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(Review Article)

Laxative effect of prebiotics in chronic constipation: Mechanisms of action

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Abstract

Constipation is a condition that affects a consistent part of the general population, with increasing numbers of incidence worldwide. Its causes can be attributed to several factors. One of these factors (and one of the most relevant causes) is dietary choices. For instance, poor nutrition habits have been shown to adversely affect the function of the digestive tract, eliciting abnormal physiological responses that might lead to constipation. Prebiotics are specialized types of fermentable fibres which have been hypothesised to play a beneficial role in the treatment of chronic idiopathic constipation. Fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS) and inulin are the most common types of prebiotics. There are several studies to demonstrate that prebiotics have many interactions with the bowel and its movements, thus they are potentially beneficial in the treatment of chronic idiopathic constipation. Some prebiotics can retain water and therefore increase stool mass and viscosity, making the passage of faeces through the gastrointestinal tract easier. In addition, prebiotics can feed the probiotic bacteria (the body's "good" bacteria that synergistically live in the digestive tract), and the fermentation of prebiotics by the probiotic bacteria leads to the production of short-chain fatty acids (SCFAs). SCFA synthesis through prebiotic fermentation has been shown to improve gastrointestinal function and bowel movement. Moreover, prebiotic fermentation in the colon might trigger both immunomodulatory responses and the production of neurotransmitters that elicit stronger contractility in the colon. Prebiotic fermentation from the gut microbiota might trigger the release of neurotransmitters that interact with the central nervous system (CNS) and enteric nervous system (ENS). These bacterial neuromodulators directly affect the digestive nerve terminals, eliciting responses from the digestive tract that result in a faster and easier defaecation. Besides the existing studies that describe the roles of prebiotics in gut health and motility, their beneficial role has not yet been fully understood and proven, thus further research is needed on the topic.

Keywords: Constipation; Dietary fibre; Prebiotics; Gut microbiota; Short chain fatty acids; Mechanisms

1 Introduction

1.1 Chronic constipation

Varying from individual to individual, the normal transit time is between 30 and 40 hours. Constipation is defined as the reduction and infrequency of bowel movement (less than three times a week, with a transit time of more than 70 hours) [1] with the result of poor passage of stool, which usually becomes hard and dry. If it persists for several weeks, it is described as chronic constipation and it is a common condition that affects millions of people every year (up to the 20% of population in determined geographic areas), representing one of the main causes of visit to the gastroenterologist yearly [2][3][4][5]. Chronic constipation has a negative impact on everyday life of the affected individuals, and it presents a socioeconomic burden since it affects nearly 10-15% of the population, with higher incidence in female patients and elderly patients. Chronic constipation has several possible aetiologies. One of the most common is attributed to dietary choices that might affect bowel movement. However, the exact pathophysiology of chronic constipation is not yet fully understood. The diagnosis of chronic constipation is usually performed with the

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Rome IV diagnostic criteria, as most of the times the diagnosis is based on symptomatology alone. Only when an underlying cause is suspected, further tests are performed [6][7]. The management of chronic constipation depends on the underlying cause of the condition, and, since most cases can be attributed to dietary issues, the most recommended first-line treatment is to switch to high fibre (including prebiotics) diets. Other treatments include laxatives and prescribed medications, which may often dissatisfy the patient due to poor outcomes and potential side effects [8][9][10].

2 Brief overview of Fibres

Dietary fibres are plant-derived polysaccharides of ten or more monomeric units that cannot be fully digested by the human digestive system [11]. Depending on their solubility in water, they are classified into soluble fibre (e.g. psyllium, pectin, etc.), which are usually fermentable, and insoluble fibre (cellulose, hemicellulose etc.), which are usually poorly fermented by the gut microbiota [11]. Dietary fibres are widely recommended in diets since they play a key role in promoting digestive health for the prevention of constipation [12][13]. Studies have shown that the recommended doses for men and women aged between 19 and 50 are 38 g/day and 25 g/day, respectively [14][15]. Many fibre supplements are available commercially. For instance, psyllium, a soluble fibre, which possesses hydrophilic properties (high solubility and viscosity), and therefore can retain water, thus increasing stool volume and viscosity, and consequently improving bowel movement [16][17].

2.1 Prebiotics

Prebiotics are a type of fermentable fibre that promotes the activity and growth of the gut microbiota. The concept of prebiotics was firstly introduced in 1995, and since then the studies over them have grown exponentially over the years [18]. In order to be classified as a prebiotic, a fibre should meet the following criteria: it must be fermented by the gut microbiota, and must selectively stimulate the growth and activity of the probiotic bacteria in the gut. The human gastrointestinal tract hosts a wide number of microorganisms and bacteria, called the “gut microbiota” [19]. The gut microbiota plays several roles in gut motility, with the immune system as well as the central nervous system involved through the gut-brain axis [20]. Prebiotics usually target bacteria such as Lactobacilli and Bifidobacteria in the colon, causing a more notable change in their interaction with Bifidobacteria in comparison with Lactobacilli. This might be because of the more prominent presence of Bifidobacteria in the human colon [21][22][23][24]. Besides the aid in constipation, prebiotics present several other benefits for the healthy individual, and their ingestion has shown to be safe tolerable up to 30-45 g per day without altering the normal functions of the gastrointestinal tract [25]. There are several types of prebiotics, but most of them belong to the family of oligosaccharide carbohydrates (OSCs). Fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and inulin are the main types of prebiotics. FOS and inulin, also known as fructans, are contained in a prominent number of plants. GOS derives from lactose through enzymatic reaction of trans-glycosylation [26].

3 Current Status of Knowledge

3.1 Prebiotics and Constipation

3.1.1 Stool Volume/Mass

Prebiotics have been shown by some researchers to increase the stool volume and enhance colonic motility. The stool increases in size and volume by absorbing water and bacteria, with this increase associated with an acceleration of the transit time [27]. In addition, water retention can also increase viscosity which might in turn improve stool consistency. Microscopically, the water is absorbed by the fibre cell wall pores, while the capillary areas outside the walls stay empty. The thinner the wall is, the higher is the water binding capacity of prebiotics [28]. Moreover, by increasing the stool volume, prebiotics reduce the bile acid and salt concentration in the faecal matter, thus increasing its osmotic load which might contribute to the transit time acceleration [28] [29].

3.1.2 Gut Microbiota Fermentation

Prebiotic fermentation produces short-chain fatty acids in the colon that increase the osmotic gradient. The increase in the osmotic gradient can increase the stool volume, and therefore accelerate transit time. Fermentation of prebiotics leads to the production of short-chain fatty acids (SCFAs), such as acetic, propionic, and butyric acid. SCFAs might contribute to the pH lowering in the colon, making the replication of several pathogens more difficult and easing the proliferation of the beneficial bacteria (Bifidobacteria and Lactobacilli) [30][31] [32][33]. Moreover, SCFAs are absorbed by the intestinal wall mostly by non-ionic diffusion but also by active transport through the sodium-coupled transporter. This can lead to water absorption with a subsequent increase of water in the stool) [34]. The concentration of SCFAs produced depends on the species and number of the probiotic bacteria present in the gut [35]. Some in vitro studies have shown the connection between SCFAs and gut mucosa through vagal nerve fibres and afferent enteric nerves, which showed to elicit increased contractility of the GI tract. Also, butyrate promotes cell differentiation and arrest, and inhibits the enzyme histone acetylase conversion of primary to secondary bile acids resulting in enhanced serotonin levels, which might lead to increased gut contractility [28][36][37][38].

3.2 Immune System

Prebiotics have been also shown to possess anti-inflammatory properties. SCFA production stimulates T cell production, which subsequently decreases the expression of the gene of histone deacetylase 9, which has been associated with decreased inflammation, allowing better colonic motility [39]. Moreover, butyric acid inhibits histone deacetylase (HDAC) through G protein coupled receptor signalling, resulting in an enhanced intestinal barrier function, with subsequent increased mucosal immunity [40]. The role of prebiotics in inducing gastrointestinal immunity might result in a more functional colon, therefore improving colonic motility [41]. In addition, prebiotic fermentation by Bifidobacteria and Lactobacilli in the gut might lead to the reduction of the number of several harmful pathogens [41]. Another crucial property of prebiotics in immunity is their ability to trigger the production of several cytokines. FOS can enhance the levels of anti-inflammatory compounds in the serum such as CD282+/TLR2+ myeloid dendritic cells and interleukin 4 (IL-4), while they can reduce the expression of interleukin 6 (IL-6) and phagocytosis by the immunity cells, hence, they can decrease inflammation [42] [43]. Enhanced immunity might result in a more functional colon, and therefore might be associated with improved colonic motility [43].

3.3 Nervous System

Prebiotic fermentation has been shown to alter the nervous and consequently the digestive system through the "gut-brain axis" [44]. The fermentation can produce bacterial metabolites that can act directly on Enteric Nervous System (ENS) nerve fibres in the gut, hence, prebiotics may trigger the release of neuromodulators in the digestive tract [45][46]. The ENS mediates most of the digestive functions (motility, immunity, secretions, etc.) through direct control of the organs that make the digestive system (gastrointestinal tract, liver, gallbladder, and pancreas) [47] [48]. One of the neurotransmitters released by prebiotic and gut microbiota interaction in the digestive tract is serotonin (5-hydroxytryptamine or 5-HT), which acts on the ENS enhancing the smooth muscle contractility, thus increasing gut peristalsis [49]. Serotonin is consistently present in the digestive tract, and it is stored in the enterochromaffin cells, whose release is mediated by several stimuli. Serotonin acts on the 5-HT3 receptors, present on the afferent vagal nerve fibres, resulting in an increased degree of colonic contraction [50][51][52][53][54][55].

4 Conclusion

Prebiotics can increase stool mass, enhance gut contractility, and thereby increase stool frequency and soften stool consistency. This can be achieved through several mechanisms involving the gut microbiota, immunomodulatory responses, and neuromodulation. Yet, their beneficial role in the treatment of chronic constipation needs further investigation as the mechanisms of action are still not fully understood to demonstrate a clear positive impact in the treatment of the condition. Further research is required to fully establish the complex interactions of the luminal environment, immune system, and nervous system on gut motility and constipation and how different prebiotics affect them.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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