Obesity is a Risk Factor for Erosive Gastroesophageal Reflux Disease: Prospective Case-Control Study

[9]. This is particularly interesting because it might suggest obesity as a pathogenetic event of GERD.

However, it has been hypothesized that obesity may promote the development of GERD symptoms and complications through mechanical and metabolic effects. An increase in BMI has been shown to positively correlate with an increase in esophageal acid exposure (AET) [10-12], and it has been observed that waist circumference might mediate a large part of the effect of obesity on esophageal AET [11], Pandolfino et al., [13] by means of high-resolution manometry, demonstrated that obese subjects are more likely to have esophagogastric junction disruption (leading to hiatal hernia) and an augmented gastroesophageal pressure gradient providing a perfect scenario for reflux to occur.

A mechanically defective lower esophageal sphincter was shown to be more frequent in patients with a higher BMI and obese patients were more than twice as likely to have a defective lower esophageal sphincter compared with normal weight patients [10]. Both intragastric pressure and the gastroesophageal pressure gradient were strongly correlated with both BMI and waist circumference. These findings support the concept that waist circumference is the mediator in the causal relationship between obesity and GERD [13]. Moreover, obesity also may alter the pharmacokinetics of acid suppressive therapies, including distribution (eg, poor blood flow in adipose tissue, obesity-related changes in plasma concentrations of binding proteins, variations in lipophilicity of drugs), metabolism (eg, fatty liver disease, common in obese patients, slowing the enzymatic metabolism of drugs), and elimination (eg, increased glomerular filtration rates and tubular secretion, associated with obesity, accelerating the elimination of some drugs) [14-16].

Another mechanism by which obesity can cause GERD is related to the metabolically active visceral fat that has been associated with low serum levels of protective cytokines, and high levels of inflammatory cytokines [17]. An increase in these inflammatory cytokines in patients with erosive esophagitis and Barrett's esophagus has also been observed [18].

The aim of the present study was to evaluate the prevalence of symptomatic GERD and esophagitis in female obese subjects.

Material and Methods

Throughout 2012, we prospectively enrolled consecutive female patients presenting to the outpatient units at the Obesity Center and Division of Gastroenterology at the University of Pisa.

From the outpatient Obesity Center, the inclusion criteria were as follows: age higher than 18 years, BMI higher than 30 from a larger group of patients who were scheduled diagnostic work-up for bariatric surgery (Group A).

Sex-matched patients were enrolled from outpatient Gastroenterology Unit. The inclusion criteria were as follows: age higher than 18 years, complaining of heartburn, with or without regurgitation, at least twice a week for six months in the previous year, although not consecutively (Group B).

The exclusion criteria were as follows: pregnancy (excluded by urine analysis) and/or breast-feeding; eating disorders; history of thoracic, esophageal or gastric surgery; underlying psychiatric illness; use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin.

During the first visit, a distinct investigator completed a structured interview to all patients, including a careful medical history (with recording of height and weight), current medications, tobacco use and alcohol consumption. GERD symptoms were evaluated by means of a validated questionnaire (GERD impact Scale: GIS) [19-21]. GIS comprises eight questions about the frequency, over the previous 2 weeks, of the following items: acid-related symptoms; chest pain; extra-esophageal symptoms; impact of symptoms on sleep, work, meals and social occasions; use of additional non-prescription medications. Four response options were allowed to describe the frequency of the above items over the previous 2 weeks: 'none of the time' (1), 'a little of the time' (2), 'some of the time' (3) and 'all of the time' (4). All patients signed an informed consent before entering the study. The study was designed and carried out in accordance with the Helsinki Declaration (Sixth revision, Seoul 2008) approved by the institutional review boards.

All patients discontinued PPI therapy at least 20 days before undergoing upper gastrointestinal endoscopy. All endoscopies were performed and recorded by two senior endoscopists, and videos were reviewed to reduce inter-operator variability. Endoscopies were performed with standard devices. The esophageal mucosal erosions, if present, were classified into four grades (from A to D) according to Los Angeles Classification [22].

Endoscopic Suspected Esophageal metaplasia (ESEM) was defined as a detectable upward displacement of the squamocolumnar junction (SCJ) at endoscopy, and it was histologically confirmed by the presence of IM. SCJ was defined as the point where the normal squamous epithelium joined the red mucosa of columnar-lined esophagus. Esophageal-gastric junction (EGJ) was defined as the level at which tubular esophagus joined saccular stomach. In patients with hiatal hernia, this junction was defined by the proximal margin of gastric folds. The length of BE was measured from EGJ to the most proximal extension of columnar epithelium. Systematic 4-quadrant biopsy specimens were collected with standard-size forceps at 2-cm intervals along the whole length of the ESEM segment, starting from the EGJ. Agreement on the presence and extension of BE mucosa and the degree of esophagitis was obtained in all cases. BE was defined as long segment when the length of ESEM was greater than 3 cm, otherwise it was defined as short segment. Biopsies were collected from ESEM to detect the presence of Barrett's esophagus and from nodules or other mucosa abnormalities.

Biopsies were formalin-fixed and paraffin-embedded. All biopsies were then stained with hemathoxylin-eosin. BE was determined as the presence of specialized intestinal-type metaplasia with goblet cells [23].

Statistical Analysis

Data were expressed as mean and standard deviation (SD). Statistical tests to compare the two groups of subjects included Student's t test for difference in mean values, Mann-Whitney U and Kruskal-Wallis tests for skewed variables, Pearson's Chi-squared test (with Yates's continuity correction as appropriated) for difference in counts and frequency. Pearson test has been performed between BMI and erosive esophagitis in group A patients to look for an association between these two variables. A multivariate analysis was performed to evaluate the "relative risk" and "attributable risk percent" for obesity to determine erosive esophageal erosion. A p-value less than 0.05 was considered statistically significant.

Results

We enrolled 193 female patients in Group A and 193 patients in Group B. Mean age (± sd) was 48.6 ± 13.6 years in Group A and 51.4 ± 15.3 years in group B. Mean BMI was 43.6 ± 9.2 in group A and 23.6 ± 3.7 in Group B (P<0.001). As expected, the body weight was higher in Group A 112.7 ± 31.6 than in Group B 68.8 ± 13.4 (P<0.001). Mean height was 159.3 ± 12.1 (cm) in group A and 171.8 ± 15.6 (cm) in group B (P <0.05).

There were no differences in voluptuary habits as coffee, tobacco and alcohol consumption between two groups (p=n.s.). Detailed results are reported in Table 1.

Mean age (sd)	48.6 ± 13.6	51.4 ± 15.3	0.0582
Mean BMI (sd)	43.6 ± 9.2	23.6 ± 3.7	<0.0001
Smoking (%)	25 (12.9%)	31 (16.1%)	0.368
Alcohol (2-3 unit/die)	20 (10.4%)	18 (9.3%)	0.729
Coffee (2 cup/die)	49 (25.4%)	53 (27.5%)	0.646

Table 1: Epidemiological characteristic of population in obese patients (Group A) and patients with GERD symptoms and normal BMI (Group B)

The perception of GERD symptoms was higher in group B: the mean value of GIS was 1.72 in this group when compared with 0.34 obtained in Group A (P<0.001). The mean value of score for typical GERD symptoms was 2.65 in group B and 0.85 in group A (P<0.001).

All patients in Group B recorded at least one typical GERD symptom (heartburn and regurgitate) but only 26.9% of patients in Group A recorded these symptoms (P<0.001). The GERD atypical and extra-esophageal symptoms were also more frequent in Group B (P<0.001). In the section of GIS questionnaire dedicated to explore the impact of GERD symptoms in quality of life showed that patients from Group B had more troublesome symptoms when compared with

2.16 (1.61–2.89) and subsequently the Attributable Risk Percent was 54.2%.

Discussion

GERD is a chronic disease, which has an impact on the everyday lives of affected individuals, and obesity is found to be a significant risk factor in the development of severe forms of GERD. Changes in gastro-esophageal anatomy and physiology caused by obesity may explain the association [5,6]. Several mechanisms by means of obesity causes reflux disease have been proposed even if the pathogenetic pathway commonly suggested is the increased abdominal pressure that increases esophageal mucosal acid exposure [24].

Results of 24 h pH-monitoring studies have shown that obesity is associated with a significant increase in the number of reflux episodes [11].

Our study showed that patients with obesity had a higher risk for developing esophageal erosion when compared with patients with GERD symptoms but normal weight. The most important information

GERD-related symptoms. A total of 10,545 (86%) returned the questionnaires, with 2306 (22%) participants reporting GERD symptoms at least once a week, 256 (11%) of whom with severe to very severe (ie, affecting/greatly affecting lifestyle) symptoms [9]. In 2005 El-Serag found similar results describing that 26% (118/453) obese patients reported weakly heartburn [32]. The authors summarized these findings as indicative that higher BMI increases the risk of GERD symptoms independent of demographic features and dietary intake.

As above described, our obese patients (group A) showed a high prevalence of erosive esophagitis and low prevalence of heartburn or other GERD-related symptoms. We can speculate that the chronic

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