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Review Article

Chronic Constipation, a Frequent and Multifaceted Condition. Can it be Helped with Probiotics, Including Fecal Microbiota Transplantation?

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Abstract

This review article aims to help patients with chronic constipation and prevent serious consequences. We evaluate the causes that must be addressed to prevent or reduce this unpleasant process. We begin with a review of the pathophysiology to understand what is happening and lay the groundwork for correction. We continue with a widely accepted concept: the correlation between the intestinal microbiome and chronic constipation, which can be for better or worse. Next, we consider intestinal dysbiosis, which accompanies the process, and how to address it. We continue with analysis of short-chain fatty acids, secondary bile acids and, microbiota metabolites, which have a variable impact on chronic constipation. We continue with topic of how the intestinal membrane is affected in chronic constipation and what can develop, such as the passage of pathogenic bacteria through it, with the resulting consequences. We review whether various biotics should be provided, such as pre-, pro-, and symbiotics, as well as postbiotics, psychobiotics, and bacteriophages. We conclude with the importance of intestinal microbiota transplantation.

Keywords: *Chronic Constipation (Cconst); Gut Microbiome (GM); Gut Dysbiosis (ID); Biotics (Biot); Fecal Microbiota Transplantation (FMT)*

Introduction

Constipation is defined as unsatisfactory defecation, characterized by infrequent bowel movements, difficulty evacuating, or both. It affects approximately 15% of the world's population, generating a significant healthcare burden. Its etiology and pathophysiology are poorly understood and are likely multifactorial. The use of biotics (Biot) is recommended for chronic idiopathic constipation in adults. This, along with the Gut Microbiota (GM), is an area of scientific research. There is evidence that it may be a cause of conditions such as cognitive impairment and cardiovascular processes [1]. The use of fiber and exercise are substantially helpful. A high Healthy Eating Index, along with high levels of physical activity and adequate water intake, is usually effective. Or the administration of laxatives, which are generally safe [2]. Remes JM and his team [3], in an electronic survey, demonstrated that physical inactivity or its reduction frequently leads to constipation, as occurred in the COVID-19 pandemic.

Pathophysiology: It can be due to primary or secondary causes. Primary causes usually occur due to anorectal or colonic disorders, and secondary causes are due to organic, systemic, or medication-related conditions. Common causes include: obstruction, metabolic evacuation disorder due to hypothyroidism or hypercalcemia. Neurological: Parkinson's disease, multiple sclerosis. Systemic: Scleroderma, amyloidosis. Psychiatric: Depression and eating disorders. Abnormal defecation could be due to pelvic floor dysfunction. It is linked to aging and dysmotility. It includes functional constipation and irritable bowel syndrome (IBS), in which there is a low presence of *Actinobacteria*, including *Bifidobacteria*, in fecal samples. It also has a high level of *Bacteroidetes* [4].

Gut microbiome and chronic constipation: All new research includes the correlation between the new organ: Gut microbiome (GM) and chronic constipation (Cconst). This is also linked to the presence of Gut Dysbiosis (GD), based on 16S rRNA or metabolomic studies. However, it should be noted that consensus is still being reached regarding the impact of GM on Cconst [5]. However, there are differences in GM composition when comparing constipated patients with healthy controls. The GM breaks down food into nutrients, stimulating the immune system, preventing bacterial growth, and producing important biological compounds [6]. The GM plays a fundamental role in the pathogenesis of constipation, although causality remains uncertain, likely due to confounding factors in observational studies. Feng C and his group concluded that the relationship between GM and Cconst interact at the genetic level, and that GM may influence the onset of constipation, while constipation may alter the gut microbiota [7]. Metabolomic advances indicate that GM metabolites such as SCFA, bile acids, neurotransmitters, and microbial gases influence the regulation of intestinal function [8].

Gut dysbiosis: (ID) can contribute to chronic constipation and related symptoms, including alterations in colony structures and their metabolites, as well as through the brain-gut-microbiota axis. Cao H and his group [9] confirmed this by using Fecal Microbiota Transplantation (FMT) in mice that received fecal microbiota from patients with constipation. They presented reduced intestinal peristalsis and abnormal defecation parameters, including pellet expulsion frequency, fecal weight, and fecal water content.

Short-chain fatty acids, secondary bile acids, and others: The decrease in SCFA affects intestinal motility and modulates it by having a trophic effect on epithelial cells, increasing blood flow in the region. It has been observed that when deoxycholic acid influences mediated signaling, it further affects motility. Conversely, imbalances in amino acid metabolism and neurotransmitter production generate neuromuscular dysfunction. Finally, the production of microbial gases further modulates intestinal transit [10]. SCFA and secondary bile acids (BA) have opposing effects on colonic inflammation at physiological levels. Primary BA play a determining role in lipid digestion, cholesterol metabolism, and the interaction between the host and microorganisms. They are also substrates for bacterial biotransformation into secondary BA. Higher dietary fiber intake has anticancer and anti-inflammatory effects. It does this by increasing butyrate and propionate [11].

Intestinal mucosal barrier: Is the first line of defense against many harmful substances and aids in intestinal homeostasis. Recent studies have reported that structural and functional changes are involved in the pathogenesis of several intestinal pathologies. Mucosal barrier dysfunction and GM alteration have been demonstrated in patients with Functional Constipation. Wang JK., *et al*. [12] found that the intestinal mucosal barrier in patients with Functional Constipation increased calciform cells and integral intercellular junctions, without activating mucosal immunity or increasing intestinal permeability. The use of SCFA and tryptophan catabolites, which 5-hydroxytryptamine pathways and Toll-like receptors, may be promising [13].

Biotics and chronic constipation: Inulin is the best prebiotic, along with fructooligosaccharides, for stimulating bacterial growth in the ileum [14]. Biot have been the subject of numerous animal trials, demonstrating an association with GM and immune markers, which leads to overall health. It has been determined that Biot consumption helps maintain bacterial diversity, improves immune homeostasis of the intestinal mucosa, and provides protection against lifestyle disorders.

Probiotics, prebiotics, symbiotics and chronic constipation: Araújo MM and team [15], in a bibliographic search in the PubMed database, indicate that supplementation with prebiotics and probiotics showed a decrease in colonic transit time and an increase in the number and water content in the feces. Increasing the frequency of defecation and improving stool consistency. There are incomplete answers regarding the optimal dose, time of consumption and duration.

No evidence to recommend use of symbiotics in chronic constipation, due to heterogeneity and risk of bias.

Other biotics: Include psyllium husks, laxatives, lactulose, lubiprostone, *Bifidobacterium*, and *Lactobacillus*.

Postbiotics: Purposefully inactivated microbial cells, with or without metabolites and cellular components, that remain stable for several years and offer reproducible results. They are not viruses, vaccines, filtrates, cellular components, purified microbial components, or bacterial metabolites. They are usually beneficial for health. Regarding Cconst Lévano CD., *et al*. [16] indicate that postbiotics are useful in Cconst, observing changes from abnormal constipation to improvement (Bristol Scale), with an increase in the presence of *Bifidobacterium longum* and *Roseburia hominis*, suggesting additional value for the administration of postbiotics. This gives it value for administration in this common pathology.

Psychobiotics: They can be useful for managing Cconst, as they modify GM and relieve gastrointestinal symptoms, as well as anxiety. The psychobiotic was used for 2 months, resulting in improvement in both depression and anxiety, with minimal side effects. Psychobiotics are new probiotics that, when consumed in adequate amounts, provide psychological benefits. They modulate the hypothalamic-pituitary-adrenal axis by influencing the immune system and through the production of neurotransmitters and neurohormones, such as proteins or SCFA [17].

Bacteriophages: Numerous members of the intestinal virobiota, which can be used when *Bifidobacterium* and *Lactobacillus* levels decrease and Cconst appears. The most frequently used are *Lactobacillus* [18]. They attack specific bacteria and have been detected in animal and human organisms (oral, gastrointestinal, respiratory, urinary, and serum tracts). They constitute an alternative to the use of antibiotics and are particularly useful in the treatment of resistant bacterial infections. They replicate through two alternative cycles: lytic and lysogenic. In the first, they infect bacteria, forming new particles. A bacteriophage particle adsorbs a bacterial cell and multiplies within it, destroying it [19].

Fecal microbiota transplantation and chronic constipation: An effective method for restoring GM and treating chronic constipation. Tian Y and colleagues [20] evaluated the technique using 16S ribosomal ribonucleic acid (rRNA) sequencing. They observed a lack of serious complications and a cure rate of 73.5% in three procedures per patient. Intestinal peristalsis was promoted, increasing motility and serum levels of NO and 5-HT. High concentrations of *Bacteroides, Klebsiella, Megamonas, Erysipelotrichaceae*, and *Epulopiscium* were found as probable causes of chronic constipation, and high concentrations of *Prevotella, Acidaminococcus*, and *Butyricimonas* were found as factors contributing to its cure. Xu X and colleagues [21] analyzed various therapeutic approaches, with special mention given to FMT, given its good results, in almost all reviews. Wang L and his group [22] evaluated 218 patients with Cconst, analyzing the presence of SIBO, detecting relief in ($P < 0.05$), and abdominal, rectal, and bowel symptoms were alleviated; while the patients' quality of life improved substantially. Finally, Tian H and his group [23], evaluating FMT, carried out daily for six days, reported that it was more effective, with no serious adverse events to regret.

Future Perspectives

Cconst represents diverse and complex combinations of disorders. Most studies use the Rome criteria for its diagnosis. Results from clinical studies on probiotics and FMT suggest that the process is caused by ID. Therefore, future studies should first categorize

constipation to identify the aims population. Studies on GM may identify bacterial species that promote the development of Cconst syndrome. Ultimately, identifying the causative bacteria may lead to the development of probiotic, prebiotic, symbiotic, postbiotic, psychobiotic, and bacteriophage treatments that can cure constipation in the future.

Conclusion

- The use of fiber, as well as exercise, water intake, laxatives, and diet, are substantially helpful.
- The integration of metabolomics with GM research clarifies how specific microbial metabolites regulate intestinal function.
- Increased dietary fiber intake has anticancer and anti-inflammatory effects.
- Metabolomic advances indicate that GM metabolites such as SCFA, bile acids, neurotransmitters, and microbial gases influence the regulation of intestinal function.
- FMT is an appropriate procedure to correct Cconst.

Conflicts of Interest

The authors declare that do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

Declaration on the Use of Artificial Intelligence

The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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