aiming to maintain the organism's homeostasis.

The term "leaky gut" commonly encountered in the literature refers to the increased ability of external antigens from the lumen of the gut to pass into the bloodstream of the host, which can affect both the local and systemic immune response. A great deal of evidence indicates that this phenomenon may play a role in the development or exacerbation of many autoimmune diseases, including inflammatory bowel disease, celiac disease, type 1 diabetes, multiple sclerosis, autoimmune hepatitis, systemic lupus erythematosus [4].

Rheumatoid arthritis is a chronic autoimmune disease with a heterogeneous clinical course. The etiology of RA is unknown. One of the suggested genetic factors predisposing to RA is HLA-DRB1. On the other hand, environmental factors include smoking, periodontal disease, diet, obesity, oral contraception and bronchiectasis [5]. The key phenomenon in the development of RA is an autoimmune reaction which is stimulating a chronic synovial membrane inflammation. The autoimmunity in RA is associated with the immune response to so-called post-translational modified proteins. All of them are recognized by the patient's immune system as foreign antigens and the immune response is propagated. Some of them (rheumatoid factor [RF] and antibodies against citrullinated proteins [ACPA]) are listed as classification criteria of RA.

THE ROLE OF INTESTINAL DYSBIOSIS IN THE PATHOGENESIS OF AUTOIMMUNE DISEASES

Disturbance of the composition, proportion and function of intestinal microbes is known as intestinal dysbiosis [6]. Changes in the amount as well as the diversity of the microbiota colonizing our body seem to alter the proportion of various T-cell subpopulation and can play a role in inflammatory disease development. Interestingly, the microbiome composition evolves along with the host's immune system to adapt to modern lifestyles [7].

The mechanisms of intestinal dysbiosis that may contribute to the development of autoimmune diseases include the activation of antigen presentation by influencing the pattern-recognition receptors, the ability to enzymatic citrullination of peptides, antigen mimicry, alteration of the permeability of the intestinal barrier, stimulation of differentiation of specific subpopulations of T lymphocytes, development of inflammation of the mucosa through T helper 17 cells, supporting the humoral response with the use of T follicular helper cells [8, 9].

It is also hypothesized that the microbiome may influence the epigenetic mechanisms of the host's gene expression (including genes responsible for intestinal permeability). Examples of epigenetic mechanisms that are modifications of gene expression unrelated to changes in the nucleotide sequence are DNA methylation, the effect of non-coding RNA, and post-translational modification of histones. The role of epigenetic mechanisms has been described in many diseases, including inflammatory bowel diseases, immune-mediated diseases and others [10–12].

Due to the likely impact of intestinal dysbiosis on the increase in intestinal permeability [2], environmental factors influencing the quantitative and qualitative composition of the intestinal microbiota are a subject of research aimed at understanding the prevention and management of RA.

PHYSIOLOGICAL FACTORS OF MICROBIOTA DEVELOPMENT

Microbiological colonization in early life by programming immune reactivity may affect human health in later life and its disturbances may be associated with the development of many non-communicable diseases [13]. It is assumed that the process of microbial colonization may already take place in the prenatal period through the microbiota present in the placenta and amniotic fluid [14]. Both in the prenatal and neonatal periods, a large role is assigned to maternal factors [15–17]. Antibiotic therapy used during pregnancy and the early postpartum period, obesity, improper diet and chronic diseases of the mother can be distinguished among the negatively influencing maternal factors.

Evidence emphasizes the key importance of the first 1000 days of life in the microbial colonization of a child influencing the development of immune tolerance by maintaining the balance between Th1 and Th2 lympho-

cytes [15, 17]. The type of delivery by caesarean section, the hospital environment in which the child is born, a method of feeding the child other than mother's milk, perinatal and postnatal antibiotic therapy, less numerous siblings, increased hygiene regime, less contact with natural human environment can be enumerated among the factors adversely affecting the microbiological colonization of a child [17, 18].

Both the route of delivery responsible for the unique colonization of microorganisms, as well as environmental selection through the supply of selective substrates, for instance, found in natural milk, shape the microbiome of infants [13]. Another important time point is the period of solid food introduction, followed by a relatively stable gut ecosystem [18]. Kaczmarczyk et al. [19] observed dynamic changes in the composition of the intestinal microbiota when assessing the gut microbiota and the concentration of zonulin (a marker of paracellular permeability) and calprotectin (a marker of the development of the immune system) in the stools of children from the neonatal period to the second year of life. The increasing concentration of zonulin in the faeces up to the sixth month of life was inversely correlated with the concentration of calprotectin in this period. The key role of this time point in the formation of the intestinal barrier and the development of postpartum immunity was emphasized.

Many studies look for the influence of environmental factors present in early life that affect health later in life. An interesting observation was revealed in an analysis of 14 clinical trials from 1926–2017 in breastfed children over the last century. A generational change was shown in faecal pH from 5.0 in 1926 to 6.5 in recent years, associated with a decrease in the number of *Bifidobacterium* bacteria correlated with a change in faecal pH [20]. It was highlighted that there was a strong influence of environmental factors on the intestinal microbiome of human beings living in highly industrialized countries possibly affecting the development of dysbiosis and its further consequences. As evidence accentuating the importance of first-time colonization of mucosal microbiota, Andersen et al. [21] showed an increased risk of chronic inflammatory diseases (diabetes, celiac disease, RA and chronic inflammatory bowel diseases) at least 40 years after delivery by caesarean section compared to natural delivery.

In addition, it is speculated that microbiological modulation using probiotic therapy in the neonatal and baby period may have an impact on autoimmune processes and neurodevelopmental disorders. It has been shown a 60% reduction in the risk of autoimmunity in the first year of life for children with the highest risk of developing type I diabetes (genotype HLA-DR3/4) who were supplemented with probiotics up to 27 days of life [22] and neurodevelopmental disorders (including attention deficit hyperactivity disorder and Asperger's syndrome) at the age of 13 in children receiving probiotics up to 6 months of life [23].

To sum up, the evidence points to a crucial role of microbial colonization in early life. It seems that factors disturbing its physiological course may influence the development of inflammatory diseases in later life.

OTHER FACTORS INFLUENCING THE MICROBIOME AND INTESTINAL PERMEABILITY

The factors affecting the human microbiome include diet, physical activity, medications administered, especially antibiotics and proton pump inhibitors and others [4, 24]. The gut microbiota is believed to be involved in maintaining the integrity of the intestinal epithelium [4]. The factors related to the increased permeability of the intestinal barrier, also concern disruption of the circadian rhythms and abnormal vitamin D levels [25–27].

It is estimated that diet is considered the factor with the strongest influence on the gut microbiome [28]. As early as 2009, using an animal model, it was shown that changing the macronutrients of the diet can alter the composition and function of the gut microbiome within one day [29]. Subsequent reports confirm the validity of the above findings in relation to the human gut microbiome, emphasizing the role of diet in the context of human health [30]. The reduction of systemic inflammation is attributed to a diet based on high-fibre plant products, including whole grains, fruit and vegetables [31]. The role of short-chain fatty acids (SCFA) as metabolites of bacterial fermentation of dietary fibre can be emphasized. SCFAs are involved in maintaining the tightness of the intestinal barrier by increasing the production of mucin, an energy source for colonocytes (trophic effect on the function of the intestinal epithelium), inhibiting the growth of intestinal pathogens, and increasing the absorption of nutrients [32]. In addition, the beneficial metabolic effect of SCFAs was demonstrated, reducing insulin resistance and obesity in the

animal model [33], as well as the anti-tumour activity of SCFAs in the inhibition of histone deacetylase in the cell nucleus. Inhibition of histone deacetylase has a positive effect on the expression of genes that regulate cell functions such as apoptosis and cell proliferation [34]. The role of moderate physical activity has been described as another beneficial factor in terms of the diversity and richness of the gut microbiota [24]. It should be noted, however, that excessive, strenuous physical activity may increase intestinal permeability.

Another factor that may exert a beneficial effect as well as promote intestinal dysbiosis are widely used antibiotics [35]. It was found that exposure to macrolides in 2–7-year-old Finnish children was associated with a long-term alteration in the composition and function of the intestinal microbiota. It has also been shown that the use of macrolides in the first two years of life predisposes the development of asthma and obesity in later life [36]. On the other hand, when examining the composition of the intestinal microbiota of adults receiving two courses of ciprofloxacin, it was observed that the composition of the microbiota was gradually stabilized after antibiotic therapy, but with no return to the same initial composition [37].

On the contrary, the beneficial effect of antibiotic therapy was evidenced by rifaximin administration in patients with inflammatory bowel diseases [38]. In those patients, antibiotic therapy promoted eubiosis by eliminating pathobionts and supported the growth of beneficial bacteria. To sum up, the obtained effect of antibiotic therapy may have far-reaching effects related to the change in the composition of the intestinal microbiota, and the significance of these changes may play a particular role in the early stage of life.

The next reported factor concerns drugs commonly used in the field of gastroenterology, from the group of proton pump inhibitors. Proton pump inhibitors appear to influence intestinal dysbiosis and the survival and migration of bacteria from the oral cavity to the lower gastrointestinal tract by long-term reduction of hydrochloric acid secretion and a change in gastric pH [39].

To conclude, many modifiable factors affect the gut microbiome and gut integrity in the long term, the mechanisms of which are different, and often complex. Proper dietary counselling, adequate sleep hygiene while maintaining the circadian rhythm, moderate physical activity and adequate exposure to UV radiation seem to be important in the context of the prevention of chronic inflammatory diseases in genetically predisposed individuals. The attempt to modulate the intestinal microbiota may be important in improving the function of the intestinal barrier and constitute a starting point for further research on the development and course of chronic inflammatory diseases.

INTESTINAL MICROBIOTA AND RHEUMATOID ARTHRITIS

A potential relationship between the pathogenesis of arthritis and the gut microbiota was suggested for the first time in 1979 by Kohashi et al. [40]. The authors published the results of a study indicating the occurrence of a more severe form of arthritis in germ-free rats compared to conventional rats. It is currently assumed that dysbiosis may be related to the loss of immune tolerance and the progression of autoimmunity [41].

The clinical phase of RA is preceded by the early development phase of RA, in which the characteristic RF and/or ACPA antibodies may be present in the blood serum. Autoimmunity associated with the presence of ACPA and/or RF antibodies can be a reversible condition that leads to chronic autoimmune disease through the action of additional factors [42]. Autoantigens in RA belong to post-translationally modified proteins such as citrullinated proteins. Post-translational modifications are believed to be of key importance for the function and antigenicity of proteins [9]. Citrullination is associated with the conversion of arginine to citrulline catalysed by the enzyme peptidyl arginine deiminase (PAD). ACPA are relatively the most specific markers of RA and may correlate with disease activity [43]. Other reported post-translational modifications related to RA include carbamylation, glycosylation, and acetylation [43]. Increasing the expression of PAD can be stimulated by various environmental factors, such as smoking. The effect of cigarette smoke on the induction of RA in genetically susceptible mice has been demonstrated [44]. The role of environmental and lifestyle factors was also highlighted in a study of 12 590 twins which found that the presence of ACPA was not synonymous with the development of arthritis in all ACPA-positive individuals [45]. It has been suggested that RA-specific immune responses may originate

in extra-articular locations related to the intestinal mucosa and/or the oral cavity and/or the respiratory system [46].

Damage to the structure of the mucosa may trigger an immune reaction with local inflammation and in some cases lead to a systemic inflammatory response. The correlation between changes at the mucosal level and the etiopathogenesis of RA was confirmed by the Kelmenson et al. [47] cohort study, which found RF IgA already 14.2 years before the onset of clinical symptoms of the disease, and ACPA IgA 6.2 years.

In 2013, Scher et al. [48] found the presence of *Prevotella copri* (*P. copri*) bacteria in the gut microbiota of newly diagnosed, untreated RA compared with chronic, treated RA, healthy controls and patients with psoriatic arthritis. Moreover, they noticed a decrease in the number of bacteria of the genus *Bacteroides* in this group of patients. Maeda et al. [49] in their work confirmed the role of dysbiosis as an environmental factor in the development of arthritis in genetically susceptible mice. Transfer of *P. copri* dominated gut microbiota of RA patients to genetically susceptible mice resulted in severe arthritis following injection of zymosan compared to mice transferred by microbiota from healthy individuals. In another study by Kishikawa et al. [50] when examining the intestinal microbiome of RA patients, they showed the presence of other species belonging to *Prevotella spp*. A statistically significant increase in the number of *Prevotella spp.* was also revealed in the preclinical stage of RA [51]. An interesting observation published by Marietta et al. [52] concerns the different effects of various species within the genus *Prevotella*. *Prevotella histolitica* (*P. histolitica*) has been shown to have an inhibitory effect on joint inflammation. The administration of *Prevotella histolitica* decreased the permeability of the intestinal epithelium by increasing the expression of tight junctions — zonulin-1 and occludin.

In another study, Chen et al. [53] showed the expansion of *Eggerthella*, *Collinsella*, and *Faecalibacterium* in stool samples of RA patients, and revealed a relationship between an increased amount of *Colinsella* bacteria and increased permeability of the intestinal epithelium probably resulting from the induction of pro-inflammatory IL-17 expression.

Zhang et al. [54] identified the presence of dysbiosis in both the intestinal microbiome and the oral cavity of RA patients compared with healthy individuals, suggesting that the composition and function of the microbiome are consistent in different parts of the body. The obtained results correlated with clinical indicators such as C-reactive protein (CRP), ACPA and RF concentration. Moreover, they showed an increased amount of *Lactobacillus salivarius* in a very active form of RA.

Interestingly, Forbes et al. [55] showed the presence of differences in the composition of the gut microbiome in patients with RA, Crohn's disease, ulcerative enteritis and multiple sclerosis compared to individuals in the control group, pointing to the potential role of the gut microbiota as a biomarker in the diagnosis of chronic inflammatory diseases.

Manfredo Vieira et al. [56] revealed the presence of bacterial nucleic acids in the synovial tissue and synovial fluid of patients presenting the role of the migration of pathobionts through the unsealed intestinal barrier, colonization of distant tissues and the possibility of inducing organ-specific immune responses. Zhao et al. [57] confirmed the presence of bacterial nucleic acids in the synovial tissue and synovial fluid of RA patients, as well as showed differences in the composition of bacterial genetic material concerning patients with osteoarthritis. Furthermore, Hammad et al. [58] identified bacterial DNA in the blood samples of RA patients that differed from DNA in controls, ankylosing arthritis and psoriatic arthritis, highlighting the role of the proper intestinal barrier in preventing bacterial translocation and stimulation of the immune system.

Xu et al. [59] speculated that there is a relationship between alleles of human leukocyte antigens (HLA) and the gut microbiome. They suggested that the composition of the gut microbiome may be dependent on the host's immune system, which is partially regulated by HLA. Moreover, the pro-inflammatory environment created by pathobionts may result from the metabolic function of microorganisms, as opposed to the direct species composition. Asquith et al. [60] confirmed the relationship between the HLA-DRB1 alleles associated with the risk of RA and the altered composition of the gut microbiota in healthy individuals, suggesting a potential for therapies targeting the gut microbiome to prevent the development of RA symptoms.

In another study, Pianta et al. [61] identified two autoantigens N-acetylglucosamine-6-sulfatase and filamine A, which

were highly expressed in the synovial tissue of joints of RA patients. The above peptides presented by HLA-DR showed sequence homology with protein epitopes of *Prevotella spp.* suggesting a cross-mechanism of specific T-response stimulation and a possible relationship between inflammation of the intestines and joints.

In conclusion, numerous research evidenced the development of intestinal dysbiosis in patients with RA. Its influence on the pathogenesis of RA remains unclear but it is suggested to be a component of complex mechanisms of the development of a clinically overt RA. The characteristic differences in the composition of the gut microbiota may play a role of a biomarker in diagnosing the disease at an early stage of development and constitute a starting point for further studies on the modulation of the gut microbiota as a method of disease prevention. Moreover, the improvement of the intestinal barrier function may be a tool in clinical practice that can be used to alleviate the course of the disease.

ATTEMPTS TO IMPROVE THE INTESTINAL BARRIER FUNCTIONS

The factors contributing to the improvement of the function of the intestinal microbiota and the strengthening of the intestinal barrier include, among others, dietary interventions, the use of prebiotics ("a substrate that is selectively utilized by host microorganisms conferring a health benefit" [62]), probiotics ("live microorganisms which when administered in adequate amounts confer a health benefit on the host" [63]), synbiotics (probiotics containing prebiotic components), as well as disease-modifying antirheumatic drugs (DMARDs).

The role of DMARDs in the partial restoration of eubiotic intestinal microbiota was emphasized. The use of methotrexate and hydroxychloroquine was associated with increased microbial richness and diversity, however, the exact mechanism of the medication-modulating effect on the microbiota remains unclear [53, 64]. Moreover, Picchianti-Diamanti et al. [65] observed a partial restoration of beneficial gut microbiota during the use of etanercept. Another study demonstrated the antimicrobial activity of sulfasalazine and gold salt against a broad spectrum of oral pathogens in RA patients, as well as methotrexate which acted on some bacterial species [66].

The impact of diet on the homeostasis of the intestinal microbiota was confirmed by Häger et al. [67]. The authors conducted a study evaluating the effect of a high-fibre diet in patients with RA. After 28 days of intervention, they observed an increase in the number of Treg, an increase in the Th1/Th17 ratio, a decrease in total IgA and IgA1, a decrease in the amount of bone resorption marker as well as an improvement in the patient's quality of life. Moreover, serum calprotectin and zonulin concentrations decreased significantly. The importance of dietary interventions and a statistically significant improvement in disease activity determined with the DAS28-ESR scale were also described concerning the Mediterranean diet, emphasizing the role of monounsaturated fatty acids [68].

The use of probiotics may be another example of an attempt to improve intestinal barrier function. Administration of a mixture of probiotics (*Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum*) in RA patients in an 8-week intervention was associated with an improvement in disease activity (estimated with the DAS-28 scale), insulin levels, HOMA-B and CRP levels [69]. In another study, using an animal model, the beneficial role of the supply of a probiotic (*Lactobacillus casei*) was evidenced to reduce intestinal dysbiosis and the severity of arthritis symptoms [70]. A meta-analysis confirmed a significant effect of the use of probiotics/synbiotics on the reduction of serum zonulin levels [71]. Furthermore, there are studies assessing the effect of the simultaneous use of diet and synbiotics. Supplementing *Bifidobacterium spp.* in combination with *Lactobacillus spp.*, fructooligosaccharides (FOS) and inulin in obese patients resulted in a decrease in faecal zonulin concentration after three months of the investigation [72].

To sum up, factors modulating the intestinal microbiota and regulating the functions of the intestinal barrier remain a subject of intense research, although the problem is found to be very complex. It seems that the important issue is the length of the intervention and the time point of its introduction. Further eating habits are likely to be one of the key aspects of maintaining eubiosis.

CONCLUSIONS

Microbiota, its influence on the integrity of the mucosal barrier and its potential role in the stimulation of the immune system in

genetically predisposed individuals is so far a partially understood subject that may play a significant role in the development, diagnosis and treatment of many inflammatory diseases. The characteristic configurations known as "microbial fingerprints" can create a new personalized approach to detecting autoimmune diseases at an early stage of their development [73]. In addition to their role as potential biomarkers concerning disease phenotype, they can be used to predict drug response, bioavailability as well as drug toxicity. The assessment of markers of intestinal permeability may be a potential clinical tool used to monitor the severity and predict disease exacerbation.

Further research is needed to elucidate the impact of microbiota modulation as a method of regulating the permeability of the intestinal barrier, modulating the immune reactivity and indirectly affecting the development and progression of RA.

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