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The Effect of *Lactobacillus reuteri* Supplementation in Adults with Chronic Functional Constipation: a Randomized, Double-Blind, Placebo-Controlled Trial*

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ABSTRACT

Background & Aims: There is a growing interest for the use of probiotics for chronic constipation. A recent randomized controlled trial (RCT) showed a positive effect of *Lactobacillus reuteri* (*L. reuteri)* on bowel movement frequency in infants with chronic constipation. The aim of the present study was to evaluate the effects of *L. reuteri* in adult patients with functional constipation.

Methods: A double-blind, placebo RCT was conducted in 40 adults (18M/22F, 35±15 years) affected by functional constipation according to the Rome III criteria. Patients were randomly assigned to receive a supplementation of *L. reuteri* (DSM 17938), or matching placebo for 4 weeks. The increase of bowel movements/week was the primary outcome, while the improvement of stool consistency was the secondary outcome.

Results: At week 4, the mean increase in bowel movements/week was 2.6 (SD±1.14, 95% CI:1.6-3.6) in the *L. reuteri* group and 1.0 (SD±1. 95% CI:0.12-1.88) in the placebo group (p=0.046). At the end of the treatment, the mean bowel movements/week was 5.28±1.93 in the *L. reuteri* group and 3.89±1.79 in the placebo group. There was a not significant difference in the stool consistency between the two groups.

Conclusions: *L. reuteri* is more effective than the placebo in improving bowel movement frequency in adult patients with functional constipation as previously demonstrated in children, even if it seems to have no effect on stool consistency.

Key words: bowel movements – bowel – constipation – evacuation – *L. reuteri* – placebo.

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INTRODUCTION

The prevalence of chronic constipation in the general population ranges from 15% to 25% [1, 2]. This condition affects patients of all ages and gender and severely impacts on their quality of life.

The diagnosis of functional constipation is normally performed according to the Rome III Criteria for Functional Gastrointestinal Disorders [3]. Several review articles on the role of different treatments for chronic constipation were recently published [2, 4, 5].

There is a growing interest in the use of probiotics in organic and functional gastrointestinal disorders, particularly for the treatment of inflammatory bowel disease, traveler's diarrhea and constipation [6]. The alteration of the normal intestinal microbiota in chronic constipation provides a rationale for the use of probiotics in this setting [6]. In fact, gut microbiota affects intestinal motility, and when imbalanced, it could play a key role in the development of some gastrointestinal disorders such as constipation [7].

Probiotics are defined as "live microorganisms which, when ingested in adequate amounts, confer a health benefit to the host". *Lactobacilli* and *Bifidobacteria* are the most studied species showing a high safety profiles. Both are able to produce short chain fatty acids reducing the level of intraluminal pH, thus promoting colonic peristalsis, which is beneficial for the treatment of constipation [7, 8].

A systematic review was recently performed to evaluate the use of probiotics in the treatment of functional constipation

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both in adults and children; the authors concluded that probiotics statistically improved the stool consistency and frequency [9].

A large randomized controlled trial (RCT) that compared the effect of different probiotics (*Lactobacillus plantarum* and *Bifidobacterium breve*, or *Bifidobacterium lactis*) to placebo, showed a significant improvement in all aspects of constipation using probiotic regimens [10]. In adults, affected by irritable bowel syndrome (IBS)-constipation type, the supplementation with *Lactobacillus casei Shirota* increased the frequency of defecations and the softness of the stool [11] .

Moreover, a recent pilot study that evaluated the effect of a mixture of various probiotics in children showed therapeutic effects both on constipation and on abdominal pain [8]. Finally, a large RCT performed on children with functional constipation demonstrated the effectiveness and safety of *Lactobacillus reuteri* (*L. reuteri)* (DSM 17938) supplementation for eight weeks in increasing the number of bowel movements and stool frequency [6].

On the basis of this last study, we carried out a similar double-blind placebo-controlled trial to evaluate the beneficial effects of *L. reuteri* (DSM 17938) in adults with functional chronic constipation.

PATIENTS AND METHODS

A double-blind, placebo-controlled, randomized trial, was conducted (from January to June 2012) on 40 consecutive adult patients (18M/22F; mean age 35.6±15 years) admitted to the Gastroenterology Unit of the Catholic University of Rome with a diagnosis of functional constipation according to the Rome III criteria.

Exclusion criteria were hypothyroidism or other metabolic or renal diseases, antibiotic treatment, probiotic or prebiotic supplementation and the use of oral laxatives in the last month. Patients were evaluated in a clinical setting by a physician at enrollment and at the end of therapy.

At enrollment, medical history (including the taken drugs), physical examination, laboratory tests (blood cell count, hepatic and renal function, electrolytes) were collected. All patients received a stool diary to record the frequency of daily bowel movements and to evaluate stool consistency, using the Bristol Stool Scale (BSS), during the four weeks of study.

Patients were asked to fill a diary card in order to record any "adverse experience" (causing discomfort and/or interrupting the subject usual activity) during the treatment periods and to record every time they did not assume the prescribed doses. The diary was analyzed by physicians.

We considered the stool consistency as hard if it was separated in hard lumps, nut- or sausage-shaped (Type 1-2-3); as normal if it was like a sausage or snake, smooth and soft (Type 4-5); and as watery if mushy or entirely liquid (Type 6-7).

At baseline, the mean of bowel movements/week in all patients of the study was 2.79 (SD: ±0. 66, 95% CI: 2.24 to 3.36).

The 40 patients were randomly assigned into two groups according to an automatically generated randomization list: group A (n= 20) received supplementation with the probiotic *L. reuteri* (DSM 17938), and group B (n = 20) was given a matching placebo.

Patients were informed by a blind investigator that such a supplement could offer help in improving constipation. Boxes containing placebo had the same shape, dimension, trade mark indication and contained the amount of sachet of boxes containing *L. reuteri*. They were provided by the probiotic producer.

L. reuteri (DSM 17938) was administered in the dose of 10^8 colony-forming units (CFU) in tablets of a commercially available preparation (Reuflor, Italchimici, Pomezia; BioGaia AB, Stockholm, Sweden), 30 minutes after feeding, twice per day for 4 weeks. The preparation was stable for 24 months at ≤25°C (as documented by the manufacturer). During the study period, patients were instructed to store the product according to the recommended temperature. In particular, the tablets could be stored at room temperature 25°C; at 30°C the product is stable for 3 months. Because *L. reuteri* is a living organism, for long storage periods it is preferable not to freeze the tablets but to refrigerate them at 2-8°C.

Finally protocol adherence was verified through a tablet count of the medication containers returned by subjects the day after finishing therapy and by directly asking the subjects about the completion of the therapy. Patients were asked not to change the usual diet and habits. The use of oral laxatives was not allowed (glycerin suppository was recommended only when there was no defecation for >5 days).

All patients gave written informed consent, and the study was approved by the independent Ethics Committee of the Catholic University of Rome and conducted in accordance with the Declaration of Helsinki. Subjects did not receive any payment for the participation in the study.

The primary endpoint was the increase of bowel movements/week frequency, while the secondary endpoint was the improvement of stool consistency according to BSS.

Intention to treat and per protocol analysis was performed.

Statistical analysis

This study has been designed as a proof-of-concept; therefore sample size calculation was not performed. All data were stored in a common database and statistically analyzed with SPSS software version 8.0 (SPSS, Chicago, Illinois). Results were expressed as means. The Student's *t* test was performed to compare the two means (group A and group B). A p value <0.05 was considered to be statistically significant.

RESULTS

Forty consecutive patients with chronic constipation were enrolled, and all patients completed the study. The number of patients per protocol and intention to treat analysis was the same. The study groups were well matched for age, gender and constipation characteristics (Table I).

All patients were well informed and took more than 95% of the prescribed doses for four weeks of treatment. No drops out were observed (0/40 patients).

None of the patients recorded an "adverse experience" that interrupted the usual activity during the treatment periods.

Bowel movements

Group A experienced a significant increase in the frequency of bowel movements/week, expressed in mean, than group B.

Table I. The demographic and clinical characteristics of the enrolled subjects divided into the two groups (*L reuteri* and placebo)

	L reuteri (n=20)	Placebo (n=20)
Gender, n (M/F)	9/11	7/13
Mean age (yrs) ± SD	34.5±16	36.7±14
Bowel movements ± SD	2.68±0.79	2.89±0.52
Stool consistency (Bristol Stool Scale) (%)		
Hard	80%	75%
Normal	20%	25%

Particularly, at week 4, the mean increase in bowel movements/week was 2.6 (SD ±1.14, 95% CI: 1.6 to 3.6) in group A and 1.0 (SD: ±1, 95% CI: 0.12 to 1.88) in group B (P=0.046), respectively (Fig. 1).

At the end of the treatment, the mean of bowel movements/week was 5.28±1.93 in group A and 3.89±1.79 in group B (95% CI 0.19 to 2.98, p=0.023), respectively (Fig. 2).

The frequency of bowel movements/week in group A (L. reuteri) increased from 2.68 at week 0 to 5.28 at week 4 (p<0.0001, 95% CI 1.65 to 3.54).

No adverse effects related to the use of probiotics were reported during the trial.

Three patients in group A and 5 patients in group B reported the use, only once, of suppositories during the 4 weeks of treatment.

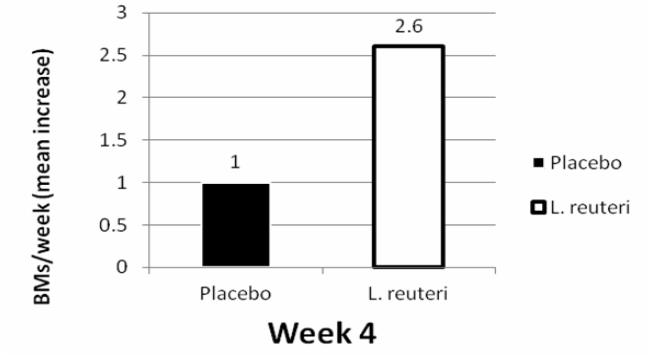

Fig. 1. The mean increase of bowel movements in the *L. reuteri* and placebo groups after four weeks of treatment.

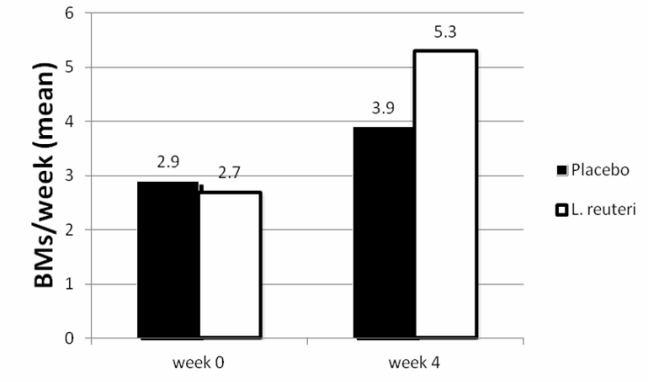

Fig. 2. Frequency of bowel movements in the *L. reuteri* and placebo groups at enrolment (week 0) and at the end of therapy (week 4).

Stool consistency

At baseline, in the *L reuteri* group, the stool consistency was reported to be hard (type 1-2-3 BSS) in 16/20 (80%) and normal (type 4-5 BSS) in 4/20 (20%) while at the end of therapy it became hard in 12/20 (60%), normal in 6/20 (30%) and watery (type 6-7) in 2/20 (10%). At baseline, in the placebo group, the stool consistency was hard in 15/20 (75%) and normal in 5/20 (25%), and at the end of the therapy (4 week) it became hard in 65%, normal in 30% and watery in 5% of the patients (Figs. 3, 4).

However, there was no statistically significant difference between *L reuteri* and placebo groups in the stool consistency at 4 weeks (p = ns, week 4).

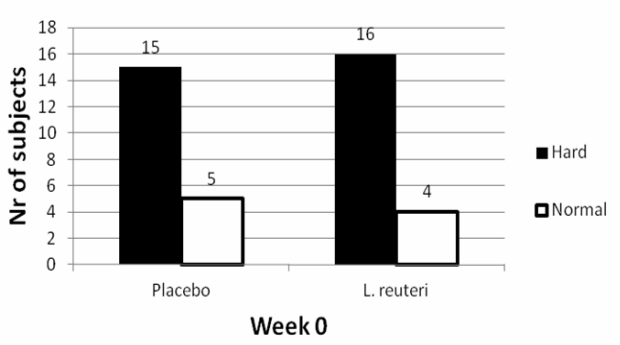

Fig. 3. Stool consistency in the *L. reuteri* and placebo groups at enrolment (week 0).

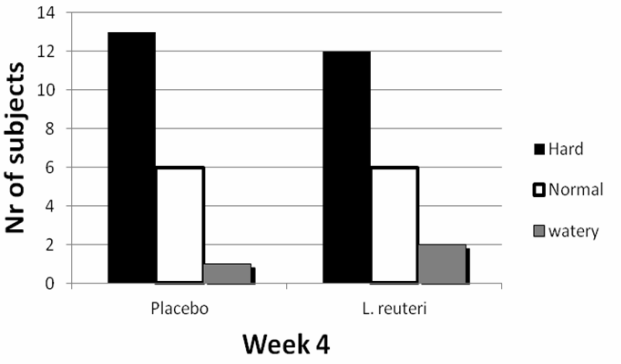

Fig. 4. Stool consistency in the *L.reuteri* and placebo groups at the end of therapy (week 4).

DISCUSSION

Our study confirmed, similarly to what was observed in children, that the supplementation with *L. reuteri* (DSM 17938) significantly improved bowel movements, increasing the frequency of evacuations per week in adult patients affected by chronic functional constipation.

Particularly, at week 4, the mean increase of bowel movements/week was higher in the group treated with *L. reuteri* than in the group treated with placebo (P 0.046). The frequency of bowel movements significantly increased (P=0.0001) in patients supplemented with *L. reuteri* twice a day for 4 weeks.

We found a slight and not significant change of stool consistency in patients treated with *L. reuteri* compared with the control group. There were no side effects that interrupted the usual activity during the treatment periods.

Chronic constipation has a high prevalence in Western countries. It reduces the patient's quality of life and imposes a significant economic burden for the health care system. The most common treatments prescribed are osmotic or stimulating laxatives, prokinetics (prucalopride), lubiprostone and others. Most of them are associated with side effects and can cause addiction; consequently, they can be used only for a limited period [12].

Many probiotics have an optimal safety profile, with multiple interesting fields of application, in particular the possibility to manipulate gastrointestinal motility in constipated patients [13].

Microbiota can control or influence gut motility according to the evidence that its disruption affects intestinal myoelectric complexes in germ-free rats. The colonization of these animals with normal feces or even with a single bacterial strain restores normal gut motility complexes [14].

The bacterial flora influences intestinal motility by anaerobic fermentation of carbohydrates and proteins. In humans, the final products of this process are mainly short-chain fatty acids (SCFA), acetate, propionate, butyrate and, in minor amount, H_2, CO_2, ammonia and amines. The activity of these SCFA on the smooth muscle contributes to the normal gut function [15, 16].

A recently published paper showed that *L. reuteri* increased both colonic mioelectric motility complex frequency and velocity. The authors, based upon the effects of *L. reuteri* on the adult mouse colon, speculated that this probiotic might have a therapeutic potential effect in constipated elderly adults [17]. However, the exact mechanisms underlying the enhancements of gastrointestinal transit by probiotics are not yet completely understood.

Many papers which evaluate the effect of different strains of *Lactobacilli spp.* (*casei, reuteri, plantarum*) or *Bifidobaterium spp.* (*breve*) showed a beneficial effect on chronic constipation with an increase in bowel movements, defecation frequency, and a decrease of abdominal pain both in children and adults [10].

Our study confirmed that the *L. reuteri* supplementation, even if only for four weeks, improves bowel movements in adults with chronic constipation. Also, in our patients, *L. reuteri* improved stool consistency, even if without a statistically significant difference compared to placebo, probably due to the limited time of treatment. One possible explanation could be the enhanced water and electrolyte secretion due to probiotic activity that may soften the stools [18, 19].

In accordance with the literature regarding the safety of *L. reuteri* DSM17938 [13, 20] and of other probiotics [21-24], no side effects in the group treated with this strain were found during our study.

Even if probiotics are not yet recommended in the pyramid of chronic constipation management [25], according to our opinion, they may be a good alternative in patients affected by functional chronic constipation.

CONCLUSION

This prospective, double blind, placebo controlled trial shows the efficacy of *L. reuteri* (DSM 17938) in adults with chronic functional constipation for increasing bowel movements.

The positive results of four weeks *L. reuteri* supplementation suggest that a long term administration of this strain could be safe and beneficial in constipated patients.

Conflicts of interests. None of the authors has a conflict of interest.

Authors' contribution: V.O. designed, drafted and revised the article, G.I. performed the statistical analysis and the graphics, A.T. and G.D.A. enrolled, randomized patients and analyzed data, T.A.D.R. enrolled, randomized patients, S.B. analyzed literature data and revised the paper, A.M. analyzed literature data and wrote the paper, A.G. revised the article. All authors approved the final manuscript version.

REFERENCES

1. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol 2004;99:750-759.
2. Tack J, Muller-Lissner S. Treatment of chronic constipation: current pharmacologic approaches and future directions. Clin Gastroenterol Hepatol 2009;7:502-508.
3. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130:1480-1491.
4. Singh S, Rao SS. Pharmacologic management of chronic constipation. Gastroenterol Clin North Am 2010;39:509-527.
5. Camilleri M, Bharucha AE. Behavioural and new pharmacological treatments for constipation: getting the balance right. Gut 2010;59:1288-1296.
6. Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. Lactobacillus reuteri (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatr 2010;157:598-602.
7. Picard C, Fioramonti J, Francois A, Robinson T, Neant F, Matuchansky C. Review article: bifidobacteria as probiotic agents -- physiological effects and clinical benefits. Aliment Pharmacol Ther 2005;22:495-512.
8. Bekkali NL, Bongers ME, Van den Berg MM, Liem O, Benninga MA. The role of a probiotics mixture in the treatment of childhood constipation: a pilot study. Nutr J 2007;6:17.
9. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. World J Gastroenterol 2010;16:69-75.
10. Del Piano M, Carmagnola S, Anderloni A, et al. The use of probiotics in healthy volunteers with evacuation disorders and hard stools: a double-blind, randomized, placebo-controlled study. J Clin Gastroenterol 2010;44 Suppl 1:S30-S34.
11. Koebnick C, Wagner I, Leitzmann P, Stern U, Zunft HJ. Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. Can J Gastroenterol 2003;17:655-659.
12. Lacy BE, Levenick J, Crowell M. Recent advances in the management of difficult constipation. Curr Gastroenterol Rep 2012;14:306-312.

13. Del Piano M, Morelli L, Strozzi GP, et al. Probiotics: from research to consumer. Dig Liver Dis 2006;38 Suppl 2:S248-S255.
14. Barbara G, Stanghellini V, Brandi G, et al. Interactions between commensal bacteria and gut sensorimotor function in health and disease. Am J Gastroenterol 2005;100:2560-2568.
15. Borriello SP. Bacteria and gastrointestinal secretion and motility. Scand J Gastroenterol Suppl 1984;93:115-121.
16. Lewis SJ, Heaton KW. Increasing butyrate concentration in the distal colon by accelerating intestinal transit. Gut 1997;41:245-251.
17. Wu RY, Pasyk M, Wang B, et al. Spatiotemporal maps reveal regional differences in the effects on gut motility for Lactobacillus reuteri and rhamnosus strains. Neurogastroenterol Motil 2013;25:e205-e214.
18. Roberfroid M. Dietary fiber, inulin, and oligofructose: a review comparing their physiological effects. Crit Rev Food Sci Nutr 1993;33:103-148.
19. Bongers ME, de Lorijn F, Reitsma JB, Groeneweg M, Taminiau JA, Benninga MA. The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial. Nutr J 2007;6:8.
20. Vanderhoof JA, Young RJ. Use of probiotics in childhood gastrointestinal disorders. J Pediatr Gastroenterol Nutr 1998;27:323-332.
21. Szymanski H, Pejcz J, Jawien M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three Lactobacillus rhamnosus strains--a randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006;23:247-253.
22. Bu LN, Chang MH, Ni YH, Chen HL, Cheng CC. Lactobacillus casei rhamnosus Lcr35 in children with chronic constipation. Pediatr Int 2007;49:485-490.
23. Banaszkiewicz A, Szajewska H. Ineffectiveness of Lactobacillus GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. J Pediatr 2005;146:364-369.
24. Borriello SP, Hammes WP, Holzapfel W, et al. Safety of probiotics that contain lactobacilli or bifidobacteria. Clin Infect Dis 2003;36:775-780.
25. DiPalma JA. Current treatment options for chronic constipation. Rev Gastroenterol Disord 2004;4 Suppl 2:S34-S42.