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REVIEW ARTICLES

Gut microbiota in axial spondyloarthritis: genetics, medications and future treatments

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ABSTRACT

Axial spondyloarthritis, also referred to as ankylosing spondylitis, is a chronic inflammatory condition that predominantly affects the axial spine but may also present with peripheral arthritis. It falls within the umbrella of disorders known as spondyloarthropathies. In addition to axial spondyloarthritis, this group includes psoriatic arthritis, enteropathic arthritis, reactive arthritis, and undifferentiated spondyloarthropathy, with axial spondyloarthritis being one of the most common. The overall mechanisms underlying the development of axial spondyloarthritis are complex and multifactorial. There is a significant and well-recognized association between axial spondyloarthritis and the HLA-B27 gene, but there have also been non-HLA genes identified in the disease process, as well as certain inflammatory cytokines that play a role in the inflammatory process, such as tumor necrosis factor (TNF). More recently, there has been research and new evidence linking changes in the gut microbiota to the disease process of axial spondyloarthritis. Research into the role of the gut microbiota and gut dysbiosis is a large, ever-growing field. It has been associated with a multitude of conditions, including axial spondyloarthritis. This mini-review highlights the symbiotic relationship of the gut microbiota with the pathogenesis, therapeutic agents and future treatments of axial spondyloarthritis .

Keywords: Axial spondyloarthritis; Gastrointestinal microbiota; Gut dysbiosis; HLA-B27

INTRODUCTION

Axial spondyloarthritis is a chronic inflammatory condition that typically affects the spine. The condition typically affects young adults, with a male predominance roughly three times that of females. The mean axial spondyloarthritis incidence per 10,000 people was 23.8 in Europe, 16.7 in Asia, 31.9 in North America and 7.4 in Africa[1]. Its classification falls under the umbrella of spondyloarthropathies, referring to a group of rheumatic diseases that are linked by common clinical and genetic features. The other related conditions include reactive arthritis, psoriatic arthritis and enteropathic arthritis. Axial spondyloarthritis may be further classified depending on joint involvement. The Assessment of Spondylarthritis International Society previously restructured the classification of spondyloarthropathies, and this is now based upon the predominant pattern of joint involvement, either axial or peripheral, acknowledging that patients may have features of both[2].

Axial spondyloarthritis presents with back pain and morning stiffness in the spine, whereas peripheral spondyloarthritis includes symptoms of peripheral joint arthritis, enthesitis and dactylitis. There may also be extra-articular features such as anterior uveitis. Regarding investigation, plain radiography is the first-line imaging modality, although further imaging with MRI may be needed to detect early and subtle changes. The available treatment options depend on the pattern of joint involvement. The first-line treatment for axial disease are NSAIDs (Non-steroidal anti-inflammatory drugs). For peripheral involvement, NSAIDs, glucocorticoids, or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) can be used. When the response to any of these treatments, in both axial and peripheral involvement, is insufficient, these drugs can be substituted or combined with biological DMARDs (bDMARDs), such as tumor necrosis factor inhibitors (TNFis)[3].

The exact etiology of this condition is not fully understood. However, in recent years, an increasing number of studies have highlighted several different factors that may be related to disease occurrence. First, the MHC class 1 allele human leukocyte antigen (HLA)-B27 plays a major genetic role in the pathogenesis of this condition. Three identified aminopeptidases, *ERAP1, ERAP 2,* and *NPEPPS,* have also been identified as having a genetic link to axial spondyloarthritis vulnerability[4].

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Furthermore, immune reactions involving specific cytokine pathways, such as the interleukin (IL)-23/17 axis, have been implicated in pathogenesis[5].

Mounting evidence indicates a potential interplay between the gut microbiota and both the development and manifestation of axial spondyloarthritis. The human microbiome is home to trillions of microorganisms, including bacteria, viruses, fungi, archaea and protozoa. Over 2000 different bacterial species have been identified, of which the majority belong to four main phyla, Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria[6].

Gut microbial changes start in utero and typically change between the first and third trimesters. Both brain-gut axis regulatory mechanisms and immune activation by the intestinal mucosa are affected by placental hormones, e.g., progesterone and estrogen[7]. By three years of age, the gut microbiota typically reaches a stable state yet remains susceptible to influences from lifestyle and host-related factors.

The vast diversity of organisms is unique to each individual and is heavily influenced by both genetic and environmental factors. Genetic predisposition is thought to explain only approximately 5-10% of bacterial variability. Environmental factors, including mode of delivery, diet and antibiotic usage, among others, are significant in determining an individual's microbial composition[8].

The gut microbiome plays a predominantly symbiotic role in shaping human physiology. These compounds contribute significantly to nutrient and drug metabolism, metabolite synthesis, immune system development and control, protection against pathogenic colonization, and maintenance of the gut mucosal barrier[9]. Alterations in the composition of the gut microbiota, known as dysbiosis, have been implicated in a multitude of neurodegenerative and autoimmune conditions, inflammatory bowel disease and type 1 diabetes mellitus[10].

Here, we review the literature to explain the relationship between gut commensal bacteria and the development and treatment options for axial spondyloarthritis.

METHODS

The main aim of this manuscript is to discuss our present knowledge of the relationships between gut microbiota alterations and axial spondyloarthritis and to understand whether probiotics have any role in axial spondyloarthritis management. Medline and Embase (OVID) were used to search for all of the studies published from the start of the database until December 2023, using keywords such as "Ankylosing/Axial Spondylitis", 'axial spondyloarthritis', "gut microbiota" and "gut dysbiosis". Duplicated articles were discarded, and a manual search of primary articles was also performed to ensure that no articles were lost. The search was limited to 42 full text articles published in English, and consisted of case studies, case–control and cohort studies, literature reviews, systematic reviews and meta-analyses.

GENETICS

Studies have attempted to investigate the role of HLA-B27 in shaping the microbial population. It is possible that HLA-B27 significantly alters the gut microbiota and therefore may be an underlying mechanism for the development of axial spondyloarthritis. Several hypotheses have been postulated, including the misfolding of HLA-B27 within the endoplasmic reticulum leading to the induction of proinflammatory cytokines and autophagy[11,12]. Molecular mimicry between bacterial peptides presented by HLA-B27 and cross-reactive peptides may also be possible; the bacterial peptide Klebsiella has been cautiously mentioned as a trigger for axial spondyloarthritis[13]. The presence of certain bacteria, including *Salmonella and Shigella,* is a well-known trigger for HLA-B27-associated reactive arthritis, while cross-reactivity between gram-negative bacteria and HLA-B27-associated monoclonal antibodies has also been reported[14].

Animal studies have also shown the development of arthritis and colitis following the introduction of commensal intestinal bacteria to germ-free HLA-B27 transgenic rats[15]. Therefore, microbial bacteria may be needed for the pathogenesis of HLA-B27-associated diseases. Lin et al. reported significant differences in the cecal microbiota of HLA-B27-transgenic rats compared with wild-type controls[16]. In particular, sequencing revealed an increase in *Prevotella spp.* and a decrease in Rikenellaceae. This was the first study that associated HLA-B27 with altered cecal microbiota. Though, it remains unclear whether these changes were the cause of the disease, a consequence of the condition, or unrelated to the disease, indicating the need for further investigation. Moreover, the sequencing techniques applied have limitations, and it's possible that some potentially harmful organisms may not have been identified.

A case-control study comparing 28 axial spondyloarthritis patients with 32 healthy controls reported decreased intestinal bacterial diversity in the axial spondyloarthritis group compared with the control group[17]. Focusing on anti-inflammatory (Bifido*bacterium, Lactobacillus*) and proinflammatory (*Bacteroides, Escherichia coli*) species, significant correlations between

HLA-B27-positive patients and decreased *Lactobacillus* and *Escherichia coli* were observed.

Furthermore Stoll et al, observed significant elevation of *Faecalibacterium prausnitzi* and *Coprococcus*, with depleted levels of *Bacteroides fragilis*, *Rumniococcus* and *Akkermansia muciniphila* in HLA-B27 positive patients against HLA-B27 positive healthy controls[18]. After adjusting for age, these findings were still maintained, except for *Coprococcus* levels, which lost statistical significance.

Genetic predisposition and its influence on gut microbial populations may play a significant role in the disease pathogenesis of axial spondyloarthritis. Significant differences in microbial composition between HLA-B27-positive and HLA-B27-negative siblings were seen[19]. Although other HLA-B alleles, including B13, B40, B47 and B52, were associated with axial spondyloarthritis, only B27 was significantly associated with microbial changes. HLA-B27 subjects were noted to have reduced levels of *Bacteroides ovatus*, *Blautia obeum* and *Dorea formicigenerans*. Conversely, increased carriage of *Roseburia* species and *Neisseriaceae* was present[20]. These overall findings suggest that HLA B27 alleles cause or increase the risk of axial spondyloarthritis through interactions with the intestinal microbiome. Given this, therapies that target and manipulate the gut microbiome to restore balance could be a ground-breaking treatment option for patients with axial spondyloarthritis.

However, the consensus between HLA-B27 and variations in the gut microbiota is not entirely uniform, with few studies showing conflicting data. For instance, a previous study noted a decreased abundance of *Faecalibacterium prausnitzi* in axial spondyloarthritis patients[21]. A decreased abundance of the *Bacteroides* genus was previously reported in adult subjects, despite increased levels in pediatric subjects, with authors highlighting that these results could be explained by developmental delays in the immune system[22]. *Ruminococcus gnavus* has been seen in increased abundance in patients with spondyloarthropathy with a history of inflammatory bowel disease, correlating directly with joint disease activity[23].

Immune System, Intestinal Permeability and Short Chain Fatty Acids

The regulation of the immune system by the gut microbiota is well founded and is known to play a fundamental role in both the innate and adaptive response[24]. Numerous immune cells, including macrophages, dendritic cells, T cells and B cells, inhabit the intestinal mucosa, suppressing inflammation. Dysbiosis triggers these cells to increase proinflammatory cytokine levels and decrease anti-inflammatory cytokine levels, subsequently contributing to auto-immune disease, such as axial spondyloarthritis [25,26,27,28].

The upregulation of proinflammatory cytokines has been associated with gut dysbiosis. ELISA revealed increased concentrations of proinflammatory cytokines, including IL-23, IL-17 and IFN-γ, in response to microbial changes[29]. An increased abundance of Actinobacteria in axial spondyloarthritis patients has been observed[29], with similar results also replicated[30]. This suggests that the unique gut microbiota pattern of axial spondyloarthritis patients may activate autoimmunity through various mechanisms, such as the upregulation of inflammatory cytokines.

The IL-23/IL-17 axis has been shown to be a key factor in axial spondyloarthritis pathophysiology[31]. Research has shown that intestinal dysbiosis triggers homeostatic changes in this pathway, leading to both axial spondyloarthritis-related intestinal and joint inflammation[32]. Colonic tissue from transgenic HLA-B27-positive rats showed a positive correlation between intestinal inflammation and increased IL-23 and IL-17[33]. *Prevotella* species have been postulated as key contributors to triggering axial spondyloarthritis in susceptible populations by altering microbial metabolites and barrier function[30]. The subsequent loss of immune tolerance and increased cytokine storms of IL-23, IL-6 and IL-8 can worsen intestinal inflammation and lead to the systemic dissemination of bacterial products[34].

Alternatively, microbiota-induced activation of mucosa-associated invariant T (MAIT) cells, a type of antibacterial lymphocyte located in the intestinal lamina propria, has also been hypothesized to play a role[35]. MAIT cells, when activated, induce a proinflammatory cytokine storm, including IL-17 and TNF alpha (TNF-α), in response to gut dysbiosis[36]. Serum levels of MAIT cells were found to be lower in axial spondyloarthritis patients but elevated in synovial fluid[37]. Besides, CD69 is a surrogate marker of MAIT cell activation, and its expression is increased and further associated with disease activity scores in axial spondyloarthritis[38].

The intestinal epithelium serves as a critical component in maintaining tissue homeostasis, acting as a robust physical and biochemical barrier against both pathogenic and commensal microorganisms[39]. The gut microbiota plays a fundamental role in maintaining the intestinal epithelial barrier. There is a connection between intestinal inflammation, gut dysbiosis, and epithelial integrity[40]. Any compromise in the integrity of the barrier leads to the phenomenon termed 'leaky gut'[41]. Multiple studies have investigated the role of increased intestinal permeability in axial spondyloarthritis. Increased intestinal permeability in both axial spondyloarthritis patients and their first-degree relatives have been noted[42] and significant presence of *Escherich-*

ia coli and *Prevotella* has been observed in the ileum of axial spondyloarthritis patients compared with healthy controls[43]. Intestinal permeability may predispose individuals to the translocation of the gut microbiota into the systemic circulation and subsequent immunological cascade. Finally, the levels of lipopolysaccharides, a type of bacterial endotoxin, are greater in patients with axial spondyloarthritis[44].

Short-chain fatty acids (SCFAs), such as acetic acid and butyric acid, are produced by gut microbiota. These metabolites are produced by anaerobic fermentation of dietary fibers by the gut microbiota and are important for regulating intestinal permeability[45]. They also induce the differentiation of Treg cells and stimulate anti-inflammatory cytokine production[46]. An imbalance of these acids is linked with several diseases, including Crohn's disease and coeliac disease[47]. Reduced levels of butyrate metabolism have been observed in axial spondyloarthritis patients, coinciding with reduced levels of species that can produce SCFAs, including *Eubacterium halli* and *Faecalibacterium prausnitzii* [21]. SCFAs have been shown to regulate and suppress (lipopolysaccharide) LPS-induced autophagy in Caco-2 cells[48]. Ileal samples from patients with axial spondyloarthritis and chronic gut inflammation were found to have significantly increased activation of autophagy within the intestinal epithelium and increased IL-23 levels[49]. Interestingly, increased levels of *Parabacteroides distasonis* in untreated axial spondyloarthritis patients has been observed. This bacterium has been implicated in regulatory T cells and the regulation of SCFAs and could be responsible for the proinflammatory state in axial spondyloarthritis[50]. Finally, significant differences in microbial composition and a lower abundance of SCFAs were noted between axial spondyloarthritis patients and healthy controls. Following treatment with TNFis, there was a positive response in the microbial composition of SCFA-producing bacteria (*Megamonas* and *Lanchnoclostridium*), and the restoration of these bacteria was negatively correlated with disease severity[51].

Current treatments

Therapeutic agents for the treatment of axial spondyloarthritis currently include NSAIDs, DMARDs, and revolutionary biological treatments. More recently, there have been studies investigating the associations between these therapeutic medications and the gut microbiota.

NSAIDs

NSAIDs are highly effective in providing symptomatic relief for patients. The inhibition of cyclooxygenase (COX) prevents the release of prostaglandins and subsequent inflammation of joints. There is marked evidence showing that NSAIDs cause shifts in the composition of the gut microbiota[52].

Only one study to date has investigated the correlation between NSAIDS use in axial spondyloarthritis and changes in the gut microbiota. The authors noted a significant decrease in bacterial diversity of *Bifidobacterium and Lactobacillus* and increased diversity of *Bacteroides*, *Clostridium coccoides, Clostridium leptum*, *Faecalibacterium prausnitzi* and *Escherichia coli* [17]. Chronic administration of NSAIDs can be harmful and can affect not only the gut microbiota but also lead to serious gastrointestinal and renal complications.

DMARDs

Disease-modifying antirheumatic drugs (DMARDs) are a class of drugs immunosuppressant and immunomodulatory drugs used in the treatment of inflammatory arthritides and other rheumatic disorders. They are classified as either conventional synthetic DMARDs (csDMARDs), or biologic DMARDs (bDMARDs).[53] The csDMARDs, such as methotrexate, sulfasalazine, and leflunomide, are used for peripheral spondyloarthritis. Therefore, there has been very limited research investigating the effect of csDMARDs on the gut microbial composition in patients with axial spondyloarthritis. Gastrointestinal side effects are common with methotrexate in patients with other rheumatic conditions due to damage to the intestinal barrier[54]. Most studies with methotrexate have been animal studies and have shown significant variances in gut microbial composition, with reduced levels of *Bacteroides fragilis* noted in low-dose methotrexate-treated mice[55]. Similarly, following monotherapy with methotrexate, there was a lower abundance of *Enterobacteriales* than in healthy controls[56]. Interestingly, the introduction of *Bifidobacterium longum* neutralized methotrexate-induced intestinal damage[57]. The gut microbiome can provide a prognostic evaluation of methotrexate efficacy in rheumatoid arthritis[58].

Sulfasalazine is also be used in the treatment of inflammatory bowel disease[59]. Few studies have also evaluated the interaction between sulfasalazine and the gut microbiota. Sulfasalazine is metabolized by the gut microbiota and is broken down into 5-ASA and sulfapyridine[60].

The administration of probiotics with sulfasalazine, e.g., *Lactobacillus acidophilus* and *Bifidobacterium lactis*, has been shown to modulate sulfasalazine metabolism in the colon[61]; however, this is still controversial[62]. Following the initiation of sulfasalazine, the abundance of *E. coli* and *Bacteroides* was significantly reduced[63]. A study on rats with induced colitis showed that Sulfasalazine not only reduced inflammation but restored balance in the gut microbiome, as evidenced by increasing amounts of SCFAs-producing bacteria and decreasing amounts of Proteobacteria[64].

Biological Agents

Biological disease-modifying anti-rheumatic drugs are monoclonal antibodies used to treat a variety of wide-ranging rheumatic conditions. These agents target the adaptive immune system and aim to inhibit cytokines, including TNFi and interleukin (IL)-1,6,17 and 23. They also target both T and B cells to dampen the immune response[65]. In Spondyloarthopathies, anti-TNF therapy is effective in reducing disease activity and spinal pain. Examples of these drugs include adalimumab, etanercept, infliximab and golimumab[66]. More recently, there have been advances in biological treatments for spondyloarthopathies, and new therapeutic options such as Janus kinase inhibitors, for example, *tofacitinib*, have been approved[67].

Previous studies have suggested that biologic agents are beneficial and modulate the gut microbial profile. TNFis have been shown to restore the gut microbiota in untreated ankylosing spondyliti patients compared with healthy controls[68] and, interestingly, were associated with a reduction in arthritogenic bacterial peptides. Zhang et al. reported that the beta diversity of the microbiota in axial spondyloarthritis patients returned to the level of that in healthy controls after one month of treatment[69]. This highlights the dynamic nature of microbial colonies, and one day could be a simple biomarker for disease activity. It is believed that TNFis inhibit vascular inflammation and induce T-cell apoptosis, which subsequently modulates the gut microbiome[70]. Etanercept therapy has been successful in restoring the gut microbiota in proteoglycan-induced axial spondyloarthritis mice, reducing inflammatory cytokine secretion, arthritis progression and shown to restore intestinal bacterial function by restoring tight junction protein levels[71]. Adalimumab restored the gut microbiome in axial spondyloarthritis patients after 6 months of therapy compared with that in healthy controls; in particular, adalimumab therapy restored the normal abundance of Bacteroidetes and Firmicutes[72]. As mentioned previously, the SCFA bacterial composition is restored successfully following TNFi treatment and is comparable to that of healthy controls[51].

A study into the effects of tofacitinib in mice with dextran sodium sulfate induced colitis, found that in the short term (3.5 days), there were no alterations in gut microbiome diversity colitis[73]. However, tofacitinib was shown to alter beta-diversity by day 21 in mice with collagen-induced arthritis, with increased amounts of beneficial members of the Firmicutes and Actinobacteria and decreased amounts of potentially pathogenic members of the phyla Proteobacteria and Chlamydiae[74].

Future Treatments

Several treatment strategies may be utilized to manipulate gut microbiota dysbiosis. These include dietary interventions, antibiotic therapy, prebiotics, probiotics, and fecal microbiota transplantation.

Dietary interventions

Studies have shown that the "Western diet", which typically consists of high fat and cholesterol, high sugar and salt, and excessive processed foods, is linked to an increased risk of several autoimmune diseases[75]. These dietary patterns play a role in shaping the gut microbiota composition and modulating its metabolites, as well as potentially disrupting intestinal tight barriers, which can then, in turn, increase the risk of certain autoimmune disease processes[76]. A low-starch diet has been associated with symptomatic relief and a reduced likelihood of needing pharmacological therapy in patients with axial spondyloarthritis[77]. A low-starch diet, in combination with traditional treatments, could be beneficial for patients with axial spondyloarthritis, particularly those with a positive family history of spondyloarthropathies or those with HLA-B27 genetic alleles, through eradication of *Klebsiella* microbes within the gut[78]. Ebringer and Wilson reported that a low-starch diet reduces the total serum IgA concentration and reduces symptoms and inflammation in patients with axial spondyloarthritis[79]. A potential dietary intervention is a low-fructose diet. Luccia et al. reported high levels of dietary fructose-induced inflammation, oxidative stress, and markers of metabolic syndrome[80]. Furthermore, increasing fiber intake may also play an important role in maintaining gut conditions. Fibers are postulated to bee metabolized into SCFAs, such as butyrate, which exert an anti-inflammatory effect[81]. Specifically, an observational study revealed that patients with axial spondyloarthritis had higher levels of IgG specific to beef, pork and crab, which all contain high levels of the natural antigen galactose-α-1,3-galactose (α-Gal), suggesting that this may play a role in the underlying disease pathology[82].

Antibiotics

Several studies have investigated the potential use of different antibiotics for the treatment of spondyloarthropathies. The fluoroquinolone antibiotic moxifloxacin has demonstrated benefits in the management of patients with axial spondyloarthritis, showing a significant reduction in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels[83]. Studies of mouse models have also shown that rifaximin is effective at modulating the intestinal microbial composition and slowing the progression of axial spondyloarthritis through downregulating cytokines, including IL-6 and IL-17A[84]. Furthermore, a systematic review with meta-analysis revealed that small intestinal bacterial

overgrowth either improved or resolved in 70.8% of patients taking rifaximin[85].

Prebiotics

Prebiotics are nutrients that can feed the gut microbiota and are degraded into short-chain fatty acids[86]. Different important groups of prebiotics are recognized to have beneficial effects on health, with most being a subset of the carbohydrate group. These groups include galacto-oligosaccharides and fructo-oligosaccharides[86]. Studies have shown that galacto-oligosaccharides can reduce the levels of the proinflammatory cytokines IL-6, IL-1β, and TNF-α and increase the levels of the anti-inflammatory cytokine IL-10[87,88], while fructo-oligosaccharides can reduce proinflammatory IL-6 expression and upregulate anti-inflammatory IL-4[89]. The rationale for administering prebiotics is to alter the structure and metabolism of beneficial commensals in the gut microbiota, strengthen epithelial barriers and modulate immune responses. Prebiotic treatment with *Lactobacillus rhamnosus* in HLA-B27 transgenic rat models has demonstrated efficacy in reducing colitis[90]. There have also been small-scale human studies showing promising results for the use of prebiotics in patients with inflammatory bowel disease[91].

Probiotics

Probiotics are live microorganisms that confer health advantages to the host when taken in adequate amounts. *Lactobacillus* and *Bifidobacterium are* two of the most commonly used probiotics. There are multiple mechanisms involved in this process, including promoting the growth of beneficial gut microbiota, strengthening intestinal barriers, producing antimicrobial compounds and organic acids, and influencing innate and adaptive immune cells through Toll-like activation of signaling pathways and modulation of cytokine pathways[92]. There have been various studies on the use of probiotics in various immune-related diseases. One such condition is inflammatory bowel disease, where probiotics have been found to modulate host cell signaling pathways and represent a potential preventative or adjunctive treatment for these patients[93]. A study on the use of probiotics in mice with collagen-induced arthritis revealed that *Lactobacillus casei* decreased inflammatory cytokines such as IL-6 and TNF-α and had an anti-arthritic effect[94]. Regarding the use of probiotics in axial spondyloarthritis, Lowe et al. reported that the combination of *Lactobacillus and Bifidobacterium* may provide pain relief, improve quality of life, and lower CRP levels in patients with spondyloarthropathies[95]. However, it was noted that the reduction in CRP was greater in patients with rheumatoid arthritis than in those with spondyloarthropathies.

Fecal microbiota transplantation

The gut microbiota can be used for therapeutic purposes, and fecal microbiota transplantation has been an area of growing interest in recent years. Fecal microbiota transplantation (FMT) can restore the entire microbiota community. The process involves the transfer of stool from a donor with a healthy gut microbiota to the intestine of a recipient, thus restoring their microbiome and modulating immune homeostasis[96]. Historically, FMT has been used for patients with *Clostridium difficile (C. difficile)* infection, for whom antibiotic therapy has failed[97]. FMT can be used to restore the microbial community and diversity in several ways to treat *C. difficile* infection, including competing for nutrients, suppression by antimicrobial peptides, and inhibition of spore germination[98]. Given its success in managing cases of *C. difficile infection,* there has been further research into the use of FMT under other conditions[99]. FMT in ulcerative colitis patients resulted in the downregulation of certain inflammatory cytokines, such as IL-1 and IL-6, as well as a reduction in the inflammatory markers CRP and ESR[100].

Two case reports observed both short- and long-term improvements in patients with axial spondyloarthritis symptoms following FMT. One patient reported a significant reduction in excruciating spine and hip pain. The second patient, who was already on infliximab, reported a complete resolution of symptoms and objectively a significant reduction in both CRP and ESR levels[101]. Another case report also highlighted similar findings[102]. This patient had refractory axial spondyloarthritis and comorbid ulcerative colitis, with a poor response to a TNFis; hence, FMT was considered. Post treatment, they found that there was a notable improvement in both ulcerative colitis and axial spondyloarthritis symptoms, with changes in the fecal microbiota.

CONCLUSION

To summarize, the etiology of axial spondyloarthritis is complex and multifactorial. Many recognized factors play a role in the disease process of axial spondyloarthritis, including the HLA-B27 gene, inflammatory cytokine pathways, certain aminopeptidases and environmental exposures. More recently, studies have investigated the potential role of gut dysbiosis in the pathophysiology of axial spondyloarthritis, given that it has been implicated in several neurodegenerative and autoimmune conditions. Research thus far has revealed several potential mechanisms through which gut dysbiosis may be related to axial spondyloarthritis, such as a reduction in short-chain fatty acid-producing bacteria. This finding suggests that there may be a role for

NSAIDs, DMARDs and biological agents outside of the traditional treatment pathway in treating gut dysbiosis in these patients. These treatments may include prebiotics, probiotics and fecal microbiota transplantation. The evidence thus far appears promising and possible life-changing, but further larger-scale clinical studies are needed to determine the effectiveness and benefits of these therapies.

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