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Epidemiologic aspects in esophageal pathology focusing on gastroesophageal reflux disease and Barrett's esophagus

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Abstract. Objective: To determine the main epidemiologic characteristics of esophageal pathology, insisting on gastroesophageal reflux disease (GERD), Barrett's esophagus (BE) and to evaluate the relationship between these conditions and some widely spread risk factors. Material and methods: Data were collected from clinical file records archive, endoscopy reports and histopatologic reports and slides for 8225 patients (01.01.2005-31.07.2007) who presented esophageal changes during upper digestive endoscopy. We used Kolmogorov-Smirnov test to assess the normality of variables distribution and then we used parametric or non-parametric tests along with multivariate analysis. Results: BE is associated with male sex (r=0.039; p<0.001), esophagitis (p=0.001), gastric surgery (r=0.027; p=0.015). BE is negatively associated with esophageal varices (r=-0.1; p<0.01) and *Helicobacter pylori* (*Hp*) infection (r=0.024; p=0.02). Age is not an important factor (OR=0.99; p=0.03). Presence of sliding hiatal hernia (SHH) is influenced by body mass index (r=0.533; p<0.001) and female sex (p=0.001). SHH size influences the severity of esophagitis (r=0.04; p<0.01). The most frequent type of metaplasia is the incomplete intestinal one and the most frequent form of esophageal cancer is adenocarcinoma. Conclusion: BE is associated positively with GERD, esophagitis, male sex and negatively with *Hp* and esophageal varices. SHH influences severity of esophagitis and is more frequent in female patients. Adenocarcinoma is more frequent that squamous esophageal cancer.
Key Words: GERD, Barrett's esophagus, esophageal adenocarcinoma, esophageal pathology.

Rezumat. Obiectiv: Determinarea principalilor indicatori epidemiologici în patologia esofagiană, insistând pe boala de reflux gastroesofagiană (BRGE), esofagul Barrett (EB) şi evaluarea relaţiei dintre aceste afecţiuni şi diverşi factori de risc. Material şi metode: pentru 8225 pacienţi (01.01.2005-31.12.2007) care au prezentat modificări esofagiene la explorarea endoscopică s-au cules date din foile de observaţie, rapoartele endoscopice şi histopatologice şi s-au examinat preparatele histologice. Pentru prelucrarea datelor am folosit testul Komogorov-Smirnov pentru a verifica distribuţia normală a acestora şi, în funcţie de aceasta, am utilizat teste parametrice, non-parametrice şi analiza multivariată. Rezultate: EB este asociat cu sexul masculin (r=0,039; p<0,001), esofagita (p=0,001), stomacul operat (r=0,027; p=0,015). EB este asociat negativ cu varicele esofagiene (r=-0,1; p<0,01) şi *Helicobacter pylori* (*Hp*) (r=0,026; p=0,02). Vârsta nu e un factor important (OR=0,99; p=0,03). Prezenţa herniei hiatale (HHA) este influenţată de indicele de masă corporală (r=0,533; p<0,001) şi sexul feminin (p=0,001). Mărimea HHA influenţează severitatea esofagitei (r=0,09; p<0,01). Cel mai frecvent tip de metaplazie întâlnită a fost cea intestinală incompletă, iar cel mai frecvent tip de cancer esofagian, adenocarcinomul. Concluzii: Apariţia EB este influenţată pozitiv de BRGE, esofagită, sex masculin şi negativ de către varicele esofagiene şi *Hp*. HHA influenţează severitatea esofagitei şi e mai frecventă la femei. Adenocarcinomul este mai frecvent decât cancerul scuamos esofagian.
Cuvinte cheie: BRGE, esofag Barrett, adenocarcinom esofagian, patologie esofagiană.

Introduction. Among various sources, Barrett`s esophagus (BE) is credited with a prevalence of 1% in general population, thus being a frequent condition and a real public health matter. If we refer to the population with gastroesophageal reflux disease (GERD) the prevalence rises up to 20%. The variety of conditions that induce GERD with or without esophagitis makes BE the possible result of these conditions also, considering that GERD is the most frequent cause of BE (Nimish et al 2006).

Hiatal hernia (HH) has been regarded for many years as an overlapped concept to the GERD and if this matter appears a little exaggerated for rolling HH, the presence of sliding HH (SHH) creates the conditions for severe persistent and pathological GER. HH size has also importance in inducing more severe symptoms, in containing more gastric material that could pass into the esophagus and in increasing reflux episodes duration (Spechler et al 2004).

Digestive and non-digestive conditions, especially esophageal ones, must be correctly inventoried and analyzed. Achalasia, esophageal varices sclerotherapy, diverticula, non-reflux esophagitis are some of the conditions that can produce or mimic GERD and aggress esophageal mucosa. There are a lot of cases when, for instance, a herpetic esophagitis, could falsely be considered intestinal metaplasia during endoscopy and only the histopathological exam will offer the exact answer.

Aim. Epidemiologic characteristics of a condition are considered primary data when investigating that condition. It is mandatory to know the real incidence, prevalence and risk factors that lead to the development of GERD and BE as well as modalities to counteract these factors. These aspects become more significant when a study is conducted in a specialized gastroenterology center that assembles patients from an extensive territory with variable individual characteristics such as: patient environment, genetic resources, accessory medical conditions, individual psychological impact toward disease a.o. All these facts are essential data when studying and following-up premalignant conditions such as BE and sometimes offer the explanation why in some people the transition to the malignant status is accelerated, while in others is slowed, or for which patient medical and interventional therapies will have the best results.

The development of low and high grade dysplasia on BE is possible and not compulsory, but will move the entire therapeutic arsenal into another direction in order to stop the evolution towards esophageal adenocarcinoma and to detect its potential presence. Undoubtedly, the treatment of associated conditions, of GERD and its complications are mandatory.

In the current study we propose an epidemiologic analysis of esophageal diseases in generally and of GERD and BE particularly. We have also insisted on esophageal cancer prevalence and esophageal adenocarcinoma and its current position towards other forms of esophageal cancer especially squamous cancer, and the correlation of various conditions with GERD and BE.

Overall, the study tries to demonstrate the importance of BE among esophageal pathology, the importance of esophageal diseases among digestive disorders and to characterize BE and GERD from epidemiologic, etiologic, surgical, evolutive and histopathological points of view.

Material and Methods. During the study we meticulously examined the endoscopy records of the patients examined in the Endoscopy Department of the 3rd Medical Clinic in Cluj-Napoca during January 1st, 2005 – December 31st, 2007. From the archive of the 3rd Medical Clinic (Internal Medicine and Gastroenterology Compartments) and the 3rd Surgical Clinic we collected important information as well as from studying and examining the tissue sampling reports and slides from the Department of Anatomopathology of the same clinical complex.

For statistical analysis we used Microsoft Office Excel XP for organization of data base and SPSS (Statistical Package for the Social Sciences) 14.0 for the analysis itself.

Data has been grouped in nominal, continuous, ordinal variables. For nominal variables we calculated frequencies, for ordinal variables we determined frequencies median value and for continuous variables we calculated central tendency (median, mean value), dispersion (standard deviation, variance). To determine the normality of variables distribution we used Kolmogorov-Smirnov test. Corresponding parametric or non-parametric statistic tests have been chosen according to normal or non-normal distribution. Univariate analysis of normal distribution continuous variables encompasses the use of T test for independent variables, Pearson correlation, partial correlation and ANOVA test. From non-parametric tests we used Spearman correlation, Mann-Whitney

test, Kruskal-Wallis test. For univariate dichotomous variables we used X^2 test. Multivariate analysis consisted of construction of predictive models using logistic binary regression. Differences have been considered statistically significant at a p parameter value less than 0.05 and we also calculated the 95% confidence intervals (CI 95%).

Results. We included in our study 8225 patients with mean age of 54.93±13.38 years. The minimal age was 18, the maximal 96. The most frequent age was 61, 362 patients being of that age. Approximately 4654 patients (56.6%) were male and 3570 (43.4%) were female. In order to check if there are significant differences between mean ages of the two sexes we applied T test for independent variables. There were no statistically significant differences between mean ages of male (54.56 years) and female (55.38 years) patients (p=0.78).

Table 1

Esophageal changes during upper digestive endoscopy

Variable	*Frequency (%)*
BE	182 (2.2%)
SHH	3140 (38.2%)
Ascension of Z line	169 (2.1%)
Xantoma	11 (0.1%)
Glycogenesis	19 (0.2%)
Foreign body	22 (0.3%)
Stenosis	97(1.2%)
Viral esophagitis	15 (0.2%)
Diverticula	77 (0.9%)
Malignant tumors	173 (2.1%)
Benign tumors	134 (1.6%)
Schatzki ring	85 (1%)
Mallory-Weiss syndrome	83 (1%)
Candidiasis	182 (2.2%)
Ulcer	190 (2.3%)
Achalasia	41 (0.5)
Esophageal varices	2953 (35.9%)
Esophagitis	2539 (30.9%)

Cases of SHH have been distributed according to hernia size: 2426 (29.4%) cases of small size SHH (<2 cm), 549 (6.7%) cases of medium size SHH (2-4cm) and 165 (2%) cases of large SHH (>4cm).

In our study we noticed 1234 (15%) patients with reflux esophagitis that were classified according to Los Angeles scale in class A (A-LA), 949 (11.5%) in B-LA, 220 (2.7%) in C-LA and 139 (1.7%) in D-LA.

We analyzed the impact of age on the development of BE, but we found no statistically significant association (p=0.07). We also searched a potential relationship between BE and patient sex, and so we established a statistically significant association between sex and BE (p=0.001). The next step was to assess the direction of this relationship so we applied a Spearman correlation and we obtained a low positive correlation highly, statistically significant, between male sex and BE (r=0.039 p<0.001).

In order to study a potential association between BE and various esophageal conditions we applied more X^2 tests with the following statistically insignificant results: SHH (p=0.15), SHH size (p=0.28), ascension of Z line (p=0.14), esophageal diverticulum (p=0.34), Schatzki ring (p=0.77), Mallory-Weiss syndrome (p=0.79), candidiasis (p=0.19) and achalasia (p=0.66).

We found a highly statistically significant association between esophageal varices and BE (p<0.001). Using a Spearman correlation we concluded that low negative correlation, high statistically significant (r=-0.1; p<0.001), exists between BE and the presence of esophageal varices.

The diagnosis of esophagitis was significantly linked to BE (p=0.001) and the Los Angeles classification has been significantly related with BE (p=0.01). After applying Spearman correlation we determined a low negative correlation, highly statistically significant, between the existence of BE and LA classification of esophagitis (r=-0.04; p<0.001).

The existence of esophagitis has been negatively correlated with BE (r=-0.04; p=0.001) and this is sustained by the majority of studies that suggest that although main cause of BE is GERD and esophagitis there are a few cases with simultaneous BE and reflux esophagitis (Darba et al 2011).

Fundus type metaplasia has been present in 23.2% of BE cases, incomplete intestinal metaplasia in 61.3% and complete intestinal metaplasia in only 15.4% of the subjects.

We calculated BMI (body mass index) for every patient. According to the classification of obesity, 340 (4.1%) of the patients had class I obesity, 348 (4.2%) class II and 259 (3.1%) class III. We applied a Spearman correlation to determine a potential link between SHH size and obesity degrees and we found a high positive correlation, highly statistically significant (r=0.533; p<0.001).

SHH has been correlated with female sex (p=0.001) and considering this, we proposed as null hypothesis the fact that the association of obesity with SHH is powerfully influenced by patient`s sex. We applied a partial correlation between obesity and SHH, having sex as control factor, and we repeated the null hypothesis (r=0.42; p<0.001). We may conclude that SHH and BMI are highly statistically significant associated independently of patients` sex.

We also analyzed a possible association between sizes of SHH and Los Angeles classification system for esophagitis. Applying a X^2 test we discovered a highly statistically significant relationship between SHH size and severity of esophagitis (p= 0.001; table 2).

We encountered a low positive correlation, highly statistically significant, between the size of SHH and the LA classification of esophagitis (r=0.04; p<0.001).

The existence of SHH has been positively correlated with the presence of esophagitis (r=0.023; p=0.03). Correlation was no longer valid when we adjusted the statistical analysis for the presence of obesity (r=0.01; p=0.37).

Table 2

LA classification according to SHH size

Variable		*Esophagitis (Los Angeles)*					*Total*
		0	A	B	C	D	
SHH	No	3556	759	559	113	98	5085
	Small	1697	382	276	50	21	2426
	Medium	337	76	83	39	14	549
	Large	93	17	31	18	6	165
Total		5683	1234	949	220	139	8225

For an independent analysis of SHH influence on reflux esophagitis we applied a binary logistic regression with age, sex and obesity adjustment.

This way we demonstrated that age is an unimportant factor for the association with esophagitis (OR=0.99). In 35% cases small size SHH has been less associated with reflux esophagitis. Medium size SHH raised 1.2 times the risk of reflux esophagitis and large size SHH has been 1.8 times more frequent correlated with esophagitis.

In order to study a possible relationship between various gastric and duodenal changes and the presence of BE we applied several X^2 tests with the results available in table 4. We found a high statistically significant association between gastric varices and BE (p<0.001) and a low negative correlation highly statistically significant (r=-0.068; p<0.001).

Table 3

Binary logistic regression for reflux esophagitis

Variable	B	S.E.	Wald	df	P	OR	CI 95% Min	CI 95% Max
Age	***-.019***	***.002***	***95.972***	***1***	***.000***	***.981***	***.978***	***.985***
Sex	.011	.024	.213	1	.645	1.011	.964	1.061
Obesity I	.076	.099	.591	1	.442	1.079	.888	1.311
Obesity II	-.067	.101	.442	1	.506	.935	.766	1.140
Obesity III	-.192	.139	1.919	1	.166	.825	.629	1.083
Small SHH	***-.430***	***.073***	***35.119***	***1***	***.000***	***.650***	***.564***	***.750***
Medium SHH	***.216***	***.082***	***6.904***	***1***	***.009***	***1.241***	***1.056***	***1458***
Large SHH	***.629***	***.158***	***15.852***	***1***	***.000***	***1.876***	***1.76***	***2.557***

Table 4

Concomitant changes of stomach and duodenum observed during upper endoscopy

Variable	*Frequency (%)*
Intestinal metaplasia	38 (0.5%)
Gastric surgery	246 (3%))
Biliary Reflux	687 (8.4 %)
Bulb inflammation	356 (4.3%)
Gastritis	1777 (21.6%)
Duodenal ulcer	505 (6.1%)
Deformed bulb	176 (2.1%)
Malignant tumors	140 (1.7%)
Benign tumors	159 (1.9%)
Gastric ulcer	360 (4.4%)
Gastric varices	1690 (19.8%)
Helicobacter pylori	1599 (18.9%)

Gastric surgery has been significantly linked to BE ($p=0.02$) and to evaluate the direction of association we applied a Spearman correlation and we found a low positive correlation highly statistically significant ($r=0.027$; $p=0.015$).

Infection with Hp have been statistically significant associated with BE ($p=0.028$), but when we applied a Spearman correlation we found a low negative correlation statistically significant ($r=-0.026$; $p=0.02$).

A complex multivariate analysis was created by including the parameters that presented a statistically significant association during univariate analysis with BE.

In order to demonstrate the independent relationship between BE and these variables we used a binary logistic regression (table 5).

The most important parameter, independently associated with BE was esophagitis ($OR=3.75$; $p<0.001$). Male sex has been an independent risk factor, rising the probability of BE up to 1.45 times ($OR=1.448$; $p<0.01$).

The presence of esophageal varices ($OR=0.247$; $p<0.001$) decreased the probability of detecting BE with 73% and the detection of *Hp* reduced the association with BE with 26% ($p=0.01$). The age was practically an insignificant factor toward BE ($OR=0.99$; $p=0.03$).

Discussion. Epidemiology and etiology of BE have been the subject of many studies, meticulously debated. The difference between our study and the existing studies in the literature is the unitary approach of epidemiological aspects and risk factors as well as data collection for a wide geographical area with particularities of these conditions among people of our country.

Table 5

Binary logistic regression for BE risk factors

Variables	*B*	*S.E.*	*Wald*	*df*	*P*	*OR*	*CI 95%*	
							Min	*Max*
Helicobacter pylori	***-.291***	***.114***	***6.565***	***1***	***.010***	***.747***	***.598***	***.934***
Age	***-.011***	***.005***	***4.680***	***1***	***.031***	***.989***	***.978***	***.999***
Sex	***.372***	***.082***	***20.478***	***1***	***.000***	***1.451***	***1.235***	***1.705***
Esophageal varices	***-1.292***	***.219***	***34.751***	***1***	***.000***	***.275***	***.179***	***.422***
Reflux esophagitis	***1.310***	***.192***	***46.554***	***1***	***.000***	***3.75***	***2.543***	***5.397***
Gastric varices	.205	.163	1.582	1	.208	1.228	.892	1.690
Gastric surgery	-.432	.351	1.514	1	.218	.649	.326	1.292

We actually wanted to note the esophageal conditions as they were detected in a diagnostic and therapeutic upper digestive endoscopy department. We also demonstrated statistically significant associations between various conditions. We tried to determine the role played by SHH in the settlement of GERD, reflux esophagitis, the correlation between the size of SHH and the severity of reflux esophagitis and with patient`s BMI.

The prevalence of BE is relatively high in general population, especially in persons with chronic esophageal reflux. BE was detected in 2,2% of the subjects in our study and this percent is a little higher than the one reported in literature for the patients undergoing upper digestive endoscopy for various accuses (1%) (Connor et al 2003). The difference between these data could be the consequence of the fact that the patients included in our study come from a large population admitted in gastroenterology highly specialized medical unit so the patients are already somehow selected into this direction. Although BE prevalence is relatively high in general population, it is much higher (5-15%) in patients that undergo upper digestive endoscopy for the investigation of chronic esophageal reflux symptoms (Shaheen et al 2009).

Although some studies determined that advanced age is associated with a higher rate of BE, in our study we did not demonstrate an increased incidence of the condition in elderly people (Eloubeidi et al 2001). During multivariate complex analysis we encounter the fact that the age is not an important risk factor in endoscopic detection of BE (OR=0.98). A possible explanation for this difference from literature data could be the fact that the mean age of our study patients was relatively low (54 years). To evaluate more exactly the impact of aging on BE incidence, studies on geriatric patients with ages over 65 years should be conducted.

Reflux esophagitis was diagnosed on 31% of the patients in the study. According to the Los Angeles classification, the majority of patients were included in class A (15%) and the minority were included in class D (1.7%). Reflux esophagitis has been highly statistically significant associated with BE, practically it rose by 3.7 times the probability of developing BE. BE is the direct consequence of chronic inflammation caused by GERD. Acid or alkaline reflux induces cell injury that finally could result in intestinal metaplasia. Cell regeneration is efficient up to the moment when lesions extend to epithelium basal membrane, thus activating esophageal pluripotent stem cells which transform themselves into columnar cells more resistant to chemical aggression. This aberrant differentiation process lies at the basis of metaplasia (Jankowski et al 2000; Seery et al 2006). Cell growth and differentiation is practically the result of a whole algorithm of expression and suppression of certain genes, of releasing cytokines and other proteins implicated in inter and intra-cell communication. This way an intense proliferative status is created on the new-formed tissue thus exponentially increasing the probability of replication errors and various grade dysplasia (Săraci et al 2009).

Depending of its extend from gastroesophageal junction we refer to short (<3cm) or long (>3 cm) BE, both conditions bearing the risk of developing esophageal adenocarcinoma on subsequent dysplasia. The risk is higher for long BE, considering the large amount of metaplasic cells but the exact way of short BE is not entirely known.

Male sex is considered a risk factor for BE (Westhoff et al 2005), fact that is confirmed also in our study as we found a 1.4 fold risk for male patients compared with female patients.

Hp is negatively correlated with BE, practically there is a lower independent probability of 25% for the patients infected with Hp to have BE, compared with patients without this infection. *Hp* infection could result in chronic gastritis, intestinal metaplasia and gastric cancer, yet the infection could reduce the risk of BE as chronic gastritis reduces the production of gastric acid (Graham et al 1998).

Esophageal squamous cancer was responsible until the 70s for approximately 95% of esophageal cancers (Vizcaino et al 2002) but for the last 30-40 years the situation changed, as 50-80% of esophageal tumors are adenocarcinomas. In our study adenocarcinoma was the most frequent type of esophageal cancer (54%) and this shift is in part consequence of the risk factors prevalence change.

For instance, smoking and obesity as well as BE are risk factors with increasing prevalence for the last 3 decades (Lagergren et al 1999; Layke et al 2006).

SHH was present in approximately 40% of the participants in our study. The prevalence of SHH increases with age and is considered frequent among women probably related to the increasing of intraabdominal pressure during pregnancy. In our study we found a high statistically significant association between female sex and SHH. Also an important risk factor is obesity, as high BMI was significantly related to SHH. Chronic esophagitis could cause shortening of the esophagus through longitudinal muscle fibrosis, that can lead to development of SHH. Anyhow it is difficult to establish the exact sequence of phenomena: SHH could augment GERD and esophagitis could induce SHH (acquired brachyesophagus) (Navtej et al 2001).

In our study we found a high statistically significant relationship between SHH size and the severity of esophagitis according to LA classification. Among the limits of the study we have to mention the lack of information concerning alimentary habits, smoking history, chronic medication a.o.

Conclusions. Barrett`s esophagus is an important problem of public health, having a prevalence of 2.2% of the people undergoing upper endoscopy. The most common esophageal changes detected during endoscopy are HH, esophageal varices and esophagitis. The most frequent class of esophagitis according to the LA classification is LA class A followed by B, C, D and esophagitis is an important risk factor for BE. BE risk is not increased by age, but it is increased by male sex. There is a positive correlation between BMI and SHH and between female sex and SHH. SHH size is also correlated with the severity of esophagitis. *Hp* and esophageal varices are negatively correlated with BE. Current tendency in esophageal cancer is the increasing of esophageal adenocarcinoma cases and the reducing of numbers of squamous cancer.

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