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Beta-glucan, inositol and digestive enzymes improve quality of life of patients with inflammatory bowel disease and irritable bowel syndrome

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Abstract. – OBJECTIVE: To evaluate the efficacy of a mixture of beta-glucan, inositol and digestive enzymes in improving gastrointestinal symptoms in patients affected by inflammatory bowel disease (IBD)-irritable bowel syndrome (IBS).

PATIENTS AND METHODS: The study was conducted at the IBD Unit of the University of Catanzaro. Forty-three IBD patients with IBS symptoms were included in the study. IBD diagnosis was performed by clinical, endoscopic, histological and radiological criteria. Patients were in clinical remission and in treatment only with systemical and topical mesalamine. All study participants fulfilled the Rome III criteria for the diagnosis of IBS. The study participants were randomized into 2 groups: group A (n=23) received conventional treatment (systemical and topical mesalamine) plus a mixture of beta-glucan, inositol and digestive enzymes (one tablet after lunch and dinner) for four consecutive weeks; group B (n=20) received only conventional treatment. The prevalence and intensity of gastrointestinal (GI) symptoms were evaluated both at the enrollment (T0) and after four weeks of treatment (T1).

RESULTS: Patients who received mesalamine plus the mixture of beta-glucan, inositol and digestive enzymes (group A) reported a reduction in abdominal pain together with reduction in bloating and flatulence after four weeks of treatment. Importantly, an overall improvement in the general well-being has been recorded. Patients who underwent only mesalamine treatment (group B) reported a mild reduction in the evacuative urgency without any other improvements.

CONCLUSIONS: We have shown that supplementation with a mixture of beta-glucan, inositol and digestive enzymes reduces bloating, flatulence and abdominal pain, improving the overall clinical condition of IBD-IBS patients.

Key Words
Intestinal permeability, Immunomodulatory function, FODMAPS, Rome III criteria, Irritable bowel syndrome, Inflammatory bowel disease.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by abdominal pain and changes in the bowel habits. With a worldwide population prevalence between 10% and 15%, IBS represents the most prevalent gastrointestinal disorder[1]. Inflammatory bowel disease (IBD) is an inflammatory disorder of the gastrointestinal tract characterized by chronic relapsing inflammation and immune activation. IBD encompasses Crohn's disease (CD), ulcerative colitis (UC) and its estimate prevalence is approximately 0.3% of the European population[2].

Despite the difference in characteristics and prevalence between IBD and IBS, these two diseases share some pathogenetic mechanisms, such as dysregulation of the immune system, alteration of the gut microbiota and of the gastrointestinal mucosa permeability[3]. Additionally, many patients with IBD continue to experience symptoms of abdominal pain and diarrhea, despite minimal or no active inflammation. For these patients it has been recently proposed the definition of a new disorder: the IBD-IBS syndrome[4,5]. The prevalence of the IBD-IBS syndrome is highly variable. A recent meta-analysis showed that 25-46% of IBD patients in clinical remission have symptoms compatible with a diagnosis of IBS[6]. Due to the high prevalence of the IBD-IBS, different treatments have been proposed ranging from dietary interventions (low FODMAPS diet)[7,8] to fibers, antispasmodics and anti-diarrheal. Recently, it has been shown that a mixture of beta-glucan, inositol and digestive enzymes improves gastro-intestinal (GI) symptoms in patients with IBS[9], while no data are available on the effect of this mixture on GI symptoms in IBD-IBS patients. Beta-glucans are a very heterogeneous

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class of d-glucose-derived polysaccharides present in cell walls of bacteria, fungi and yeasts. Yeasts derived beta-glucans have an immunomodulatory function and have also been considered for cancer therapy[10]. Specifically, yeast-derived beta-glucans seem to help the immune system by stimulating type 2 T helper cells, which in turn, modulate and mitigate type 1 T helper cells. This modulation leads to a balance between the two lymphoid systems, which results in a decrease of the intestinal inflammatory process. Additionally, b-glucans stimulate phagocyte activity, enhance protection against sepsis, infections and inflammation-associated tumour, and also against IBD development[11-14]. Inositol ($C_6H_{12}O_6$) is a natural nutrient which occurs in animal and plant tissue. The most prominent form of inositol is the myo-inositol, which was obtained for the first time by muscle tissue. Myo-inositol is a member of the vitamin B complex (namely vitamin B8), present in a variety of foods including vegetables, fruits, liver, pork and veal. Myo-inositol is a component of plasma membrane and represents a key-role player in many biological processes including intracellular signaling, intracellular calcium concentration control, and cell membrane potential maintenance[15]. Myo-inositol has been proposed as therapy for many diseases including constipation. Specifically, it has been shown that myo-inositol stimulates contractility of the gastrointestinal tract improving intestinal regularity and bloating[9].

Digestive enzymes are a group of enzymes (proteases and peptidases, lipases, carbohydrases amyloglucosidases, nucleases, lactase and cellulases) that catalyze the break down of complex macromolecules into simple molecules in order to facilitate their absorption by the intestinal tract. Given the action of beta-glucan, inositol and digestive enzymes, the administration of a mixture of these 3 molecules may be effective also in the treatment of IBD-IBS patients. Thus, the aim of this study was to evaluate the efficacy of a mixture of beta-glucan, inositol and digestive enzymes (in addition to mesalamine) in improving gastrointestinal (GI) symptoms in IBD-IBS patients.

Patients and Methods

The study was conducted at the IBD Unit of the University of Catanzaro. Inclusion criteria for the study were as follows: IBD patients in clinical remission (defined as Crohn disease activity index score < 150 or Mayo score < 2 for CD and UC respectively), with IBS symptoms and with reactive C-protein (RCP) < 5 mg/l, erythrocyte sedimentation rate (ESR) < 30 mm/h, fecal calprotectin < 50 µg/g, and in treatment only with systemical and topical mesalamine. A total of 100 patients with an established diagnosis of IBD, performed by clinical, endoscopic, histological and radiological criteria, were screened. Among these, 43 individuals fulfilled the inclusion criteria and were included in the study. All study participants fulfilled the Rome III criteria for the diagnosis of IBS[16]. Exclusion criteria were as follows: treatment with steroids, antibiotics, immunosuppressants or biological agents for at least 6 months before the beginning of the study. Additionally, patients who underwent abdominal surgery were not included in the study. Study participants were simple randomized into 2 groups: group A (n=23) received conventional treatment (systemical and/or topical mesalamine) plus a mixture of beta-glucan, inositol and digestive enzymes (one tablet after lunch and dinner) for four consecutive weeks; group B (n=20) received only conventional treatment. All patients underwent a questionnaire to investigate the prevalence and intensity of gastrointestinal (GI) symptoms both at the enrollment (T0) and after four weeks of treatment (T1). Specifically, prevalence and intensity of GI symptoms were graded as follow:

- Meteorism (from 0 to 10);
- Flatulence (from 0 to 10);
- Abdominal pain (from 0 to 10);
- Evacuative urgency (from 0 to 10);
- Number of daily evacuation;
- Feeling of incomplete defecation (yes/no);
- Stool transit (from 1/helping with the hands to 7/inability to keep stool inside);
- Stool shape (Bristol stool scale).

Statistical Analysis

Categorical variables distribution across the 2 study groups was compared by Fisher exact test. Continuous variables distribution across the 2 study groups was compared by Mann-Whitney non-parametric test for independent samples. Changes in intensity of GI symptoms after 4 weeks of treatment were evaluated by Wilcoxon non-parametric test for related samples. *p*-value < 0.05 was considered significant. All analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 100 consecutive IBD patients were screened at the IBD Unit of the University of Catanzaro. Of these, 43 met the inclusion criteria and were included in the study. No drop out occurred; all the included patients successfully concluded the four weeks treatment. Anthropometric, clinical and biochemical characteristics of the study participants are shown in Table I. Briefly, patients were adults (mean age 49±14 years) with a mean BMI of 25±4 kg/m^2. Approximately half of them were male and 14% were smokers. 65% of patients had UC with a mean Mayo score of 1.9±1.5 while 35% had CD with a mean Crohn disease activity index score (CDAI) of 1.5±1. There were no differences in the anthropometric, clinical and biochemical characteristics between the 2 study groups at the enrollment (T0) (Table I).

A mixture of beta-glucan, inositol and digestive enzymes improves gastrointestinal symptoms after four weeks of treatment

Patients who underwent treatment with mesalamine plus the mixture of beta-glucan, inositol and digestive enzymes (group A), reported a 64% reduction in abdominal pain (Figure 1A) together

Table I. Anthropometric, clinical and biochemical characteristics of the study participants.

	Overall Cohort	Group A	Group B	*p**
N	**43**	**23**	**20**	
Demographic and Anthropometric				
Male gender n (%)	23 (54)	15 (65)	8 (40)	0.131
BMI (kg/m^2)	25±4	24±3	26±5	0.137
Age (years)	49±14	49±13	51±15	0.836
Smoke	6 (14)	5 (22)	1 (5)	0.192
Disease characteristics				
Ulcerative Colitis/Crohn's Disease n (%)	28/15 (65/35)	12/11 (52/48)	16/4 (80/20)	0.107
Disease duration	6±6	7.9±7.6	4.9±3.8	0.302
Disease location n (% of CD patients)				
Ileal	6 (40)	4 (36)	2 (50)	0.999
Ileo-Colonic	9 (60)	7 (64)	2 (50)	0.999
Disease location n (% of UC patients)				
Proctitis	3 (11)	2 (17)	1 (6)	0.560
Proctosigmoiditis	3(11)	1 (8)	2 (12)	0.999
Left-side	8 (29)	4 (33)	4 (25)	0.691
Pancolitis	14 (50)	5 (42)	9 (56)	0.704
CDAI	1.5±1.0	1.3±0.8	2.0±1.4	0.454
Mayo Score	1.9±1.5	1.8±1.3	1.9±1.6	0.873
ESR (mm/h)	16.8±20	10±12	10±11	0.116
RCP (mg/l)	3.7±4.2	2.6±3.4	5.1±4.8	0.460
Fecal Calprotectin (µg/g)	45.4±8.7	44.8±8.4	46.1±9.1	0.608
IBS subtype				
Diarrhea	26 (60)	16 (69)	10 (50)	0.704
Constipation	15 (35)	6 (26)	9 (45)	0.219
Mixed	2 (5)	1 (4)	1 (5)	0.999
Gastrointestinal symptoms*				
Abdominal pain	5±3	5.0±3.0	5.0±3.0	0.883
Bloating	7±3	7.0± 2.6	7.3±2.4	0.702
Flatulence	6±3	6.0±3.6	6.1±3.2	0.951
Evacuative urgency	3±3	3.0±3.0	3.4±3.0	0.413
Stool shape (Bristol stool scale)	4±1	3.3±1.6	3.7±1.1	0.491
Number of daily evacuation	2±2	2.0±2.0	2.0±1.2	0.612
General being	6±2	7.0±1.6	6.3±1.4	0.453

Continuous variables are shown as mean ± standard deviation. Categorical variables are presented as number and proportion (%).
*p-value has been calculated comparing Group A vs. Group B. Categorical variables distribution across treatment was compared by χ^2-test. Continuous variables distribution across treatment was compared by Mann-Whitney test.
**Prevalence and intensity of gastrointestinal (GI) symptoms have been investigated using a self-administered questionnaire as described in Materials and Methods section.

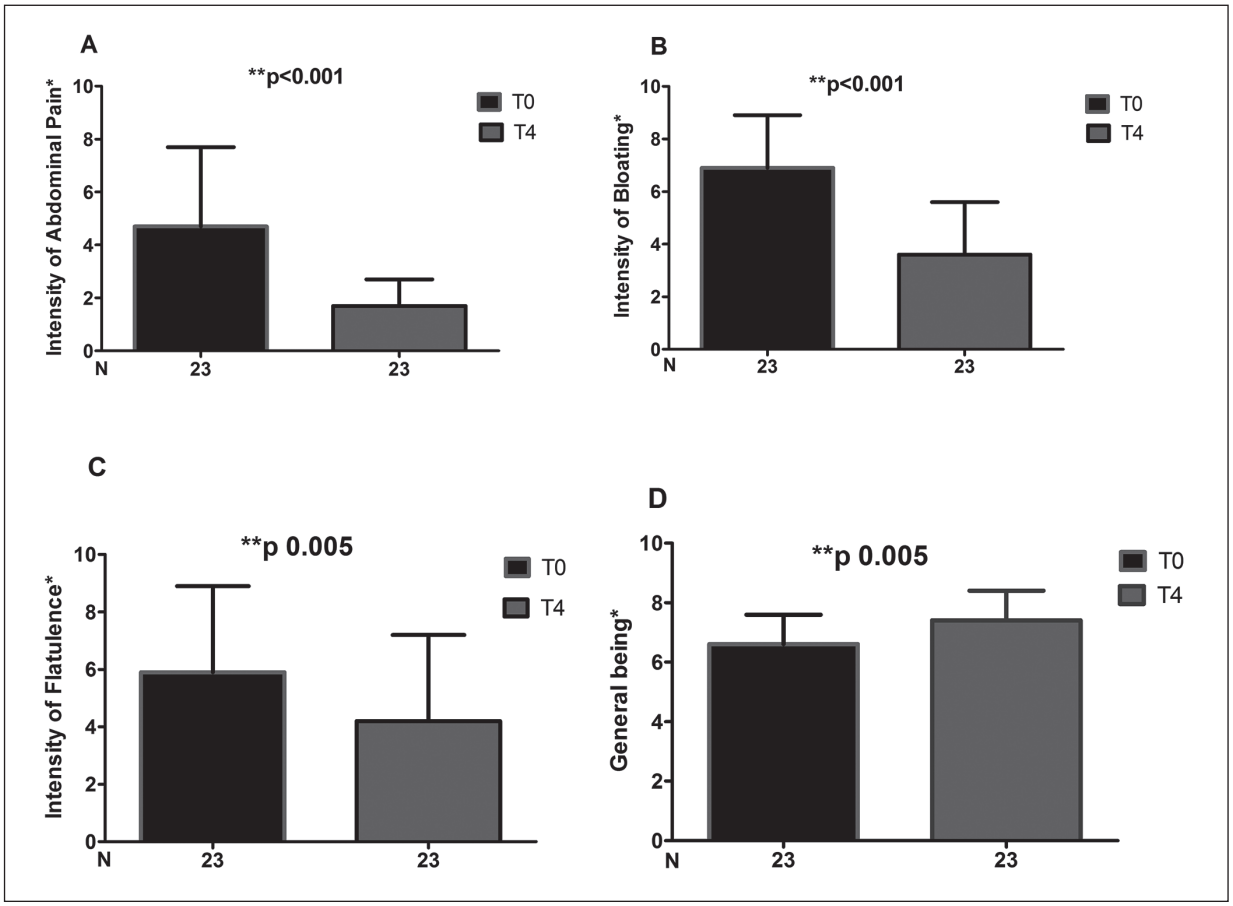

Figure 1. . A mixture of beta-glucan, inositol and digestive enzymes improves gastrointestinal symptoms after four weeks of treatment. Patients who underwent treatment with the mixture of beta-glucan, inositol and digestive enzymes (group A) reported a reduction in: **A**, Abdominal pain; **B**, Bloating; **C**, Flatulence. These patients reported additionally an improvement in the general well-being (**D**). Variables are shown as mean ± standard deviation. *p*-values were calculated by Wilcoxon non-parametric test.

with 48% reduction in bloating (Figure 1B) and 29% reduction in flatulence (Figure 1C), after four weeks of treatment. Importantly, a 12% improvement in the general well-being has been recorded (Figure 1D). Patients who underwent only mesalamine treatment (group B) reported a mild reduction in the evacuative urgency (18% *vs.* 84% reduction observed in patients from group A). No other improvements in GI symptoms have been observed in this study group, after four weeks of treatment (Table II). No changes in inflammatory markers and in fecal calprotectin have been detected in both study groups (Tables II-III).

Discussion

In this study we investigated the effectiveness of a mixture of beta-glucan, inositol and digestive enzymes (in addition to mesalamine) in improving GI symptoms in IBD-IBS. To do this, we performed a randomized study with 43 IBD patients with IBS-like symptoms. The study participants were randomly assigned to 2 groups: group A received mesalamine plus the mixture for 4 weeks; group B received only mesalamine for 4 weeks. Our results show that patients who received mesalamine plus the mixture had a strong reduction in abdominal pain, bloating and flatulence, reflecting an overall improvement in the quality of life of these patients. These findings indicate that treatment with mesalamine plus a mixture of beta-glucan, inositol and digestive enzymes is more effective in improving quality of life of IBD-IBS patients than the treatment with only mesalamine, also in terms of savings in the use of steroids and immunosuppressant. Our study failed to detect changes in the inflammatory markers currently used for the

Table II. Intensity of gastrointestinal symptoms, inflammatory markers and fecal calprotectin at the entry and after four weeks in group B.

	T0	T1	p
ESR (mm/h)	10±11	9.2±11	0.999
RCP (mg/l)	5.1±4.8	4.3±3.0	0.092
Fecal Calprotectin (μg/g)	46.1±9.1	45.8±8.6	0.320
Gastrointestinal symptoms*			
Abdominal pain	5.0±3.0	4.4±2	0.061
Bloating	7.3±2.4	7.1±1	0.050
Flatulence	6.1±3.2	6.0±2	0.084
Evacuative urgency	3.4±3.0	2.8±2	0.047
Stool shape (Bristol stool scale)	3.7±1.1	3.4±0	0.059
Number of daily evacuation	2.0±1.2	2.1±1	0.999
General being	6.3±1.4	6.1±1	0.660

Continuous variables are shown as mean ± standard deviation. Continuous variables distribution across treatment was compared by non-parametric Wilcoxon test.

Table III. Inflammatory markers and fecal calprotectin in group A.

	T0	T1	p
ESR (mm/h)	10±12	8.25±12	0.999
RCP (mg/l)	2.6±3.4	4.0±5.0	0.999
Fecal Calprotectin (μg/g)	44.8±8.4	44.7±8.6	0.876

Continuous variables are shown as mean ± standard deviation. Continuous variables distribution across treatment was compared by non-parametric Wilcoxon test.

definition of disease remission. This may support the idea that these markers could not be considered valid standards for the definition of IBD remission and that the identification of more sensible markers is needed. The efficacy of this mixture in improving IBS-related GI symptoms has been previously shown[9]. Specifically, it has been shown that the treatment with a mixture of beta-glucan, inositol and digestive enzymes reduces bloating, flatulence and abdominal pain in IBS patients after 4 weeks of treatment. Our study extends the efficacy of the mixture in improving GI symptoms to IBD patients with IBS-like symptoms. We speculate that improvement of the GI symptoms could be due to the anti-inflammatory effect of the beta-glucan. Indeed, beta-glucan reduces the production of pro-inflammatory cytokines such us IL10, IL12 and TNF-alpha. Furthermore, beta-glucan may have a prebiotic effect. It has been shown that beta-glucan supplementation modifies lactic acid bacteria level and the short chain fatty acid profiles in rat feces, thus reducing the risk of direct impact on the pathogenic microflora and the toxic effects of its metabolites[17,18]. The amelioration of GI symptoms could be additionally due to the effect of the inositol supplementation on intracellular calcium homeostasis. Specifically, inositol restores the intracellular calcium homeostasis, which is compromised in chronic inflammatory diseases of the intestine. This compromised calcium homeostasis determines intestinal dysmotility in mice and inositol supplementation, restoring the calcium homeostasis, re-establish the normal intestinal motility[15]. The main limit of our study is that it has been conducted on a relatively small number of individuals and for a relatively short period (only 4 weeks). Further studies are required to evaluate the long-term effect of the mixture.

Conclusions

Our findings provide new evidence on the synergistic function of beta-glucan, inositol and digestive enzymes in improving GI symptoms and extend the efficacy of this mixture from IBS to an IBD-IBS model.

Conflict of interest

The Authors declare that they have no conflict of interests.

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