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REVIEW

Manipulation of the gut microbiome may be a promising pathogenic approach in rheumatic inflammatory diseases – A review

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Abstract: *A symbiotic association between humans and microbes has been established over time. Disruptions in gut homeostasis have been linked to immune-mediated inflammatory diseases.*

Factors such as genetics, environment, diet, age, and medication play a major role in shaping the intestinal microbiome. An altered gut microbiome seems to modulate the progression and severity of inflammatory rheumatic diseases. Disruptions in the eubiotic state of the intestinal microbiome might promote intestinal and extraintestinal autoimmune and inflammatory disorders, although the mechanisms involved are not well understood.

In this review, we provide a general overview of several studies concerning intestinal microbiome perturbations and their implications in rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus. Furthermore, we discuss the relationship between diet, intestinal microbiota, and inflammation.

Keywords: *intestinal microbiome, intestinal dysbiosis, probiotics, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus*

INTRODUCTION

The human digestive tract is inhabited by somewhere between 300 and 1000 different species of bacteria. Microorganisms like bacteria, yeast, and viruses compose the gut microbiota. Bacteria are classified into phyla, classes, orders, families, genera, and species. [1]

There are four dominant bacterial phyla: Bacteroides spp., Firmicutes spp., Actinobacteria spp., and Proteobacteria spp. The Firmicutes phylum contains more than 200 genera such as Lactobacillus spp., Bacillus spp., Clostridium spp. (95% of the Firmicutes), Enterococcus spp., and Ruminicoccus spp. The Bacteroidetes phylum consists of predominant genera such as Bacteroides and Prevotella. Actinobacteria phylum is less abundant and represented by the Bifidobacterium genus. [2]

The relationship between humans and gut flora is a symbiotic one. The microbial colonization occurs before birth and stabilizes around the age of three. The intestinal microbiome has various roles: fermentation and degradation of dietary fibers, modulation of antibody production, defense against pathogenic bacteria colonization, production of vitamins, and maintenance of intestinal epithelium integrity.

The most important end products of microbial fermentation processes are short-chain fatty acids (SCFA), acetate, propionate, and butyrate. These molecules promote the immunity of the intestinal mucosa and protect it from pathogens. [3]

Only 1% of bacteria can be grown in cultures. New

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techniques like the extraction of DNA and the amplification of the 16S ribosomal RNA gene (rRNA) allowed researchers to analyze nucleic acids (DNA and RNA) from the stool. The Human Microbiome Project (HMP) focused on identifying, studying, and cataloging uncultivated bacteria.

The intestinal microbiome is influenced by diet and the environment. People who eat more carbohydrates and simple sugars have more Prevotella, while Bacteroides are associated with saturated fats and proteins. Plant-based diets are associated with a greater abundance of Prevotella and a greater diversity of microbes [4, 5].

It is believed that high-fiber diets ameliorate autoimmune, metabolic, and allergic diseases mainly through their microbiota dependent fermentation to SCFAs that promote tissue barrier integrity, mucus production, immune serum globulin (IgA) secretion, and regulatory lymphocyte T (Treg) differentiation, sustaining an anti-inflammatory environment [6].

Some microbes, such as Bacteroides fragilis, can drive the immune system to create anti-inflammatory cytokines while some segmented filamentous bacteria favor the production of pro-inflammatory cytokines. Bacteroides promote the production of immuno-regulatory T cells that suppress immune responses to self and bacterial antigens and stimulate epithelial repair. [7]

Manipulation of the intestinal microbiota through diet and probiotics may be the target for future strategies and preventive interventions in rheumatic diseases.

METHODS

Relevant literature relating to the gut microbiome and autoimmune diseases was selected through searching online medical databases. Search terms used were: “intestinal microbiome”, “gut microbiota”, “intestinal dysbiosis”, “manipulation of the gut microbiome”, “rheumatic diseases and intestinal microbiome”, “probiotics”. Only English-written studies published from 2011 to date were selected and analyzed.

RHEUMATOID ARTHRITIS (RA)

Rheumatoid arthritis is a chronic, autoimmune disease that primarily affects joints and the first study that links intestinal microbiome to arthritis was published in the late 1970s, suggesting that bacterial flora may be a stimulus for induction of cell-mediated immunity and may also have suppressive effects on the disease evolution. [8]

The patient microbiome plays a big role in the progression of rheumatoid arthritis. Together with the lymphoid tissue, the microbiome helps maintain immune homeostasis. Changes at this level can damage the intestinal mucosa and the systemic immune system, triggering the onset of autoimmune diseases.

Using zonulin as a serological marker, some recent studies have demonstrated the increased gut permeability in rheumatoid arthritis patients. This finding has been shown in about 1/3 of pre-RA patients. [9]

In rheumatoid arthritis, studies have shown that patients present a dysbiotic state, with the depletion of gram-negative bacteria and an increase of gram-positive bacteria. Furthermore, these patients present a higher concentration of Collinsella and Eggerthella lenta than normal individuals. [10]

As well, these patients have a high level of Prevotella copri and a low level of Bacteroides. P. copri pathogenicity was explained through its capacity of stimulating Th1 cells. Some patients produce antibodies against P. copri (IgA, IgG). Moreover, an over-abundance of P. copri has been identified in individuals at risk of rheumatoid arthritis (patients without arthritis but anti-citrullinated protein antibody – ACPA/ rheumatoid factor – RF positive). [11, 12, 13]

A study showed that a Prevotella strain, Prevotella histicola, suppresses arthritis in humanized HLA-B27 mice. [14] P. histicola treatment can reduce pain and improve motor function as a response to an increase in T regulatory cells and a decrease in IL-6 levels. [15]

Lactobacillus salivarius is more abundant in rheumatoid arthritis patients but its effects are unclear. Administration of L.salivarius in mice showed a significant improvement of collagen-induced arthritis and it may help reduce interleukin-17 and increase anti-inflammatory interleukin-10. Thus, it may help reduce clinical manifestations in RA patients. [16]

A study conducted on 60 women with rheumatoid arthritis, showed the beneficial role of Lactobacillus casei. Used as adjuvant therapy, it reduces the symptoms, lowers the pro-inflammatory cytokines, and lowers serum C - reactive protein and DAS28 score. [17]

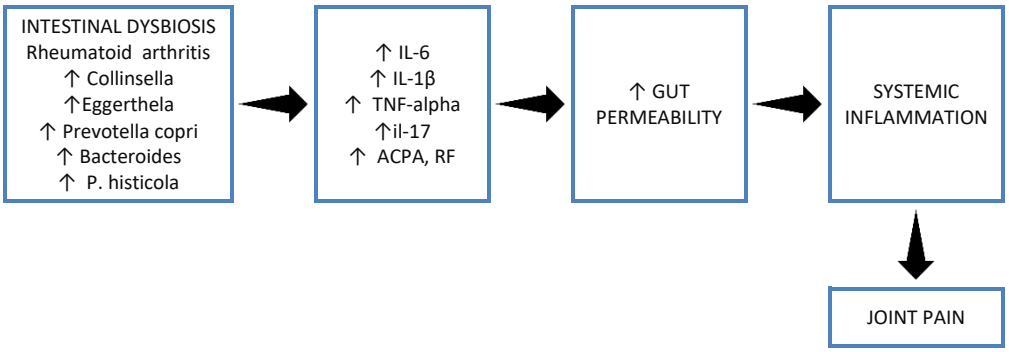
A more recent study, conducted on P. histicola treated mice, showed a decrease in the incidence and severity of arthritis. P. histicola decreases the intestinal permeability and lowers the pro-inflammatory IL-17 cytokine and increases IL-10. [14] Because P. histicola is normally present in the gut, the treatment as a probiotic in humans is beneficial, with minimum adverse effects.

A study conducted in China found a greater abundance of

Enterobacteriaceae spp. and Klebsiella spp. and a lower abundance of Bifidobacterium spp. in rheumatoid arthritis patients with high levels of TNF-α or IL-17A. Moreover, ACPA-positive patients had a greater abundance of Blautia spp., Akkermansia spp. and Clostridiales spp. then patients with negative ACPA. In conclusion, patients with RF/ACPA seropositivity exhibited a different microbial composition than RF/ACPA negative patients, suggesting an association between intestinal microbiome alteration and disease activity. [18]

Porphyromonas gingivalis, a periodonthopathogenic bacteria that exist in dental plaque can be swallowed with saliva and can affect the composition of the gut microbiome. Several studies have shown a strong correlation between P. gingivalis infection and systemic disease. Intestinal dysbiosis by oral inoculation of P. gingivalis has been shown to contribute to the progression of arthritis. [19, 20]

Figure 1: Associated microbiome in rheumatoid arthritis



Rheumatoid arthritis treatment and intestinal microbiota

The use of disease-modifying anti-rheumatic drugs (DMARDs) can modulate the intestinal microbiome and has the potential to shift the intestinal flora towards a healthy microbiome.

Two studies showed a significant decrease in Bacteroides fragilis and an increase in Prevotella maculosa after treatment with Methotrexate (MTX). Dysbiosis associated with RA was partially resolved after treatment. [21, 22] Another study suggests that patients that were treated with Methotrexate showed increased species richness and diversity compared to other patients receiving different treatments. [23] These studies suggest that MTX could correct intestinal dysbiosis.

Some studies concluded that pharmacological treatment in rheumatoid arthritis increased the Firmicutes and Bacteroidetes phyla. MTX induced a significant growth in Firmicutes over the Bacteroidetes that was associated with improved drug response and reduced inflammation. [24, 25] In a study conducted in 2018, the microbial profile of Etanercept treated patients (in monotherapy or combination with Methotrexate) was compared to normal individuals. There has been reported a significant decrease of Faecalibacterium compared to healthy individuals. In Etanercept treated patients there has been reported a great abundance of Cyanobacterium compared to patients without treatment.

Some species of Cyanobacterium produce some metabolites and bioactive substances that have cytotoxic properties and are involved in gastroenteritis. On the contrary, some metabolites have anti-inflammatory and immunosuppressive properties that are beneficial in rheumatoid arthritis. [26]

ANKYLOSING SPONDYLITIS (AS)

Ankylosing spondylitis is a chronic, autoimmune disease characterized by long-term inflammation of the sacroiliac joints and spine with or without HLA-B27. But the most important genetic factor in ankylosing spondylitis, HLA-B27, could change the intestinal microbiome, contributing to multisystemic inflammation and the production of IL-23 and other proinflammatory cytokines.

HLA-B27 positive patients had changes in Faecalibacterium prausnitzii, Bacteroides vulgares, and Akkermansia muciniphila. An abundance of Bacteroides vulgatus has been discovered in HLA-B27 rats, suggesting that HLA-B27 may alter the intestinal microbiome composition. [27]

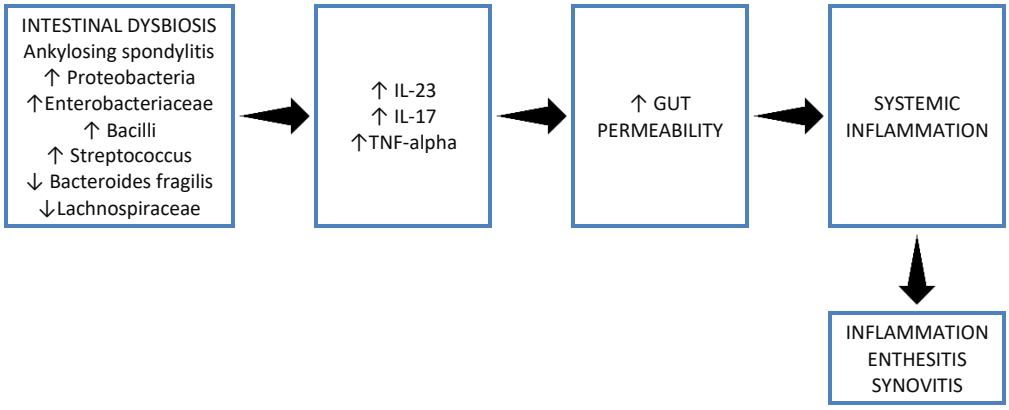
In ankylosing spondylitis, 87% of the patients have an altered microbiome (dysbiosis). Their microbiome was characterized by an abundance of species of Proteobacteria spp., Enterobacteriaceae spp., Bacilli spp., Streptococcus spp., Actinobacteria spp. and a low number of Bacteroides and Lachnospiraceae. [28] Dysbiosis is also associated with disease activity.

Akkermansia muciniphila, of the phylum Verrucomicrobia spp., resides in the mucus layer of the large intestine. It is implicated in maintaining intestinal integrity and can cause the degradation of the mucin in the gut epithelium. [29]

Prevotella can increase Th17-mediated immune response in the intestinal mucosa. Increased Prevotella abundance stimulates the production of IL-1, IL-6, IL-8 and also stimulates neutrophil recruitment. The mucosal inflammation caused by Prevotella leads to systemic dissemination of inflammatory mediators and promotes chronic inflammation. [30]

Some microbes, such as Faecalibacterium prausnitzii, administered to mice, have been found to protect them against induced intestinal inflammation, thus concluding that F. prausnitzii has anti-inflammatory effects. [31] A decreased abundance of F. prausnitzii was observed in fecal samples of patients with ankylosing spondylitis. [28, 32]

Figure 2: Associated microbiome in ankylosing spondylitis



Ankylosing spondylitis treatment and intestinal microbiota

Patients with ankylosing spondylitis treated with biological treatment have shown a greater abundance in Proteobacteria spp. (especially the Enterobacteriaceae family) and Veillonella genus compared to patients without treatment. [33]

A perturbation of the intestinal fungal microbiome (mycobiome) has been observed in patients with ankylosing spondylitis after biological treatment. An increase in the abundance of Saccharomycetales was found after anti-TNF and anti-IL17 treatment. [34]

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic lupus erythematosus is an autoimmune disease that is characterized by severe inflammation that can affect almost all organs of the body. Lopez et al. observed the influence of the microbiota over T lymphocyte differentiation in healthy and SLE groups. These authors found a rise in lymphocyte activation and differentiation toward Th17 in SLE patients. [35]

There were some studies on SLE patients which demonstrated that the abundance of Firmicutes is decreased and that of Bacteroidetes is increased compared to healthy control groups. If the intestinal epithelial barrier is damaged, Enterococcus gallinarum and Lactobacillus reuteri, possible gut pathobionts, can translocate into the systemic tissue, inducing autoantibody production. In addition, Ruminococcus gnavus can trigger an anti-double-stranded DNA antibody response. [36, 37]

A study conducted in Spain has proved that there is a gut microbial dysbiosis related to SLE in Caucasian female patients. SLE patients developed intestinal dysbiosis with a decrease within the Firmicutes spp. and a rise in the Bacteroides spp. It also showed that SLE patients with inactive lupus disease had significantly lower Firmicutes/ Bacteroidetes ratios than healthy control individuals did. [38]

A study conducted by Van der Meulen et al also showed that in SLE patients, the intestinal microbiota composition is characterized by lower bacterial richness, lower Firmicutes/ Bacteroidetes ratio, and a greater abundance of Bacteroides species. [39]

Similarly, a study by Greiling et al concluded that the Firmicutes/Bacteroidetes ratio in SLE patients decreased compared to healthy controls. In addition, commensal bacteria which contain Ro60 orthologs could induce the production of autoantibodies that cross-react with human Ro60, therefore triggering autoimmune diseases like SLE. [40, 41]

On the contrary, a study concluded that Firmicutes/

Bacteroidetes ratio is not significantly different between SLE patients and healthy controls. Also, this study concluded that Gram-negative bacteria, like Proteobacteria spp. and Blautia spp. were increased and Odoribacter spp. was decreased in SLE patients. [42]

A study explored whether the alteration of the intestinal microbiome in SLE patients from China was according to the intestinal dysbiosis of SLE patients from Spain. The depletion of Firmicutes spp. and the abundance of Bacteroidetes spp. in SLE patients from China was in keeping with the SLE patients from Spain. This study also showed that nine genera of intestinal microbiota were SLE-related microorganisms: Rhodococcus spp., Eggerthella spp., Klebsiella spp., Prevotella spp., Eubacterium spp., Flavonifractor spp. and Incartae spp. sedis were found in great abundance but Dialister spp. and Pseudobutyrivibrio spp. were depleted in SLE subjects. These nine genera have the potential to distinguish SLE patients from healthy controls. Also, the gut microbiome profiles of SLE patients were found to be more influenced by disease than ethnicity. [43]

Another study conducted in China concluded that the genera Streptococcus spp., Campylobacter spp., Veillonella spp. and the species Anginosus spp. and Dispar spp. were in direct correlation to lupus activity, while the genus Bifidobacterium spp. was in negative correlation to the disease activity. [44]

A study conducted in New York, on SLE female patients, investigated the fecal microbiota for possible pathobionts. Patients with a high disease activity index had a greater abundance of Ruminococcus gnavus. The highest levels of serum anti-Ruminococcus gnavus strain-restricted antibodies were found in patients with active nephritis. These findings showed evidence of altered fecal commensal taxa and increased immunoglobulin levels and other biomarkers, as evidence of altered gut barrier function. The study concluded that some strains can contribute to the immunological pathogenesis of lupus nephritis. [45]

Treatment with probiotics composed by Lactobacillaceae members has been used as anti-inflammatory therapy. Studies found the up-regulation of anti-inflammatory cytokine genes and down-regulation of the pro-inflammatory ones.

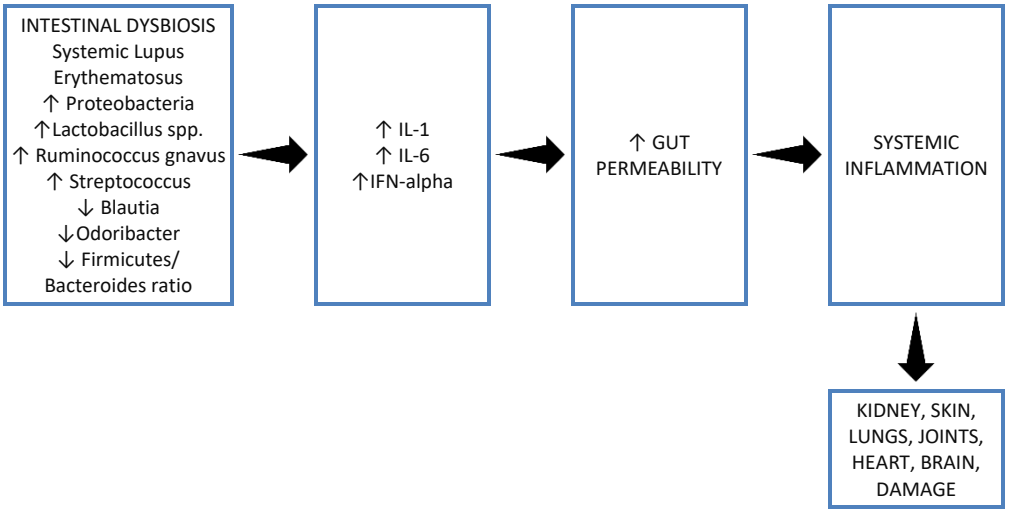
Moreover, the probiotic-treated group exhibited higher anti-oxidant activities and low levels of lipid peroxides. CRP levels were found to be in the normal range in comparison with the untreated group which levels were elevated.

Immunohistochemistry found high levels of IL-10 and low levels of IL-6, demonstrating the anti-inflammatory properties of L. mucosae and L.fermentum. [46, 47]

Lactobacillus rhamnosus and Lactobacillus delbrueckii have been found beneficial in the management of newly diagnosed SLE patients. [48] L. rhamnosus stimulates IL-12 and IL-10 production. Moreover, it secretes soluble factors that decrease TNF-α production, a potent pro-inflammatory cytokine. [49]

Although there is still no clarity about the role of microbiota within the development of SLE, the evidence suggests that the dysbiosis observed within SLE patients might be associated with this disease.

Figure 3: Associated microbiome in systemic lupus erythematosus



Systemic lupus erythematosus treatment and intestinal microbiota

Nonselective immunosuppressive therapies, like Dexamethasone and azathioprine, in SLE patients, may have vast effects on the intestinal microbiome. It is believed that at the same time as immunosuppressive medications are acting directly onto suppressing inflammation, these medications can also help in the formation of a microbiome that promotes the regulation of local inflammation within the bowels and potentially at distant sites within the body. A study showed that the gut microbiota tended to be more diverse after Dexamethasone treatment. Also, a greater abundance of lactobacilli was found after the treatment with Dexamethasone. [42]

On the contrary, no significant results were found between gut microbiota and methotrexate use in a recent study within the British TwinsUK cohort. [39] Chloroquine and hydroxychloroquine are reported to inhibit the intracellular growth of bacteria in vitro, but these drugs do not seem to own any antibacterial activity or effect on extracellular bacterial growth. Regarding the use of NSAIDs, a study observed no significant effect on the gut microbiome. Also, oral corticosteroid use didn't significantly affect the gut microbiome. [50]

DIET

Diet and the intestinal microbiota may be the target for future treatments and preventive interventions in rheumatic diseases. Diet can modulate the symptoms in rheumatoid arthritis through the metabolites produced by the intestinal microbiome. The intestinal microbiome has the capacity of modifying the circulating pro and anti-inflammatory mediators. [51]

Western diets are characterized by increased consumption of refined carbohydrates, red meat, and salt, which can induce a pro-inflammatory state and trigger the onset of autoimmune diseases. [52, 53]

Patients with a positive rheumatoid factor or anti-citrullinated protein antibody had a decreased concentration of omega-3 fatty acids in the red blood cell membranes, suggesting the potential beneficial effect in individuals with genetic susceptibility to rheumatoid arthritis. [54]

Some studies suggest that there might be a link between high salt consumption and the increasing incidence of autoimmune diseases, especially rheumatoid arthritis. A high concentration of sodium chloride can induce the activation of some signaling pathways, the activation of Th1, the overproduction of pro-inflammatory cytokines (IFN-gamma, IL-17), and the differentiation of macrophages. [55, 56]

For example, trimethylamine-N-oxide, a pro-inflammatory metabolite that derives from choline and carnitine, found in red meat, eggs, and dairy, is produced by Prevotella copri. [57][58]. Prevotella copri was found in great concentrations in newly diagnosed patients with rheumatoid arthritis. [59]

Probiotic use of Lactobacilli spp. improves intestinal immune function and stimulates anti-inflammatory cytokines (IL-10).

In general, Lactobacillus spp. and Bifidobacterium spp. are considered beneficial. Both species produce catabolites that decrease intestinal permeability and have anti-inflammatory and antioxidant properties, with the enforcement of the intestinal barrier function. Fermented foods that contain Bifidobacterium spp. and Lactobacillus spp. genera can have a protective role against immune-mediated diseases. [60]

A study evaluated the effects of L. casei supplementation on disease activity and inflammatory markers levels in rheumatoid arthritis females. A decrease in CRP, DAS28, and inflammatory cytokines was observed. [17]

The microbial degradation of complex carbohydrates will increase short-chain fatty acids that are beneficial for the intestinal immune response. [61] Several foods (highly refined flours, gluten, saturated and trans fats, red meat, dairy) have been identified as proinflammatory foods. Some vegetables as tomatoes, eggplants, and potatoes, contain solanine and increase intestinal permeability.

Foods high in omega 3 (chia seeds, flax seeds, sesame seeds, avocados), fruit that contain enzymatic proteins (pineapple, mango, papaya), turmeric, black pepper, green tea, and legumes offer multiple benefits.

To decrease inflammation, an ITIS diet has been suggested. It consists of a modified Mediterranean diet with several changes: the separation of carbohydrates and proteins, gluten-free foods, fruit with enzymes, and other anti-inflammatory foods mentioned above. [62]

A study regarding intestinal microbiome and Mediterranean diet observed that an increased ratio of Firmicutes/ Bacteroides was related to lower adherence to the Mediterranean diet. A lower animal protein intake was associated with an abundance of Bacteroides. Moreover, high consumption of sugars, saturated fats can affect the intestinal microbiota diversity. A plant-based diet was related to higher bifidobacterial counts. [63]

A case report discussing a fecal matter transplant (FMT) for a rheumatoid arthritis patient found that HAQ-DI (Health

Assessment Questionnaire – Disability Index) dropped seven days after FMT. [64] Therefore, fecal matter transplant may be an effective treatment for rheumatoid arthritis through the restoration of beneficial microbiota.

DISCUSSIONS

The treatment in rheumatology has made great advances with the potential to significantly impact the evolution of inflammatory diseases. A promising area of active research is the targeted manipulation of the microbiome to improve the outcome of rheumatic diseases.

The Fecal Matter Transplant in rheumatic diseases is not studied enough and more data is needed to achieve durable responses. Extensive donor testing is mandatory to guarantee patients' safety.

The use of prebiotics and probiotics can promote the growth of beneficial microbes. Probiotics supplements may be used as adjunctive therapy for rheumatic patients.

The microbiome composition can be used for prognosis and diagnosis, but most importantly, the manipulation of the intestinal microbiome through diet may be a promising future therapeutic approach. Large, long-term clinical trials are needed for specific dietary recommendations to rheumatic patients.

CONCLUSIONS

Current literature shows the link between the intestinal microbiome and the activity and severity of rheumatic diseases.

The imbalance of bacterial phylum, especially Firmicutes spp. and Bacteroidetes spp., is believed to be one of the most important causative factors for autoimmune diseases.

Although a lot of progress had been made in the past years regarding the intestinal microbiome, the research still requires more data. Targeted manipulation of the intestinal microbiome is needed for better treatment and management of inflammatory rheumatic diseases. Although 16S rRNA sequencing provides information about microbial identity, its function remains unknown.

Fecal matter transplant may have a good therapeutic effect on rheumatic diseases through its capacity of restoring and maintaining eubyosis.

Diet has been shown to influence the evolution and severity of autoimmune diseases. The use of pre and probiotics may be useful. The use of Lactobacillus species, as an adjuvant treatment, has been found beneficial.

Dietary or targeted manipulation of the intestinal microbiome may restore homeostasis and restrain disease-promoting pathobionts.

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