Prevalence and risk factors for Barrett’s esophagus. Study in a hospital population in a tertiary care center

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Abstract. Objectives: to study the prevalence and risk factors of Barrett’s esophagus (BE) in the inpatient population referred for upper endoscopy. Methods: prospective study including patients undergoing upper endoscopy between 7 January 2013 and 31 May 2013. Patients with upper bleeding and esophageal tumors were excluded. A specific chart was completed for each patient, including the following parameters: demographic information, body mass index (BMI), the presence of heartburn, endoscopic appearance (the presence and length of BE: short < 3 cm, long > 3 cm, the presence of Helicobacter pylori (HP) and biopsy findings. Results: from an initial number of 1,585 patients, only 1,261 were enrolled. Of these, 44 patients (3.48%) had an endoscopic appearance compatible with BE (1 long BE, 34 short BE, 9 BE islands). Only 36 (2.85%) of them were documented as intestinal metaplasia in biopsy specimens. The mean age in BE patients was 55±16.8 years (vs. 53±14.3 years in patients without BE), with a male/female ratio of 1:11. We used heartburn as the main clue that the patient has gastroesophageal reflux disease (GERD). Thus, 26 (4.93%) patients with heartburn had BE, whereas the rate was only 1.19% (10) in patients without reflux symptoms (p<0.001). There were no statistically significant differences between the two groups of patients (with and without BE) in terms of BMI (the patients without BE had a mean BMI of 26.4±6.7 kg/m² and those with BE had a mean BMI of 25.2±5.7 kg/m², p=0.2), smoking (the ratio of non-smokers/smokers was 1.87:1 in patients without BE and 2:1 in patients with BE, p=1) and the presence of hiatal hernia (HH)(HH was present in 20.3% of patients without BE vs 22.9% of patients with BE, p=0.7). In contrast, the number of patients without alcohol consumption was significantly higher in the group with BE (the ratio 6:1) compared to the group without BE (the ratio 2:1, p=0.01). Similarly, the prevalence of HP in patients with BE was higher than in the group of patients without BE (82.9% vs 64.6%, p=0.02). Conclusion: In our inpatients population the prevalence of BE was 2.85 %. We found that the presence of GERD and HP are risk factors for BE, meanwhile the alcohol was found to be a protective factor. We have not found a relationship between BE and BMI, smoking and the HH.

Key Words: Barrett’s esophagus, prevalence, risk factors, gastroesophageal reflux disease.

Introduction

Barrett’s esophagus (BE) is defined as the abnormal transformation (metaplasia) of the squamous epithelium, a complication of gastroesophageal reflux disease (Spechler et al 2014). The presence of BE is determined using endoscopy (a change in the distal esophageal epithelium of any length), histopathology being mandatory in establishing the diagnosis of metaplasia. There has been an increasing interest in BE in recent studies due to its progression to esophageal adenocarcinoma, whose risk of occurrence is 30-40 times higher than in the general population (Spechler et al 2014; Sharma et al 2004).

The risk factors for the onset of BE were intensely studied over the years. Today there is an unanimous accepted fact that BE is an acquired disease, with gastroesophageal reflux being the main risk factor, through its severity and lengthiness. The acid reflux is the mainly blamed for BE, but there are evidences that prove that the alkaline reflux is also implicated in the onset of BE (Spechler et al 2014). The frequency of BE increases with age and with the family history of BE. BE is found frequently in men, and especially in those with high body mass index (BMI) and abdominal obesity. Regarding the role that Helicobacter pillory (HP) infection is playing in BE pathogenesis, things are not completely clear, but the majority of studies indicate a lower prevalence of HP infection in patients with BE (Spechler et al 2014; Gatenby et al 2014).

This study aimed to examine the risk factors involved in the incidence of BE, the study being performed on the population admitted to a gastroenterology regional center with high addressability.

Material and method

This was a prospective, observational, cohort study performed between 7 January 2013 and 31 May 2013 on the patients admitted
as well as those with esophageal tumors.

The study protocol was approved by the Hospital Ethics Committee and patients signed an informed consent for study inclusion. The following parameters were charted in all remaining 1,261 patients: patient demographics (age, gender), anthropometric data (weight and height) to calculate BMI, clinical data - heartburn, presence or absence of alcohol consumption and smoking. We used heartburn as the main clue that the patient has gastroesophageal reflux disease (GERD).

Data provided by upper gastrointestinal endoscopy was an important part of the patient chart. Thus, the distance from the dental arch of the Z-line and the cardia were recorded in order to assess the presence of hiatal hernia (HH). Suspicion of Barrett’s mucosa was considered when endoscopy revealed mucosal areas of reddish color on the pink background of normal esophageal mucosa, divided into three categories: isolated islands, short BE (discolored areas less than 3 cm in size) and long BE (discolored areas larger than 3 cm in size) (Sharma et al 1998). The presence or absence of HP was also considered, being assessed by means of urease test.

The last part of the chart recorded the presence or absence of biopsies (one biopsy in each quadrant) and their results. Statistical analysis was performed using descriptive statistical methods (dispersion and centrality indices) and inferential statistical methods: Fisher’s exact test, chi-square test unpaired Student’s t test/Mann-Whitney test, in accordance with standard rules of application. The selected threshold of statistical significance was p ≤0.05. SPSS 17.0 statistical package was used for data processing.

Results

As mentioned above, there were 1,261 patients taken into consideration for the final assessment, with a gender ratio being substantially equal (669-53% men, 592-47% women). The average age of the patient group was 57±14.4 years, with a maximum age of 89 and a minimum of 18 years.

Of the 1,261 patients taken into consideration, endoscopic changes compatible with BE were found in 44 cases (3.48%), with only one case of long BE, 9 cases (20.45%) of BE islands and short BE in the remaining 34 cases (77.27%). Morphopathologic examination only confirmed 36 cases of BE (2.85%), all with intestinal metaplasia, none with dysplasia. Most cases (32 cases - 88.88%) revealed short BE, there were 3 cases of BE islands (8.3%) and the case of long BE was confirmed as metaplasia as well.

In the group of patients with BE, only 3 patients had cirrhosis (8.33%) and none of them had ascites, while among those without BE there were 282 (21.13%) patients with cirrhosis, 95 of them presenting ascites.

Of the 36 biopsy-confirmed patients, 19 (52.8%) were men and 17 (47.2%) women. The gender ratio was not statistically significantly different from the group without BE (p=0.9) (fig. 1).

No statistically significant differences were observed (p=1) in the smokers and non-smokers ratio between the group of patients with BE and that of those without BE, with a predominance of non-smokers in both cases (about twice more than smokers in both groups).

In terms of reflux symptoms, of the 1,261 patients, 527 had heartburn, while the remaining 734 did not have heartburn. Of the patients with heartburn, 26 (4.93%) patients had BE, compared to only 10 (1.19%) patients of those without reflux symptoms (p<0.001).

On the other hand, in the group of patients with BE, the number of patients with heartburn prevails, while in the group of patients without BE, the number of patients without heartburn prevails. There is a statistically significant difference between patients with and without BE in terms of symptoms (p<0.001) (figure 3).
The presence of HP was recorded in 82.9% of patients with BE, compared to only 64.6% of those without BE, the difference being statistically significant (p=0.02) (figure 4).

Figure 4. The presence of Helicobacter Pylori (HP) in patients with and without BE

Discussion

In literature, the prevalence of BE varies in different studies from 0.3 to up to 25% (Spechler et al 2014; Hirota et al 1999; Westhoff et al 2005) according to the target population investigated, the prevalence generally being lower if the studies addressed asymptomatic populations, increasing in the case of patients with chronic reflux symptoms, with the highest prevalence to be found when using data obtained at autopsy (Cameron et al 1990). There were exceptions to this trend, for example, a study carried out on asymptomatic patients who have also undergone screening for colorectal cancer, 25% of them having BE (Gerson et al 2002). Another study performed on patients undergoing colorectal cancer screening tests revealed a 16.7% prevalence of BE, also taking into account patients with reflux symptoms (Ward et al 2006).

The main results obtained in different studies are summarized in Table 1.

Table 1. BE prevalence in different regions around the globe

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population studied</th>
<th>Results (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayeck et al 2010</td>
<td>Estimate of general population based on computer modeling</td>
<td>5.6</td>
</tr>
<tr>
<td>Westhoff et al 2005</td>
<td>Subjects with chronic GERD symptoms</td>
<td>13.2</td>
</tr>
<tr>
<td>Gerson et al 2002</td>
<td>Asymptomatic subjects older than 50 years undergoing colorectal cancer screening</td>
<td>5.6 to 25</td>
</tr>
<tr>
<td>Veldhuyzen van Zanten et al 2006</td>
<td>Patients with dyspepsia undergoing endoscopy</td>
<td>2.4</td>
</tr>
<tr>
<td>Ronkainen et al 2005</td>
<td>Population-based study</td>
<td>Overall: 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reflux symptoms: 2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No reflux symptoms: 1.2</td>
</tr>
<tr>
<td>Zagari et al 2008</td>
<td>Population-based study</td>
<td>1.3</td>
</tr>
<tr>
<td>Playford 2006</td>
<td>Patients with GERD symptoms</td>
<td>12</td>
</tr>
<tr>
<td>Van Soest et al 2005</td>
<td>A population study that utilized the Integrated Primary Care Information Database</td>
<td>1997: 1.98</td>
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<td></td>
<td></td>
<td>2002: 4.05</td>
</tr>
<tr>
<td>Odemiş et al 2009</td>
<td>Patients undergoing endoscopy</td>
<td>1.2</td>
</tr>
<tr>
<td>Barr et al 2006</td>
<td>Patients undergoing endoscopy</td>
<td>1990: 0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2002: 1.89</td>
</tr>
<tr>
<td>Sărăci et al 2011</td>
<td>Patients undergoing endoscopy</td>
<td>2.2</td>
</tr>
</tbody>
</table>

However, even if morphopathology could only confirm 36 of the 44 cases with suspected BE, BE prevalence is likely to be underdiagnosed, as many studies have only demonstrated a 34% positive predictive value of conventional video-endoscopy (i.e. without the use of modern diagnostic methods) when identifying intestinal metaplasia (Eloubeidi et al 1999). This hypothesis is supported by the fact that 20% of cases showed a diagnostic mismatch, even in the same patient, when endoscopy was performed by two different specialists (Kim et al 1994). In addition, the presence of metaplastic cells was shown in the lower esophagus in patients with gastroesophageal reflux without existing macroscopic changes detected by endoscopy (Melson et al 2014).
In terms of BE structure, the particularity of our study is given by the fact that there was only one patient with long BE (2.77% of all patients with BE and 0.18% of the patients with reflux), a percentage lower than literature studies where the percentage is somewhat higher (between 3.5 and 7% of patients with reflux) (Spechler et al 2014; Sampliner 2002). On the other hand, 35 patients had short BE (also considering those with very short BE), which account for 6.64% of patients with reflux symptoms, the result being this time lower than the average 10-15% that we found in different studies (Spechler et al 2014).

Unlike the literature, where the male-female ratio is about 2:1 (Spechler et al 2014; Westhoff et al 2005; Gerson et al 2002; Ward et al 2006; van Soest et al 2005; Cook et al 2005), the male-female ratio in the present study was approximately equal to that of the group without BE, with a slight predominance of men. The average age of the group with BE was 55 years, age that overlaps with other studies in the literature. (Spechler et al 2014; Gerson et al 2002). One of the common risk factors for reflux disease, and therefore for BE, is obesity, especially abdominal obesity (Kamat et al 2009; Jacobson et al 2009; Yates et al 2014).

However, a meta-analysis performed on 11 studies only showed a slight increase (OR 1.4) in patients with a BMI of over 30 kg/m², compared to those with a BMI below this value (Yates et al 2014). In the present study, there was no statistically significant relationship between the prevalence of BE and BMI, patients with BE having an average BMI of 25.25 kg/m², even lower than those with BE (26.41 kg/m²), although the difference was not statistically significant. The limitation of this study is given by the absence of complete data on abdominal circumference, which was initially considered, but data was only partially filled in patient charts and could not be later used for the final calculation. In addition, the slight increase in the group of patients without BE may have been due to cirrhosis patients (some of them suffering from ascites), whose BMI was 27.61 kg/m², thus increasing the BMI of the group without BE.

Regarding alcohol and smoking, studies have shown a higher prevalence of BE in alcoholics (Spechler et al 2014; van Soest et al 2005; Zimmerman et al 2014; Gatenby et al 2014) especially if they are smokers too. In our study, there was no relationship between smoking and the presence or absence of BE. However, in terms of alcohol consumption, we achieved a relatively surprising result when compared to the literature, where alcohol is a risk factor for BE (Spechler et al 2014; Yates et al 2014), as the percentage of patients without alcohol consumption in our study was statistically significantly higher in patients with BE than in those without BE. The features of the study group might have contributed to the final result, with a higher percentage of patients with cirrhosis in the group without BE (25.21%), many cases caused by ethanol, compared to only 8.4% patients with cirrhosis in the group with BE. Supporting this hypothesis, there are several studies that showed the fact that the alcohol consumption does not enhance the risk for BE (Thrift et al 2011; Anderson et al 2009; Kubo et al 2009). In addition, the beer (Thrift et al 2011) or wine consumption might have a protective role for onset of BE (Anderson et al 2009; Kubo et al 2009).

Our results were consistent with the literature in terms of the prevalence of BE in patients with reflux symptoms, BE being present in a higher percentage in patients with reflux symptoms than in those without reflux (Spechler et al 2014; Sharma et al 2004; Westhoff et al 2005; Hayeck et al 2010; Zagar et al 2008; Cook et al 2005). On the other hand, BE patients have reflux symptoms in a much higher and statistically significant percentage than those without BE. Although the results regarding heartburn were predictable, an apparently surprising result was obtained related to the presence of HH, with no differences in its presence in the groups of patients with and without BE.

The alteration of the antireflux barrier is known to be influenced by three major components: the frequency and duration of transient lower esophageal sphincter relaxation, the drop in the resting pressure of the lower esophageal sphincter and the presence of HH and decreased efficiency of crural diaphragm contraction. Although most studies have shown a direct relationship between the severity of HH type and the severity of gastroesophageal reflux (Spechler et al 2014; Westhoff et al 2005; Zagar et al 2008; Cook et al 2005), there have also been studies showing that gastroesophageal reflux is not directly influenced by the existence of HH itself or by the decreased esophageal sphincter tone, the reflux being rather present when there is an abnormal contraction of the crural diaphragm during inspiration (Pandolfino et al 2007). Therefore, there are patients with HH without reflux and patients with reflux and without HH which may explain the results found in the present study.

Regarding the prevalence of HP, our results differ from those reported by other studies in the literature (Spechler et al 2014; Wang et al 2009; Rokkas et al 2007; Gatenby et al 2014; Fischbach et al 2014) which showed a low prevalence of HP in patients with BE compared to controls. In the present study, patients with BE had a statistically significantly greater prevalence of HP than the group without BE.

HP is known to be responsible for gastric intestinal metaplasia. There is discussion in the literature showing that, given the identical morphological features of metaplasia in the case of very short BE, biopsy taken from the vicinity of the esophagogastric junction cannot distinguish between cardiac metaplasia as part of gastric intestinal metaplasia and intestinal metaplasia as part of a very short BE (Oksanen et al 2003; Hackelsberger et al 1998). The particularity of our study was given by the fact that of the 32 BE cases confirmed by biopsy, 3 were BE islands (very short BE) and, as discussed above, they could be interpreted as metaplasia of the cardia. But even under these circumstances, if we reed the calculations by removing these three patients from the assessment (all being HP positive), the percentage of patients with BE and HP positive would be 78.78%, greater than the group without BE. Due to this result, one of our main future objectives is to continue to study the prevalence of HP in patients with BE in order to certify or invalidate this result and to identify the factors that influence it.

Conclusion
The prevalence of BE in the hospital population studied herein was 2.85%. In the present study, gastroesophageal reflux disease and HP proved to be risk factors for BE, while alcohol consumption was a protective factor. BMI, smoking and the presence of HH were correlated with the presence of BE.
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Dina et al 2015

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