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Effect of Body Weight and Esophageal Damage on the Severity of Gastroesophageal Reflux Symptoms. Mexican GERD Working Group

Juan Carlos Lopez-Alvarenga^{a,b}, José Antonio Vargas^c, Luis Humberto Lopez^d, Ronnie Fass^e, Sergio Sobrino-Cossio^f, Paul Higgins^a, and Anthony Comuzzie^a

^aSouthwest Foundation for Biomedical Research, San Antonio, Texas

^bDepartment of Research, Hospital Regional de Veracruz, Veracruz, Mexico

^cALTANA Pharma SA de CV, Mexico, Naucalpan de Juarez, Estado de México, Mexico

^dFacultad de Medicina, Universidad de Guanajuato, León, Guanajuato, México

^eHealth Sciences Center and University Medical Center, University of Arizona, Tucson, Arizona

^fServicio de Endoscopia, Instituto Nacional de Cancerología, Mexico, D.F., Mexico

Abstract

Background and Aims—Several studies have demonstrated overweight and obesity are strong independent risk factor of GERD symptoms and esophageal erosions. Our aim was to analyze the joint effect of BMI with the grade of esophageal damage over symptoms' intensity of GERD.

Methods—We used a questionnaire with a Likert scale for severity of symptoms related to GERD. The distal portion of the esophagus was evaluated to determine the presence of mucosal injury, classified by Los Angeles criteria (LA).

Results—We included 917 subjects (53.76% females) with average age 36.8 ± 7 years. Males had higher BMI than females (26.8 ± 3.5 vs. 25.2 ± 4.5 , $p < 0.001$). Severe damage (C–D ulcers) was associated with overweight (BMI 25–30), severity of heartburn, retching, halitosis, regurgitation, and chest oppression. BMI > 30 had high score for heartburn and retching, but low score for nausea, compared with lower weight. The model with interaction showed a non-linear association between BMI and LA. Overweight (but not obese) patients with damage scored C–D had the highest score for intensity of heartburn and retching.

Conclusions—BMI and LA do not have additive effects on the severity of symptoms of GERD. Those with BMI between 25 and 30 had severe symptoms score, but those with BMI > 30 showed lower scores. These findings could explain controversial results found in other studies.

Keywords

Gastroesophageal reflux; Endoscopy; Heartburn; Obesity; Esophageal disease; Pain sensation

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Address reprints requests to: Juan Carlos Lopez-Alvarenga, Department of Genetics, Southwest Foundation for Biomedical Research, 7620 NW Loop 410, San Antonio 78227, TX; Phone: 78245-0549; jalvaren@sfbgenetics.org or jclalvar@yahoo.com.

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Introduction

Obesity is considered a risk factor for chronic illnesses such as diabetes, hypertension, cardiovascular disease, and type 2 diabetes mellitus (T2DM). Several recent cross-sectional studies have demonstrated a positive association between gastroesophageal reflux disease (GERD) and high body mass index (BMI) (1,2), but this relationship is still controversial (3, 4).

The physiopathology for the association of GERD and BMI can be explained by inappropriate lower esophageal sphincter relaxation arising from hiatal hernia (5) or increase in intra-abdominal pressure (6), both leading to increase in acid reflux. Regarding food ingestion, GERD has no association with fatty foods (7), coffee (8), alcohol, tea (9), or chili consumption. Moreover, capsaicin can help to alleviate esophageal motor disorders (10).

Endoscopy has demonstrated that overweight and obesity are strong independent risk factors for esophageal erosions and correlate with GERD symptoms.¹¹ The association between GERD and obesity is supported by the observation that moderate weight gain among persons of normal weight may cause or exacerbate reflux symptoms (12).

GERD and obesity are complex traits. Both are heritable, meaning that they are due, in part, to gene function. Complex traits are multifactorial variables with genetic and environmental effects that interact between the two, influencing the trait. Advances in the understanding of other complex diseases such as diabetes, obesity, and asthma have been made by examining the interaction of genetics and environment (13). Examining GERD using these methods may yield similar insights.

Most studies analyze BMI and symptoms as they are in linear relationship, using odd ratios as risk association (2). None of the studies has focused on the effect that one variable can change the other (interaction between anatomic damage and BMI) to explain the symptom intensity of GERD. We measured the severity of symptoms related to GERD and endoscopy to determine mucosal injury of the esophagus damage using the Los Angeles (LA) classification (14).

In this study we evaluated the joint effect of BMI and LA on the severity of symptoms in patients with GERD. We hypothesized a positive additive linear effect of BMI with LA on the severity of GERD symptoms. Consequently, our aim was to explore this joint effect as we suspected the nonadditive effect of both variables, which can explain the controversies.

Materials and Methods

Participants

This clinical trial was conducted in 556 private and state clinics and hospital-based gastroenterology practices and gathered data from 954 patients with GERD symptoms who underwent endoscopy. The advantage of using such a number of centers was the increase of external validity for daily clinical practice. The increase in variability due to heterogeneous sources was controlled using a model corrected by the specialty of the practitioner (see Statistical Analyses for details). We included subjects between 18 and 45 years old (we restricted older people to decrease the risk of malignancy) with clinical history of heartburn, acid regurgitation, or both during the previous 3 months. These symptoms are reliable indicators of the presence of GERD, as has been found in other questionnaires (15,16).

All subjects were interviewed by the physician, and their weight (with minimal clothing) and standing height were recorded at the clinic.

We excluded subjects with major symptoms of malignancy, esophageal stenosis, previous gastrointestinal surgery (except cholecystectomy), cardiovascular disease, intake of alcohol, drugs, severe psychiatric disorder, pregnancy, or breastfeeding. Also, those subjects using of proton pump inhibitors, H2 antagonist, glucocorticoid or ketoconazol 2 weeks before endoscopy were excluded. The recruitment of subjects was performed in 2005.

Questionnaire

Researchers conducted a structured interview and used a 5-point Likert scale questionnaire (ranked from 0–4) to determine the severity and duration of symptoms of GERD. This questionnaire included severity of heartburn, reflux, retching, halitosis, flatulence, nausea, sialorrhea, globus, discomfort, oppressive chest pain, dyspnea, chronic cough, early satiety, and sleeping disturbances. The scale included categories such as never, rare, sometimes, most of the time, and always.

This alpha coefficient (17) of the questionnaire was 0.85, and this result shows high internal consistency. We demonstrated that this questionnaire has sufficient sensitivity to detect group differences or changes with treatment (18,19).

Upper Endoscopy

After overnight fasting, endoscopy was performed by a trained endoscopist. The stomach and duodenum were inspected to exclude possible lesions. The distal portion of the esophagus was evaluated carefully to determine the presence of mucosal injury. The definition of reflux esophagitis rested on the demonstration of diffuse or streaking erythema, mucosal friability, erosions, and ulcers, i.e., mucosal breaks. The severity of mucosal breaks was categorized according to LA classification (grades A, B, C, and D) (20). For the analysis, severe disease was defined as grades C or D.

Statistical Analyses

Data are expressed as mean $\pm$ standard error. One-way ANOVA for anatomic damage and post hoc comparisons were made using the Fisher method. A general linear method for multivariate analysis of covariance (MANCOVA) was used to assess the interaction between BMI and grade of esophageal damage. We used three categories of BMI: normal weight (BMI <25), overweight (BMI between 25 and 30), and obese (BMI >30). They were used as fixed factors. Other fixed factors were sex, LA classification, and the interaction between BMI and LA classification. We considered the background of the practitioner as a random factor, and age was considered as a covariate. This helped to control the expected high standard error in this sample and increased the internal validity of the study. The statistical value (*a priori*) for statistical significance in this interaction model was $p < 0.10$. Surface graphics were set to show smooth function of interaction between BMI and anatomic damage.

Ethics

All applicable international regulations concerning the ethical participation of our volunteers were followed during this research protocol. The study and signed informed consent were approved by the Ethics Committee of Research of the Dr. Maximiliano Ruiz Castañeda General Hospital of Naucalpan, Estado de Mexico, Mexico and the Center of Bioethics of the Faculty of Medicine, University of Guanajuato, Mexico.

Results

Study Participants

We recruited 954 patients. Of these, 917 (53.76% females) subjects had complete data and were included in the analysis. Average age was 36.8 ± 7 years (no gender difference). BMI for males was higher than females (26.8 ± 3.5 vs. 25.2 ± 4.5 , $p < 0.001$).

Esophageal Damage

General comparisons related to anatomic damage are described in Table 1 and those related to BMI can be seen in Table 2. Esophageal damage was associated with the symptom severity of heartburn, regurgitation, retching, halitosis, and chest oppression.

Esophageal damage differed by sex: men had severe LA (C–D damage) [OR = 3.7, 95% CI 1.7–8.2] and mild damage (B damage) [OR = 1.56, 95% CI 1.1–2.3] compared to women and was associated with BMI: lesions grade C–D in BMI between 25 and 30 was OR = 2.8 (95% CI 1.16–6.7) and for those with BMI >30, the OR = 2.1 (95% CI 0.65–6.8), compared to BMI <25.

Interaction Between BMI and Esophageal Damage for Symptom Severity

The MANCOVA model showed significant interaction between BMI and LA for severity of heartburn and retching. The surface response graphics and tables are showed in Figure 1. Severest symptoms for heartburn and retching were for BMI between 25 and 30 and were associated with LA damage C–D. Interestingly, those with no anatomic damage showed an increase in symptom score for heartburn as the BMI increased (Point 2 in Figure 1A). Retching decreased for those with BMI >30, whereas LA damage increased (Figure 1B).

Nausea was a very interesting symptom. Its score increased significantly for C–D damage but was negatively related to the BMI categories (Figure 2). BMI and anatomic damage maintained an independent effect on regurgitation, whereas nausea was affected only by BMI. There was no interaction between BMI and LA damage. Other important symptoms positively associated with obesity were flatulence and halitosis, the latter was independently associated with severe LA (C–D).

Discussion

This study demonstrates that BMI >30 has increased risk of esophageal damage, but the symptom intensity may be lower compared with overweight subjects with the same LA damage. To our knowledge, this is the first study that demonstrates that this interaction has a lack of additive effect, especially for heartburn severity. Threshold for pain sensation could change with obesity. Our study suggests that pain threshold in obese subjects may be different from lean subjects. Nausea was related to anatomic damage; meanwhile, increase in BMI blunted this response. Interestingly, as a subject gained weight, he or she was less likely to suffer from nausea in spite of the anatomic damage.

Obesity appears to be a factor that can change pain produced by esophageal lesions or digestive tract sensitivity. Other reports considered different factors that can change pain perception. Studies based on ethnic differences show that Indians complain more about heartburn and acid regurgitation and have more structural damage compared with Chinese and Malaysian populations. Malaysians complain more about reflux symptoms than exhibiting signs of reflux damage (21). Older age is associated with a high prevalence of erosive esophagitis but less sensitivity to severity of heartburn (22). Moreover, older age is also associated with decreased sensitivity to pain after balloon distension (23). Some speculate that acute acid exposure can

sensitize the esophagus to pain (24), but this notion is still controversial (25). To our knowledge there are no specific studies that analyze visceral pain for GERD in obese subjects.

Gender Affects Symptom Intensity and LA Damage

Another interesting finding published elsewhere was that males had a higher risk than females of suffering more severe disease (26), and this difference may be due to the effect of sex hormones on parietal cell mass (27). The higher BMI found in males was not associated with the severity of heartburn or retching. Genetic influences account for 31% of the likelihood of having GERD, with differences in the functional genes according to gender (28).

Other Studied Symptoms

Extra-esophageal symptoms showed that BMI was associated with severity of flatulency, as reported by Danish researchers (29). Other studies have shown obese women with BMI >35 are at increased risk for mild to moderate flatus incontinence (30).

Halitosis has been described as an extra-esophageal manifestation of GERD. We found a positive association with obesity and the severity of esophageal damage. Other researchers have described that halitosis is positively correlated with obesity (31), the intensity of heartburn, and reflux but not with functional dyspepsia, peptic ulcer disease and *Helicobacter pylori* infection (32). A strong association with halitosis and gastroesophageal reflux has recently been described (33).

Limitations and Advantages of the Study

The main limitation of this study is the fact that the subjects were self-selected and cannot be assumed to be representative of the population. To partially solve this inconvenience, we used intercorrelational analysis of the variables. The strength of our study was that we used semiquantitative scales for the variables instead of the dichotomous variables that other studies used. BMI, pain, and anatomic damage are continuous variables. This strategy allowed us to analyze interaction quantitatively for a complex phenotype. The interaction we found showed a nonlinear relationship. This finding may explain some of the conflicting findings reported in different studies. Some studies have dichotomized the BMI to compare obese vs. non-obese. This approach can have the advantage of increased power but loses information regarding details on obesity grades. Studies focusing on specific responses for patients in different obesity groups should be done in order to understand how anatomic damage is affecting defensive responses (e.g., pain, retching, nausea). A partial limitation was the use of the BMI instead of waist circumference; however, these two variables can be used as surrogate to each other. Coefficient correlation in previous studies was $r = 0.90$ for women and $r = 0.92$ for men.

Complex traits for GERD are the combination of pain threshold, anatomic damage, and BMI, and they can be used in genomic analysis for explanation of underlying complexity of the disease. The present findings can help to detect bias in analysis, including intensity of GERD symptoms due to BMI increase. Extremely obese subjects may suffer mild symptoms of GERD and have a significant anatomic lesion. It is important to recognize the relationship between these variables because GERD is a risk factor of Barrett's esophagus, which in turn increases the risk of developing adenocarcinoma of the esophagus (34,35).

Further Research and Conclusions

Further studies about symptom intensity should be done in different obese populations, among them those with morbid obesity and mild anemia (Hb ~11 g/dL). This group of subjects may suffer from esophageal lesions and may not show important symptoms. Other interesting aspects would be to understand the subjacent cellular physiopathology that explains the lack

of sensation in obese subjects. The response of obese subjects and esophageal lesions to pantoprazol is another aspect for future studies. Finally, we conclude that the joint effect of BMI and LA endoscopic grade on the severity of GERD is not linear, and some subjects with mild symptom intensity may have significant esophageal damage. This relationship can help to interpret some of the conflicting findings reported in different publications.

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	None	A	B	C-D
BMI >30	2.51 ± 0.1	2.26 ± 0.1	2.36 ± 0.2	2.58 ± 0.3
25 – 30	2.20 ± 0.1	2.26 ± 0.1	2.57 ± 0.1	2.68 ± 0.2
BMI <25	2.18 ± 0.1	2.29 ± 0.1	2.32 ± 0.1	2.31 ± 0.2

	None	A	B	C–D
BMI >30	0.63 ± 0.2	0.61 ± 0.1	0.38 ± 0.2	0.05 ± 0.5
25 – 30	0.74 ± 0.1	0.71 ± 0.1	0.67 ± 0.1	1.55 ± 0.3
BMI <25	0.59 ± 0.1	0.77 ± 0.1	0.91 ± 0.1	0.76 ± 0.5

Figure 1.

Significant joint effect of body mass index and anatomic damage on severity of symptoms. The level curves at the surface response graphic show the score for severity symptoms. Panel A, heartburn: Point 1 shows the highest score. Point 2 shows subjects with BMI >30 and no esophageal lesions. Point 3 shows subjects with BMI <25 and no esophageal lesions, they had the lowest score for heartburn intensity. Interaction $p < 0.10$. Panel B, retching. Point 1 shows the highest score. Interaction $p < 0.025$.

Figure 2.
The graph shows the independent effect of BMI and esophageal anatomic damage on severity of nausea. Different significant groups are marked by letters.

Table 1

General data and symptoms associated with grade of esophageal damage (mean $\pm$ SE)

	Grade of esophageal damage				<i>p</i> value
	None	A	B	C-D	
<i>n</i> (F/M)	116/81	247/188	121/132	9/23	<0.001
Age (years)	37.3 (0.5)	36.3 (0.4)	37.4 (0.4)	37.9 (1.2)	0.159
BMI <25*	86 (20.6)	209 (51.4)	107 (26.3)	7 (1.7)	-
BMI 25–30*	85 (22.6)	158 (42.0)	113 (30.1)	20 (5.3)	-
BMI >30*	28 (20.9)	68 (50.7)	33 (24.6)	5 (3.7)	-
Heartburn (pyrosis)	2.26 (0.05) ^a	2.29 (0.03) ^a	2.45 (0.04) ^b	2.52 (0.12) ^b	0.002
Regurgitation	2.19 (0.06) ^a	2.20 (0.03) ^a	2.36 (0.04) ^b	2.36 (0.14) ^{a,b}	0.015
Retching	0.66 (0.08) ^a	0.72 (0.05) ^a	0.70 (0.07) ^a	1.24 (0.28) ^b	0.058
Halitosis	1.05 (0.09) ^a	1.21 (0.06) ^a	1.19 (0.07) ^a	1.58 (0.18) ^b	0.095
Discomfort	1.89 (0.07) ^a	2.00 (0.04) ^{a,b}	2.10 (0.05) ^b	1.87 (0.18) ^{a,b}	0.067
Nausea	1.28 (0.08)	1.25 (0.05)	1.19 (0.06)	1.50 (0.21)	0.447
Flatulence	1.19 (0.09)	1.33 (0.06)	1.22 (0.08)	1.48 (0.23)	0.367
Chest oppression	1.37 (0.09) ^a	1.39 (0.05) ^a	1.45 (0.07) ^a	1.93 (0.18) ^b	0.062
Dysphony	0.71 (0.08)	0.80 (0.05)	0.93 (0.07)	0.83 (0.21)	0.248

^{a-c} Homogeneous groups by post hoc Scheffe analysis.

* Frequency (percentages by row).

 $\chi^2 = 13.5$, $p = 0.036$.

F/M, female/male.

Table 2General data and symptoms contrasted by BMI (mean $\pm$ SE) or frequency (percentage)

	BMI			<i>p</i> value
	<25	25–30	>30	
<i>n</i> (F/M)	272/158	158/218	63/71	<0.001
Age (years)	35.07 (0.39) ^a	37.94 (0.32) ^b	39.47 (0.50) ^c	<0.001
BMI	22.45 (0.09) ^a	27.18 (0.07) ^b	39.47 (0.28) ^c	<0.001
Heartburn (pyrosis)	2.29 (0.03) ^a	2.37 (0.03) ^b	2.36 (0.06) ^{a,b}	0.172
Regurgitation	2.21 (0.04)	2.31 (0.04)	2.22 (0.06)	0.119
Retching	0.79 (0.06) ^a	0.73 (0.06) ^a	0.53 (0.08) ^b	0.053
Halitosis	1.09 (0.06) ^a	1.31 (0.06) ^b	1.24 (0.09) ^{a,b}	0.031
Discomfort	2.05 (0.04)	1.95 (0.04)	2.03 (0.07)	0.295
Nausea	1.37 (0.05) ^a	1.17 (0.06) ^b	1.04 (0.08) ^b	0.001
Flatulence	1.13 (0.06)	1.34 (0.06)	1.56 (0.10)	0.001
Chest oppression	1.41 (0.06)	1.42 (0.06)	1.51 (0.10)	0.683
Dysphony	0.72 (0.06) ^a	0.87 (0.06) ^b	1.01 (0.10) ^b	0.028

^{a–c} Homogeneous groups by post hoc Scheffe analysis.* *p* value from χ^2 for all grades of esophageal damage.

F/M, female/male.