Role of Probiotics in Reducing GERD

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Abstract

Probiotic is little known for its benefits on upper gastrointestinal health. The objective of this systematic review was to examine the efficacy of probiotics in alleviating the frequency and severity of symptoms in gastroesophageal reflux disease (GERD) in the general adult population.. In total, 13 prospective studies that were published in 12 articles were included in the analysis and scored per the Jadad scale as high- (five studies), medium- (two), and low- (six) quality. One article reported on two probiotic groups; thus, 14 comparisons were included in the selected studies, of which 11 (79%) reported positive benefits of probiotics on symptoms of GERD. Five out of 11 positive outcomes (45%) noted benefits on reflux symptoms: three noted reduced regurgitation; improvements in reflux or heartburn were seen in one study; five (45%) saw improvements in dyspepsia symptoms; and nine (81%) saw improvements in other upper gastrointestinal symptoms, such as nausea (three studies), abdominal pain (five), and gas-related symptoms (four), such as belching, gurgling, and burping. In conclusion, probiotic use can be beneficial for GERD symptoms, such as regurgitation and heartburn.

Keywords: *gastroesophageal reflux disease, regurgitation, heartburn, probiotics*

Introduction

The World Gastroenterology Organization defines GERD as 'troublesome symptoms sufficient to impair an individual's quality of life, or injury or complications that result from the retrograde flow of gastric contents into the esophagus, oropharynx, and/or respiratory tract' [1]. The Rome IV criteria include functional heartburn (FH) and reflux hypersensitivity (RH), which can overlap with GERD [2]. Further, the Rome IV criteria describe infant regurgitation (IR) as follows: regurgitation 2 or more times per day for 3 or more weeks [3], spontaneous resolution with age, and no association with negative long-term consequences [4]. IR is not included in this systematic review.

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Typical symptoms of GERD are heartburn and regurgitation, rendering the distinction between GERD, FH, and RH complicated. To improve the diagnosis of GERD, the Gastroesophageal Reflux Disease Working Group of the International Working Group for Gastrointestinal Motility and Function created a consensus document to determine modern indications for esophageal testing in GERD and define criteria for the clinical diagnosis of GERD [5]. Diagnosis and investigation of GERD is commonly based on questionnaires, including the Gastrointestinal Symptom Rating Scale (GSRS) [6] and Frequency Scale for Symptoms of GERD (FSSG) [7].

Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' . Probiotics are available in a variety of forms, such as powders, capsules, foods, and infant formula . The administration of probiotics has been recognized to benefit the health of the gut by improving bowel functions and abdominal symptoms . The mechanisms of probiotics have been suggested to involve a wide range of activities, including direct

interactions with the gut luminal microbiota, metabolic effects that result from enzymatic activities, effects on barrier function, and crosstalk with the central nervous system and enteric immunity . Notwithstanding this, there is a lack of a thorough mechanistic understanding of probiotics' functionality in general; this is also the case for GERD.

The clinical implications of probiotics in gut health have been studied extensively in various clinical trials . Although their ingestion does not appear to influence gastrointestinal microbiota in healthy adults , the consumption of probiotics during dysbiosis can promote gastrointestinal homeostasis and stimulate the growth of beneficial indigenous gut microbes.

Materials and Method

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

An advanced-mode electronic search was performed in the PubMed and Web of Science databases for prospective controlled studies using the terms "GERD OR dyspepsia OR heartburn OR regurgitation AND probiotic" in all age groups. We also performed focused searches of the Directory of Open Access Journals, Google Scholar, and reference lists of the included papers and applicable meta-analyses. The final search was performed in June 2019; eligible articles up to that date were considered for inclusion.

Two independent reviewers (J.C., A.C.O.) identified studies for inclusion and analyzed the selected articles. Discrepancies were resolved by discussion. Titles and abstracts were first reviewed to exclude manuscripts that were published in non-English-language journals, systematic and literature reviews, commentaries, meeting abstracts, letters, case reports, animal studies, and clearly irrelevant studies. The remaining full-text articles were assessed for eligibility, based on the research questions. Data on subject characteristics (gender, age), study characteristics (study design, randomization, blinding, sample size, probiotic delivery vehicle, probiotics species/strain, daily probiotic dose, intervention duration), and clinical outcomes were recorded.

Results

The database searches retrieved 232 titles and abstracts, and a manual search of relevant bibliographies identified one additional record. After the removal of duplicates, 182 unique titles remained. These titles and abstracts were screened for eligibility; 128 records were excluded, and 54 full-text articles were reviewed. In the analysis, 12 articles were included. One of the articles reported two interventions , and one article reported two probiotic study arms and one shared placebo arm . Thus, the analysis ultimately included 14 comparisons.

A total of 951 subjects (mean: 68, range: 8–249/comparison) were analyzed in the 14 comparisons that were published in the 12 included articles. The subjects were healthy adults, including elderly persons. In most studies, both genders were evenly distributed in the analyzed population . Daily probiotic doses ranged from 0.05×10^9 to 46×10^9 colony-forming units (CFU) (mean 5.8×10^9 CFU). Treatment durations ranged from 1 to 12 weeks (mean six weeks).

A total of eight probiotic or synbiotic products were studied, containing between one and six strains . Ten were single-strain products—*L. gasseri* LG21, *B. bifidum* YIT 10347, *Bifidobacterium animalis* subsp. *lactis* HN019, and *Lactobacillus reuteri* DSM 17938—whereas the four remaining products were multi-strain products, containing various strains in species of *B. bifidum*, *B. lactis*, *Bifidobacterium longum* subsp. *longum*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, and *Lactobacillus acidophilus*. Four study products also contained other ingredients, such as antioxidants and prebiotics. In the included studies, the probiotics were administered in various formats: fermented dairy (seven comparisons), pill-like (four comparisons), powder (two comparisons), and olive oil (one comparison) .

Of the 13 included studies, six were randomized and seven performed blinding of the patients; various study designs were used, including parallel groups (six studies), before–after comparisons (five studies), and crossover designs (two studies) . After qualitative rating of the study design, per the Jadad scale, five randomized controlled trials (RCTs) with a parallel-group design were defined as high-quality, two RCTs with a parallel-group or crossover design were medium-quality, and

the six remaining studies were low-quality . Although it is not part of the Jadad score, reporting on compliance is an important marker of quality. Nearly half of the comparisons (n = 6) did not report compliance with the product .

Discussion

In this systematic review, 13 prospective clinical studies, comprising 14 comparisons, were reviewed to determine the potential of probiotics to alleviate upper-GI symptoms in GERD in the general adult population. The mechanism of action of probiotics has focused primarily on the lower digestive tract, and the activities of probiotics in the upper-GI tract remain largely unknown .

Nevertheless, probiotics of the genera *Lactobacillus* and *Bifidobacterium* are associated with modulations in the immune response and antagonistic activity toward potential pathogens through the production of short-chain fatty acids, such as lactic acid. Further, probiotics accelerate gastric emptying by interacting with stomach mucosal receptors, which are suspected of triggering transient lower esophageal sphincter relaxation, one of the pathophysiological mechanisms of GERD . In addition, probiotics can be beneficial for small intestinal bacterial overgrowth, interfering with immunity or intestinal motility under various conditions . These properties might be relevant to their effects in GERD, as discussed here.

A majority (79%) of the included comparisons reported probiotic benefits on the symptoms of GERD, such as regurgitation, heartburn, dyspepsia, nausea, abdominal pain, and gas-related symptoms (belching, gurgling, burping). However, the heterogeneity in the outcomes made it impossible to perform a meta-analysis.

Probiotics have positive effects on reflux with regards to the presence of episodes and frequency scores [9]. The presence of reflux episodes fell significantly by 40% in 20 pregnant women [10]. To our knowledge, de Milliano et al. (2012) is the first trial to supplement with multi-strain probiotics, and reported benefits for reflux, particularly in constipated pregnant women. The product in this study contained six probiotic strains from six species, including *Bifibacterium* and *Lactobacillus*, providing efficacy for a wide range of upper- and lower-GI symptoms, such as abdominal pain and constipation .

Based on the FSSG, the frequency scores for reflux declined significantly from 6.2 to 4.8 on supplementation with *L. gasseri* LG21 for 12 weeks . Notably, in the same study, pepsinogen (PGI) level was the only stomach-related biomarker that had a significant negative correlation with the reflux symptom score, after the effects of gender and age were adjusted. PGI was suspected to be involved in the occurrence of symptoms; thus, a higher PGI level indicates accelerated protein digestion in the stomach. This explanation is one basis for the inverse relationship between increased PGI levels and reduced reflux symptoms, particularly in the presence of increased dysmotility-like dyspepsia, from 3.5 to 4.0 on the FSSG .

Conclusion

Most studies reported positive outcomes for probiotics regarding the symptoms of GERD. However, there was substantial heterogeneity in the outcomes and symptoms. Thus, although the results are encouraging, it is difficult to draw any general conclusions on the effects of probiotics. The heterogeneity in endpoints also made it impossible to quantitively evaluate the results. Further, the quality of the studies is concerning—only 5 of 14 studies were good quality. Nevertheless, despite the diversity in the studied product formats, populations, and experimental designs, the efficacy of the probiotic treatment does not appear to be influenced by the study quality.

Properly designed, randomized, double-blind, placebo-controlled studies with a sufficient number of participants and well-defined endpoints are needed. Studies with a longer duration should also be considered, with an intermediate analysis of the endpoints—for example, through questionnaires—to determine the period in which the benefits can be expected and whether they are long-lasting.

Gram Staining showed that GM+Budding yeast cells & hypae among 5.0%, GM+Budding yeast psudo hypae among 17.0% and GM + septate fungal hypae seen among 75.0%. The present study highlights the increased prevalence of otomycosis in females as compared to males with majority of the cases occurring in the rainy

season.*Aspergillus* species was the most common fungi isolated.

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