

## Probiotic beverage containing *Lactobacillus casei* Shirota improves gastrointestinal symptoms in patients with chronic constipation

Corinna Koebnick PhD<sup>1</sup>, Irmtrud Wagner PhD<sup>2</sup>, Peter Leitzmann MD<sup>3</sup>, Udo Stern<sup>4</sup>, HJ Franz Zunft PhD<sup>1</sup>

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RÉSUMÉ :

**BACKGROUND:** The aim of the present study was to investigate the effect of a probiotic beverage on gastrointestinal symptoms in patients with chronic constipation.

**METHODS:** A double-blind, placebo-controlled, randomized study was conducted over a four-week period in patients with symptoms of chronic constipation (n=70). To all patients, 65 mL/day of a probiotic beverage containing *Lactobacillus casei* Shirota (LcS) or a sensorially identical placebo was administered. Patients completed a questionnaire on gastrointestinal symptoms, well-being and stool habits and underwent a medical examination weekly. Severity of constipation, flatulence and bloating was summarized into three {four? add 'no symptoms?'} categories (severe, moderately severe and mild).

**RESULTS:** The consumption of LcS resulted in a significant improvement in self-reported severity of constipation and stool consistency, starting in the second week of the intervention phase (P<0.0001). Severe and moderately severe constipation was observed less in the LcS group. The occurrence and degree of flatulence or bloating sensation did not change. In the final examination, 89% of the LcS group and 56% of the placebo group showed a positive effect of their beverage on constipation (P=0.003). No adverse reactions were reported.

**CONCLUSIONS:** The results indicate a beneficial effect on gastrointestinal symptoms of patients with chronic constipation. The administration of probiotic foodstuffs may be recommended as an adjunctive therapy of chronic constipation.

**Key Words:** Constipation; Gastrointestinal disorders; Probiotics

Probiotics are defined as living microorganisms that enter the gastrointestinal tract in an active form in sufficient numbers to exert positive effects (1-3). The concept of a stabilization of intestinal microflora and the associated health-promoting effect of lactic acid bacteria goes back to the beginning of the last century. During the past ten years, a large number of scientific studies have been conducted on the effects of probiotic cultures (4-15).

The consumption of probiotic microorganisms has beneficial effects on gastrointestinal disorders (such as the course of

various types of diarrhea), promotes lactose digestion and lowers the concentration of several metabolic products suggested to be injurious to health, including markers of carcinogenesis in the colon (4,7,16-18). Probiotic microorganisms also exert several immunomodulating effects (15,19).

Constipation is a gastrointestinal ailment encountered often in Western countries, especially in elderly people (20). With a view toward improving colonic function in patients suffering from constipation, the influence of nutrition on the intestinal ecosystem has been a subject of great interest.

<sup>1</sup>German Institute of Human Nutrition, Department of Intervention Studies, Bergholz-Rehbrücke, Germany; <sup>2</sup>Yakult Deutschland GmbH, Neuss, Germany; <sup>3</sup>Institute of Nutritional Science, University of Giessen, Germany; <sup>4</sup>Büdingen, Germany

Correspondence and reprints: Dr Corinna Koebnick, Department of Intervention Studies, German Institute of Human Nutrition, Arthur-Scheunert-Allee 114-116, D-14558 Bergholz-Rehbrücke, Germany. Telephone?, fax?, e-mail Koebnick@mail.dife.de  
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**TABLE 1**  
**General patient characteristics in the placebo and verum groups**

	Verum n=35	Placebo n=35	P
Age (years)	43.3 ± 6.9	44.6 ± 9.7	0.535
Body mass index (kg/m <sup>2</sup> )	23.8 ± 2.4	22.7 ± 2.1	0.077
Women (%)	60	49	0.472
Smokers (%)	40	51	0.472
Good general condition (%)	97	83	0.106
Occurrence of solid stool* (%)	97	94	0.555

\*In the preceding four weeks

Research on the relationship between constipation and nutrition during the last few decades have focused on fibre and non-digestible oligosaccharides (21-27). The effect of fermented milk products and probiotic lactic acid bacteria on various forms of constipation has been explored in only a few studies, most of which were carried out without controls (28-34). Nevertheless, constipation has a significant impact on the quality of life (35,36) and beneficial effects of probiotics in the therapy of constipation seem to be promising. In addition, studies investigating effects of probiotics are mostly conducted with highly concentrated isolates that are not available in the supermarket.

In the present placebo-controlled, randomized trial the effect of a commercially available probiotic beverage containing *Lactobacillus casei* Shirota (LcS) on gastrointestinal symptoms and general well-being in patients with chronic constipation was investigated. Primary study outcomes were severity of constipation, stool consistency and defecation frequency. The survival of LcS in the gastrointestinal tract has been investigated previously (13,37,38).

## PATIENTS AND METHODS

In October 2000 a placebo-controlled, double-blind, randomized trial with two parallel arms was conducted with 70 men and women aged 18 to 70 years suffering from chronic idiopathic constipation who were recruited from patients in a naturopathic practice. The exclusion criteria were pregnancy, regular ingestion of probiotic products within the preceding four weeks and the use of laxatives, anticholinergics, medication against diarrhea and antibiotics. Persons with a milk protein allergy, or constipation of organic or neurological origin, were also excluded. All patients were advised not to modify their habitual diet and lifestyle during the run-in and the intervention phase. None of the patients interrupted or terminated the study participation. All patients gave signed informed consent.

At the initial examination, the demographic data and medical history of the study participants were assessed by a questionnaire. In addition, the gastrointestinal symptoms were assessed (eg, severity of constipation, defecation frequency, stool consistency, occurrence and degree of flatulence, occurrence and degree of bloating). **Degree of constipation, flatulence and bloating was assessed on a four-point scale (severe, moderately severe, mild or no symptoms).**

Stool consistency was assessed by a five-point scale modified according to the Bristol Stool Form Scale (watery or mushy, soft blobs, normal sausage, hard shaped sausage, hard lumps) (39). Subjective severity of constipation was assessed by a four-point scale (no constipation, mild, moderately severe and severe constipation) on a patient's questionnaire.

The initial examination was followed by a run-in period of two weeks and an intervention period of four weeks. The final evaluation was carried out one week after the intervention period. The gastrointestinal symptoms were assessed each week by a questionnaire that was filled out by the participant at the examiner's office. Additionally, the patients were asked weekly for product tolerability during the intervention phase.

During the four weeks of intervention, the patients were administered 65 mL/day of a probiotic beverage containing at least  $6.5 \times 10^9$  colony forming units LcS, or 65 mL/day placebo. LcS has been isolated from the feces of a healthy infant (37). The LcS and the placebo beverages also contained 1.3 g of protein, 0.004 g of fat and 18.0 g of carbohydrates per 100 mL, and 580 mg of lactic acid. All ingredients were identical in the treatment and placebo products except for the content of LcS. The placebo was also sensorially identical. The small bottles with the probiotic beverage and the placebo were externally indistinguishable by appearance, taste, texture or odor. The bottles were handed out weekly to assure high quality of beverages and a constant amount of LcS. Compliance was checked by a weekly interview with the examiner. **High compliance was maintained by frequent visits and frequent contact with the examiner {ok?}.**

Data are shown as mean and SD. General characteristics of the study groups and rating of the product efficacy were compared by using Student's *t* test and Fisher's exact test. The longitudinal effect of the probiotic beverage was estimated by generalized estimating equations with logit link using the occurrence of severe and moderately severe constipation and hard, lumpy stool as a dependent variable. Poisson link was used within the generalized estimating equations model to estimate treatment effect on degree of constipation, flatulence or bloating, and defecation frequency. For estimating the time point of significant effect, an interaction term between treatment group and week of intervention was included. Statistical analysis was carried out using SAS Version 8.02 (SAS Institute Inc, USA).

## RESULTS

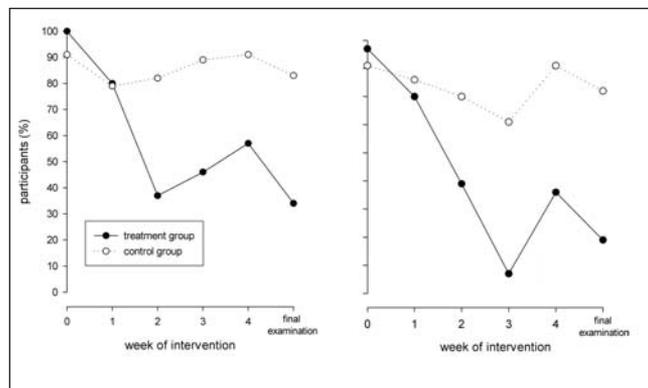
There were no differences between the treatment and the placebo groups with respect to age, body mass index, sex or general health status. Moreover, the occurrence of flatulence, a bloated feeling or solid stool was similar in both groups (Table 1).

At the beginning of the intervention phase, the percentage of participants with severe or moderately severe constipation was similar in the treatment and the placebo groups ( $P=0.239$ ). Severe symptoms of constipation were reported by 3% of participants in both the intervention group and the control group. Moderately severe symptoms of constipation were reported by 97% of the intervention group and 88% of the control group (Figure 1, left).

In the treatment group, the occurrence of severe or moderately severe constipation decreased ( $P<0.001$ ), whereas no change could be observed in the control group (Table 2). The effect became apparent from the second week ( $P=0.001$ ) to the fourth intervention week.

Also, the occurrence of hard and lumpy stool in the treatment group was lower starting in the second week of intervention than at the beginning ( $P<0.011$ ). No changes could be observed in the placebo group (Figure 1, right).

At the initial examination of the study, median defecation frequency was three times per week (range two to five) in both groups. In the treatment group, 54% reported a defecation frequency of three times or less per week, compared with 51% in



**Figure 1**) Occurrence of severe and moderately severe constipation in verum and placebo group (left). Occurrence of hard or lumpy stools in verum and placebo group (right)

the control group. During the run-in phase, the median defecation frequency increased to five times per week (range three to six times per week) in the treatment group and four times per week (range two to six times per week) in the control group. The occurrence of a defecation frequency of three times or less per week decreased to 3% in the treatment group and 14% in the control group. During the intervention phase, defecation frequency increased to six times per week (range five to six times per week) in the treatment group and five times per week (range four to six times per week) in the control group ( $P=0.001$ ). The differences between groups were significant starting in the second week of the intervention phase ( $P<0.001$ ). After the intervention phase, a defecation frequency of three times or less per week was reported by 4% of the treatment group and 15% of the control group ( $P=0.198$ ). Stool consistency, assessed on a five-point scale, decreased in the treatment group but not in the control group ( $P<0.001$ ; Table 2).

During the complete intervention period, a marginal or noticeable improvement of constipation symptoms was reported by 94% in the treatment group, compared with 57% in the control group ( $P<0.001$ ). In the final examination, 89% in the treatment group and 56% in the control group reported a positive effect of the probiotic drink on constipation ( $P=0.003$ ). No effect was reported by 11% in the treatment group and 37% in the control group. A worsening of constipation was

### *Lactobacillus casei* Shirota treatment for chronic constipation

reported by 3% in the control group and none in the treatment group. No side effects were reported.

Moreover, the general well-being was distinctly improved in the treatment group compared with the placebo group ( $P=0.008$ ): 17% of the treatment group reported a distinct improvement and 34% reported a slight improvement. In 49% of the treatment group, the intervention had no effect on general well-being. In the placebo group, none of the participants observed a distinct improvement, whereas eight participants (23%) reported a slight improvement and 27 (77%) saw no improvement at all. A deterioration of general well-being did not occur in either group.

The tolerability of verum and placebo was given a similar rating. It was rated between "very good" and "good" by 91% of the participants in the verum group and by 80% in the placebo group.

## DISCUSSION

There are a large number of therapeutic approaches to the treatment of constipation. Successful forms of nutritional treatment for constipation, such as the ingestion of larger amounts of fibre, are due to elevated metabolic activity of the colonic flora and a lowering of the pH value in the colon (26, 40). These results emphasise the importance of intestinal flora in the prevention and treatment of constipation (7,10,19).

In the present study, the severity of constipation was reduced by the daily consumption of LcS, as demonstrated by a significant improvement in stool consistency and bowel movement frequency.

The composition of the colonic flora is related to bowel motility (7). Differences in the intestinal flora between constipated and healthy subjects have been observed. In constipated children, the numbers of bifidobacteria were decreased, while nonpathogenic *Escherichia coli*, *Bacteroides species* {OK?} and the total number of microorganisms increased (41). However, the question of whether there is a cause-and-effect relationship between constipation and the composition of the intestinal flora has not yet been conclusively answered.

The effect of fermented milk products and/or probiotic microorganisms on constipation has only been investigated in some small, nonplacebo-controlled studies; these studies yielded controversial results (6,28,30,32,42-44). Various studies carried out in the past in Japan have already demonstrated the positive effects of LcS on constipation (33,34,43). Due to diverging dietary habits of Japanese and European populations,

**TABLE 2**  
Constipation, flatulence and bloating in the verum and placebo group

Parameter	Baseline (n=70)	End of intervention		P <sup>‡</sup>
		Verum (n=35)	Placebo (n=35)	
Occurrence of moderate and severe constipation (%)	96	34	83	< 0.001
Degree of constipation* (range)	2 (2-3)	1 (1-2)	2 (1-3)	0.003
Defecation frequency (range)	3 (2-5)	6 (5-6)	5 (4-6)	0.004
Occurrence of hard stools (%)	94	29	82	< 0.001
Degree of stool consistency <sup>†</sup> (range)	5 (4-5)	3 (2-4)	5 (3-5)	< 0.001
Occurrence of flatulence (%)	47	6	17	0.259
Degree of flatulence* (range)	1 (0-2)	1 (0-1)	1 (0-2)	> 0.999
Occurrence of bloating (%)	22	11	3	0.356
Degree of bloating* (range)	1 (1-2)	1 (1-1)	1 (1-1)	> 0.999

Data are shown as median and range (minimum;maximum). \*Degree on a 4 point scale (0 to 3) anchored to no symptoms as zero; <sup>†</sup>Degree on a 5 point scale (1 to 5) anchored to watery as 1 and hard lumps as 5; <sup>‡</sup>Significance of treatment effect estimated from generalized estimating equations model

further results are needed from the European population to confirm these observations. In addition, some of these studies can be criticized for failing to distinguish between the effects of probiotics and sour milk products, and possible placebo effects (31).

The beneficial effects of probiotics may be explained by various mechanisms. Changes in the composition of the intestinal flora may result in changes of metabolites of bacterial fermentation and in enhanced intestinal motility, attributable to a lowering of the pH value or a shortening of transit time (44). Some studies support the hypothesis that the oral administration of LcS modifies the composition and metabolic activity of the intestinal microflora (2,13). These mechanisms may be an explanation for the slightly delayed onset of the beneficial effect on constipation in the second week of the present study, following the regular ingestion of LcS.

In two studies (37,45) carried out with probiotic beverages containing LcS in children, the fecal pH decreased on average by 0.4 to 0.7 after LcS administration. This result could not be reproduced in healthy adults (13). A decrease in pH in the large intestine is due to the bacterial production of organic acids (butyric acid, propionic acid and lactic acid) that stimulate motility in the colon (44). These acids also affect the reabsorption of water and electrolytes, thus, promoting intestinal motility and changing the osmotic pressure (27).

The ingestion of the investigated LcS-containing beverage can not only lead to a rise of LcS in the intestine but also in the total number of intestinal microorganisms (13,38). The water content of feces is also altered by the ingestion of LcS (13). In healthy adults, the ingestion of LcS ( $3 \times 10^{11}$  colony forming units per day) brought about a significant increase in the water content of stool after four weeks in the treatment group in comparison with the control group. The authors attribute this to a shortening of transit time and/or to the osmotic effects of the short-chain fatty acids. Nevertheless, there is no evidence that exogenously administered probiotics adhere to the mucosal cells. Instead, they seem to pass into the feces without having adhered (2). As a consequence, the probiotic culture has to be ingested continually to exert beneficial effects.

Although bowel frequency is easy to determine, only a few conclusions can be drawn from it concerning colon function, transit time and stool weight. Stool consistency, in contrast, is related to a number of factors, including transit time (39). The significant improvement in stool consistency observed during the present study may be explained by a shortened transit time. Together with potential changes in the intestinal microflora, this, in turn, exerts beneficial effects, ie, shorter contact times during which the intestinal mucosa is exposed to carcinogenic, mutagenic or toxic substances and other carcinogenic mechanisms in the colon (9).

The patients' ability to achieve normal bowel habits without being in pain, and to control bowel movements, are important elements of physical well-being. This was shown by studies investigating the relationships between quality of life and gastrointestinal symptoms in persons with functional constipation (35,46). The surveys revealed an impaired quality of life in constipated individuals in comparison with healthy persons, depending on the severity of constipation. Against this background, the subjective statements made by the study participants, in particular, are worth mentioning. An improvement in general well-being was reported by about half of the study participants in the treatment group. The tolerability

and taste of the administered probiotic drink was assessed positively.

## CONCLUSIONS

The regular ingestion of LcS resulted in an improvement of gastrointestinal parameters, in particular, bowel movement frequency and stool consistency, in otherwise healthy individuals suffering from constipation. In addition to a high-fibre diet containing whole grain products, fruits and vegetables, modern constipation therapy should include the administration of probiotic food products. The improvement of gastrointestinal symptoms achieved by the ingestion of LcS indicates changes in the microflora and the intestinal milieu. Furthermore, the general well-being of the subjects improved. Further studies are needed to investigate the effect of probiotics on gut transit time.

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**Lactobacillus casei** Shirota treatment for chronic constipation

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