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Research Article

Effects of Probiotic Supplementation in Non-Celiac Gluten Sensitivity Patients

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Abstract

Non-celiac gluten sensitivity (NCGS) is a clinical condition characterized by gastrointestinal and extra intestinal symptoms that occur shortly after ingestion of gluten, improve or disappear when gluten is withdrawn from the diet and recur if gluten is reintroduced. NCGS patients miss the biochemical markers of celiac disease and wheat allergy.

The aim of this study was to analyze the effects of oral administration of probiotics on the overall symptoms of NCGS patients. Twenty-two NCGS patients have been recruited in this study. Both the experimental (n=11) and the control (n=11) groups have been treated with a gluten free diet (GFD); only the patients of the experimental group received an oral supplementation of probiotics for 60 days. The occurrence of symptoms (related to NCGS) has been recorded before starting the GFD (baseline survey) and in four later follow-up visits.

The results have shown a decrease of the number of symptoms in patients of the experimental group from 30 days onwards, indicating that probiotic administration for a period of 30 days begins to improve the overall symptoms in NCGS patients. Probiotic administration has led to an improvement and, in some cases, to a complete remission of some symptoms, suggesting that it acts as a promising support for the diet therapy in NCGS treatment.

ABBREVIATIONS

NCGS: Non-Celiac Gluten Sensitivity; CD: Celiac Disease; GFD: Gluten-free Diet; IBS: Irritable Bowel Syndrome

INTRODUCTION

Worldwide, the growing consumption of gluten-containing foods is associated with an increase in the incidence of gluten-related disorders such as celiac disease (CD) and non-celiac gluten sensitivity (NCGS). Gluten is a structural protein in wheat and other cereals (such as barley, rye and spelt) and its components (gliadins and glutenins) give elasticity to gluten-containing foods when flours are mixed with water [1].

NCGS is an emerging clinical condition in the context of gluten-related disorders. In NCGS patients symptoms occur after gluten ingestion, disappear with a GFD and relapse when gluten is reintroduced. NCGS consists of a combination of symptoms similar to those of CD and irritable bowel syndrome (IBS): bloating and abdominal pain, alternating bowel habits with diarrhea or constipation. Sometimes NCGS is also characterized by systemic manifestations such as dizziness, headache, tiredness, joint and/or muscle pain, numbness in legs and/or arms, dermatitis and skin rash, aphthous stomatitis, anemia and, in some cases, associated autoimmune diseases represented by autoimmune thyroiditis, psoriasis and Grave's disease.

Because there are no biomarkers available, NCGS diagnosis is based on the exclusion of wheat allergy (negativity for specific IgE antibodies to wheat and/or skin prick test) and CD (absence of the typical serological, histological and genetic markers of CD). The lack of diagnostic criteria for NCGS diagnosis makes its prevalence difficult to define: an Italian prospective multicenter survey on patients suspected of having NCGS estimated that the likely NCGS prevalence in the general Italian population should be slightly higher than 1% [2,3,4].

It's been observed that some symptoms (such as bloating and abdominal pain, flatulence, bowel habits abnormalities with diarrhea or constipation) persist in NCGS patients even after

gluten withdrawal from the diet; this observation suggested to associate the GFD with probiotics administration, since probiotics represent a realistic therapeutic strategy in the maintenance of human health and in the treatment of various intestinal disorders [5]. Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host [6]. Probiotics differ greatly in their mechanism of action. They are able to enhance the beneficial components of the gut microbiota with healthy effects on epithelial barrier function, intestinal inflammation and immune system [7]. Probiotics belonging to the genera *Lactobacillus* and *Bifidobacterium* demonstrated to act as an interesting adjuvant in the dietetic management of CD [8], while studies on the effects of probiotics on NCGS symptoms are not available.

The aim of this study was to analyze the effects of oral administration of probiotics in association with a GFD on the overall symptoms of NCGS patients. NCGS patients treated with a GFD in association with probiotic administration have been compared with patients treated with a GFD only. The major decrease of the number of symptoms in NCGS patients treated with a GFD in association with probiotic administration (in comparison with NCGS patients treated with a GFD only) would confirm the role of the gut microenvironment in gluten response.

MATERIALS AND METHODS

This study was a longitudinal not randomized trial; each patient has been followed for 60 days. In all 22 study patients, celiac disease and wheat allergy have been ruled out by the absence of the specific biochemical, histological and genetic markers. All patients have been voluntarily enrolled (in the basis of symptoms) and they have been divided into two groups: an experimental group (n=11) and a control group (n=11). The experimental group included 8 females (72.7%) and 3 males (27.3%) with a mean age of 34.8 ± 4.7 years for females and 32.3 ± 8.2 years for males; the control group included 7 females (63.6%) and 4 males (36.4%) with a mean age of 35.0 ± 10.8 years for females and 34.3 ± 10.7 years for males (Table 1). In this study we didn't include a group of patients who received a gluten-containing diet to avoid the risk of diet interruption because of the symptoms.

All study patients have been treated with a GFD and only the individuals of the experimental group received a supplementation of an oral administrated probiotic pill (to take once a day between meals) for 60 days. In this study we have tested the multistrain probiotic supplement IDA® (see Table 2 for probiotic supplement composition) because of the high heterogeneity and the high number of probiotic microorganisms contained. The patients of the experimental group have been informed that the purpose of the study was to investigate the possible benefits of the probiotic supplementation on NCGS symptoms and this awareness could contribute to a placebo effect, conditioning their expectation of a positive outcome.

The data of both groups have been recorded during the baseline survey (before starting the gluten-free diet therapy) and in four later follow-up visits: first follow-up after 15 days from the baseline survey, second follow-up after 30 days, third follow-up after 45 days and fourth follow-up after 60 days from the baseline survey. During each visit we asked patients to refer the presence or absence of symptoms commonly associated to NCGS [7,9]: diarrhea, constipation, abdominal bloating, flatulence, nausea and/or vomit, eczema and/or rash, musculoskeletal and neurological symptoms (joint and/or muscle pain, numbness in legs and/or arms), headache, dizziness and difficulty concentrating [9,10]; we have also analyzed the total number of symptoms (total score of symptoms) as a single variable.

Table 1: Patients distribution between the two arms of the study.

	Experimental group n=11)		Control group (n=11)	
	Female	Male	Female	Male
n. (%)	8 (72,7%)	3 (27,3%)	7 (63,6%)	4 (36,4%)
Mean age ± st dev (years)	34,8 ± 4,7	32,3 ± 8,2	35,0 ± 10,8	34,3 ± 10,7

St dev: Standard Deviation

Table 2: Probiotic supplement composition.

Probiotic	Number of cells/500 mg
Streptococcus thermophilus	6.000 mln
Lactobacillus acidophilus	5.500 mln
Lactobacillus rhamnosus	5.000 mln
Lactobacillus plantarum	5.000 mln
Lactobacillus reuteri	4.000 mln
Lactobacillus lactis	2.000 mln
Bacillus coagulans	1.500 mln
Saccharomyces boulardii	1.000 mln

Data have been analyzed using STATA IC/12.1 software. The statistical analysis has been performed with mean value and standard deviation, and median and interquartile range (which showed to be more appropriated for the total score of symptoms). The statistical significance of the differences between the occurrence of symptoms in the two groups has been evaluated using the Chi-square test (χ^2) with the Fisher correction or Fisher's exact test; the statistical significance of the differences between the total number of s ymptoms (score) reported by the patients of the two groups in each follow up has been evaluated with the Wilcoxon's test and with the Cuzick's test for the whole observation period.

RESULTS AND DISCUSSION

Table 3 shows the percentage of individuals affected by each symptom (at the baseline survey and in the four later follow-up), a P value referred to the statistical significance of the differences between the percentage of NCGS patients affected by each symptom at baseline survey and in each follow up visit (P value obtained with Fisher's exact test) and a P value for the statistical significance of each symptom's decrease in each group during the whole observation period (P value obtained with Cuzick's test).

A detailed analysis of each symptom is reported below.

Diarrhoea

Patients were asked to indicate if they experienced diarrhoea

(three or more watery or soft bowel movements in a day) during the last three days prior the baseline survey and during the whole observation period. In the baseline survey all patients have reported the presence of diarrhoea; both groups have shown a decrease of such symptom: in the 4th follow up 3 subjects of the control group (27.3%) still reported its presence, while there has been a full remission in the experimental group. The reduction trend of the symptom diarrhea during the whole observation period is statistically significant for both groups to Cuzick's test ($p<0.001$), whereas there is no statistic significance to Fisher's exact test in the different percentage of subject reporting diarrhea in the experimental and control group in each phase of the study ($p>0.05$ at the baseline survey and in the four later follow up). Symptom's full remission in the control group can be explained with the mechanism of action of some probiotic microbes, especially *Lactobacillus* strains, which can enhance gut barrier function through the stimulation of mucus secretion by the epithelial cells of the intestinal tract [11].

Constipation

NCGS clinical picture is often characterized by alternating bowel habits with constipation (fewer than three bowel movements in a week) followed by diarrhea. Patients were asked to indicate if they experienced constipation during the last two weeks prior the baseline survey and during the whole observation period.

Constipation has been reported by all patients enrolled in the experimental group and by 8 subjects (72.7%) of the control group. The experimental group has shown a complete remission of such symptom from the 3rd follow up onwards; the control group has shown a persistence of constipation in 3 patients (27.3%) in the 4th and last follow up. Cuzick's test for the significance of the reduction trend during the whole observation period is statistically significant for both groups with a higher level of significance for the experimental group ($p<0.001$ vs $p<0.05$ in the control group). Fisher's exact test shows statistic significance in the decrease of the number of subject affected by constipation of each group only at the 3rd follow up ($p<0.05$). The reasons why probiotics might have beneficial effects in the treatment of constipation are several: many data demonstrate that there are differences in the composition of gut microbiota between patients with constipation and healthy individuals. Constipated individuals have an increased number of *Clostridia* and *Bifidobacteria*, but it is still unclear whether dysbiosis is a cause for constipation or a factor which contributes to it. Due to the probiotic bacterial production of short-chain fatty acids (SCFAs), including butyric acid, propionic acid and lactic acid, probiotics lower the pH in the colon and, subsequently, enhance peristalsis and reduce the colonic transit time [12].

Abdominal bloating

All 22 patients enrolled in the study have reported abdominal bloating at the baseline survey. In the 4th last follow up, 8 patients

Table 3: Time trend of symptoms in the two groups during the whole observation period.

Symptoms	Baseline (0 dd)			1st follow up (15 dd)			2nd follow up (30 dd)			3rd follow up (45 dd)			4th follow up (60 dd)			P value (Cuzick test)	
	Exper.	Contr.	Pvalue	Exper.	Contr.	P value	Exper.	Contr.	P value	Exper.	Contr.	P value	Exper.	Contr.	P value	Exper.	Contr.
Diarrhea (%)	100.0%	100.0%	n.s.	90.9%	100.0%	n.s.	45.4%	81.8%	n.s.	18.2%	36.4%	n.s.	0.0%	27.3%	n.s.	<0,001	<0,001
	(11/11)	(11/11)		(10/11)	(11/11)		(5/11)	(9/11)		(2/11)	(4/11)		(0/11)	(3/11)			
Constipation (%)	100.0%	72.7%	n.s.	81.8%	63.6%	n.s.	27.3%	36.4%	n.s.	0%	36.4%	<0,05	0%	27.3%	n.s.	<0,001	<0,05
	(11/11)	(8/11)		(9/11)	(7/11)		(3/11)	(4/11)		(0/11)	(4/11)		(0/11)	(3/11)			
Abdominal bloating (%)	100.0%	100.0%	n.s.	81.8%	90.9%	n.s.	18.2%	90.9%	<0,01	0%	81.8%	<0,001	0%	72.7%	<0,01	<0,001	<0,05
	(11/11)	(11/11)		(9/11)	(10/11)		(2/11)	(10/11)		(0/11)	(9/11)		(0/11)	(8/11)			
Flatulence (%)	72.7%	63.6%	n.s.	18.2%	63.6%	<0,05	0%	45.5%	<0,05	0%	27.3%	n.s.	0%	18.2%	n.s.	<0,001	<0,01
	(8/11)	(7/11)		(2/11)	(7/11)		(0/11)	(5/11)		(0/11)	(3/11)		(0/11)	(2/11)			
Nausea and/or vomit (%)	45.4%	63.6%	n.s.	9.1%	27.3%	n.s.	0%	9.1%	n.s.	0%	0%	n.s.	0%	0%	n.s.	<0,01	<0,001
	(5/11)	(7/11)		(1/11)	(3/11)		(0/11)	(1/11)		(0/11)	(0/11)		(0/11)	(0/11)			
Eczema and/or skin rash (%)	36.4%	36.4%	n.s.	36.4%	36.4%	n.s.	27.3%	36.4%	n.s.	9.1%	27.3%	n.s.	9.1%	27.3%	n.s.	<0,05	n.s.
	(4/11)	(4/11)		(4/11)	(4/11)		(3/11)	(4/11)		(1/11)	(3/11)		(1/11)	(3/11)			
Muscolo-skeletal and neurological symptoms (%)	45.4%	36.4%	n.s.	27.3%	27.3%	n.s.	0%	18.2%	n.s.	0%	9.1%	n.s.	0%	0%	n.s.	<0,001	<0,05
	(5/11)	(4/11)		(3/11)	(3/11)		(0/11)	(2/11)		(0/11)	(1/11)		(0/11)	(0/11)			
Headache (%)	54.5%	63.6%	n.s.	45.4%	45.4%	n.s.	9.1%	54.5%	<0,05	0%	45.4%	<0,05	0%	45.4%	<0,05	<0,001	n.s.
	(6/11)	(7/11)		(5/11)	(5/11)		(1/11)	(6/11)		(0/11)	(5/11)		(0/11)	(5/11)			
Difficulty concentrating (%)	63.6%	72.7%	n.s.	36.4%	54.5%	n.s.	9.1%	18.2%	n.s.	0%	9.1%	n.s.	0%	0%	n.s.	<0,001	<0,001
	(7/11)	(8/11)		(4/11)	(6/11)		(1/11)	(2/11)		(0/11)	(1/11)		(0/11)	(0/11)			

Exper: Experimental group; Contr: Control group; P value: P value obtained with Fisher's exact test; P value (Cuzick test): P value obtained with Cuzick's test; n.s.: not significant

(72.7%) of the control group have continued to be affected by that symptom, whereas a marked improvement has been observed in the experimental group in the 2nd follow up. A complete remission of such symptom has been observed from the 3rd follow up onwards. Cuzick's test is more significant in the experimental group ($p<0.001$) compared to the control group ($p<0.05$). Fisher's exact test shows the presence of statistic significance between the percentage of patients of the two groups affected by such symptom in the 2nd follow up ($p<0.01$) and in the later follow up ($p<0.001$ at 3rd follow up and $p<0.01$ at 4th follow up).

Flatulence

In the baseline survey, 7 patients of the control group (63.6%) and 8 patients of the experimental group (72.7%) have reported the presence of flatulence. The GFD alone have led to a reduction of the number of patients affected by such symptoms; in the 4th follow up 2 patients (18.2%) of the control group have continued to report the persistence of such symptom. Probiotic supplementations have led to a full remission of flatulence in the experimental group from the 2nd follow up onwards. The reduction trend during the whole observation period (evaluated with the Cuzick's test) is statistically significant for both groups, with a higher level of significance for the experimental group ($p<0.001$) compared to the control group ($p<0.01$). Fisher's exact test, used to analyze the presence of statistic significance between the percentage of patients of the two groups affected by such symptom in every single phase of the study, shows statistic significance in the 1st follow up ($p<0.05$) and in the 2nd follow up ($p<0.05$). Many probiotics, including *Lactobacillus* and *Bifidobacteria*, ferment unabsorbed polysaccharides to generate SCFAs, but they don't produce gas on fermenting carbohydrate; SCFAs acidifies the colonic contents and inhibit some bacteria to flourish, such as *Clostridia* spp. that produce gas, reducing some symptoms like abdominal bloating and flatulence [13].

Nausea and/or vomit

The symptoms nausea and/or vomit have been reported by 7 patients (63.6%) of the control group and by 5 patients (45.5%) of the experimental group; both groups have shown a complete remission of such symptoms, even if this remission occurred in a faster manner in the experimental group (from the 2nd follow up onwards in the experimental group vs the 3rd follow up in the control group). Cuzick's test shows that the reduction of nausea and/or vomit during the whole observation period is less significant for the experimental group than the control group ($p<0.01$ vs $p<0.001$) because of the lower percentage of patients of the experimental group who have reported such symptoms in the baseline survey. Fisher's exact test don't show any statistic significance between the different percentage of patients of the two group affected by such symptoms in all the single phases of the study ($p>0.05$ in the baseline survey and in all the later follow up). It is important to consider that probiotic supplementation have accelerated the reduction of such symptoms in the experimental group.

Eczema and/or skin rash

NCGS is also characterized by extra intestinal manifestations like eczema and/or skin rash. At baseline 4 patients (36.4%) in both groups have reported such symptom; in the 4th follow up, 3 subjects (27.3%) of the control group and 1 subject (9.1%) of the experimental group have continued to be affected by such symptoms. The reduction trend during the whole observation period (analyzed with Cuzick's test) shows statistic significance only for the experimental group ($p<0.05$). Fisher's exact test don't show any statistic significance between the different percentage of patients of the two groups affected by eczema and/or skin rash in all the single phases of the study ($p>0.05$ in the baseline survey and in all the later follow up). The improvement of eczema and/or skin rash could be explained with the immunomodulatory effect of probiotics on the T cells responses: probiotics can alleviate the symptoms of atopic dermatitis due to their effects of balancing T helper1/T helper2 immunity and enhancing regulatory T cells (Treg) activity through their interaction with dendritic cells [14].

Musculo-skeletal and neurological symptoms

Musculo-skeletal and neurological symptoms include joint and/or muscle pain and numbness in legs and/or arms. In the baseline survey 4 patients (36.4%) of the control group and 5 patients (45.5%) of the experimental group have reported such symptoms; both groups have shown a full remission of such symptoms but in different times: from the 2nd follow up onwards for the experimental group and from the 4th follow up onwards for the control group. Cuzick's test shows a higher level of statistic significance of the symptom's reduction trend during the whole observation period for the experimental group ($p<0.001$) compared to the control group ($p<0.05$). Fisher's exact test don't show any statistic significance between the different percentage of patients of the two groups affected by such symptoms in all the single phases of the study ($p>0.05$ in the baseline survey and in all the later follow up). Due to the unknown etiology of this type of symptoms [2], it is not possible to give an exact explanation of the improvement observed in the patients of the experimental group.

Headache

At baseline survey headache has been reported by 7 subjects (63.6%) of the control group and by 6 patients (54.5%) of the experimental group. The control group has shown a slight reduction at the end of the whole observation period: in the 4th follow up 5 patients (45.5%) have continued to recount such

Table 4: Time trend of the total score of symptoms in the two groups during the whole observation period.

Total Score	Baseline (0 dd)		1st follow up (15 dd)		2nd follow up (30 dd)		3rd follow up (45 dd)		4th follow up (60 dd)	
	Exper.	Contr.	Exper.	Contr.	Exper.	Contr.	Exper.	Contr.	Exper.	Contr.
Median value	6	7	5	5	2	4	0	2	0	2
Interquartile range	2	4	4	4	2	2	0	2	0	2

Exper: Experomental group; Contr: Control grouP

symptom. The experimental group has shown a faster reduction of headache until its complete remission from the 3rd follow up onwards. The reduction trend during the whole observation period (evaluated with the Cuzick's test) is statistically significant only for the experimental group ($p<0.001$). Fisher's exact test shows the presence of statistic significance between the percentage of patients of the two groups affected by such symptom in the 2nd, 3rd and 4th follow ups ($p<0.05$).

Difficulty concentrating

At baseline survey, difficulty concentrating has been reported by 8 patients (72.7%) of the control group and by 7 patients (63.6%) of the experimental group. Both groups have experienced a reduction of that symptom, which completely disappeared from the 3rd follow up onwards in the experimental group and from the 4th follow up onwards in the control group. Symptom's reduction trend during the whole observation period is statistically significant at Cuzick's test for both groups ($p<0.001$): such symptom has decreased homogeneously in both groups so Fisher's exact test don't show any statistic significance between the different percentage of patients affected by difficulty concentrating of the two group in all the single phases of the study ($p>0.05$ in the baseline survey and in all the later follow up). Due to the uncertain etiology of this type of symptoms [2], it is not possible to give an exact explanation of the improvement observed in the experimental group; however, recent studies evidenced the existence of a connection between the gut microbiota and the brain: this bidirectional network is called gut microbiota-brain axis [15]. Enterochromaffin cells act like bidirectional transducers that regulate communication between the gut lumen and the nervous system; a disruption of the bidirectional interactions between the enteric microbiota and the nervous system may be involved in the modulation of pain, immune response and other homeostatic functions [16].

Total score of symptoms

The total score of the number of symptoms reported by the patients is expressed as median value (range from 0 to 9) and interquartile range; such parameter has been analyzed to determine symptom's reduction trend in both groups during the whole observation period by Cuzick's test (Table 4). In both groups the reduction trend of the total number of symptoms during the whole observation period is statistically significant at Cuzick's test ($p<0.001$). From the 2nd follow up onwards the total number of symptoms reported by the patients of the experimental group is statistically lower ($p<0.001$) than the total number of symptoms reported by the patients of the control group: this result has been evaluated with Wilcoxon's test. The statistically significant reduction of the total number of symptoms reported by the patients of the experimental group from the 2nd follow up onwards indicates that probiotic intake started to improve the overall symptoms commonly associated with NCGS after 30 days of supplementation.

CONCLUSION

In the last few years many studies have analyzed the role of probiotics in the anti-inflammatory response and their influence in the gut microbiota composition in different gastrointestinal problems [17], but the effects of probiotic supplementation in NCGS patients are still poorly investigated. The overlaps between NCGS and IBS symptoms [18] and the effects of probiotics in alleviating some of IBS symptoms [19,20], have suggested us to test probiotic supplementation on NCGS patients and analyze the effects on the symptoms reported by such individuals.

The data coming out from this study have shown that probiotics have a considerable potential for therapeutic application in the treatment of symptoms (especially gastrointestinal symptoms) associated to NCGS due to their capacity to influence gut microbiota composition [21] and to the absence of side-effects reported by the patients who made use of them. However further studies are needed to identify the exact mechanisms of action of probiotics on NCGS symptoms.

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