



Associations of the microbiome and esophageal disease

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Abstract: The incidence of esophageal diseases such as esophageal adenocarcinoma (EAC) and gastroesophageal reflux disease (GERD) have been increasing over the last 40 years. The esophageal microbiome appears to have a role in the development of some disease processes, and could also serve as markers of early diseases of the esophagus. A literature review was performed examining the role of the microbiome in the development of esophageal disease. In addition, the results of several studies and experiments were included in the review. Both EAC and GERD have increased in incidence over the last 40 years. Barrett's esophagus (BE) is a risk factor for EAC. Patients with BE appear to have a microbiome expression pattern distinct from patients without BE. The distinct pattern may be related to factors within the distal esophagus such as a more acidic environment, intraluminal stasis and other elements. It remains unclear whether the change in microflora leads to esophageal disease, or whether the disease process within the esophagus allows these particular organisms to experience overgrowth compared to other microflora. Patient factors such as body mass index (BMI), diet and geographic location also appear to affect the esophageal microbiome. There is an association with the esophageal microbiome and several esophageal diseases. Future studies should examine these correlations more closely. The distinct patterns may be able to serve as a marker of early disease, and possibly lead to a mechanism for the development of esophageal disease.

Keywords: Microbiome; adenocarcinoma; gastroesophageal reflux disease (GERD)

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Introduction

Several diseases of the esophagus have been increasing over the last few decades. While most other solid organ tumors have seen a decrease in incidence over the last 40 years, esophageal adenocarcinoma (EAC) has become more prevalent with time. This increase in the number of cases of EAC has been especially evident in Western countries and Asia. In the United States, EAC is rising more rapidly than any other cancer/malignant growth (1). It is reported that EAC has increased 6-fold in the United States since

1970 (2). Barrett's esophagus (BE), characterized by a metaplastic change of the mucosa of the distal esophagus from squamous to columnar cells, is a precursor condition for EAC. Although only 1 in 860 patients with BE will develop EAC (3), this rate means that there is a 10-fold risk increase compared to patients without BE (4). Many patients with BE are also obese. The exponential increase of obesity in the United States is likely one of the reasons that EAC has increased in incidence with time. The rise in obesity can be explained by several factors, including

more sedentary lifestyles and an increase in the number of people who consume high fat diets (HFD). Several studies have shown that waist circumference can be used as a measurement which correlates to the presence of BE (5). The increased circumference would be expected to increase intra-abdominal pressure, which could make acid reflux into the distal esophagus more severe. Increased intra-abdominal pressure may also cause gut dysbiosis and may be related to a HFD (6-8).

Gut dysbiosis has been associated with several esophageal disease processes, such as BE, gastroesophageal reflux disease (GERD), irritable bowel syndrome, and colitis. It is unclear, however, whether changes in gut flora cause these esophageal diseases versus changes in the esophageal intraluminal environment leading to the altered microbial composition (9).

In addition, other diseases have shown to alter the natural gastrointestinal (GI) microbiota. Diabetes, asthma and interstitial pulmonary fibrosis have all been seen to have correlations with changes in the gut microflora (10,11). Social factors such as diet, waist circumference, and living in urban versus rural areas can also shift the natural gut microbiome into an ecology that promotes disease (12-14).

Discussion

Microbiota of GERD, BE, and EAC

GERD leads to esophageal inflammation at the gastroesophageal junction (GEJ) and can lead to development of metaplastic columnar epithelium, replacing the natural squamous epithelium. Continued inflammation can ultimately lead to EAC (15-17). Both BE and EAC have been found to host unique microbiomes, including the presence of *Helicobacter pylori* and *Escherichia coli* (18,19). The microbiota dysbiosis could be a side effect of the highly acidic environment created from GERD (20,21). The lower esophageal tract microbiome is also unique for patients with GERD and BE, showing high levels of gram negative species such as *Proteobacteria*, *Fusobacteria*, *Spirochaetes*, *Rothia*, and *Campylobacter* (22,23). This bacterial shift can be an indication that dysbiosis is potentially the cause of GI diseases (21). BE patients have a dysbiotic shift of the *Bacteroidetes* to *Firmicutes* ratio, which has also been observed by people who consume HFD (24). The natural microbial ecosystem in the gut holds many functional roles such as digestion, nutrient uptake, eradication of toxic materials and bacteria and production of essential

vitamins (10,25). Dysbiosis of the bacterial community can cause disruption in one, if not many, of these systems and create GI pathology (26). Dietary modifications and the use of antibiotics can help to regulate the gut microbiome to create a less pathogenic environment (27).

The mucosal immune system acts as the first line of defense for preventing infections and helps to reduce inflammation. Chronic inflammation is a known factor in the promotion of GI disease, as seen in patients with BE, GERD, EAC, colon cancer, inflammatory bowel syndrome (IBS), etc. (28-30). Chronic inflammation has also been shown to create systemic immune responses that can alter natural microbiota, which further promotes the advancement of GI diseases. HFD can directly alter GI microbiota, and this altered microbiota pattern can change the intraluminal environment to make conditions more favorable for the development of BE and EAC (31,32).

Elevated levels of pro-inflammatory cytokines and toll-like receptor (TLR) are found in the GEJ of both human and mice models with BE (33). TLR signaling creates dysbiosis in the gut microbiota and induces the activation of chemokine IL-8. In BE mice models, IL-8 was secreted by epithelial mucosa and created a systemic inflammatory response which accelerated the progression of BE and EAC (34).

Urban versus rural diet

Obesity is increasing worldwide and has been heavily influenced by a diet high in fats and ultra-processed materials. This diet is typically characterized by having high levels of simple sugars, animal protein, and fats. People living in urban areas have increased exposure to this type of diet, as these foods are more accessible and cheaper than healthier options. People in rural areas, alternatively, are more likely to have balanced diets and an intake which is much higher in fiber than people living in urban areas. These two different diet types also have different GI microbiota profiles associated with them.

People in rural areas tend to have microbiota patterns which are high in *Prevotella*, *Treponema*, and *Succinivibrio*. These organisms have been seen to aid in the digestion of polysaccharides and fiber (14). People in urban areas, on the other hand, show an increased level of *Bacteroidetes* and decreased level of *Firmicute*. People who have longstanding dietary intakes similar to those in urban areas have been shown to have chronic inflammation of the esophagus and dysbiosis which may favor the development of pathogenesis.

The differences between urban and rural diets have also been associated with changes in the intraluminal environment of the esophagus. People who consume an urban diet and eat less fiber are more prone to have a decreased mucus growth rate in the intestinal tract, which aids in mucosal permeability (35). HFD diets and gut dysbiosis are correlated with obesity, disease, and GI disorders. The global rise of obesity and diabetes are correlating factors. Gut microbiota play an important role in regulating metabolism and overall adiposity. Both human and mice studies show that the dysbiosis caused by obesity is a leading factor for the development of Type II diabetes.

Though mice do not serve as an identical model to human with regards to esophageal disease development, a recent study highlighted the correlation between obesity and BE. In this study, wild type (WT) mice and genetically modified BE mice were both given a normal diet and an HFD. The WT HFD mice showed increased weight gain while the BE HFD mice did not (34).

In another experiment, the BE mice were crossbred with mice modified to express high levels of IL-8 expression. When these crossbred mice were given a HFD, there was twice the number of dysplastic changes as in the BE mice which were not crossbred. Both of these experiments reinforce the idea that chronic inflammation coupled with a HFD can work synergistically to lead to the development of esophageal pathology (34).

BMI and waist circumference

Although elevated BMI is associated with the development of BE and EAC, waist circumference may be an independent risk factor for these diseases as well. Even though obesity is increasing worldwide across most demographics, particular demographic groups have seen an increase in the incidence of BE and EAC. There are likely many unknown factors, including changes in the microbiome expression pattern, which account for the different rates of disease development in different populations.

An increase in waist circumference (adjusted for BMI) leads to intra-abdominal pressure and an increased propensity for acid reflux into the distal esophagus. Patients who experience reflux on at least a weekly basis tend to have more reflux symptoms as waist circumference increases (36).

IBS

IBS is associated with multiple factors, including diet

and microbiome composition. Dysbiosis of the intestinal microbiome disrupts the natural immune response and allows for proliferation of pathogenic bacteria. Commensal gut microbiota, such as *Bacteroides* and *Firmicutes*, are important in regulating T cells and the immune response to intestinal inflammation. Patients with IBS have been shown to have decreased level of gut *Firmicutes* and correspondent chronic intestinal inflammation. The inflammation activates T lymphocytes, which increases pro-inflammatory cytokines. IBS patients given a low carbohydrate diet showed improvements in the *Bacteroidetes* to *Firmicutes* ratio and experienced a decreased level of symptomatology. Other treatments for IBS currently include immunosuppressive therapy, targeting inflammatory pathways, and the use of antibiotics and probiotics. Immunomodulators also have been shown to effectively treat both IBS and colitis by enriching the gut microbiome (37).

Association between respiratory and GI microflora

The “gut-lung axis” is the relationship between the immune health of the GI tract and the respiratory tree. Changes in the GI microbiome by disease, diet or medications can cause an alteration in the lung microbiome. The microbiome plays an important role in immunity, and fluctuations in the microbiome can affect homeostasis. It has been established that there is a difference in the microbial composition of the upper and lower airway regions (38). The oral cavity is mainly colonized by *Streptococcus*, *Prevotella*, and *Veillonella*. The oropharynx and hypopharynx are composed of *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*. Finally, the microbiome of the lobar bronchi and lung tissue in healthy individuals are mainly made up of *Bacteroidetes* and *Firmicutes*. Disruptive dysbiosis of the pulmonary tree and intestinal tract is linked to increased incidence pulmonary disease (39-41). There is a higher prevalence of pulmonary disease in patients with chronic intestinal inflammation such as inflammatory bowel disease. It has also been shown that the chronic lung diseases like asthma, COPD, and cystic fibrosis are associated with irritable bowel disease. Lung microbiota have been shown to migrate to the GI tract and cause infections after pulmonary infections. The relationship between dysbiosis of the lung microbiome and carcinogenesis of lung cancer may be linked to inflammation and immune pathways.

Evidence suggests that idiopathic pulmonary fibrosis (IPF) is associated with an increased bacterial burden in the respiratory tree, which is related to disease progression

and mortality. Treatment with antibiotics to decrease the bacterial burden is under investigation for the treatment of IPF. Two mouse models found that infections with *Streptococcus pneumoniae* resulted in exacerbation of lung fibrosis (42). It was also found that patients having an acute IPF exacerbation had a bacterial burden that was four times higher than stable IPF. Infectious agents have the ability to induce alveolar injury and apoptosis in IPF (43). Interestingly, these patients had elevated levels of *Campylobacter*, a known GI pathogen. The association between *Streptococcus pneumoniae* and lung fibrosis was shown to be linked to the cytotoxin pneumolysin in a mouse model. The infection-induced fibrosis was terminated in mice that were treated with antibiotics.

Conclusions

Although increases in obesity and BMI have been thought to be the leading reasons for the increases in esophageal diseases, dietary factors are in all likelihood more influential than previously thought. The pandemic rise of obesity and esophageal diseases correlates with the spread of a HFD worldwide. A HFD causes an increase in chronic inflammation of the esophagus and dysbiosis, which have both been linked to esophageal disease. High fiber, low fat diets create a commensal gut microbiome that promotes healthy metabolism, nutrient and vitamin uptake, proper digestion and eradication of harmful bacteria and toxins. Changes in microbiota from other non-GI sites, such as the lung, can also further exacerbate gut dysbiosis and increase the risks of BE and EAC. Though the GI tract and pulmonary tree have unique functions, there is a microbiome crossover at the laryngopharynx. *Bacteroidetes* and *Firmicutes* are highly developed in the healthy lung. GI disease has been correlated with pulmonary infections, and multiple previous studies have shown that the *Bacteroidetes* to *Firmicutes* ratio correlate with a HFD, development of BE and development of EAC.

Future studies are needed and are ongoing to understand further the correlation between the microbiome and esophageal disease. Future directions can help to explain these associations and possibly find preventative treatments to reduce the development of esophageal diseases.

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Footnote

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References

1. Chen Z, Ren Y, Du X, et al. Incidence and survival differences in esophageal cancer among ethnic groups in the United States. *Oncotarget* 2017;8:47037-51.
2. Malhotra GK, Yanala U, Ravipati A, et al. Global trends in esophageal cancer. *J Surg Oncol* 2017;115:564-79.
3. Hvid-Jensen F, Pedersen L, Drewes A, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;365:1375-83.
4. Wild CP, Hardie L. Reflux, Barrett's oesophagus and adenocarcinoma: Burning questions. *Nat Rev Cancer* 2003;3:676-84.
5. Corley DA, Kubo A, Levin T, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology* 2007;133:34-41.
6. Leng Y, Zhang K, Fan J, et al. Effect of acute, slightly increased intra-abdominal pressure on intestinal permeability and oxidative stress in a rat model. *PLoS One* 2014;9:e109350.
7. Martinez KB, Leone V, Chang E. Western diets, gut dysbiosis, and metabolic diseases: Are they linked? *Gut Microbes* 2017;8:130-42.
8. Kaakoush NO, Lecomte V, Maloney CA, et al. Cross-talk among metabolic parameters, esophageal microbiota, and host gene expression following chronic exposure to an obesogenic diet. *Sci Rep* 2017;7:45753.
9. Yang L, Lu X, Nossa C, et al. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. *Gastroenterology* 2009;137:588-97.
10. Tilg H, Moschen A. Microbiota and diabetes: an evolving relationship. *Gut* 2014;63:1513-21.
11. Musso G, Gambino R, Cassader M. Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. *Annu Rev Med* 2011;62:361-80.
12. De Filippo C, Di Paola M, Ramazzotti M, et al. Diet, environments, and gut microbiota. A preliminary investigation in children living in rural and urban Burkina Faso and Italy. *Front Microbiol* 2017;8:1979.

13. Sedibe MH, Pisa P, Feeley A, et al. Dietary habits and eating practices and their association with overweight and obesity in rural and urban black South African adolescents. *Nutrients* 2018;10. doi: 10.3390/nu10020145.
14. Martin JC, Moran L, Teede H, et al. Exploring diet quality between urban and rural dwelling women of reproductive age. *Nutrients* 2017;9. doi: 10.3390/nu9060586.
15. Snider EJ, Freedberg DE, Abrams JA. Potential role of the microbiome in Barrett's esophagus and esophageal adenocarcinoma. *Dig Dis Sci* 2016;61:2217-25.
16. Blackett KL, Siddhi S, Cleary S, et al. Oesophageal bacterial biofilm changes in gastro-oesophageal reflux disease, Barrett's and oesophageal carcinoma: association or causality? *Aliment Pharmacol Ther* 2013;37:1084-92.
17. Yang L, Chaudhary N, Baghdadi J, et al. Microbiome in reflux disorders and esophageal adenocarcinoma. *Cancer J* 2014;20:207-10.
18. Tian Z, Yang Z, Gao J, et al. Lower esophageal microbiota species are affected by the eradication of *Helicobacter pylori* infection using antibiotics. *Exp Ther Med* 2015;9:685-92.
19. Polyzos SA, Zeglinas C, Artemaki F, et al. *Helicobacter pylori* infection and esophageal adenocarcinoma: a review and a personal view. *Ann Gastroenterol* 2018;31:8-13.
20. Amir I, Konikoff F, Oppenheim M, et al. Gastric microbiota is altered in oesophagitis and Barrett's esophagus and further modified by proton pump inhibitors. *Environ Microbiol* 2014;16:2905-14.
21. Yap YA, Marino E. An insight into the intestinal web of mucosal immunity, microbiota, and diet in inflammation. *Front Immunol* 2018;9:2617.
22. Paull G, Yardley J. Gastric and esophageal *Campylobacter pylori* in patients with Barrett's esophagus. *Gastroenterology* 1988;95:216-8.
23. Nardone G, Compare D, Rocco A. A microbiota-centric view of diseases of the upper gastrointestinal tract. *Lancet Gastroenterol Hepatol* 2017;2:298-312.
24. Devaraj S, Hemarajata P, Versalovic J. The human gut microbiome and body metabolism: implications for obesity and diabetes. *Clinical Chemistry* 2013;59:617-28.
25. Elliott DR, Walker A, O'Donovan M, et al. A non-endoscopic device to sample the oesophageal microbiota: a case-control study. *Lancet Gastroenterol Hepatol* 2017;2:32-42.
26. Huang CH, Yu X, Liao W. The expensive-tissue hypothesis in vertebrates: Gut microbiota effect, a review. *Int J Mol Sci* 2018;19. doi: 10.3390/ijms19061792.
27. Kaakoush NO, Morris M. The oesophageal microbiome: an unexplored link in obesity-associated oesophageal adenocarcinoma. *FEMS Microbiol Ecol* 2016;92. doi: 10.1093/femsec/fiw161.
28. Ghoshal UC, Shukla R, Ghoshal U, et al. The gut microbiota and irritable bowel syndrome: Friend or foe? *Int J Inflam* 2012;2012:151085.
29. Deshpande NP, Riordan S, Castaño-Rodríguez N, et al. Signatures within the esophageal microbiome are associated with host genetics, age, and disease. *Microbiome* 2018;6:227.
30. Chumpitazi BP, Hollister E, Oezguen N, et al. Gut microbiota influences low fermentable substrate diet efficacy in children with irritable bowel syndrome. *Gut Microbes* 2014;5:165-75.
31. Ahn J, Chen C, Hayes R. Oral microbiome and oral gastrointestinal cancer risk. *Cancer Causes Control* 2012;23:399-404.
32. Gall A, Fero J, McCoy C, et al. Bacterial composition of the human upper gastrointestinal tract microbiome is dynamic and associated with genomic instability in Barrett's esophagus cohort. *PLoS One* 2015;10:e0129055.
33. Zaidi AH, Kelly L, Kreft R, et al. Associations of microbiota and toll-like receptor signaling pathway in esophageal adenocarcinoma. *BMC Cancer* 2016;16:52.
34. Münch NS, Fang H, Ingermann J, et al. High-fat diet accelerates carcinogenesis in a mouse model of Barrett's esophagus via IL-8 and alterations to the gut microbiome. *Gastroenterology* 2019;157:492-506.e2.
35. Llewellyn SR, Britton G, Contijoch E, et al. Interactions between diet and the intestinal microbiota alter intestinal permeability and colitis severity in mice. *Gastroenterology* 2018;154:1037-46.e2.
36. Yang HJ, Chang Y, Park S, et al. Sex differences in the relation between waist circumference within the normal range and development of reflux esophagitis. *J Clin Med* 2019;8. doi: 10.3390/jcm8010067.
37. Rooks MG, Veiga P, Wardell-Scott L, et al. Gut microbiome composition and function in experimental colitis during active disease and treatment-induced remission. *ISME J* 2014;8:1403-17.
38. Chotirmall SH, Gellatly S, Budden K, et al. Microbiomes in respiratory health and disease: An Asia-Pacific perspective. *Respirology* 2017;22:240-50.
39. Mao Q, Jiang H, Yin R, et al. Interplay between the lung microbiome and lung cancer. *Cancer Lett* 2018;415:40-8.
40. Salisbury ML, Han M, Dickson R, et al. Microbiome in interstitial lung disease. *Curr Opin Pulm Med* 2017;23:404-10.

41. Moffatt MF, Cookson W. The lung microbiome in health and disease. *Clin Med Lond* 2017;17:525-9.
42. Molyneux PL, Maher T. The role of infection in the pathogenesis of idiopathic pulmonary fibrosis. *Eur Respir* Rev 2013;22:376-81.
43. Fastrès A, Felice F, Roels E, et al. The lung microbiome in idiopathic pulmonary fibrosis: a promising approach for targeted therapies. *Int J Mol Sci* 2017;18:2735.

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