PROBIOTICS AND PREBIOTICS IN THE MANAGEMENT OF CONSTIPATION IN THE ELDERLY

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ABSTRACT

The prevalence of constipation and its impact on quality of life are high among elderly people, with a incidence of 26% in men and 34% in women aged 65 or more. The current standard treatment consists of laxatives administration, lifestyle modifications such as regular physical activity and increased fluids and fibers intake. Several studies have demonstrated that modifications in the intestinal microflora of elderly could alter the metabolic environment of the colon with important changes in the concentration of physiologically active substances that may alter the motor and secretory functions of the bowel. Probiotics are live microorganisms (such as Bifidobacteria and Lactobacilli), which, when administered in adequate amounts, confer a health benefit to the host. Studies examining the effects of probiotics on constipation in elderly are limited, and different strains have been used so far. The aim of this review is to summarize the best available data and indications regarding probiotics as a tool for the management of constipation in the elderly.

Key words*: Probiotics, Constipation, Bifidobacterium, Prebiotics, Elderly.*

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Introduction

Constipation is a common condition affecting elderly people. According to "Rome criteria III" it is characterized by the presence of two or more of the following symptoms occurring for at least 12 weeks: hard or lumpy stools, painful and strained defecation, a sense of incomplete evacuation, the need to use manual manoeuvres to pass stool or sense of anorectal obstruction with >25% of bowel movements and/or <3 bowel movements per week, no evidence for irritable bowel syndrome (IBS)(1). The prevalence of constipation and its impact on quality of life are high among elderly, with a incidence of 26% in men and 34% in women aged 65 or more(2). The prevalence rises to 80% in people living in nursing homes and hospitals because of many risk factors, including immobility, chronic medical conditions (e.g. diabetes mellitus, hypothyroidism, dementia, Parkinson disease, neuropathy), and drugs (e.g. anticholinergic, antidepressants, opiod analgesics, nonsteroidal anti-inflammatory drugs)(3).

Primary or idiopathic constipation is divided into three subtypes:

a) functional constipation (normal transit and pelvic floor function)(4);

b) slow transit constipation (abnormal bowel motor function)(5);

c) outlet delay constipation (inability to coordinate actions of abdominal musculature, anorectum and pelvic floor musculature)(6).

Secondary constipation is caused by medical conditions (gastrointestinal, neurologic, endocrine and metabolic diseases) and medications. The current standard treatment consists of laxatives administration that promotes bowel movements and the passing of soft stools without pain(7) (Table 1).

Class	Agents	Mechanism of action
Bulk-forming laxatives	*Psyllium, bran, methylcellulose, calcium polycarbophil.*	Increase water absorption from the intestinal lumen, thereby softening stool consistency, and increasing stool bulk.
Osmotic laxatives	*Polyethyleneglicol, lactulose, sorbitol and saline laxative.*	Increase the amount of water in the large bowel, either by osmotic secretion of water into the intestinal lumen.
Stimulant laxatives	*Senna, bisacodyl.*	Stimulate the myenteric nerve plexus and increase intestinal motility. They also increase secretion of water into the bowel.
Stool softeners and emollients	*Docusatesodium, docusatecalcium.*	Ionic agents that moisten the stool through a detergent action.
Chloride channel activators	*Lubiprostone*	Bicyclic fatty acid that acts as a selective chloride channel activator. It increases intestinal water secretion.
Other agents	*Tegaserod*	Selective 5-HT4 receptor agonist, reduces constipation
		symptoms and increases bowel movements.

Table 1: Classification of laxatives.

Other treatments include lifestyle modifications such as regular physical activity and increased fluid and fibers intake. However there is no evidence to support an increased fluid intake in older people and caution is required in patient with renal or cardiac failure[8]. Regular exercise is frequently recommended for the management of constipation basing on the assumption that exercise may reduce the gastrointestinal time transit[9]. “Dietary fibers” consists of non digestible carbohydrates and lignin that are intrinsic and intact in plants. Dietary fibers or non-starch polysaccharide are composed of cellulose, non cellulose polysaccharide and lignin. It can be decomposed by colonic bacterial flora but not by human digestive enzymes. In the colon, anaerobic enzymes produce substances as short-chain fatty acids and gases, as well as energy, which bacteria use for growth and maintenance. Grains, legumes, vegetables and fruits are main foods rich in “dietary fibers”. The “functional fiber” is defined as a non-digestible carbohydrate extract from food that have positive effects in people. The “total fibers” is the sum of dietary fibers and functional fibers[10]. Different types of fibers have different effects on stool weight. The cellulosic polysaccharides increase the stool weight, decrease the transit time and resist the digestion better than non-cellulosic polysaccharides. Soluble fibers (e.g. pectins, inulin, fructo-oligosaccharides) are less effective on increasing the stool weight and some of them are totally fermented in the colon. Moreover, in the colon fermented fibers contribute to increase bulk by increasing microbial mass, while less well fermented fibers increase bulk by their water-holding properties. Non-degraded fibers increase bulk in the colon thus leading to a decreased transit time and a less water reabsorption. The consequence of this process is an increasing stool weight[11]. The diminished intake of dietary fibers contribute to constipation. In fact several studies showed that adequate fibers supplementation increases stool weight and intestinal transit time[12]. Dietary fibers intake is the simplest, most physiologic and cheapest treatment for constipation[13].

Gut microflora

The gastrointestinal tract is a complex ecosystem and our knowledge about the intestinal microbiota is still limited. The gut of human adult is colonised by approximately 1014 microbial cells, about 10 times more than all tissue cells of the body taken together[14]. This great metabolic potential suggests important regulatory effects on body functions, especially in the colon where the largest concentration of up to 5x1011 bacterial cell per g is found. The “autochthonous” microorganisms include more than 400 species and diverse bacterial genera, of which the Gram-positive, anaerobic genera Bacteroides, Eubacterium, Bifidobacterium are predominant.

On the other hand, Peptostreptococcum, Streptococcum, Lactobacillus, Fusobacterium, Ruminococcus, Clostridium and Escherichia also play a role in the maintenance of a stable gut mucosa and in the generation of short chain fatty acids (SCFA) in a favourite ratio[15]. Several studies have demonstrated a decrease in bifidobacteria and an increase in clostridia, lactobacilli, streptococci and Enterobacteriaceae in the gut microflora of elderly people[16]. These modifications in the intestinal microflora could alter the metabolic environment of the colon with important changes in the concentration of physiologically active substances that may alter the motor and secretory functions of the bowel. Consequently, bifidobacteria, more generally the lactic acid bacteria (LAB), are an important component of a good balanced intestinal microbiota and are often used as probiotics[17]. Further changes in the microflora increase susceptibility to gastrointestinal functional disorders, infections, inflammation or cancer[18, 19]. Conversely, probiotics and prebiotics can promote the homeostasis of the colonic microbiota[20]. Causes of changes in the microflora with age are still unclear. Several physiological and immunological modifications occur in the old person[21] (Table 2).

Genera	Young-adult people	Elderly people
Bacteroides	+++	--+
Bifidobacterium	+++	--+
Clostridium	-+	+++
Streptococcus	+--	+++
Lactobacillus	++-	+++
Enterobacteriaceae	+--	+++
Fungi	+--	+++

Table 2: Age-related changes in gut microflora.
+: increase
-: decrease

It has been suggested that some bacterial strains could take advantage of new ecological niches, thereby inducing a shift in the composition of the gut microflora[22]. The decreasing colonisation of elderly people by certain species of bifidobacteria could be caused by a reduced adhesion to the mucosa[23].

Probiotics

According to the Joint FAO/WHO Working Group 2002 the definition of probiotics: “live microorganisms which when administered in adequate amounts, confer a health benefit on the host”[24]. Probiotic microorganisms live mainly in the large intestine but also in other organs where they modulate immunological parameters, intestinal permeability and bacterial translocation and provide bioactive or regulatory metabolites. Probiotics modulate the bowel microflora and inhibit colonization of the gut by pathogens and translocation of bacteria through the intestinal wall[25]. Mechanisms of these effects include a decrease of intestinal pH, production of antimicrobial substances, agglutination of pathogenic bacteria[26, 27] integrity of the gut mucosa, competition for substrates or receptors on the mucosa wall, release of gut-protective substances (arginine, short chain fatty acids (SCLA)[28, 29] and neutralization of toxic or cancerogenic molecular substances, modulation of immune system[30] and stimulation of peristalsis[31]. Most probiotic products contain bacteria from the genera Lactobacillus or Bifidobacterium, although many other genera have been marketed as probiotics (Table 3).

Lactobacilli and Bifidobacteria are Gram positive, lactic acid-producing bacteria. In particular, lactobacilli are non-spore forming rod-shaped bacteria. They are strictly fermentative, aerotolerant or anaerobic, aciduric or acidophilic. Lactobacilli are available on animal and human mucosal membranes, on plants or material derived plant, sewage and fermented milk products fermenting or spoiling food. Bifidobacteria are the main strain of the human microflora. The number of bifidobacteria in the colon of adults ranges between1010-1011 CFU/g, but this number decrease with age. They are non-spore forming rods, non-motile and strictly anaerobic. As effects of probiotics have been shown to be strain specific, it is essentially to report health benefits for single strains or for a mix of strains separately[32, 33, 34]. According to the definition of Food and Nutrition Board, a functional food can be defined as “any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains”. Functional food may contain health-promoting microorganisms. Also, foods must be healthy, safe and free of pathogenic and toxic effects. Probiotic microorganisms must resist to gastric acid, bile and digestive enzymes. Effects on human health are bacterial strains specific, clearly defined with modern molecular biological detection methods. 108-109 probiotic bacteria daily are often sufficient to achieve healthy effects. Furthermore, the effects of probiotics change with age, gender, health and diet environment (rural or urban) (Table 4).

Prebiots

A prebiotic is “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a

LACTOBACILLI	BIFIDOBACTERIA	OTHERS
L. acidophilus-group	B. longum(BB536)	Enterococcusfaecium
L.acidophilus(LA-5)	B. longum (SP 07/3)	Enterococcusfaecalis
L. crispatus (L. acidophilus "Gilliland")	B. bifidum(MF 20/5)	Lactococcuslactis
L. johnsonii (LA1)	B. infantis	Streptococcusthermophilus
L. gasseri (PA 16/8)	B animalis (B. animalisssp. lactisBB-12)	Propionibacteria
L. casei- group	B. adolescentis	E. colic (E. coli"Nissle 1917")
L.(para) casei- L. (para)casei (L. casei) "shirota" L. casei "defensis")	B. breve	Sporolactobac. Inulinus
L. rhamnosus(LGG)		Spores of Bacillus cereus
L. reuteri		"toyoi"
L. plantarum(299 and 299v)		Saccharomyces boulardii

Table 3: Bacteria genera with probiotic effects.

limited number of bacteria in the colon"[35]. Thus, health-promoting bacteria, especially, but not exclusively, lactobacilli and bifidobacteria, may become predominant in the colonic microflora[35,36]. So, a prebiotic can be defined as a "bifidogenic" substance. Roberfroid introduced the prebiotic index defined as the absolute increase of the fecal bifidobacteria concentration per gram of daily-consumed prebiotics[37].

• Yogurt-like, solid or liquid milk products
• Sour milk, sour whey, sour cream, buttermilk
• Fresh cheese
• Ice cream
• Sweets, e.g cookies and chocolate
• Meat products

Table 4: Examples of probiotic foods.

According to the definition, prebiotics are non digestible carbohydrates but they can be fermented by the intestinal microbiota. These oligosaccharides (chains consisting of 3 to 10 carbohydrate monomers) include inulin, oligofructose (FOS), galactooligosaccharides (GOS), lactulose, lactosucrose and xylooligosaccharides[38]. Effects of prebiotics include a increase of bifidobacteria or lactobacteria cell counts on the intestinal microflora and a decrease of pathogenic bacteria as well as stabilization of the intestinal environment by lowering of pH and release of short chain organic acids. These effects depend on the type and concentration of the prebiotic and on the bifidobacteria concentration on the gut of the host. So, inulin, oligofructose or GOS, as well as their synbyotic combination with probiotic bacteria (strains of L. Plantarum, L. Paracesei or B. Bifidum), increased bifidobacteria and lactobacilli or inhibited various human- and animal pathogenic bacteria strains (Clostridium spec, E. Coli, Campylobacter jejuni, Enterobacterium spec., Salmonella enteritis or S. Typhimurium) in vitro or in mice, piglets or humans[39-41] (Table 5). It is not the prebiotic by itself but rather the changes induced in microbiota composition that is responsible for its effects. Many studies showed an increase in bifidobacteria and lactobacilli on the intestinal microflora after administration of prebiotics[40, 42, 43]. Bifidobacteria are thought to improve the immune system, produce B vitamins, inhibit pathogen growth, reduce blood ammonia and blood cholesterol levels, and help to restore the normal flora after antibiotic therapy[34, 44]. Lactobacilli may help digestion of lactose in lactose-intolerant individuals, reduce constipation and infantile diarrhea, help to resist infections such as salmonellae and relieve irritable bowel syndrome[45]. Criteria for classification of a food ingredient as prebiotic include resistance to gastric acid, bile, enzymatic digestion and intestinal absorption, fermentation by intestinal microbiota, beneficial effect to the host health, selective stimulation of probiotics and stability to food processing treatment. In humans, intestinal fermentation can be studied measuring breath hydrogen or fecal recovery of the administered carbohydrates after a single prebiotic meal[46].

Prebiotic	Proven effect
Oligosaccharides, undigestible but fermentable in the colon	
Lactulose	B +, P -, PM -
Lactosucrose	B +
Xilooligosaccharides	B +
Glucooligosaccharides	B +
Prebiotic oligosaccharides	
Fructooligosaccharides	B +, P-
Galactooligosaccharides	B +, P-
Oligofructose	B +, P-
Inulin	B +, P-

Table 5: Effects of prebiotics on gut microbiota.
B: bifidogen, P: putrefactive/pathogenic bacteria, PM: putrefactive metabolites

Selective promotion of the growth and activity of the gut bacteria are difficult to measure. The best in model vitro is the measure of bacterial counts in fecal samples before and during exposure to the test material in batch or multichamber fermentation systems. Carbohydrates have a positive prebiotic activity score if they aremetabolized, as well as glucose, by probiotic strains and are selectivelymetabolized by probiotics but not by other intestinal bacteria. Candidate prebiotics are reported to be particularly suited tothe growth and activities of the probiotics such as bifidobacteria and lactobacilli. Beneficial effects of prebiotics on constipation include an increased biomass, fecal stool weight and frequency and healthy benefits on the mucosa of the bowel[47, 48]. Adverse effects of prebiotics include headache, belching, flatulence, bowel contractions or liquid stool. Several prebiotics are found in vegetables and fruits and can be industrially processed from renewable materials.

In food formulations, they can significantly improve organoleptic characteristics, upgrading both taste and mouth feel. To serve as functional food ingredients, prebiotics must be chemically stable to food processing treatments, such as heat, low pH, and Maillard reaction conditions. In fact, a prebiotic would no longer provide selective stimulation of beneficial microorganisms if it was degraded to its component mono- and disaccharides or chemically altered and unavailable for bacterial metabolism. Huebner et al showed that heating at low pH (30 min at 85 °C, pH 4-7) caused an important reduction in prebiotic (FOS and inulin) activity. Low pH (pH 3 to 6) and Maillard reaction conditions (up to 6 h at 85 °C with 1% glycine, pH 7) caused only little change in activity[49].

Most prebiotics and prebiotic candidates identified today are non-digestible oligosaccharides. They are obtained either by extraction from plants (e.g., chicory inulin), possibly followed by an enzymatic hydrolysis (e.g., oligofructose from inulin) or by synthesis (by trans-glycosylation reactions) from mono - or disaccharides such as sucrose (fructooligosaccharides) or lactose (trans-galactosylated oligosaccharides or galactooligosaccharides)[50]. Among these prebiotics, inulin and oligosaccharides are the most studied prebiotics and have been recognized as dietary fibers in most countries[51]. Prebiotics can be used for either their nutritional advantages or technological properties, but they are often applied to offer a double benefit: an improved organoleptic quality and a better-balanced nutritional composition[52]. Food applications of prebiotics are summarized in Table 6.

Yoghurts and desserts
Breads and fillings
Beverages and drinks
Meat products
Dietetic products
Chocolate
Cake and biscuits
Sugar confectionary
Soups and sauces
Baby food

Table 6: Food applications of prebiotics.

Effects of probiotics and prebiotics on constipation in thr elderly

Probiotics might have therapeutic potential for the treatment of constipation for several reasons. Some studies showed differences in the intestinal microbiota between individuals in good health and patients with chronic constipation in which an increased number of Clostridia and Enterobacteriaceae are frequently isolated[53].

The origin of this dysbiosis is unclear. It is not clear if dysbiosis is a secondary manifestation of constipation, or it is a factor that promotes the constipation. Probiotics may reduce pH in the colon by the bacterial production of short chain fatty acids (butyric acid, propionic acid, and lactic acid).

A lower pH enhances peristalsis in the colon and, subsequently, might decrease the colonic transit time[7]. It has been reported a reduction of transit time after 10-day intervention with Bifidobacterium animalis DN-173 010[54], and an increase in stool frequency after a 2 weeks intervention with Lactobacillus casei Shirota[55]. On the contrary, no beneficial effect on constipation was reported in a clinical trial performed on subjects receiving Lactobacillus rhamnosus GG[56]. Many studies reported beneficial changes in the microbial metabolism in the colon of people with gut function disorders. The main metabolic markers of probiotic benefits include short chain fatty acid levels (SCFAs), faecal enzyme activity and certain toxic or carcinogenic compounds[57]. SCFAs in the gut, for example, stimulate host receptors for gut motility and the immune response, and regulate mucosal gene expression. The SCFA butyrate, an important energy source for colon cells, is involved in regulation of their growth. Probiotics have also been associated with production of substances that inhibit tumour growth, neutralisation of harmful molecular substances in the gut, and inhibition of species that can produce promoters, mutagens and carcinogens[58, 59, 60]. Phenol, cresol and ammonia are metabolites produced by colonic fermentation.

A significant reduction of such substances was associated with consumption of a probiotic containing L. casei Shirota, in double-blind placebo-controlled trials involving healthy subjects[61, 62], and similar results have been reported after administration of other probiotics[63-66]. Bifidobacterium animalis intake reduced gut transit time in a group of subjects free of anygastrointestinal pathology[54]. In an open trial on elderly subjects, a commercial mixture of Lactobacillus rhamnosus and Propionibacterium freudenreichii improved defecation frequency in 24% of subjects, but no reduction in laxative use was observed[66]. Thus, probiotics may be effective in patients with mild to moderate constipation. However, theeffect of lactic acid bacteria ingestion may be dependent on the bacterial strain used andthe population being studied. On the other hand, there are no studies evaluating theeffect of probiotics as compared to fibre supplements[67]. In a clinical trial, 19 old patients suffering from chronic constipation were assigned to receive Lactic acid bacteria (LAB) (3.0 × 1011 CFU/g) twice a day for 2 weeks. Subjects draw up a questionnaire on defecation habits (frequency of defecation, amount and state of stool).

Analysis of data showed that there was an increase in the frequency of defecation and amount of stool excreted in defecation habit after LAB treatment, but there were no significant changes. LAB treatment also affected the intestinal environment, through significantly increase ($p<0.05$) of fecal LAB levels. In addition, tryptophanase and urease among harmful enzyme activities of intestinal microflora were significantly decreased ($p<0.05$) after LAB treatment[3]. Data suggested that Bifidobacterium animalis, Lactobacillus caseiShirota, Lacidophilus, L paracasei, L rhamnosus and Propionibacterium freudenreichii might increase the frequency of defecations and reduce the time of bowel transit[7]. Prebiotics such as FOS, galacto-oligosaccharides (GOS), lactulose, and inulin act as substrates for lactic acid bacteria, thus improving their growth in the intestine. The widely used laxative lactulose is not digested by human disaccharidases, and is a substrate for the Bifidobacteria in the colonic flora. Placebo-controlled trials have shown that lactulose (15–30 ml twice a day) is effective in increasing stool frequency and stool consistency in patients with mild to moderate chronic constipation[68, 69]. Other prebiotics could be a promising therapy for chronic constipation[70].

A study was initiated to test the effects of lactose or inulin on the bowel habits of constipated elderly patients. Two groups of 15 and 10 patients received lactose and inulin, respectively, for a period of 19 days. Only inulin stimulated the growth of Bifidobacteria and suppressed other microorganisms such as Enterococci in number and Enterobacteria in frequency. The latter microorganisms are potentially pathogenic, causing autogenous infections when host resistance mechanisms fail, possibly as a result of gastrointestinal disorders in aging[71].

A recent study has associated the use of a synbiotic (a combination of prebiotics and probiotics) of lactitol and Lactobacillus acidophilus twice daily in healthy elderly subjects, with increased stool frequency, as well as other indications of positive results in the intestinal microbiota composition and mucosal function[72].

Conclusion

The role of normal intestinal flora in the maintenance of health and in the prevention of functional bowel disorders is well known.

Studies examining the effects of probiotics and prebiotics on constipation in elderly people are limited, and different strains have been used in those published so far. Although results are conflicting, the evidence is that specific probiotic strains are more effective than others. In general probiotics are safe and rare cases of adverse effects occurred in immunocompromised subjects or in patients with other life-threatening illnesses, who were managed in intensive care units[7].

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