Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review

Vaidota Maksimaityte, Augustinas Bausys, Marius Kryzauskas, Martynas Luksta, Ieva Stundiene, Klaudija Bickaite, Bernardas Bausys, Tomas Poskus, Rimantas Bausys, Kestutis Strupas

ORCID number: Vaidota Maksimaityte 0000-0002-9307-0037; Augustinas Bausys 0000-0003-1848-2960; Marius Kryzauskas 0000-0002-6373-9721; Martynas Luksta 0000-0001-8023-9908; Ieva Stundiene 0000-0002-2569-3638; Klaudija Bickaite 0000-0003-3952-3223; Bernardas Bausys 0000-0002-6542-4045; Tomas Poskus 0000-0002-6931-6941; Rimantas Bausys 0000-0003-4718-6810; Kestutis Strupas 0000-0002-1690-937X.

Author contributions: Maksimaityte V and Bausys A contributed equally to this work; Bausys R and Strupas K conceptualized and designed the work; Maksimaityte V, Bausys A, Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, and Poskus T performed the literature review and critical revision of the studies; Bausys A and Maksimaityte V prepared the manuscript; Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, Poskus T, Bausys R, and Strupas K revised the manuscript; all authors read and approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Open-Access: This article is an open-access article that was

Abstract

Gastric cancer is one of the most common malignancies worldwide and gastrectomy remains the only potentially curative treatment option for this disease. However, the surgery leads to significant physiological and anatomical changes in the gastrointestinal (GI) tract including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion after gastrectomy. These changes in the GI tract influence the composition of the gut microbiome and thus, host health. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. Furthermore, this dysbiosis is linked to intestinal inflammation, small intestinal bacterial overgrowth, various GI symptoms, and an increased risk of colorectal cancer.

Key Words: Gut microbiota; Dysbiosis; Gastric cancer; Gastrectomy; Microbiome; Comprehensive review

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Lithuania

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** March 13, 2021
**Peer-review started:** March 13, 2021
**First decision:** April 6, 2021
**Revised:** April 19, 2021
**Accepted:** May 25, 2021
**Article in press:** May 25, 2021
**Published online:** July 27, 2021

**P-Reviewer:** Chen F, Liang Y, Socea B
**S-Editor:** Fan JR
**L-Editor:** Webster JR
**P-Editor:** Wang LL

---

**Core Tip:** In most cases of gastric cancer (GC) the only life-saving treatment is gastrectomy. Gastrectomy results in significant changes in gut microbiota: Higher abundance of oral cavity bacteria, aero-tolerant bacteria, and bile transforming bacteria, and these changes in the microbiome are related to host health. In this review we discuss current knowledge and the results of recent studies on the changes in gut microbiome after gastrectomy in patients with a history of GC.

**Citation:** Maksimaityte V, Bausys A, Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B,Poskus T, Bausys R, Strupas K. *Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review.* World J Gastrointest Surg 2021; 13(7): 678-688

**URL:** https://www.wjgnet.com/1948-9366/full/v13/i7/678.htm

**DOI:** dx.doi.org/10.4240/wjgs.v13.i7.678

---

**INTRODUCTION**

Gastric cancer (GC) is an important oncological problem responsible for over 1000000 new cases and more than 783000 deaths worldwide annually, making it the fifth most common cancer and the third leading cause of cancer death[1]. Surgery remains the only potentially curative treatment option for this disease[2]. However, gastrectomy has some adverse effects in long-term survivors, including persistent gastrointestinal (GI) symptoms[3-5] and an increased risk of metachronous cancers[6-8]. Gastrectomy leads to significant changes in the GI tract, including changes in pH, oxygenation levels, and biliary diversion. These alterations of the GI tract create a strong impetus on changes in the gut microbiome (Figure 1), which was suggested to be involved in postoperative outcomes[6]. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria.

The microbiome of the human gut is a complex and diverse population of bacteria, fungi, archaea, and viruses that inhabit the intestinal tract, mainly the large intestine[9,10]. The stable human gut bacterial species are divided into six main phyla: *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Verrucomicrobia*, and *Euryarchaeota* [11]. These microbes have tremendous potential to impact host physiology, both in health and disease[12]. They contribute metabolic functions, protect against pathogens, educate the immune system, and, through these basic functions, affect directly or indirectly most of our physiologic functions[12]. Recent advancements revealed the gut microbiome's role in a series of different diseases including Alzheimer’s disease [13,14], obesity[15], inflammatory bowel diseases (IBD)[16,17], cancer[18,19], functional GI disorders[20], and others. Furthermore, the role of the microbiome in postoperative weight loss and other outcomes are documented after sleeve gastrectomy and Roux-en-Y gastric bypass in bariatric patients[21-26]. Several recent studies investigated the gut microbiome after gastrectomy for GC[6,27-29]. This comprehensive review provides an overview of the current evidence on gut microbiome after gastrectomy for GC and its clinical implication.

---

**LITERATURE SEARCH**

A comprehensive literature search was conducted using the PubMed database up to 31st December, 2020. The search terms used were “gastrectomy AND microbiome”. No time restrictions for publications were used, but only manuscripts published in the English language were reviewed. All titles and abstracts were independently reviewed by two reviewers (V.M. and A.B.) to identify clinical studies investigating the impact of gastrectomy on the gut microbiome in GC patients. After relevant abstracts were identified the full-text articles were retrieved. To ensure a comprehensive literature search an additional manual search of the reference lists was performed.
Following a comprehensive review of the current literature, we identified 4 studies which investigated the gut microbiome after total or subtotal gastrectomy for GC, and these are summarized in Table 1. Three of these four studies were cross-sectional and investigated gut microbiome composition in GC patients at a median time of 3.75 years [27], 5 years [6], and 8.25 years [28] after gastrectomy and compared it with the corresponding controls. One small-scale study was longitudinal and investigated the gut microbiome composition before and approximately one week after gastrectomy [29].

Gut microbiome diversity and richness may be related to host health [30]. A reduction in the GI microbiome biodiversity was reported in obesity, inflammatory bowel disease, colorectal malignancy, and type 2 diabetes [21,30-33]. The impact of gastrectomy on bacterial richness and alpha diversity remains controversial because of conflicting results in current studies. Erawijantari et al [6] showed increased richness and diversity by increased Chao1 and Shannon indices in gastrectomized patients [6]. However, bacterial richness and alpha diversity may depend on the type of GI tract reconstruction. The study by Lin et al [28] showed increased richness and alpha diversity only after subtotal gastrectomy with Roux-en-Y reconstruction (RYGJ), but not in the case of Billroth II reconstruction (B2) [28]. Furthermore, similar richness and even decreased alpha diversity after subtotal gastrectomy with B2 reconstruction was reported by Horvath et al [27]. The impact of gastrectomy on bacterial richness and alpha diversity seems to be a long-term effect of the surgery since these changes were not observed by Liang et al [29] in the early perioperative period [29]. All the studies managed to identify and highlight specific features of the gut microbiome composition in the postsurgical period [27-29,34].

GASTRIC BARRIER LOSS AFTER GASTRECTOMY AND ITS IMPACT ON GUT MICROBIOME COMPOSITION

One of the typical changes in the GI tract after subtotal gastrectomy includes loss of the gastric barrier [27] due to reduced gastric acid secretion [27,35-37]. A pH of 4 is considered a threshold value for a powerful bactericidal effect [38] and it is significantly exceeded after subtotal gastrectomy, as the gastric pH increases from physiological levels to values above 6.0, irrespective of the type of reconstruction [39]. A very similar increase in gastric pH from approximately 2.0 to over 6.0 is described following proton pump inhibitor (PPI) intake [27]. In such conditions oral bacteria may survive during gastric passage and colonize the distal part of the GI tract, causing gut microbiome oralization, the phenomenon previously described in PPI users [40-43]. The comparable loss of gastric barrier function after subtotal gastrectomy and by PPI use may result in a similar impact on the gut microbiome.

Thus, it was not surprising that a higher abundance of typical oral cavity bacteria - Streptococcus, Veillonella, Prevotella, Orbibacterium, and Mogibacterium [44] - were observed in the gut microbiome of gastrectomized patients [6,27,28]. Some of these bacteria are linked to host health and treatment efficacy. A recent study linked Veillonella with tumor response to Nivolumab in patients with progressive GC [45]. Streptococcus is a prevalent bacterial taxon in the oral cavity and the most commonly described...
## Table 1 Clinical studies investigating gut microbiome composition in patients after gastrectomy for gastric cancer

| Ref.        | Type of study | Participants (groups) | Exclusion criteria | Type of gastrectomy and method of reconstruction | Main findings of the study | Other metabolites investigated |
|-------------|---------------|-----------------------|-------------------|-------------------------------------------------|---------------------------|--------------------------------|
| Erawijantari et al[6], 2020 | CSS | Gastrectomy group: Patients with a history of gastrectomy for GC (n = 50). Control group: Healthy controls without a history of gastrointestinal surgery (n = 56) | Recurrence of gastric cancer (gastrectomy group). History of gastrointestinal surgery (for controls) | Total (n = 12) gastrectomy and subtotal gastrectomy (n = 38). Types of reconstruction: Stomach-stomach (n = 1); Billroth I (n = 2); jejunal interposition (n = 6); Pylorus-preserving gastrectomy (n = 8); Roux-en-Y (n = 29) | Higher species diversity and richness in gastrectomized patients. Higher abundance of aerobes, facultative anaerobes, and oral microbes in gastrectomized patients | Phosphate and amino acid transporters were more abundant in gastrectomized patients. Primary and conjugated forms of bile acid enriched in the control group and deoxycholic acid more abundant in gastrectomized patients |
| Liang et al[29], 2019 | LS | Gastrectomy group: Patients with a diagnosed GC one week before (n = 20) and a 7 d after (n = 6) gastrectomy. Control group: Healthy controls (n = 22) | History of antibiotics, PPI or H2 receptor antagonist use 1 mo prior to inclusion. Endoscopic finding of peptic ulcer, tumor rupture, pyloric obstruction. Patients with a history of radiotherapy/chemotherapy and/or previous surgery | Distal gastrectomy (n = 6). Types of reconstruction: Billroth II (n = 1); Roux-en-Y (n = 5) | Increased abundance of Bacteroidetes, Fusobacteria, and Verrucomicrobia and decreased abundance of Proteobacteria, Firmicutes, and Actinobacteria after distal gastrectomy. The richness and diversity by Chao1, ACE; Shannon; and Simpson indices were similar before and after distal gastrectomy. LEfSe analysis attributed Verrucomicrobiae (genus Akkermansia) and genus Escherichia/Shigella, Lactobacillus, and Dialister to patients after gastrectomy, and the genus Klebsiella to patients before gastrectomy | Significantly decreased level of valeric acid after distal gastrectomy |
| Horvath et al[27], 2021 | CSS | Gastrectomy group: Patients with a history of distal gastrectomy with Billroth II reconstruction for early gastric cancer (n = 14). Control group: Patients’ in-house relatives without a history of gastric surgery (n = 8) | Chemotherapy or radiotherapy 12 mo before inclusion. Gastric stump cancer. Usage of antibiotics, pro-, pre-, or symbiotics, H2-blocker, or PPI 1 month before inclusion. History of any gastrointestinal tract resections other than SGB2. Recurrence of gastric cancer, and current nongastric malignancies | Distal gastrectomy (n = 14). Types of reconstruction: Billroth II (n = 14) | Alpha diversity assessed by Shannon index was significantly decreased in gastrectomy patients. Median bacterial richness quantified by Chao1 index was similar. Beta diversity analysis showed significant differences between the microbiome composition of patients and controls; ANCOM identified the genus Enterobacter-Sigella to be more abundant in gastrectomized patients. LEfSe attributed 11 additional genera to the gastrectomy group and 17 genera to the control (approximately half of them already have been implicated in PPI-induced or PPI-associated dysbiosis in previous reports). Increased abundance of Enterobacter-Sigella, Enterococcus, Streptococcus, and other typical oral cavity bacteria (Veillonella, Orbitobacterium, and Megabacterium) in gastrectomized patients | Fecal calprotectin marker was higher in gastrectomized patients. Fecal calprotectin was positively correlated with the abundance of Streptococcus and negatively correlated with the abundance of Ruminococcaceae, Bacteriella, Ruminococcus 2, Ruminococcus 1, and Anaerostipes. Abdominal discomfort was associated with a significantly higher abundance of Holdemanella and lower abundance of Agathobacter; Diarrhea was associated with a significantly higher abundance of Agathobacter and Streptococcus. Patients who suffered from diarrhea also showed significantly higher serum levels of CRP and a trend to higher calprotectin level in stool compared with patients without diarrhea |
| Lin et al[28], 2018 | CSS | Gastrectomy group: Patients with a history of distal gastrectomy | Age < 20 yr. Other underlying malignancies. Pre- and postoperative chemotherapy or chemoradiotherapy for GC. Other endocrine disorders such as DM, | Distal gastrectomy (n = 111). Types of reconstruction: Billroth | Significantly increased richness of gut microbiome after RYJ by Chao1 index. Tendency of increased richness of gut microbiome after SGB2 by Chao1 | GC patients after subtotal gastrectomy with RYGJ had a lower occurrence of metabolic syndrome and type II diabetes |
Gastrectomy impact on the gut microbiome

for early GC ($n = 111$). Control group: Age and sex-matched subjects without a history of GI tract surgery ($n = 344$). Patients who received proton pump inhibitors, histamine-2 receptor antagonists, nonsteroidal anti-inflammatory drugs, antibiotics, or probiotics within one month of sample collection.

CSS: Cross-sectional study; LS: Longitudinal study; GC: Gastric cancer; PPI: Proton pump inhibitors; SGB2: Subtotal gastrectomy with Billroth II reconstruction; CRP: C-reactive protein; RYGJ: Subtotal gastrectomy with Roux-en-Y reconstruction.

bacterium in PPI-induced dysbiosis.[27,41,43,46,47] Previously, this bacterium was linked to intestinal inflammation and gut permeability in cirrhosis patients.[40] Similarly, Streptococcus was also associated with intestinal inflammation in gastrectomized patients.[27] Chronic intestinal inflammation may be involved in the pathogenesis of intermittent or permanent chronic diarrhea, which is present in up to 40% of long-term survivors after gastrectomy.[3,48-50] Previously post-gastrectomy diarrhea was attributed to vagotomy, endocrine hypofunction-related dyscoordination of the digestive tract, and abnormalities in the regulation of GI tract hormone secretion.[50] Although, as shown in IBD patients, chronic inflammation leads to damage of intestinal mucosa, dysregulation of intestinal ion transport, impaired and increased accessibility to the intestinal mucosa for pathogens.[51] Dysregulation of the expression and/or function of epithelial ion transporters and channels leads to electrolyte retention and water accumulation causing diarrhea.[30] Loss of epithelial barrier function contributes to diarrhea via a leak-flux mechanism, while mucosal penetration of enteric pathogens drives subsequent tissue damage.[51] Furthermore, patients suffering diarrhea after gastrectomy showed an increased abundance of Mogibacterium and decreased abundance of Ruminococcus 1.[27] Mogibacterium is increased in Crohn’s patients[52] and decreased Ruminococcus 1 was associated with diarrhea in an experimental porcine model.[53]

Other common GI symptoms in gastrectomized patients are abdominal discomfort and bloating.[27,48-50] Both of these symptoms were associated with a decrease in Agathobacter.[27] These butyrate producers live in symbiosis with Bifidobacteria, which provides acetate as a substrate for butyrate production.[54] Abdominal discomfort was also, associated with increased abundance of Holdemanelia.[27] There is a lack of evidence on the impact of Holdemanelia on host health, although, their taxonomic family Erysipelotrichaceae contains highly immunogenic species and is associated with
pro-inflammatory conditions[27,55].

INCREASED OXYGEN LEVEL IN THE GUT AFTER GASTRECTOMY AND ITS IMPACT ON THE GUT MICROBIOME

The important anatomical and physiological changes in the GI tract after gastrectomy include increased oxygen in the distal part of the gut[56], which may provide an appropriate niche for aerobic and facultative anaerobic microbes. The studies on the gut microbiome after gastrectomy consistently showed an increased abundance of aero-tolerant microorganisms[27,28,34]. Erawijantari et al[6] demonstrated an increased abundance of aerobes (Streptococcus, Enterococcus) and facultative anaerobes (Escherichia, Enterobacter, and Streptococcus) in patients after gastrectomy. The study by Lin et al[28] showed a higher amount of aero-tolerant Proteobacteria phylum microorganisms including Streptococcus, Escherichia, and Klebsiella[28]. Similar, studies by Liang et al[29] and Horvath et al[27] demonstrated increased numbers of aerobes (Streptococcus) and facultative anaerobes (Escherichia) in patients after subtotal gastrectomy[27,29]. The increase in Escherichia was the most prominent difference between the microbiome of gastrectomy patients and controls documented in all studies[27-29,34]. Escherichia is a common protagonist in small intestinal bacterial overgrowth (SIBO)[57], which is a heterogeneous syndrome characterized by an increased number and/or abnormal type of bacteria in the small bowel[57]. SIBO occurs in the majority of patients after gastrectomy[58], and the clinical manifestation of this syndrome includes bloating, flatulence, abdominal discomfort, diarrhea, and abdominal pain[57], symptoms which are common in long-term survivors after gastrectomy[3,48-50].

Taken together, there is evidence associating GI symptoms after gastrectomy with specific changes in the gut microbiome composition, although further studies are warranted to confirm these findings and the exact mechanisms involved.

THE IMPACT OF BILIARY DIVERSION AFTER GASTRECTOMY ON THE GUT MICROBIOME

GI tract reconstruction following gastrectomy may lead to biliary diversion. The altered bile acid flow potentially stimulates the growth of bile acid-transforming bacteria[34]. The study by Erawijantari et al[6] extensively analyzed the fecal metabolomic profile and showed increased abundance of the secondary bile acid - deoxycholic acid (DCA) in gastrectomized patients[6]. Deconjugation of human primary bile acids and their subsequent biotransformation to secondary bile acids is a well-recognized function carried out by the human gut microbiome with its implications for human health[59]. The 7α-dehydroxylation reaction has been described as the most quantitatively important process for the formation of secondary bile acids performed by the gut microbiome, specifically the bacteria that belong to the genus Clostridium[60]. The increased abundance of Clostridium following gastrectomy was confirmed in several studies[28,34]. Altered bile acid pool composition has been associated with several diseases including colorectal cancer[61,62], IBD, and metabolic syndrome[60].

DCA is a carcinogen in liver cancer and colorectal cancer[34,61,62]. Increased DCA in the intestine causes DNA damage through oxidative stress in intestinal epithelial cells and activates the epidermal growth factor receptor or Wnt pathways to promote colorectal cancer (CRC)[63]. These mechanisms may be responsible for the increased risk of metachronous CRC in GC patients[7,8]. Furthermore, the altered bile flow-induced gut microbiome changes were suggested as one of the potential mechanisms for the metabolic effect of gastrectomy[28]. Patients after subtotal gastrectomy with RYGJ or B2 reconstruction were shown to have a lower body mass index or waist circumference compared to age and sex-matched healthy controls in the study by Lin et al[28]. Also, subtotal gastrectomy had some more positive effects such as higher serum high-density lipoprotein, lower total cholesterol, and triglyceride levels[28]. Only patients who underwent RYGJ showed a lower prevalence of metabolic syndrome and type 2 diabetes[28]. The exact mechanisms linking subtotal gastrectomy with metabolic improvement remain unclear; however, some gut microbiome involving pathways were suggested[28]. They include: (1) The impact of the gut microbiome on the enteroendocrine function; (2) Altered bile acid flow, which is a
driver for changes in microbiome composition; and (3) Decreased levels of circulating lipopolysaccharides and altered bacterial components promoting hepatic insulin sensitivity[28].

LIMITATIONS OF THE CURRENT KNOWLEDGE AND PERSPECTIVES FOR FUTURE RESEARCH

The knowledge provided by the current studies has some limitations. First, most of the studies were cross-sectional design[27,28,34], and the only longitudinal study by Liang et al[29] was limited by a very small sample size and short follow-up[29]. Thus, there is a lack of data showing microbiome composition changes pre- and post-gastrectomy. Second, some studies included controls who were on gastric acid suppression medications or did not record the history of antibiotic use. These medications have a strong effect on the gut microbiome, thus, the impact of gastrectomy may have been underestimated[64]. Third, the current studies included patients with different extents of gastrectomy (total vs subtotal) and different types of reconstructions (B2, RYGJ, Billroth I). The impact of gastrectomy on the gut microbiome may be specific for the type of surgery; thus, future studies should clarify the impact of types of reconstruction after gastrectomy. Together, the present knowledge provides evidence on the impact of gastrectomy on the gut microbiome. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion. Further well-designed and appropriate size longitudinal studies are necessary to confirm this concept. These studies should incorporate data on health-related quality of life, especially on GI symptoms, metabolomics, and markers on intestinal inflammation and permeability to provide robust evidence on the impact of gastrectomy-induced dysbiosis on host health.

Several ongoing studies are already investigating gut microbiome changes through the GC treatment pathway. The LEGACY-2 trial (NCT04015466) is a large-scale international study aiming to study biological factors, including microbiome impact on clinical outcomes. The NeoChance trial (NCT04196465) is investigating the microbiome as a predictive/prognostic biomarker in patients who receive neoadjuvant immune checkpoint inhibitor IMC-001 for resectable GC. The NutriGIT (NCT04476082) study is investigating the nutritional status of patients with various GI cancers, including GC, and one of the study outcomes is changes in the gut microbiome. Together, these studies will increase the knowledge on microbiome changes through GC treatment and will highlight the impact of these changes on treatment outcomes. However, current studies are not designed to specifically investigate gastrectomy-induced dysbiosis; thus, such studies are still necessary.

The recent studies linked gut microbiome composition with the effectiveness of anti-cancer therapy[45,65]. An exploratory analysis of genus from the DELIVER trial showed that Odoribacter and Veillonella were associated with tumor response to Nivolumab in patients with advanced GC[45]. As mentioned previously, the abundance of typical oral bacteria-Veillonella increases following subtotal gastrectomy, due to the oralization phenomenon[27]. However, there is currently a lack of evidence to reliably characterize the impact of gastrectomy-induced dysbiosis on the effectiveness of anti-cancer therapy. As systemic therapy before and/or after surgery is the modern standard for GC, it would be of interest to investigate the association between gut microbiome and the efficacy of therapy in future studies.

CONCLUSION

Gastrectomy for GC impacts the composition of the gut microbiome. These changes are characterized by oralization, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and the biliary diversion after gastrectomy. Gastrectomy-induced dysbiosis is associated with host health. However, current evidence is limited; therefore, further longitudinal studies looking at different reconstructions of the GI tract are needed to confirm the concept and to investigate the mechanisms related to the impact of the gut microbiome on the health of GC patients.
REFERENCES

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jamal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J Clin* 2018; 68: 394-424 [PMID: 30207593 DOI: 10.3322/canjclin.21492]

2 Stratilatovas E, Bauly's A, Bauly's R, Sangaila E. Mortality after gastrectomy: a 10 year single institution experience. *Acta Chir Belg* 2015; 115: 123-130 [PMID: 26021945 DOI: 10.1080/00015458.2015.1168108]

3 Yu W, Park KB, Chung HY, Kwon OK, Lee SS. Chronological Changes of Quality of Life in Long-Term Survivors after Gastrectomy for Gastric Cancer. *Cancer Res Treat* 2016; 48: 1030-1036 [PMID: 27004956 DOI: 10.14143/crt.2015.398]

4 Lee SS, Chung HY, Kwon OK, Yu W. Quality of life in cancer survivors 5 years or more after total gastrectomy: a case-control study. *Int J Surg* 2014; 12: 700-705 [PMID: 24866609 DOI: 10.1016/j.ijsu.2014.05.067]

5 Brenkman HJF,egelsersberg R; LOGICA Study Group. Factors influencing health-related quality of life after gastrectomy for cancer. *Gastric Cancer* 2018; 21: 524-532 [PMID: 29067597 DOI: 10.1007/s10120-017-0771-0]

6 Erawijantari PP, Mizutani S, Shiroma H, Shibayama K, Sakamoto T, Saito Y, Fukuda S, Yachida S, Yamada T. Influence of gut microbiota due to gastric bypass reduce host weight and adiposity. *Microbiota Axis: Antibiotics and Functional Gastrointestinal Disorders.* [PMID: 20722058 DOI: 10.1016/j.jso.2016.10.015]

7 Ikeda Y, Saku M, Kawanaka H, Nonaka M, Yoshida K. Features of second primary cancer in patients with gastric cancer. *Oncology* 2003; 65: 113-117 [PMID: 12931016 DOI: 10.1159/000072335]

8 Eom BW, Lee HH, Yoo MW, Cho JI, Kim WH, Yang HK, Lee KL. Synchronous and metachronous cancers in patients with gastric cancer. *J Surg Oncol* 2008; 98: 106-110 [PMID: 18452218 DOI: 10.1002/jso.21027]

9 Bäumler AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* 2016; 535: 85-93 [PMID: 27383983 DOI: 10.1038/nature18849]

10 Clemente JC, Ursell LL, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell* 2012; 148: 1258-1270 [PMID: 22424233 DOI: 10.1016/j.cell.2012.01.035]

11 Bliss ES, Whiteside E. The Gut-Brain Axis, the Human Gut Microbiota and Their Integration in the Development of Obesity. *Front Physiol* 2018; 9: 900 [PMID: 30050464 DOI: 10.3389/fphys.2018.00900]

12 Shreiner AB, Kao JY, Young VB. The gut microbiome in health and in disease. *Curr Opin Gastroenterol* 2015; 31: 69-75 [PMID: 25394236 DOI: 10.1097/MOG.0000000000000139]

13 Zhao Y, Saku M, Kawanaka H, Nonaka M, Yoshida K. Features of second primary cancer in patients with gastric cancer. *Cancer Res Treat* 2016; 38: 213-218 [PMID: 27383983 DOI: 10.1016/j.jso.2016.10.015]

14 Moulaert KE, Pahor M, Bäumler AJ. Antibiotics, the gut microbiota and the brain. *Nat Med* 2015; 21: 150-157 [PMID: 25248007 DOI: 10.1038/nm.3607]

15 Doherty MM, Sperandio V. Interaction between the microbiota and the human brain. *Brain Behav* 2015; 5: 690-702 [PMID: 26021945 DOI: 10.1007/s10120-017-0771-0]

16 Messaoudi I, Sperandio V. The gut-brain axis: a bidirectional communication. *J Neurogastroenterol Motil* 2016; 22: 13-23 [PMID: 26021945 DOI: 10.1007/s10120-017-0771-0]

17 Everard A, Belzer C, Geurts L, Ouwerkerk JP, DeCarli C, McSweeney C, Morrison M, Marteau P, Doré J, Crettaz D, Pacheco A, Martin L, Calugi S, Vellone E, Suruda J, Janssens S, Scharre V, Riva G, Sonnenberg A, Cani PD, Dore J, Darche S, Dieterich D, Deroo S, Dethy E, Denninger T, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and host beneficial intestinal epithelial cells. *Cell* 2015; 162: 709-719 [PMID: 26021945 DOI: 10.1007/s10120-017-0771-0]

18 Andler A, Sperandio V. The gut-brain axis: a bidirectional communication. *Gastroenterol Hepatol* 2015; 29: 153-162 [PMID: 26021945 DOI: 10.1007/s10120-017-0771-0]

19 Zhang H, Ostrosky-Wegman P, Sung J, Olszowka AJ, Pacheco A, Cani PD, Dore J, Darche S, Dethy E, Denninger T, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and host beneficial intestinal epithelial cells. *Cell* 2015; 162: 709-719 [PMID: 26021945 DOI: 10.1007/s10120-017-0771-0]

20 Everard A, Belzer C, Geurts L, Ouwerkerk JP, DeCarli C, McSweeney C, Morrison M, Marteau P, Doré J, Leclerc M. Highlighting new phylogenetic specificities of Crohns disease microbiota. *Inflamm Bowel Dis* 2015; 21: 139-153 [PMID: 25248007 DOI: 10.1097/MIB.0000000000000215]

21 Mondot S, Kang S, Furet JP, Aguierre de Carcer D, McSweeneey C, Morrison M, Marteau P, Dore J, Leclerc M. Highlighting new phylogenetic specificities of Crohns disease microbiota. *Inflamm Bowel Dis* 2011; 17: 185-192 [PMID: 20722058 DOI: 10.1002/ibd.21436]

22 Wei B, Su TT, Duhwadi H, Stephan RP, Fujiwara D, Huang TT, Brewer S, Chen L, Arditi M, Borneman J, Rawlings DJ, Braun J. Resident enteric microbiota and CD8+ T cells shape the abundance of marginal zone B cells. *Eur J Immunol* 2008; 38: 3411-3425 [PMID: 19009525 DOI: 10.1002/eji.200838432]

23 Wu S, Rhee JK, Albesiano E, Rabizadeh S, Wu X, Yen HR, Hsu DL, Brancati FL, Wick E, McAllister F, Houssseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat Med* 2009; 15: 1016-1022 [PMID: 19701202 DOI: 10.1038/nm.2015]

24 Karakan T, Ozkul C, Kupeli Akkol E, Bilici S, Sobarzo-Sánchez E, Capasso R. Gut-Brain-Microbiota Axis: Antibiotics and Functional Gastrointestinal Disorders. *Nutrients* 2021; 13 [PMID: 33513791 DOI: 10.3390/nu13020389]

25 Liu AP, Paziuk M, Luevano JM Jr, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. *Sci Transl Med* 2013; 5: 178ra41 [PMID: 23536015 DOI: 10.1126/scitranslmed.3005687]

26 Palleja A, Kashani A, Allin KH, Nielsen T, Zhang C, Li Y, Brach T, Liang S, Feng Q, Jørgensen NB, Bojsen-Moller KN, Dirksen C, Burgdorf KS, Holst JJ, Madsbad S, Wang J, Pedersen O, Hansen T,
Maksимайте V et al. Gastrectomy impact on the gut microbiome

Arumugam M. Roux-en-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. *Genome Med* 2016; 8: 67 [PMID: 27306058 DOI: 10.1186/s13073-016-0312-1]

23 Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R. Human gut microbiota in obesity and after gastric bypass. *Proc Natl Acad Sci USA* 2009; 106: 2365-2370 [PMID: 19164566 DOI: 10.1073/pnas.0812600106]

24 Karami R, Kermansaravi M, Pishgharoudsari M, Talebi M, Mohammadzadeh N, Pazouki A. Changes in gut microbial flora after Roux-en-Y gastric bypass and sleeve gastrectomy and their effects on post-operative weight loss. *Updates Surg* 2020 [PMID: 33067675 DOI: 10.1007/s13304-020-00900-9]

25 Xu G, Song M. Recent advances in the mechanisms underlying the beneficial effects of bariatric and metabolic surgery. *Surg Obes Relat Dis* 2021; 17: 231-238 [PMID: 33036939 DOI: 10.1016/j.soard.2020.08.028]

26 Sanchez-Carrillo S, Ciordia S, Rojo D, Zubeldia-Varela E, Méndez-García C, Martínez-Martínez M, Barbas C, Ruiz-Ruiz S, Moya A, Garriga M, Salazar N, Botella-Carretero JI, Vega-Piñero B, de los Reyes-Gavilán CG, Del Campo R, Ferrer M. A body weight loss- and health-promoting gut microbiota is established after bariatric surgery in individuals with severe obesity. *J Pharm Biomed Anal* 2021; 193: 113747 [PMID: 32217711 DOI: 10.1016/j.jpba.2020.113747]

27 Horvath A, Bausys A, Sabaliauskaite R, Stratilatovas E, Jarmalaitė S, Schuetz B, Stiegler P, Bausys R, Stadlbauer V, Strupas K. Distal Gastrectomy with Billroth II Reconstruction is Associated with Oralization of Gut Microbiome and Intestinal Inflammation: A Proof-of-Concept Study. *Anal Cancer* 2021; 5: DOI: 10.1093/jcancer/jox377

28 Lin XH, Huang KH, Chuang WH, Luo JC, Lin CC, Ting PH, Young SH, Fang WL, Hou MC, Lee FY. The long term effect of metabolic profile and microbiota status in early gastric cancer patients after subtotal gastrectomy. *PLoS One* 2018; 13: e0206930 [PMID: 30395589 DOI: 10.1371/journal.pone.0206930]

29 Liang W, Yang Y, Wang H, Yu X, Lu Y, Shen S, Teng L. Gut microbiota shifts in patients with gastric cancer in perioperutive period. *Medicine (Baltimore)* 2019; 98: e16626 [PMID: 31464899 DOI: 10.1097/MD.0000000000016626]

30 Heiman ML, Greenway FL. A healthy gastrointestinal microbiome is dependent on dietary diversity. *Mol Metab* 2016; 5: 317-320 [PMID: 27110483 DOI: 10.1016/j.jomel.2016.02.005]

31 Turnbaugh PJ, Hamady M, Yatsunenko T, Fischline M, Gevers D, Knights D, Ley RE, Sogin ML, Relman DA. A core gut microbiome in obese and lean twins. *Nature* 2009; 457: 480-481 [PMID: 19434044 DOI: 10.1038/nature07540]

32 Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010; 5: e9085 [PMID: 20140211 DOI: 10.1371/journal.pone.0009085]

33 Kowalska-Duplaga K, Gosiewski T, Kapusta P, Sroka-Oleksiak A, Wędrzynowicz A, Pieczarkowski S, Ludwig-Słomczyńska AH, Wolkow PP, Dyderek K. Differences in the intestinal microbiome of healthy children and patients with newly diagnosed Crohn's disease. *Sci Rep* 2019; 9: 18880 [PMID: 31827911 DOI: 10.1038/s41598-019-55290-9]

34 Dhakan DB, Maji A, Sharma AK, Saxena R, Puliikkann J, Grace T, Gomez A, Scaria J, Amato KR, Sharma VK. The unique composition of Indian gut microbiome, gene catalogue, and associated fecal metabolome deciphered using multi-omics approaches. *GigaScience* 2019; 8 [PMID: 30698687 DOI: 10.1093/gigascience/giz004]

35 Huang L, Xu AM, Li TJ, Han WX, Xu J. Should peri-gastrectomy gastric acidity be our focus among gastric cancer patients? *World J Gastroenterol* 2014; 20: 6981-6986 [PMID: 24944492 DOI: 10.3748/wjg.v20.i22.6981]

36 Rieu PN, Jansen JB, Hopman WP, Joosten HJ, Lamers CB. Effect of partial gastrectomy with Billroth II or Roux-en-Y anastomosis on postprandial and cholecystokinin-stimulated gallbladder contraction and secretion of cholecystokinin and pancreatic polypeptide. *Dig Dis Sci* 1990; 35: 1060-1072 [PMID: 2390021 DOI: 10.1007/BF01537576]

37 Jepson K, Johnston D. Effect of vagotomy on human gastric acid secretion stimulated by gastrin pentapeptide and by histagol. *Gastroenterology* 1968; 55: 669-669 [PMID: 5727781]

38 Martinsen TC, Bergh K, Waldum HL. Gastric juice: a barrier against infectious diseases. *Basic Clin Pharmacol Toxicol* 2005; 96: 94-102 [PMID: 15679471 DOI: 10.1111/j.1742-7843.2005.tb09020.x]

39 Carboni M, Guadagni S, Pistoia MA, Amicucci G, Tuscano D, Negro P, Smith PL, Walters CL. The microflora of the gastric juice after Billroth I and Billroth II partial gastrectomy. *Scand J Gastroenterol* 1986; 21: 461-470 [PMID: 3726452 DOI: 10.3109/00365528609015163]

40 Horvath A, Rainer F, Bashir M, Leber B, Schmerboeck B, Klymiuk I, Groselj-Strele A, Durdevic M, Freedenberg DE, Abrams JA, Fickert P, Stiegler P, Stadlbauer V. Biomarkers for oralization during long-term proton pump inhibitor therapy: prediction of gastric acid suppression in cirrhosis. *Sci Rep* 2019; 9: 12000 [PMID: 31427714 DOI: 10.1038/s41598-019-48352-5]

41 Imhann F, Bonder MJ, Vich Vila A, Fu J, Mujagic Z, Lork V, Tigeheelaar EF, Jankipersadsing SA, Cenit MC, Harnsen HJ, Dijkstra G, Franke L, Xavier RJ, Jonkers D, Wijmenga C, Weersma RK,
Zhernakova A. Proton pump inhibitors affect the gut microbiome. *Gut* 2016; 65: 740-748 [PMID: 26657899 DOI: 10.1136/gutjnl-2015-310376]

Bajaj JS, Cox IJ, Betrapally NS, Heuman DM, Schubert ML, Rameswaran M, Hylemon PB, White MB, Daia K, Noble NA, Sikaroodi M, Williams R, Crossley MM, Taylor-Robinson SD, Gillevet PM. Systems biology analysis of omeprazole therapy in cirrhosis demonstrates significant shifts in gut microbiota composition and function. *Am J Physiol Gastrointest Liver Physiol* 2014; 307: G951-G957 [PMID: 25259407 DOI: 10.1152/ajpgi.00268.2014]

Jackson MA, Goodrich JK, Maxan ME, Feedberg DE, Abrams JA, Poole AC, Sutter JL, Welter D, Ley RE, Bell JT, Spector TD, Steses CJ. Proton pump inhibitors alter the composition of the gut microbiota. *Gut* 2016; 65: 749-756 [PMID: 26719299 DOI: 10.1136/gutjnl-2015-310861]

Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol* 2005; 43: 5721-5732 [PMID: 16272510 DOI: 10.1128/JCM.43.11.5721-5732.2005]

Sunakawa Y, Matoba R, Inoue E, Sakamoto Y, Kawabata R, Ishiguro A, Akamaru Y, Kito Y, Takahashi M, Matsuyma J, Yabuzaki H, Makiyama A, Suzuki T, Tsuda M, Yaisi H, Kawakami H, Muro K, Nakajima TE, Ichikawa W, Fujii M. Genomic pathway of gut microbiome to predict efficacy of nivolumab in advanced gastric cancer: DELIVER trial (JACCRO GC-08). *J Clin Oncol* 2021; 39: 161-161 [DOI: 10.1200/JCO.2021.39.3_supp.161]

Tsuda A, Suda W, Morita H, Takanashi K, Takagi A, Koga Y, Hattori M. Influence of Proton-Pump Inhibitors on the Luminal Microbiota in the Gastrointestinal Tract. *Clin Transl Gastroenterol* 2015; 6: e89 [PMID: 26605717 DOI: 10.1038/ctg.2015.20]

Clooney AG, Bernstein CN, Leslie WD, Vagianos K, Sargent M, Laserna-Mendieta EJ, Claesson MJ, Targownik LE. A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. *Aliment Pharmacol Ther* 2016; 43: 974-984 [PMID: 26923470 DOI: 10.1111/apt.13568]

Karanicolas PJ, Graham D, Gönen M, Strong VE, Brennan MF, Coit DG. Quality of life after gastrectomy for adenocarcinoma: a prospective cohort study. *Ann Surg* 2013; 257: 1039-1046 [PMID: 23665970 DOI: 10.1097/SLA.0b013e31828e4a19]

Kim AR, Cho J, Hwu YJ, Choi MG, Noh JH, Sohn TS, Bae JM, Yun YH, Kim S. Changes of quality of life in gastric cancer patients after curative resection: a longitudinal cohort study in Korea. *Ann Surg* 2012; 256: 1008-1013 [PMID: 23154395 DOI: 10.1097/SLA.0b013e31827661c9]

Aoki T, Yamaji I, Hisamotou T, Sato M, Matsuda T. Irregular bowel movement in gastrectomized patients. *Gastroenterol Res Pract*. 2011; 2011: 1-8 [PMID: 21967065 DOI: 10.1155/2011/382145]

Anbazhagan AN, Priyamvada S, Alrefai WA, Dudeja PK. Pathophysiology of IBD associated diarrhea. *Tissue Barriers* 2018; 6: e1463897 [PMID: 29737913 DOI: 10.1080/21688370.2018.1463897]

Qu Z, Yang H, Rong L, Ding W, Chen J, Zhong L. Targeted Metagenome Based Analyses Show Gut Microbial Diversity of Inflammatory Bowel Disease patients. *Indian J Microbiol* 2017; 57: 307-315 [PMID: 28904415 DOI: 10.1007/s12088-017-0652-z]

Yang Q, Huang X, Wang P, Sun W, Zhao S, Guan S. Longitudinal development of the gut microbiota in healthy and diarrheic piglets induced by age-related dietary changes. *Microbiologyspen* 2019; 8: e923 [PMID: 31496126 DOI: 10.1002/mbo3.923]

Rivière A, Gagnon M, Weckx S, Roy D, De Vuyst L. Mutual Cross-Feeding Interactions between Bifidobacterium longum subsp. longum NCC2705 and Eubacterium rectale ATCC 33656 Explain the Bifidogenic and Butyrogenic Effects of Arabinoxylan Oligosaccharides. *Appl Environ Microbiol* 2015; 81: 7767-7781 [PMID: 26319874 DOI: 10.1128/AEM.02089-15]

Kaakoush NO. Insights into the Role of Erysipelotrichaceae in the Human Host. *Front Cell Infect Microbiol* 2015; 5: 84 [PMID: 26636046 DOI: 10.3389/fcimb.2015.00084]

Celiker H. A new proposed mechanism of action for gastric bypass surgery: Air hypothesis. *Med Hypotheses* 2017; 107: 81-89 [PMID: 28915970 DOI: 10.1016/j.mehy.2017.08.012]

Sachdev AH, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. *Ther Adv Chronic Dis* 2013; 4: 223-231 [PMID: 23997926 DOI: 10.1177/2040622313496126]

Paik CN, Choi MG, Lim CH, Park JM, Chung WC, Lee KM, Jun KH, Song KY, Jeon HM, Chin HM, Park CH, Chung IS. The role of small intestinal bacterial overgrowth in postgastrectomy patients. *Neurogastroenterol Motil* 2011; 23: e191-e196 [PMID: 21324030 DOI: 10.1111/j.1365-2982.2011.01686.x]

Heiken A, Ravcheev DA, Baldwin F, Heirendt L, Fleming RMT, Thiele I. Systematic assessment of secondary bile acid metabolism in gut microbes reveals distinct metabolic capabilities in inflammatory bowel disease. *Microbiome* 2019; 7: 75 [PMID: 31092280 DOI: 10.1186/s40168-019-0689-3]

Staley C, Weingarden AR, Khourts A, Sadowsky MJ. Interaction of gut microbiota with bile acid metabolism and its influence on disease states. *Appl Microbiol Biotechnol* 2017; 101: 47-64 [PMID: 27888332 DOI: 10.1007/s00253-016-8006-6]

Yachida S, Mizutani S, Shiroma H, Shiba S, Nakajima T, Sakamoto T, Watanabe H, Masuda K, Nishimoto Y, Kubo M, Hosoda F, Rokutan H, Matsumoto M, Takamura H, Yamada M, Matsuda T, Iwasaki M, Yamaji T, Yachida T, Soga T, Kurokawa K, Toyoda A, Ogura Y, Hayashi T, Hatakeyama M, Nakagama H, Saito Y, Fukuda S, Shibata T, Yamada T. Metagenomic and metabolomic analyses
reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. *Nat Med* 2019; 25: 968-976 [PMID: 31171880 DOI: 10.1038/s41591-019-0458-7]

62 Wirbel J, Pyl PT, Kartal E, Zych K, Kashani A, Milanese A, Fleck JS, Voigt AY, Palleja A, Ponnudurai R, Sunagawa S, Coelho LP, Schrotz-King P, Vogtmann E, Habermann N, Niméus E, Thomas AM, Manghi P, Gandini S, Serrano D, Mizutani S, Shiroma H, Shibata S, Shibata T, Yachida S, Yamada T, Waldron L, Naccarati A, Segata N, Sinha R, Ulrich CM, Brenner H, Arumugam M, Bork P, Zeller G. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. *Nat Med* 2019; 25: 679-689 [PMID: 30936547 DOI: 10.1038/s41591-019-0406-6]

63 Liu L, Dong W, Wang S, Zhang Y, Liu T, Xie R, Wang B, Cao H. Deoxycholic acid disrupts the intestinal mucosal barrier and promotes intestinal tumorigenesis. *Food Funct* 2018; 9: 5588-5597 [PMID: 30339173 DOI: 10.1039/c8fo01143e]

64 Vich Vila A, Collij V, Sanna S, Sinha T, Imhann F, Bourgonje AR, Mujagic Z, Jonkers DMAE, Masclee AAM, Fu J, Kurilshikov A, Wijmenga C, Zhemakova A, Weersma RK. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. *Nat Commun* 2020; 11: 362 [PMID: 31953381 DOI: 10.1038/s41467-019-14177-z]

65 Ma W, Mao Q, Xia W, Dong G, Yu C, Jiang F. Gut Microbiota Shapes the Efficiency of Cancer Therapy. *Front Microbiol* 2019; 10: 1050 [PMID: 31293523 DOI: 10.3389/fmicb.2019.01050]
