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Review Article

Faecal transplant therapy for Arthritis: Diagnostic and therapeutic tool Tinea faciei as the main mimicker of cutaneous lupus erythematosus

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Abstract

In the recent past the gut microbiota has emerged as a critical factor in human health and disease. The plasticity of the gut microbiome allows for adjustment in its composition to achieve a balanced micro-ecosystem in the gut to maintain a healthy state. Impressive advances in sequencing technologies, compelling animal data and human evidence suggest that dysbiosis of gut microbiota play a vital role in the pathogenesis of autoimmune arthritis. Fecal microbiota transplantation was found to have the potential to revert the altered microbiota to a balanced state. In this review we discuss the types autoimmune arthritis, mechanism operated by the microbiota for the prognosis of the disease and the studies performed to evaluate the efficacy of the Faecal transplant therapy, since no permanent treatment is available for this disease. This therapy has been standardized for the treatment of recurrent Closteridium difficil infection in therapeutics. The main focus on this therapy is to avoid the side effects of drugs available to treat the disease temporarily.

Key words: types; mechanism; gut microbiota; dysbiosis; human trials

Introduction

Arthritis is the manifestation of inflammation or swelling of joints [1]. There are more than 100 conditions that affect the joints, and nearby tissues. Specific symptoms vary depending on the type of arthritis, but usually include joint pain and nearby tissue stiffness. Etiology of arthritis is still an enigma though; a few causal factors are suggested but not confirmed. There are various types of arthritis [2; 3] such as Rheumatoid arthritis (RA), Fibromyalgia, Lupus erythematosus and Infectious and reactive arthritis. Though there is no known cure for arthritis, proper early diagnosis and creation of a personalized treatment plan can help to prevent permanent joint damage. Arthritis treatment options include lifestyle changes, medication and even surgery for severely damaged joints. The treatment goal is to limit pain and inflammation and preserve joint function. Treatment options include medicines, weight reduction, exercise, and surgery. There lies a hope not for complete cure but at least for its management in 'Faecal transplant therapy (FMT)". Lately, scientists are trying FMT in animal models as well as human trials to standardize the modality to use it as an effective therapeutic tool. A number of randomized controlled trials (RCTs) have found that the efficacy of FMT in the treatment of autoimmune diseases is significantly better than that of conventional treatment, and no serious adverse reactions have been observed during follow-up [4]. In Certain types of arthritis, it is successful whereas in others it is not at all, may be due to different aetiologies.

Types of Arthritis

1. Osteoarthritis (OA) commonly called "degenerative joint disease or wear and tear arthritis" is the most common form of arthritis affecting the hands, hips, and knees in old age. Breakdown of the cartilage and underlying bone begins to change slowly and get worse over time. The patients suffer with severe pain, stiffness, and swelling. Some experience reduced function, disability and inability to daily tasks or work. Personalized combination of therapies such as increasing physical activity, physical therapy with muscle strengthening exercises, weight loss, medications including over-the-counter pain relievers and prescription drugs, supportive devices such as crutches or canes and surgery (if other treatment options have not been effective) are tried based on the response from the patient.

2. Rheumatoid arthritis (RA), is an autoimmune and inflammatory disease where the immune system attacks healthy cells in the body by mistake, causing inflammation (painful swelling) in the affected parts of the body. In one stroke many joints are damaged, commonly joints in the hands, wrists, and knees. The lining of the joint becomes inflamed damaging the joint tissue having a long-lasting or chronic pain, unsteadiness (lack of balance), and deformity (misshapenness). RA damage multiple immune cell types and signalling network malfunction to elicit a maladaptive tissue repair process leading to organ damage, predominantly in the vascular system, lungs, and joints lungs,

heart, and eyes. Its pathogenesis may be linked to genetic and environmental factors [5]. Rheumatoid arthritis can be one of the most painful types of arthritis; this inflammatory, autoimmune disease attacks healthy cells by mistake, causing painful swelling in the joints, like hands, wrists and knees So far identified risk factors for the prognosis of RA is age, sex, genetics/inherited traits, smoking, nulliparity, obesity, etc. Women who have breastfed their infants have a decreased risk of developing RA.

3. Juvenile arthritis (JA) is a group of autoimmune disorders that can impact children's joints causing permanent physical damage. JA, an umbrella term for several types of arthritis such as juvenile dermatomyositis, juvenile lupus, juvenile scleroderma, Kawasaki disease, mixed connective tissue disease [6] below 16 years. Juvenile idiopathic arthritis (JIA) is a common type formerly called juvenile rheumatoid arthritis. Muscle and soft tissue tighten, bones erode, growth patterns change, and joints misalign. Months of aching joints, swelling, stiffness, fatigue, and fevers may indicate juvenile idiopathic arthritis.

4. Modality for treatment is wanting, though some children with arthritis achieve permanent remission implying that disease is no longer active in spite of permanent physical damage to the joint.

5. Fibromyalgia:a syndrome [6], in which the brain processes pain in the muscles and joints in a way that amplifies the perception of the pain. It causes pain all over the body (also referred to as widespread pain), sleep problems, fatigue, and often emotional and mental distress more sensitive to pain. The cause of fibromyalgia is not known, but it can be effectively treated and managed. Fibromyalgia patients suffer with pain and stiffness all over the body, fatigue and tiredness, depression and anxiety, sleep problems, problems with thinking, memory, and concentration, headaches, including migraines, tingling or numbness in hands and feet, temporo-mandibular joint syndrome (also known as TMJ) and digestive problems. Known risk factors include age, Lupus or RA and few more not yet established.

6. Gout is caused by too much uric acid in the body (hyperuricemia). This is when uric acid crystals can build up in joints, fluids, and tissues within the body. Hyperuricemia may not always cause gout. Gout can only be diagnosed only during a flare when the joint is hot, swollen, and painful. The lab test will confirm the deposition of uric acid crystals in the affected joint [6].

7. Systemic Lupus erythematosus (SLE) is a disease that can affect people of all ages, races, and ethnicities. This disease is "the great imitator" since the signs and symptoms mimic those of other diseases, making it hard to diagnose. SLE' s the most common type of lupus which can affect multiple organs. The possible mechanisms of gut microbiota dysbiosis in SLE have not yet been well identified to date, although they may include molecular mimicry, impaired intestinal barrier function and leaky gut, bacterial biofilms, intestinal specific pathogen infection, gender bias, intestinal epithelial cells autophagy, and extracellular vesicles and micro RNAs [7]. Observed symptoms include fatigue or extreme exhaustion, muscle and joint pain or swelling, skin rashes (in particular a butterfly-shaped face rash across the cheeks and nose), fever, hair loss, recurring mouth sores. Incidence of Lupus is more in females [6].

8. Infectious and reactive arthritis is caused by bacteria, viruses, parasites, or fungi. The origin of the condition may be in one region but spread to joints. This kind of arthritis is often accompanied by fever and chills. The infection triggers immune system dysfunction and inflammation in a joint elsewhere in the body. Often infection starts in the gastrointestinal tract, bladder, or sexual organs [2,3].

9. Psoriatic arthritis (PsA) affects the fingers, and this painful condition affects other joints as well. Pink-coloured fingers that appear sausage-like, and pitting of the fingernails, may also occur. Probability of spine getting damaged as is in ankylosing spondylitis.

10. **Scleroderma**, an **autoimmune** condition in which inflammation and hardening in the skin, and connective tissues can lead to organ damage and joint pain.

Influence of gut microbiota in the prognosis

We all get an initial dose of microbes from mother [9], during the passing of the birth canal and recently also shown through placenta [10-13], they multiply and grow up in the human body in a range of 30 to 40 trillion in numbers. The microbiota present in the human body produce many chemicals, some are beneficial to the host and others are harmful. In the recent past studies on the relationship between bacteria and the human body gave clues for the existence of the gut-brain axis responsible for influencing the brain. Hundreds of neuro-chemicals produced by the gut microbes regulate basic physiological processes [9]. Dysbiosis and inflammation of the gut are responsible for many human diseases [14-23], that are prevalent in society today. Many of the bacteria that colonize the gut and other mucosal sites are essential for digestion of food and acquisition of vital nutrients.

Dysbiosis and inflammation of the gut are responsible for many human diseases in the brain [13-23], that are prevalent in society today. Many of the bacteria that colonize in the gut and other mucosal sites are essential for digestion of food and acquisition of vital nutrients.

The immune system is essential for human living. More than 1600 genes are involved in innate and adaptive immune responses. Gut microbiota also has an impact on the development of the immune system. Indirectly it is that immunologic deregulation is the cause of many non-infectious autoimmune human diseases such as arthritis. The gastrointestinal tract is the primary site of interaction between the host immune system and microbiota [24].

Mammalian gut microbiota have long been appreciated for the benefits they provide to the host through provision of essential nutrients, metabolism of indigestible compounds, defence against colonization by opportunistic pathogens and even contribution to the development of the intestinal architecture [9,25]. In addition, certain basic developmental features and functions of the mammalian immune system depend on interactions with the human microbiota. Microbiota has the potential to exert both pro- and anti-inflammatory responses, and balances in the community structure of gut bacteria may be intimately linked to the proper function of the immune system.The collective genomes of the microbiota) are responsible for protection from various diseases and dysbiosis disturb the partnership between the microbiota and the human immune system, ultimately leading to altered immune responses that may underlie various inflammatory disorders in humans. Sprinz, et al. [26] showed that Germ-free animals are more susceptible to infection by certain bacterial, viral and parasitic pathogens. Challenged with the Gram-negative enteric pathogen Shigella flexneri, germ-free animals expressed decreased immune resistance to infection and increased mortality compared with conventionally colonized animals [26]. Hyperactive microbiota may be the causal factor for the development of autoimmune disease or allergy, a price paid for the overall benefit.

The bacterial genera Bacteroides, *Escherichia-Shigella*, and *Prevotella* species were more in RA patients. On the other hand, Lactobacillus, Alloprevotella, Enterobacter, and Odoribacter were less in the RA group than in the control group. Spearman's correlation analysis of blood physiology of RA showed that bacterial genera such as Dorea and Ruminococcus were positively correlated with RF-IgA and anti-CCP antibodies. In addition, Alloprevotella and Parabacteroides were positively correlated with the erythrocyte sedimentation rate, and Prevotella-2 and Alloprevotella were positively correlated with C-reactive protein, both biomarkers of inflammation [27].

Preclinical and established RA studies suggest a vital role of the gut microbiota in immune dysfunction characteristic of RA. Since multiple therapies commonly used to treat RA have been observed to alter gut microbiota diversity, modulation of the gut microbiota may help prevent or treat RA.

Mechanism operated by the gut microbiota for the prognosis of RA may be related to regulation of immune function by the metabolites produced by these gut microbes. Intestinal microbiota imbalance in autoimmune diseases leads to abnormal synthesis or degradation pathways and then to intestinal ecological damage and pathological damage to the body [28]. For example, a study involving a Japanese cohort of 47 SLE patients and 203 healthy control participants reported that the altered gut microbiome of SLE patients was characterized by the increased abundances of Streptococcus intermedius and Streptococcus anginosus and the activation of various bacterial pathways (e.g., sulphur metabolism and flagella assembly) [29].

Marian, A. et al. [30] demonstrated that Firmicutes/Bacteroidetes (F/B) ratio in SLE patients (mean ratio: 0.66%) compared to healthy subjects (mean ratio: 1.79%) was found. Lactobacillus showed a significant decrease in SLE patients ($p=0.006$) in comparison to healthy controls. The study consisted of Twenty Egyptian SLE patients (female/male = 18/2) with a mean age of 25.6 ± 6.3 years at the time of diagnosis, as well as twenty healthy subjects (female/male = 16/4) with a mean age of 29.9 ± 6.6 years, were recruited for this case/control study. Similar results were obtained for the ratio of Firmicutes/Bacteroidetes (F/B) ratio in SLE patients in Spain as significantly lower F/B ratio in SLE patients (median ratio: 1.97) than in healthy subjects (median ratio: 4.86; $p < 0.002$). This low ratio was found to be ethnicity independent [30]. Ma, Y.et al. [31] observed from their study a causal factor of aberrant gut microbiota in contributing to the pathogenesis of SLE. Their study gave evidence that significantly 5 species including Turicibacter genus and other 5 species were different [31].

Dysbiosis of specific bacterial lineages and alterations in host gut microbiota metabolism led to changes in the immune profile, a causal factor responsible for the development of the disease. It has been established that immune T and B cells have position-specific phenotypes whose function in the mucosa is influenced by the microbiota. In the joint, bacterial peptidoglycan components are found in the synovial tissue of RA patients, probably responsible for the inflammation within the microenvironment of the joint. Substantial data published in the past few years demonstrate the presence of altered composition of the gut microbiota in RA patients, major factors triggering aberrant systemic immunity.

Presence of some strains are found to stimulate an immune response, benefiting immunocompromised patients, while others can suppress the immune response, affecting immune regulation in RA patients. For example, the ability of segmented filamentous bacteria (SFB) to drive T helper 17 (Th17) cell accumulations in the small intestine's lamina propria through SFB-derived antigens presented by dendritic cells is the best example. In contrast, the colonization of *Bacteroides fragilis* is closely associated with increased activity of regulatory T cells (Tregs), which may reduce the intensity of the disease [32].

Maeda, et al. [33] identified that *Prevotella* had a high capacity to induce Th17 cell-related cytokines, such as IL-6 and IL-23 suggesting that increased Prevotella abundance is associated with augmented T helper type 17-mediated mucosal inflammation [33]. *Prevotella* is capable of driving Th17 immune responses in vitro also. Studies on mice have shown that disruptions in the intestinal microbiota could induce production of proinflammatory cytokines, interleukin-17, and increased levels of Th17 cells, even in extra-intestinal tissues. Th17 cells could migrate into the peripheral lymphoid tissue and secrete IL-17. These cells act directly on B cells to induce systemic B-cell differentiation and antibody production and induce the prognosis of the disease. In conclusion the gut microbiota could induce Th17 cell differentiation, which was consistent with the reported elevated circulating Th17 cells populations in patients with RA [27]. Evidence is available for the pathogens or microbial derivatives with pro-inflammatory capabilities over activate innate immunity and aberrant antigen presentation resulting in aberrant activation of the adaptive immune system. It has been understood that dendritic cells and macrophages are capable of obtaining microbial cells and their derivatives from the intestinal lumen as antigens and further transport to secondary lymphoid tissues to activate T and B cells. The abnormal activation of the latter two often promotes autoimmune diseases [34]. Depression is common in patients with RA. Accumulating evidence suggests the role of gut–microbiota–brain axis [14] in depression. Pu, et al. [35] found that FMT of depression-related microbes from RA patients could induce depression-like phenotypes in ABX-treated mice through the activation of T cell immunization. Their vital observation that FMT from RA patients induced T cells differentiation in Peyer's patches (a gut-associated lymphoid tissue) and spleen. Peyer's patches probably can receive signal molecules from gut bacteria and differentiate naïve T cells into regulatory T (Treg) cells or T helper (Th) cells [35; 36]. Ma, Y.et al., [31] carried out 16s rDNA sequencing analyses in a cohort of 18 female un-treated active SLE patients and 7 female healthy controls, and performed faecal microbiota transplantation from patients and healthy controls to germ-free mice. The interplay of aberrant gut microbiota gut microbial and histidine metabolism could be one of the mechanisms intertwined with autoimmune activation in SLE [31].

Periodontal disease and its polymicrobial burden are also correlated as a causal factor RA. For several decades, teeth extraction was a prevalent treatment of disease and was used very intensively in the treatment of RA. Most recently, *Porphyromonas gingivalis*, a periodontopathic bacteria, has been recognized as a possible link between periodontitis, peptide citrullination, autoantibody formation and joint inflammation extensively reviewed. Therefore, the relative abundance of different bacterial lineages probably creates changes in the host immune profile to drive inflammatory responses observed [37-39].

In addition, the leaky gut phenomenon increases the transfer of gut microbes and their constituents may trigger autoimmunity through various mechanisms. This mechanism is substantiated by the presence of Enterococcus *gallinarum* in the liver of patients with systemic *lupus erythematosus* or autoimmune hepatitis, but not in healthy subjects. Similarly, *E. gallinarum* inoculated in the stomach of lupus-prone mice cross the intestinal barrier and enter the liver [34]. Similarly, Mu, Q *et al.* [40] observed *Lactobacillus reuteri* to be translocated from gut to the peripheral organs resulting in systemic immune activation; and it can drive autoimmunity in a Toll-like receptor 7-dependent mouse model of SLE [40].

Roseburia intestinalis, *Bacteroides thetaiotaomicron*, etc., can trigger lupus-like symptoms. Studies have shown that dysbiosis of gut microbiota and their derivatives (e.g., nucleic acids, polysaccharides, metabolites, and toxins) may create aberrant activation of innate immune cells leading to inflammation [34].

As it is reported in the literature, clinical trial suggests that FMT is a potentially safe and effective treatment for SLE. In order to elucidate the potential effect of FMT on peripheral immune cells of patients with SLE, they were collected. Peripheral blood mononuclear cells PBMCs ($n = 30$) of 13 SLE patients who participated in the clinical trial before and after the FMT-treatment, and performed single-cell RNA sequencing. The results first revealed that peripheral T lymphocytes of SLE patients decreased and NK cells increased after the FMT treatment. Then, sub-clustering analysis discovered that total $CD4^+$ T cells highly expressed genes of IL7R, CD28, and $CD8^+$ T cells highly expressed genes of GZMH and NKG7 after FMT treatment. Moreover, FMT treatment reduced the expression of interferon-related genes (IRGs) in $CD4^+$ T, $CD8^+$ T, DP, NK, and B cells of SLE patients. More importantly, interferon-related pathways were more enriched in cells of the FMT non-responder group, and further the interferon genes expression of lymphocytes and myeloid cells was negatively correlated with the efficiency of FMT treatment. Collectively the data identified various immunophenotypic and associated gene set changes following FMT treatment, illustrating the heterogeneity of response to FMT treatment in SLE [41].

Evaluation of therapeutic trial of Faecal transplant therapy for arthritis

Some antirheumatic drugs may fail to treat RA and cause serious adverse reactions. Zeng, J. et al. [27] the first one to present a case of a 20-year-old patient with 5 years' history of RA, successfully treated with fecal microbiota transplantation (FMT) [27]. In a Phase 2, human trial 30 patients with active RA FMT is the engraftment of microbiota from a healthy donor into a recipient to achieve restoration of the normal gut microbial community structure. This is a randomized, 24-week, double-blind, parallel group study, and refractory to MTX (FARM) will be randomized in a 1:1 ratio to one of the following 2 parallel treatment arms [42]. Later Zeng et al. [34] observed that after FMT in SLE, the alpha diversity of the gut microbiota of the patients was increased, with significant enrichment of short-chain fatty acid production-related genera, while inflammation-related bacterial taxa decreased, and short-chain fatty acid production in the gut increased [34].

Xin et al., [41] demonstrated for the first time that Fecal microbiota transplantation (FMT) to be safe and efficient in recovering gut microbiota structure of SLE patients and reducing lupus activity from their recent clinical trial [43]. Huang, et al. [44] performed a single-arm pilot clinical trial (ChiCTR2000036352) of oral encapsulated fecal microbiome clinical trial to explore and ascertain the efficacy and safety for 12 weeks. Their pilot study proved that a significant enrichment of SCFAs-producing bacterial taxa, reduction of inflammation-related bacterial taxa along with increased production of SCFAs in the gut and reduced levels of IL-6 and $CD4^+$ memory/naïve ratio in the peripheral blood. This first signature on active SLE patients provides promising evidence for the feasibility, safety, and potentially effective therapy in SLE patients by modifying the gut microbiome and its metabolic profile [44]. Subsequently, Ciccia and Gandolfo [45] from their similar first FMT trial in SLE patients and provides supportive evidence that FMT appears to be a safe, feasible and potentially effective treatment modality in SLE [45]. Repaired gut microbiota can be used for FMT to treat control lupus mice after an acidic water diet to restore the balance of gut microbiota in lupus mice. It was observed that short term antibiotic treatment of early-stage MRL/lpr lupus mice promoted SLE progression, though the disease burden in these mice was reduced after FMT treatment in the following week. The progression of the disease is suppressed by FMT at the same time impaired the therapeutic effect of glucocorticoid therapy. In mouse model studies have shown that FMT is effective in the treatment of SLE to avoid adverse glucocorticoid reactions [7]. A 58-year-old patient diagnosed with fibromyalgia, non-responsive to a variety of treatments over the years, suffered from significant social and occupational disabilities. The patient was interested in fecal microbiota transplantation (FMT), but given that FMT is not approved for these indications, he used an online protocol for FMT screening and preparation and self-instilled the filtrate using an enema 6 times. FMT resulted in a gradual improvement of symptoms and 9 months after the last treatment, the patient reported full recovery of symptoms, going back to work at full time employment. Improvement of symptoms was associated with major alterations of the enteric microbiota, according to next generation sequencing analysis performed before the first FMT and after the last FMT. Most prominent alterations at the genus level included a decrease in fecal Streptococcus proportion from 26.39% to 0.15% and an increase in *Bifidobacterium* from 0% to 5.23%. This case is added to several additional case reports that demonstrated the effectiveness of FMT in these functional disorders that are lacking an otherwise good medical therapeutic intervention [46].

Conclusion:

The reconstruction of a healthy microbiota is found to alleviate or stop the prognosis of the disease from the clinical trials as well as with the mouse model. FMT proved to give promising results in all the studies performed without serious side effects. Information, thus obtained from larger randomized FMT clinical trials with a longer follow-up to confirm the long-term safety, effectiveness, and potential benefits of FMT-based intervention in autoimmune arthritis will help to standardize FMT procedures in therapeutics

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