e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(2); 1283-1296

Original Research Article

Correlation between Barrett's Esophagus and Hiatal Hernia in Chronic GERD patients in rural population of Northern India

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Received: 11-01-2024 / Revised: 03-02-2024 / Accepted: 17-02-2024
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Conflict of interest: Nil

Abstract:

Hiatal Hernia (HH) and Barrett's esophagus (BE) are the two important complications of Chronic Gastroesophageal Reflux Disease (cGERD). The prevalence and the risk factors for HH and BE in the patients with cGERD of rural Northern India were investigated. The relationship between Size of HH and BE with clinical and endoscopic findings were also evaluated.

Materials and Methods: A total of 156, chronic gastroesophageal reflux disease (cGERD) patients (male-96, female-60) previously confirmed by clinical and endoscopic findings, were enrolled in the Department of general surgery, Hind Institute of Medical Sciences, Mau, ataria, Sitapur, UP, India, for upper gastrointestinal endoscopy. Upper endoscopy reports were examined retrospectively from patients with symptoms of cGERD for prevalence of HH and BE and associated factors. On endoscopic suspicion of columnar lined epithelium (CLE), the patients were randomly divided in two groups for either 4-quadrant conventional biopsies at 2 cm interval or Methylene Blue (MB) directed biopsies, were also obtained. The two groups were compared for the detection of Specialized Intestinal Metaplasia (SIM), which was diagnosed if the intestinal goblet cells were present. Size of BE and HH were also measured for correlation.

Results: Out of 156 patients with cGERD, were randomly divided in two groups (Group A= Conventional Endoscopy and Group B= Chromoendoscopy, 78 patients in each group). A total of 88 (56.41%) patients were suspected of CLE on endoscopy (A+B). After taking biopsy samples from the 88 patients, only 84 (53.84%) had specialized intestinal metaplasia on histopathological examination. 41 (46.59%) patients in the conventional group and 43 (48.86%) patients in the chromoendoscopy group (p=0.64) were diagnosed as having BE. It was also observed that 132 (84.61%) cGERD patients were having as Hiatal Hernia. Hiatal hernia size, lower esophageal sphincter pressure, esophageal acid exposure, and number of reflux episodes ≥6 min significantly correlated with BE. Stepwise regression identified hiatal hernia size (p =0.001) and lower esophageal sphincter pressure (p =0.001) as significant predictors of BE. Age and BMI ≥25 were also related to BE and HH.

Conclusions: Prevalence of HH and BE in the rural northern India were 46.32% and 12.5% respectively in cGERD patients and the presence of hiatal hernia was strong risk factor for Barrett's esophagus in old age with ≥25 BMI.

Keywords: cGERD, Hiatal Hernia, Barrett's esophagus.

Introduction

Gastroesophageal reflux disease (GERD) has a multifactorial pathophysiology which affected about 10% to 20% of general population [1]. Barrett's esophagus (BE) and Hiatal Hernia (HH) are the two commonly seen complications of chronic GERD. Different risk factors have been proposed for chronic GERD in eastern and western countries, but the data regarding how these factors contribute to the development of BE complications and its relation with HH are inconsistent[2]. Barrett's esophagus is

recognized as a pre malignant condition that may lead to the development of esophageal adenocarcinoma, a malignancy with an incidence that is increasing faster than any other cancer Worldwide [3].

It is estimated that the prevalence of BE in the general population is 376 per 100,000 and that it is significantly higher in patients with chronic symptoms of GERD particularly in the patients with Hiatal Hernia. The highest prevalence of histologically confirmed BO among patients with gastro-oesophageal reflux symptoms occurred in North American countries (14.0%) and the lowest in the Middle East (3.0%) [figure-1A][2]. The pooled prevalence of histologically confirmed BO was 8.2% (95% CI 6.2% to 10.3%). The lowest prevalence was 0.6%, reported by a study conducted in Turkey,41 and the highest prevalence was 20.7%, reported in a study from the USA,as per the Montreal definition [figure-1B] [2].

Figure-1 A & B: Prevalence of Barrett's oesophagus in GERD patients[2]

→1A↓ **→ 1B↓**

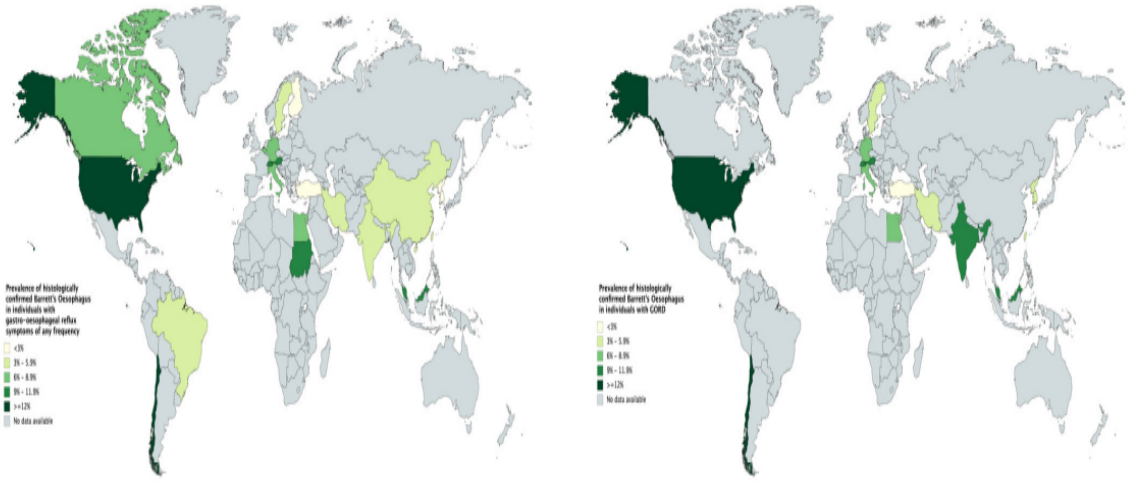
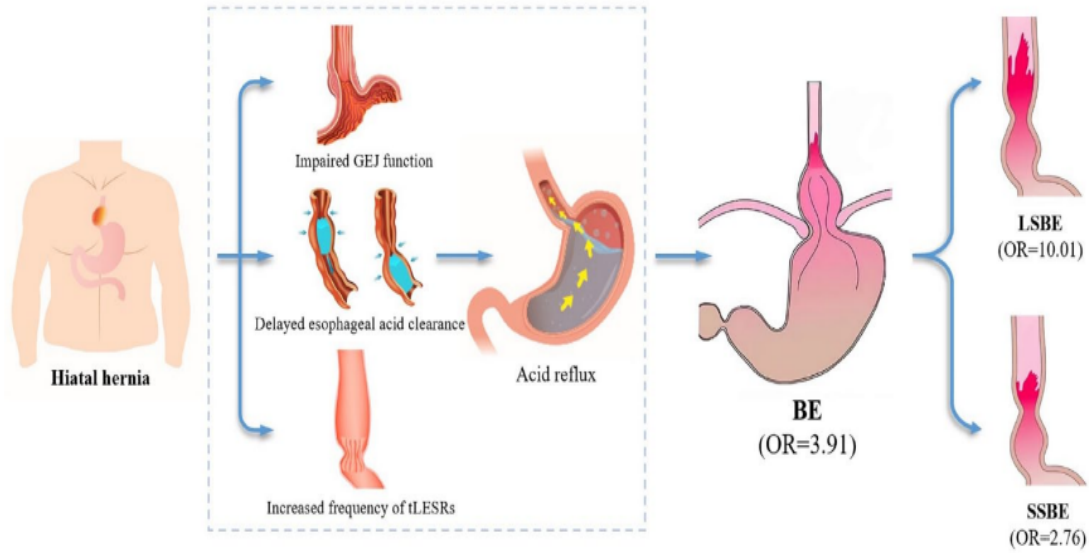


Figure 1A: Prevalence of histologically confirmed Barrett's oesophagus in individuals with gastro oesophageal reflux symptoms of any frequency by individual country.Figure-1B: Prevalence of histologically confirmed Barrett's oesophagus in individuals with GORD by individual country.

Gastro-oesophageal reflux disease (GERD) is characterised by symptoms of heartburn and regurgitation, and by oesophageal complications such as oesophagitis, Barrett's oesophagus, Hiatal Hernia and oesophageal adenocarcinoma [5]. Both HH and Barrett's oesophagus are important because they are thought to indicate an increased risk of oesophageal adenocarcinoma, but, because of the difficulties associated with performing endoscopy in rural population-based studies. A previous study has reported their population prevalence which advocated that in northern Sweden showed that 10.5% of the general population had HH and 1.6% had Barrett's oesophagus [5].

Figure-1C: Graphic description of Hiatal Hernia and Barrett's oesophagus in GERD patient [1].



Barrett's Esophagus:

Barrett esophagus can be defined as the replacement of the squamous epithelium that normally lines the distal esophagus with columnarappearing epithelium on upper endoscopic examination, with histologicfindings of specialized intestinal metaplasia. Traditionally, BE has been defined as columnar-appearing epithelium extending at least 3cm above the gastroesophageal junction. However, it has become clear that shorter segments of columnarappearing epithelium may contain specialized intestinal metaplasia, and thus have malignant potential. No standardized definitions have been established. Generally, longsegment and short-segment BE are defined, respectively, as the presence of a specialized intestinal metaplasia 3 cm or greater, or less than 3 cm—but the latter definition of short-segment BE may be problematic. As there is no gold standard of what defines an endoscopically normal-appearing squamocolumnar junction, distinguishing the intestinal metaplasia of BE from that of the proximal stomach, which is found in 18% of the healthy population[6], can be difficult and lead to unnecessary surveillance. As a result, one must decide whether to sacrifice the sensitivity or the specificity of endoscopic criteria when determining whether longer (≥3 cm) or shorter (≤3cm) segments of columnar-appearing mucosa are used to define BE morphologically. It is estimated that 5% to 15% of patients with GERD will have BE. Patients with long-standing GERD are at greatest risk for developing BE, which is considered the precursor lesion to adenocarcinoma. The presence of BE increases an individual's relative risk of cancer 30 to 120 times compared with persons without BE[7-9]

Pathophysiological factors might play a role in the genesis of BE which is delineated bellow.

The esophagogastric junction:

The EGJ is the barrier against reflux of gastric content into the esophagus. It is mainly composed of the lower esophageal sphincter (LES) and the crural diaphragm. EGJ anatomy and physiology are complex, but warrant careful consideration. The esophagus enters the abdomen through a teardrop-shaped opening, the diaphragmatic hiatus, which is formed by the right diaphragmatic crus originating from lumbar vertebral bodies and forming a loop around the distal esophagus. The esophagus is normally anchored to the diaphragm at the hiatus by the phrenoesophageal membrane, which also closes the potential space between the esophagus and the margins of the hiatus. The phrenoesophageal membrane is formed by fused elements of the peritoneum and the parietal pleura, inserting circumferentially into the esophagus at the level of SCJ. At the distal extreme of the esophagus, the thickened muscularis propria corresponds to the LES. Together, the right diaphragmatic crus, the phrenoesophageal membrane, and the LES form the EGJ. In absence of swallowing, the EGJ is closed and the pH interface between the gastric and esophageal pH environments is precisely localized at the SCJ; a relationship that has been carefully studied by relating to positions of the intraluminal pH transition, a mucosal clip affixed to the SCJ and the intraluminal high-pressure-zone (HPZ) of the EGJ with fluoroscopy (Figure 1) [8]. A corollary of these relationships is that the distal aspect of the EGJ HPZ normally resides distal to the SCJ and that the proximal margin of the HPZ is normally 1-1.5 cm proximal to the SCJ. During swallowing, the LES relaxes and the EGJ opens. Alternatively, transient LES relaxations (tLESRs) can occur in absence of swallowing; they correspond to the physiological mechanism of belching, but also represent a major mechanism of gastroesophageal reflux [9,10]. Major distinctions between swallow induced relaxation and tLESRs are: 1) the crural diaphragm is inhibited

with tLESR, but not swallow-induced LES relaxation, 2) tLESRs persist significantly longer that the roughly 6 seconds of relaxation associated with a swallow, and 3) tLESRs also entail contraction of the longitudinal muscle of the esophageal muscularis propria[11].

Hiatus hernia:

Hiatal hernia is a condition in which elements of the abdominal cavity, most commonly the stomach, herniate through the esophageal hiatus into the mediastinum [12]. The major subcategorization is between sliding hernias, which are most pertinent to reflux pathogenesis and paraesophageal hernias, which involve either inversion of the stomach as it herniates, or involvement of other organs. Sliding hernia is part of a continuum of anatomic disruption of the native EGJ also involving dilatation of the diaphragmatic hiatus and circumferential laxity of the phrenoesophageal ligament. This causes progressive exaggeration of the 'physiologic herniation' that occurs with swallowing as the cardia of the stomach herniates symmetrically upward in conjunction with contraction of the esophageal longitudinal muscle. When fully established, sliding hiatal hernia is characterized by a separation between the LES and the crural diaphragm, which normally work in synergy to augment the anti-reflux barrier [13]. Hence, with hiatus hernia, the mechanistic profile of reflux events extends to mechanisms other than tLESR, specifically strain-induced reflux and even swallow-induced reflux. This is especially true in a recumbent posture. Equally important, hiatus hernia profoundly disrupts the normal process of acid clearance by permitting the 'rereflux' of gastric juice into the distal esophagus during swallow-induced LES relaxation, a circumstance normally prevented by crural diaphragm contraction. Epidemiologically, the incidence of hiatal hernia increases with age and with body mass index (BMI). Kyphosis and scoliosis also favor the occurrence of hernia [14]. Finally, thoraco-abdominal trauma (secondary to road traffic accidents, or falls from height) and complications of surgery (antireflux procedures, esophagomyotomy, or partial gastrectomy) are risk factors for the occurrence of both sliding and paraesophageal hernias [15,16].

Diagnosis of hiatal hernia:

There is no gold standard for diagnosis of a sliding hiatal hernia because it is not inherently a dichotomous condition. Rather, it is a progressive degradation of normal anatomy that becomes increasingly obvious as it progresses. The most accurate diagnosis is achieved during surgery in the region of the EGJ with the caveat that hiatal hernia might be intermittent. Sliding hiatus hernia is diagnosed endoscopically when the apparent separation between the SCJ and the diaphragmatic impression exceeds 2 cm. However, the level of accuracy associated with this was apparent in a recent study performed among Barrett's esophagus experts and community hospital endoscopists that showed absolute agreement in the assessment of hiatal hernia length to be 63% (95% confidence interval (CI) 56-70) compared to 74% (95%CI 68-80) and 68% (95% CI 62-75) for the assessment of circumferential and maximal Barrett's esophagus length respectively according to the Prague Classification [17]. Confounding factors that help explain the discrepancies are that Barrett's mucosa can make it difficult to ascertain the location of the native SCJ and that an extremely patulous hiatus makes it difficult to precisely localize the diaphragmatic pinch. Finally, excess insufflation of the stomach can exaggerate the apparent size of the hernia [18]. Another approach to the endoscopic grading of sliding hernia is to assess the appearance of the EGJ from a retroflexed position and to incorporate an assessment of hiatal integrity along with the assessment of axial displacement. Barium swallow examination identifies the relative position of the EGJ and the diaphragmatic hiatus [19](Figure-2). A muscular ring (the A ring) can be visible during swallowing demarcating the superior margin of the LES. A second ring (the B ring) corresponds to the SCJ; a B ring with an internal aperture <13 mm is called a Schatzki ring. A separation exceeding 2 cm between the A and B ring is required to define a sliding hernia. However, these rings are not always present and not always easy to identify. In their absence, the demonstration of gastric rugal folds traversing the diaphragm is used as the defining criterion for hiatal hernia [19,20]. Finally, separation between LES and crural diaphragm can be evidence using high resolution manometry (HRM). Combining many closely spaced pressure sensors and topographic plotting methods (Clouse plots), HRM facilitates the localization of discrete elements within the EGJ. Hence, distinct EGJ morphologic subtypes have been described using HRM [21]. With type I EGJ morphology, there is complete overlap of the crural diaphragm and LES with no spatial separation evident on the Clouse plot and no double peak on the associated spatial pressure variation plot. With type II EGJ morphology, the LES and CD are separated (double-peaked spatial pressure variation plot), but the nadir pressure between the two peaks does not decline to gastric pressure: the separation between the pressure peaks is 2 cm or less. With type III EGJ morphology, the LES and CD are clearly separated as evidenced by a double-peaked spatial pressure variation plot and the nadir pressure between the peaks equal to or less than gastric pressure. Type III EGJ morphology is further divided into subtypes IIIa and IIIb. With type IIIa the pressure inversion point remains at the CD level, while in type IIIb it is located at the LES level. Type II and type III EGJ

morphology correspond to manometric hiatal hernia. On average, patients with GERD have significantly greater LES-CD separation than controls [22,23]. It is important to note that this separation can fluctuate over time during long-interval manometric recordings and gastro-esophageal reflux episodes preferentially occur in the hernia configuration rather than when in type I morphology [24].

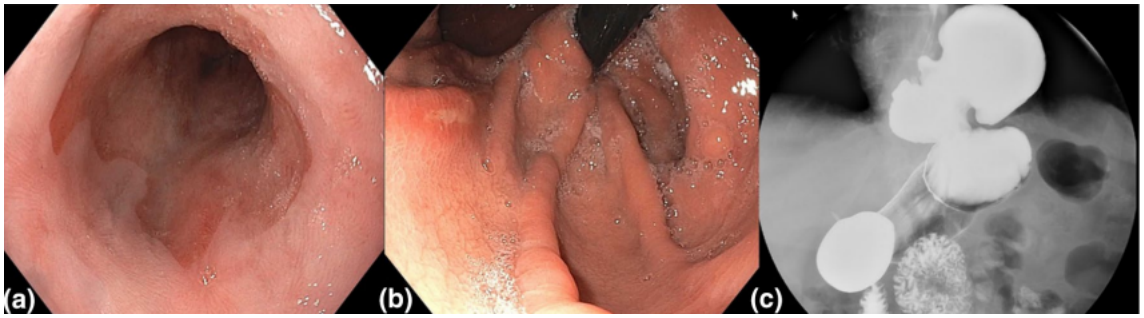


Figure 2: Hiatal hernia & Berrett's of a patients [19].

a. Upper endoscopy demonstrating a 4-cm-long salmon-colored mucosa consistent with Barrett's esophagus classifed C3-M4 per Prague criteria, along with LA grade B esophagitis. b. Endoscopic view in retrofexion within the hiatal hernia sac with the visible site of the paraesophageal gastric protrusion, as well as a Cameron's lesion. c. Contrast esophagram demonstrating a type III paraesophageal hernia with 30% of the stomach above the hiatus.

b. Association with Barrett's esophagus:

Hiatal hernia is commonly encountered in patients with Barrett's esophagus; up to 96% of patients in one estimate [25]. A recent meta-analysis found that hiatal hernia was associated with an increased risk of Barrett's esophagus (odds ratio (OR) 3.94, 95% confidence interval (CI) 3.02-5.13) [26]. This risk was even present after adjusting for BMI and reflux symptoms (OR=2.99, 95%CI 2.24-3.96). Hiatal hernia size was also greater in patients with Barrett's esophagus than in controls (for example mean length 3.95 cm versus 2.81 cm in the study of Cameron [27] , $p<0.005$). Interestingly, a Japanese series found that kyphosis, which is a risk factor for hiatal hernia, might also be independently associated with the occurrence of long-segment Barrett's esophagus [28].Some authors propose that hiatal hernia increases the risk of progression to esophageal adenocarcinoma. A case-control study found that the size of hiatal hernia was associated with the occurrence of high-grade dysplasia (OR 1.20, 95% CI 1.04-1.39 versus patients with Barrett's esophagus, p=0.013) [29]. In another series of 550 patients with Barrett's esophagus, the size of hiatal hernia (≥ 6 cm) was independently associated with progression to high-grade dysplasia or adenocarcinoma (OR = 4.51, 95%CI 1.18-17.15) [30]. However, that association disappeared when patients without dysplasia and with low-grade dysplasia were entered in the model. That finding was confirmed in another series of 713 patients with Barrett's esophagus with no dysplasia or low-grade dysplasia; the size of hiatal hernia was not predictive of progression to high-grade dysplasia or adenocarcinoma (OR 0.9, 95% CI 0.7-1.2, ns) after 4 years of follow-up [31]. Finally, in another case-control study, hiatal hernia was associated with the occurrence of cronic GERD and Barrett's esophagus but not with high-grade dysplasia or esophageal adenocarcinoma [32]. Hence, the role of hiatal hernia in the development of Barrett's esophagus is clear, but its role in the progression to high-grade dysplasia and adenocarcinoma is questionable.

It was documented in a previous study that the GERD symptoms occured at least once a month in 44%, once a week in 20%, and daily in 7% of the adult US population [33].The epidemiological studies of GERD in India are sparse. In a questionnaire-based study, it was reported that the weekly prevalence of GERD symptoms was 7.6% of the Indian population [34]. Other questionnaire-based cross-sectional studies showed prevalence rates of 16.2% to 18.7% for cGERD in the Indian population. These studies emphasize that the prevalence of GERD in India was likely to be between 8% and 19%, which is comparable to the prevalence rates in western countries[8]. Although the prevalence of cronic gastroesophageal reflux is increasing in Asia, the prevalence of HH, BE and esophageal adenocarcinoma (EAC) have so far remained low in most Asian countries[35]. It was also documented that the prevalence of BE in Asia outside Japan was ranges from 0.06% to 6.2%. In Japan, the prevalence of BE was reportedly 19.9% in a series where biopsy was employed and as high as 43% in those series without biopsy [36]. Till date, few studies from India had reported a prevalence rate of BE ranging from 2.6% to 23%.[13-15]. Hiatal Hernia and Barrett's oesophagus can be assessed only by endoscopy. Methylene blue is a vital stain which is used for most of the chromoendoscopic studies in BE . However, the use of this agent, either for the diagnosis of Barrett's metaplasia or for the detection of Barrett's dysplasia and early cancer, remains controversial because of a wide range of

reported diagnostic sensitivities (32%-98%) and specificities (23%-100%) [16, 1737]. Two of 3 randomized, controlled, cross-over trials showed an increased yield in the diagnosis of BE with MB–directed biopsies compared with random biopsies [17].

Esophageal acid exposure is in turn determined by the balance between factors allowing refluxate access to the esophageal mucosa and factors promoting acid clearance. Factors promoting refluxate access into the esophagus include transient or permanent incompetence of the lower esophageal sphincter (LES), hiatal hernia, and possibly delayed gastric emptying .Factors impairing acid clearance include impaired esophageal motility , hiatal hernia , and deficiencies in salivary bicarbonate production (18).

Hence, the putative risk factors for symptoms and complications of cGERD, provide useful information for the screening, prevention and treatment of cGERD and its complications. The aim of the present study was to assess the prevalence of, and risk factors for HH and BE in a representative sample of the population of villages in northern India.

Materials and Methods:

Materials:

Study Site: Hind Institute of Medical Sciences, Mau, Ataria, Sitapur, UP, India.

Study Design: Prospective comparative and analytical study

Study Periods: 18 months, after obtaining IHEC clearance.

Study Groups: two groups, 4-quadrant conventional biopsies at 2 cm interval (Group A) and MethyleneBlue (MB) directed biopsies (GroupB)

Sample Size: 156 (78 in each Group, both sex)

The present study was a single-center, prospective comparative study conducted on patients admitted with cGERD (Based on previous Clinical and Endoscopic findings) in the surgical wards of Hind Institute of Medical Sciences and Hospital, Ataria, Sitapur, UP. from July 2022 to December 2023. A total of 156 cGERD patients admitted in ward were randomely divided into the two groups of 78 patients in each group who underwent 4-quadrant conventional biopsies at 2 cm interval (Group A) and Methylene Blue (MB) directed biopsies (GroupB) as per patients consent. Patients were included in the study based on the inclusion and the exclusion criteria as mentioned below:

Inclusion criteria:

Inclusion criteria for current study were, Confirmed GERD, in the age group of ≥20 to 80 years.(Patients with Grade B or higher according to Los Angeles classification). Complications ≥ 6 months and with ≤ 6 month old endoscopic report of GERD.

Exclusion criteria:

Exclusion criteria for current study were; age extremities ≤20 and ≥80 years, patients who had other significant systemic illnesses including coagulopathy and diagnosed case of upper GI malignancy.Pregnant women. Previous gastric or upper gastrointestinal surgery.

Patients fulfilling inclusion criterion were subjected to endoscopy with an Olympus GIF-Q180 videoendoscope (Olympus Co. Tokyo, Japan) after induction of oropharyngeal anaesthesia with 10% lidocaine spray. The gastroesophageal junction(GEJ) was defined as the ‘‘pinch” at the distal end of the esophagus, coinciding with the most proximal margin of the gastric folds. Endoscopic esophagitis (esophageal mucosal breaks), if present, were graded according to the Los Angeles classification system. The CLE was described as endoscopic findings consistent with BE and HH that awaited histological evaluation. CLE was identified as columnar epithelium above gastroesophageal junction which had a reddish color and a velvety texture which could be distinguished easily from normal pale and glossy esophageal squamous epithelium. The length of CLE was estimated by subtracting the distance from incisors to the squamocolumnar junction (Z-line) from the distance from incisors to the gastroesophageal junction. Patients were classified into short-segment BE (SSBE) if the length of columnar appearing mucosa was less than 3 cm above the gastroesophageal junction and long-segment BE (LSBE) if the length of columnar mucosa was equal to or more than 3 cm.

Endoscopy:

Patients with characteristic symptoms of GERD were subjected to upper endoscopy using the conventional method. The appearance and location of the squamocolumnar junction, location of GEJ, the presence or absence of hiatus hernia, endoscopic esophagitis, BE and the presence or absence of columnar lined esophagus, its length and morphological types were carefully evaluated, identified and the findings were recorded. On endoscopic suspicion of BE either conventional biopsies or MB-directed biopsies were obtained randomly. In the first group ie “Group A” of patients, the biopsy specimens were obtained conventionally in a 4-quadrant fashion at intervals of 2 cm from the circumferential endoscopic Barrett’s epithelium in the distal esophagus. In patients with small islands or irregular tongues of columnar appearing mucosa, at least two specimens were obtained within the abnormal appearing

mucosa at intervals of 1cm from the GEJ to the proximal extent of the abnormality. All biopsy specimens were obtained using standard biopsy forceps and placed in bottles containing 10% of buffered formalin solution.

In the second group, ie "GroupB" chromoendoscopy was done with methylene blue on columnar appearing mucosa with the help of a spray catheter (PW-5L, Olympus America, Inc., Melville, NY) for spraying reagents onto the CLE in the following order. First, the distal esophagus was washed with 10% acetylcysteine (Mucomyst) to dissolve the mucus layer and clear the esophagus of saliva and gastric secretions. The volume sprayed varied according to the length of ESEM (endoscopically suspected esophageal metaplasia), an average of 6 ml for short segment and 12 ml for long segment was used. Next, a 0.5% solution of MB was sprayed on the columnar-lined portion of the distal esophagus until dark blue staining was achieved. The volume of MB solution sufficient to cover the CLE was used (≥ 5-20 ml). After 1 to 2 minutes, the distal esophagus was irrigated vigorously with tap water (30-100 ml) until there was no further loss of staining within the columnar mucosa. Positive staining was defined as blue staining that persisted despite vigorous washing. After MB staining, the mucosal pattern was classified as described in previous study [19]. Diffuse pattern (at least 75% of columnar epithelium stained blue), non-diffuse pattern (less than 75% of columnar epithelium stained blue) and unstained (predominance of pink columnar epithelium). MB directed biopsy specimens were obtained from stained or heterogeneously stained mucosa. From unstained areas, random biopsy samples were taken from CLE and included in the group of patients in whom the biopsy samples were obtained in a conventional way.

Histopathology:

All biopsy specimens obtained either in the conventional way or after MB chromoendoscopy were stained with H&E in combination with alcian blue stain at pH 2.5. The specimens were examined for the presence of SIM, which was diagnosed if intestinal goblet cells were present in the columnar epithelium with blue staining [19]. The biopsy specimens were evaluated by pathologists, who were blinded to the method used to obtain the biopsy specimens (MB-directed or conventional) and the status of MB staining (MB-stained or unstained specimen). The presence of dysplasia was assessed using the standard criteria and classified as no dysplasia, low grade dysplasia, high grade dysplasia, and adenocarcinoma according to the Vienna classification of epithelial neoplasia of the digestive tract [21].

Satistical Analysis:

Statistical analyses were performed using statistical package for Social Sciences (SPSS), version 21.6 (Chicago, IL). Statistics were presented as mean±SD for continuously distributed variables and as frequency (%) for categorical variables. The prevalence of endoscopically suspected BE and that of biopsy-proven BE were calculated as percentage prevalence. Patients with biopsy-proven BE were compared with those in whom biopsy did not show evidence of BE. The two groups were compared using Student's t-test in case of continuously distributed variables and Chi-square and Fisher's exact tests in the case of categorical variables. Next, the predictors of biopsy-proven BE (SIM) were determined using logistic regression analysis with the presence of metaplasia as the dependent variable and a number of clinical and endoscopic variables as independent variables. A two-sided p value of <0.05 was considered as statistically significant. This study was carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association in a tertiary care hospital in North India and approved by the medical ethics committee. Patients older ≥20 years, with troublesome symptoms of cronic GERD in the past 6 months with previous positive (Erosive Oesophagitis) endoscopic reports were recruited from Northern India after obtaining written informed consent.

A hiatal hernia was deemed to be present if either gastric folds or a hernia pouch was present above the diaphragm between swallows. Hiatal hernia size was measured between swallows as the distance between the center of the diaphragmatic hiatus and the superior aspect of the gastric folds.

Results:

A total of 156 patients, 96 males and 60 females with cGERD, of different age groups (20-80 years) were randomly divided in two groups and subsequently examined using two endoscopic methods (Group A= Conventional Endoscopy and Group B= Chromoendoscopy, 78 patients in each group). (Table-1 Demographic distribution of cGERD patients).

Table 1: Characteristics of Chronic GERD patients

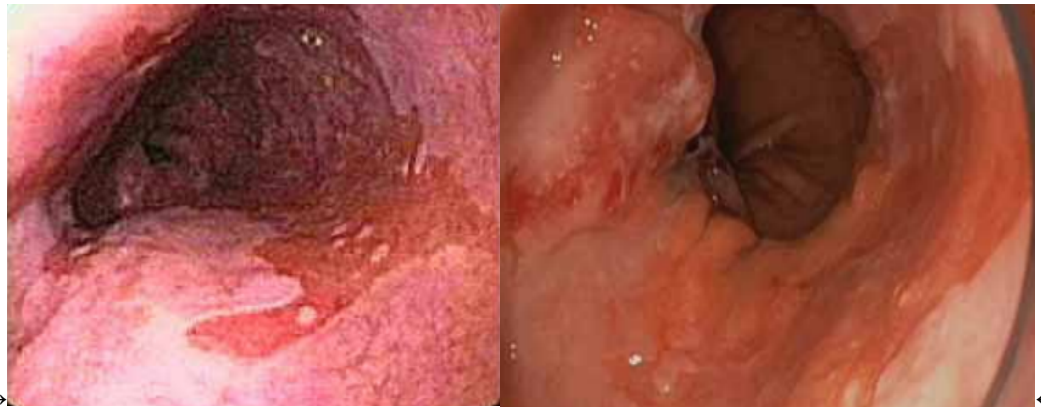
Variables		No of patients (n=156)		Percentage %		P value
Gender	Male	96				0.05
	Female	60				
Age (Years)		Male	Female	Male	Female	0.05
	20-30	2	0	1.28	0.00	
	31-40	5	3	3.20	1.92	

	41-50	27	17	17.30	10.89	
	51-60	18	10	11.53	6.41	
	61-70	32	21	20.15	13.46	
	71-80	12	9	7.69	5.76	
BMI Kg/m2	≤ 20	4	5	2.56	3.20	0.05
	20-24.9	9	8	5.76	5.12	
	25-29.9	64	37	41.02	23.71	
	≥30	19	10	12.17	6.41	
Smoking Status/Tobacco	Never	36	34	23.07	21.49	
	Former	51	20	32.69	12.82	
	Current	9	6	5.76	3.84	
Alcohol	None	36	53	23.07	33.97	0.05
	weekly	18	6	11.53	3.84	
	Daily	42	1	26.92	0.64	
Coffee/Tea	No	21	24	13.46	15.38	0.68
	Yes	75	36	48.07	23.07	
Medicine	No	77	41	49.35	26.28	0.06
	NSAIDs	11	16	7.05	10.25	
	Aspirin	5	2	3.20	1.28	
	Corticosteroids	3	1	1.92	0.64	
Insomnia	Yes	78	48	50.00	30.76	0.05
	No	18	12	11.53	7.69	

A total of 88 (56.41%) patients were suspected of CLE on endoscopy (A+B). After taking biopsy samples from the 88 patients, only 84 (53.84%) had specialized intestinal metaplasia on histopathological examination. 41 (46.59%) patients in the conventional group and 43 (48.86%) patients in the chromoendoscopy group (p=0.64) were diagnosed as having BE. It was also observed that 132 (84.61%) cGERD patients were having as Hiatal Hernia. Hiatal hernia size, lower esophageal sphincter pressure, esophageal acid exposure, and number of reflux episodes ≥6 min significantly correlated with BE. Stepwise regression identified hiatal hernia size (p =0.001) as significant predictors of BE. Age ≥ 60 years in both gender was related to BE and HH, subsequently BMI ≥ 25 in both sex was also related to BE and HH. Out of 84 BE patients, 27.38% was having short segment BE, whereas 72.61% was long segment BE, subsequently, long length ≥3 cm, Hiatal hernia was observed in 72.61% BE patients with LSBE whereas, ≤ 2cm in 4.76% and ≥ 2cm in 22.61% BE patients with SSBE≤ 3cm. It was also found significant (p=0.01). HH was more prevalent in patients with BE than in cGERD.The prevalence of HH was similar in male and female subjects, 46% versus 42% (NS). HH was found in 12.30% (male)and 8.89% (female) of cGERD, aged 41-50 yr, whereas it was 17.54% (male) and 11.32% (female) aged 61-70 years.It was also found significant. [table-2].

Table 2: Prevalence of Hiatal Hernia (HH) in Barrett's esophagus (BE)with size

Variables		No. of Patients (n=156)	Hiatal Hernia		P value
			SL ≥ 2 cm	SL ≤2 cm	0.005
Barrett's esophagus	Short Segment BE≤3cm	23 (27.38%)	19 (22.61%)	4 (4.76%)	
	Long Segment BE≥3cm	61 (72.61%)	61 (72.61%)	0	0.001



3A→ ←3B

Figure-3 A,: Barrett's oesophagus ; 3 B, Hiatal Hernia

Hiatal Hernia and Barrett's esophagus size was shown in Table 3 & figure 3A &3B. Mean HH length was 3.92 cm in BE, 2.93 cm in SSBE, 2.77 cm in HH, and 2.86 cm in cGERD. The length of HH was significantly greater in BE than cGERD (p =0.001) It was also observed that the patients with BE had wider hiatal orifices than did the other cGERD.The mean maximum hiatal width seen at endoscopy was 4.76±1.024 cm in BE. This was significantly wider than in any of the other patient of cGERD, the minimum width being 2.08 ± 1.36 cm in SSHH, 2.93 ± 1.32 cm in SSBE and 2.21 ± 0.26 cm in CGERD. The widened hiatal orifice was usually oval in shape. On quiet inspiration during endoscopy, the hiatal diameter usually decreased by 0–1 cm but did not occlude the lumen around the endoscope shaft. Patients with longer hernias had wider openings in the diaphragm; the correlation coefficient between HH length and hiatal width was r 5 ±0.433 [table-2,3 and figure-3A & 3B].

Table 3: Endoscopic findings on the size of HH and BE

Variables	HH (n, %)	BE (n,%)	BE+HH (n, %)
Long segments in cm	3.92±1.91 (91%)	4.76±0.45 (78%)	5.11±0.86 (82%)
Short segments in cm	2.08 ±1.36 (24%)	2.93±1.32 (22%)	3.00±1.4 (12%)

With respect to clinical symptoms, heartburn and dysphagia and regurgitation were the symptoms correlated significantly with endoscopy-positive cGERD (p = 0.05 and p = 0.005, 0.05 respectively.). There were significant differences in above clinical findings between the BE and HH.There were also significant relationship between each LA classification grade and typical reflux symptoms (p = 0.005) as well. Table-4,5,6 and figure-4 illustrated the distribution of reflux symptoms in patients with and without HH and BE in cGERD.

Table 4: Comparison of reflux symptoms in Chronic GERD patients (n=156)

Symptoms	cGERD n=156,%)	HH (n= 132 , %)	HH+BE (n=88,%)	BE(n= 84,%)	P value
Heartburn (HRB)	68.2	66.7	71.9	67.8	0.005
Regurgitation (RGG)	73.2	74.3	77.1	76.4	0.05
Heartburn+ Regurgitation (HRB+ RGG)	75.9	77.3	79.2	78.9	0.001
Atypical Chest Pain (ACP)	34.7	35.8	36.2	36.00	0.056
Abdominal Pain (AP)	22.9	23.7	24.3	24.9	0.05
Water Brash (WB)	39.8	40.6	44.3	43.8	0.001
Nausea\ Vomiting (NAVO)	15.4	16.7	17.2	16.9	0.69
Anorexia (ANORX)	14.7	15.2	16.3	15.9	0.72
Dysphagia (DYSP)	66.8	79.1	74.9	77.3	0.05
Chronic Cough (CHC)	18.9	19.8	20.7	19.6	0.61
Hoarseness (HORSN)	10.8	11.3	12.8	12.2	0.05
Hiccup (HUP)	0.7	0.8	1	0.9	0.86
Weight loss (WL)	14.7	15.5	17.3	17.01	0.73

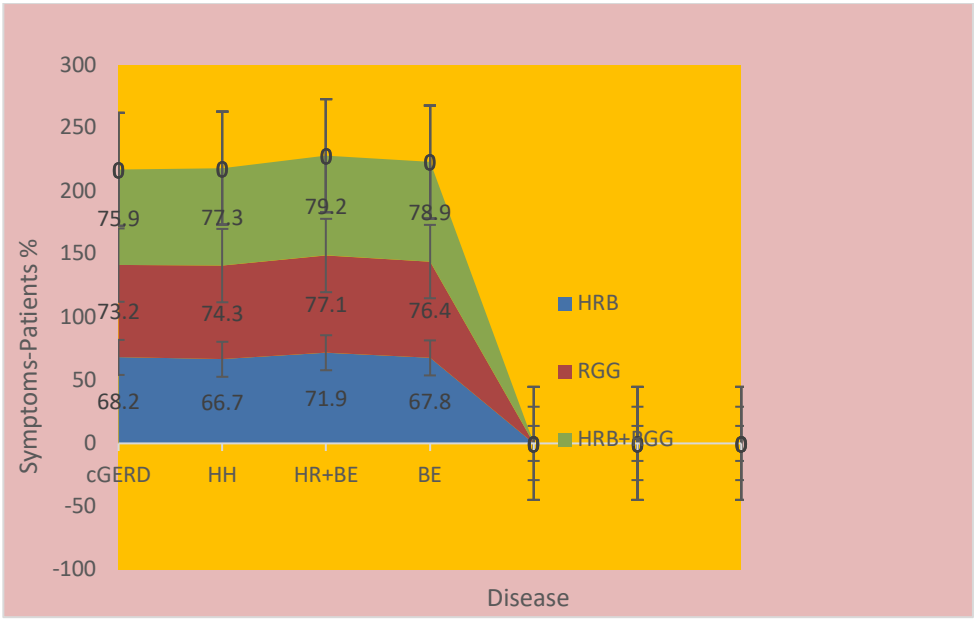


Figure-4:Correlation of Symptoms[Heartburn (HRB),Regurgitation (RGG),Heartburn+ Regurgitation (HRB+ RGG)] with Hiatal Hernia, Berrett's esophagus and chronic GERD.

The most frequent symptoms prompting endoscopy were heartburn in 68.2%, 66.7%, 71.9% and 67.8% in cGERD, HH, HH+BE and BE patients respectively. Regurgitation was observed in 73.2%, 74.3%, 71.1% and 76.4% respectively. Heartburn and Regurgitation were also observed in 75.9%, 77.3%, 79.2& and 78.9% respectively. Dysphagia was also observed in 66.8%, 79.1%, 74.9% and 77.3% respectively and thoracic pain was found in 34.7%, 35.8%, 36.2% and 36% respectively. It was found significant (p=0.005) Comorbidities were infrequent, with 78.2% of patients.

Table 5: Correlation of Dysphagia Characteristics with the patients of LS/SS BE and HH

Variables	Berrett's esophagus (n=84)		Hiatal Hernia (n=132)		BE+HH (n=88)		P value
	SSBE	LSBE	SSHH	LSHH	SSBEHH	LSBEHH	
	Yes (N=63)		Yes (104)		Yes (N=68)		
Dysphagia % Yes	29 (34.52%)	34 (40.47%)	38 (28.78%)	66 (50%)	31 (35.22%)	37 (42.04%)	0.05
Duration in Year (Median)	27	34	32	65	31	37	0.68
Daily frequency %	80	97	83	89	98.9	99.9	0.05
Severity % Very Sever	76	97	74	86	98	99	0.05
Intensity Score (Median)	5	6	4	6	6	7	0.81
Pain During Swallowing %	82	88	75	84	97	98	0.73

Table 6: Correlation of Different symptom Characteristics with the Length (cm) of LS/SS BE and HH

Symptoms with Characteristics		Berrett's esophagus (n=84)		Hiatal Hernia (n=132)		BE+HH (n=88)		P value
		Spearman Correlation		Spearman Correlation		Spearman Correlation		
		SSBE	LSBE	SSHH	LSHH	SSBEHH	LSBEHH	
Heartburn	Duration	0.15	0.19	0.14	0.18	0.20	0.23	0.05
	Frequcecy	-0.11	-0.14	-0.13	-0.04	-0.05	-0.04	
	Severity	-0.15	-0.16	-0.16	-0.17	-0.19	-0.28	
	Intensity Score	-0.11	-0.14	-0.13	-0.15	-0.16	-0.23	
Acid regurgitation	Duration	0.03	0.06	0.05	0.07	0.08	0.09	0.05
	Frequcecy	-0.02	-0.04	-0.03	-0.04	-0.07	-0.09	
	Severity	-0.02	-0.05	-0.03	-0.04	-0.06	-0.08	
	Intensity Score	-0.01	-0.03	-0.04	-0.05	-0.07	-0.09	
Chest Pain	Duration	0.45	0.65	0.59	0.66	0.89	0.92	0.75
	Frequcecy	-0.20	-0.31	-0.29	-0.32	-0.41	-0.49	
	Severity	-0.25	-0.34	-0.32	-0.33	-0.37	-0.52	
	Intensity Score	-0.09	-0.12	-0.11	-0.12	-0.18	-0.21	
Dysphagia	Duration	0.20	0.31	0.27	0.32	0.47	0.59	0.55
	Frequcecy	0.06	0.09	0.06	0.08	0.09	0.10	
	Severity	0.31	0.81	0.76	0.79	0.97	0.98	
	Intensity Score	0.14	0.72	0.69	0.71	0.88	0.93	

Patients with larger HH (≥ 4cm) had more frequent episodes of dysphagia,Heartburn, regurgitation and chest pain were associated with episodes of reflux which worsen existing anti-reflux dysfunction and then further aggravated reflux. The correlation of different symptoms with size/ length of HH/BE were found significant (p=0.05).

Table 7 Endoscopic findings based on Chronic GERD symptoms Reflux

Variables	Reflux Symptoms (R)	Airway Symptoms (A)	Airway and Reflux Symptoms (A + R)	P value
Erosive esophagitis (Reflux)	18.6	19.7	24.8	0.05
Grade 0	11.4	14.8	18.6	0.69
Grade-A-B (Mild)	78.3	88.6	89.6	0.73
Grade-C-D (Severe)	12.3	13.5	13.4	0.56
Barrett's esophagous	44.9	46.7	58.3	0.05
Hiatal Hernia	45.8	53.2	56.9	0.05
Hiatal Hernia + Barrett's esophagus	51.7	67.4	71.9	0.05

The table- 7, illustrated that the R + A group had a significantly higher point prevalence of (24.8 % vs. 18.6 % and 19.7 %; $P < 0.05$) and HH (56.9 % vs. 45.8 % and 53.2 %; $P < 0.05$) compared to the R or A groups, respectively. The R+A group had a significantly higher point prevalence of BE compared to the A or R groups, respectively (18.3 % vs. 14.9 % and 16.7 %, $P < 0.05$). It has also been observed that the The R+A group had a significantly higher point prevalence of BE +HH compared to the A or R groups, respectively (71.9% vs.51.7% and 67.4%). EGD revealed that patients with HH had a higher incidence of esophagitis than patients without hernia.In addition, the degree of mucosal injury increased with the size of the hernia, with 82 percent of the cGERD patients with HH ≥ 4cm presenting BE.

Discussion:

This study showed that most patients with BE (95.45%) have HH. In addition to an increased prevalence of HH, patients with BE had larger hernias and wider openings in the diaphragm than did the other patients. The prevalence of HH in BE was greater in LSBE\SSBE as compared to cGERD. The diagnosis of a ≥ 3-cm segment of BE, and its confirmation on biopsy, seemed straight forward, but the definition of SSBE appeared less satisfactory. SSBE patients were defined by a short (, ≤ 3-cm) length of columnar appearing mucosa, with intestinal metaplasia on biopsy.

A previous reports illustrated that the biopsies are routinely taken from the esophagogastric junction, in the absence of endoscopically evident BE, intestinal metaplasia is found in about 20% of patients undergoing endoscopy [24,25], suggested that the distinction between SSBE, and a normal variation of the z-line with intestinal metaplasia of the cardia, was frequently impossible to define. It was found difficult to recognize HH when the length was ≤ 2 cm [26], so a 2-cm minimum length was used for this diagnosis. Measurements were made at the end of the endoscopic examination, after the endoscope had been pushed into the distal stomach and duodenum and then withdrawn and with the stomach fully inflated with air. This reduced a few small hernias, and the measurements given were for non reducing hernias. The method of measuring hiatal width was probably accurate within 1 cm. The true width of the hiatal opening in the diaphragm was greater than the width recorded in this study, because the thickness of the stomach wall was not taken into account. The prevalence of HH in BE in the present report was consistent with older studies in which HH was found in a combined total of 94% of 170 BE patients [6–10,39]. The increased prevalence of HH in patients with reflux esophagitis previously reported (40-41) was also confirmed in the present study, HH being found in 84.61% of patients with cGERD. The prevalence of HH in SSBE was the same as in other cGERD without BE.

A recent reports was advocated that the gastroesophageal reflux was more strongly associated with HH than with low LES pressure {22, 27, 37]. The mechanisms by which HH can cause reflux have been described [38]. Esophageal acid clearance was impaired in the presence of HH [29]. Gastric content trapped in the hernia may reflux when the LES relaxes [21, 22]. The zone of elevated pressure at the esophagogastric junction was the result of both the intrinsic LES smooth muscle tone and the squeeze from the striated muscle of the crural diaphragm [23]. In patients with HH observed in the present study, the widened hiatal opening had no squeeze effect during quiet respiration. It was unlikely that reflux esophagitis causes esophageal shortening and HH to develop, although this had been proposed [23]. In an endoscopic study of 109 patients with large HH, only 14% had esophagitis and 6% had BE [30]. It was also suggested that, in many patients with large HH, there were endoscopy kinking and tortuosity of the lower esophagus; this suggested the esophagogastric junction has been pushed rather than pulled upward. The evidence indicates that HH was not a result of reflux [30,31]. Twenty-four-hour esophageal monitoring has shown that patients with reflux esophagitis have greater esophageal exposure to acid [2, 4] and bile [4] than do controls. Patients with BE, however, have even greater exposure to acid [2, 4] and bile [4] than do patients with reflux esophagitis. LES pressure may be similar in patients with esophagitis and BE [3] or lower in patients with BE [2].

A previous study observed that patients with gastroesophageal reflux disease and large HH (by x-ray) had lower LES pressure, greater acid exposure, and more severe esophagitis than did those with small or no HH [40]. The prevalence of BE is variable, depending on the population and the definition used.[2,20]. In 2008, Fan and Snyder conducted a retrospective study in the United States evaluating the medical records and endoscopic reports of 4,500 patients. They reported a prevalence of BE of 4.4% and 1.5%, in those with and without gastroesophageal reflux symptoms, respectively[12]. In Mexico, the prevalence of BE is not clear. The data reported more than a decade ago vary widely, with a prevalence of 0.26 to 9.2%. [13,14] A study which considered BE as the presence of intestinal metaplasia with goblet cells, they did not specify what type of biopsy protocol was used [15]. A study has established only the presence of metaplasia as a condition for the diagnosis of BE, contrary to the American guidelines, in which the presence of intestinal metaplasia with goblet cells is required to make the diagnosis [16,2].

Symptoms of gastroesophageal reflux have been identified as the main risk factor associated with BE (OR: 12, 95% CI: 7.64-18.7),[21] with a high prevalence in the Mexican population (19.6-40%), compared with reports in the United States (18.1-27.8%) and Europe (8.8-25.9%). [22] In our study, 71.9% of the patients presented with gastroesophageal reflux symptoms, which was also the main risk factor associated with BE (OR: 20.09, 95% CI: 2.44-165.18). The prevalence of BE in patients with gastroesophageal reflux symptoms in our study was 58.3%. as this study evaluated only cGERD patients. In connection with cGERD, it has been observed that patients with short segment BE was also presented with gastroesophageal reflux symptoms. Likewise, up to 40% of patients with EAC do not report a previous history of GERD [23].

A study using esophageal impedance demonstrated an increase in acid and non-acid reflux episodes in patients with short-segment and long-segment BE, compared with healthy individuals [24]. In our study, 71.9% (A+R) of the patients with short and long-segment BE +HH had reflux symptoms. However, a meta-analysis assessing 26 studies showed a significant symptomatic association with BE in those patients with long-segment BE (OR: 4.92, 95% CI: 2.01-12.0, p = 0.30), but not in those with short-segment BE (OR: 1.15, 95% CI: 0.763-1.73, p = 0.84)[25]. In this regard, acid exposure in the most distal part of the esophagus was a theory proposed to explain the development of short-segment BE, a phenomenon demonstrated in healthy individuals with no endoscopic evidence of esophagitis or hiatal hernia[26].

Current clinical guidelines recommend screening patients with chronic GERD and additional risk factors, such as obesity, smoking, age > 50 years, male sex, etc.[2]. Over the past decades, a screening and surveillance plan has been implemented in patients with GERD in search of BE, with the main purpose of preventing death by EAC, through early-stage detection of neoplasia [41]. However, the quality of available evidence on the effectiveness of this strategy was not conclusive[44,45].On the other hand, the increase in the incidence of EAC in the last decades [33], subsequently the low incidence of EAC in patients with BE without dysplasia reported in recent studies,[42] as well as the low frequency of BE (<10%) in patients with EAC,[30,43] raised doubts as to the cost-effectiveness of current screening and surveillance strategies.

The present study observed only 12 patients with dysplasia (high grade) originating in BE (13.63%), which was lower than the previously reported prevalence of dysplasia/cancer in BE in Mexico (15.1-19.3%).[13,15] A previous study also reported that 81 out of 420 patients with BE presented with some degree of dysplasia or cancer (11.4% with low-grade dysplasia, 4.8% with high-grade dysplasia, and 3.1% with esophageal cancer). This information plus the knowledge of BE epidemiology at our center could help to develop costeffective strategies for the identification and surveillance of patients with BE.

Conclusion

Hiatal hernia, hypotensive EJG and peristaltic dysfunction are involved in the pathophysiology of GERD as well as in the pathophysiology of Barrett's esophagus; hiatal hernia might even be independently associated with the development of Barrett's mucosa. However, it did not seem that hiatal hernia might be a risk factor for progression to highgrade dysplasia and adenocarcinoma. Based on the results, the following was proposed. Patients with BE have more and larger HHs than patients with uncomplicated reflux disease. As a result of their HH, probably combined with other factors including a low LES pressure, they have more severe reflux. Thus, they were more liable to damage to the normal squamous lining of the esophagus and its subsequent replacement by specialized columnar (Barrett's) epithelium. HH was likely one etiological factor in the development of BE. BE was the principal risk factor for the development of esophageal adenocarcinoma. However, from a clinical perspective, discussion of malignant risk or endoscopic surveillance in patients with HH was not advised, Because HH was so common in the general population, the risk of an individual with HH developing adenocarcinoma might be very low. This study supported a close relationship between hiatal hernia and an increased risk of BE. Additionally, hiatal hernia was correlated more strongly with LSBE compared with SSBE. More large-scale

prospective cohort studies are required to confirm our findings in future.

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