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

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**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

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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.

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Research on the relationship between constipation and nutrition during the last few decades has focused on fibre and nondigestible 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 $6.5 \times 10^{6}$ 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
the control group. During the run-in phase, the median defe-
cation 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, defe-
cation 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 report-
ed 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 pos-
itive 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
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 gen-
eral 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 consti-
pated 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 car-
ried 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,
water content of feces is also altered by the ingestion of LcS. can not only lead to a rise of LcS in the intestine but also in sorption of water and electrolytes, thus, promoting intestinal late motility in the colon (44). These acids also affect the reab-
tions 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 LeS 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 LeS.

In two studies (37,45) carried out with probiotic beverages containing LeS in children, the fecal pH decreased on average by 0.4 to 0.7 after LeS 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 stimu-
late 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 LeS-containing beverage can not only lead to a rise of LeS 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 LeS (13). In healthy adults, the ingestion of LeS (3×10^11 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 mecha-
nisms 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 LeS 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 LeS 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.

REFERENCES
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