

From Heartburn to Barrett's Esophagus, and Beyond

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Abstract

Background Gastroesophageal reflux disease (GERD) affects an estimated 20% of the population in the USA, and its prevalence is increasing worldwide. About 10–15% of patients with GERD will develop Barrett's esophagus (BE). **Aims** The aims of this study were to review the available evidence of the pathophysiology of BE and the role of anti-reflux surgery in the treatment of this disease.

Results The transformation of the squamous epithelium into columnar epithelium with goblet cells is due to the chronic injury produced by repeated reflux episodes. It involves genetic mutations that in some patients may lead to high-grade dysplasia and cancer. There is no strong evidence that anti-reflux surgery is associated with resolution or improvement in BE, and its indications should be the same as for other GERD patients without BE.

Conclusions Patients with BE without dysplasia require endoscopic surveillance, while those with low- or high-grade dysplasia should have consideration of endoscopic eradication therapy followed by surveillance. New endoscopic treatment modalities are being developed, which hold the promise to improve the management of patients with BE.

Introduction

Gastroesophageal reflux disease (GERD) affects an estimated 20% of the population in the USA, and its prevalence is increasing worldwide [1]. Furthermore, it is a disease with a high annual cost in the USA, estimated around 9 billion dollars [2]. The largest contributor to the

cost is drug therapy to suppress gastric acid production (around \$5.8 billion). While these medications have shown excellent results in controlling GERD symptoms, they have not averted the malignant complications of this disease. In fact, esophageal adenocarcinoma, a cancer associated with the presence of chronic GERD symptoms, is one of the fastest rising cancers in the last 30 years [3]. Although treatment modalities have improved during the past decade, survival rates for esophageal adenocarcinoma remain poor, with an overall 5-year survival of less than 20% [4].

In about 10–15% of patients, GERD causes a metaplasia of the squamous epithelium into intestinalized epithelium with a characteristic endoscopic appearance, termed Barrett's esophagus (BE). This condition in a small proportion of patients can eventually progress to dysplasia and cancer.

This review will focus on the pathophysiology of BE and the potential role of anti-reflux surgery in the treatment of this disease.

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Barrett's esophagus: definition and epidemiology

BE has been traditionally defined as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus. Currently, the presence of intestinal metaplasia—columnar epithelium with goblet cells—is also needed for the diagnosis of BE in the USA [5]. The reason that intestinal metaplasia is mandated in the definition of BE is related to the higher risk of developing cancer in columnar epithelium containing goblet cells as compared to columnar epithelium without intestinal metaplasia [6, 7].

The real prevalence of BE in the general population is uncertain because upper endoscopy is required for diagnosis. Previous reports have suggested a prevalence of 1–2% [8, 9]. However, there is evidence that the prevalence of BE is increasing dramatically in recent years, independent of the number of upper gastrointestinal endoscopies that are being performed [10]. Interesting findings were reported by Cameron et al. [11] who found that the prevalence of BE in autopsies was five times higher than the clinical prevalence reported in the same area. Many patients with BE are asymptomatic or present minor reflux symptoms, such that they may go undiagnosed.

Pathophysiology: from GERD to Barrett's esophagus

About 10–15% of patients with GERD will develop BE [12]. The transformation of normal esophageal squamous mucosa into a simple columnar epithelium is thought to be due to the chronic injury produced by repeated reflux episodes. In fact, in patients with GERD, symptom duration has been shown to be a risk factor for the presence of BE. Lieberman [13] showed that compared with patients with GERD symptoms for less than 1 year, the odds ratio for BE in patients with GERD symptoms for 5 years was 3.0 and increased to 6.4 in patients with symptoms for more than 10 years. Interestingly, columnar mucosal metaplasia is also seen in the esophageal remnant in patients with a gastric pull-up following an esophagectomy, where the reflux of gastric contents into the residual esophagus is common because there is no lower esophageal sphincter. Oberg et al. [14] reported that 46.9% of the patients had metaplastic columnar mucosa within their cervical esophagus following an esophagectomy, and the length of that metaplastic mucosa was significantly correlated with the degree of the esophageal acid exposure. Similar findings were reported by O'Riordan et al. [15] with 50% of patients developing columnar metaplasia in the remnant esophagus, with the

duration of reflux being the most important factor influencing that transformation.

The molecular pathway by which the normal squamous mucosa of the distal esophagus is transformed into a columnar mucosa remains uncertain. Tobey et al. [16] showed that acid damage of the esophageal epithelium produces dilated intercellular spaces, which in turn reduces the transepithelial resistance and increases transepithelial permeability. This change in permeability permits molecules as large as 20 kD to diffuse across the epithelium, exposing stem cells in the basal layer to refluxate. The intercellular acidification exposes the squamous basolateral membrane to acid, initiating a cascade of events leading to loss of cell osmoregulation, cell edema and ultimately cell death [17]. Cell death is counterbalanced by tissue reparative processes, including restitution and replication. It is worth mentioning that during the normal growth process of the embryo, the esophageal cells undergo a columnar to squamous transition under the influence of a combination of active prosquamous and inactivated procolumar homeobox genes. The cellular phenotype may reverse if the opposite set of cell patterning genes is reactivated. An acidic milieu, combined with other components of refluxate, may induce phenotypic transformation of squamous cells into columnar mucosal cells. The reason why pluripotent esophageal stem cells turn into columnar cells in this “acid environment” may be related to the better adaptability of this epithelium due to its acid resistance. Nevertheless, the origin of BE remains obscure. There are several hypotheses concerning the origin of these stem cells that will give rise to BE: (1) migration and differentiation of stem cells from the gastric cardia, (2) differentiation of stem cells residing in the crypts of the esophageal mucosal glands and (3) migration of stem cells from the bone marrow (circulating stem cells that can hone in to areas of injury to repair damaged tissue) [18–20].

While the transition between squamous and columnar epithelium likely occurs within a few years, the development of intestinal metaplasia may take over 5–10 years [21]. Once the columnar epithelium is established, two possible pathways are observed. The first one, “gastric differentiation,” implies the formation of parietal cells within glands and may represent a favorable change, as this mucosa is not thought to be premalignant. The second one, “intestinal differentiation,” induces the expression of intestinalizing genes, causing the formation of goblet cells within the columnar epithelium. The development of intestinal metaplasia is considered a detrimental change because this mucosa is capable of further progression to epithelial dysplasia and adenocarcinoma. The specific cellular event(s) that induce the “intestinalization” of the columnar epithelium is unknown. However, it is likely to occur in response to multiple noxious luminal contents

rather than to acid reflux only. In fact, previous studies have demonstrated the association between BE and the exposure of a mixture of acid and bile salts on the esophagus [22–24]. The role of refluxed bile in the development of intestinal metaplasia was suggested by Oberg et al. [25] as patients with intestinal metaplasia had similar esophageal acid exposure to those with GERD and no BE, but significantly higher frequency of abnormal bilirubin exposure. It has been hypothesized that in a weakly acidic environment (pH 3–5), certain bile acids become non-ionized and able to cross the cell membrane. Once inside the cell (pH 7) they become ionized and remain trapped causing mitochondrial injury, cellular toxicity and mutagenesis [26]. The molecular mechanism by which bile acids promote the development of goblet cells may be related to the activation of the caudal-related homeobox 2 (Cdx2) promoter via nuclear factor kappa B (NF- κ B) with the consequent production of Cdx2 protein in esophageal immature keratinocytes, resulting in the production of MUC2 (intestinal-type protein found in Barrett's metaplasia) [27]. Recently, bile acids have shown to enhance cytoplasmic expression of the signaling ligand Delta-like 1 (Dll1) which facilitates the intestinal metaplasia in conjunction with Cdx2 expression [28].

Barrett's esophagus malignant transformation

BE is a premalignant mucosa with increased proliferation rates and decreased apoptosis rates compared to normal epithelium [29]. In fact, it is the only known precursor of esophageal adenocarcinoma. However, only a small percentage of patients with BE will develop cancer, and more than 90% of the patients with the diagnosis of esophageal adenocarcinoma have no prior history of BE [30, 31]. The question as to why some cases of BE progress to esophageal adenocarcinoma and some do not remains unanswered. Currently, the presence and grading of dysplasia is the most important predictive factor for the development of adenocarcinoma. The known risk factors for the development of dysplasia in BE include: increasing length of BE, advancing age, central obesity, tobacco usage, lack of nonsteroidal anti-inflammatory agent use, lack of proton-pump inhibitors (PPI) use and lack of statin use [5].

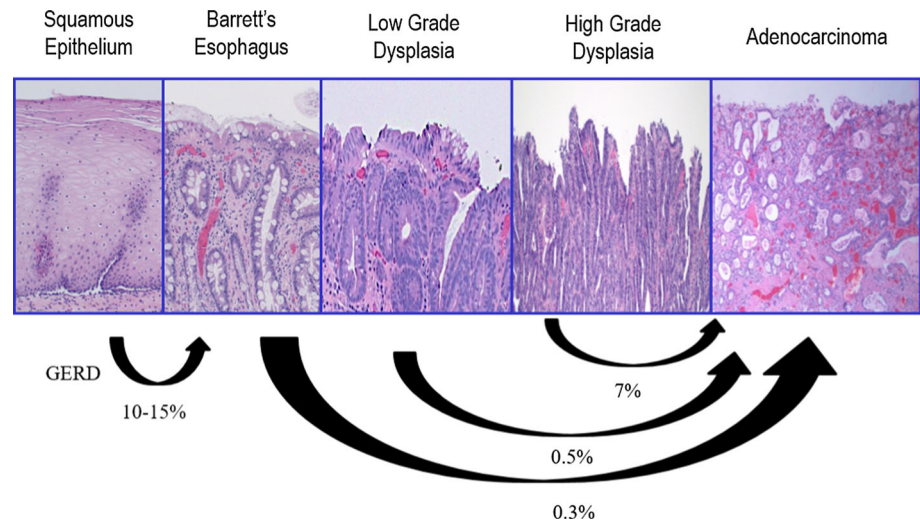
Gopal et al. [32] showed that the prevalence of dysplasia was strongly associated with age and length of BE. Patients with BE without dysplasia were younger than those with dysplasia (62 ± 0.8 vs. 67 ± 1.7 years, $p = 0.02$), and the risk of dysplasia increased by 3.3%/year of age. Patients with BE length ≥ 3 cm also had a significantly greater prevalence of dysplasia compared to length < 3 cm (23 vs. 9%, $p = 0.0001$), and the risk of dysplasia increased by 14%/cm of increased length. Hampel et al. [33] reported

that obesity was associated with a statistically significant increase in the risk for GERD complications and esophageal adenocarcinoma. Interestingly, Singh et al. [34] found that, compared with patients with normal body habitus, patients with central adiposity had a higher risk of BE, even after adjusting for body mass index and the presence of GERD, suggesting a reflux-independent association between truncal obesity and BE. Added to this, central adiposity was associated with higher risk of adenocarcinoma (OR 2.5, 95% CI 1.54–4.06) compared with normal body habitus. The relationship between BE and cigarette smoking was reported by Andrici et al. [35] who found that having ever smoked was associated with an increased risk of BE compared with non-GERD controls but not when compared with patients with chronic GERD, suggesting that the increased risk of BE associated with tobacco usage may be due to the increased incidence of GERD in cigarette smokers.

Some medications have been shown to reduce the risk of progression to dysplasia or esophageal cancer in patients with BE. A recent meta-analysis [36] showed that PPI use was associated with a substantial reduction in risk of high-grade dysplasia and/or esophageal adenocarcinoma in patients with BE (OR 0.29 95% CI 0.12–0.79). There was also a trend toward a dose–response relationship with PPI use for >2 –3 years. Another meta-analysis [37] reported that aspirin use also reduced the risk of high-grade dysplasia/adenocarcinoma, as well as non-aspirin cyclooxygenase inhibitors in patients with BE. The chemopreventive effect seemed to be independent of duration of therapy. Finally, statin usage was also associated with a significant (41%) decrease in the risk of esophageal adenocarcinoma within patients with BE [38].

There are four categories to stratify the dysplastic process: (1) no dysplasia; (2) indefinite for dysplasia; (3) low-grade dysplasia; and (4) high-grade dysplasia. Patients with non-dysplastic BE have very low risk for malignant progression, and a recent meta-analysis reported that the pooled annual incidence of adenocarcinoma in this cohort was 0.33% (95% CI 0.28–0.38) [39]. For patients with low-grade dysplasia, Singh et al. [40] reported a pooled annual incidence of 0.5% for adenocarcinoma (95% CI 0.3–0.8). Patients with high-grade dysplasia present an annual incidence of adenocarcinoma of 7% (95% CI 5–8) [41] (Fig. 1). Unfortunately, the grading of dysplasia remains subjective and is often inaccurate, especially in centers without expert gastrointestinal pathologists [42]. Issues with the diagnosis of low-grade dysplasia are especially vexing, with frequent disagreement between pathologists [43, 44]. This may explain the substantial heterogeneity in outcomes reported in LGD, with studies reporting progression rates as low as 0.9%/patient-year [45] and as high as 26.5% [46]. Due to interobserver variability in the

Fig. 1 Pathological progression from normal esophageal squamous epithelium to adenocarcinoma



interpretation of dysplasia, current guidelines of the American College of Gastroenterology [5] recommend that patients with BE and any dysplasia undergo a review by two pathologists, at least one of whom has specialized expertise in gastrointestinal pathology.

Role of anti-reflux surgery for Barrett's esophagus

Several studies have shown the efficacy of acid suppression therapy with PPIs in neutralizing gastric acid, and therefore, they remain the main treatment for GERD. These medications make the reflux less aggressive, with symptom relief and healing of esophagitis [47]. However, while PPIs modify the pH of the refluxate, they do not change the occurrence and number of reflux episodes [48, 49]. In contrast, anti-reflux surgery restores the competence of the gastroesophageal junction and blocks reflux of all gastric contents into the esophagus. A recent meta-analysis [50] showed that surgical management of GERD was more effective than medical treatment with respect to symptoms relief and GERD-specific quality of life. Moreover, it seems that laparoscopic fundoplication is a cost-effective alternative to continued medical management over 5 years [51]. Nevertheless, several studies have tried to determine the value of anti-reflux surgery in the prevention of esophageal adenocarcinoma in the setting of BE with conflicting results.

Oelschlager et al. [52] analyzed a cohort of patients with BE who underwent laparoscopic anti-reflux surgery and reported that endoscopy and pathology revealed complete regression of intestinal metaplasia (absence of any signs of BE) in 55% of the patients with short-segment BE (<3 cm) but in none of those with long-segment BE (≥ 3 cm), suggesting that fundoplication may have a salutary effect in

patients with short-segment BE. Katz et al. [53] performed endoscopic surveillance on 102 patients with BE and reported that by 3 years, almost 8% of the medically treated patients had developed dysplasia, while none of the patients who had received anti-reflux surgery presented dysplasia. Similarly, Oberg et al. [54] studied the development of dysplasia and esophageal adenocarcinoma during long-term endoscopic and histologic surveillance in 140 patients with BE free from dysplasia and found that successful anti-reflux surgery was associated with a decreased risk of high-grade dysplasia and esophageal adenocarcinoma, possibly by better control of reflux of gastric contents. In a systematic review performed by Chang et al. [55] to determine the effect of anti-reflux surgery on esophageal carcinogenesis in patients with BE, the probability of progression was 2.9% (1.2–5.5) in surgical patients and 6.8% (2.6–12.1) in medical patients ($p = 0.054$). The probability of regression was 15.4% (6.1–31.4) in surgical patients and 1.9% (0.4–7.3) in medical patients ($p = 0.004$), suggesting that, while fundoplication was not significantly associated with a decreased risk of BE progression, it was strongly associated with regression of BE.

On the other hand, a prospective randomized trial that compared the results of medical treatment and anti-reflux surgery in patients with BE with a long-term follow-up showed that high-grade dysplasia appeared in two of the 43 patients (5%) in the medical treatment group and in two of the 58 patients (3%) in the surgical treatment group, concluding that there were no differences between the two types of treatment with respect to preventing BE from progressing to dysplasia and adenocarcinoma [56]. While this study represents the only level one evidence on this question, the small number of patients in the trial makes a type II error more likely and makes it difficult to draw firm

conclusions. Similarly, a Swedish population-based study showed that the risk of esophageal adenocarcinoma was not decreased after anti-reflux surgery [57].

Overall, the available evidence about the resolution or improvement in BE after anti-reflux surgery is inconclusive. Given the paucity of data in the literature with the lack of a well-conducted randomized trial, anti-reflux surgery should not be suggested as a modality to prevent the malignant transformation of BE, but its indications should be the same as for other GERD patients.

Management of Barrett's esophagus

Based on the recent guidelines from the American College of Gastroenterology for the diagnosis and management of BE [5], we recommend:

BE without dysplasia: endoscopic surveillance at intervals of 3–5 years.

BE indefinite for dysplasia: repeat endoscopy after optimization of acid suppressive medications for 3–6 months.

BE with low-grade dysplasia: without life-limiting comorbidity, endoscopic therapy (radiofrequency ablation) is the preferred treatment modality. Endoscopic surveillance every 12 months is an acceptable alternative.

BE with high-grade dysplasia: endoscopic therapy (radiofrequency ablation) * unless life-limiting comorbidity is present.

*Given the costs and side-effect profile of photodynamic therapy and the strong evidence about the safety and efficacy of radiofrequency ablation, this modality is the preferred therapy for most patients. The role of cryotherapy is promising but still under investigation.

Future directions

Significant advances have been made in endoscopic imaging techniques. Electronic chromoendoscopy enhances imaging of the mucosal and vascular patterns in BE without the need for dye sprays and may increase the detection of dysplasia [58]. More recently, confocal and volumetric laser endomicroscopy has shown promising results for endoscopic diagnosis of BE [59, 60]. Added to enhanced imaging devices, better sampling tests are studied. Wide-area transepithelial sampling (WATS) consists of a brush biopsy technique for acquiring wide-area sampling of BE tissue, followed by a computer-assisted analysis of dysplasia. The diagnosis of BE-associated dysplasia using the WATS technique has higher interobserver agreement among pathologists compared with the use of standard histopathology [61].

A non-endoscopic screening test for BE (Cytosponge), consisting of gelatin-coated sponge attached to a string that is swallowed and then pulled out, obtaining esophageal cytology samples as it is withdrawn, is currently undergoing investigation. The device is safe, well-tolerated and, when combined with immunocytochemistry for trefoil factor 3, has a sensitivity of 73% and specificity of 94% for the diagnosis of BE in screening populations [62]. This procedure may be a cost-effective and useful screening test for BE if validated by future studies.

Molecular markers to predict the risk of progression are also under investigation. Interestingly, accumulation of multiple genetic mutations may be necessary for cancer development. Thus, genetic mutations may be detectable in early stage of disease prior to the progression to malignancy [63]. Kastelein et al. [64] reported that aberrant p53 protein expression (loss or overexpression by immunohistochemistry) was associated with an increased risk of neoplastic progression in patients with BE and appeared to be a more powerful predictor of neoplastic progression than histological diagnosis of LGD. Recently, microRNA expression has shown to be altered in neoplastic progression, and its analysis may be useful for prediction of progression risk [65]. Although most biomarkers currently under investigation are not yet ready for clinical practice, they may be used to define patients at increased risk for progression to cancer in the near future.

Conclusion

GERD is a very prevalent disease, and its incidence is increasingly worldwide. Around 15% of the patients affected by this disease will develop Barrett's esophagus. This metaplastic lesion due to the chronic injury produced by repeated reflux episodes involves genetic mutations that can lead to a malignant transformation. There is no strong evidence that anti-reflux surgery is associated with resolution or improvement in BE and its indications should be the same as for other GERD patients. Patients with BE without dysplasia require endoscopic surveillance, while those with low- or high-grade dysplasia should have consideration of endoscopic eradication therapy. Several new diagnostic and therapeutic technologies are being developed, which hold the promise to improve the management of patients with BE.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

References

- El-Serag HN, Sweet S, Winchester CC et al (2014) Update on the epidemiology of gastro-esophageal reflux disease: a systematic review. *Gut* 63:871–880
- Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R (2002) The burden of selected digestive diseases in the United States. *Gastroenterology* 122:1500–1511
- Pohl H, Welch HG (2005) The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 97:142–146
- National Cancer Institute: Surveillance, Epidemiology, and End Results Program. <http://seer.cancer.gov/statfacts/html/esoph.html>
- Shaheen NJ, Falk GW, Iyer PG, Gerson LB (2016) ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol* 111:30–50
- Bhat S, Coleman HG, Yousef F et al (2011) Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* 103:1049–1057
- Bandla S, Peters JH, Ruff D et al (2014) Comparison of cancer-associated genetic abnormalities in columnar-lined esophagus tissues with and without goblet cells. *Ann Surg* 260:72–80
- Zagari RM, Fuccio L, Wallander MA et al (2008) Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano–Monghidoro study. *Gut* 57:1354–1359
- Ronkainen J, Aro P, Storskrubb T et al (2005) Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 129:1825–1831
- van Soest EM, Dieleman JP, Siersema PD, Sturkenboom MC, Kuipers EJ (2005) Increasing incidence of Barrett's esophagus in the general population. *Gut* 54:1062–1066
- Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA (1990) Prevalence of columnar lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings. *Gastroenterology* 99:918–922
- Johansson J, Hakansson HO, Mellblom L et al (2005) Prevalence of precancerous and other metaplasia in the distal oesophagus and gastro-oesophageal junction. *Scand J Gastroenterol* 40:893–902
- Lieberman DA (1997) Risk factors for Barrett's esophagus in community-based practice. *Am J Gastroenterol* 92:1293–1297
- Oberg S, Johansson J, Wenner J, Walther B (2002) Metaplastic columnar mucosa in the cervical esophagus after esophagectomy. *Ann Surg* 235:338–345
- O'Riordan JM, Tucker ON, Byrne PJ, McDonald GS, Ravi N, Keeling PW, Reynolds JV (2004) Factors influencing the development of Barrett's epithelium in the esophageal remnant post-esophagectomy. *Am J Gastroenterol* 99:205–211
- Tobey NA, Hosseini SS, Argote CM, Dobrucali AM, Awayda MS, Orlando RC (2004) Dilated intercellular spaces and shunt permeability in non-erosive acid-damaged esophageal epithelium. *Am J Gastroenterol* 99:13–22
- Tobey NA, Orlando RC (1991) Mechanisms of acid injury to rabbit esophageal epithelium. Role of basolateral cell membrane acidification. *Gastroenterology* 101:1220–1228
- Souza RF, Krishnan K, Spechler SJ (2008) Acid, bile, and CDX: the ABCs of making Barrett's metaplasia. *Am J Gastrointest Liver Physiol* 295:211–218
- Sarosi G, Brown G, Jaiswal K, Feagins LA, Lee E, Crook TW, Souza RF, Zou YS, Shay JW, Spechler SJ (2008) Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus. *Dis Esophagus* 21(1):43–50
- Nakagawa H, Whelan K, Lynch JP (2015) Mechanisms of Barrett's oesophagus: intestinal differentiation, stem cells, and tissue models. *Best Pract Res Clin Gastroenterol* 29(1):3–16
- DeMeester SR, DeMeester TR (2000) Columnar mucosa and intestinal metaplasia of the esophagus: fifty years of controversy. *Ann Surg* 231:303–321
- Oberg S, Ritter MP, Crookes PF, Fein M, Mason RJ, Gadenstätt M, Brenner CG, Peters JH, DeMeester TR (1998) Gastroesophageal reflux disease and mucosal injury with emphasis on short-segment Barrett's esophagus and duodenogastroesophageal reflux. *J Gastrointest Surg* 2:547–553
- Fein M, Ireland AP, Ritter MP, Peters JH, Hagen JA, Bremner CG, DeMeester TR (1997) Duodenogastric reflux potentiates the injurious effects of gastroesophageal reflux. *J Gastrointest Surg* 1:27–32
- Kauer WK, Peters JH, DeMeester TR, Ireland AP, Bremner CG, Hagen JA (1995) Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy re-emphasized. *Ann Surg* 222:525–531
- Oberg S, Peters JH, DeMeester TR, Lord RV, Johansson J, DeMeester SR, Hagen JA (2000) Determinants of intestinal metaplasia within the columnar-lined esophagus. *Arch Surg* 135(6):651–655
- Theisen J, Peters JH, Fein M, Hughes M, Hagen JA, DeMeester SR, DeMeester TR, Laird PW (2005) The mutagenic potential of duodenoesophageal reflux. *Ann Surg* 241:63–68
- Kazumori H, Ishihara S, Rumi MA et al (2006) Bile acids directly augment caudal related homeobox gene Cdx2 expression in esophageal keratinocytes in Barrett's epithelium. *Gut* 55:16–25
- Tamagawa Y, Ishimura N, Uno G, Aimi M, Oshima N, Yuki T, Sato S, Ishihara S, Kinoshita Y (2016) Bile acids induce Delta-like 1 expression via Cdx2-dependent pathway in the development of Barrett's esophagus. *Lab Invest* 96(3):325–337
- Reid BJ, Sanchez CA, Blount PL, Levine DS (1993) Barrett's esophagus: cell cycle abnormalities in advancing stages of neoplastic progression. *Gastroenterology* 105:119–129
- Hvid-Jensen F, Pedersen L, Drewes AM et al (2011) Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 365:1375–1383
- Dulai GS, Guha S, Kahn KL et al (2002) Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. *Gastroenterology* 122:26–33
- Gopal DV, Lieberman DA, Magaret N et al (2003) Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. *Dig Dis Sci* 48:1537–1541
- Hampel H, Abraham NS, El-Serag HB (2005) Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 143:199–211
- Singh S, Sharma AN, Murad MH et al (2013) Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 11:1399–1412
- Andrici J, Cox MR, Eslick GD (2013) Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 28:1258–1273
- Singh S, Garg SK, Singh PP et al (2014) Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut* 63:1229–1237
- Zhang S, Zhang XQ, Ding XW et al (2014) Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a meta-analysis. *Br J Cancer* 110:2378–2388
- Singh S, Singh AG, Singh PP et al (2013) Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 11:620–629

39. Desai TK, Krishnan K, Samala N et al (2012) The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut* 61:970–976
40. Singh S, Manickam P, Amin AV et al (2014) Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 79:897–909
41. Rastogi A, Puli S, El-Serag HB et al (2008) Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc* 67:394–398
42. Alikhan M, Rex D, Khan A, Rahmani E, Cummings O, Ulbright TM (1999) Variable pathologic interpretation of columnar lined esophagus by general pathologists in community practice. *Gastrointest Endosc* 50:23–26
43. Montgomery E, Bronner MP, Goldblum JR et al (2001) Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Hum Pathol* 32:368–378
44. Curvers WL, ten Kate FJ, Krishnadath KK et al (2010) Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol* 105:1523–1530
45. Wani S, Falk GW, Post J et al (2011) Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology* 141:1179–1186
46. Phoa KN, van Vilsteren FG, Weusten BL et al (2014) Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *JAMA* 311:1209–1217
47. Katz PO, Zavala S (2010) Proton pump inhibitors in the management of GERD. *J Gastrointest Surg* 14:62–66
48. Tamhankar AP, Peters JH, Portale G, Hsieh CC, Hagen JA, Bremner CG, DeMeester TR (2004) Omeprazole does not reduce gastroesophageal reflux: new insights using multichannel intraluminal impedance technology. *J Gastrointest Surg* 8(7):890–897
49. Blonski W, Vela MF, Castell DO (2009) Comparison of reflux frequency during prolonged multichannel intraluminal impedance and pH monitoring on and off acid suppression therapy. *J Clin Gastroenterol* 43(9):816–820
50. Rickenbacher N, Kötter T, Kochen MM, Scherer M, Blozik E (2014) Fundoplication versus medical management of gastroesophageal reflux disease: systematic review and meta-analysis. *Surg Endosc* 28(1):143–155
51. Faria R, Bojke L, Epstein D, Corbacho B, Sculpher M, REFLUX trial group (2013) Cost-effectiveness of laparoscopic fundoplication versus continued medical management for the treatment of gastro-oesophageal reflux disease based on long-term follow-up of the REFLUX trial. *Br J Surg* 100(9):1205–1213
52. Oelschlager BK, Barreca M, Chang L, Oleynikov D, Pellegrini CA (2003) Clinical and pathologic response of Barrett's esophagus to laparoscopic antireflux surgery. *Ann Surg* 238(4):458–464
53. Katz D, Rothstein R, Schned A, Dunn J, Seaver K, Antonioli D (1998) The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. *Am J Gastroenterol* 93(4):536–541
54. Oberg S, Wenner J, Johansson J, Walther B, Willén R (2005) Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. *Ann Surg* 242(1):49–54
55. Chang EY, Morris CD, Seltman AK, O'Rourke RW, Chan BK, Hunter JG, Jobe BA (2007) The effect of antireflux surgery on esophageal carcinogenesis in patients with barrett esophagus: a systematic review. *Ann Surg* 246(1):11–21
56. Parrilla P, Martínez de Haro LF, Ortiz A, Munitiz V, Molina J, Bermejo J, Canteras M (2003) Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. *Ann Surg* 237(3):291–298
57. Lagergren J, Ye W, Lagergren P, Lu Y (2010) The risk of esophageal adenocarcinoma after antireflux surgery. *Gastroenterology* 138(4):1297–1301
58. Qumseya BJ, Wang H, Badie N, Uzomba RN, Parasa S, White DL, Wolfsen H, Sharma P, Wallace MB (2013) Advanced imaging technologies increase detection of dysplasia and neoplasia in patients with Barrett's esophagus: a meta-analysis and systematic review. *Clin Gastroenterol Hepatol* 11(12):1562–1570
59. Canto MI, Anandasabapathy S, Brugge W, Falk GW, Dunbar KB, Zhang Z, Woods K, Almario JA, Schell U, Goldblum J, Maitra A, Montgomery E, Kiesslich R, Confocal Endomicroscopy for Barrett's Esophagus or Confocal Endomicroscopy for Barrett's Esophagus (CEBE) Trial Group (2014) In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). *Gastrointest Endosc* 79(2):211–221
60. Suter MJ, Gora MJ, Lauwers GY, Arnason T, Sauk J, Gallagher KA, Kava L, Tan KM, Soomro AR, Gallagher TP, Gardecki JA, Bouma BE, Rosenberg M, Nishioka NS, Tearney GJ (2014) Esophageal-guided biopsy with volumetric laser endomicroscopy and laser cautery marking: a pilot clinical study. *Gastrointest Endosc* 79(6):886–896
61. Vennalaganti PR, Naag Kanakadandi V, Gross SA, Parasa S, Wang KK, Gupta N, Sharma P (2015) Inter-observer agreement among pathologists using wide-area transepithelial sampling with computer-assisted analysis in patients with Barrett's esophagus. *Am J Gastroenterol* 110(9):1257–1260
62. Kadri SR, Lao-Sirieix P, O'Donovan M, Debiram I, Das M, Blazeby JM, Emery J, Boussioutas A, Morris H, Walter FM, Pharoah P, Hardwick RH, Fitzgerald RC (2010) Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. *BMJ* 341:c4372
63. Weaver JM, Ross-Innes CS, Shannon N, Lynch AG, Forshaw T, Barbera M, Murtaza M, Ong CA, Lao-Sirieix P, Dunning MJ, Smith L, Smith ML, Anderson CL, Carvalho B, O'Donovan M, Underwood TJ, May AP, Grehan N, Hardwick R, Davies J, Oloumi A, Aparicio S, Caldas C, Eldridge MD, Edwards PA, Rosenfeld N, Tavaré S, Fitzgerald RC, OCCAMS Consortium (2014) Ordering of mutations in preinvasive disease stages of esophageal carcinogenesis. *Nat Genet* 46(8):837–843
64. Kastelein F, Biermann K, Steyerberg EW, Verheij J, Kalisvaart M, Looijenga LH, Stoop HA, Walter L, Kuipers EJ, Spaander MC, Bruno MJ, ProBar-study group (2013) Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus. *Gut* 62(12):1676–1683
65. Cabibi D, Caruso S, Bazan V, Castiglia M, Bronte G, Ingrao S, Fanale D, Cangemi A, Calò V, Listì A, Incorvaia L, Galvano A, Pantuso G, Fiorentino E, Castorina S, Russo A (2016) Analysis of tissue and circulating microRNA expression during metaplastic transformation of the esophagus. *Oncotarget* 7(30):47821–47830