Clinical and Endoscopic Differences Between Patients With Barrett's Esophagus With and Without Dysplasia/Adenocarcinoma

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Abstract

Introduction: Barrett's esophagus (BE) is the main precursor of esophageal adenocarcinoma (EAC). This study aimed to identify the risk factors associated with BE progression to dysplasia or EAC in a Latin population.

Methods: The study is a retrospective analysis of a single-center cohort of patients with BE, evaluated from 2002 to 2012.

Results: We identified 420 patients with BE; 281 (66.9%) of them were men with a mean age of 57.2 ± 15.3 years. Among all BE patients evaluated, 81 (19.3%) had progression to some degree of dysplasia/EAC. The mean follow-up was 5.6 years. Multivariate analysis showed that age (OR = 1.03), cigarette smoking (OR = 3.05), long-segment BE (OR = 4.81), and a visible lesion on BE (OR = 6.94) were associated with progression to dysplasia/EAC.

Conclusion: In Latin patients with BE, age, cigarette smoking, long-segment BE, and the presence of lesions were associated with the presence of dysplasia/EAC.

Introduction

Barrett's esophagus (BE) is a metaplastic change in the distal esophagus involving the replacement of the normal squamous epithelium by a specialized intestinal columnar epithelium. It is the main known precursor lesion of esophageal adenocarcinoma (EAC) [1,2]. In the general population, its prevalence is estimated at 1-2%. It is found in 10-15% of all patients with gastroesophageal reflux symptoms of several years of evolution [3]. In Mexico, BE studies have reported a prevalence of 0.26%, 1.8%, and 9.6% [4-6]. Compared with the general probability, patients with BE have a 50 to 55 times higher risk of developing EAC [7]. In addition, the annual risk of progression of BE to EAC in patients without dysplasia is 0.33% [8]. However, in BE patients with low- and high-grade dysplasia, the annual rates of progression to EAC could be as high as 1% and 6%, respectively [9]. In recent decades, the incidence of EAC has been on the increase, while the five-year survival prognosis is less than 15% [10,11].

Since BE is the known precursor of EAC, it is pertinent that once diagnosed, an initial evaluation be performed and endoscopic follow-up instituted, both with the aim of early detection of cancer or dysplasia, and hence subsequent curative treatment. Nevertheless, consensus is lacking on the follow-up intervals between the different medical societies [12-15]. In addition, it should be borne in mind that there is no conclusive evidence of the benefits and the impacts on mortality of these actions [16]. Attempts have been made to establish the risk factors for progression from BE to EAC. In a multicenter longitudinal study of the Caucasian and Anglo-Saxon populations, the authors identified male gender, smoking, BE length, and initial presence of low-grade dysplasia as risk factors for progression [17,18]. A meta-analysis found similar results but included "age at diagnosis" as a risk factor for progression [18]. In our population, these risk factors are unknown. Detecting factors associated with the presence or development of EAC in BE cases could impact the different screening and prevention strategies in our population. On this basis, the objective of the present study was to identify differences between patients with and without dysplasia/EAC in patients with BE in a Latin population.

Materials And Methods

It is a comparative retrospective study. Patients with a histological diagnosis of BE from January 2002 to December 2012 were included. BE data were collected from the databases of the Gastrointestinal Endoscopy and Pathology Departments of the National Institute of Medical Sciences and Nutrition, Salvador Zubirán (INCMNSZ) in Mexico City. Affiliated physicians and residents were responsible for performing the endoscopic procedures. Biopsies were obtained using white-light, high-definition Olympus GIF 160® and 180® model endoscopes (Olympus Corporation, Tokyo, Japan), with the application of vital chromoendoscopy or narrow-band imaging (NBI) at the discretion of the endoscopist, based on the Seattle protocol and with biopsies directed at observed lesions (nodule, stricture, and ulcer) within the BE. All procedures were done under moderate sedation or monitored anesthesia care. The biopsies were processed in accordance with the standard protocol of the INCMNSZ Pathology Department and reviewed by physicians assigned to this department.

In all the patients, data on age, sex, body mass index (BMI), the presence or absence of tobacco use, alcohol, proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), presence of hiatal hernia, Nissen fundoplication, and symptoms of gastroesophageal reflux at BE diagnosis (based on patient history documenting heartburn or regurgitation) were recorded. In the endoscopic studies, the length of the BE was documented and divided into short-segment BE (less than 3 cm) and long-segment BE (greater than or equal to 3 cm). The presence of lesions, defined as a nodule, stricture, and ulcer, within the BE was recorded. Our hospital follow-up recommendation for patients with BE is based on clinical management guidelines, which depend on the type of histopathological results obtained [12-14].

The samples were divided, considering the pathology report at study entry, into two groups: BE without dysplasia (only intestinal metaplasia) and BE with dysplasia (low-grade dysplasia, high-grade dysplasia, and the presence of EAC). Subsequently, the variables, previously mentioned, were compared to establish significant differences and to identify variables associated with the presence of dysplasia/EAC.

In all patients, the follow-up time was documented and changes or no changes of BE without dysplasia to BE with dysplasia/EAC and vice versa were recorded. In addition, patients' treatment and type or no treatment were registered.

Statistical analysis

Descriptive statistics with measures of central tendency and dispersion for a population with a parametric or non-parametric distribution that is appropriate for the variable were used. To evaluate differences between the groups, we used chi-square or Fisher's exact test for categorical variables and Student's t-test for continuous variables. Variables with a p-value < 0.2 were included in the multivariate analysis. A p-value <0.05 was considered significant. SPSS v20 statistical program (IBM Corp., Armonk, NY) was used.

Ethical considerations

This study was performed with strict observance of the bioethical precepts of human research and Helsinki principles. The study consisted of a retrospective review of data from INCMNSZ files and collected at the moment of review. Due to the retrospective nature and review of the data in the file, the consent of each of the patients involved was not necessary. However, care was taken at all times to guard the anonymity of the patients. The protocol was approved by the INCMNSZ Ethics and Research Committee with registration number END-3085-20-21-1.

Results

A total of 43,639 upper digestive tract endoscopies were performed in the period evaluated and 420 patients were diagnosed with BE (9.6 patients with BE for every 1000 studies performed); 66.9% were men with mean age ± SD of 57.2 ± 15.3 years, 223 (53%) of the patients presented long-segment BE and 197 (47%) with short-segment BE, 339 (80.7%) were found without dysplasia, while 81 (19.3%) had some degree of dysplasia or cancer. In Table *1*, the clinical and endoscopic characteristics of included patients are shown.

Characteristics	BE without dysplasia (n = 339), n (%)	BE with dysplasia/EAC (n = 81), n (%)	P
Gender, male	223 (65.7)	58 (71.6)	0.5
Age, years (mean ± SD)	56.3± 15.4	62.5 ± 13.3	0.002
BMI kg/m2 (mean ± SD)	26± 5	26.3 ± 3.9	0.66
Smoking	177 (52)	62 (76.5)	0.001
Alcohol	126 (37.2)	40 (49.4)	0.011
GERD symptoms	254 (74.9)	64 (79)	0.06
PPI	183 (53.9)	52 (64.2)	0.14
NSAIDs	37 (11)	13 (16)	0.29
Nissen surgery	55 (16.2)	8 (9.9)	0.052
Hiatal hernia	219 (64.6)	52 (64)	0.75
Lesion*	30 (8.8)	25 (30.9)	0.001
BE large	163 (48)	62 (76.5)	0.001

TABLE 1: Clinical and endoscopic characteristics of BE patients without dysplasia and BE patients with dysplasia/EAC.

* Ulcer, estenosis, or nodule. BE: Barrett's esophagus; EAC: esophageal adenocarcinoma; BMI: body mass index; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs. P-value < 0.05 was considered significant.

Diagnosis and follow-up

According to the pathology report at study entry, the patients were divided into those without dysplasia (n = 339) and those with dysplasia/EAC (n = 81), including those with low-grade dysplasia and high-grade dysplasia/EAC. Twenty-one patients were diagnosed with high-grade dysplasia at study entry and in eight cases, high-grade dysplasia coexisted with EAC. Thirteen patients were diagnosed with EAC only, without dysplasia at biopsies.

In the follow-up of the 339 patients without dysplasia at study entry, 25 (7.4%) progressed to low-grade dysplasia and five to high-grade dysplasia (1.5%). For the 47 patients with low-grade dysplasia at baseline, 15 (31.9%) remained unchanged during follow-up, 29 (61.7%) subsequently presented BE without dysplasia, and four (8.5%) progressed to EAC. In those with high-grade dysplasia at study entry, one progressed to cancer, four remained unchanged (three received endoscopic treatment), three were reported with low-grade dysplasia after mucosectomy, and four underwent esophagectomy. The mean follow-up time was 5.6 years.

Univariate and multivariate analysis

In Table 2, univariate and multivariate analyses are shown. Age, tobacco use, BE lesions, and segment length ≥ 3 cm (long-segment BE) were associated with the presence of dysplasia/EAC.

Characteristics	OR	CI	P
Univariate			
Age	1.02	1.004 – 1.039	0.014
Gender	0.76	0.448 – 1.298	0.32
Reflux	1.47	0.808 – 2.670	0.21
Smoking	2.99	1.712 – 5.210	<0.001
Alcohol	2.12	1.298 – 3.460	0.003
PPI	1.66	1.008- 2.747	0.047
NSAIDs	1.56	0.787 – 3.094	0.203
Lesion	6.36	3.507 – 11.53	<0.001
Hiatal hernia	1.11	0.665 – 1.853	0.69
Nissen	0.58	0.264 – 1.269	0.17
Length	4.77	2.649 – 8.573	<0.001
Multivariate			
Age	1.03	1.012 – 1.053	0.02
Smoking	3.05	1.65 – 5.66	<0.001
Lesion	6.94	3.56 – 13.45	<0.001
Length	4.81	2.52 – 9.12	<0.001

TABLE 2: Univariate and multivariate analysis of the factors associated with the presence of dysplasia/EAC in patients with BE.

BE: Barrett's esophagus; EAC: esophageal adenocarcinoma; OR: odds ratio; CI: confidence interval; BMI: body mass index; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs. Variables with a p-value < 0.2 were included in the multivariate analysis. P-value < 0.05 was considered significant.

Discussion

The results of the present study depict an association between age >60 years, tobacco use, the presence of lesions and long-segment BE, and the presence of dysplasia/EAC in biopsies from Mexican patients with BE.

Most of the patients (80.7%) in our study population did not present dysplasia. Of those with dysplasia (19.3%), low-grade dysplasia (11.2%) predominated in relation to high-grade dysplasia (5%). The evolution over time presented differences according to the type of dysplasia. It was observed that in the 339 patients without dysplasia at study entry, only 25 (7.4%) progressed to low-grade dysplasia and five to high-grade dysplasia (1.5%). Previous studies that monitored BE patients without dysplasia reported that the probability of dying from a cause unrelated to EAC is 10 times higher [8]. That is, BE patients without dysplasia have a lower risk of progressing to EAC (0.1% to 0.5% per patient-year) when compared with those with low- and high-grade dysplasia [19]. Although the increased risk of high-grade dysplasia progression to EAC is well established, there are studies where the rate of progression was reported to vary from 16% in a seven-year period to 50% in a five-year period [10,20]. A more recent meta-analysis in patients with BE estimated an annual incidence of EAC in patients with high-grade dysplasia of 6% [21].

An interesting group in the present study is patients with low-grade dysplasia; 15 (31.9%) of the 47 patients with this condition remained unchanged while 29 (61.7%) presented BE without dysplasia and four (8.5%) progressed to EAC at the end of their follow-up. A possible explanation for these situations may be sampling error in obtaining the endoscopic biopsies or inter-observer variability in the interpretation of the biopsies and/or the regularity in the analysis by two expert pathologists, situations that have been documented in other works [22,23]. This highlights the importance of adequately confirming both low-grade and high-grade dysplasia.

There are several reports where the degree of abdominal fat content has a greater impact on BE than BMI per

se [24,25]. In our study, it was not possible to obtain the percentage of abdominal fat in our patients, and weight and BMI were not found to be associated with dysplasia/cancer in the patients evaluated.

Currently, surveillance intervals for BE > 3 cm are three years while shorter segments (<3 cm) could surveyed every five years. It is important to notice that endoscopic surveillance can conclude when the patient is not a good candidate for endoscopic eradication therapy. Our hospital followed international recommendations for patients with BE [26].

Management of BE with low-grade dysplasia includes endoscopic surveillance or endoscopic eradication therapy while management of BE with high-grade dysplasia includes endoscopic eradication therapy. In this study, four patients with high-grade dysplasia were managed with esophagectomy [26].

The present study has its limitations and strengths. Within the limitations, we can highlight the retrospective design and that some variables were categorized as binary variables (smoking, alcohol, use of PPIs, or NSAIDs), which could cause data loss. The BE groups with and without dysplasia are different risk populations, so they have different follow-ups. Another limitation is that the follow-up time is too short for the appropriate establishment of the progression of each group. Apart, the expert vs. resident variable in the detection of BE was not compared. Despite these limitations, this work is the largest series reported so far in our country, and where factors associated with the presence of dysplasia/EAC in patients with BE are evaluated.

Conclusions

In conclusion, the results of the present study found an association between age, cigarette smoking, long-segment BE, and the presence of lesions in BE and progression of BE to dysplasia (30 of 339 patients, 8.8%) or dysplasia to EAC (five of 59 patients, 8.4%) in a Latin population during a mean follow-up of 5.6 years.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. National Institute of Medical Sciences and Nutrition Salvador Zubiran, Ethics and Research Committee issued approval END-3085-20-21-1. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ: American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011, 140:1084-91. 10.1053/j.gastro.2011.01.030
2. Thrift AP: Global burden and epidemiology of Barrett oesophagus and oesophageal cancer . Nat Rev Gastroenterol Hepatol. 2021, 18:432-43. 10.1038/s41575-021-00419-3
3. Ronkainen J, Aro P, Storskrubb T, et al.: Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005, 129:1825-31. 10.1053/j.gastro.2005.08.053
4. Trujillo-Benavides OE, Baltazar-Montúfar P, Ángeles-Garay U, et al.: Association between symptomatic gastroesophageal reflux and Barrett's esophagus. (Article in Spanish). Rev Gastroenterol Mex. 2005, 70:14-9.
5. Peña Alfaro NG, Manrique MA, Chávez García MA, Pérez Valle E, Ladrón de Guevara L, López Gutierrez J: Prevalence of Barrett's esophagus in non-selected patients submitted to esophagogastroduodenoscopy and associated risk factors. (Article in Spanish). Rev Gastroenterol Mex. 2005, 70:20-4.
6. Herrera Elizondo JL, Monreal Robles R, García Compean D, González Moreno EI, Borjas Almaguer OD, Maldonado Garza HJ, González González JA: Prevalence of Barrett's esophagus: an observational study from a gastroenterology clinic. Rev Gastroenterol Mex. 2017, 82:296-300. 10.1016/j.rgmxen.2017.07.001
7. Cook MB, Coburn SB, Lam JR, Taylor PR, Schneider JL, Corley DA: Cancer incidence and mortality risks in a large US Barrett's oesophagus cohort. Gut. 2018, 67:418-529. 10.1136/gutjnl-2016-312223
8. Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S, Howden CW: The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut. 2012, 61:970-6. 10.1136/gutjnl-2011-300730
9. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P: Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc. 2008, 67:394-8. 10.1016/j.gie.2007.07.019
10. Sikkema M, de Jonge PJ, Steyerberg EW, Kuipers EJ: Risk of esophageal adenocarcinoma and mortality in

patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2010, 8:235-44. 10.1016/j.cgh.2009.10.010

11. Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, Feuer EJ: Trends in esophageal adenocarcinoma incidence and mortality. Cancer. 2013, 119:1149-58. 10.1002/cncr.27834

12. Fitzgerald RC, di Pietro M, Ragunath K, et al.: British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014, 63:7-42. 10.1136/gutjnl-2013-305372

13. Shaheen NJ, Falk GW, Iyer PG, Gerson LB: ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016, 111:30-50. 10.1038/ajg.2015.322

14. Wani S, Rubenstein JH, Vieth M, Bergman J: Diagnosis and management of low-grade dysplasia in Barrett's esophagus: expert review from the Clinical Practice Updates Committee of the American Gastroenterological Association. Gastroenterology. 2016, 151:822-35. 10.1053/j.gastro.2016.09.040

15. Uscanga-Domínguez L, Huerta-Iga F: Clinical guidelines for diagnosis and treatment of Barrett s esophagus. Medical, surgical and endoscopic treatment. (Article in Spanish). Rev Gastroenterol Mex. 2010, 75:118-21.

16. Otaki F, Iyer PG: Point-counterpoint: screening and surveillance for Barrett's esophagus, is it worthwhile? . Dig Dis Sci. 2018, 63:2081-93. 10.1007/s10620-018-5065-9

17. Parasa S, Vennalaganti S, Gaddam S, et al.: Development and validation of a model to determine risk of progression of Barrett's esophagus to neoplasia. Gastroenterology. 2018, 154:1282-9.e2. 10.1053/j.gastro.2017.12.009

18. Krishnamoorthi R, Singh S, Ragunathan K, Visrodia K, Wang KK, Katzka DA, Iyer PG: Factors associated with progression of Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018, 16:1046-55.e8. 10.1016/j.cgh.2017.11.044

19. Vaezi MF, Kahrilas PJ: Barrett's esophagus surveillance: time to rethink if one size fits all? . Gastroenterology. 2013, 145:503-5. 10.1053/j.gastro.2013.07.020

20. Avidan B, Sonnenberg A, Schnell TG, Chejfec G, Metz A, Sontag SJ: Hiatal hernia size, Barrett's length, and severity of acid reflux are all risk factors for esophageal adenocarcinoma. Am J Gastroenterol. 2002, 97:1930-6. 10.1111/j.1572-0241.2002.05902.x

21. Wang JS, Canto MI: Predicting neoplastic progression in Barrett's esophagus. Ann Gastroentol Hepatol. 2010, 1:1-10.

22. Sharma P: Low-grade dysplasia in Barrett's esophagus . Gastroenterology. 2004, 127:1233-8. 10.1053/j.gastro.2004.07.061

23. Curvers WL, ten Kate FJ, Krishnadath KK, et al.: Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. 2010, 105:1523-30. 10.1038/ajg.2010.171

24. Wiseman EF, Ang YS: Risk factors for neoplastic progression in Barrett's esophagus . World J Gastroenterol. 2011, 17:3672-83. 10.3748/wjg.v17.i32.3672

25. Kubo A, Corley DA: Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006, 15:872-8. 10.1158/1055-9965.EPI-05-0860

26. Shaheen NJ, Falk GW, Iyer PG, Souza RF, Yadlapati RH, Sauer BG, Wani S: Diagnosis and management of Barrett's esophagus: an updated ACG guideline. Am J Gastroenterol. 2022, 117:559-87. 10.14309/ajg.0000000000001680