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Original Article

Differences of risk factors and clinical presentations in male and female Taiwanese individuals with Barrett's esophagus

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Abstract

Background: Barrett's esophagus (BE) is a disorder more often found in obese men. Differences between the two genders are not known in the Asian countries. Here, we studied their gender differences in the Taiwanese population in terms of risk factors and clinical presentations.
Methods: Data from Taichung Veteran General Hospital were prospectively collected during an approximately two year-period (October 2012 to December 2014). Patients all underwent endoscopic surveillance, and BE was diagnosed based on the typical pattern of intestinal metaplasia. The patient characteristics were compared between the two genders.
Results: We enrolled 152 BE patients: 103 men and 49 women. We found in the males, when compared with the females, significantly older mean age, higher waist circumference, greater BMI (ratio of obesity BMI $\geqq 25$ kg/m^2), and more cases with dyslipidemia and hiatus hernia. Long-segment BE and high-grade dysplasia/adenocarcinoma appeared only in males. Self-reported reflux symptoms were noted 80.6% in men and 89.8% in women. In those with dysplastic BE, we found these patients having higher ratios of obesity, hiatus hernia, alcohol drinking, cigarette smoking and reflux symptom.
Conclusion: Gender differences were found in our BE patients, males were older in age, more obese, and suffered more serious signs from BE in terms of both endoscopic and pathologic presentations.

Keywords: Barrett's esophagus; Endoscopic; Gender

1. Introduction

Barrett's esophagus (BE) is a disorder defined as an abnormal transformation of the squamous epithelium (viz., intestinal metaplasia, IM), and is considered as a complication of gastroesophageal reflux disease (GERD).[1] Recently, interest in BE has grown due to its likely progression to esophageal adenocarcinoma (EAC), with elevated risk 30−40 times higher than that of the general population.[1,2] Symptoms of GERD, such as heartburn or regurgitation, are associated with the increased risk of BE or EAC.[3−5] However, some patients of BE or EAC report no history of GERD.[3] Traditionally, in the Western countries, BE is often found in male and obese individuals[6] but similar findings in the Asian countries are lacking. The aim of this study is therefore to determine the gender differences of BE in the Taiwanese population in terms of risk factors and clinical presentations.

2. Methods

We prospectively analyzed clinical data collected from subjects with BE at the Medical Screening Center at Taichung

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Table 1
The demographic data of enrolled individuals with Barrett's esophagus.

	Male (N = 103, 67.8%)			Female (N = 49, 32.3%)			p
	M ± SD	N	%	M ± SD	N	%	
Age (years)	61.67 ± 15.27			55.48 ± 14.27			0.019[b]
Waist (cm)	91.49 ± 8.41			81.63 ± 9.32			0.001[b]
BMI (kg/m^2)	24.72 ± 3.12			23.65 ± 4.42			0.132[b]
Obesity[c]		62	(60.2%)		16	(32.7%)	0.001[a]
Cholesterol (mg/dl)	184.77 ± 69.79			200.42 ± 60.61			0.017[b]
TG (mg/dl)	135.76 ± 69.79			92.05 ± 60.61			0.001[b]
HDL (mg/dl)	52.28 ± 13.28			66.56 ± 17.77			0.001[b]

p-values were analyzed with Pearson's Chi-square test[a]; independent t test[b].
BMI = body mass index; HDL = high density lipoproteins; TG = triglyceride; N = numbers.
[c] Definition of obesity: BMI ≧ 25 kg/m^2.

Veteran General Hospital during the period from October 2012 to December 2014. This study was approved by Institutional Review Board of the Taichung Veterans General Hospital (No. CF14040). The general data of patients included age, gender, body weight, body mass index (BMI), and waist circumference. Lipid profiles of the following items: cholesterol, triglyceride (TG), and high density lipoproteins (HDL), were also recorded. All patients underwent an open-access trans-oral upper gastrointestinal (UGI) endoscopy. Specifically, white light and narrow band imaging (NBI) were used in the high-resolution endoscopy and four-quarter tissue biopsy was taken in accordance with the AGA recommendations. BE was diagnosed by the typical IM pattern. We also collected the endoscopic findings, that included hiatus hernia, erosive esophagitis (EE), short segment BE (SSBE, extend <3 cm into the esophagus) or long segment BE (LSBE, extend ≧3 cm into the esophagus), and pathologic appearance of BE tissue, such as low- and high-grade dysplasia (LGD and HGD) or EAC. Exclusion criteria were total esophagectomy, severe cardiopulmonary deficiency, malignancy, or other conditions unsuitable for UGI endoscopy.

All patients were asked to complete a questionnaire on lifestyle habits and reflux symptoms. The lifestyle habits included drinking of alcohol, tea or coffee, and cigarette smoking. The positive of lifestyle habits were defined as ongoing consumption of a particular item in excess of one day in a week. Reflux presentation referred to typical symptoms like acid regurgitation, heartburn or chest pain, and atypical symptoms like sore throat, lump sensation or chronic cough. A positive symptom was defined as one that occurred in excess of twice in a week. Patients were divided into one of two groups according to their gender. Their characteristics were subsequently compared.

For each of the measured parameters, data were expressed as mean and standard deviation. Hiatus hernia, endoscopic and pathologic findings of BE tissue, lifestyle habits and presentation of reflux symptom of each stratified group, were expressed as the percentage of total patient numbers of the respective groups. Statistical comparisons were made using Pearson's chi-square test to compare the effects of gender and positive ratios of the stratified groups. Independent t-test was used to analyze age, BMI, waist circumference and lipid profiles. *p*-values <0.05 were considered statistically significant.

3. Results

Among the 152 enrolled subjects, 103 were men (67.8%) and 49 were women (32.2%). The general data and lipid profiles are shown in Table 1. The male group, in comparison with the female, was found to have significantly older ages (mean 61.67 vs. 55.48 years, $p = 0.019$), larger waist circumferences (mean 91.49 vs. 81.63 cm, $p = 0.001$), and more classified with obesity (BMI ≧25 kg/m^2) (60.2% vs. 32.7%, $p = 0.001$). Men compared with women, also had higher levels of TG (mean 135.76 vs. 92.05, $p = 0.001$) and lower levels of HDL (mean 52.28 vs. 66.56, $p = 0.001$), Cholesterol levels were similar across gender.

Some subjects received anti-secretory medications, such as proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs). In the male group, 55 (53.4%) took PPIs, and 9 (8.7%) took H2RAs. In the female group, 27 (55.1%) took PPIs and 4 (8.2%) took H2RAs.

The endoscopic and pathologic appearances of BE of these two groups are shown in Table 2. The male group had a higher

Table 2
The endoscopic, pathologic appearance and lifestyle habits of men and women with Barrett's esophagus.

	Male (N = 103, 67.8%)		Female (N = 49, 32.3%)		p
	N	%	N	%	
Hiatal hernia	47	(45.6%)	12	(24.5%)	0.012
BE length					0.031
SSBE	93	(90.3%)	49	(100%)	
LSBE	10	(9.7%)	0		
Pathologic findings					0.514
No dysplasia	97	(94.2%)	46	(93.9%)	
LGD	3	(2.9%)	3	(6.1%)	
HGD	1	(1.0%)	0		
EAC	2	(1.9%)	0		
Lifestyle habits					
Alcohol	18	(17.5%)	7	(14.3%)	0.884
Tea	40	(40.8%)	12	(25.5%)	0.072
Coffee	36	(35.0%)	19	(38.8%)	0.647
Smoking	19	(18.6%)	6	(12.2%)	0.609

All *p*-values were analyzed with Pearson's Chi-square test.
BE = Barrett's esophagitis; EAC = esophageal adenocarcinoma; HGD = high grade dysplasia; LGD = low grade dysplasia; LSBE = long segment Barrett's esophagus; N = numbers; SSBE = short segment Barrett's esophagus.

Table 3
The portion of erosive esophagitis and reflux disease of men and women with Barrett's esophagus.

	Male (N = 103, 67.8%)		Female (N = 49, 32.3%)		p
	N	%	N	%	
EE					0.599
Nil	69	(67.0%)	35	(71.4%)	
LA Gr. A/B	29	(28.2%)	14	(28.6%)	
LA Gr. C/D	5	(4.8%)	0		
GERD symptoms					
Nil	20	(19.4%)	5	(10.2%)	0.152
Acid regurgitation	52	(50.5%)	26	(53.1%)	0.767
Heartburn	21	(20.4%)	11	(22.4%)	0.771
Chest pain	17	(16.5%)	12	(24.5%)	0.242
Sore throat	24	(23.3%)	10	(20.4%)	0.689
Lump sensation	39	(37.9%)	24	(49.0%)	0.194
Chronic cough	21	(20.4%)	4	(8.2%)	0.057

All *p*-values were analyzed with Pearson's Chi-square test
EE = erosive esophagitis; GERD = gastroesophageal reflux disease; N = numbers.

ratio of hiatus hernia than the female group (45.6% vs. 24.5%, $p = 0.012$). Most enrolled subjects (93.4%) were SSBE, and all LSBE cases (n = 10) were men. Regarding pathologic findings, in the male group, one case had a high-grade dysplasia (HGD), and two had EAC. On the contrary, in the female group, no cases of HGD nor EAC were found. Altogether, 6 cases of LGD were found, equally distributed to both groups (3:3 patients). Their lifestyle habits, such as alcohol, tea or coffee consumption, and cigarette smoking, are shown in Table 2. Male patients had tea drinking most often (40.8%), followed by coffee drinking (35.0%). Female patients on the other hand, had coffee drinking most often (38.8%), followed by tea drinking (25.5%). But we found no gender-differences for the consumed items.

The positive numbers of EE and reflux symptoms are listed in Table 3. We found 34 (33.0%) cases of EE in the male group and 14 (28.6%) cases in the female group again with no gender-differences. Most EE cases (89.6%) belonged to L.A. classification A or B, and all the 5 subjects with L.A. classification C or D EE were men. Among all patients, 20 (19.4%) male and 5 (10.2%) female reported no reflux symptoms. For those cases with reflux symptoms, most complaints were acid regurgitation (50.5% in men and 53.1% in women) followed by lump sensation (37.9% in men and 49.0% in women). Here again, no gender-differences were found. General data of subgroups with or without EE are shown in Table 4. We found EE males having significantly higher waist circumferences than females (mean 91.63 vs. 80.69 cm, $p = 0.001$); and in the non-EE males, higher waist circumferences (mean 91.42 vs. 82.00 cm, $p = 0.001$) and more in obesity (56.5% vs. 28.6%, $p = 0.007$) (see Table 4).

The clinical and endoscopic presentations of the patients with dysplasia (n = 9) are shown in Table 5. Most of them had obesity, hiatus hernia, lifestyle habits of alcohol drinking or cigarette smoking, and reflux related symptoms, especially in those subjects with severe dysplasia, including HGD and EAC. On the contrary, almost none of these patients were LSBE or EE during endoscopic surveillance.

4. Discussion

BE, which is defined as a metaplastic change of cells (from squamous epithelium to columnar epithelium in the distal esophagus), has been considered as a pre-malignant disease.[1] Identifying risk factors and specific symptoms associated with BE is therefore important for early detection, and for timely management when dysplasia is found. Here we have examined gender differences of BE in a Taiwanese population.

Male predominance in BE is well documented.[1,8] The distribution of male:female in our study was about 2:1, a ratio quite comparable to those reported.[1,7] For example, a meta-analysis reported a male:female ratio of 2.13:1 (95% CI: 1.87–2.46).[8] Such gender difference might be accounted for mainly by female sex hormones that prevent the development of IM by reducing EE, and through anti-inflammatory actions that take place at the esophageal epithelium.[6] Another minor contributor is the estrogen up-regulated expression of esophageal occludin, a tight junction protein that plays a crucial role in the esophageal

Table 4
The demographic data of with Barrett's esophagus subjects with or without erosive esophagitis.

	Male			Female			p
	M ± SD	N	%	M ± SD	N	%	
EE		34			14		
Age (years)	63.00 ± 15.76			53.36 ± 14.75			0.056[b]
Waist (cm)	91.63 ± 8.58			80.69 ± 8.70			0.001[b]
BMI (kg/m^2)	24.83 ± 2.96			23.79 ± 3.83			0.374[b]
Obesity[c]		23	(67.6%)		6	(42.9%)	0.110[a]
Non-EE[c]		69			35		
Age (years)	61.01 ± 15.09			56.34 ± 14.21			0.131[b]
Waist (cm)	91.42 ± 8.38			82.00 ± 9.66			0.001[b]
BMI (kg/m^2)	24.67 ± 3.22			23.59 ± 4.69			0.230[b]
Obesity[c]		39	(56.5%)		10	(28.6%)	0.007[a]

p-values were analyzed with Pearson's Chi-square test[a]; independent t test[b].
BMI = body mass index; EE = erosive esophagitis; N = numbers.
[c] Definition of obesity: BMI ≧ 25 kg/m^2.

Table 5
The clinical and endoscopic presentations of the individuals with dysplasia.

	HGD/EAC (N = 3)		LGD (N = 6)	
	N	%	N	%
Obesity	2	(66.7%)	3	(50.0%)
Hiatal hernia	2	(66.7%)	2	(33.3%)
LSBE	0		0	
EE	0		1	(16.7%)
Life style habitus				
Alcohol	2	(66.7%)	4	(66.7%)
Tea	2	(66.7%)	3	(50.0%)
Coffee	1	(33.3%)	3	(50.0%)
Smoking	2	(66.7%)	2	(33.3%)
GERD symptoms	3	(100%)	5	(83.3%)

EAC = esophageal adenocarcinoma; EE = erosive eosphagitis; GERD = gastroesophageal reflux disease; HGD = high grade dysplasia; LGD = low grade dysplasia; LSBE = long segment Barrett's esophagus; N = numbers.

mechanical defense system, further enhancing the esophageal structural resistance to refluxed acid.[9] BE is known to associate with old ages. The prevalence of BE in women rises after 60 years of age, and during the postmenopausal period, even surpassing that of men.[10,11] A large cohort study of BE in Netherlands reported that the mean age of women patients of the disease is significantly higher than that of men (men/women; 59.3/65.5, $p < 0.01$).[7] Our study on the other hand, showed dissimilar results, with males significantly older than females. This difference might be related to the sample bias at a male-patient dominated veteran hospital.

One common risk factor for BE is obesity.[12] Our previous study on BE revealed a positive association of metabolic syndrome in a Taiwanese population,[13] and the female cases showed an increasing rate of obesity.[14] In this study, we found male cases, compared with female, having a greater proportion of obesity and dyslipidemia. Here we further showed that in males, higher waist circumference (or central obesity) was a risk factor of BE, regardless of having EE or not. These results need to be confirmed with a better control group.

Hiatus hernia is considered as a major cause of severe reflux and is strongly associated with BE.[15] Our present results further showed that such association was more predominant in the males. According to the previous reports, BE measured longer in length in males than in females.[11,16] Those with longer segments of BE are at a higher risk for the progression to EAC,[17] and consequently EAC is more commonly found in males than in females.[6]

Our results showed a similar distribution, with males, in compared with females, having a higher proportion of LSBE and more severe pathology of dysplasia, such as HGD or EAC. Interestingly, our patients with dysplasia showed no concomitant LSBE or EE during endoscopic surveillance. The reason might be due to ethnic differences between the Western and Eastern countries. Therefore in the Taiwanese population, LSBE and severe EE are not risk factors for tumor in BE patients. Other factors for associating subjects at risk with dysplastic BE progression remain to be explored in the Eastern countries.

Earlier studies in Western countries reported a higher prevalence of BE with lifestyle like alcohol drinking,[1,7] and cigarette smoking increases the risk for progression to HGD and EAC by almost two fold.[18] In the present study, on the one hand, our patients had no history of large consumption of tea, coffee, alcohol, or smoking. On the other hand, some of them had a relatively high consumption of alcohol and were heavy smokers especially those patients with dysplasia. Although the sample size is small, this result seemed to suggest that alcohol and smoking might play a role of carcinogenesis in the BE tissue.

Chronic presentation of GERD is considered a risk factor for BE. BE presents more likely in patients with reflux symptoms than those without.[1,2] According to literatures, the prevalence of BE lies between 1 and 2% in population-based studies, but in patients with GERD symptoms, the prevalence of BE is elevated to over 10 and upto 18%.[19,20] Individuals who have severe chronic reflux symptoms, and those with nocturnal symptoms, also appear to be at the greatest risk of progressing to malignancy.[21] Despite of these findings still some BE patients are asymptomatic. Large, randomly selected population studies in Sweden and in Italy both reported that about 40% of BE patients have no reflux symptoms.[20,22]

In our study, EE was found in 33.3% of men and 28.6% of women. Presentation of reflux symptoms was recalled at 80.6% in men and 89.8% in women. This means that most BE subjects with reflux symptoms belong to non-erosive reflux disease (NERD), and the symptoms could be typical (such as acid regurgitation) as well as atypical (such as lump sensation). Not surprisingly, almost all our patients with dysplasia had reflux symptoms. Therefore, reflux symptoms, rather than EE or LSBE, had a positive association with BE with dysplastic changes. Our study has several limitations. First, it data were collected at a single tertiary care center, hospital-based. Selection bias could not be ruled out and results therefore failed to truly reflect the general population. Second, medications for controlling lipids were not determined. Consequently the ratio of dyslipidemia could have been underestimated. Third, the questionnaires of lifestyle habits and reflux symptoms were obtained through self-reporting, with likely uncontrolled errors. Finally, the status of *Helicobacter pylori* infection of each case was not determined. Further research on this topic incorporating analyses of more variables is needed.

In conclusion, in the studied population, we found that men prone to BE, when compared with women, were older, more obese, and more having dyslipidemia. These men were also suffered the disease to a greater severity, both in the endoscopic and pathologic dysplastic degree. Factors of obesity, hiatus hernia, lifestyle like alcohol drinking and cigarette smoking, and the presentation of reflux symptoms, were all associated with severe dysplastic changes in the BE patients.

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