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Effect of probiotics on small intestinal bacterial overgrowth in patients with gastric and colorectal cancer

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ABSTRACT

Background/Aims: Small intestinal bacterial overgrowth (SIBO) may be related to the presence of gastrointestinal cancer. The exact link, however, between SIBO and cancer prevalence as well as cancer symptoms remains unclear, especially in Asian populations. In addition, there is a paucity of data documenting the influence of probiotic treatment of SIBO on cancer symptoms. Here, the aims were to correlate the presence of SIBO with cancer prevalence and cancer symptoms, as well as to investigate the effect of probiotic intervention on SIBO and cancer symptoms.

Materials and Methods: Employing a case-control design, 112 gastric and 88 colorectal cancer patients were evaluated. Questionnaires were used to assess gastrointestinal symptoms and a glucose-H2-breath test (GHBT) was used to determine SIBO status. Patients with SIBO were administered Bifidobacterium triple viable capsule therapy or placebo. Subsequently, SIBO status and gastrointestinal symptom scores were reanalyzed.

Results: In our study group, 63.0% of patients versus 16.3% of controls was tested positive for SIBO. In patients with cancer, SIBO was associated with proton pump inhibitor (PPI) use. Bifidobacterium triple viable capsule was effective in combating SIBO and was associated with a significant improvement in gastrointestinal cancer-related symptoms.

Conclusion: In a Chinese cohort, SIBO is associated with gastrointestinal cancer. Based on the preliminary intervention study, we conclude that probiotic intervention combats SIBO in patients with gastrointestinal cancer and alleviates its symptoms.

Keywords: Small intestinal bacterial overgrowth, digestive diseases, malignancies, glucose-hydrogen breath test, proton pump inhibitors

INTRODUCTION

Gastrointestinal cancer is usually accompanied by various clinical manifestations such as anorexia, low grade fever, diarrhea, constipation, abdominal distension and ascites, pleural effusion, repeated infection, fatigue, and weight loss (1). Although these manifestations often directly relate to the presence of the cancer, such symptoms may also result from small intestinal bacterial overgrowth (SIBO) (2). Patients suffering from gastrointestinal malignancies usually are compromised with respect to the integrity of the intestinal mucosa barrier as a consequence of the damage by the tumor or as a side effect of radiotherapy and chemotherapy. In addition, gastrointestinal cancer and its treatment often result in reduced functionality of cellular and humoral immune system, inadequate nutritional functionality, and secondary infection due to the long-term use of broad spectrum antibiotics used to prevent and treat post-operative infection. In conjunction, these factors substantially impair the ability of patients to control intestinal bacterial proliferation, ultimately resulting in SIBO (3). However, the actual incidence of SIBO in patients with gastrointestinal cancer remains unclear.

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Small intestinal bacterial overgrowth is a very heterogeneous syndrome characterized by an increase in the number and/or alteration in the type of bacteria in the upper gastrointestinal tract. Most authors define SIBO based on the detection of $\geq 10^5$ bacteria [i.e., colony-forming units (CFU)] per mL upon culturing upper gut aspirates (4). Affected patients may be asymptomatic or have non-specific symptoms, such as bloating, abdominal pain, diarrhea, steatorrhea, flatulence, dyspepsia, nutrient malabsorption, weight loss, and/or absence of weight gain (5). To which extent, however, such SIBO-evoked symptoms contribute to diminished quality of life in cancer patients has not been established.

The gold standard for the diagnosis of SIBO remains aspiration and direct culture of the jejunal aspirate; however, in practice, the use of such methodology is hampered by its high cost, invasiveness of the associated procedure, absence of laboratories equipped to perform such analyses, and resistance of many species of bacteria to cultivation (6-9).

Currently, glucose-hydrogen breath tests (GHBTs) are the most common diagnostic tool for SIBO diagnosis because they are noninvasive, cheap, simple, and safe (10). Glucose is rapidly absorbed in the proximal small bowel and usually does not reach the colon; thus, it is a suitable substrate to detect proximal small bowel overgrowth. After the consumption of the substrate, a rise in H_2 release signifies the presence of bacteria in the small bowel that metabolize the substrate before absorption by the body occurs. This test is well accepted in the literature. Earlier, it was shown that the sensitivity and specificity of GHBT for SIBO were 62.5% and 82%, respectively, against the gold standard of a jejunal aspirate (11). Hence, we view the use of GHBT to diagnose SIBO as valid and that increased hydrogen release by cancer patients most likely demonstrates SIBO in these patients. Thus, we feel that studies employing GHBT to test for SIBO constitute a rational approach.

Furthermore, there is a substantial body of literature (12,13) showing that use of antibiotics or probiotics to treat SIBO can greatly improve the symptoms of patients, warranting further research exploring the possible therapeutic role of probiotic therapy for treating SIBO in cancer patients.

The abovementioned considerations prompted us to explore SIBO incidence and its relation to clinical symptoms in a large cohort of patients suffering from gastrointestinal cancer and to assess the effect of an experimental intervention.

MATERIALS AND METHODS

Study population

In this study, a case-control design was employed, using patients suffering from gastric or colorectal cancer who were referred to either the department of digestive internal medicine, the department of general surgery, or to the oncology clinic of the Qingdao Municipal Hospital from July 2013 to November 2015. We included 200 patients suffering from gastrointestinal cancer between the ages of 25 and 75 who based on the gastrointestinal endoscopic appearance and pathological examination report (e.g., tumor markers). Finally, we selected 112 patients with gastric cancer and 88 patients with colorectal cancer. As controls, 80 healthy volunteers between the ages of 20 and 65 were recruited. All participants signed informed consent. The exclusion criteria were as follows: use of antibiotics in the month preceding the study and use of acid inhibitors or gastrointestinal actuation, use of prednisone, antidepressants, opioids, patients suffering from diabetes, thyroid disease, scleroderma, pseudo-obstruction, or functional gastrointestinal diseases, and patients who had undergone colonoscopy or enema in the month preceding the study. During the study, subjects were not allowed to smoke and were instructed to refrain from eating high fiber and indigestible carbohydrates the day before H_2BT examination.

Glucose hydrogen breath test (1)

All subjects were asked to fast for 12 h, and brush their teeth and rinse their mouth with an antiseptic mouth wash or tap water in the morning prior to the test. GHBT was performed using a breath gas analyzer, model HHBT-01 (Shenzhen ZHONGHEHAIDEWEI Biological Technology Co, Ltd; Shenzhen, China). The test was started by measuring baseline hydrogen levels; the subjects were then asked to consume 50 g of glucose dissolved in 200 mL water. Thereafter, breath hydrogen release values were determined every 20 min for the next 2 h. A persistent rise in breath hydrogen 12 ppm above the basal value was considered as SIBO. Patients with high basal breath hydrogen levels were scheduled for retesting on another day.

Clinical intervention

Patients with gastrointestinal malignancies who were tested positive for SIBO were included in the intervention arm of the study. Clinical symptoms, such as diarrhea, abdominal pain, bloating, constipation, abdominal discomfort, anorexia, and fever, present at the start of the study were determined and recorded for later analysis. Patients were randomly assigned to either the probiotics or the placebo group in a double-blind manner. The study group was administered Bifidobacterium triple viable capsule (offered by Shanghai Pharmaceutical Co., Ltd; Shanghai, China), 250 mg of each tablet, once 2 tablets, 3 times per day, for 4 weeks and the control group was administered placebo. Otherwise, the groups were identically treated and were asked to refrain from the use of antimicrobial agents or other drugs that could influence intestinal flora composition. After the treatment, GHBT was performed again and clinical symptoms were reassessed.

Symptom questionnaire (14)

For determining gastrointestinal symptoms, a questionnaire was employed, which asked the subjects to assess their abdominal pain, bloating, constipation, appetite, diarrhea and fe-

ver. If present, patients were asked to estimate each symptom's frequency, intensity, and duration on a 0–3 Likert-like scale. The score indication on this scale was as follows: Intensity: 0=no symptoms, 1=mild, 2=moderate, 3=severe symptoms; frequency: 0=none, 1=Less than 1 episode/week, 2=1 episode/week, 3=More than 1 episode/week; duration: 0=none, 1=Less than 10 min, 2=10–30 min, 3=greater than 30 min. On this scale, the total score for each symptom could range from 0 to 9. A mean total score for all six symptoms was calculated for each patient before and after the experimental intervention.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 19.0 (IBM Corp.; Armonk, NY, USA). Data measured are described as mean±standard deviation ($\bar{x}\pm s$). Two groups were compared using at test and three groups were compared using analysis of variance. For comparing non-continuous variables, a Chi-square test was employed. Results are regarded as statistically significantly different when the p value is less than 0.05.

RESULTS

Characteristics of the patient and control cohort

In this study, 200 patients with gastrointestinal malignant tumors were included. The patient cohort included 84 (42.0%) females and 116 (58.0%) males, whose age ranged from 25 to 75 years. Of these patients, 112 suffered from gastric cancer and 88 had colorectal cancer. Another patient cohort was composed of 80 individuals, of which 40 (50%) were males and 40 (50%) were females. In this control cohort, the age ranged from 20 to 65 years. No significant difference was detected between the two groups with respect to age and gender (p>0.05; Table 1). We concluded that our study population was suitable for making statements on the prevalence of SIBO in cancerous disease.

Increased prevalence of patients with gastrointestinal cancer

To assess SIBO, GHBT was used. Test results contrasted between the groups of patients with gastric cancer, patients with colorectal cancer, and the control group. Importantly, both constitutive and post-prandial expiratory hydrogen concentrations were higher in patients with both forms of cancer, and these effects reached statistical significance (p<0.05; Figure 1). Of the 112 gastric cancer patients, 73 (65.2%) were positive for SIBO, whereas of the 88 colorectal cancer patients, 53 (60.2%) were positive. In contrast, in the control group, only 13 (16.3%) of the 80 subjects were positive for SIBO. When either the gastric or the colorectal cancer group was compared to the control group for SIBO positivity (rather than for expiratory hydrogen concentration), statistical significance reached p<0.01 for both groups of cancer, whereas the comparison between the gastric cancer group and the colorectal cancer group was not significant (p>0.05; Figure 2). Thus, cancers in the gastrointestinal tract may be associated with SIBO.

Table 1. General information in each group

Group	Number	Male	Female	Age (year)*
Gastric cancer	112	68	44	51.36±10.78
Colorectal cancer	88	48	40	49.78±11.63
Control group	80	40	40	48.43±11.39

*Single factor analysis of variance

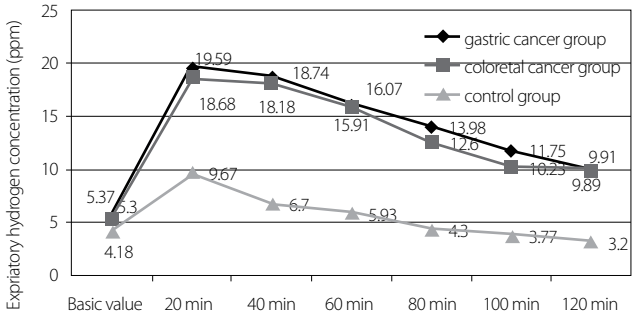

Figure 1. The results were contrasted between the groups of patients with gastric cancer, the patients with colorectal cancer, and the control group. Importantly both contitutive and post-prandial expiratory hydrogen concentrations were higher in patients with either form of cancer, and these effects all reached statistical significance (p<0.05)

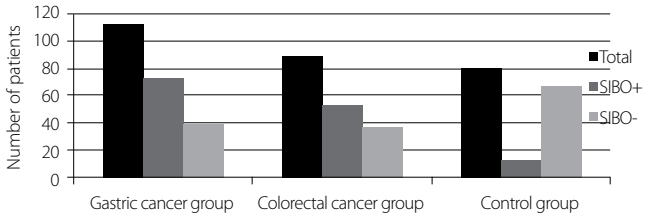

Figure 2. Of the 112 gastric cancer patients, 73 (65.2%) were positive for small intestinal bacterial overgrowth (SIBO) whereas of the 88 colorectal cancer patients, 53 (60.2%) were positive. In contrast, in the control group, only 13 (16.3%) of the 80 subjects were positive for SIBO. When either the gastric or the colorectal cancer group was compared to the control group for SIBO-positivity (rather as expiratory hydrogen concentration), statistical significance reached p<0.01 for both groups of cancer, whereas between the gastric cancer group and the colorectal cancer group was not significant (p<0.05).

Influence of proton pump inhibitor (PPI) use

Of the 200 patients with gastrointestinal malignancies, 116 (58.0%) were long-term PPI users and of these, 86 (74.1%) were positive for SIBO. In the same group, 84 (42.0%) patients did not use PPIs and of these, 39 (46.4%) were positive for SIBO. In the control group, there were no PPI users and thus this parameter could not be evaluated for these subjects for a relation to SIBO. The apparent association of SIBO positivity with the use of PPIs was statistically significant (p<0.05; Table 2). Hence, it appears that application of PPIs in patients with gastrointestinal malignancies makes SIBO more likely to occur.

SIBO is related to gastrointestinal symptom development

Cancer patients often suffer from gastrointestinal symptoms. To investigate whether these symptoms might possibly relate

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to the presence of SIBO, we contrasted the clinical symptom scores of SIBO positive and negative patients. We observed that the difference was statistically significant ($p<0.05$; Table 3) and thus gastrointestinal symptoms in cancer patients may possibly partially be because of SIBO.

Probiotic therapy counteracts SIBO in patients with gastrointestinal malignancies

We decided to study the effect of intervention on SIBO positivity in cancer patients. To this end, 126 patients were included in an intervention study in which 63 patients received probiotic (Bifidobacterium triple viable capsule) therapy whereas 63 were allotted to a placebo group, employing a double-blind design. Following 4 weeks of treatment, the SIBO prevalence between the Bifidobacterium triple viable capsule group and placebo group was compared. We observed that the group receiving probiotic treatment had 19.0% SIBO-positive patients, whereas the group that was administered placebo showed 74.6% SIBO-positive patients. A comparison of both groups for conversion to SIBO negative status showed a highly statistically significant difference ($p<0.01$; Figure 3). Thus, Bifidobacterium triple viable capsule therapy is effective in combating SIBO in patients with gastrointestinal malignancy.

Treating SIBO reduces gastrointestinal symptoms in patients with gastrointestinal malignancies

When the placebo group and the Bifidobacterium triple viable capsule-receiving group were compared for clinical symptoms before the onset of the intervention, no statistically significant difference was noted ($p>0.05$). Importantly, clinical symptoms were much diminished in the Bifidobacterium triple viable capsule-receiving group, and this difference reached statistical significance on comparison with the placebo arm of the study ($p<0.05$). In addition, in the Bifidobacterium triple viable capsule group, treatment provoked a statically significant reduction in clinical symptoms ($p<0.05$), whereas in the placebo group, such an effect was not noted ($p>0.05$; Table 4). Thus, counteracting SIBO reduces gastrointestinal symptoms in patients with cancer of the digestive tract.

DISCUSSION

SIBO prevalence in patients with cancer is unclear. In the present study, we evaluated the prevalence of SIBO in patients with malignant gastrointestinal cancer using GHBT and observed a very high incidence of SIBO on comparing results to a control cohort, irrespective of whether constitutive or post-prandial hydrogen was used as measure. These data fit well with a growing momentum that relates SIBO development to gastrointestinal cancer (15-17) and also with the study by Bustillo et al. (18), which successfully counteracted diarrhea in patients with advanced pancreatic cancer by treatment for SIBO. Thus, a picture emerges that high SIBO prevalence is characteristic for intestinal oncological disease.

There is an abundance of mechanistic explanations underlying SIBO development in cancer patients: the integrity of the intestinal mucosa barriers suffers the damage inflicted by radiotherapy and chemotherapy used to treat such cancers, either through direct effects on the epithelial stem cell compartments (19) or by causing diminished intestinal blood circulation. The latter effect provokes ischemia hypoxia, in turn activating the xanthine oxidase and oxygen free radical production, and then damages the intestinal mucosa, furthering bacterial growth (20). Furthermore, the ionizing radiation associated with cancer therapy can provoke intestinal cell necrosis, reduce intestinal survival and change the general aspect of the enterocytes, thus making them less capable to counteract bacterial growth and invasion (21). Finally, reduced intestinal immunity in cancer patients may hamper the control of the size of the intestinal microbiological compartment. Thus, our observation that SIBO is highly prevalent in patients with gastric or colorectal cancer is in agreement with the data available in the medical literature and fits well with the processes likely to occur in such patients.

Table 2. Gastrointestinal malignancies with and without use of PPI, regarding SIBO

Group	SIBO+	SIBO–	χ^2	p
PPI group	86	30	15.961	0.000
Non-PPI group	39	45		

PPI: proton pump inhibitor; SIBO: small intestinal bacterial overgrowth

Table 3. SIBO positive and SIBO negative patients, in relation to clinical symptom scores

Group	Number	Mean symptom integral
SIBO+	126	10.87±2.26
SIBO-	74	10.14±1.98
T		2.345
P		0.022

Table 4. Clinical symptom scores before and after treatment in the study and placebo groups

Group	No	Score before treatment	Score after treatment	T	P
Study group	63	10.91±2.32	9.73±1.87	3.231	0.002
Placebo group	63	10.86±2.17	10.47±2.03	1.137	0.300
T		0.067	-2.193		
P		0.901	0.035		

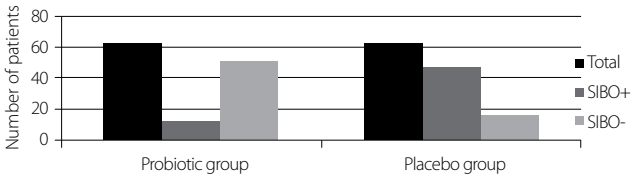

Figure 3. We observed taht the group receiving probiotic treatment had 19.0% SIBO-positive patients, whereas the group that was administered placebo showed 74.6% SIBO-positive patients. Comparng both groups for conversion to SIBO negative status showed a highly statistically significant difference ($p<0.01$).

In the present study, we observed that 116 (58.0%) of 200 patients with gastrointestinal malignancies had been administering PPIs for a long term, and of these, 86 (74.1%) were tested positive for SIBO; 84 (42.0%) did not use PPIs, and of these, 39 (46.4%) showed SIBO positivity. In the control group, no PPI use was reported. We observed a higher prevalence of SIBO in patients with gastrointestinal malignancies who were long-term users of PPIs. These results are in good agreement with those reported in the studies by Lombardo et al. (22) and Jacobs et al. (23). These studies also illustrate a positive association between SIBO and PPI administration. Thus, our results suggest that SIBO should be considered in PPI-administering patients, especially oncological patients, reporting gastrointestinal complaints.

The most evident reason for the relation of PPI use and SIBO is the inhibition of gastric acid secretion by this medication and a resulting diminished anti-bacterial action of the stomach secretion. Recent studies demonstrate that gastric acidity and intestinal motility are major mechanisms for the gastrointestinal flora control (24). Gastric acid is an important barrier in the prevention of the stomach and proximal small intestine bacterial colonization (25). The use of PPIs inhibits gastric acid secretion, increases gastric pH, and facilitates the survival and colonization of the intestinal wall by bacteria, thus favoring SIBO development (26,27). Previous studies have also implicated that abnormal small bowel motility is one of the indications in the pathogenesis of SIBO (28,29). Thus, the observed link between PPI use and SIBO fits well with the expected effects on intestinal physiology.

An important aspect of our study is that SIBO relates to clinical symptom scores in gastrointestinal cancer patients. Thus, the development of SIBO appears to aggravate clinical symptoms of cancerous disease. Successful treatment of SIBO through probiotic intervention was effective in reducing clinical symptom scores. Thus, our results show that in patients with gastric or colorectal cancer, vigilant monitoring for SIBO should take place, and if detected, it should be treated to improve quality of life in this patient group.

Our results also document that probiotic intervention is a suitable mode of clinical action for the treatment of SIBO in such patients. In apparent agreement, various studies have demonstrated that either probiotics (30,31) or antibiotics (32,33) can counteract SIBO and clinical symptoms in patients with gastrointestinal diseases. In addition, many studies (13,34) indicated that the combination of antibiotics and probiotics was more effective than antibiotics used alone in eradicating SIBO. Thus, in conjunction with the available literature data, our results support the use of probiotics in patients with gastrointestinal cancer.

The underlying mechanisms remain somewhat controversial but appear to include the following: competition with pathogens; production of bacteriocins; inhibition of bacterial translocation; enhancement of mucosal barrier function; down-regulation of inflammatory responses; modulation of gut motor and sensory responses; and modulation of signaling between luminal bacteria, the intestinal epithelium, and the immune system (11,35-37). Our present results suggest that bacteriocidal effects may especially be important, as they are the most likely to explain the anti-SIBO effects of this preparation. However, further research is necessary to substantiate this notion.

In conclusion, this preliminary study demonstrates a high prevalence of SIBO in patients with gastrointestinal malignant tumors, especially in those on long-term use of PPIs. In addition, we show that treatment with Bifidobacterium triple viable capsule is effective in combating SIBO and simultaneously improves gastrointestinal symptoms in patients. Our results therefore call for further research on the possible use of the therapy in the treatment of gastric cancer and colon cancer patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - L.X., S.L.; Design - L.X., S.L.; Supervision - L.X.; Funding - L.X.; Materials - L.X., S.L., D.Z., Z.W.; Data Collection and/or Processing - S.L.; Analysis and/or Interpretation - S.L.; Literature Review - L.X., S.L.; Writer - S.L.; Critical Review - L.X.

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Conflict of Interest: No conflict of interest was declared by the authors.

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