endogenous inhibitor of angiogenesis and tumor growth / M.S. O'Reilly // Cell. – 1997. 88:277-285.

15. Terman B.I., Stoletov K.V. VEGF and Tumor Angiogenesis / B.I. Terman // Einstein Quart. J. Biol. and Med. – 2001. 18:59-66.

16. Nissen M.J. et al Efficacy of intra-articular bevacizumab for relapsing diffuse-type giant cell tumour / M.J. Nissen // In:Ann Rheum Dis. – 2014. 73(5), P. 947–948.

17. Manchini G. Immunological quantitation of antigenes by single radial diffusion / G. Manchini// Immunochemistry. – 1965. – № 2. – P. 235 – 239.

18. Haskova V. Novy spusob stanoveni circulyjcich immunokomplexes v lidskych serech / V. Haskova // Z Cas. Lek. Ceb. – 1977. – № 14 (116). – C. 437 – 438.

19. Bentley G., Kreutner A., Ferguson A.B. Synovial regeneration and articular cartilage changes after synovectomy in normal and steroid-treated rabbits / G. Bentley // J Bone Joint Surg Br. – 1975.;57(4):454-62. – PMID: 1194312.

20. Ostergaard M., Ejbjerg B., Stoltenberg M., Gideon P., Volck B., Skov K. et al Quantitative magnetic resonance imaging as marker of synovial membrane regeneration and recurrence of synovitis after arthroscopic knee joint synovectomy: a one year follow up study / M. Ostergaard // Ann Rheum Dis. – 2001.; 60(3): 233–236. – doi: 10.1136/ard.60.3.233. – PMID: 11171684

21. Григоровский В.В., Сильченко В.П., Григоровская А.В. Гистологическое строение, клеточный состав и клинико-морфологическая дифференциальная диагностика синовиальной гигантоклеточной опухоли диффузного типа / В.В. Григоровский // Онкология. – 2015. Т. 17, № 2. – с. 119-128.

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ENDOSCOPIC APPEARANCE OF GASTROESOPHAGEAL REFLUX DISEASE AND ITS ASSOCIATION WITH BODY MASS INDEX

Abstract. Introduction. Gastroesophageal reflux disease (GERD) is a common condition characterized by the presenting symptoms of heartburn and/or regurgitation.

GERD affects millions of people worldwide and has an estimated worldwide prevalence of 8-33%. An important risk factor for GERD is obesity, which has been increasing in prevalence and is strongly associated with adverse metabolic, cardiovascular, chronic inflammatory and malignant health outcomes.

The aim of the study. To study the association between the BMI and endoscopic appearance of GERD. **Materials and methods.** Retrospective study, medical documentation of 250 patients in Health center 4, Riga, Latvia has been analyzed. Data included patients gender, age, weight, height, calculated BMI (body mass index), stage of GERD using Los Angeles classification. The association between BMI and endoscopic appearance of GERD was studied using various statistical tests - Shapiro-Wilk test, Kolmogorov-Smirnov test, nonparametric test - Kruskal-Wallis test, Pairwise Comparisons and Chi Square test.

Results. From 250 total cases of endoscopic positive GERD, 59% (147) representatives were women and 41% (103) were men. The median age of the patients was 40(31.75-50.00) years. The median BMI was 27.16(23.79-30.13) kg/m^2. The median BMI in GERD groups A – 25,24 (22.75-28.73), B - 28.91(26.04-30.31) and C - 30.04(27.71-32.01) kg/m^2. The distribution of BMI differs across GERD stages ($p<0.001$). BMI is statistically significantly higher between patients with diagnosed GERD, stage B (28.91(26.04-30.31) kg/m^2) than stage A (25.24(22.75-28.73) kg/m^2) ($p<0.05$). And BMI is statistically significantly higher between patients with diagnosed GERD, stage C (30.04(27.71-32.01)) kg/m^2) than stage A (25.24(22.75-28.73) kg/m^2) ($p<0.001$).

Conclusion. This study demonstrates an association between the BMI and endoscopic appearance of GERD. The median BMI is higher in GERD stages where mucosal damage is greater.

Key words: GERD (gastroesophageal reflux disease), BMI (body mass index), upper gastrointestinal endoscopy, obesity, risk factors.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which acid backs up from the stomach into the esophagus and even up to the throat, irritating their lining tissues. GERD is a common chronic disorder in developed countries of the world. **GERD affects millions of people worldwide and** has an estimated worldwide prevalence of 8-33%, the prevalence in the Western world was found to be 10-20% and less than 5 percent in Asia. Gastroesophageal reflux disease is one of the most frequent diseases encountered by primary care physicians and gastroenterologists. [1.2.4.]

The classic and most common symptoms of GERD is heartburn and regurgitation. Other symptoms

include globus sensation, dysphagia, odinophagia and chest pain. If symptoms are left untreated, a major concern is the potential risk of peptic strictures, Barret`s metaplasia and esophageal adenocarcinoma associated with GERD. Extraesophageal manifestations are also common, but not always diagnosed, symptoms include chronic cough, asthma, laryngitis, sinusitis, hoarseness, pharyngitis and dental erosion syndrome. [3.7.]

Risk factors include older age, excessive body mass index (BMI), smoking, anxiety/depression, and less physical activity at work. [1.]

Maev, Yurenev et al published that epidemiological data indicate that obesity is a significant risk factor for developing GERD due to increased intra-abdominal pressure and gastroesophageal gradient, slowing of gastric evacuation and formation of hiatal hernia. Abdominal obesity increases complications of GERD: erosive esophagitis, Barrett's esophagus and adenocarcinoma. [9.]

Body mass index (BMI) is an index of weight-for-height that is commonly used to classify overweight and obesity in adults. World health organization defines that overweight people are these who have BMI greater than or equal to 25 kg/m^2; and obesity - BMI greater than or equal to 30 kg/m^2. (Table 1) [8.]

Table 1

Classification of body mass index

Classification	BMI (kg/m^2)	Risk of comorbidities
Underweight	< 18.5	Low
Normal range	18.5-24.9	Average
Overweight	25.0-29.9	Mildly increased
Obese	≥ 30.0	
Class I	30.0-34.9	Moderate
Class II	35.0-39.9	Severe
Class III	≥ 40.0	Very severe

WHO report that in 2016, more than 1.9 billion adults aged 18 years and older were overweight. Among them over 650 million adults were obese. The prevalence of overweight and obesity among children and adolescents aged 5-19 has been risen dramatically from just 4% in 1975 to just over 18% in 2016. [8.]

Mandeep Singh, Jaehoon Lee et al published that the overall prevalence of GERD symptoms is high (37%) in overweight and obese subjects. A structured weight loss program can lead to complete resolution of GERD symptoms in the majority of these subjects. [5.]

GERD classification is based on the apperance of the esophageal mucosa on upper endoscopy. First, erosive esophagitis or endoscopy positive GERD is characterized by endoscopically visible breaks in the distal esophaeal mucosa with or witout symptoms of GERD. Second, nonerosive reflux disease or endoscopy negative reflux disease is characterized by the presence of symptoms without visible esophageal mucosal injury. [1.2.]

The most commonly used diagnostic test for the evaluation of GERD is the upper gastrointestinal endoscopy or esophagogastroduodenoscopy (EGDS). The benefit of endoscopy is visualization of the esophageal mucosa. [6.]

The Los Angeles classification is the most thorougly evaluated classification for esophagitis and is the most widely used. (Table 2) [1.]

Table 2

Los Angeles classification of GERD

Grade	Endoscopic description
A	One or more mucosal break < 5mm that does not extend between the tops of two mucosal folds.
B	One or more mucosal break ≥ 5mm that does not extend between the tops of two mucosal folds.
C	One or more mucosal break that is continuous between the tops of two or more mucosal folds but that involves < 75 % of the circumference.
D	One or more mucosal break that involves ≥ 75 % of the esophageal circumference

MATERIALS AND METHODS

The retrospective research was carried out at Health center 4, Riga, Latvia by analyzing medical documentation of 250 patients that had referred for upper gastrointestinal endoscopy and have been diagnosed with endoscopic positive GERD between January 2018 and October 2019. Data included patients gender, age, weight, height (obtained from patient self-administered questionnaire) and stage of GERD (obtained from endoscopists conclusion of procedure – upper gastrointestinal endoscopy).

By using data of weight and height from self-administered questionnaire BMI was calculated for all patients by using formula:

$$BMI = \frac{weight(kg)}{(height(m))2}$$

and they were classified as underweight (BMI <18.5), normal weight (BMI 18.5 -24.9), overweight (BMI 25-29.9) and obese (BMI≥30) according to WHO BMI classification. Patients were divided into groups regarding GERD stage by using Los Angeles staging system – grade A, B, C or D.

Data was statistically processed in IBM SPSS Statistics 22. Descriptive statistics (median, quartiles, mean, standard deviation, minimum, maximum) and

frequencies were used to describe included patients in common and also to describe researched groups.

The association between the BMI and endoscopic appearance of GERD was studied using various statistical tests. To identify normality of data Shapiro-Wilk test and Kolmogorov-Smirnov test was used. According to these tests variables do not follow normal distribution, so further there were nonparametric tests used in analysis. Independent sample nonparametric test (Kruskal-Wallis test) was performed. To compare GERD groups in pairs Pairwise Comparisons were used. Last the Chi Square test was performed to identify if there is a statistically significant difference between BMI groups. Level of statistical significance was accepted at p value less than 0,05.

RESULTS

From 250 total cases of endoscopic positive GERD, 59% (147) representatives were women and 41% (103) were men.

To identify normality of data Shapiro-Wilk test and Kolmogorov-Smirnov test was used. According to these tests variables (gender, age, weight, height, BMI) do not follow normal distribution, so further there were nonparametric tests used in analysis that are based on median data.

The median age of the patients was 40(31.75-50.00) years (Table 3). The median BMI was 27.16(23.79-30.13) kg/m^2 (Table 3).

Table 3

Overall description of patients

	M(SD)	Me(Q1-Q3)	Min-Max
Age, years	41.62(12.66)	40(31.75-50.00)	17-78
Height, m	1.75(0.10)	1.76(1.68-1.82)	1.35-2.06
Weight, kg	85.11(18.00)	85.00(72.00-97.00)	44-174
BMI, kg/m^2	27.60(5.24)	27.16(23.79-30.13)	18.11-52.53

Among these cases the most common endoscopic finding was GERD, grade A (61.2%(153)), followed by grade B (20.4%(51)), grade C (18.4%(46)), none of the patients had GERD, grade D.

Similar as in common divided by GERD groups data of variables do not follow normal distribution. The description of GERD groups is shown in Table 4. The median BMI in GERD groups A, B and C is as follows - 25.24(22.75-28.73), 28.91(26.04-30.31) and 30.04(27.71-32.01) kg/m^2. In conclusion – the median BMI is higher in GERD stages where mucosal damage is greater. Further analysis is necessary to identify if these differences described above are statistically significant.

Table 4

Description of patients by GERD groups

	GERD, stage		
	A	B	C
	Me(Q1-Q3)	Me(Q1-Q3)	Me(Q1-Q3)
Age, years	40.00(32.00-50.00)	39.00(30.00-46.00)	40.50(31.75-51.00)
Height, m	1.76(1.66-1.81)	1.80(1.73-1.86)	1.76(1.70-1.82)
Weight, kg	77.00(67.50-90.00)	92.00(85.00-104.00)	93.00(82.75-102.50)
BMI, kg/m^2	25.24(22.75-28.73)	28.91(26.04-30.31)	30.04(27.71-32.01)

Nonparametric data was compared through independent sample nonparametric test (Kruskal-Wallis test). The distribution of BMI differs across GERD stages ($p<0.001$). Distribution of the BMI according to the GERD stages is graphically depicted in box plot chart (Figure 1).

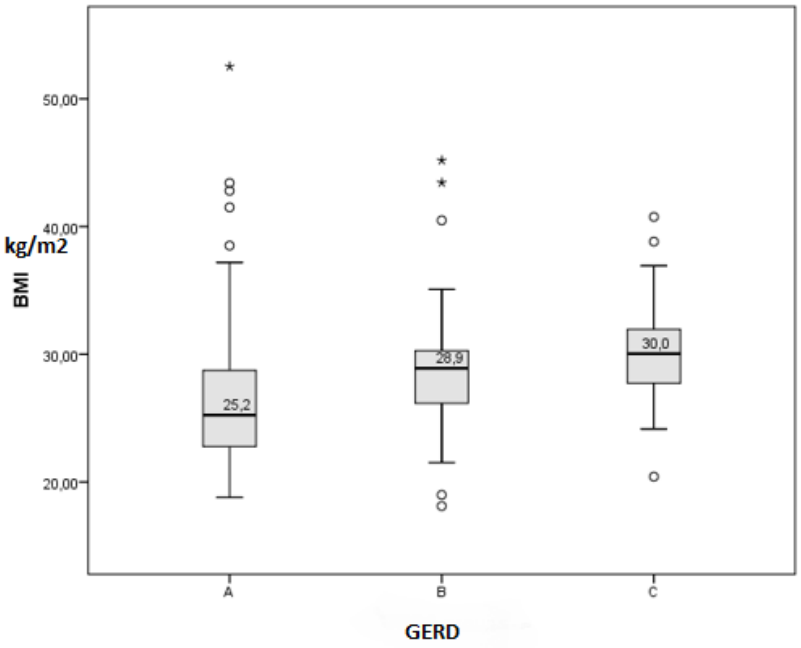

Figure 1. Distribution of the BMI according to the GERD stages

To compare GERD groups according to BMI in pairs Pairwise Comparisons were performed. The test shows that BMI is statistically significantly higher between patients with diagnosed GERD, stage B (28.91(26.04-30.31) kg/m^2) than stage A (25.24(22.75-28.73) kg/m^2) ($p<0.05$). And BMI is statistically significantly higher between patients with diagnosed GERD, stage C (30.04(27.71-32.01)) kg/m^2) than stage A (25.24(22.75-28.73) kg/m^2) ($p<0.001$).

Patients were divided in groups regarding BMI and these groups were ranked as follows in a descending order: overweight – 96 cases (38.4%), normal weight – 86 (34.4%), obese – 67 (26.8%), underweight – 1 (0.4%).

By performing Chi Square test it was identified that there is a statistically significant difference between BMI groups ($x^2(4) = 36.95$, $p<0.001$). Cluster bar chart depicts association between GERD stages and BMI groups (Figure 2). There are statistically significantly more patients in group of patients with normal weight who have been diagnosed with GERD, stage A (48%) than stage B (18%) and stage C (9%). There are no statistically significant differences between GERD stages among overweight patients. In group of obese patients there are statistically significantly more patients with GERD, stage C (50%) than stage A (19%).

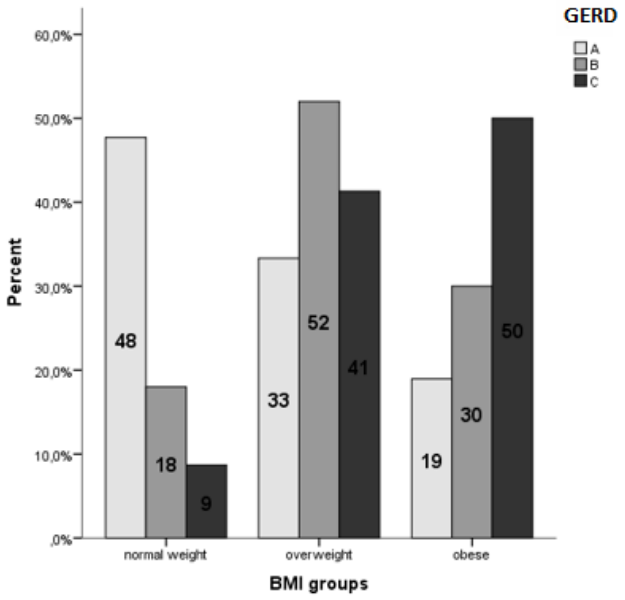

Figure 2. Association between GERD stages and BMI group.

DISCUSSION

First, to improve the study, we could include control group of healthy individuals, who have not been diagnosed with reflux esophagitis by endoscopy and have not experienced symptoms of GERD. We suggest that individuals with normal weight or underweight do not have reflux disease or have GERD, grade A by Los Angeles classification.

Second, in our study we included patients only from Health center 4, in Riga, Latvia, which is an outpatient private clinic. To improve the study, we could include other outpatient private clinics and other hospitals in Latvia to get data that characterize overall population.

Third, as we know, GERD risk factors are older age, excessive body mass index (BMI), smoking, anxiety/depression and less physical activity. For that reason we could include in the reaserch other risk factors such as smoking, because it has been identified as a significant risk factor in several studies. In our study we are not aware about patient`s smoking status.

The main problem in our study was, that group of GERD, grade C esophagitis had a small number of patients and none of the patients had GERD, grade D by Los Angeles classification.

CONCLUSIONS

GERD is a common chronic disorder in developed countries of the world. Epidemiological data indicate that obesity is a significant risk factor for developing GERD.Abdominal obesity increases complications of GERD: erosive esophagitis, Barrett's esophagus and adenocarcinoma. The prevalence of overweight and obesity among children and adolescents aged 5-19 has risen dramatically from just 4% in 1975 to just over 18% in 2016.

In our study the median BMI is higher in GERD stages where mucosal damage is greater. The study shows that BMI is statistically significantly higher between patients with diagnosed GERD, stage B than stage A ($p<0.05$). And BMI is statistically significantly higher between patients with diagnosed GERD, stage C than stage A($p<0.001$). There were statistically significantly more patients in group of patients with normal weight who have been diagnosed with GERD, stage A than stage B and stage C. In group of obese patients there are statistically significantly more patients with GERD, stage C than stage A.

REFERENCES

1. Stephan Vavricka, Martin Wilhelmi, Essentials in gastroenterology and hepatology, 2017, 386 pages.

2. Danisa M.Clarrett, Christine Hachem, Gastroesophageal Reflux Disease, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140167/

3. Elif Saritas Yuksel, MD and Michael F. Vaezi New Developments in Extraesophageal reflux disease, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3594960/

4. Harland S Winter et al Clinical manifestations and diagnosis of gastroesophageal reflux disease in children and adolescents, 2018. https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-gastroesophageal-reflux-disease-in-children-and-adolescents?search=GERD&source=search_result&selectedTitle=8~150&usage_type=default&display_rank=8

5. Mandeep Singh, Jaehoon Lee et al Weight Loss Can Lead to Resolution of Gastroesophageal Reflux Disease Symptoms: A Prospective Intervention Trial, 2013, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853378/#__ffn_sectitle

6. Michael AJ Sawyer et al, Gastroesophageal Reflux Disease (GERD) Imaging, 2019. https://emedicine.medscape.com/article/368861-overview

7. Peter J Kahrilas et al, Clinical manifestations and diagnosis of gastroesophageal reflux in adults, 2019. https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-gastroesophageal-reflux-in-adults?search=GERD&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4

8. World health organisation, obesity and overweight, 2018. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

9. Maev, Yurenev et al, Phenotype of obesity and gastroesophageal reflux disease in the context of comorbidity in patients with cardiovascular diseases, 2019. https://www.ncbi.nlm.nih.gov/pubmed/31094183