

BARRETT'S ESOPHAGUS AND ASSOCIATED RISK FACTORS AMONG PATIENTS IN NORTH OF IRAQ

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ABSTRACT

Background: Gastroesophageal reflux disease is a common condition affecting the upper gastrointestinal tract and results in substantial health loss. Its burden is increasing due to global population aging and growth. Barrett's esophagus is an important complication of this disease and is the precursor of esophageal adenocarcinoma which remains a malignancy with poor prognosis.

Objective: To determine the prevalence of Barrett's esophagus and its risk factors in Duhok, Iraq.

Patients and methods: This prospective study extended from February 2016 to August 2024 in 3 health facilities in Duhok-Iraq. It included 10000 patients referred to diagnostic endoscopy for any indication. The endoscopy was done using high definition gastroscopes and when Barrett's esophagus was suspected on endoscopy, biopsies were taken using Seattle protocol.

Results: The age range was 18-92 years (mean=44.3 years). The prevalence of BE was 0.5% on histopathology and 1.4% on endoscopy. Risk factors associated with BE were erosive reflux disease (OR= 23.7, P-value <0.0001), hiatus hernia (OR= 10.9, P-value <0.0001), smoking (OR= 2.8, P-value 0.0001), male sex (OR= 2.5, P-value 0.001), obesity (OR= 1.9, P-value 0.02) and age more than 50 years (OR= 1.8, P-value 0.03). Alcohol intake was not associated with BE (P-value 0.07).

Conclusion: The prevalence of BE in our area is lower than the rates reported in the literature. The risk factors for BE are erosive reflux disease, hiatus hernia, smoking, male sex, obesity and age more than 50 years. Alcohol intake was not associated with BE.

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Keywords: Barrett's esophagus, reflux disease, upped endoscopy, Duhok.

Gastroesophageal Reflux Disease (GERD) is a chronic upper gastrointestinal condition characterized by troublesome symptoms and / or complications resulting from the retrograde refluxate of gastric contents to the esophagus which results from variable pathophysiologic derangements in the mechanisms controlling the lower esophageal sphincter^[1].

GERD affects all age groups and can have an adverse impact on health-related life quality and job productivity^[2]. It is a common disease with an estimated prevalence of 10–20% in the Western populations and its prevalence is increasing

in Asian countries^[3]. In the USA, GERD symptoms are reported once monthly by 44%, once weekly by 20% and once daily by 7% of the adult population^[2].

When GERD is left untreated, it can lead to complications like stricture, Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC)^[4]. BE, first described in 1950, was classically defined as a replacement of distal esophageal squamous mucosa by columnar epithelium^[5]. This definition has been modified over time and currently the American College of Gastroenterology and American and European Societies for Gastrointestinal Endoscopy warrants the

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existence of intestinal metaplasia (i.e. contains goblet cells) with a minimum length of 1 cm in the distal esophagus while the American Gastroenterological Association accepts any extent of intestinal metaplasia but the British Gastrointestinal Society still uses the classic definition of any columnar mucosa with a minimum length of 1 cm lining the distal esophagus^[6]. The attention drawn to BE is attributed to the fact that it is a premalignant condition for esophageal adenocarcinoma which has two noticeable features; first is its raising annual average incidence ranging from 3.5% in Scotland to 8.1% in Hawaii and second is its poor prognosis (at best 5-year survival is 15–20%)^[7,8]. The risk of esophageal adenocarcinoma in BE patients is 30–125 folds greater than the risk in general population^[9].

Generally, Barrett's esophagus is suspected on endoscopy (by identifying the salmon-color of the mucosa above the GE junction by more than 1 cm) and is confirmed on histopathology (by finding the intestinal metaplasia with goblet cells on biopsy from the suspected mucosa)^[10]. The prevalence of BE has been variable which is attributed to differences in study population, definition used for BE and time period of the study^[11]. Some studies estimated the prevalence of BE in those with GERD to be 15% while the prevalence of BE in general population is estimated to be 1-2%^[6].

In Iraq, the data about BE are scarce. Owing to the increasing prevalence of esophageal adenocarcinoma especially in Asian countries which are adopting the western lifestyles more and the fact that BE is a preventable risk factor for esophageal adenocarcinoma^[11], it is important to have an insight to the prevalence of this premalignant condition which could guide the health providers about the necessity of any screening strategy. The aim of this study was to determine the prevalence of BE in 10000 patients undergoing endoscopy for any indication and the risk factors for BE in this study population.

PATIENTS AND METHODS:

This prospective study extended from February 2016 to August 2024 and was conducted in the endoscopy units of Azadi teaching hospital, Vin hospital and Jeen clinics in Duhok city which is located in Kurdistan region-Iraq. The study design was approved by the scientific committee of the college of medicine in Duhok University and the informed consent was taken from all patients.

A total of 10000 patients were included in the study. Adult patients aging more than 18 years referred to diagnostic endoscopy for any indication were included. Data were collected by special questionnaire which included age, sex, smoking status, alcohol use, body mass index, indication of endoscopy and the final diagnosis on endoscopy.

The majority of endoscopies (8992, 89.9%) were done under conscious sedation using fentanyl, midazolam and in some cases propofol infusion. The endoscopes used were Pentax EPK-i5000 with EG-2990i and Olympus EXERA III with GIF-HQ190, both of which are high-definition scopes with electronic chromoendoscopy characteristics. During endoscopy, all the measurements were made during withdrawal after gastric deflation and the same technique was used for all procedures. The GE junction was identified using upper border of the gastric folds. The Z-line was identified as the line where the salmon-colored columnar gastric mucosa changes to the pale-colored squamous esophageal mucosa. BE was suspected endoscopically when the Z-line extends above the GE junction by more than 1cm^[12]. The Prague classification was used to determine the extent of BE^[13] and the ESGE guidelines were used for BE inspection time^[14]. The size of hiatus hernia was documented by measuring the distance between the GE junction and the diaphragmatic pinch. When erosive reflux disease was found, the Los Angeles classification was used. When the BE was suspected endoscopically,

biopsies were taken from distal esophagus using Seattle protocol and were processed and examined for presence of intestinal metaplasia containing goblet cells. Dysplasia, when present, was classified into low grade and high grade dysplasia. The diagnosis of BE was finalized based on both endoscopic verification and histological confirmation^[12].

The statistical analysis of data was performed using Statistical Package for the Social Sciences (SPSS) program version 29.0 for windows to calculate the P-value using χ^2 test (or Fisher's exact test if an expected number in any of the cells was less than 5) for categorial variables and t-test for continuous variables. A P-value less than 0.05 was used to define any associations or differences to be significant.

RESULTS

of the total 10000 patients who underwent endoscopy, 5629 (56.3%) were females and 4371 (43.7%) were males with female: male ratio being 1.3:1. The age range was 18-92 years with a mean of 44.3 years (95% confidence interval (CI) = 43.9-44.6 years). The most common indication for endoscopy was dyspepsia (N=5579, 55.8%) followed by heartburn and/or regurgitation (N=2101, 21%) then GI bleeding (N=976, 9.8%). The most common diagnosis on endoscopy was gastritis (N=3029, 30.3%) followed by GERD (N=1903, 19%) then gastric or duodenal erosions (N=908, 9.1%) as shown in table-1.

Table-1: Indications for endoscopy and endoscopic diagnosis (N=10000)

Parameter	Number	Percentage
<i>Indications for endoscopy</i>		
Dyspepsia	5579	55.8%
Heartburn and/or regurgitation	2101	21 %
GI bleeding	976	9.8%
Dysphagia	549	5.5%
Persistent vomiting	513	5.1%
Weight loss	148	1.5%
Others	134	1.3%
<i>Endoscopic diagnosis</i>		
Gastritis	3029	30.3%
GERD	1903	19%
Gastric or duodenal erosions	908	9.1%
Duodenal and / or gastric ulcers	809	8.1%
Varices and /or PHG	497	5%
Benign upper GI strictures or achalasia	203	2%
Malignancies	104	1%
Normal	709	7.1%
Multiple findings	1838	18.4%

In GERD patients, the disease was non-erosive in 61 % (N=1161), LA grade A in 22% (N=419), LA grade B in 8% (N=152), LA grade C in 6% (N=114), LA grade D in 3% (N=57). Hiatus hernia was identified in 11.6% (1162) of the patients.

In the total sample population, the prevalence of BE on endoscopy was 1.4% (N=142) and on histopathology was 0.5% (N=48). In patients with GERD, the prevalence of BE on endoscopy was 7.5% and on histopathology was 2.5%. Among

patients with BE confirmed with histopathology, the prevalence of no dysplasia was 85.4% (N=41), low-grade dysplasia was 8.3% (N=4) and high-grade dysplasia was 6.3% (N=3). A total of 26 esophageal adenocarcinomas were diagnosed in this study and BE was present in 5 patients of these (19%). The length of BE was short (<3 cm) in 38 patients (79%) and long segment in 10 patients (21%) with a mean BE length of 2.4 cm (SD=1.7).

The risk factors for BE were investigated during this study and are shown in table-2. The mean age of patients with BE was 51.7 years (SD=12 years) which was statistically significantly different from those without BE (mean =44.2 years, SD=17.2 years)

with a P-value <0.0001. Also the mean BMI was significantly different (P-value <0.0001) among patients with BE (30.1 Kg/m², SD = 2.3 Kg/m²) from patients without BE (27.8 Kg/m², SD=4 Kg/m²).

Table-2: Risk factors for BE (N = 10000)

Parameter	Patients with BE (N=48)	Patients without BE (N=9952)	Odds Ratio	P-value
Age >50 years	24	3542	1.8	0.03
Male sex	32	4339	2.5	0.001
Smoking	20	1989	2.8	0.0001
Alcohol intake	3	230	2.8	0.07
Obesity (BMI >30 Kg/m ²)	21	2893	1.9	0.02
Hiatus hernia	28	1134	10.9	<0.0001
Erosive reflux disease	31	711	23.7	<0.0001

Among the risk factors associated with BE, the presence of erosive reflux disease had the strongest association (OR= 23.7, P-value <0.0001) followed by presence of hiatus hernia (OR= 10.9, P-value <0.0001), smoking (OR= 2.8, P-value 0.0001), male sex (OR= 2.5, P-value 0.001), obesity (OR= 1.9, P-value 0.02) and age more than 50 years (OR= 1.8, P-value 0.03). Alcohol intake was not associated with BE (P-value 0.07).

DISCUSSION:

GERD is a common disease having a worldwide prevalence of 13.3% and can have a wide range of presentations including esophageal and extra-esophageal symptoms^[15]. Although the natural history of GERD is poorly understood and disease progression is usually limited, the complications of GERD can cause considerable morbidity and mortality^[16]. BE is a premalignant condition that is asymptomatic and is important only because it is currently a major risk factor for esophageal adenocarcinoma which remains a deadly cancer despite all advances in oncology^[17]. The poor prognosis of this malignancy has strengthened the efforts to detect and treat BE hoping that this strategy will reduce the burden of esophageal adenocarcinoma^[18].

BE has not been investigated in our area adequately and studies about it are scarce. This has been an encouragement to conduct this study to determine the prevalence of BE in a large cohort of patients undergoing endoscopy for various indications. Most of our endoscopies were done under sedation which provided the endoscopist with adequate time to inspect the GE junction adequately as the minimum time for BE examination is 1 minute inspection time for each 1 cm of BE length according to the ESGE guidelines^[14]. This study included patients referred for endoscopy with any indication. The most common indication was dyspepsia and the most common endoscopic finding was gastritis. These findings are generally reported by other studies^[10,19].

The prevalence of BE in this study was 0.5%. This is generally lower than that reported in the literature. In a recent systemic review, the pooled prevalence of BE was 0.96% in the general population^[6]. The prevalence of BE has been subjected to variability from many factors but the lower prevalence of BE in our study could be explained by three means. First, there is a significant (P=0.002) decline in the prevalence of BE during the period from 1998–2003 (24.3%) to 2013–2015 (13.5%). This is thought to be due to the increasing use of proton pump inhibitors & aspirin &

the decline in the smoking noted over the same period^[12]. Second, the general prevalence of BE in Asian countries has been reported to be lower than that of Western population probably due to lower frequency of GERD attributed to the smaller parietal cell mass & the lower fatty diet^[3]. Third, the diagnosis of BE has been more homogenous in recent studies after the definition of BE has been more unified by most GI societies and the establishment of Prague classification^[6].

The prevalence of suspected BE on endoscopy was 1.4%. This is also lower than the reported pooled rate of 7.8% in a meta-analysis of endoscopic BE prevalence in Asian countries^[11]. Despite the use of high-definition endoscopes in this study, depending on endoscopic characteristics can be inaccurate as endoscopy alone cannot determine the exact type of epithelium covering the lower esophagus and histopathology is more accurate in this regard^[10]. Fortunately, most of the BE cases had no dysplasia and were short segment BE. These findings are consistent with figures reported elsewhere^[3,11].

The risk factors for BE also have been a subject of controversy and many risk factors have been proposed which are mostly the risk factors for esophageal adenocarcinoma also^[17]. In this study, the strongest risk factor was the presence of erosive reflux disease. The prevalence of BE in patients with GERD features was 2.5% which is higher than that in general population and this has been observed in other studies^[10,11,20]. Many studies revealed that GERD patients are 6-8 times riskier to develop BE. This risk increases with symptom severity and duration although GERD symptom severity has poor correlation with BE risk^[9]. Studies have shown that patients with BE have longer acid exposure episodes, lower pH values, weaker peristaltic contractions and diminished lower esophageal sphincter tone compared to those without BE^[9]. Hiatus hernia is another important risk factor for

BE which has been found in another study^[10] and a recent meta-analysis which concluded that hiatus hernia increased the risk of BE by 3.9 folds^[21]. The effect of hiatus hernia may be attributed to anatomical factor as it decreases the diaphragmatic crus effect in augmenting the lower esophageal sphincter^[22].

Smoking is one of the modifiable risk factors associated with BE which has been shown in the majority of studies although some studies have found no association. The risk appears to be more in smokers with erosive reflux disease which may imply a possible synergism between GERD and smoking in BE pathogenesis^[9,17]. The mechanism of BE in smokers is unclear but it can be due to methylation of DNA in the esophagus^[23]. BE has been 2-3 times more prevalent in males, tends to develop 20 years earlier in males than in females and the rate of neoplastic progression is more in males^[24,25]. This sex difference is thought to be due to female hormones which have anti-inflammatory actions reducing erosive esophagitis and thereby intestinal metaplasia. Also estrogen upregulates esophageal occludin expression which is a tight junction protein that enhances the esophageal barrier function to acid injury^[26].

Obesity has been associated with BE in this study. A recent systemic review showed that obesity is associated with neoplastic progression in BE and this has a dose-response relationship^[27]. The exact mechanism is not clear but it could operate through GERD and also it is thought that the increased adipose tissue may release leptin and inflammatory cytokines (TNF- α , IFN- β , IL-1 and IL-6) which with adiponectin deficiency and insulin resistance can cause chronic inflammation that will potentiate the inflammatory process in esophageal epithelium^[22,27]. Age more than 50 years was associated with BE. This has been observed in other studies as well^[23]. On average, BE is diagnosed at the age of 60-70 years, but the age is usually

variable as many patients are asymptomatic and are diagnosed incidentally on endoscopy^[9]. Studies have shown that the yield of BE increases proportionally to age reaching a peak in the sixth decade and maintaining a plateau thereafter^[23].

In this study alcohol was not associated with BE. Whether this is due to the low prevalence of alcohol intake in this study or reflects a real fact may need further study. Alcohol intake association with BE has been variable. It was thought initially to be a minor risk factor for BE but more studies have shown that the association between BE and wine intake is inverse. Currently the bulk of evidence suggests no association and more study is warranted^[9].

Converting the results of this study into practical recommendations for screening will need some considerations. The 0.5% prevalence of BE in this study means that we must do 200 endoscopies to detect 1 case of BE and among the detected cases, most of them would have no dysplasia. In addition, in this study, only 26 cases of esophageal adenocarcinoma were diagnosed, of which only 5 cases (19%) had BE on endoscopy. But the association of BE with age more than 50 years might give us a clue to incorporate BE screening into programs of colorectal screening (as the age is similar) by doing screening upper endoscopy at the time of colonoscopy for patients with chronic GERD features who have at least one other risk factor for BE.

Limitations of this study include lack of data about the protective factors for BE like *H. pylori*. Data about medication use and family history of BE or esophageal cancer were not included in this study. The details of smoking and alcohol use were also not measured in this study including the type, amount and duration of use. Future studies could include these factors in consideration. In conclusion, the prevalence of BE in our area is lower than the rates reported in the literature. The risk factors for BE are erosive reflux disease, hiatus hernia, smoking, male sex, obesity and age more

than 50 years. Alcohol intake was not associated with BE.

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Author contributions: The author collected the data, did the endoscopies and write down the article and made the statistics. Informed consent was taken from all the patients.

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پوخته

نهخۆشی مریی باریت و هۆکارین گرنج یین په یوه ندیبار له نیوان نهخۆشان ل باکورئ عیراق

پیشهکی: نهخۆشی گهرانهوهی مادهی شهیری میده بو میری (GERD) نهخۆشیهکی زور بلاوه و دژه تهنروستی تاییهته به بهر هوبیشچوونی بهشیکه سهرهوهی گوازمهکانی ههس. بهردهوامی ئەم نهخۆشییه له جیهان دا بهرز دهییت بههوی گهورههوه و پیربوونی دانیشتون. سورینچکی باریت یهکیکه له عواقبه گرنهکانی ئەم نهخۆشییه، وه پیشهکییه بو شیرپهجهی گرنکی میری (adenocarcinoma) که هیشتا شیوهیهکی نهخۆشی خراب و به دنیایی کهمه.

نامانج: ناساندنی ریزهی بلاوههوه و هۆکاره خهتهرهکانی سورینچکی باریت له ناوچهی دهۆک – عیراق.

نهخۆشان و شیواز: ئەم توێژینهوهی پیشچووهیه له مانگی شوبات 2016 دا دهستپێ کردوه و تا ته باخ 2024 بهردهوام بوو، له سێ ناوهندی تهنروستی ناوچهی دهۆک. 10,000 نهخۆش له توێژینهوهکدا بهشداریان کردوه، ئەوانهی بو هه هۆکاریهک بو نهخۆسکۆپی ههنازن. نهخۆسکۆپی به مێشینه بهرز رووناکراوهکان کرا، و کاتیک گومان له باریت بوو، بايوپسی به پروتوکۆلی سیاتل گرت.

نهجام: تهمنی بهشداریان 18–92 سال بوو (ناوند=44.3 سال). ریزهی باریت 0.5% بوو له ریهگی تهواوی نپوانهکاندا و 1.4% به تهها له روی نهخۆسکۆپیهوه. هۆکاره خهتهرهکان بریتین له: گهرانهوهی تیکشکاو (OR=23.7، P<0.0001)، هیرنیا (OR=10.9، P<0.0001)، جکاره کیشان (OR=2.8، P<0.0001)، پیاو بوون (OR=2.5، P=0.001)، قهلهو بوون (OR=1.9، P=0.02)، و تهمنی زیاتر له 50 سال (OR=1.8، P=0.03). (P=0.07)

کۆتایی: ریزهی سورینچکی باریت له ناوچهی تهمههه کهمتره لهوهی که له سهراوه پزیشکییهکاندا باسکراوه. هۆکاره خهتهرهکانی بریتین له گهرانهوهی تیکشکاو، هیرنیا، سیگیر خواردن ئ، پیاو بوون، قهلهزی و تهمنی زیاتر له 50 سال. سهراوه پهیهندی نهبوو.

وشهه سهرهکی: بلاوههوه، سورینچکی باریت، نهخۆشی گهرانهوه، نهخۆسکۆپی بهرز، دهۆک

الخلاصة

مرض مريء باريت وعوامل الخطورة المرتبطة به بين المرضى في شمال العراق

الخلفية: يعد مرض الارتجاع المعدي المريئي حالة شائعة تصيب الجهاز الهضمي العلوي، وتؤدي إلى خسائر صحية جسيمة. ويتزايد عبئه بسبب شيخوخة السكان العالميين ونموهم السكاني. ويعد مريء "باريت" من المضاعفات المهمة لهذا المرض، ويعد الحالة التمهيدية لسرطان المريء الغدي، وهو من الأورام الخبيثة التي لاتزال ذات توقعات سير مرضي ضعيف.

الهدف: تحديد مدى انتشار مريء "باريت" وعوامل الخطر المرتبطة به في دهوك، العراق.

المرضى وطرق البحث: امتدت هذه الدراسة الاستباقية من فبراير 2016 حتى أغسطس 2024 في ثلاث مؤسسات صحية في دهوك - العراق. شملت الدراسة 10000 مريض أُحيلوا لإجراء التنظير الهضمي العلوي لأي سبب. تم إجراء التنظير باستخدام مناظير معدية عالية الدقة، وعند الاشتباه بوجود مريء باريت أثناء التنظير، تم أخذ خزعات وفقا لبروتوكول سيائل.

النتائج: تراوحت أعمار المرضى بين 18 و92 سنة (المتوسط = 44.3 سنة). بلغت نسبة انتشار مريء باريت 0.5% وفقًا للفحص النسيجي، و1.4% وفقًا للتنظير. العوامل المرتبطة بمريء باريت شملت: مرض الارتجاع التآكلي (نسبة الأرجحية = 23.7، OR = 23.7، القيمة الاحتمالية) $P < 0.0001$ ، الفئق الحجابي (OR = 10.9، $P < 0.0001$)، التدخين (OR = 2.8، $P = 0.0001$)، الجنس الذكري (OR = 2.5، $P = 0.001$)، السمنة (OR = 1.9، $P = 0.02$)، والعمر أكثر من 50 سنة (OR = 1.8، $P = 0.03$). لم يكن هناك ارتباط بين تناول الكحول ومريء باريت ($P = 0.07$).

الاستنتاج: إن معدل انتشار مريء باريت في منطقتنا أقل من المعدلات المذكورة في البحوث الطبية. وتشمل عوامل الخطر المرتبطة بمريء باريت: مرض الارتجاع التآكلي، الفئق الحجابي، التدخين، الجنس الذكري، السمنة، والعمر فوق 50 سنة. لم يُلاحظ ارتباط بين تناول الكحول ومريء باريت.

الكلمات المفتاحية: مريء باريت، داء الارتجاع، التنظير الداخلي العلوي، دهوك.