TOPIC HIGHLIGHT

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Effect of medical and surgical treatment of Barrett's metaplasia

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Abstract

Barrett's esophagus (BE) is a change in the esophageal mucosa as a result of long-standing gastroesophageal reflux disease. The importance of BE is that it is the main risk factor for the development of esophageal adenocarcinoma, whose incidence is currently growing faster than any other cancer in the Western world. The aim of this review was to compare the common treatment modalities of BE, with the focus on proton pump inhibitors and operative fundoplication. We performed a literature search on medical and surgical treatment of BE to determine eligible studies for this review. Studies on medical and surgical treatment of BE are discussed with regard to treatment effect on progression and regression of disease. Although there is some evidence for control of reflux with either medical or surgical therapy, there is no definitive evidence that either treatment modality decreases the risk of progression to dysplasia or cancer. Even though there is a trend toward antireflux surgery being superior, there are no definitive studies to prove this.

Key words: Barrett's esophagus; Intestinal metaplasia;

INTRODUCTION

Barrett's esophagus (BE) is defined as a change of any length in the distal esophageal epithelium, which can be recognized as columnar-type mucosa at endoscopy and confirmed as intestinal metaplasia (IM) by biopsy of the tubular esophagus[1]. BE is a complication of gastroesophageal reflux disease (GERD) through damage of the esophageal mucosa from refluxed contents[2,3]. It is thought to be present in around 10% of patients with GERD[3,4], although the exact incidence is unknown. As a result of the substantial increase of esophageal adenocarcinoma (AC) in patients with BE, it is considered the major risk factor for this form of cancer. In fact, over the past decade there has been acceleration in the incidence of AC in the Western world, presumably from a rise in GERD, its treatment, or other environmental factors. In the United States, it is estimated that 1.5-2 million people have BE[5].

It has been estimated that the risk for developing esophageal AC when IM is present is approximately 0.5% per year[6]. Although the factors that affect progression are not completely known, it is tempting to assume that the risk is increased by continued exposure of the IM to gastric contents[7].

Screening for BE in patients with chronic heartburn is not widely considered to be cost-effective, but surveillance in patients with BE is generally advised[8]. This, however, puts a heavy burden on resources for endoscopists. To prevent the development of esophageal cancer and to try and reduce the need for surveillance, the available treatment modalities for BE have been evaluated. The goal for treating patients with BE is generally directed at controlling associated symptoms of GERD, because quelling symptoms is a much more immediate endpoint for adjusting or changing therapy. Nevertheless, in this review, we discuss the possible treatment options for BE, with a focus on their effect on the Barrett's mucosa itself. The two most common treatments of GERD and associated BE are medical (proton pump inhibitors, PPIs) and surgery (fundoplication). Recently, more attention has been paid to other possible (medical) treatment options of BE that are not specifically aimed at reducing reflux. We briefly cover these treatment options as well.

LITERATURE SEARCH

A PubMed search was performed to identify publications using the following MeSH terms: "Barrett esophagus" and "proton pump inhibitors" or "surgical procedures, operative". Publications had to be published in the English language in peer-reviewed journals. Only studies published from 2000 onward with endoscopic biopsy results after treatment were deemed eligible. If publications were from the same research group, the most recent or most applicable study was chosen.

The abstracts of the results were read to determine eligibility for this review. If deemed eligible, full-text versions of the studies were acquired. From these full-text articles, references were checked to find publications that were missed using the search with MeSH terms[9-12]. Twenty studies were found to be eligible for this review. Five were on medical treatment (PPIs), 11 were on surgical treatment and four compared the two treatments.

DEFINITIONS

Progression of BE in this review is defined as a change in histological findings on biopsy from either IM to any form of dysplasia or an increase in grade of dysplasia. Development of AC is also considered progression of disease. Regression is defined as change from high-grade dysplasia (HGD) to low-grade dysplasia (LGD) or no dysplasia, change from LGD to metaplasia or loss of metaplasia, and change from IM to complete loss of metaplasia. Shortening of the segment or development of squamous cell islands, although considered by some as regression, usually is not accurately measured and reported, and is therefore, not considered regression in our report. Short-segment BE (SSBE) is defined as a length ≤ 3 cm seen at endoscopy and confirmed by biopsy. Long-segment BE (LSBE) is defined as > 3 cm.

LIMITING PROGRESSION

Ultimately, the goal of treatment for BE is to prevent cancer. Both medical and surgical treatment studies therefore have traditionally been focused on showing results of preventing progression of disease. We first discuss the results for PPI treatment, then those of operative treatment using fundoplication, and finally, studies that have compared these two treatment modalities.

Medical treatment

Three recent studies have investigated the effect of PPI treatment on the risk of progression of BE to dysplasia or AC[9,13,14]. The results of studies of PPI treatment with regard to progression and regression of disease are shown in Table 1. The results of these studies suggest a protective effect of PPIs in limiting the progression of BE.

In the study by Hillman *et al*[13], (350 patients with BE over a 20-year period), patients were stratified according to delay in starting PPI therapy after the diagnosis of BE was established. Patients who delayed PPI therapy for ≥ 2 years after being diagnosed with BE had 5.6 times higher risk of developing LGD than patients who used PPI within the first year after diagnosis. Furthermore, patients with BE had up to a 20 times higher risk of developing HGD or AC when PPI therapy was delayed for 2 years after diagnosis of BE. Although this suggests a substantial protective effect, the absolute risk of developing HGD or AC was low ($n = 11$; 3%) at a median follow-up of 4.7 years.

The small rate of progression of BE makes it very difficult to show a difference between treatments. In another study, the risk of developing LGD within 5 years of the diagnosis of BE was around 2.5%, and the risk of HGD/AC was around 2% while taking PPI therapy. Cooper *et al*[9] have shown this in a study of 188 patients with IM who were treated with a PPI. However, when following patients for > 5 years, Nguyen *et al*[14] recently have found a much higher risk of developing AC. They have studied 344 patients diagnosed with BE without dysplasia, with a mean follow-up of 7.6 years. They found that the chance of developing HGD or AC was 7.4%. Moreover, this risk was even higher when not taking PPIs (14.2%). Taken together, the results of these non-controlled studies suggest that PPIs have a protective effect, but they do not eliminate the risk of developing AC.

Surgical treatment

Surgical treatment of BE most often involves fundoplication for GERD. Where PPIs are only able to decrease acid content in the stomach (and thus change the pH of the refluxate), surgery has the ability to prevent any type of reflux. Therefore, many have argued that surgery is a more effective therapy for BE. All 11 publications on surgical treatment for BE that met our screening criteria included results on prevention of progression, as well as regression of metaplasia or dysplasia[15-25]. In this section, we discuss only the results of the effect of fundoplication on the rate

Table 1 Medical therapy and surgery for limiting progression and causing regression of Barrett's esophagus *n* (%)

Publication	No. of patients	Follow-up (yr)	Adenocarcinoma	Dysplasia	Regression
Medical therapy					
Hillman *et al*[13], 2004	279	4.7	7 (2.5)	5 (1.8)	NA
Cooper *et al*[9], 2006	188	5.1	3 (1.6)	6 (3.2)	NA
Nguyen *et al*[14], 2009	231	7.6	17 (7.4)	53 (23)	NA
Heath *et al*[10], 2007	82	0.9	6 (7.3)	9 (11)	34 (41)
Horwhat *et al*[11], 2007	67	3.8	2 (3.0)	21 (31)	13 (19)
Total	847	4.4	35 (4.1)	94 (11.1)	47 (31.5)
Surgery					
Hofstetter *et al*[15], 2001	79	5.0	0	4 (5)	16 (20)
Bowers *et al*[16], 2002	64	4.6	0	1 (2)	31 (48)
Mabrut *et al*[17], 2003	13	3.8	0	0	6 (46)
Oelschlager *et al*[18], 2003	90	2.6	1 (1)	3 (3)	30 (33)
Desai *et al*[19], 2003	50	3.1	0	1 (2)	9 (18)
O'Riordan *et al*[20], 2004	57	3.8	2 (4)	2 (4)	14 (25)
Abbas *et al*[21], 2004	33	1.5	1 (3)	2 (6)	13 (39)
Zaninotto *et al*[22], 2005	35	2.3	0	0	6 (17)
Ozmen *et al*[23], 2006	37	1.6	0	1 (3)	6 (16)
Biertho *et al*[24], 2007	70	4.2	0	3 (4)	23 (33)
Biertho *et al*[25], 2009	23	4.5	0	0	14 (61)
Total	551	3.4	4 (0.7)	17 (3.4)	168 (30.5)

NA: Not applicable.

of progression. The results of studies on surgical treatment for limiting progression and causing regression are summarized in Table 1.

In the reported case series, the number of patients is relatively low since a minority of patients is referred for surgery. As a result, because progression can take a long time and is still a relatively rare event (especially on medical therapy), large studies with several hundred patients would be needed to show a clinically significant benefit. Still, it is interesting to look at several trends, and as can be seen in Table 1, almost uniformly there is a low incidence of progression to dysplasia and even a lower incidence to AC.

Hofstetter *et al*[15] have published the study with the longest follow-up. They showed results for a series of 97 patients, with complete endoscopic follow-up in 79, at a median of 5 years. No patients developed HGD or AC, but four had progression of metaplasia to LGD (5%). Bowers *et al*[16], have reported a similar series with a mean follow-up of 4.6 years. Their 104 patients underwent open or laparoscopic fundoplication. Of these, 64 patients had endoscopic follow-up with biopsy. None of the patients developed HGD or AC. Only one patient had progression to LGD (1.5%).

Control of reflux

The hypothesis that surgery is superior to medical therapy comes from the assumption that surgery provides better control of GERD than do PPIs, and this should translate into lower progression rates. Indeed, there is some circumstantial evidence for this. Lagergren *et al*[26] and Csendes *et al*[27] have suggested that, when esophageal AC occurs after antireflux surgery, it is usually in the face of persistent or recurrent reflux. This observation, that control of reflux is essential in preventing progression of disease, is backed up by the fact that, in most studies, the patients with progression after surgical treatment seem to have recurrent reflux. In a series of 58 patients by O'Riordan *et al*[20] who underwent open or laparoscopic Rossetti-Nissen fundoplication, four were found to have progression of disease after a follow-up of 45 mo. All four patients were found to have abnormal postoperative acid scores[20]. In another study, Biertho *et al*[24] have published the results of 70 patients with BE who had endoscopic follow-up for 4.2 years after laparoscopic fundoplication. Three patients had progression of disease, but none developed HGD or AC. All three patients with progression had recurrence of GERD symptoms. We published our results of 106 patients with BE who underwent laparoscopic fundoplication[18]. Endoscopic follow-up with biopsies was performed in 90 patients with a median follow-up of 30 mo. One patient was found to have developed AC at 10 mo after the operation (and thus likely had at least dysplasia at the time of operation). One patient developed HGD and one LGD. The patient with HGD had LGD preoperatively and for 3 years thereafter, and then developed recurrent GERD symptoms with an abnormal 24-h pH. One year later this patient was found to have developed HGD despite being on medical therapy. Still, despite the fact that surgery is not perfect, the rate of progression to HGD or AC seems around 1.5%, which is lower than that typically seen in medical treatment.

One of the difficulties in evaluating the results of these treatments is the overall low incidence of patients with BE progressing to AC. Although decreasing the total burden of BE might actually decrease the risk of cancer, it is difficult to track. The results of the studies suggest that surveillance after medical treatment is necessary. After surgical treatment, there is also still progression of

Table 2 Medical therapy *vs* surgery for Barrett's esophagus *n* (%)

Publication	Treatments	PPI	Nissen	Progression PPI	Progression Nissen	Regression PPI	Regression Nissen	Study type
Gatenby *et al*[6], 2009	PPI *vs* Nissen	646	41	154 (24)	4 (10)	NA	NA	Cohort
Parrilla *et al*[28], 2003	H2RA/PPI *vs* Nissen	43	58	10 (23)	5 (9)	2 (5)	5 (9)	RCT
Rossi *et al*[29], 2006	PPI *vs* successful Nissen	19	16	NA	NA	12 (63)	16 (100)	Case comparison
Total		708	115	164 (23.8)	9 (9.1)	14 (22.6)	21 (28.4)	

PPI: Proton pump inhibitor; H2RA: H2 receptor antagonist; RCT: Randomized controlled trial; NA: Not applicable.

disease (particularly in patients with LSBE), although the risk seems to become very small when this treatment is successful. Patients are generally reluctant to have surveillance, as shown by the low number of patients who actually have endoscopy after fundoplication. Another difficulty in interpreting the results is the follow-up of these studies that ranges from 0.9 to 7.6 years. With a disease that, in general, progresses only slowly, studies with follow-up of 10-20 years are needed. In contrast, studies on surgical treatment with the longest follow-up have still shown very low incidence of progression. The study on medical treatment with the longest follow-up did show a higher chance of progression of disease[14], although that study was possibly confounded by selection bias.

Medical *vs* surgical treatment

There have been very few studies comparing medical and surgical therapy; in fact, in our review, we only found two studies on progression of disease worthy of comment. The results of these are summarized in Table 2.

In one, Gatenby *et al*[6] published the results of their review of a cohort of 738 patients with BE enrolled in a national registry. They compared patients with anti-reflux surgery (*n* = 41) to those treated medically with PPIs (*n* = 551), H2 receptor antagonists (H2RAs) (*n* = 42), H2RA followed by PPI (*n* = 95), or no treatment (*n* = 9). Their outcome parameters were progression of disease to LGD, HGD or AC. They could not control for many other selection factors, which might have confounded the results, such as severity of disease. After a follow-up of 5 years after medical therapy and 6 years after surgical therapy, there was however a trend toward antireflux surgery being more protective. No patients in the antireflux group developed HGD or AC as compared to 4.3% in the all-medical therapies group (*P* = 0.13). There were not enough patients in the surgical arm to determine if this was a significant difference.

Parrilla *et al*[28] have published the only randomized study comparing medical treatment (*n* = 43) and antireflux surgery (*n* = 58). In that study, 101 patients with BE were treated between 1982 and 2000. Medical treatment consisted of H2RA treatment initially and then omeprazole from 1992 onward. Surgery was performed through laparotomy with Nissen fundoplication in 56 patients and a Collis-Nissen procedure in the other two because of short esophagus.

All patients had annual clinical, endoscopic and histological follow-up, and patients who had an operation also had a pH study and manometry at 1 year postoperatively and every 5 years thereafter, or if they presented with recurrent GERD symptoms. Mean follow-up was 6 years for the medical therapy group and 7 years for the surgical group. Progression of BE to any dysplasia was found in eight patients (19%) in the medical treatment group and in three in the surgical group (5%). Although the *P* value was not specified in their paper, according to our calculations using Fisher exact test, there was a protective effect of fundoplication (*P* = 0.05). Two patients in each group progressed to AC, which was confirmed after esophageal resection. Although differences in progression rates between the two groups were not significant according to the authors, when a sub-analysis was performed including only patients in the surgical arm with normal pH, the progression rate dropped to 2%, which was a significantly lower chance of progression of disease than in the medical group (*P* < 0.05).

CAUSING REGRESSION

IM without dysplasia is a benign condition, therefore, inducing regression is not considered as important as limiting progression. Nevertheless, if IM is no longer present, then it theoretically can no longer progress to cancer, thus it has been reported as a surrogate for measuring the response of various therapies. Disappearance of IM seems to be a slightly more common occurrence after effective treatment of GERD and therefore is a more easily studied endpoint.

Medical treatment

The only two studies that we found that have published results of regression of BE following medical treatment are by Heath *et al*[10] and Horwhat *et al*[11]. The results of these studies are shown in Table 1, together with the studies on progression of disease.

The purpose of the study by Heath *et al*[10] was to investigate the effect of long-term celecoxib in patients with BE with dysplasia. The mechanism for chemoprevention of celecoxib is thought to be through inhibition of cyclooxygenase (COX)[30]. They randomized 100 patients with low or high-grade Barrett's dysplasia to treatment with either celecoxib (*n* = 49) or placebo (*n* = 51). Although this study did not focus on PPI therapy, > 90% of these patients were concomitantly on a PPI. After 48 wk of treatment, endoscopic biopsy results showed a regression of dysplasia in 41.9% of patients on celecoxib and 41%

on placebo (*P* = 0.89), either from LGD to no dysplasia or from HGD to LGD (although differentiation between those events in this study was not possible). In contrast, 14% (*n* = 6) and 15.4% (*n* = 6) respectively had an increase in highest grade of pathology, with three patients in each group developing AC. These mixed results might say more about the variability in interobserver reliability of dysplasia, as has been reported[31]. However, the results do suggest that patients with dysplasia can regress with medical therapy alone.

Horwhat *et al*[11] looked at LSBE and SSBE. They contacted 101 patients after a mean follow-up of 46 mo. Most patients received PPI therapy but seven underwent fundoplication. Of the 38 patients with LSBE, 23 underwent endoscopy. Six patients developed dysplasia (26%) and two cancer (9%). No patient with LSBE had regression of disease. Of the 63 patients in the SSBE group, 44 underwent endoscopy. Three patients were found to have progression of disease (7%) *vs* 13 with regression (30%). They found an almost linear relationship between BE segment length and normalization of the epithelium, that is, the chance of progression of disease is significantly higher in LSBE compared with SSBE. Unfortunately, it is unclear in this study whether the patients with regression or progression had medical or surgical treatment.

Surgical treatment
The results of regression of BE with surgical treatment are shown in Table 1, together with the results of progression. The literature suggests that regression of BE occurs with some regularity after fundoplication, even regression to completely normal squamous epithelium. Hofstetter *et al*[15] have reported that 16 of their 79 patients (20%) had regression of disease in some fashion. Of the 16 patients with LGD, seven had regression (44%), and of the 63 patients with IM, nine had complete loss of metaplasia (14%).

It is important to consider that LGD is sometimes over-reported because of inflammation from ongoing GERD, and surgery could make it easier for the pathologist to interpret the biopsies. Nevertheless, other studies have suggested regression in a substantial number of BE patients. Desai *et al*[19] have found a loss of metaplasia in seven of 50 patients (14%) postoperatively. Two out of the three patients with LGD had regression to non-dysplastic BE. In the study by Bowers *et al*[16], it has been found that 31 of 66 patients had loss of IM (47%) after antireflux surgery. Patients with regression had shorter lengths of BE preoperatively and longer follow-up after the operation.

That patients with SSBE have a higher incidence of regression than those with LSBE seems logical, and it has been consistently seen in studies where long and short-segment BE has been distinguished. In the study by O'Riordan *et al*[20], eight of 57 patients (14%) were found to have complete regression. Six of these patients had SSBE preoperatively. They have also found regression from LGD to non-dysplastic BE in six of eight patients. Biertho *et al*[24] have reported that complete regression

was found in 23 of their 70 patients (33%). All patients with regression had SSBE preoperatively. Regression from LGD to non-dysplastic BE occurred in two of three patients.

Our experience mirrors that of other authors who have found that complete regression occurs only in patients with SSBE. Of the 54 patients with SSBE before surgery, 30 (54%) had no evidence of IM at last follow-up. In contrast, none of the 38 patients with LSBE before surgery had complete regression[18]. These observations suggest that the chance of accomplishing regression is especially high in patients with earlier disease. Therefore, earlier referral for surgery might increase the chance of cure from BE even further.

Medical vs surgical treatment
Only one small study comparing medical and surgical treatment directly has been published that focuses on regression of BE. The results are summarized in Table 2.

Rossi *et al*[29] prospectively studied 19 patients with high-dose PPI and 16 patients with fundoplication. All patients had LGD. After 18 mo follow-up, a high percentage of patients were found to have regressed to IM after medical (63%) as well as surgical treatment (100%). Although the rate was higher in the surgical group, the small numbers make it difficult to use the study to draw any definitive conclusions. Parrilla *et al*[28] also have reported data on regression of disease in their randomized study, although they do not comment on this, with 2/43 (4.6%) having regression from LGD to IM with medical therapy, and 5/58 (8.6%) after surgical therapy (*P* > 0.05).

When comparing both treatment modalities, antireflux surgery seems to be more successful in prevention of progression and in promoting regression than medical treatment with PPI. The number of patients studied and the quality of the studies however were low, therefore, a firm conclusion cannot be drawn. Complications from the operation are also not taken into account and these studies generally come from surgical centers of excellence. On the other hand, the patients that underwent an operation are more likely to have had more severe disease than the patients that are treated medically.

OTHER MEDICAL TREATMENT
Almost all patients with BE, because of their associated GERD, are treated with PPIs (unless they have surgery), therefore, it makes sense to evaluate the effect of acid reduction on the natural history of BE. However, there have been other medical therapies investigated for the purpose of addressing IM primarily. For example, Vaughan *et al*[32] have shown a potential role for nonsteroidal anti-inflammatory drugs (NSAIDs). The effect of NSAIDs is thought to be through their anti-inflammatory effect through inhibition of COX-2 production[33]. Ogunwobi *et al*[34] have made a theoretical argument for statins, stating that they might affect proliferation and apoptosis in esophageal cancer cells. The protective effect of these medications is further supported by a

recent study by Nguyen *et al*[35]. In this retrospective observational study using pharmacy data, they have shown a reduced risk of developing AC in patients with BE and filled NSAID prescriptions. They have also studied statins as chemopreventive medications, however, they are concerned about confounding with statin therapy because patients had short periods of use, therefore, conclusions cannot be drawn about these medications.

Other publications contradict the role of NSAIDs in preventing progression. One is the study by Heath *et al*[10] that was discussed earlier, which did not find a difference when comparing patients on or off celecoxib. Gatenby *et al*[36] have published results of a national registry in the United Kingdom of BE, where they did not find a difference in development of dysplasia or AC between patients on or off aspirin. To evaluate further the effect of aspirin treatment of BE on progression to cancer, a large randomized trial (AsPECT) is ongoing, which is comparing patients on PPI therapy with and without aspirin[37].

Many other medications, such as ursodeoxycholic acid, hormone replacement therapy and n-3 fatty acids have been studied[38-41], but all have too little information to recommend their use currently. Dietary interventions through antioxidants, fiber and vitamins have been studied for their effect on risk of cancer in general and for prevention of esophageal AC. However, mixed results have been reported[42].

Very few clinical studies have been carried out on treatment modalities other than antireflux surgery using fundoplication, or medical treatment using PPIs. Therefore more (large) studies are necessary before any firm conclusions can be drawn on the chemopreventive qualities of agents such as aspirin, selective COX inhibitors or diet modifications.

CONCLUSION

Consensus on the best treatment for BE remains elusive, because there has not been a large definitive study to date that has compared PPIs and fundoplication (nor is there likely to be one). There is, however, a trend toward lower risk of progression with anti-reflux surgery compared with anti-acid medication, especially when anti-reflux surgery is successful. In addition, there seems to be a greater chance of regression of disease with anti-reflux treatment, but the importance of this regression is unclear. Theoretically, surgery controls gastroesophageal reflux better than PPIs do (which mostly reduces the acid component), therefore, it is appealing for some to consider this a real difference, and therefore, recommend surgery for patients with BE, even though it is not definitively proven. As a result, treatment of BE has to be given based on the patient's preference and control of GERD symptoms. Just like GERD without IM, those with IM should consider fundoplication if symptomatic, despite appropriate medical therapy. The effect of fundoplication on the natural history of the epithelium should be a secondary concern. Whichever treatment is pursued, surveillance remains important, because the risk of cancer is not eliminated despite the decrease in risk through both PPIs and surgery.

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