Leading Article

Gastroesophageal Reflux Disease: New evidence defining the pathology and pathogenesis of early GERD

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DOI: <http://doi.org/10.4038/jdp.v13i2.7756>

Submitted on 12.06.2018 Accepted for publication on 02.08.2018

Introduction

Throughout history, the success and failure of management of a disease has been determined by the level of understanding of its pathology at an anatomic, histologic, and molecular level.

Gastroesophageal reflux disease (GERD) is a common human disease. In the western world, it has a prevalence of 30% (1). In the Eastern world, the prevalence is lower, but shows signs of increase (1). The cause of GERD is conceptually simple; it results when the mechanism that normally prevents reflux of gastric contents into the esophagus fails. That mechanism is the lower esophageal sphincter (LES). In a patient with a competent LES, reflux does not occur.

Despite this obvious etiology, present medical management is largely aimed at reducing gastric acid with a naïve and incorrect belief that the disease will be cured by making the refluxed gastric juice less acid. In fact, the common name for GERD is “acid reflux disease.” No amount of acid in the stomach will cause GERD if the LES is competent. No amount of acid suppression will cure reflux if the LES is defective. Patients on acid suppressive therapy

continue to reflux gastric contents of higher pH, i.e. weak acid reflux (2).

The belief that acid suppression is the answer to GERD has induced the pharmaceutical industry to provide physicians with increasing power to suppress gastric acid secretion; from H₂ receptor antagonists in the 1960s to proton pump inhibitors (PPI) in the 1980s. These have been heralded as cures for GERD and still remains the mainstay of GERD treatment. They have been successful in healing erosive esophagitis and controlling heartburn, the latter leading to an improvement in quality of life (3).

However, the drugs have not prevented progression of GERD to Barrett esophagus (BE) and esophageal adenocarcinoma. Esophageal adenocarcinoma, which always results as a complication of GERD, has increased 7-fold in the Western world from 1973 to 2010; it continues to increase (4).

If acid suppression can claim to heal erosive esophagitis and control heartburn, we must explain how and why it has failed to protect the progression to adenocarcinoma. The Pro-GERD study in Europe provides insight into the progression of GERD over a 5-year period. Over 6200 patients with GERD were recruited for this study from clinics in Western Europe, had an index endoscopy performed in study centers by trained endoscopists and then returned to the care of their primary physicians (5). After 5 years, the patients were brought

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back to the study centers for repeat endoscopy. This showed that patients had excellent control of erosive esophagitis during the 5 years. However, 9.7% of patients without BE at the index endoscopy had developed BE at 5 years. The incidence was significantly associated with the severity of erosive esophagitis at the index endoscopy (19.7% of patients with Los Angeles grade C/D compared with 5.4% of patients with no erosive esophagitis), and with regular PPI use compared to intermittent PPI use or use of H₂ receptor antagonists (6). It has been suggested that the association with regular PPI use was the result of indication bias, i.e. the relationship was due to the fact that regular PPI use was more common in patients with more severe GERD. Indication bias is not likely to be the full answer because no significant association was present between severity of symptoms in detailed questionnaires and the occurrence of BE.

Whether or not PPI use is responsible, the fact that 10% of GERD patients under standard GERD therapy in the primary care setting develop BE in 5 years cannot be disputed. In a disease with a prevalence of 30% in the population, the conversion of a benign disease to its premalignant complication can explain the rapid increase in the incidence of esophageal adenocarcinoma over the past 20 years. With no changes in the way GERD is managed, the probability is that the increasing incidence of esophageal adenocarcinoma will continue.

PRESENT UNDERSTANDING OF NORMAL ANATOMY AND HISTOLOGY

The present management of GERD is based on the present understanding of the normal anatomy and histology of the esophagus, LES and proximal stomach (Fig 1). At endoscopy, the esophagus is a tube that is lined entirely by squamous epithelium. At the end of the tube, the esophagus flares into what is believed to be the saccular stomach. The stomach is lined by columnar epithelium with longitudinal rugal folds. Normally, the rugal folds reach the horizontal line of the squamocolumnar junction (SCJ) at the point of

flaring of the esophagus. The SCJ is below the diaphragm because the distal 2 - 4 cm of the esophagus is in the abdomen. When a sliding hiatal hernia is present, the SCJ is above the diaphragm; in these patients, the gastroesophageal junction is defined as the proximal limit of rugal folds. When a patient has BE, the SCJ is displaced cephalad and the GEJ is defined as the point of flaring of the tubular esophagus, which is concordant with the proximal limit of rugal folds (Fig 2).

The distal 5 cm of the esophagus is surrounded by the lower esophageal sphincter (Fig 1), a high pressure zone designed to prevent reflux along the pressure gradient that exists from the stomach (intraluminal pressure + 5 mmHg) to the mid thoracic esophagus (- 5 mmHg).

Fig. 1. Diagram of esophagus showing the presently accepted normal state. The entire esophagus is tubular and lined by squamous epithelium (white). The stomach is lined by columnar epithelium with rugal folds (blue), histologically of cardiac (proximal 30 mm), oxyntic (body) and antral type. The lower esophageal sphincter surrounds the distal 50 mm of the esophagus, including the entire abdominal esophagus. The circles show the biopsies taken in the DeMeester biopsy protocol in the endoscopically normal person. These include biopsies at the squamo-columnar junction (SCJ), biopsies within 10 mm distal to the SCJ, and biopsies in the distal body and antrum.

Fig 2. The present interpretation of the gross pathology and endoscopy in a patient with long segment Barrett esophagus with adenocarcinoma. The esophagus is a tube that flares into the saccular stomach at a point that is concordant with the proximal limit of rugal folds, which defines the gastroesophageal junction. The esophagus is lined proximally by squamous epithelium and distally by Barrett-type columnar epithelium. In such a patient, the DeMeester protocol will take biopsies at 1-2 cm intervals from the Barrett segment in addition to the biopsies taken in a person with normal endoscopy.

The normal histology, as it is presently believed, is that the entire esophagus is lined by squamous epithelium. It is presently believed that the proximal stomach has a variable amount of cardiac mucosa distal to the endoscopic GEJ followed by gastric oxyntic epithelium. Hayward, in 1961 (7), stated without evidence that the proximal 30 mm of the stomach was normally lined by cardiac mucosa. He suggested that this mucus secreting epithelium acted as a buffer zone that prevents squamous epithelial digestion by gastric acid.

The present guidelines for endoscopy and biopsy are based on this understanding of anatomy and histology. If the patient with GERD has no abnormality at endoscopy, biopsies are not recommended because the epithelium distal to the normal SCJ where it meets the proximal limit of rugal folds is gastric. Biopsy is only indicated if there is a visible columnar lined esophagus (CLE) (8); the objective of biopsy is to identify intestinal metaplasia, which defines BE and neoplastic changes. The GERD patient who does not have BE has not been studied histologically because of the failure to take biopsies before BE has developed.

FINDING THE FUNDAMENTAL FLAW IN THE PRESENT UNDERSTANDING

An error that causes a failure of management of a disease is frequently based on one fundamental mistake. Correcting that fatal flaw is the basis of positive change. A recent example of that is the discovery that *Helicobacter pylori* and not acid was the cause of peptic ulcers. Correction of that error has greatly improved the management of peptic ulcer disease and increased our understanding of gastric adenocarcinoma, and gastric lymphoma. The change following the discovery was extremely slow with severe resistance by the medical establishment to the idea for over two decades.

In 1990, Dr. Tom DeMeester took the position of Chairman, Department of Surgery at the University Hospital of the University of Southern California. He brought a team of surgeons and technical staff to establish what became a world-renowned esophageal surgery program. I was assigned to be his pathologist. Most importantly, Dr. DeMeester brought with him an endoscopic biopsy protocol that he used for all patients undergoing endoscopy (Fig 1).

Over the next three decades, I received biopsy specimens according to protocol from over 15000 patients. At the weekly clinicopathologic conferences of the unit, it quickly became apparent that the belief that cardiac mucosa lined 30 mm of the proximal stomach was incorrect. This was initially the

result of two observations: (a) cardiac mucosa was sometimes absent in the two biopsies at and within 10 mm distal to the endoscopic gastroesophageal junction, and (b) when present, the amount of cardiac mucosa was correlated with the severity of GERD.

These observations led to a clinical study that correlated cardiac mucosa to esophageal acid exposure by a 24-hour pH test and evidence of lower esophageal sphincter damage by manometry. These were the most reliable feature of objective criteria for GERD. This resulted in the first abstract in 1994 (9) followed by a larger study in 1997. In that study of 334 patients, Oberg *et al.*, (10) showed that patients who had cardiac mucosa in the biopsies distal to a normal squamocolumnar junction had a significantly higher probability of an abnormal 24-hour pH test and abnormalities in the LES.

The medical establishment resistance to the finding that cardiac mucosa was a GERD-related pathologic finding and not a normal proximal gastric mucosa was intense. The finding was ignored by most, but stimulated numerous important studies over the next two decades. Mainstream belief about cardiac mucosa has evolved towards the concept. At the present, most pathologist still incorrectly believe that a small amount (less than 4 mm) of cardiac mucosa normally lines the proximal stomach. However, there is evidence that the new concept is very close to mainstream acceptance. In a review of Barrett esophagus in the August 2019 issue of *Gastroenterology*, Stuart Spechler's group writes (11): "... *there is considerable indirect evidence to support a hypothesis, proposed by Chandrasoma in 1997, that cardiac mucosa is not normal but an acquired, GERD-induced metaplasia, and that cardiac mucosa is the precursor of intestinal metaplasia in BE.*"

As soon as the fatal flaw that cardiac mucosa is normal in the proximal stomach is corrected, the definition of the GEJ will change and the early changes of GERD in the most distal abdominal esophagus will be recognized. At present, because of the incorrect definition of the GEJ at endoscopy as the proximal limit of

rugosal folds, the critical early changes of GERD are mistaken for normal proximal stomach.

EVIDENCE THAT CARDIAC MUCOSA IS A METAPLASTIC ESOPHAGEAL AND NOT A NORMAL PROXIMAL GASTRIC MUCOSA

1. Cardiac mucosa is not present in the entire circumference of the GEJ in all persons

In a study of autopsies in 18 persons without clinical GERD during life (12), we showed that pure cardiac mucosa was absent in 10/18 (56%). Oxyntocardiac mucosa (= cardiac mucosa with parietal cells in the glands) was present in all persons. However, both cardiac and oxyntocardiac mucosae were absent in some part of the circumference of the SCJ in 9/18 (50%). This proves that cardiac mucosa is absent in some persons in some part of the GEJ. In these persons, the esophageal squamous epithelium transitions directly to gastric oxyntic mucosa (the zero squamo-oxyntic gap (13); Fig 3).

Other studies have disputed the finding that cardiac mucosa can be absent. Kilgore *et al.*, (14), in an autopsy study showed that cardiac mucosa was present in all persons to a length of 1 – 4 mm. Marsman *et al.*, (15), in an endoscopic study, reported that cardiac mucosa was present at the normal squamocolumnar junction in 62% of patients; in the other 38%, the squamous epithelium transitioned to oxyntocardiac mucosa. No patient had a zero squamo-oxyntic gap. It should be understood that a negative finding (i.e. absence of cardiac mucosa) is not proved by these findings. A single photograph (Fig 3) of a zero-oxyntic gap over-rides claims that cardiac mucosa is universal.

2. When present, cardiac mucosa correlates with GERD

The study of Oberg *et al.*, (10) established the relationship of the presence of cardiac mucosa with abnormal reflux and LES abnormalities. Cardiac mucosa between the SCJ and gastric oxyntic mucosa (i.e. in the squamo-oxyntic gap) is therefore a GERD-induced metaplasia of squamous epithelium of

the distal abdominal esophagus (Fig 4). When found, cardiac mucosa always shows chronic inflammation (Fig 4). Carditis is the earliest specific histologic manifestation of GERD (16).

Fig 3. The zero squamo-oxyntic gap in a child with no GERD at autopsy. The esophageal squamous epithelium transitions at the squamocolumnar junction to gastric oxyntic mucosa with straight tubular glands composed of parietal and chief cells. There is no cardiac mucosa.

Fig 4. A 2 mm squamo-oxyntic gap in a resected specimen of a patient with squamous carcinoma of the esophagus. The squamous epithelium has been displaced cephalad (to the left in the picture) by cardiac and oxyntocardiac epithelium that separates it from the proximal limit of gastric oxyntic mucosa. Note the disorganized mucous cell containing glands in cardiac mucosa and the presence of inflammation and reactive changes in the foveolar region ("carditis").

3. The length of cardiac mucosa distal to the endoscopic GEJ correlates with severity of GERD

Glickman *et al.*, (17) showed that the presence of > 1 mm of cardiac mucosa in children was associated with a significantly higher prevalence of reflux esophagitis in the squamous epithelium compared with patients with < 1 mm. Chandrasoma *et al.*, (18) showed a significantly higher acid exposure in patients with > 20 mm of cardiac mucosa compared to patients with < 20 mm. Chandrasoma *et al.*, (19) showed, in esophagectomy specimens, that patients with squamous carcinoma had lengths of cardiac mucosa similar to the non-GERD autopsy population (< 5 mm) whereas patients with GERD-induced adenocarcinoma had lengths of 10 – 20 mm.

4. The pathogenesis of cardiac metaplasia

In an elegant study of asymptomatic volunteers, Robertson *et al.*, (20), from Professor McColl's unit in Glasgow, showed that gastric over-distension caused by heavy meals resulted in a temporary shortening of the LES that caused the squamous epithelium of the distal esophagus to become exposed to gastric contents. With cumulative exposure, the squamous epithelium underwent increasing expression of trefoil family factor 3 (TFF3) that triggered metaplasia into cardiac mucosa (21). Derakhshan *et al.*, (21) also showed that the small amounts of cardiac mucosa found in these asymptomatic volunteers was similar to non-intestinalized columnar epithelium in Barrett esophagus.

Robertson *et al.*, (20) also showed that the length of cardiac mucosa was significantly shorter (median of 1.75 mm) in volunteers without central obesity than in obese persons. The correlation between cardiac mucosal length and central obesity suggest that over-eating is a common etiology for these two entities. Bu *et al.*, (22) showed that there was a dose related relationship between the presence of cardiac mucosa and body mass index.

All this evidence conclusively shows that cardiac mucosa distal to the normal SCJ is

a metaplastic GERD-induced epithelium and not a normal proximal gastric mucosa.

THE DEFINITION OF THE GASTROESOPHAGEAL JUNCTION

When it is accepted that cardiac mucosa *distal* to the endoscopic GEJ (defined as the proximal limit of rugal folds) is a metaplastic esophageal epithelium derived from GERD-induced damage to the squamous epithelium, it must follow that the proximal limit of rugal folds is not the true GEJ. The evidence that the proximal limit of rugal folds is the true GEJ is a single unconvincing and flawed report by McClave *et al.*, in 1987 (23). It must be rejected in the light of presence evidence. The true GEJ is the junction between metaplastic cardiac and oxyntocardiac mucosa with gastric oxyntic epithelium (20). It can be defined only by histology.

The measured length of cardiac mucosa distal to the endoscopic GEJ in a limited number of resected and autopsy specimens is zero to 28 mm (12,24). When more studies are done, the length is likely to be greater. This length of cardiac mucosa is mistaken at endoscopy for proximal stomach because of the erroneous use of the proximal limit of rugal folds to define the GEJ at endoscopy.

In a study of resected specimens, Chandrasoma *et al.*, showed that the length of cardiac and oxyntocardiac mucosa distal to the proximal limit of rugal folds was < 5 mm in two patients with squamous carcinoma and between 10 and 20.5 mm in 8 patients with GERD-induced adenocarcinoma (19). Mapping of esophageal submucosal glands showed that the distal extent of the submucosal glands was concordant with the distal limit of cardiac and oxyntocardiac mucosa (Fig 5). Submucosal glands were never seen under gastric oxyntic mucosa. This finding proves that cardiac and oxyntocardiac mucosa distal to the proximal limit of rugal folds is esophageal.

In that study, the anatomy of the region distal to the endoscopic GEJ that was lined by cardiac and oxyntocardiac mucosa was

dilated and its mucosa was lined by rugal folds. This was termed the dilated distal esophagus (25) and defined as that area distal to the end of the tubal esophagus that is dilated, lined by cardiac and oxyntocardiac mucosa, and containing rugal folds (Fig 5). This exactly mimics the stomach at gross examination and endoscopy; the error is only revealed by the histologic presence of metaplastic cardiac mucosa.

Korn *et al.*, (26) measured the circumference at the anatomic GEJ, which is marked accurately by the peritoneal reflection, at surgery. They showed that the mean circumference in persons without GERD was 6.3, that of GERD patients without Barrett esophagus was 8.9 cm, and that of patients with Barrett esophagus was 13.8 cm. This confirms the increasing dilatation of the distal esophagus with increasing GERD severity.

WHAT CAUSES DILATATION OF THE ESOPHAGUS WHEN CARDIAC METAPLASIA OF SQUAMOUS EPITHELIUM OCCURS?

The abdominal esophagus that is first affected by GERD is normally surrounded by the high pressure zone of the abdominal segment of the LES. This high pressure is necessary to maintain the tubular shape of the abdominal esophagus.

Normal LES tone is likely maintained by a local reflex arc with the afferents likely in the squamous epithelium, the relay in the ganglion cells of the submucosal and myenteric plexus, and the efferents passing to the smooth muscle to maintain tonic contraction. When cardiac metaplasia occurs in the esophagus, the nerve endings in the squamous epithelium are lost, the afferent arc of the local reflex is disrupted, and the LES tone disappears. Without LES tone, the affected abdominal esophagus dilates because of the positive intraluminal pressure and the fact that it distends with every gastric over-distension (Fig 6). It essentially becomes "gastricized", behaving physiologically like the stomach, distending and collapsing in the full and fasting state. This results in the development of rugal folds which are a feature of all reservoir organs.

RESULT OF THIS NEW UNDERSTANDING

The abdominal esophagus surrounded by the abdominal segment of the LES is the critical barrier that prevents reflux of gastric juice from the esophagus. The only recognized measurement that is presently used is the manometric length of the abdominal LES. It is known that LES shortening occurs in GERD. However, without knowledge of its original length, manometric length of the abdominal LES cannot define LES shortening. Lee *et al.*, (27) showed that, in patients with clinical GERD, the length of the abdominal segment of the LES bears an inverse linear relationship to acid exposure by the 24-hour pH test. In that study, the length of the abdominal segment of the LES decreased from 18 mm to 3 mm with increasing reflux (27). Zaninotto *et al.*, (28) showed that an abdominal LES length of < 10 mm is indicative of a defective LES and is associated with an abnormal 24-hour pH test. This criterion for an abnormal LES is of value to identify an LES that needs to be surgically repaired.

Fig 5. Patient in Fig 2 showing the distribution of metaplastic columnar epithelium in the esophagus. The red line is the squamocolumnar junction; the yellow line is the distal extent of intestinal metaplasia. Cardiac and oxyntocardiac epithelia extend 20 mm distal to the proximal limit of rugal folds (black line). The black dots represent mapping of the submucosal glands in the specimen; their distribution is concordant with the extent of cardiac and oxyntocardiac epithelium, proving that the area distal to the proximal limit of rugal folds is esophageal ("the dilated distal esophagus"). The true GEJ is defined histologically as the proximal limit of rugal folds.

Fig 6. Diagram showing why the abdominal esophagus dilates when it loses the protection of the high pressure zone by lower esophageal sphincter damage. The sphincterless abdominal esophagus can no longer resist the dilatatory tendency of the positive intraluminal pressure which is accentuated with every meal.

	STAGE OF GERD	REFLUX 24-hour pH Test	CELLULAR CHANGES
35 mm	Severe GERD	pH < 4 > 4.5%	Presence or Risk of Visible CLE
30 mm			Erosive esophagitis
25 mm			CE in DDE
20 mm	Mild GERD	pH < 4 > 1.1 to 4.5%	Erosive esophagitis
15 mm			NERD
10 mm	Phase of compensated LES damage	pH < 4 > zero to 1.1%	CE limited to DDE
5 mm			CE limited to DDE
0 mm			CE limited to DDE

Fig 7. Diagram showing the correlation between damage to the lower esophageal sphincter and newly understood stages of gastroesophageal reflux disease. The first stage, where LES damage is within its reserve capacity, is not associated with reflux because the LES is competent. As LES damage progressively shortens the abdominal LES from its distal end, there is progression from postprandial reflux to fully established reflux disease with a defective lower esophageal sphincter.

The relationship between metaplastic cardiac mucosa distal to the endoscopic GEJ, and concordant dilatation of the esophagus in the area of the damaged LES enables a simple formula to be developed regarding the abdominal esophagus:

Length of abdominal esophagus

(= length of abdominal segment of the LES)

=

Length of the tubular abdominal esophagus

(= manometric length of the functional abdominal segment of the LES)

+

Length of the dilated distal esophagus/cardiac mucosa distal to endoscopic GEJ

(= length of damaged/shortened abdominal segment of the LES)

A new pathologic test now emerges that measures damage (shortening) of the abdominal segment of the LES, the critical causative factor in determining the absence, presence and severity of GERD. Accurate measurement of the length of cardiac mucosa cannot be made with present biopsy technology. Multi-level biopsies distal to the endoscopic GEJ provide results that may lack precision of measurement (29). A quantitative biopsy device that can remove a 20-25 mm longitudinal piece of mucosa vertically on the lesser curvature distal to the endoscopic GEJ (the SCJ in a patient without Barrett esophagus) needs to be developed.

The available data suggest that a length of dilated distal esophagus < 15 mm represents a competent LES and absence of GERD while a length > 15 mm predicts early

GERD, increasing progressively till the entire abdominal segment of the LES has been destroyed (length 30-35 mm) (Fig 7).

The measurement of abdominal LES damage by histology is possible in the asymptomatic person. If LES damage has a linear progression, this information may allow prediction of GERD and its severity in the person's future, allowing development of new methods to prevent progression of LES damage in selected persons (30).

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