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REVIEW ARTICLE

Osteoarthritis Can Also Start in the Gut: The Gut–Joint Axis

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Abstract

Background Osteoarthritis is a common cause of pain and disability with an increasing prevalence among the global population (Hunter and Bierma-Zeinstra in Lancet 393(10182):1745–1759, 2019; Zhang and Jordan in Clinics in Geriatric Medicine 26(3):355–369, 2010). Altered immune responses and low-grade systemic inflammation driven by gut dysbiosis are being increasingly recognized as contributing factors to the pathophysiology of OA (Tan et al. in International Journal of Rheumatic Diseases. https://doi.org/10.1111/1756-185X.14123, 2021; Binvignat et al. in Joint, Bone, Spine 88(5):105203, 2021; Ramasamy et al. in Nutrients 13(4):1272, 2021), which increased the interest in the so-called "gut-joint axis". The various microbiota in the gastrointestinal tract is commonly referred to as the gut microbiome. The gut microbiome is affected by age, sex, and immune system activity as well as medications, environment, and diet (Arumugam in Nature. https://doi.org/10.1038/nature09944, 2011). The microbiome is pivotal to maintain host health and contributes to nutrition, host defense, and immune development (Nishida et al. in Clinical Journal of Gastroenterology 11:1–10, 2018). Alterations in this microbiome can induce dysbiosis, which is associated with many human disease states including allergies, autoimmune disease, diabetes, and cancer (Lin and Zhang in BMC Immunology 18(1):2, 2017). A gut-joint axis is proposed as a link involving the gastrointestinal microbiome, the immune response that it induces, and joint health.

Results Emerging evidence has shown that there are specific changes in the microbiome that are associated with osteoarthritis, including increased Firmicutes/Bacteroides ratio, *Streptococcus spp.* prevalence, and local inflammation (Collins in Osteoarthritis and Cartilage. https://doi.org/10.1016/j.joca.2015.03.014, 2015; Rios in Science and Reports. https://doi.org/10.1038/s41598-019-40601-x, 2019; Schott in JCI insight. https://doi.org/10.1172/jci.insight.95997, 2018; Boer et al. in Nature Communications 10:4881, 2019). Both the innate and adaptive immune systems are affected by the gut microbiome and can become dysregulated in dysbiosis which ultimately triggers events associated with joint OA.

Conclusions The gut is an intriguing and novel target for OA therapy. Dietary modification or supplementation with fiber, probiotics, or prebiotics could provide a positive impact on the gut joint axis.

Keywords Osteoarthritis · Joint · Microbiome · Dysbiosis · Inflammation · Obesity · Diet · Gut–joint axis · Immune response

Introduction

Osteoarthritis is the most common joint disorder worldwide [1]. It is a common cause of pain and disability and its prevalence continues to rise [1, 2]. Though OA is one of the most widely studied musculoskeletal conditions, the pathophysiology of OA is still an important area of study. Biomechanical factors contributing to OA are well established but a systemic contribution is being increasingly recognized [3–5]. This systemic contribution includes inflammatory and immune responses to alterations in the gastrointestinal microbiome.

The joint space is considered to be sterile, however, there is emerging evidence that biochemical factors can travel from subchondral bone to overlying cartilage in joints affected by osteoarthritis [6]. Microfractures are present at the osteochondral junction in osteoarthritic joints. These microfractures can be invaded by blood vessels providing an avenue for the transportation and translocation of factors present in the bloodstream to the joint space [13].

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A "gut joint axis" is proposed as a link involving the gastrointestinal microbiome, the immune response that it induces, and joint health. The gastrointestinal microbiome is comprised of the various bacteria, viruses, fungi, and archaea present in the GI tract [14, 15]. Though the exact composition is believed to be unique to each individual [16], studies have identified the predominant bacterial phyla, genera, and species that make up the gut microbiome. Firmicutes and Bacteroides are the main phyla of gut bacteria in humans, comprising about 90% of the total gut microbiome. The gut microbiome can be influenced by a number of factors both modifiable and non-modifiable. These factors include age, sex, and immune system activity as well as medications, environment, and diet [6]. The presence of a connection between the gut microbiome and osteoarthritis (OA) has become clearer as basic science and transitional research have demonstrated a correlation between the two [17, 18].

Physiologic Role of the Gut Microbiome

The gut microbiome is essential to normal host health. The gut microbiota contributes to host nutrition, defense, and immune development [7]. Bacteria can synthesize vitamins used by the host [19]. Gastrointestinal bacteria such as bacteroides also produce short chain fatty acids from indigestible carbohydrates [20]. These are used by colonic epithelial cells as a primary energy source [21].

Immune system maturation is dependent on the host's specific microbiome [22]. Germ-free mice (mice lacking gastrointestinal flora) exhibit impaired immune development, evidenced by immature lymphoid tissue [23], decreased intestinal lymphocyte numbers and decreased IgA production [24, 25]. Reconstitution of the intestinal microbiome restores immune function in previously germ-free mice [26], though this is only seen in murine-specific microbiome restoration. The immune system remains underdeveloped in mice colonized with human microbiota [22]. Components of the microbiome also affect the immune composition of the gut through the maturation and differentiation of immune cells [27]. For example, *Bacillus fragilis*, a known commensal bacterium in the human gut facilitates the maturation of regulatory T cells in mice [28].

The gut microbiota provides colonization resistance: competitive inhibition of invading pathogens [29]. This contribution can occur through direct competition for resources in the GI tract, induction of a physiologic immune response, or the production of inhibitory substances. For example, *Bacteroides thuringiensis* secretes a substance that directly targets spore-forming bacteria such as *C. difficile* [30]. Gut microbiota and their microbial products also induce physiologic inflammation [31]. The activation of TLRs by the gut microbiome leads to the expression of antimicrobial peptides and RegIIIγ [32, 33]. Specific commensal bacteria have also been shown to promote the secretion of antimicrobial peptides, IgA, and the development of Th17 cells [34, 35].

Changes in Microbial Composition Associated with Osteoarthritis

Changes in the microbial composition of the gut microbiome associated with osteoarthritis have been studied in humans as well as animal models. In rodent models, when obesity was induced by a high-fat diet, the most common finding was an increased *Firmicutes/Bacteroidetes* (F/B) phyla ratio relative to mice fed a standard chow diet [9–11]. This finding was also found to be strongly correlated with OA severity. This change in F/B ratio was mostly due to a decrease in the Bacteroidetes population, especially *Bacteroides* and *Prevotella* genera. While the total of Firmicutes remained relatively stable in HFD models, the relative composition was altered with a decrease in Lactobacillus species and an increase in *Clostridiales* [9]. The correlation between altered bacterial composition of the gut microbiome and OA severity in model organisms suggests that there are systemic implications to the disruption of the delicate balance within the gut microbiome.

Broadly speaking, changes in the gut microbiome associated with osteoarthritis alter the delicate balance of pro and anti-inflammatory signaling and activity. The largest study of the gut microbiome in humans with OA identified a specific microbiome signature with a correlation between WOMAC pain score and the levels of pro-inflammatory bacteria such as *Streptococcus* [12]. Increases in proteobacteria are associated with increased concentrations of IL6 and IL8, proinflammatory cytokines. These cytokines are also associated with a decrease in the amount of Firmicutes [36]. Some members of the Firmicutes phylum are able to produce metabolites such as microbial anti-inflammatory molecule, which impair the production of pro-inflammatory cytokines NFkappaB and IL-8 [37, 38].

Effect of Diet on Gut–Joint Axis

Poor diet is associated with obesity, one of the most common risk factors for OA. Animal studies have extensively shown diet itself can affect OA severity through alterations of the gut microbiome. High fat diet and steroid-deficiency induced obesity are common models of gut epithelium disruption, gut dysbiosis, and low-grade systemic inflammation. OA-like changes were observed on histological analysis of rodents on a HFD [9]. Interestingly, when pre and probiotics

were administered the inflammatory effects on the gut-joint axis were partially reversed and prevented [9, 10, 39].

Role of the Immune Response in the Gut–Joint Axis

The integral role of the immune system in mediating the connection between gut inflammation and the joint is supported by emerging research. A recent study describes intricate immune system responses to gut dysbiosis and an association between this immunologic response and spondyloarthritis [40]. Obesity, one of the most well-known risk factors for OA, also involves the immune response by inducing low-grade systemic inflammation [41, 42]. The presence of research in rheumatology, oncology, and orthopaedics into the connection between the gut microbiome and specific disease pathophysiology represents an exciting new frontier of research and therapeutic targets. It is important to note, however, that though these various fields are investigating the gut microbiome, the mechanisms by which it exerts its effect seems to differ.

Specifically, there are important distinctions between the effect of the gut microbiome on osteoarthritis and ankylosing spondylitis (AS). First, AS is a genetically driven disease, with HLA-B27 being the classic risk factor [43, 44]. As a genetically driven disease, much of the gut inflammation associated with AS may have a genetic basis. It has been demonstrated that IBD and AS have significant overlap at the genetic level [40]. IBD is also recognized as a disease with significant genetic components. The best explanation for gut dysbiosis and inflammation in osteoarthritis is that it develops primarily due to environmental factors. Additionally, the pattern of GI inflammation in AS patients has been described as Crohn's like, a pattern not found or described in the osteoarthritis literature [40]. Finally, specific bacteria including *Klebsiella pneumoniae* and *Bacteroides vulgatus* have been identified as essential for the pathogenesis of AS [45]. While particular groups of bacteria such as *Firmicutes, Bacteroidetes,* and *Streptococcus* have been implicated in the pathogenesis of gut dysbiosis associated with OA, there is no indication that any bacteria are essential for the pathogenesis of OA.

Both adaptive and innate immune responses are impacted by the gut microbiome and altered by gut dysbiosis. The microbiota of the gastrointestinal system affects the host immune system in several ways. Not only does the microbiota induce various signaling pathways in the gut but the microbiome contributes to the development of the immune system itself.

The microbiome produces microbial components and metabolites which are recognized by the innate immune system. This induces constitutive signaling, much of which occurs via toll-like receptors [12, 27]. This signaling produces factors that induce a physiologic level of inflammation [31]. Nucleotide oligomerization domain receptors (NOD) are receptors that are also constitutively activated by the gut microbiota. This activity primes the innate immune system and enhances its function [46]. NOD1 detects microbial components found mostly in gram-negative bacteria including *Shigella flexneri, E. coli*, and *H. pylori* [47, 48]. NOD 1 is broadly expressed and recognizes commensal and pathogenic bacteria within the intestine, contributing to the regulation of local and systemic innate and adaptive immune response [27]. The recognition of the GI microbiota by the innate immune system prevents intestinal barrier injury and bacterial translocation and induces the presence of the diverse intestinal immune cell population [27].

The pro-inflammatory signaling by TLR in the innate immune system must be appropriately balanced or excessive and harmful inflammation occurs [27]. For example, IFN-γ and TNF-α, inflammatory cytokines produced by TLRs, are primary culprits in IBD responsible for epithelial barrier disruption [49]. A particularly important anti-inflammatory cytokine in the intestinal steady state is IL-10. This cytokine is produced by regulatory T cells, dendritic cells, and macrophages in the intestine and its role in balancing TLR signaling has been demonstrated extensively in mouse models [50–53].

Regulatory T cell differentiation may be induced by specific members of the gut microbiome in addition to metabolic products. *Bacteroides* produce high levels of short-chain fatty acids. These molecules play a role in the differentiation of regulatory T cells, primary effectors of the suppression of inflammation [31]. It is therefore reasonable to propose that a decrease in *Bacteroides*, as is seen in patients with OA, alters the delicate balance of pro and anti-inflammatory mechanisms across the gut-joint axis. Treatment of mice with probiotics has demonstrated an increased prevalence of Treg cells in the gut [54]. This increase is not well understood and may be due to the direct induction of Treg cells, or changes in the overall microbiome [27].

Effect of Dysbiosis on the Immune System

In intestinal dysbiosis, the aforementioned intricate balance of immune pathways is altered. This dysbiosis is associated with a vast range of human diseases. It is commonly discussed in relation to IBD and the defects in mucosal tolerance seen in that condition. Intestinal dysbiosis is also being investigated in relation to gastric cancer, asthma, allergies, and infectious disease [55].

In OA, macrophage activation has been implicated as one of the predominant immune responses responsible for increased pain and inflammation [56]. Macrophages can

be activated by the presence of bacterial products systemically or in their resident tissue. Specifically, LPS, produced by many bacteria including *Streptococcus*, can bind TLR4 expressed by macrophages [4]. This can induce pro-inflammatory mediators and lead to increased intestinal permeability. Increased intestinal permeability allows greater passage of bacteria, bacterial fragments, and pro inflammatory mediators into systemic circulation [57].

The abundance of streptococcus is strongly correlated with higher knee OA pain and primes local and systemic inflammation by LPS induced macrophage activation [12]. The hypothesis to explain the association between *Streptococcus* and knee pain/effusion is that strep species produce metabolites and membrane vesicles, both of which interact with the host immune system. These products are able to pass the intestinal barrier, enter the bloodstream, and activate macrophages within the synovium or systemic circulation creating a pro-inflammatory state which can invoke or exacerbate joint inflammation [12].

Small numbers of commensal bacteria translocate in a healthy human gut. These are removed by Th1 and Th17 cells. Bacteroides and mucosa adherent segmented filamentous bacteria produce polysaccharides that induce the development of Th1 and Th17 cells. Decreased Bacteroides populations have been demonstrated to be associated with OA [9], likely contributing to a pro-inflammatory state [11]. Bacterial invasion in higher numbers occurs in dysbiosis results in overactivity of TLRs, overproduction of proinflammatory cytokines, and pathologic chronic inflammation. This pattern can be seen in a variety of disease states, particularly autoimmune diseases [58].

Therapeutic Perspectives

The gut is an intriguing novel target for OA therapies. Diet modification for the purpose of weight loss has been prescribed for OA, but more targeted dietary interventions could have positive impacts on the gut joint axis. Randomized, double-blind, placebo-controlled studies have demonstrated an association between the use of probiotics and a decrease in OA symptoms. One of these studies found an association between oral *Streptococcus thermophilus* and decreased OA serum biomarkers and WOMAC pain score [59]. Another clinical trial showed a significant decrease in WOMAC pain score after 6 months of treatment with *Lactobacillus casei Shirota* [60]. The prebiotic oligofructose has shown promise in reducing inflammation and OA markers in model organisms [12].

High fiber diet has been studied in non-interventional cohorts. These studies have demonstrated a correlation between high fiber intake and the reduction of OA pain. The elimination of a high-fat diet is a logical therapeutic approach, though it is unlikely that this alone would be able to reverse or completely halt OA progression [61].

Additional interesting areas of research are antibiotic administration to shape the gut microbiome, restoration of barrier integrity of the intestine, and exercise. Exercise is already a common recommendation for patients with OA. It may help to improve stiffness and other mechanisms of joint function and can have a positive impact on the metabolic comorbidities that are often seen with OA. Additionally, it may directly impact the gut microbiome [62], providing another avenue by which it can exert a positive effect.

Conclusion

This review emphasizes that a more intimate understanding of the interaction between the immune system and microbes and their products is vital to a more intimate understanding of joint health. The concepts discussed here are also relevant in the study of musculoskeletal infection, where better understanding of the effect of bacterial toxins and products has been identified as an integral aspect of MSKI research moving forward [63].

Declarations

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Standard Statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed Consent For this type of study informed consent is not required.

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