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ORIGINAL ARTICLE

Does Impaired Gallbladder Function Contribute to the Development of Barrett's Esophagus and Esophageal Adenocarcinoma?

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Abstract

Introduction Esophageal adenocarcinoma is aetiologically associated with gastro-esophageal reflux, but the mechanisms responsible for the metaplasia–dysplasia sequence are unknown. Bile components are implicated. Impaired gallbladder function may contribute to duodenogastric reflux (DGR) and harmful GERD.

Aims This study aims to compare gallbladder function in patients with Barrett's esophagus, adenocarcinoma, and controls.

Methods Three groups of patients, all free of gallstone disease, were studied. Group 1: (n=15) were normal controls. Group 2: (n=15) were patients with >3-cm-long segment of Barrett's esophagus. Group 3: (n=15) were patients with esophageal adenocarcinoma. Using real-time ultrasonography unit, gallbladder volume was measured in subjects following a 10-h fast. Ejection fraction was calculated before and after standard liquid meal and compared between the groups.

Results The mean percentage reduction in gallbladder volume was 50% at 40 min in the adenocarcinoma group compared with 72.4% in the control group (p<0.001). At 60 min, gallbladder filling had recommenced in the control group to 64.1% of fasting volume while continuing to empty with further reduction to 63% in the Barrett's group and to 50.6% (p=0.008) in the adenocarcinoma group. The mean gallbladder ejection fraction decreased progressively from controls to Barrett's to adenocarcinoma and was significantly lower in Barrett's group (60.9%; p=0.019) and adenocarcinoma group (47.9%; p< 0.001) compared with normal controls (70.9%).

Conclusion Gallbladder function is progressively impaired in Barrett's esophagus and adenocarcinoma. Gallbladder malfunction increases duodenogastric reflux, exposing the lower esophagus to an altered chemical milieu which, in turn, may have a role in promoting metaplasia–dysplasia–neoplasia sequence in the lower esophageal mucosa.

Keywords Gallbladder function · Barrett's esophagus · Adenocarcinoma esophagus

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Introduction

The chief risk factor for esophageal adenocarcinoma is Barrett's esophagus, which in turn results from mucosal injury secondary to gastro-esophageal reflux disease (GERD). Impaired lower esophageal sphincter function and the composition of the refluxate are key factors in any resultant mucosal injury. Disturbance of lower esophageal sphincter function allows reflux of gastric contents into the esophagus.[1–4] In addition to gastric acid,[5–7] other components of the refluxate such as pancreatic enzymes,[8–12] intestinal enzymes,[8,13–15] and bile, in particular,[8,16] are all implicated in esophageal mucosal injury.

Bile is stored in the gallbladder between meals and is expelled into the duodenum by contraction of the gallbladder in response to meal-stimulated CCK secretion from the duodenum (Fig. 1). In addition to inducing gallbladder contraction, CCK causes relaxation of the sphincter of Oddi and relaxation of the lower esophageal sphincter (LES). The resultant bile bolus in the duodenum switches off CCK release by a negative feedback mechanism. (Fig. 2). Thus, when the gallbladder is functioning normally, bile is mixed with food in the duodenum and little is free to enter the stomach or come into contact with the esophageal mucosa.[18,19]

This orderly sequence of bile processing can be disturbed in a number of circumstances,[20–23] such as a non-functioning gallbladder or following cholecystectomy. When the gallbladder is removed or full of gallstones, the storage facility is destroyed. Instead of storage followed by meal-stimulated release, bile trickles constantly from the liver into the duodenum permitting retrograde reflux into the stomach.[24–26] Furthermore, as the bile is delivered constantly into the duodenum the mechanism for switching off CCK secretion is impaired. Plasma CCK levels remain elevated after meals[27] which in turn may contribute to altered cardia function[28–32] and increased gastro-esophageal reflux. When the gallbladder is non-functioning or poorly functioning bile storage and release by the gallbladder is compromised. The absence of a bolus fails to provide a negative switch-off signal. Gallbladder function may be altered by increasing volumes of gallstones[33,34] chronic cholecystitis, chronic pancreatitis,[35] and by diabetes mellitus[36] amongst other diseases.[37–39]

There is evidence that implicates duodenogastric-esophageal reflux in the pathogenesis of Barrett's esophagus[40–42] and adenocarcinoma. We have previously shown that cholecystectomy is associated with an increased incidence of GERD.[22,27,70] Others have shown a link between

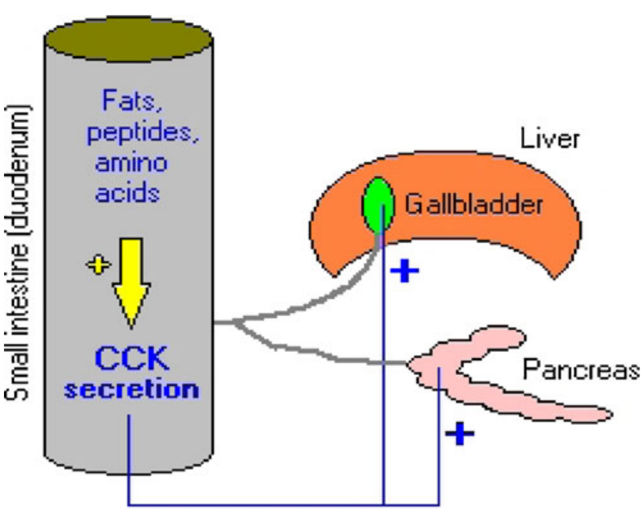

Fig. 1 Normal mechanism of CCK release. Meal-stimulated CCK release from the duodenum results in gallbladder emptying. Impaired CCK release is a potential cause of impaired gallbladder emptying

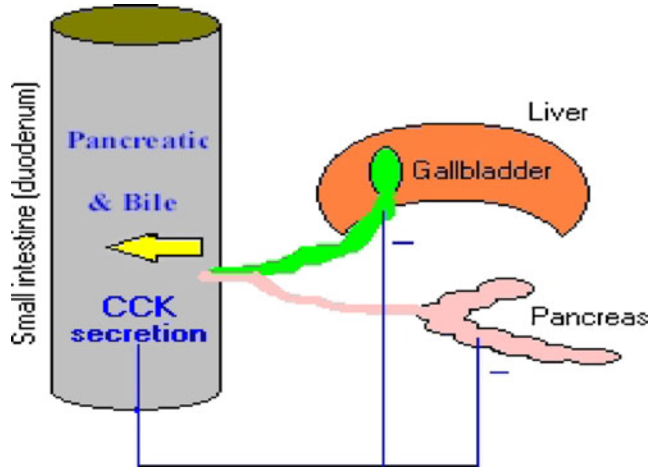

Fig. 2 Normal mechanism of CCK inhibition. CCK release from the duodenum is inhibited by the negative feedback of a bile bolus in the duodenum. Modulation of CCK release is the chief mechanism of control of gallbladder emptying

cholecystectomy and adenocarcinoma.[20,22,24] Studies have also demonstrated that foregut and gallbladder function are impaired in Barrett's esophagus.[33,34] There are no studies on gallbladder function in esophageal adenocarcinoma.

As a unifying concept to weave together these strands of evidence, we hypothesized that gallbladder function may be impaired in patients with Barrett's esophagus and adenocarcinoma of the esophagus, which may in turn contribute to duodenogastric reflux and to the metaplasia–dysplasia–neoplasia sequence. The aim of this study, therefore, was to compare gallbladder function between patients with Barrett's esophagus, adenocarcinoma, and controls.

Patients and Methods

Study Groups

Three study groups were enrolled. Since the prevalence of gallstone disease in patients with Barrett's is higher than patients without Barrett's[43], we screened all patients prior to study to exclude gallstone disease.

- Group 1 (n=15) were healthy volunteers attending the radiology department for non-GI radiological investigations. None had symptoms of GERD.
- Group 2 (n=15) were patients with histologically confirmed long segment Barrett's esophagus (>3 cm from the OGJ) who were off all medication that might impact on the gastrointestinal tract for at least 14 days.
- Group 3 (n=15) were patients with newly diagnosed adenocarcinoma of the esophagus without evidence of metastatic disease, all of whom were able to swallow fluids without a difficulty.

Ethics Approval

Approval for the study was obtained from the ethics committee in the hospital before enrolment. All participants were interviewed and a study information proforma was completed. Informed consent was signed by each participant prior to recruitment to the study.

Exclusion Criteria

Participants with conditions known to affect gallbladder motility were excluded from the study. These included patients with diabetes, chronic liver disease or cholelithiasis. Also excluded were patients being prescribed pharmacological agents known to affect acid secretion or GI or gallbladder motility. A previous history of esophageal, gastric, duodenal, hepatic, pancreatic, or biliary surgery was also an exclusion factor. Esophageal adenocarcinoma patients with advanced cancer, an esophageal stent in situ, severe dysphagia that might compromise the ingestion of the test meal, or patients receiving chemoradiotherapy or post-chemoradiotherapy were also excluded. Apart from the adenocarcinoma group none had a history of cancer.

Sample Size

Sample size was calculated using "PS: Power and Sample Size Calculation© software (version 2.1.31, 2003, Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN).

The Standard Test Meal

All patients were given a standard test liquid meal to stimulate gallbladder contraction. The meal used as the standard test meal was the commercially available Fortisip® Strawberry (Nutricia Clinical NZ, Auckland, New Zealand). Fortisip® Strawberry is a commercially available nutritionally complete food commonly used for patients with increased energy or protein requirements or for those who have little appetite for food. A liquid preparation was chosen as standard to facilitate rapid ingestion into the stomach for patients with some degree of stenosis. The meal provided 300 kcal in each 200 ml fluid preparation (1.5 kcal/ml) in the form of 10.2% saturated fatty acids, 9.4% monounsaturated fatty acids, and 30.4% polyunsaturated fatty acids. It was felt that this would facilitate gallbladder emptying in a more physiological manner than using a purely fatty meal which may have resulted in exaggerated emptying. The standard test meal (Fortsip) was ingested at a rate of 50–100 ml/min via a straw.[44,45]

Measurement of Gallbladder Function

A real-time ultrasonography unit (Model: GE Logiq 9, GE Healthcare Technologies, Clinical Systems Information Technologies, Hatfield, UK) was used for measuring gallbladder volume.[46] The transducer used was a real-time multi-frequency (2–4 MHz) sector transducer.

Ultrasonographic scanning was performed after a 10-h overnight fast to ensure adequate gallbladder distension. The fasting gallbladder volume (FGV) was calculated and the common bile duct caliber was measured before meal ingestion. The gallbladder volume (GBV) was also calculated at 20, 40, and 60 min following the standard test meal.

Study participants remained in the sitting position after meal and between scans to facilitate passage of the meal through the stomach to the duodenum. Any participant who was unable to tolerate sitting comfortably adopted the right lateral position. Images and measurements were obtained in suspended deep inspiration.

Gallbladder volume was calculated using software capable of automatically capturing the gallbladder length, width and depth (Model: GE Logiq 9, GE Healthcare Technologies, Clinical Systems Information Technologies, Hatfield, UK). To verify the software produced readings, duplicate readings were also obtained to calculate the gallbladder volume manually by using the ellipsoid formula:[39,46,47]

$$\frac{\text{Volume} = \pi \times \text{Length} \times \text{Width} \times \text{Depth}}{6}$$

The FGV was taken as the base line volume.

Calculation of Gallbladder Emptying

Gallbladder emptying (GBE) was taken as the difference between the FGV and the GBV at a specific time, expressed as a percentage of the basal gall bladder volume:

$$\frac{\text{GBE}(X_{\min}) = (\text{FGV} - \text{GBV}(X_{\min})) \times 100}{(\text{FGV})}$$

Data Collection and Statistical Analysis

Data were collected using a computer-generated database (Microsoft Office Access 2003, Microsoft Windows XP Professional™, Microsoft Corporation, Redmond, WA). Statistical analysis was performed using SPSS 10.0 software for Windows™ (SPSS Inc., Chicago, IL) to calculate the mean, the standard deviation (SD) and the any significant difference between the different groups. The t test for independent samples was used to compare gallbladder emptying and ejection fraction between the study groups and the control group using a p value of <0.05 and a power of 0.8.

Results

Demographic Data

A total of forty-five participants had gallbladder emptying assessed with a male/female ratio of 2.4:1. There was no significant difference between the ages of the different groups. The mean (SD) age of the control group was 69.7 (8.7) years which compared with 66.0 (9.9) years for the Barrett's group (p=0.542) and 64.5 (14.9) years for the adenocarcinoma group (p=0.622).

Gallbladder Volume

The mean resting gallbladder volume was 26(1.1) mls in controls, compared with 38.1 (26.8) ml in the Barrett's group (p=0.005) and 27.6(16.1) ml in the adenocarcinoma group (p=0.054) (Table 1).

Gallbladder volume decreased gradually after the standard meal in all groups. This decrease was more significant at 20-min posttest meal in the control group, where gallbladder volume fell to 10.5 (5.1) ml than in the Barrett's group 22.7 (21.2) ml compared with the control group (p<0.001), or the adenocarcinoma group 15.5 (15.7) ml compared with the control group (p=0.003).

Gallbladder volume reached its lowest level in the control group at 40 min to 7.5[4] ml and had started to fill again by 60 min to 9.4 (4.3) ml. Both the Barrett's and the adenocarcinoma groups continued to show significant decrease in volume at 60 min confirming continuation of emptying with volumes of 14.9 (14.5) ml (p=0.007) and 14.4[13] ml (p=0.01), respectively. The gallbladder volume decrease was slower in the Barrett's group and the cancer group than in normal controls and continued up to 60 min with no recovery.

Percentage of Gallbladder Emptying

Because the mean starting fasting gallbladder volume showed slight variability among the three groups, the percentage gallbladder emptying was used to provide better comparison between the three study groups. The fasting gallbladder volume was taken as the base line volume from which subsequent emptied volumes were calculated as the percentage of gallbladder emptying at a specific point of time.

The mean percentage gallbladder volume emptied at 20 min following a standard meal in the control group was 60.5% (12.5%) which was not significantly different from the 48.5% (18%) in the Barrett's group. The percentage emptying in the adenocarcinoma group was 41% (26%) which was significantly reduced compared with the control group (p=0.021).

At 40 min, the mean percentage gallbladder volume reduction in the control group was 72.4% (6.9%), which was similar to the Barrett's group 58.4% (11.6%; p=0.213) but was significantly different from the adenocarcinoma group 44.9% (20.7; p<0.001).

At 60 min, gallbladder filling had recommenced in the control group to 64.1% (10.2). Both the Barrett's and the adenocarcinoma groups continued to show progression of emptying with further reduction to 63%[13] (p=0.427) in the Barrett's group and 50.6% (26.5; p=0.008) in the adenocarcinoma group.

The gallbladder emptying was faster and more significant in the control group compared with the cancer group but not the Barrett's group, mirroring the volume changes, and reaching maximal emptying at 40 min after which recovery was seen. Gallbladder emptying was delayed in the Barrett's and the cancer group particularly as seen after 40 min and continued up to 60 min posttest meal.

Gallbladder Ejection Fraction

The gallbladder ejection fraction was taken as gallbladder emptying at 40 min. The ejection fraction was taken as the study's end-point at which the statistical test for the study power was taken. The ejection fraction was calculated as 72.4% (6.9) in the control group, 58.4% (11.6) in the Barrett's group (p=0.213), and 44.9% (20.7) in the adenocarcinoma group (p<0.00 1) using the Student's t test for independent samples.

Table 1 Gallbladder volumes

	Fasting GBV (ml)	20 min (ml)	40 min (ml)	60 min (ml)
Controls	26	10.5	8	9.4
Barrett's group	38.1	22.7	15	15
Adenocarcinoma	27.6	15.5	18	14.4

Gallbladder volume decreased gradually after the standard meal in all groups. The gallbladder volume decrease was slower in the Barrett's group and the cancer group and continued up to 60 min with no recovery

Discussion

The increase in the incidence esophageal adenocarcinoma is multifactorial, but the contribution of Barrett's esophagus is beyond question.[48] The aetiology of Barrett's mucosa, which represents the severest end of the reflux spectrum, is in turn a consequence of altered gastrointestinal anatomy and physiological mechanisms[49] the most significant of which are the alteration in intestinal motility[50] and the toxicity of the resultant refluxate.[16,51,52] The motility disturbances identified in Barrett's include esophageal body dysmotility leading to impaired clearance[53,54] lower mean basal LES pressure and increased transient lower esophageal sphincter relaxation episodes, which allow increased gastro-esophageal reflux, gastric dysmotility leading to delayed gastric emptying which could promote reflux and prolong contact with toxic refluxate[55–60] and possible antro-duodenal motility disorders.[61,62]

The toxicity of the refluxate is clearly a co-contributing factor to the resultant injury. While we are unclear about the exact chemical components which inflict most injury, it is clear that injury may result from gastric acid alone[52] or from acid combined with duodenal refluxate.[63,64] The role of acid and bile in the genesis of esophageal mucosal damage and reflux symptoms is complex. Acid combined with pepsin and unconjugated bile acids are critical to the development of esophagitis and Barrett's esophagus.[40,42] Bile alone or duodenal refluxate alone may be the principal factor in determining the severity of esophagitis as Barrett's has been described following total gastrectomy.[65,66] Patients with reflux disease have an increased concentration of bile acids in their esophageal aspirates.[12] Nearly half of the patients with reflux symptoms have combined pathological acid and bile reflux.[67]

Duodenogastric reflux (DGR) of duodenal content into the stomach occurs physiologically but anything that alters the structure or function of the duodeno-pancreatobiliary system will promote DGR. Thus, surgical destruction of the pylorus after distal gastrectomy,[68] pyloroplasty or Whipples procedure increase DGR.[17] Similarly, anything that disturbs the orderly sequence of bile secretion, storage, and release may contribute to DGR.[69] The most dramatic alteration in this environment occurs after cholecystectomy when bile is no longer stored between meals but streams continuously into the duodenum and the stomach.[22,23] We, and others, have previously shown that cholecystectomy results in increased gastro-esophageal reflux[70] and elevated levels of CCK.[27] Amongst the effects of CCK is the reduction in LOS pressure.[27] These combined disturbances may contribute to an abnormal concentration of bile refluxate for a longer duration in the lower esophagus. These findings support a possible contribution of gallbladder malfunction in the development of Barrett's esophagus and adenocarcinoma.[21]

In this study we have shown that gallbladder emptying is progressively impaired in the Barrett's esophagus and adenocarcinoma groups. In normal subjects gallbladder emptying in response to a meal was complete by 40 min after which it began to fill again. Approximately two thirds of resting volume had emptied within the first 20 min and three quarters by 40 min and the filling process had commenced within 60 min of a meal, which is consistent with the literature.[71] The pattern of emptying was altered in the Barrett's group and even more so in the adenocarcinoma group where both groups continued to show significant decrease in volume to 60 min confirming continuation of emptying suggesting abnormal gallbladder motility. Thus, patients with Barrett's and adenocarcinoma had an impaired response to meals suggesting that their gallbladder function was impaired and incapable of storing and releasing bile normally, a condition approaching non-functioning gallbladder. Patient following cholecystectomy[21–23] or patients with poorly functioning gallbladders have increased bile reflux into the stomach and increased potential toxicity.

The cause of the abnormal gallbladder function in Barrett's and cancer is unclear. It may be that there is a common motility disorder that predisposes to both Barrett's esophagus and gallbladder malfunction. This may have a neural basis or a hormonal basis, most likely through CCK secretion. Whatever the cause, it is likely that a lifetime of altered gallbladder function may predispose to chronic toxic bile exposure in the stomach and lower esophagus. Barrett's esophagus is associated with motility disorders of the esophagus and of the stomach and a recent report has observed an association between Barrett's and gallbladder function.[43] Our study is the first report to describe an association between gallbladder malfunction and adenocarcinoma. It is possible that there is a primary motility disorder in Barrett's esophagus affecting the entire upper gastrointestinal tract affecting the esophagus, stomach and the biliary system.

In conclusion, patients with Barrett's esophagus and esophageal adenocarcinoma have abnormal gallbladder function. Whether this is cause or consequence is unclear. Further studies are needed to determine whether impaired gallbladder function contributes significantly to the reflux milieu and in particular to the mucosal change of Barrett's esophagus or adenocarcinoma.

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