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GASTRIC MICROBIOME

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Abstract – Considering the gastric microbiota, *Helicobacter pylori* is the most famous bacterium discovered in the 80s and is known to be implicated in gastric diseases. Its role in ulcer peptic disease and in gastric cancers is now very well described. However, other bacteria, like Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria and Fusobacteria, can reside in the stomach, and this review will present the different studies published in 2022 considering the gastric microbiome.

Keywords: Helicobacter, Probiotics, Microbiota.

HELICOBACTER PYLORI AND GASTRIC MICROBIOTA

Previous studies in the past years showed that the gastric microbiota differs from *H. pylori*-infected patients and from uninfected patients. This past year, two meta-analyses[1,2] reported modifications of the gastric microbiome occurring during gastric carcinogenesis. The first one performed a meta-analysis of nine publicly available 16S datasets with standard tools of the state-of-the-art[1]. They found significant changes in the composition of the gastric microbiome during the progression of gastric carcinogenesis, especially when the *Helicobacter pylori* reads were removed from analyses to mitigate its compositional effect, as they accounted for extremely large proportions of sequencing depths in many gastric samples. Differential bacteria, including *Fusobacterium*, *Leptotrichia*, and several lactic acid bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Streptococcus anginosus*, which were frequently and significantly enriched in gastric cancer patients compared with gastritis across studies, had good discriminatory capacity to distinguish gastric cancer samples from gastritis. This meta-analysis[2] confirmed that novel and consistent microbial patterns are present in gastric carcinogenesis. Another meta-analysis aimed to identify universal microbial signatures in gastric carcinogenesis considering gastric microbiome from multiple studies. The authors showed that compositional and ecological profiles of gastric microbes across stages of gastric carcinogenesis were significantly altered. The meta-analysis revealed that opportunistic pathobionts *Fusobacterium*, *Parvimonas*, *Veillonella*, *Prevotella* and *Peptostreptococcus* were enriched in gastric cancer, while commensals *Bifidobacterium*, *Bacillus* and *Blautia* were depleted in comparison to superficial gastritis. Eight bacterial taxa, including *Veillonella*, *Dialister*, *Granulicatella*, *Herbaspirillum*, *Comamonas*, *Chryseobacterium*, *Shewanella,* and *Helicobacter*, were newly identified by this study as universal biomarkers for robustly discriminating gastric cancer from superficial gastritis, with an area under the curve of 0.85. Finally, these 2 articles identified gastric mucosa microbial features associated with histological stages of gastric carcinogenesis, including gastric cancer-associated bacteria, diagnostic biomarkers, bacterial network alteration, and *H. pylori* influence.

Another meta-analysis[3], including 9 papers, was published last year and aimed to evaluate the influence of successful *H. pylori* eradication on the short-term and long-term alterations of human gastric microbiota. It showed that regarding quadruple therapy, alpha diversity indexes increased within 1 month after eradication; significant differences in gastric microbial community structure between before and after eradication were also seen within 1 month. The trends of the above-mentioned diversity changes persisted with a follow-up of 6 months. Regarding the triple therapy, similar trends of alpha diversity and beta diversity changes were observed in the short-term and long-term follow-ups. In the 2 different types of therapy, the microbial composition altered significantly and logically after eradication, and the relative abundance of *H. pylori*-related taxa decreased. Accordingly, gastric commonly dominant commensals were enriched. The authors concluded that successful *H. pylori* eradication could reverse gastric microbiota dysbiosis and show beneficial effects on gastric microbiota.

PROBIOTICS USE AND GASTRIC MICROBIOTA

Different studies published this past year concerned the impact of different substances on gastric microbiota. An Italian team, decided to investigate the impact of yogurt consumption on gastric cancer[4]. It has been suggested that yogurt might have a beneficial effect on gastrointestinal diseases, potentially by promoting healthy gut microbiota. They conducted a meta-analysis of 16 studies that assessed yogurt intake using food frequency questionnaires. The analysis included 6,278 gastric cancer cases and 14,181 controls. The results of the study-specific odds ratio calculations indicated no significant association between yogurt consumption and gastric cancer, despite some indications of a protective effect in sensitivity analyses[4].

Regarding the use of probiotics, as defined by the World Health Organization (WHO) as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, gastric cancer is usually treated with gastrectomy, which is the most effective treatment. However, postoperative recovery is significantly affected by the induced pathophysiological changes. *Clostridium butyricum*, an anaerobic gram-positive bacillus, has been shown to promote the proliferation and development of some gut bacteria, inhibit the growth of pathogenic and spoilage bacteria in the intestines, correct gut microbiota imbalance, and reduce the occurrence of enterotoxins. However, there have been few published reports on the treatment of postoperative complications in cancer patients using *C. butyricum* administration. Cao et al[5] conducted a randomized, double-blind experiment to evaluate the effect of *C. butyricum* on recovery after gastric cancer surgery. The study included 92 gastric cancer patients who underwent gastrectomy. Of these, 47 patients received Ataining (containing *C. butyricum*, CGMCC0313.1, Qingdao East Sea Pharmaceutical Co., Ltd, Qingdao, China), while 45 patients received a placebo for 21 days after gastrectomy. Early postoperative recovery was assessed by monitoring inflammatory immune response through blood indicators, analyzing the gut microbiota using high-throughput sequencing, and examining short-chain fatty acids (SCFAs) through targeted metabolomics. The results of their study revealed that *C. butyricum* significantly reduced the number of leukocytes ($p < 0.001$), the percentage of neutrophils ($p < 0.001$), and the expression of IL-1β ($p < 0.01$), IL-6 ($p < 0.05$), and TNF-α ($p < 0.01$). The nutrition indexes, including albumin and total protein, were improved ($p < 0.05$). Additionally, the use of *C. butyricum* significantly increased the relative abundance of *Bacteroides*, *Faecalibacterium*, and *Gemmiger*, while reducing the abundance of *Streptococcus*, *Desulfovibrio*, and *Actinomyces* at the genus level. The study also reported a significant up-regulation of SCFAs after *C. butyricum* administration in patients who underwent gastrectomy. They concluded that oral administration of *C. butyricum* after gastrectomy can reduce early postoperative inflammation, enhance immune function, restore intestinal microbiota balance, increase intestinal SCFAs, reduce the occurrence of postoperative complications, and ultimately could promote early patient recovery[5].

It has been frequently reported that *H. pylori* eradication can lead to short-term disruption of the gut microbiota. He et al[6] conducted a multicenter, double-blind, randomized trial in China to evaluate the impact of probiotics on the gastrointestinal microbiota after *H. pylori* eradication with antibiotics. The study included 276 patients, where 140 patients received a 14-day bismuth quadruple therapy in combination with probiotics (Bifidobacterium Tetravac-

cine Tablets, SiLianKang, Hangzhou Grand Biologic Pharmaceutical Inc., Hangzhou, China), while 136 patients received a placebo for 28 days. After the therapy, saliva, gastric mucosa, and fecal samples were collected for 16S rRNA gene sequencing. No differences in the eradication rate between the two groups were observed, but side effects, especially nausea and vomiting, were lower in the probiotic group. Significant modifications of the gut microbiota were observed immediately following eradication, notably a significant decrease in richness, which gradually returned to baseline as early as 2 weeks after the completion of the quadruple therapy. The reduction of *Bacteroides* spp. in the gut after eradication was counteracted by the use of probiotics. Regarding the fluctuation in gastric microbiota, an increased alpha diversity was observed after *H. pylori* eradication in the placebo group, as measured by Chao1 and Shannon indices, while no significant change was observed in patients treated with probiotics. Unlike the fecal microbiota, the gastric microbiota in patients with *H. pylori* infection was predominantly composed of Phyla of Proteobacteria, followed by Firmicutes and Bacteroidetes. With the reduction of Proteobacteria after eradication, the relative abundances of Firmicutes and Bacteroidetes were enhanced. At the genus level, eradication was accompanied by enrichment of *Lactobacillus*, *Prevotella*, and *Bifidobacterium*. Interestingly, some taxa, including *Faecalibacterium* spp., *Bacteroides* spp., and *Streptococcus* spp., displayed differential abundances 8 weeks after eradication compared to baseline in the placebo group, while their abundances remained unchanged in patients treated with probiotics. Additionally, the amplitude of fluctuation was smaller in the probiotic group compared to the placebo group for certain genera, such as *Shigella* spp., *Ruminococcus* spp., and *Bifidobacterium* spp. In saliva samples, the expansion of certain pathogenic genera, including *Porphyromonas* and *Leptotrichia*, was suppressed by the use of probiotics. This study demonstrated the beneficial effect of implementing probiotics to mitigate side effects during *H. pylori* eradication and also provided a comprehensive profile of microbiome alterations along the gastrointestinal tract modulated by probiotics[6].

The use of probiotics has also been studied by Carlos et al[7] in patients who underwent Roux-en-Y gastric bypass surgery to investigate their effects on binge eating and food addiction. A randomized, double-blind, placebo-controlled trial[7] was conducted involving 101 patients who received either a probiotic supplement (containing *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* Bi-07) or a placebo for 90 days after bariatric surgery, starting from the 7th postoperative day. The Yale Food Addiction Scale (YFAS) and Binge Eating Scale (BES) were administered to assess food addiction and binge eating, respectively, before the surgery, at 90 days, and at 1 year after the surgery. The results showed that the number of symptoms on the YFAS and the BES score significantly decreased in both groups at 90 days after surgery compared to baseline. However, a significant treatment effect of probiotics was observed at 1 year after surgery. The probiotic group exhibited a lower number of food addiction symptoms and a lower binge eating score compared to the placebo group (p=0.037 and p=0.030, respectively). This study demonstrated that the use of probiotic supplementation for 90 days in the immediate postoperative period may lead to a reduction in food addiction symptoms and binge eating scores up to 1 year after surgery compared to the control group[7].

Finally, concerning bariatric surgery for patients with obesity, Lahtinen et al[8] conducted a randomized clinical trial to assess the effectiveness of Fecal Microbiota Transplantation (FMT) in promoting weight loss. They aimed to investigate whether FMT from a lean donor could reduce body weight and enhance the outcomes of bariatric surgery. The study employed a double-blinded, placebo-controlled, multicenter, randomized clinical trial design and included 41 patients who were eligible for bariatric surgery. During the study, FMT from a lean donor or an autologous placebo (patient's own fecal material) was administered *via* gastroscopy into the duodenum. Bariatric surgery, either laparoscopic Roux-en-Y gastric bypass (LRYGB) or laparoscopic sleeve gastrectomy (LSG), was performed 6 months after the baseline intervention. Weight reduction was measured as the percentage of total weight loss (TWL). At 18 months from the baseline, which corresponds to 12 months after surgery, the FMT group achieved a TWL percentage of 25.3%, while the placebo group had a TWL percentage of 25.2%. No significant difference in weight loss was observed between the two groups. FMT did not appear to influence weight loss before or after bariatric surgery. Further research is necessary to explore the potential role of FMT in the context of obesity[8].

Regarding bypass surgery and sleeve gastrectomy, a Canadian team[9] analyzed the changes in microbial and metabolomics in the fecal microbiota following bariatric surgery and sleeve gastrectomy. They identified pathways, such as aminoacyl-transfer RNA biosynthesis, that are associated with the beneficial metabolic effects of surgery[9].

CONCLUSIONS

The different papers published in the area of gastric microbiome in this past year mainly concerned the impact of probiotics on gastric microbiota. Some meta-analyses were also performed and confirmed that the gastric microbiota was evaluated with gastric carcinogenesis.

Conflict of Interest

The authors declare no conflict of interest.

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Informed Consent

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Authors' Contribution

Marine Jauvain and Emilie Bessède both wrote this review and contributed equally to this work.

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