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## **The importance of diet, intestinal microbiome and physical activity in Rheumatoid Arthritis (RA) - Review**

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## ABSTRACT

### Introduction and objective

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic inflammation and joint damage resulting from an excessive production of inflammatory cytokines.

The objective of this text is to describe the interplay between the gut microbiome, dietary factors, physical activity and RA pathogenesis. By synthesizing current knowledge, we aim to provide potential insights into the development of personalized therapeutic strategies to improve outcomes for individuals with RA.

### Review methods

Literature review was carried out using PubMed, Scopus and Google Scholar databases. The following search terms were used: “rheumatoid arthritis gut microbiome”, “rheumatoid arthritis diet”, “rheumatoid arthritis sport”. Articles published from 2016 to 2023 were analyzed. Earlier articles were sometimes included, if referenced by later works.

### State of knowledge

While there is no cure for RA, several treatments aim to manage its symptoms and improve quality of life for those affected. The most common treatments include medications: nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, corticosteroids. Recent attention has turned to the role of sport, diet, and the gut microbiome in modulating RA severity, offering promising avenues for holistic management approaches.

## Summary

Recent research highlights the role of diet in modulating RA severity, with evidence suggesting alterations in gut microbiota composition in RA patients, including the impact of dietary interventions, probiotics, prebiotics, fecal microbiota transplantation, antibiotics, and vitamin D supplementation on the gut microbiome and their potential efficacy in mitigating RA-associated symptoms. Physical activity has also been shown to reduce the severity of RA symptoms.

Key words: rheumatoid arthritis, gut microbiome, “Mediterranean diet”, physical exercise

## INTRODUCTION

Rheumatoid arthritis (RA) stands as a paradigmatic autoimmune disorder, characterized by chronic inflammation and destructive joint pathology, affecting approximately 1% of the global population. This debilitating condition results from an intricate interplay of genetic predisposition and environmental triggers, leading to an aberrant immune response targeting synovial joints. Central to the pathogenesis of RA is the dysregulated activation of immune cells, particularly T lymphocytes, and synovial fibroblasts, accompanied by an excessive production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 $\beta$ ). (Edilova et al., 2021)

As our understanding of RA's complex etiology deepens, a myriad of therapeutic interventions has emerged, aiming to alleviate symptoms, halt disease progression, and enhance the overall quality of life for affected individuals. Despite significant therapeutic advancements, RA patients continue to face challenges associated with long-term disability and compromised joint function. (Ajeganova & Huizinga, 2017)

In recent years, the role of diet in modulating the course of rheumatoid arthritis has garnered increasing attention. While a definitive causative link remains elusive, accumulating evidence suggests that certain dietary patterns may contribute to the modulation of inflammation and disease activity. (Gioia et al., 2020) Omega-3 fatty acids, abundant in fatty fish and flaxseeds, exhibit anti-inflammatory properties that may attenuate the systemic inflammation observed in RA. (Lee et al., 2012) Conversely, a diet rich in saturated fats, prevalent in certain processed foods, has been associated with increased inflammatory markers, potentially exacerbating RA symptoms. (Patterson et al., 2012) The impact of specific diets, such as the Mediterranean diet,

characterized by its anti-inflammatory components, is currently under scrutiny for its potential benefits in ameliorating RA severity.(Oliviero et al., 2015)

#### BENEFITS OF GUT MICROBIOME:

The intricate interplay between the gut microbiome and the immune system is a dynamic and essential aspect of maintaining overall health. Within the gastrointestinal tract, trillions of microorganisms collectively form a complex ecosystem, influencing the host's immune responses through various mechanisms.(Velasquez-Manoff, 2015)

Commensal microorganisms contribute to immune modulation by producing bioactive molecules, such as short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. These SCFAs interact with immune cells like regulatory T cells (Tregs) and dendritic cells, fostering an anti-inflammatory milieu and contributing to immune homeostasis (Figure 1).(Morrison & Preston, 2016)

Additionally, the gut microbiome actively participates in educating the immune system through the presentation of microbial antigens. Dendritic cells in the gut mucosa capture these antigens, engaging with T cells in lymphoid tissues. This process plays a crucial role in developing immune tolerance, wherein the immune system recognizes commensal microbes as harmless and refrains from mounting unnecessary inflammatory responses.(Yang & Cong, 2021) Recent studies have also shown a link between gut microbiome and obesity, with a potential for therapies aimed at restoring microbial balance.(Liu et al., 2021)

Another critical role of the gut microbiome is in maintaining the integrity of the gut epithelial barrier, the first line of defense against invading pathogens. Commensal microorganisms contribute to barrier function by enhancing mucin production and reinforcing tight junctions between epithelial cells. A robust epithelial barrier prevents the translocation of bacteria and microbial products into the bloodstream, thereby averting systemic inflammation and potential autoimmune responses.(Duerkop et al., 2009) Furthermore, the overall composition and diversity of the gut microbiome have significant immunomodulatory effects. A balanced microbial community, characterized by diversity in bacterial species, contributes to a harmonious immune response. Conversely, dysbiosis, an imbalance in the microbial composition, has been associated with inflammatory and autoimmune conditions, highlighting the pivotal role of the gut microbiome in shaping immune function.(Kim et al., 2016)

## GUT MICROBIOME AND RHEUMATOID ARTHRITIS:

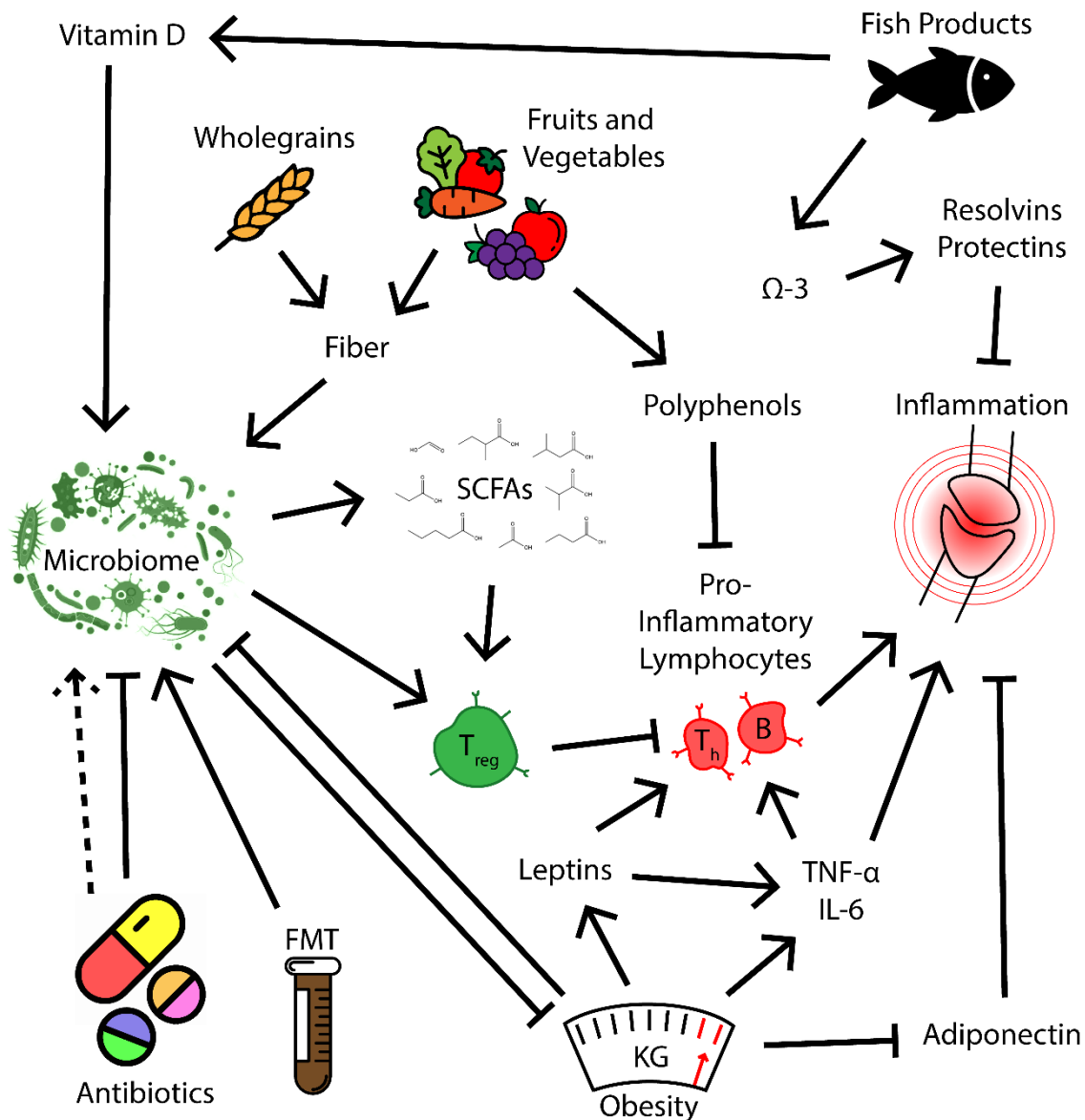
The complex interaction between the gut microbiome and the immune system is increasingly recognized as a critical element in the development of autoimmune conditions such as rheumatoid arthritis. Recent studies have indicated alterations in the composition and diversity of the gut microbiota in individuals with RA, suggesting a potential link between gut dysbiosis and disease development.(Horta-Baas et al., 2017)

While the intricate crosstalk between diet, gut microbiome, and RA pathogenesis continues to unfold, the exploration of these factors presents promising avenues for holistic approaches to managing and understanding the complexity of this autoimmune condition.(Dourado et al., 2020) As we delve deeper into the molecular intricacies of rheumatoid arthritis, the integration of dietary considerations and the modulation of the gut microbiome may prove essential in refining therapeutic strategies and improving patient outcomes.(Küçükdeveci, 2019)

Research on the microbiome in individuals with rheumatoid arthritis (RA) suggests the presence of altered gut microbiota and a potential link between RA development and intestinal dysbiosis.(Reyes-Castillo et al., 2021) However, there is limited published data addressing whether the observed intestinal dysbiosis in RA patients results from a complex interaction involving genetic susceptibility and environmental factors or is a consequence of systemic inflammation affecting the intestines.(Taneja, 2014) Recent clinical studies involving pre-clinical RA individuals, including those with autoantibodies or genetic predispositions, have yielded intriguing results, indicating that alterations in gut microbiota precede the onset of RA.(Wells et al., 2020)

Significant changes in concentrations of microbiome-derived metabolites in RA patients have been reported through metabonomic analysis, implying that similar alterations may occur during the pre-clinical stage.(Yang & Cong, 2021) Within the gastrointestinal tract, the detection of toxic components secreted by gram-negative bacteria, mediated by Toll-like receptor (TLR) 4 and subsequent pathway activation, may induce intestinal inflammation in pre-clinical RA individuals.(Di Lorenzo et al., 2019) Indeed, reports suggest that alterations in gut microbiota can induce autoreactive T cell activation, potentially serving as a latent trigger for systemic inflammation.(Maeda et al., 2016)

Specific bacterial strains, such as those belonging to the genera *Bacteroides*, *Firmicutes*, and *Actinobacteria*, have been implicated in the regulation of immune responses. (Wilmanski et al., 2021) *Bacteroides fragilis*, for instance, has been shown to induce anti-inflammatory signals and promote the development of regulatory T cells (Tregs), which play a key role in immune tolerance. (Carrow et al., 2020) Additionally, certain strains of *Clostridium* within the *Firmicutes* phylum, through the fermentation of dietary fiber, contribute to the generation of anti-inflammatory molecules, such as short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, which possess immunomodulatory properties important for maintaining intestinal homeostasis. (Guo et al., 2020) Furthermore, in RA patients, a decreased abundance of bacteria capable of producing SCFAs, such as *Faecalibacterium prausnitzii*, and an increase in potentially pathogenic bacteria like *Prevotella*, have been noted. The imbalance in these regulatory bacteria and their metabolites may contribute to the disruption of immune tolerance and the progression of autoimmune responses characteristic of RA. (Moon et al., 2023)



**Figure 1. The interplay between diet, healthy microbiome, obesity, and inflammation discussed in this article.**

#### OBEASITY:

High body mass index (BMI), obesity, and increased waist circumference collectively represent a significant risk factor for the development of RA, with intricate pathogenic mechanisms involving adipose tissue dysfunction and dysregulated immune responses.(Poudel et al., 2020) Adipose tissue, particularly visceral adipose tissue, serves as a dynamic endocrine organ, secreting various cytokines (adipokines) that modulate immune and inflammatory processes. Obesity is characterized by chronic low-grade inflammation, with adipose tissue acting as a major source of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6). These cytokines play pivotal roles in RA pathogenesis by promoting

synovial inflammation, cartilage degradation, and bone erosion.(Ogata et al., 2019) Moreover, adipose tissue-derived leptin, an adipokine elevated in obesity, has been implicated in RA development as leptin exhibits pro-inflammatory properties, stimulating the production of TNF- $\alpha$ , IL-6, and other cytokines involved in RA pathophysiology. Additionally, leptin promotes T-cell activation and differentiation, contributing to autoimmune responses characteristic of RA (Figure 1).(Wang et al., 2018)

The dysregulation of adipokines and cytokines in obesity fosters a pro-inflammatory milieu conducive to autoimmunity. Adiponectin, another adipokine, exhibits anti-inflammatory properties, but its levels are often reduced in obesity, further exacerbating inflammation and insulin resistance. Moreover, adipose tissue macrophages in obesity undergo phenotypic changes, adopting a pro-inflammatory M1 phenotype and further amplifying inflammation and potentially promoting insulin resistance.(Apostolopoulos et al., 2016) Insulin resistance, a hallmark of obesity, may also contribute to RA development through its pro-inflammatory effects and dysregulation of immune responses.(Nicolau et al., 2017) Obesity is also linked to dysbiosis of the gut microbiome, leading to further complications.(Liu et al., 2021)

#### EXPERIMENTAL TREATMENT:

Intensive investigation into potential interventions for rheumatoid arthritis has delved deeply into the realm of intestinal microbial treatments. Among these approaches are probiotics, prebiotics, dietary adjustments, antibiotic therapy, and fecal microbiota transplantation. These strategies represent a multifaceted approach to harnessing the therapeutic potential of the gut microbiome in the context of RA prevention and management. Through targeted manipulation of the intestinal microbial milieu, these interventions aim to rebalance dysbiosis, mitigate systemic inflammation, and potentially halt the progression of RA.(Lu et al., 2021; Marietta et al., 2016; Zeng et al., 2021)

##### 1. Probiotics and Prebiotics:

Probiotics, comprising live microorganisms, predominantly bacteria and yeast, are garnering attention for their potential immunomodulatory effects in the context of RA. Preliminary studies suggest that specific probiotic strains may influence the composition and function of the gut microbiota, thereby mitigating systemic inflammation associated with RA.(Mohammed et al., 2017) Lactobacillus and Bifidobacterium species, among others, have been investigated for



their ability to restore microbial balance and suppress aberrant immune responses.(Paul et al., 2021)

Concomitantly, prebiotics, non-digestible fibers with fermentative properties, represent an intriguing avenue for modulating the gut microbiome. By serving as substrates for beneficial bacteria, prebiotics foster a microenvironment conducive to the proliferation of commensal organisms, potentially counteracting dysbiosis observed in RA (Figure 1). The synergistic administration of probiotics and prebiotics aims to create an environment conducive to microbial diversity and resilience, fostering an anti-inflammatory milieu within the gut ecosystem.(Lin et al., 2023; Sredkova et al., 2020)

## 2. Fecal Microbiota Transplantation (FMT):

Fecal Microbiota Transplantation (FMT) emerges as a pioneering therapeutic paradigm, leveraging the symbiotic relationship between the gut microbiome and the immune system. While primarily employed for gastrointestinal disorders, FMT has shown promise in addressing dysbiosis associated with autoimmune conditions, including RA.(Belvoncikova et al., 2022) The rationale lies in the transfer of a diverse microbial consortium from a healthy donor to the recipient, with the objective of reinstating a balanced microbial community and ameliorating systemic inflammatory responses (Figure 1). FMT for RA represents a novel frontier, necessitating meticulous investigation into its safety, efficacy, and potential long-term consequences. Robust clinical trials are imperative to elucidate the nuanced interplay between the gut microbiome and RA pathology, ultimately establishing FMT as a viable therapeutic avenue.(Zeng et al., 2021)

## 3. Dietary Interventions:

The exploration of dietary interventions in the context of rheumatoid arthritis draws inspiration from the profound influence of nutrition on both the gut microbiome and immune responses.(Dourado et al., 2020) Central to this paradigm is the Mediterranean diet, a nutritional pattern characterized by the consumption of fruits, vegetables, whole grains, lean proteins, and healthy fats. This dietary approach is rich in polyphenols, omega-3 fatty acids, and fiber, all of which have been implicated in modulating inflammation and promoting a healthier gut microbiome (Figure 1).(Michalsen et al., 2005)

Polyphenols, abundant in fruits, vegetables, and beverages such as tea and red wine, exhibit antioxidant and anti-inflammatory properties. These bioactive compounds may act as prebiotics, nourishing beneficial gut bacteria and fostering an environment that curtails inflammatory responses (Plamada & Vodnar, 2022). Moreover, polyphenols have been associated with the inhibition of pro-inflammatory pathways, potentially mitigating the systemic inflammation observed in RA.(González-Gallego et al., 2010)

Omega-3 fatty acids, predominantly found in fatty fish like salmon and mackerel, contribute to the anti-inflammatory milieu of the Mediterranean diet. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two key omega-3 fatty acids, serve as precursors to anti-inflammatory lipid mediators, resolvins, and protectins. These molecules actively participate in resolving inflammation and maintaining immune homeostasis,(Calder, 2015) offering a potential avenue for managing the chronic inflammatory nature of RA.(Lee et al., 2012)

Fiber, another cornerstone of the Mediterranean diet derived from whole grains, fruits, and vegetables, plays a pivotal role in shaping the gut microbiome. High-fiber diets have been associated with increased microbial diversity and the promotion of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*.(Holscher, 2017) As fermentation of dietary fiber produces short-chain fatty acids (SCFAs), these microbial metabolites contribute to immune regulation,(Koh et al., 2016) potentially influencing the systemic inflammatory milieu associated with RA.(Häger et al., 2019)

Clinical investigations into the impact of adopting a Mediterranean diet or incorporating specific dietary components as adjunctive measures in RA management are ongoing.(Michalsen et al., 2005) These studies aim to elucidate the nuanced mechanisms through which dietary interventions modulate the gut microbiome and immune responses, providing valuable insights for personalized therapeutic strategies in the realm of autoimmune disorders.(Guerreiro et al., 2018) While dietary interventions represent a promising avenue, their integration into the broader spectrum of RA management warrants further exploration and validation through rigorous scientific inquiry.

#### 4. Antibiotics:

Antibiotics, traditionally employed for their antimicrobial properties, are under scrutiny for their potential impact on the gut microbiome and, consequently, autoimmune conditions such

as RA.(Ogrendik, 2013) While antibiotics indiscriminately target pathogenic bacteria, they concurrently alter the composition of commensal microbes, potentially influencing immune responses.(Haak et al., 2019) Tetracyclines, for instance, have exhibited anti-inflammatory properties beyond their antimicrobial effects, prompting investigations into their utility in dampening RA-associated inflammation (Figure 1).(Gompels et al., 2006)

Nevertheless, some studies have brought to light a concerning association between antibiotic prescriptions and an increased risk of rheumatoid arthritis (RA). This correlation underscores the potential role of disrupted gut microbiota induced by antibiotic use in otherwise healthy populations as a contributing factor to the onset of RA. By disturbing the delicate balance of the gut microbiome, antibiotic therapy may inadvertently promote conditions conducive to the development of autoimmune disorders such as RA.(Armstrong et al., 2020) Rigorous clinical evaluations are indispensable to delineate the precise effects of antibiotics on the gut microbiome, discern optimal dosages, and ascertain their role in the broader therapeutic landscape of RA.

## 5. Vitamin D

Emerging research suggests a link between vitamin D levels and the gut microbiome, unveiling an additional layer to the intricate interplay within the human body. Vitamin D, renowned for its role in calcium metabolism and bone health, exhibits immunomodulatory properties that extend to the gut. Studies propose that vitamin D can influence the composition and diversity of the gut microbiome, potentially contributing to the maintenance of a balanced microbial ecosystem. Moreover, vitamin D may enhance the production of antimicrobial peptides, fortifying the gut's defense against pathogenic invaders and fostering a microenvironment conducive to the flourishing of beneficial bacteria (Figure 1).(Yamamoto & Jørgensen, 2020)

It's essential to emphasize that while these interventions show promise, their efficacy and safety in the context of RA treatment require further investigation through rigorous clinical trials.

## THE IMPACT OF SPORT ON RHEUMATOID ARTHRITIS PATIENTS:

The impact of physical activity on the clinical condition of patients with RA is multi-faceted. Sport has a beneficial effect on the physical and mental health of patients, helping to achieve better results in treatment. increased physical activity in RA has been associated with a reduced number and duration of hospitalizations. (Metsios et al., 2011)

### 1. Reducing Inflammation

Physical activity has been shown to shift the balance of cytokine production towards an anti-inflammatory profile. Exercise induces the release of myokines—cytokines produced by muscle cells during contraction—which have systemic anti-inflammatory effects. Key myokines involved include IL-10, which inhibits the synthesis of pro-inflammatory cytokines like TNF- $\alpha$  and IL-1; and interleukin-1 receptor antagonist (IL-1ra), a natural inhibitor of IL-1 that reduces inflammation by blocking its interaction with cell surface receptors.(Pedersen, 2011) In addition to cytokines, exercise promotes the release of other anti-inflammatory factors such as adiponectin, which can improve metabolic health and reduce inflammation, as well as reducing the levels of pro-inflammatory leptin. (Becic et al., 2018)

Exercise affects T cell function and distribution by increasing the number and functionality of Tregs, which help control the autoimmune response in RA, while also reducing the number of Th17 cells, a subset of T helper cells that produce IL-17, a potent pro-inflammatory cytokine involved in RA pathology. (Benatti & Pedersen, 2015)

## 2. Reduction of Adipose Tissue

Exercise can help reduce the size of adipocytes and lower levels of inflammation, even in populations with non-communicable, low-grade inflammatory diseases such as diabetes. (Hayashino et al., 2014) It is therefore thought that the long-term anti-inflammatory effects of exercise are mainly due to reduction of the size of adipocytes.

## 3. Enhancing Joint Mobility and Function

Engaging in regular physical activity can help maintain joint flexibility and function. Sports such as swimming, cycling, and low-impact aerobics are particularly beneficial as they provide cardiovascular exercise without putting excessive strain on the joints, helping to avoid long-term damage.(Law et al., 2015) Swimming, for instance, supports the body while allowing full range of motion, which can be particularly therapeutic for individuals with RA. Animal studies on RA models show that swimming can be beneficial to maintaining joint health, reducing stiffness, and preventing the loss of muscle mass that often accompanies inactivity.(Saremi et al., 2021)

## 4. Psychological Benefits

Physical activity has also been shown to positively affect the quality of sleep and fatigue levels of RA patients, as well as their general mental health, which might be considered equally important to the aforementioned physiological benefits.(Durcan et al., 2014; Noreau et al., 1995)

It is crucial for individuals with RA to engage in sports and physical activities that are tailored to their specific needs and limitations. Consulting with healthcare providers, such as rheumatologists and physical therapists, can help design a safe and effective exercise regimen. This personalized approach ensures that the activities chosen do not exacerbate symptoms and are adjusted according to disease activity and overall health status.

#### SUMMARY:

Rheumatoid Arthritis (RA), characterized by chronic inflammation and joint damage, results from genetic predisposition and environmental triggers, leading to dysregulated immune responses. Recent research highlights the role of body weight, as well as diet and the gut microbiome in modulating RA severity, with evidence suggesting alterations in gut microbiota composition in RA patients. Dysbiosis may precede RA onset and contribute to systemic inflammation through microbial metabolites and immune dysregulation. The data discussed points to the benefits of physical activity on regulating the balance of pro- and anti-inflammatory cytokines, which is skewed in RA. Additionally, sport is one of the only certain ways to reduce body weight, also aiding in maintaining this healthy balance. Just the mechanical movement of joints may be beneficial on its own. Psychological benefits of physical activity have also been shown.

Dietary interventions, such as the Mediterranean diet, rich in polyphenols and omega-3 fatty acids, show promise in modulating inflammation and promoting gut health. Probiotics, prebiotics, fecal microbiota transplantation, antibiotics, and vitamin D supplementation are emerging therapeutic strategies targeting the gut microbiome to mitigate RA-associated inflammation. However, further research is needed to elucidate their efficacy and safety in RA treatment.

#### DISCLOSURE:

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**Investigation:** Joanna Antczak, Anna Kajka, Olga Skupińska, Julia Hamerska, Laura Hamerska, Julia Lipska, Bogumił Bocianiak, Damian Ruta

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**Project administration:** Joanna Antczak;

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