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Original Research

Specific prebiotic composition for precision bacterial therapy in patients with irritable bowel syndrome

Abstract

Various factors can alter the balance of the gut microbial ecosystem, including food imbalances, gastroenteritis, dyspepsia, inflammatory bowel diseases and antibiotic therapy, potentially causing the condition generally identified as dysbiosis. The objective of this observational study was to evaluate the impact of a precision prebiotic mixture based on inulin, galacto-oligosaccharides (GOS), fruit-oligosaccharides (FOS), isomaltooligosaccharide (IMO), lactulose and polydextrose marketed under the name Fibradis® on gut microbiota. Fibradis® is formulated with the specific intent of promoting the physiological development of bifidobacteria and lactobacilli in patients diagnosed with irritable bowel syndrome (IBS) and already receiving treatment where treatment had successfully resolved painful symptoms but symptomatic residues remained such as discomfort, meteorism, flatulence, diarrhoea (IBS-D) and constipation (IBS-C) or alternating episodes of diarrhoea and constipation (IBS-M), potentially suggestive of a residual intestinal dysbiosis. In addition to their normal treatment, to which no changes were made, 24 patients took one sachet of 3.3 g Fibradis® on an empty stomach every day before breakfast for 14 days. A symptomatology assessment was performed at t0 and t1 using a score between 0 and 10 according to the visual analogue Scott-Huskisson scale. In patients undergoing IBS therapy but with residual symptoms, taking one sachet of Fibradis® for 14 days is related to a significant reduction in meteorism and flatulence and improved intestinal function, demonstrating good tolerability. Further larger studies, with a more articulated protocol and more specific recruitment dynamics will further clarify the potential of this first precision prebiotic formulation in the management of intestinal dysbiosis.

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Introduction

The human intestine is an extremely complex organ both anatomically and biologically. Anatomically, the small intestine reaches lengths between 7 m and 11 m with diameters between 27 mm and 47 mm, with a total volume of 6000 ml. It has an estimated absorbent surface of around 400 m2 thanks to its structural architecture with folds, villi, and microvilli.

The colon, with an average length of 1.8 m, has remarkable distensibility with the ability to reach circumferences between 14 cm and 28 cm [1]. These anatomical and microstructural features encourage the development of a considerably complex ecosystem, both along the course of the intestine and in the thickness of the mucosa [2]. The gut microbiota hosts between 150 and 400 bacterial species, viruses and fungi and is a fundamental element for human health [3]. The development of the gut microbiota begins at birth via contact with the maternal anatomical structures [4], progressively evolving towards adulthood through food dynamics and through every element capable of intervening at the level of the microbial ecosystem [2–4].

The gut microbiota acts as a polyfunctional 'organ' [5] promoting digestive processes, producing some micronutrients and substances useful for the well-being and maintenance of the intestinal microenvironment, promoting immune development and protecting against pathogenic microorganisms through competition for the ecological niche and through the production of antimicrobial substances defined as bacteriocins [8, 9]. Various factors can alter the quantitative and qualitative balance of the gut microbial ecosystem, including food imbalances, gastroenteritis (with diarrhoea) of different aetiology, dyspepsia, inflammatory bowel diseases with or without malabsorption, antibiotic treatment (or drug treatments capable of altering the dynamics of the gut microbiome), causing the condition generally identified as dysbiosis. Intestinal dysbiosis generally manifests itself with a wide range of symptoms such as borborygmus, abdominal distention, meteorism, changes in bowel movement (diarrhoea, constipation, or alternating between the two) pain, etc. [10–15]. Among the many possible interventions are administration of live and vital microorganisms (probiotics) or energetic substrates for the resident microbiota (prebiotics) or a mixture of the two (synbiotics) [16–18]. One of the biggest limitations of prebiotics, and therefore of synbiotic applications also, is a non-specific action that can result in a series of side-effects similar to some IBS symptoms, including abdominal distension, pain, meteorism and flatulence. Although it remains a macroscopically non-specific approach in supporting the intestinal microbiota, prebiotic treatment can be specialized to create a precision prebiotic therapy, considering at least two of the main targets generally believed to aid intestinal well-being and used in probiotic therapies: lactobacilli and bifidobacteria. From the evaluation of their quantitative ratios and their metabolic affinity for different types of fibres, it is possible to create a blend that, considering these aspects, assumes a certain rational character of specificity. In an intestine considered healthy, bifidobacteria and lactobacilli are found in a ratio of approximately 10:1. Rationally, a first fundamental measure for a precision prebiotic therapy would involve the provision of energy substrates with a high affinity for bifidobacteria and lactobacilli in this same ratio [19–20]. Considering the high bifidogenic effect of fibre, inulin (a mixture of fructose oligosaccharide polymers with 10–12 subunits joined by beta-2-1-glucosidic bond and naturally present in many plant species), galacto-oligosaccharides (GOS) (galactose oligomers) and fruit-oligosaccharides (FOS) (polymers with 3–5 subunits with alternation of D-fructose and D-glucose) represents a good

choice of prebiotic treatment and have been widely researched. In addition, GOS and FOS occurs in a 9:1 ratio in breast milk and have metabolism and fermentability times such as to allow their use in the first portion of the colon, while inulin is metabolized and fermented mainly in the final colon tract. Considering these characteristics and to favour a balanced development, the GOS/FOS mixture (in a 9:1 ratio) must be in a 1:1 ratio respectively with inulin [21–28]. Considering the high lactogenic effect of fibre, it is necessary to consider a suitable effect that would allow a proportionate production of butyrate, propionate, acetate and lactate, favouring the development of the relative bacteria, the well-being of the intestinal epithelia and defence from pathogenic microorganisms. Drawing on what is suggested by the scientific literature, the most favourable choice may be represented by the mixture of isomaltooligosaccharide (IMO) (isomalt polymers, disaccharide formed by glucose and mannitol), lactulose (D-lactose and D-fructose disaccharides obtained semi-synthetically) and polydextrose (dextrose polymer) in the ratio 2:1:1 [29–34].

Materials and methods

Patient selection criteria

A total of 24 participants – 18 women and 6 men – aged between 18 and 62 years were evaluated. All participants were currently being treated for IBS and had experienced a resolution of painful symptoms but retained symptomatic residues such as discomfort, meteorism, flatulence, diarrhoea (IBS-D) and constipation (IBS-C) or alternating episodes of diarrhoea and constipation (IBS-M), potentially suggestive of residual intestinal dysbiosis.

Individuals with other ongoing pathologies, pregnant women, individuals receiving drug treatment (other than for treatment for IBS) or taking any other nutraceutical product, individuals diagnosed with psychiatric or behavioural disorders, and those who consumed alcohol, drugs, tobacco and its derivatives were excluded from evaluation.

Evaluated products and evaluation scheme

The objective of this observational study was to evaluate the impact of a mixture of fibres with the aim of obtaining a precision prebiotic effect at the level of bifidobacteria and lactobacilli on patients diagnosed with IBS and already receiving treatment where treatment had successfully resolved painful symptoms but symptomatic residues remained such as discomfort, meteorism, flatulence, diarrhoea (IBS-D) and constipation (IBS-C) or alternating episodes of diarrhoea and constipation (IBS-M), potentially suggestive of residual intestinal dysbiosis.

The observational study and data analysis were carried out in accordance with good clinical practice rules fixed by the Declaration of Helsinki and in accordance with the European Union Directive 2001/20 / EC [35]. Each patient signed a consent form and privacy policy documents and approved data analysis and publishing.

The nutraceutical product considered is a mixture of prebiotic fibres constituted with the logic previously discussed and as indicated in **Table 1**, notified to the Italian Ministry of Health as a food supplement by Pharmextracta SpA (Pontenure, PC, Italy) complying with Law no. 169/2004 (notification number: 40633), marketed under the name Fibradis®.

Table 1 Composition of precision prebiotic product

Name	%	Total Bifidogenic/Lactogenic
Inulin	45	90
GOS	40	
FOS	5	
IMO	5	10
Lactulose	2.5	
Polydextrose	2.5	
Total prebiotic fibres	100	

In addition to their regular treatment, to which no changes were made, the 24 evaluated patients took one 3.3 g sachet containing the mixture of fibres described every day for 14 days, on an empty stomach before breakfast. At t0 and t1 a symptomatology assessment was performed using a score between 0 and 10 according to the visual analogue Scott-Huskisson scale, evaluating the symptoms listed in **Table 2**. Tolerability was also assessed for the entire treatment period with a score from 0 to 4, where 0 = absent; 1 = poor; 2 = fair; 3 = good; 4 = excellent (see **Table 2**).

Table 2 Symptom score and tolerability score

Symptom	Minimum score	Maximum score
Meteorism	0	10
Flatulence	0	10
Alternating constipation and diarrhoea (14/24)	0	10
Constipation (5/24)	0	10
Diarrhoea (5/24)	0	10

Tolerability: 0 = absent; 1 = poor; 2 = fair; 3 = good; 4 = excellent

Results

After 14 days of use, an evaluation of symptoms showed a significant reduction in gastric discomfort and the production of intestinal gas, helping to counteract the alternating episodes of constipation and diarrhoea, albeit to a lesser extent, as indicated in **Table 3**. The tolerability was very positive: apart from one reported headache no other adverse effects could be identified as attributable to the treatment; no patients dropped out of the evaluation, as indicated in **Table 4.**

Table 3 Symptom score (M±SD) at t0 and t1 in 24 patients

Symptom	t0 Score (day 0)	t1 Score (day 14)
Meteorism	8±2	2±2
Flatulence	8±2	2±2
Alternating constipation and diarrhoea (14/24)	9±3	0
Constipation (5/24)	8±2	3±0
Diarrhoea (5/24)	9±2	0

Table 4 Tolerability score and adverse events

Parameter	Result	Patients
Tolerability	Excellent	5/24
	Good	19/24
Adverse events	Headache	1/24
Drop out	Absent	0

Discussion

Based on the results obtained, the blend of fibres created with the aim of obtaining a precision prebiotic effect at the level of bifidobacteria and lactobacilli shows good applicative potential in reducing symptoms of IBS in patients undergoing treatment but without complete symptomatological remission.

Compared with other approaches, prebiotic fibres have the considerable advantage of remaining easily stable in their finished pharmaceutical forms [36], of not requiring a demonstrable ability to overcome the gastric and biliary barriers in a living and vital form and, above all, of not having the need to demonstrate colonizing capacity [37]. The fibres discussed, after being metabolized by the relative bacteria, allow the production of acetic acid, lactic acid, butyric acid and propionic acid with the function of promoting the trophism of the intestinal epithelia, the maintenance of a physiological pH, the maintenance of physiological dynamics of transit and defence against pathogenic microorganisms [38]. These results confirm how any disadvantages related to the phenomenon of gas production following fermentation (a possible cause of meteorism and flatulence) can be managed through the rationalization of dosages and the use of different sources of fibre rather than a single one, high- dose fibre [39]. Being the result of an articulated and rational analysis, Fibradis® can be considered the first real example of precision prebiotic therapy, with targeted action on two specific components of the intestinal microbiota.

Conclusions

In conclusion, in patients undergoing IBS therapy with residual symptoms, taking of 3.3 g/day for 14 days of a precision prebiotic mixture based on inulin, GOS, FOS, IMO, lactulose and polydextrose (Fibradis®), formulated with the specific intent of promoting the physiological development of bifidobacteria and lactobacilli is related to a significant reduction in meteorism and flatulence scores and improved intestinal function. Furthermore, it demonstrates a good tolerability in the study period under consideration. Further larger studies, with a more articulated protocol and more specific recruitment dynamics will contribute to further clarification of the potential of this first precision prebiotic formulation in the management of intestinal dysbiosis.

Author contributions All authors contributed equally to writing of the manuscript; all authors read and approved the final version of the manuscript.

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Conflict of Interest A Bertuccioli works as a scientific consultant for the company responsible for developing Fibradis®.

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