CLINICAL—ALIMENTARY TRACT

Central Obesity in Asymptomatic Volunteers Is Associated With Increased Intrasphincteric Acid Reflux and Lengthening of the Cardiac Mucosa

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See editorial on page 708.

BACKGROUND & AIMS: In the West, a substantial proportion of subjects with adenocarcinoma of the gastric cardia and gastroesophageal junction have no history of reflux. We studied the gastroesophageal junction in asymptomatic volunteers with normal and large waist circumferences (WCs) to determine if central obesity is associated with abnormalities that might predispose individuals to adenocarcinoma. **METHODS:** We performed a study of 24 healthy, *Helicobacter pylori*–negative volunteers with a small WC and 27 with a large WC. Abdominal fat was quantified by magnetic resonance imaging. Jumbo biopsy specimens were taken across the squamocolumnar junction (SCJ). High-resolution pH-metry (12 sensors) and manometry (36 sensors) were performed in upright and supine subjects before and after a meal; the SCJ was visualized fluoroscopically. **RESULTS:** The cardiac mucosa was significantly longer in the large WC group (2.5 vs 1.75 mm; $P = .008$); its length correlated with intra-abdominal ($R = 0.35$; $P = .045$) and total abdominal ($R = 0.37$; $P = .034$) fat. The SCJ was closer to the upper border of the lower esophageal sphincter (LES) in subjects with a large WC (2.77 vs 3.54 cm; $P = .02$). There was no evidence of excessive reflux 5 cm above the LES in either group. Gastric acidity extended more proximally within the LES in the large WC group, compared with the upper border (2.65 vs 4.1 cm; $P = .027$) and peak LES pressure (0.1 cm proximal vs 2.1 cm distal; $P = .007$). The large WC group had shortening of the LES, attributable to loss of the distal component (total LES length, 3 vs 4.5 cm; $P = .043$). **CONCLUSIONS: Central obesity is associated with intrasphincteric extension of gastric acid and cardiac mucosal lengthening. The latter might arise through metaplasia of the most distal esophageal squamous epithelium and this process might predispose individuals to adenocarcinoma.**

Keywords: Cardia Histology; Intrasphincteric Reflux; Overweight; Cancer Risk.

Esophageal adenocarcinoma is a condition of increasing incidence and poor prognosis. It is believed to develop from columnar metaplasia of esophageal squamous epithelium (Barrett's esophagus), resulting from gastroesophageal reflux of acid and possibly bile. Reflux occurs when there is complete loss of lower esophageal sphincter (LES) tone, allowing gastric juice to flow up into the body of the esophagus. This trans-sphincteric reflux occurs most commonly during transient lower esophageal sphincter relaxations (TLESRs).

There is a strong association between esophageal adenocarcinoma and both body mass index (BMI) and waist circumference.[1,2] This may be explained partly by these morphometric characteristics being associated with impaired function of the lower esophageal sphincter.[3–5] In addition, increased visceral fat might promote the carcinogenic pathway by humoral mechanisms.[6]

Several observations make it difficult to attribute the majority of esophageal adenocarcinomas to traditional reflux and Barrett's esophagus. Only 42% of men and 46% of women with esophageal adenocarcinoma have a history of weekly reflux symptoms,[7] and only 22% have a previous diagnosis of gastroesophageal reflux disease.[8] In one study, of those endoscoped more than 6 months before surgery for esophageal adenocarcinoma, only 36% were reported to have evidence of Barrett's esophagus.[9] Furthermore, Barrett's esophagus is apparent in only 31% of patients presenting with esophageal adenocarcinoma.[9]

There is an even greater problem with the etiology of adenocarcinoma of the gastric cardia, which is more prevalent than esophageal adenocarcinoma.[10,11] In the Western world this cancer shares epidemiologic characteristics with esophageal adenocarcinoma.[12–14] However, its association with traditional reflux is particularly weak, with only 29% having a history of reflux symptoms[15] and Barrett's mucosa being detected in only 12% at the time of cancer diagnosis.[9]

Abbreviations used in this paper: BMI, body mass index; GEJ, gastroesophageal junction; GI, gastrointestinal; IGP, intragastric pressure; IQR, interquartile range; LES, lower esophageal sphincter; MRI, magnetic resonance imaging; PIP, pressure inversion point; SCJ, squamocolumnar junction; TLESRs, transient lower esophageal sphincter relaxations; WC, waist circumference.

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An observation that may provide a clue to the etiology of adenocarcinoma of the gastric cardia and gastroesophageal junction (GEJ) in subjects with no reflux history is the frequent finding of pathologic changes at the cardia and GEJ in asymptomatic volunteers. Inflammation of the gastric cardia, sometimes accompanied by intestinal metaplasia, has been reported in a high proportion of asymptomatic subjects.[16,17] Although *Helicobacter pylori* infection can cause inflammation and intestinal metaplasia in the most proximal stomach, these changes also occur in the absence of the infection or evidence of traditional reflux.[16,17] The earlier-described observations suggest that mucosal damage at the gastroesophageal junction might occur by mechanisms other than traditional reflux, with its complete loss of LES tone. We previously suggested that pathology occurring at the gastroesophageal junction might be related to opening of the distal segment of the lower esophageal sphincter, allowing ingress of gastric juice, while the more proximal segment of the sphincter retains tone, preventing trans-sphincteric reflux.[18,19]

Cardiac mucosa is non–acid-secreting columnar mucosa laying between the squamous mucosa of the esophagus and the acid-secreting mucosa of the stomach. The origin and even universal existence of cardiac mucosa has been hotly debated. In neonates, the cardiac mucosa is less than 1 mm in length,[20] but increases in length with age. Previous investigators also have shown lengthening of the cardiac mucosa in association with acid reflux.[21] These observations have led some to suggest that the cardiac mucosa is a pathologic phenomenon arising through a process of metaplasia of the most distal esophageal squamous mucosa akin to the development of Barrett's esophagus.[22] The short length of cardiac mucosa and its circumferential pattern also would fit with it arising from the opening of the most distal segment of the LES rather than by conventional reflux.

The first aim of our current study was to examine the association between central obesity and the length of non–acid-secreting columnar epithelium (cardiac mucosa) laying between esophageal squamous mucosa and acid-secreting gastric mucosa. In addition, our study was designed to determine whether central obesity disrupts the structure and functioning of the distal segment of the lower esophageal sphincter, allowing acid ingress without trans-sphincteric reflux. To avoid confusion related to *H pylori*–induced histologic changes in the proximal stomach we limited our study to subjects without the infection. In addition, because we were interested in subjects without traditional reflux, we also excluded subjects with hiatus hernia.

Materials and Methods

Subjects

Study participants were healthy volunteers recruited by word of mouth and newspaper advertisement. Those who had ever taken proton pump inhibitors or ever attended primary or secondary care with reflux symptoms were excluded. All subjects were screened for *H pylori* by urea breath test and those testing positive or who had a past history of the infection were excluded. Subjects who were found to have hiatus hernia during the study protocol were excluded from the current analysis.

Subjects were recruited to the study to achieve 2 groups defined by small or large waist circumference (WC) and matched with respect to age and sex. Large WC was defined on entry as greater than 102 cm in males and greater than 88 cm in females. Small WC was defined as less than 94 cm in males and less than 80 cm in females. Waist circumference has been validated as a noninvasive assessment of visceral fat mass.[23]

Study Design

Study day 1: clinical and magnetic resonance imaging assessment of fat distribution. Demographic details and waist circumference were recorded and magnetic resonance imaging (MRI) scans of the abdomen were performed using the Philips T1.5 MRI scanner (Philips Healthcare, Surrey, UK) before and 45 minutes after a standardized meal.

Study day 2: upper gastrointestinal endoscopy with biopsy and attachment of a radio-opaque clip. An upper gastrointestinal (GI) endoscopy was performed after a 12-hour fast. Biopsy specimens were taken across the squamocolumnar junction using a large-capacity radial jaw 4 forceps (Boston Scientific, Hemel Hempstead, Herts, UK) with a jaw span of 8 mm. Junctional biopsy specimens were taken perpendicular to the squamocolumnar junction and targeted to include just enough squamous mucosa at the proximal end to confirm positioning. Biopsy specimens were examined during the endoscopy procedure for the presence of glandular and squamous mucosa and intraprocedure feedback was given for biopsy accuracy. Up to 3 junctional biopsy specimens were taken to optimize the chances of capturing the full span of the cardiac mucosa in a single biopsy sample, allowing accurate length measurement. Biopsy specimens also were taken of the body and antrum of the stomach. Finally, the squamocolumnar junction was marked by 2 endoclips placed endoscopically (HX-610-135; Olympus, Southend-on-Sea, UK).

Biopsy specimen processing

Biopsy specimens were placed immediately on dental wax, which has a nonadherent surface, and oriented flat. An isotonic solution of Hyoscine N butyl bromide (1 mg/mL) was applied to minimize sample contraction and preserve the length. Biopsy specimens were transferred to filter paper using a non-touch technique and re-oriented where necessary. Samples were transported in conventional formalin and embedded in agar on the filter paper without further manipulation. Staining was performed with conventional H&E.

Study day 3: combined recording of pH and manometry. After a 12-hour fast, a combined high-resolution manometer catheter and high-resolution pH catheter was passed nasally. Recordings were taken for 15 minutes fasting with subjects seated in an upright position and for a further 15 minutes supine. Subjects then consumed a standardized meal over a 20-minute period and were asked to eat until full. The meal consisted of battered fish and chips with 150 mL of water. After the meal, combined recording of pH and pressure was continued for 45 minutes with patients in an upright position and for 30 minutes supine. In each of the 4 periods of recording (fasting upright, fasting supine, post-prandial upright, and post-prandial supine), fluoroscopic screening was performed for 30 seconds to visualize the endoscopically placed clips.