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Protective Role of Intermittent Fasting and Probiotics on Inflammatory bowel diseases

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Abstract:

Inflammatory Bowel Diseases (IBD) which include Crohn's disease and ulcerative colitis are chronic, relapsing-remitting inflammatory disorders of the gastrointestinal tract. While their precise etiology is multifactorial implicating genetic susceptibility, immune dysregulation, microbiota imbalance, and environmental triggers—emerging non-pharmacological interventions such as intermittent fasting (IF) and probiotic supplementation have shown promise in modulating disease activity and gut homeostasis.

Keywords: Intermittent Fasting, Probiotics, Inflammatory bowel diseases.

Introduction:

The incidence and prevalence of IBD markedly increased over the second half of the 20th century, and since the beginning of the 21st century, IBD has been considered one of the most prevalent gastrointestinal diseases with accelerating incidence in newly industrialized countries **(1)**. IBD also has significant impacts on patient health, quality of life, mental health, work productivity and healthcare resources **(2, 3)**.

Inflammatory bowel diseases are mainly divided into ulcerative colitis (UC) and Crohn's disease (CD) which are considered two highly heterogeneous, debilitating, incurable, persistent, worsening, immune-arbitrated inflammatory pathologies of the digestive system canal. Both of them have been described as chronic IBD that cause digestive disorders and inflammation in the gastrointestinal tract **(4).**

Ulcerative colitis causes inflammation and ulceration of the epithelial layer and, to a lesser degree, the submucosae layer of the larger intestine (colon and rectum only) in a continuous pattern. However, Crohn`s disease impacts the whole digestive system from the mouth to the anus. It also causes inflammation in a discontinuous pattern that affect all the intestinal layers (mucosa, submucosa, muscularis and serosa) **(5, 6).**

Scientists believe that the main objective of the diagnosis and treatment of the disease is to reduce the symptoms and improve the patient's health. Also to keep the disease at a fixed stage and to avoid the surgical treatment. Inflammatory bowel disease can be treated by a combination of self-care and medical treatments **(7).**

Drug treatment in IBD depends on the location of inflammation, the severity of the disease, the side effects of the disease, and the patient's response to drug treatment **(5, 7, 8).** Several therapies have been used for the management of IBD, such as anti-inflammatory drugs (such as sulfasalazine or corticosteroids) and immunosuppressive agents (azathioprine) which demonstrated biological activities. Also, some antibiotics as amoxicillin , ciprofloxacin and metronidazole can improve the symptoms of CD. However, these drugs resulted in adverse effect especially with long treatment periods in addition to high relapses rates **(8, 9).**

Sulfasalazine, which contains 5-ASA, was the first aminosalicylate used to treat CD. This drug could improve the clinical symptoms of patients with mild to moderate CD. Unfortunately, this drug was associated with side effects **(9)**.

Corticosteroids were also suggested for moderate to severe chronic conditions in order to improve the symptoms of the disease **(10).**

Although the etiology of inflammatory bowel diseases is still unclear, it was also reported that the balance of gut microbial environment which is influenced by dietary composition and patterns plays an important role in regulating the inflammation and oxidative damages of colon through linking the diet and host physiology and pathology **(11-13).**

Probiotics

It has been found that the composition of gut microbes and microbial metabolites are enormously altered in IBD patients and colitis mouse models, including the increase of Shigella and Escherichia Coli and the decrease of the enrichment of Lactobacillus. It has been reported that the transplantation of microbiota from healthy donors could reverse the colitis symptoms. Supplementation of Lactobacillus significantly alleviated the inflammatory responses in a murine colitis model **(13, 14).**

Probiotics are living microorganisms, including bacteria and yeast, that can benefit the body. Probiotics are naturaly found in fermented foods , Yogurt, kimchi, pickles, Kombucha ,Sour cream, cottage cheese, aged cheese and Buttermilk, they also could be taken as supplements produced by pharmaceutical companies (**15**).

Probiotics contain a larger variety and number of microorganisms, ranging from 108 to more than 1010 organisms. Most strains of probiotics were developed for their capacity to resist low gastric pH, giving rise to a number of variants with unknown physiological properties **(16, 17).**

Probiotics are not equally potent in their impact on different metabolic and their effects are strain specific and hence consuming a mixture of different strains rather than one particular strain could provide earlier positive effect **(17).**

Scientists believe that positive effects of probiotics can be obtained in cases of consuming a mixture of different strains rather than one particular strain. Also, they believe that probiotic properties can be strongly dependent on the metabolic activity of the strains and its affection on host cells **(16, 18)**

The bacterial wall can directly interact with immune cells especially when gut barrier permeability is altered. A published report indicated that certain strain of probiotics had modulatory effect on activated B cells **(19)**. It was reported Faecalibacterium prausnitzii improved the tightness of the gut barrier in mice model **(20),** Lactobacillus rhamnosus was proved to increase the occludin and E-cadherin proteins **(21)**. The effect of probiotics could lead to immune regulatory functions or it could lead to endo toxemia associated with insulin resistance, diabetes, and increased cardiovascular morbidity **(16, 17).**

The exact path of the influence, mechanisms, and structures involved in the effect of probiotics are still unknown and under studies. The studies highlight their effect on the intestinal epithelial cells including the intestinal barrier, the immune cells and the resident microbiota. Probiotics bind with the host epithelium and produce metabolites and antimicrobial peptides (AMP) with potential immunomodulatory, anti-inflammatory activities and ability to reduce microbial growth (**22).** By its ability to influence other bacterial growth , it could cause an alteration in luminal microbiata which could be considered focal ecosystem of organisms favoring certain species leading to changes in the produced metabolites which will affect the surrounding cells of the host **(23)**.

Some studies suggested that some strains of probiotics had an influence on the mucus structure , increased the expression of the Muc2 gene with sligh increase of MUC1 and MUC3 also the secretion of the non-mucin glycoprotein increased. These changes lead to enrichment of the intestinal mucus content and improved the intestinal barrier. Other studies highlighted its effect on tight junction proteins. They increase the expression of zoludin-1 (ZO-1) and occluding **(16)**.

Probiotics also interact with both intestinal epithelial cells and immune cells probably by its outer membrane proteins. Scientists discovered certain protein called Amuc_1100 in certain strain which directly interact with the TLR-2

receptor resulting in improving the gut barrier and decreasing inflammation **(24).** Some scientists believe in its effect on T cell subpopulation proportions as they interact in case of gut barrier dysfunction **(25)**. Another study highlighted the ability of certain strain of bacteria to adapt by lateral gene transfere mechanism. They believe it`s the reason behind the Japanese population inherited ability to digest algae polysaccharide porphyrin **(26, 27)**.

Some scientists studied the short chain fatty acid produced by probiotics as butyrate and propionate and their involvement in regulation of numerous functions. They also could influence gene expression in enterocytes through histone deacetylases to binding to specific G protein-coupled receptors, such as GPR-43 and GPR-41. Activating these proteins lead to the secretion of gut peptides such as glucagon-like peptide-1 and−2 (GLP-1 and GLP-2) which are important in regulation insulin sensitivity and gut barrier function **(28, 29)**.

Probiotics produce metabolites and antimicrobial peptides (AMP) with potential immunomodulatory, anti-inflammatory activities and ability to reduce microbial growth and control deterioration in many foods so it could be used as biopreservatives in the food industry **(30, 31).**

Probiotics have been used in many industries as biopreservatives in the food industry due to their anti-inflammatory activities and ability to reduce microbial growth and control food deterioration or spoilage **(30).** They are also considered as beneficial therapeutic alternative that has many promising results. For example in antibiotic-based therapy **(32)**, antibacterial activities against multidrug resistant E. coli and Staphylococcus aureus **(30, 33)**, to decrease blood cholesterol level **(14)**, the treatment of local infections (**34**), even in veterinary medicine and it has positive effect on eggs quality (**35).** Probiotics also have properties for the immunomodulation of many processes **(36).**

Recent advances in assessing the therapeutic potential of microbiota in the treatment of IBD support the reconstitution of microbial resident populations by administration of appropriate microbes. Prebiotics, probiotics, synbiotics, and fecal microbiota transplantation (FMT) are currently considered to be the most common treatments **(37).**

Intermittent fasting

Intermittent fasting (IF) is an umbrella term including a group of periodic energy restriction dietary patterns, including alternate-day fasting (ADF), time-restricted fasting (TRF), and intermittent energy restriction (IER) **(38, 39)**. ADF involves a “feast day”, where individuals eat ad libitum, alternated with a “fast day”, where participants can choose to consume only water or consume ∼25% of energy needs. TRF involves confining the eating window to a specified number of hours per day (usually 4 to 10 h) and fasting with zero-calorie beverages for the remaining hours. IER involves two days where the animals were provided with 50% of their normal calorie intake and the next two days were provided with 10% of their normal calorie intake. Previous research has reported that ADF, TRF, and IER had beneficial regulatory effects on the compositions of gut microbes in various animal models and human trials **(40, 41).**

Intermittent fasting has gained popularity over the last decade mainly as a weight loss regimen. Accumulating evidence indicates that these various intermittent fasting regimens are effective for decreasing body weight and improving insulin sensitivity, blood pressure, and markers of oxidative stress in adults with obesity **(42, 43).**

Multiple studies highlighted the role of intermittent fasting in metabolic state. It plays an important role maintaining a healthy circadian rhythm which have favorable effects on organ systems of animal models (white adipose tissue, brown adipose tissue, and gut) **(44, 45).** It also affects glucose–fatty acid cycle in which glucose and fatty acids compete for oxidation **(46)** causing metabolic shift which will lead to oxidation of fatty acids instead of glucose. This mechanism will be a trigger shifting metabolism from lipid/cholesterol synthesis leading to mobilization of fat and preserving both muscle mass and function **(47).**

Intermittent fasting was also reported to have great effect on adipose tissue which controls the inflammatory state of the body through adipokine secretion which could be proinflammatory or antiinflammatory. Inflammatory state affects muscle mass, hepatic fatty acid oxidation, hepatic gluconeogenesis, glucose uptake and levels of Adenosine

monophosphate-activated protein kinase which likely plays a role in the improvements in insulin sensitivity and glucose homeostasis **(48).**

Studies proved that increased inflammation, including elevated C-reactive protein, decreased adiponectin, lower low-density lipoprotein (LDL) particle size and additional metabolic factors are associated with fluid retention, congestive heart failure, development of atherosclerosis and coronary artery disease. Thus, controling insulin levels through intermittent fasting would be expected to reduce major adverse cardiovascular events **(49, 50).**

Intermittent fasting is proved to be protecrive and effective in animal models as in a research conducted to study autophagy induced by fasting and its effect on fatty liver **(51),** protection against food allergy **(52)** and some scientists even believed that time restricted energy restriction participates in keeping the body healthy at old age and even promotes longevity **(35, 53, 54).**

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