Effect of body weight and obesity on esophageal function

Running title: Effect of obesity on esophageal function

Yi Yang[1], MD, Jia-rong Lin[1], MD, Yan-qiu Li[1], MD, Yu-shan Wei[2], MD, Zhi-jun Duan[1*], Ph.D, MD

1. Department of Gastroenterology, The First Affiliated Hospital of Dalian Medical University, Dalian, 116011, China;

2. Department of the Scientific Research Management, The First Affiliated Hospital of Dalian Medical University, Dalian, 116011, China

***Corresponding author**

Zhi-jun Duan

Department of Gastroenterology,

The First Affiliated Hospital of Dalian Medical University,

No.222 of Zhongshan Road, Xigang District

Dalian 116011,

China

Tel:+86 18098875588

Email: duanzhijundzj@126.com

Competing interests

The authors declare that they have no competing interests.

Funding

No external funding received to conduct this study.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Abstract

Background: The incidence of obesity in the population is gradually increasing. Obesity can cause a variety of complications in the digestive system such as gastroesophageal reflux disease, and impacts the integrity of the esophageal mucosal barrier and esophageal motility. However, not many studies have focused on the effect of varying degrees of obesity on the esophagus.

Methods: A total of 611 participants were included in this study. We divided them into three groups according to their body mass index (BMI): the normal weight group, the overweight group, and the obesity group. We performed a retrospective comparison between groups based on indicators from high resolution esophageal manometry (HREM) and 24-hour pH impedance monitoring, and did a correlation analysis on multiple indicators such as esophageal mucosal barrier, esophageal motility, and acid reflux.

Results: The mean nocturnal baseline impedance (MNBI) in the overweight and obesity groups was lower than that in the normal group. The MNBI of the subjects in Z5–Z6 channels in the overweight group was significantly lower than that in the normal group. With respect to Z3–Z6 channels, MNBI values in the obesity group were significantly lower than those in the normal group. The acid exposure time (AET) was

significantly higher, while the DeMeester scores (DMS), and 24-hour total reflux episodes were significantly lower in the obesity group than those in the normal and overweight groups. The upper esophageal sphincter (UES) residual pressure, and intrabolus pressure (IBP) in the overweight and obesity groups were significantly higher than those in the normal group. In addition, lower esophageal sphincter (LES) resting pressure, and esophagogastric junction contractile integral (EGJ-CI) in the obesity group were significantly higher than those in the normal group.

Conclusion: We found that increase in body weight affected the integrity of esophageal mucosa, and different degrees of increase associated with different degrees and different aspects of changes in esophageal motility.

Keywords: esophageal barrier; gastroesophageal reflux; manometry; obesity; 24h pH-impedance

1. Background

Obesity is a widespread metabolic disease in the 21st century. Over the years, the number of persons with obesity is gradually increasing[1]. In 2016, the World Health Organization (WHO) reported that 650 million adults were obese, accounting for 34% of the total overweight population[2]. Obesity contributed to 3.4 million deaths indirectly or directly, and 4% of disability-adjusted life-years (DALY)[3]. Obesity can affect the functioning of multiple organs in the body, leading to a variety of complications in the cardiovascular system, respiratory system, digestive system, and psychological health.[4] Gastroesophageal reflux disease (GERD), Barrett's esophagus, and esophageal cancer are among the common diseases of the digestive system[5]. Obesity, especially abdominal visceral obesity, is a risk factor for reflux esophagitis (RE)[6,7], and has also been associated with non-erosive gastroesophageal reflux disease (NERD)[8]. Multiple studies have found that obesity can cause damage to the esophageal mucosa[9,10,11,12], and may also lead to changes in esophageal motility[13,14].

Esophageal 24-hour pH-impedance test is the gold standard for diagnosis of gastroesophageal reflux disease (GERD) [4]. During pH monitoring, the impedance when reflux or swallowing does not occur reflects the intrinsic conductivity of the mucosa, that is, the baseline impedance (BI). The mean nocturnal baseline impedance (MNBI) is obtained by taking the mean value of the measured BI over a fixed nocturnal period. MNBI reflects esophageal mucosal integrity, and its decrease reflects impairment of esophageal mucosal integrity[15], which may not be detected endoscopically[16,17].

High-resolution esophageal manometry (HREM) is currently the preferred investigation for evaluating esophageal motility[18]. Studies have shown that obese

patients have esophageal motility changes[19,20,21], but most of the existing studies are based on HREM to determine the type of esophageal motility disorders in obese patients, and only a few studies have included a comprehensive analysis of changes in HREM indicators in obese patients.

Therefore, in this study, we evaluated Asian obesity and the extent of its impact on the esophagus by measuring esophageal 24-hour pH-impedance and HREM, as well as the integrity of the esophageal mucosal barrier, motility indicators, and reflux indicators. We investigated the effects of different degrees of obesity on the esophageal mucosal barrier, and other functional indicators of the esophagus, so as to provide guidance for the clinical management and treatment of patients with various body weights.

2. Materials and Methods

2.1 Study population and design

This study retrospectively collected data from patients who attended the Gastrointestinal Dynamics Center of our hospital from April 2019 to June 2022. Patients who were treated with regular PPI for at least 8 weeks after the onset of reflux-like symptoms and remained ineffective and required further determination of the esophageal function and reflux were qualified for enrollment. All patients underwent upper gastrointestinal endoscopy, HREM and ambulatory 24-hour pH-impedance monitoring. The general data of enrolled patients, including age, sex, height, and weight, were collected by the same physician. This study was approved by the first affiliated hospital of Dalian Medical University, Liaoning, China.

Inclusion criteria: Patients aged over 18 years, and who had not taken proton pump inhibitor (PPI) treatment or prokinetic drugs within two weeks prior to the study.

Exclusion criteria: Patients with incomplete data; patients whose endoscopy

showed achalasia of cardia, peptic ulcer, tumor and other diseases; and patients who had previous abdominal surgery.

We enrolled a total of 611 individuals based on the inclusion and exclusion criteria.

We divided the participants into three groups based on their body mass index (BMI): normal group (BMI < 23 kg/m^2), overweight group (BMI ≥ 23 kg/m^2 and < 25 kg/m^2), and obesity group (BMI ≥ 25 kg/m^2)[22,23]. In addition, participants whose BMI ≥ 35 kg/m^2 were classified as morbidly obese[24,25].

2.2 Upper gastrointestinal endoscopy

Patients underwent a gastrointestinal endoscopy within two months prior to completing the HREM and 24-hour pH impedance monitoring. Upper gastrointestinal endoscopy was performed according to international guidelines. The examinations were performed by experienced physicians.

2.3 High-resolution esophageal manometry (HREM)

We performed the HREM using GAP-36A (Medkinetic Incorporated, Ningbo, China) to evaluate esophageal functioning. Before undergoing the HREM, patients were instructed to stop taking PPI and prokinetic drugs for at least 14 days[26]. Participants were required to fast eight hours or more before the investigation. The catheter was passed trans-nasally, and passed from the hypopharynx to the stomach. We adjusted the tubes for three to five minutes. When the upper esophageal sphincter (UES) pressure and the lower esophageal sphincter (LES) pressure were stable, we recorded the resting pressure for at least 30 seconds. The patients were then asked to swallow 5 ml of water kept at room-temperature every 30 seconds, for more than 10 times in total. Patients were advised to avoid repeated swallowing and only swallow once. We used the Manoview 3.0 software for analysis, and followed the Chicago classification

v4.0[27].

In this study, we included the following indicators that reflect esophageal motility: LES resting pressure, residual pressure, length, UES resting pressure, residual pressure, length, distal contractile integral (DCI), distal latency (DL), intrabolus pressure (IBP), number of peristaltic contractions, and esophagogastric junction contractile integral (EGJ-CI).

2.4 24-hour pH-Impedance Monitoring

24-hour pH-impedance testing was performed immediately after the HREM. A SleuthVR Multichannel Intraluminal Impedance ambulatory system (Sleuth; Sandhill Scientific, Inc., Highlands Ranch, CO, USA) was used. A pH sensor was positioned 5 cm above the upper edge of the LES, a catheter was fixed at the nasal ala, and we recorded the start time. The patient was given instructions to fill in a monitoring diary accurately, including details such as the start and the end time of eating and lying down, the type of symptoms, and their respective start times. Patients were advised to follow their regular routine, reduce their intake of acidic food, beverages, and alcohol, avoid lying in bed all day, avoid strenuous exercise after a meal, and flush the catheter with warm boiled water. The catheter was removed after 24 hours of monitoring. We connected the monitor to a computer, and used a professional software (BioViewanalysisVR; SandHill Science, Inc.) for analysis.

The reduction of esophageal baseline impedance (BI) can reflect esophageal inflammation, and damage to the integrity of esophageal mucosa that does not show up in the endoscopic examination can be detected in this method. As swallowing and reflux activities during the day can affect the measurement of BI, the BI values were recorded when patients were asleep three different times, early in the morning (at 1 am, 2 am and 3 am). We took the average value of these as the mean nocturnal baseline impedance

(MNBI)[28,29]. We included the MNBI values for the six channels (Z1–Z6) in the study to assess the integrity of the esophageal mucosal barrier.

We also included the following indicators: acid exposure time (AET), DeMeester score (DMS), and total reflux episodes, which were used to reflect esophageal reflux.

3. Statistical analysis

Statistical analysis was done using IBM SPSS 26.0 (Armonk, NY, USA). Count data was described as percentage (%). The Pearson's chi-square test was used to compare the three groups on baseline patient characteristics. Kolmogorov-Smirnov test was used for checking the normal distribution of data, and continuous variables were expressed as quartiles. The comparison of continuous variables between two groups was performed using the Mann-Whitney U test. Spearman correlation analysis was used to analyze dependence between ariales, and the correlation parameter was expressed by correlation coefficient, r. The Durbin-Watson test statistic was used for single factor regression analysis, and the parameters were expressed by β. $P < 0.05$ indicated that the difference was statistically significant.

We compared data between groups using the Kruskal-Wallis test. We used this test because we were analyzing multiple sets of data, and the data was from participants who were divided into three groups, namely, normal weight, overweight, and obesity. When conducting multiple tests, Bonferroni correction [30] was used to divide the significance level $P = 0.05$ by 3, and the difference was statistically significant at $P < 0.017$.

4. Results

4.1 General information

A total of 611 participants were enrolled in the study, and of these, 255 (41.73%)

were in the normal group, 129 (21.12%) were in the overweight group, and 227 (37.15%) were in the obesity group. Basic data included age, gender, and height. The results showed that the basic data of the three groups were comparable (Table 1). In the normal group, there were 12.5% cases with reflux esophagitis (RE) and 3.5% with Barrett's esophagus. In the overweight group, there were 13.2% with RE and 5.4% with Barrette's esophagus. In the obese group, there were 20.7% with RE and 7% with Barrette's esophagus. The percentages of cases with esophageal HH were 15.3%, 14.7%, and 18.5% in the three groups, respectively. The 24-hour pH monitoring results showed that GERD accounted for 16.86% in the normal group, 21.71% in the over-weight group, and 38.33% in the obese group. The rest cases were with esophageal hypersensitivity or functional heartburn, i.e., functional esophageal disease.

4.2 Comparison of MNBI between the three body weight groups

The results of six channels among the three groups of participants indicated that there were no significant differences between the Z1 and Z2 channels ($P = 0.659$, $P = 0.535$), but there was a significant difference among the three groups between the Z3 and Z6 channels ($P < 0.05$), as shown in Table 1. Further pairwise comparison showed that MNBI of the subjects in Z5–Z6 channels in the overweight group was significantly lower than that in the normal group ($P < 0.017$). With respect to Z3–Z6 channels, MNBI values in the obesity group were significantly lower than those in the normal group ($P < 0.01$). However, there were no significant differences in Z1–Z6 channels between overweight and obesity groups. The results are shown in Figure 1.

4.3 Comparison of 24-hour pH- impedance parameters among the three body weight groups

Our results suggested that there were significant differences ($P = 0.000$) in the 24-

hour acid exposure time, DMS, and total reflux episodes among the three groups, as shown in Table 1. Further pairwise comparison showed that for the three parameters of AET, DMS, and total reflux episodes, these levels in the obesity group were significantly higher than the normal group and the overweight group ($P = 0.000$), but there was no significant difference between the normal group and the overweight group, as shown in Figure 2.

4.4 Comparison of esophageal manometry indicators among the three body weight groups

The comparison of esophageal manometry indicators among the three groups revealed that there were inter-group differences in the LES resting pressure, UES residual pressure, IBP, and EGJ-CI ($P < 0.05$), as shown in Table 1. Further pairwise comparison showed that the UES residual pressure and IBP of the overweight group were significantly higher than those of the normal group ($P < 0.017$). The LES resting pressure, UES residual pressure IBP, and EGJ-CI of the obesity group was significantly higher than that of the normal group ($P = 0.000$), and the LES resting pressure and EGJ-CI in the obesity group was significantly higher than that of the overweight group ($P < 0.01$), as shown in Figure 3.

4.5 Correlation analysis and regression analysis between BMI and different indicators of esophageal functioning

Inter-group comparisons revealed differences among participants of different body weights in the following indicators: Z3-Z6 in MNBI, AET, DMS, total reflux episodes, LES resting pressure, UES residual pressure, IBP, and EGJ-CI. To further verify that the above indicators were associated with change in body weight, we performed correlation and regression analysis of BMI and the above indicators on data from all

participants. (Figure 4a&b)

The results of our correlation analysis indicated that BMI had significant positive correlation with LES resting pressure (r = 0.241, *P*=0.00), UES residual pressure (r = 0.19, *P* = 0.00), IBP (r = 0.249, *P* = 0.00), EGJ-CI (r = 0.215, *P* = 0.00), AET (r = 0.286, *P* = 0.00), DMS (r = 0.285, *P* = 0.00), and total reflux episodes (r = 0.184, *P* = 0.00). BMI had a significant negative correlation with Z3 (r = −0.142, *P* = 0.000), Z4 (r = −0.126, *P* = 0.002), Z5 (r = −0.173, *P*= 0.000), and Z6 (r = −0.207, *P* = 0.000), as shown in Table 2.

Regression analysis indicated that BMI had a significant positive correlation with LES resting pressure (OR: 5.83, 95%CI: 3.44−8.23, *P* = 0.00), UES residual pressure (OR: 6.00, 95%CI: 4.54−7.46, *P* = 0.009), IBP (OR: 5.65, 95%CI: 3.45−7.85, *P* = 0.000), EGJ-CI (OR: 14.61, 95%CI: 6.91−22.31, *P* = 0.000) and had a positive correlation trend with the total reflux episodes (OR: 24.14, 95%CI: 14.62−33.66, *P* = 0.059); BMI had a significant negative correlation with Z3 (OR: 2134.56, 95%CI: 1915.77−2353.34, *P* = 0.000), Z4 (OR: 2183.94, 95% CI: 1948.45−2419.43, *P* = 0.000) Z5 (OR: 2306.76, 95%CI: 2067.58−2545.95, *P* = 0.000) and Z6 (OR: 2318.72, 95%CI: 2087.74−2549.70, *P* = 0.000),as shown in Table 2.

4.6 Correlation analysis of indicators of esophageal functioning and body weight

To further explore whether different degrees of obesity would cause different changes in esophageal function, we divided the data into three groups according to BMI, i.e., normal weight group, overweight group, and obesity group. The intra-group correlation analysis of the above indicators was performed again, and the results showed that the BMI in overweight group was not significantly different from the above indicators, but BMI in obesity group had significant positive correlation with LES resting pressure (r = 0.466, *P* = 0.00), IBP (r = 0.243, *P* = 0.00), EGJ-CI (r = 0.435, *P*

= 0.00), Z4 (r = 0.133, *P* = 0.046). Results are shown in Table 3.

5. Discussion

Obesity is a condition that has a high incidence, and it is both a stand-alone disease and a condition associated with type 2 diabetes, cardiovascular disease, multiple cancers, and digestive system disorders. Studies have shown that the incidence of Barrett's esophagus and esophageal cancer are higher in obese persons than in the normal population[31,32]. In our study, we included both parameters of esophageal manometry and 24-hour pH-impedance monitoring of patients . We grouped patients according to different degrees of body weight to explore different effects of obesity on esophageal function. Our main conclusions were: 1. Esophageal mucosal integrity was damaged in overweight and obesity groups; 2. Different degrees of obesity were associated with different aspects of esophageal motility changes and different reflux conditions. As these results suggest that different degrees of obesity were associated with different aspects of esophageal motility changes and reflux conditions, management strategies may need to be tailored based on the severity of obesity, with more intensive interventions for severely obese patients compared to those who are overweight or mildly obese. It is also important to note that management of overweight and obese patients should be based on a comprehensive evaluation of individual patient characteristics, medical history, and overall health status, and should be guided by evidence-based guidelines and the expertise of qualified healthcare professionals.

In this study, we compared the MNBI values of patients in the normal weight group, the overweight group, and the obesity group. We found significant differences among the three groups, highlighting the differences in esophageal mucosal function among patients with different body weights. Further, pairwise comparison showed that the Z5 and Z6 channel data of the overweight group were significantly lower than those of the

normal group, while Z3-Z5 channel data of the obesity group were significantly lower than those of the normal group. There was no significant difference between the obesity group and the overweight group. This finding is consistent with that of Blevin's research[11],which indicated that obesity can lead to a decrease in esophageal multi-channel MNBI. Gibbens[9] found that central obesity impairs the structural and functional integrity of the esophageal barrier, with increased intercellular space, decreased desmosomal density, and increased fluorescein leakage.

In summary, there is no doubt that obesity destroys the integrity of esophageal mucosa. Findings of a study by Savarino[33] found that being overweight/ obese was an important risk factor for both erosive and non-erosive esophagitis. The results of this study suggest that being overweight or obese may cause damage to the esophageal mucosal barrier, but obesity may have a broader range of damage.

In the 24-hour pH-impedance test, the levels of all three indicators reflecting reflux were significantly higher in the obesity group than the normal group and the overweight group, that is, obesity was more likely to be accompanied by pathological reflux. An increase in BMI increases the risk of GERD[34], and there is a linear relationship between BMI and esophageal acid exposure[35]. The results of our study are consistent with this. Compared with the normal group, there was no significant difference in reflux parameters of the overweight group. In a study, Wu[36] found that individuals with BMI > 25 kg/m^2 had higher acid exposure time. Along with the MNBI data in this study, we infer that being overweight might cause mucosal damage, but it does not cause pathological reflux. Obesity damages the mucosal barrier, and there is reflux.

Comparison of esophageal function indicators from esophageal manometry revealed distinct changes in esophageal function among overweight and obese individuals. For overweight individuals, UES residual pressure, and IBP were increased,

while for obese individuals, LES resting pressure, UES residual pressure, IBP, and EGJ-CI were increased. With respect to IBP, Madigan[37] found that the abnormal increase of the elevated average maximum IBP (AM-IBP) during the examination might be related to esophageal motility disorders. Our results also suggested that there were significant differences in IBP among participants of different weights, indicating that the food bolus transmission ability significantly decreased with the increase of body weight.

We propose to further explore the role of IBP in esophageal motility in forthcoming follow-up research. The UES compliance of overweight and obese patients may be low, all of which show the increase of UES residual pressure. Increased UES residual pressure is often associated with cardia failure [38]. However, patients with cardia achalasia have been excluded from this study, and it has been found that in patients with GERD, the UES exhibits a shorter and low tension [39,40]. The obese patients in this study were different from them probably related to the extrusion of fat. However, in a study conducted by Edani[41] on 89 participants, the results indicated that there was no significant correlation between BMI and UES residual pressure. We speculate that this could be because all the participants enrolled in our study were symptomatic. But symptomatic subjects were excluded in their study. A study conducted by Vardar[42] found that UES residual pressure was significantly higher in patients with pharyngeal reflux. The results of this study also suggested that LES resting pressure and EGJ-CI increased in obese individuals. Our results in this study are consistent with the findings of Pandolfino[43] that esophageal pressure is high in obese population, but studies have also shown that esophageal LES pressure is significantly lower in obese people than in normal weight people[35,44], and this is possibly because fewer participants with morbid obesity were included in this study. There can be

different probable explanations for the different parameters we found among the overweight and obesity groups: being overweight and obese may affect the esophageal peristalsis, leading to an increase in IBP, gradual increase of food bolus pressure, slow food bolus transmission, and increase of UES residual pressure. Following obesity, extra-esophageal adhesion fat increases, which compresses LES and also affects the function of esophagogastric junction (EGJ). Wu et al.[45] found a significant correlation between BMI and SUVmax increase in the upper esophageal sphincter, middle esophagus, and EGJ during PET-CT examination. This, and results from our study indicate that the increase of BMI has an impact on esophageal function.

To again prove the correlation between the changes in BMI and the above indicators, we performed correlation analysis and regression analysis between BMI and various esophageal parameters , and the results showed that Z3, Z4, Z, and Z6 in MNBI, ALES resting pressure, UES residual pressure, IBP， EGJ-CI and total reflux episodes were all statistically significant ($P < 0.05$).

Our results showed that an increase in BMI affected the Z3-Z6 of MNBI total reflux episodes, LES resting pressure, UES residual pressure, IBP, and EGJ-CI. Functionally, the increase in BMI may be associated with the integrity of esophageal mucosa, gastroesophageal reflux, upper and lower esophageal sphincter pressures, and food bolus transport. We further investigated whether the severity of obesity had varying impacts on esophagus. In the obesity group, 41 participants with morbid obesity (MO) (BMI $\geq$ 35 kg/m^2) were taken as one group, while the remaining obese patients were defined as simple obesity group (OB) [24,25]. We did the inter-group comparison of individuals with simple obesity and morbid obesity in the same manner as earlier, and found that the LES static pressure, IBP, and EGJ-CI in the morbid obesity group were higher. There was no significant statistical difference in other parameters, and the

results are shown in Table 4.

This indicates that in individuals who are morbidly obese, esophageal motility may be affected more, while reflux parameters and integrity of esophageal mucosal barrier may not be affected to that extent. From the perspective of pathophysiology, persons with morbid obesity have increased abdominal fat and esophageal adhesion fat, which may compress the lower end of the esophagus. Therefore, the LES pressure is higher, the influence of EGJ function is greater, and peristalsis of the food bolus is more difficult. However, the number of morbidly obese participants in this study was small, and the majority of the morbidly obese people included were patients who were about to undergo sleeve gastrectomy, generally were younger, and most had no reflux symptoms. We recommend that the sample size of the morbid obesity group can be increased in subsequent research.

Previous studies have suggested that the possible reasons for the damage to the integrity of esophageal mucosa caused by obesity are as follows: First, when obesity occurs, the number of adipose tissues attached to esophagus increases, and adipose tissues may release inflammatory substances [12], such as TNF-α, which can inhibit esophageal mucosal cell repair [46] and promote oxidative stress to aggravate the damage of esophagus and destroy mucosal barrier [47]. This damage to the mucosal barrier is independent of the presence of gastroesophageal reflux [9]. Second, obesity results in increased gastroesophageal reflux, excessive esophageal mucosa, and exposure to gastric fluid due to corrosive and irritant components of gastric fluid can cause mucosal barrier damage [48]. In addition, elevated levels of IL-1β were observed in both obese and GERD patients [49,50], and it is well known that IL-1β can significantly affect esophageal muscle contractile function [51-53]. These findings may help explain the significant correlation between BMI and esophageal motility index.

According to the previous results, the extent of esophageal mucosal damage may be more extensive in overweight compared with obese subjects, and the altered esophageal dynamics may be different. To further determine whether such different mucosal damage alterations caused by different BMI are related to different altered esophageal dynamics, we further correlated esophageal dynamics with esophageal mucosal damage indexes in overweight and obese subjects. It was found that for overweight patients, esophageal mucosal injury was mainly related to reflux indicators, while for obese patients, mucosal injury may have a role of UES residual pressure in addition to reflux indicators.

In this study, all the patients discontinued PPI and gastrointestinal motility drugs for more than one week before esophageal manometry, thus reducing the impact on the results of PPI and drugs that regulate gastrointestinal motility. All 24-hour pH-impedance monitoring tests were performed after the completion of esophageal manometry with accurate positioning of the MNBI catheter. The total number of participants included in the sample size was more.

A limitation of the study was that symptom scores were not combined, so the symptoms could not be included together as a variable for correlation analysis of symptoms and parameters. Morbid obesity patients were too few and all were hospital-based, so further research on a representative population needs to be conducted.

6. Conclusions

Our study showed that the integrity of esophageal mucosa was damaged in overweight and obese persons. Different degrees of body weight gain were associated with different aspects of esophageal motility changes and reflux conditions. Mucosal injury in both obese and overweight is associated with esophageal reflux conditions, but mucosal injury in obese patients may also have the involvement of altered UES

pressure.

References

[1]WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies [published correction appears in Lancet. 2004 Mar 13;363(9412):902]. *Lancet*. 2004;363(9403):157-163.

[2]NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants [published correction appears in Lancet. 2016 May 14;387(10032):1998]. *Lancet*. 2016;387(10026):1377-1396.

[3]Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013 [published correction appears in Lancet. 2014;384(9945):746]. *Lancet*. 2014;384(9945):766-781.

[4]Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, Vaezi M, Sifrim D, Fox MR, Vela MF, Tutuian R, Tack J, Bredenoord AJ, Pandolfino J, Roman S. Modern diagnosis of GERD: the Lyon Consensus. *Gut*. 2018;67(7):1351-1362.

[5]Bou Daher H, Sharara AI. Gastroesophageal reflux disease, obesity and laparoscopic sleeve gastrectomy: The burning questions. *World J Gastroenterol*. 2019;25(33):4805-4813.

[6]Savarino E, Tutuian R, Zentilin P, Dulbecco P, Pohl D, Marabotto E, Parodi A, Sammito G, Gemignani L, Bodini G, Savarino V. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. *Am J Gastroenterol*. 2010;105(5):1053-1061.

[7]Wu YW, Tseng PH, Lee YC, Wang SY, Chiu HM, Tu CH, Wang HP, et al. Association of esophageal inflammation, obesity and gastroesophageal reflux disease: from FDG PET/CT perspective. PLoS One. 2014;9(3):e92001.

[8]Kim KJ, Lee BS. Central Obesity as a Risk Factor for Non-Erosive Reflux Disease. Yonsei Med J. 2017;58(4):743-748.

[9]Gibbens YY, Lansing R, Johnson ML, Blevins CH, Katzka DA, Iyer PG. Effects of Central Obesity on Esophageal Epithelial Barrier Function. Am J Gastroenterol. 2021;116(7):1537-1541.

[10]Singh S, Sharma AN, Murad MH, Buttar NS, El-Serag HB, Katzka DA, Iyer PG.

Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399-1412.e7.

[11]Blevins CH, Dierkhising RA, Geno DM, Johnson ML, Vela MF, Ravi K, Iyer PG, Katzka DA. Obesity and GERD impair esophageal epithelial permeability through 2 distinct mechanisms. Neurogastroenterol Motil. 2018;30(10):e13403.

[12]Paris S, Ekeanyanwu R, Jiang Y, Davis D, Spechler SJ, Souza RF. Obesity and its effects on the esophageal mucosal barrier. Am J Physiol Gastrointest Liver Physiol. 2021;321(3):G335-G343.

[12]Kristo I, Paireder M, Jomrich G, Felsenreich DM, Nikolic M, Langer FB, Prager G, Schoppmann SF. Modern Esophageal Function Testing and Gastroesophageal Reflux Disease in Morbidly Obese Patients. Obes Surg. 2019;29(11):3536-3541.

[14]Mushref MA, Srinivasan S. Effect of high fat-diet and obesity on gastrointestinal motility. Ann Transl Med. 2013;1(2):14.

[15]Ye B, Wang Y, Lin L, Jiang L, Wang M. Sex-Based Differences in pH Parameters and Esophageal Impedance of Patients With Gastroesophageal Reflux Disease. Front Med (Lausanne). 2021;8:629302.

[16]Farré R, Blondeau K, Clement D, Vicario M, Cardozo L, Vieth M, Mertens V, Pauwels A, Silny J, Jimenez M, Tack J, Sifrim D. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. Gut. 2011;60(7):885-92.

[17]Kessing BF, Bredenoord AJ, Weijenborg PW, Hemmink GJ, Loots CM, Smout AJ. Esophageal acid exposure decreases intraluminal baseline impedance levels. Am J Gastroenterol. 2011;106(12):2093-7.

[18]Riva CG, Siboni S, Ferrari D, Sozzi M, Capuzzo M, Asti E, Ogliari C, Bonavina L. Effect of Body Position on High-resolution Esophageal Manometry Variables and Final

Manometric Diagnosis. J Neurogastroenterol Motil. 2020;26(3):335-343.

[19]Popescu AL, Costache RS, Costache DO, Balaban VD, Jinga M, Ionita-Radu F, Caruntu A, Fierbinteanu-Braticevici C. Manometric changes of the esophagus in morbidly obese patients. Exp Ther Med. 2021;21(6):604..

[20]Aggarwal N, Lopez R, Gabbard S, Wadhwa N, Devaki P, Thota PN. Spectrum of esophageal dysmotility in systemic sclerosis on high-resolution esophageal manometry as defined by Chicago classification. Dis Esophagus. 2017;30(12):1-6.

[21]Yen HH, Tseng PH, Shih MC, Yang PJ, Lin MT, Lee PC. Derangement of esophageal anatomy and motility in morbidly obese patients: a prospective study based on high-resolution impedance manometry. Surg Obes Relat Dis. 2020;16(12):2006-2015.

[22]Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol. 2017;67(4):862-873.

[23]Wong VW, Wong GL, Chan RS, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol. 2018;69(6):1349-1356.

[24]Chiang KM, Chang HC, Yang HC, Chen CH, Chen HH, Lee WJ, Pan WH. Genome-wide association study of morbid obesity in Han Chinese. BMC Genet. 2019;20(1):97.

[25]World Health Organization (WHO) Global Strategy on Diet, Physical Activity and Health. [(accessed on 3 June 2019)];

[26]Gyawali CP, Carlson DA, Chen JW, Patel A, Wong RJ, Yadlapati RH. ACG Clinical Guidelines: Clinical Use of Esophageal Physiologic Testing. Am J Gastroenterol. 2020;115(9):1412-1428.

[27]Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-

resolution manometry: Chicago classification version 4.0©. Neurogastroenterol Motil. 2021;33(1):e14058.

[28]de Bortoli N, Martinucci I, Savarino E, Tutuian R, Frazzoni M, Piaggi P, Bertani L, Furnari M, Franchi R, Russo S, Bellini M, Savarino V, Marchi S. Association between baseline impedance values and response proton pump inhibitors in patients with heartburn. Clin Gastroenterol Hepatol. 2015;13(6):1082-8.e1.

[29]Frazzoni M, de Bortoli N, Frazzoni L, Tolone S, Furnari M, Martinucci I, Mirante VG, Marchi S, Savarino V, Savarino E. The added diagnostic value of postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance in refractory reflux disease studied with on-therapy impedance-pH monitoring. Neurogastroenterol Motil. 2017;29(3):e12947.

[30]Gunning MN, Sir Petermann T, Crisosto N, van Rijn BB, de Wilde MA, Christ JP, Uiterwaal CSPM, de Jager W, Eijkemans MJC, Kunselman AR, Legro RS, Fauser BCJM. Cardiometabolic health in offspring of women with PCOS compared to healthy controls: a systematic review and individual participant data meta-analysis. Hum Reprod Update. 2020;26(1):103-117.

[31]Schlottmann F, Dreifuss NH, Patti MG. Obesity and esophageal cancer: GERD, Barrett´s esophagus, and molecular carcinogenic pathways. Expert Rev Gastroenterol Hepatol. 2020;14(6):425-433.

[32]Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Mol Oncol. 2021;15(3):790-800.

[33]Savarino E, Zentilin P, Marabotto E, Bonfanti D, Inferrera S, Assandri L, Sammito G, Gemignani L, Furnari M, Dulbecco P, Savarino V. Overweight is a risk factor for both erosive and non-erosive reflux disease. Dig Liver Dis. 2011;43(12):940-5.

[34]Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal Reflux Disease: A Review. JAMA. 2020;324(24):2536-2547.

[35]Derakhshan MH, Robertson EV, Fletcher J, Jones GR, Lee YY, Wirz AA, McColl KE. Mechanism of association between BMI and dysfunction of the gastro-oesophageal barrier in patients with normal endoscopy. Gut. 2012;61(3):337-43.

[36]Wu JC, Mui LM, Cheung CM, Chan Y, Sung JJ. Obesity is associated with increased transient lower esophageal sphincter relaxation. Gastroenterology. 2007;132(3):883-9.

[37]Madigan KE, Smith JS, Evans JK, Clayton SB. Elevated average maximum intrabolus pressure on high-resolution manometry is associated with esophageal dysmotility and delayed esophageal emptying on timed barium esophagram. BMC Gastroenterol. 2022; 22(1):74.

[38] Menezes MA, Herbella FA, Patti MG. High-Resolution Manometry Evaluation of the Pharynx and Upper Esophageal Sphincter Motility in Patients with Achalasia. J Gastrointest Surg. 2015;19(10):1753-7.

[39]Nadaleto BF, Herbella FA, Pinna BR, Patti MG. Upper esophageal sphincter motility in gastroesophageal reflux disease in the light of the high-resolution manometry. Dis Esophagus. 2017;30(4):1-5.

[40]Passaretti S, Mazzoleni G, Vailati C, Testoni PA. Oropharyngeal acid reflux and motility abnormalities of the proximal esophagus. World J Gastroenterol. 2016;22(40):8991-8998.

[41]Edeani FO, Kern M, Ulualp K, Kovacic K, Sanvanson P, Mei L, Shaker R. Variables influencing manometric parameters of deglutitive and non-deglutitive upper esophageal sphincter: A study of 89 asymptomatic participants. Neurogastroenterol Motil. 2022;34(2):e14175.

[42]Vardar R, Sweis R, Anggiansah A, Wong T, Fox MR. Upper esophageal sphincter and esophageal motility in patients with chronic cough and reflux: assessment by high-resolution manometry. Dis Esophagus. 2013;26(3):219-25.

[43]Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology. 2006;130(3):639-49.

[44]Petersen WV, Meile T, Küper MA, Zdichavsky M, Königsrainer A, Schneider JH. Functional importance of laparoscopic sleeve gastrectomy for the lower esophageal sphincter in patients with morbid obesity. Obes Surg. 2012;22(3):360-6.

[45]Wu YW, Tseng PH, Lee YC, Wang SY, Chiu HM, Tu CH, Wang HP, Lin JT, Wu MS, Yang WS. Association of esophageal inflammation, obesity and gastroesophageal reflux disease: from FDG PET/CT perspective. PLoS One. 2014;9(3):e92001.

[46] Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr. 2006;83(2):461S-465S.

[47] Meigs JB, Larson MG, Fox CS, Keaney JF Jr, Vasan RS, Benjamin EJ. Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: the Framingham Offspring Study. Diabetes Care. 2007;30(10):2529-35.

[48]Tack J, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. Gastroenterology. 2018;154(2):277-288.

[49]Maedler K, Sergeev P, Ehses JA, Mathe Z, Bosco D, Berney T, Dayer JM, Reinecke M, Halban PA, Donath MY. Leptin modulates beta cell expression of IL-1 receptor antagonist and release of IL-1beta in human islets. Proc Natl Acad Sci U S A. 2004;101(21):8138-43.

[50] Rieder F, Cheng L, Harnett KM, Chak A, Cooper GS, Isenberg G, Ray M, Katz JA, Catanzaro A, O'Shea R, Post AB, Wong R, Sivak MV, McCormick T, Phillips M, West GA, Willis JE, Biancani P, Fiocchi C. Gastroesophageal reflux disease-associated

esophagitis induces endogenous cytokine production leading to motor abnormalities. Gastroenterology. 2007;132(1):154-65.

[51] Pan Q, Zhang ZQ, Tian CY,Yu T,Yang R, Chai XL. Effect and signaling pathways of Nelumbinis folium in the treatment of hyperlipidemia assessed by network pharmacology. World J Tradit Chin Med,2021;7(4):445-455.

[52]Zhang ZQ, Chen AP, Yu T, Yang SJ, Yu DS, Yang R, et al. Exploring the pharmacological mechanism of danhe granulesagainst hyperlipidemia by means of network pharmacology and verified by preliminary experiments. World J Tradit Chin Med 2021;7:436-44.

[53]Miftahussurur M, Doohan D, Nusi IA, Adi P, Rezkitha YAA, Waskito LA, Fauzia KA, Bramantoro T, Maimunah U, Thamrin H, Masithah SI, Sukadiono S, Uchida T, Lusida MI, Yamaoka Y. Gastroesophageal reflux disease in an area with low Helicobacter pylori infection prevalence. PLoS One. 2018;13(11):e0205644.

Figure Legends:

Figure 1 Pairwise comparison of MNBI and 24-hour pH-impedance parameters between the three body weight groups

Note: $P < 0.017$ was considered statistically different because multiple tests required correction of the *P*-value (0.017 = 0.05/3).

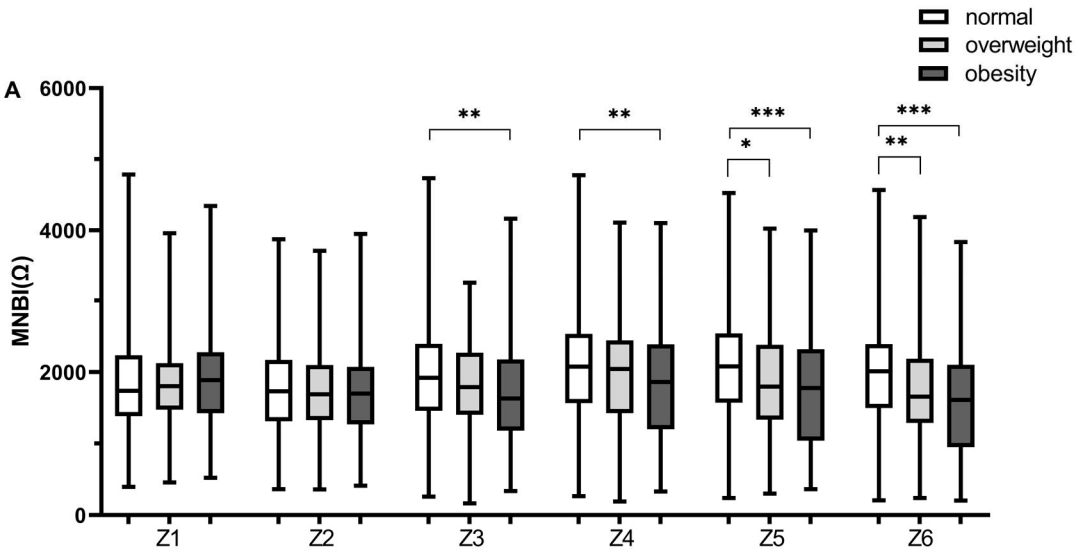

Figure 2 Pairwise comparison of 24-hour pH-impedance parameters between the three body weight groups

Note: $P < 0.017$ were considered statistically different because multiple tests required correction of the P-value (0.017 = 0.05/3).

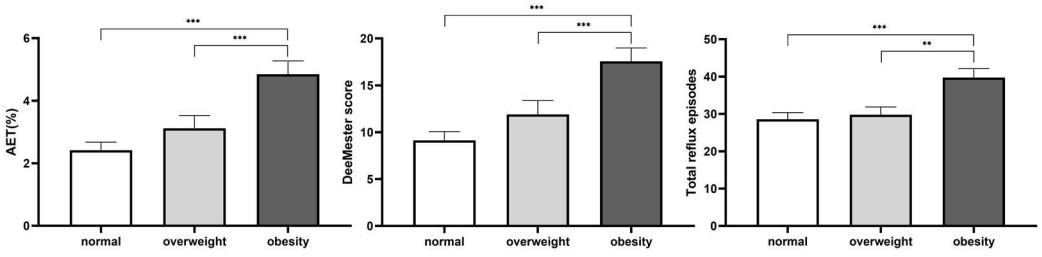

Figure 3 Pairwise comparison of esophageal manometry parameters between the three body weight groups

Note: $P < 0.017$ were considered statistically different because multiple tests required correction of the P-value (0.017 = 0.05/3).

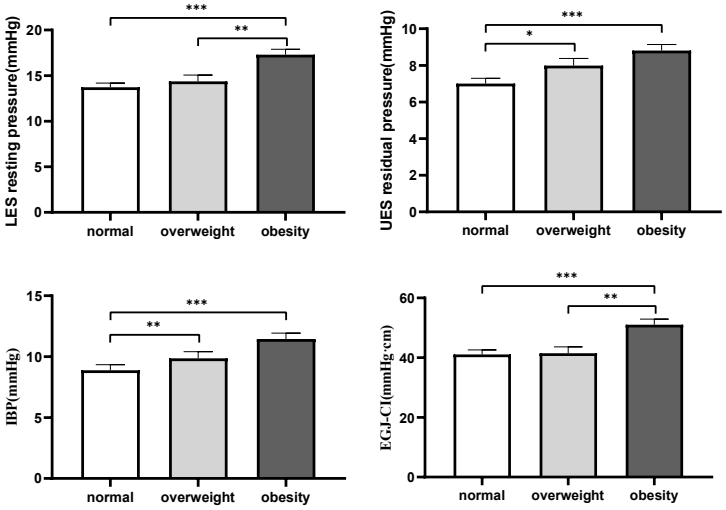

Figure 4a Correlation analysis between esophagus motility, reflux coefficients, and MNBI of the overweight group

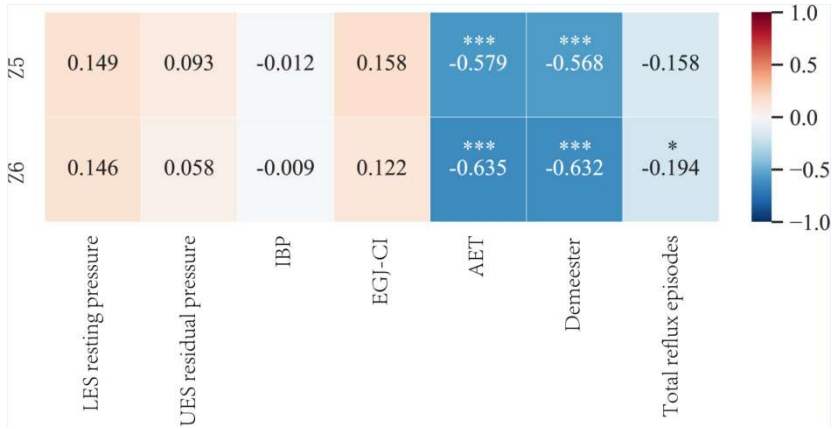

Figure 4b Correlation analysis between esophagus motility, reflux coefficients, and MNBI of the obesity group

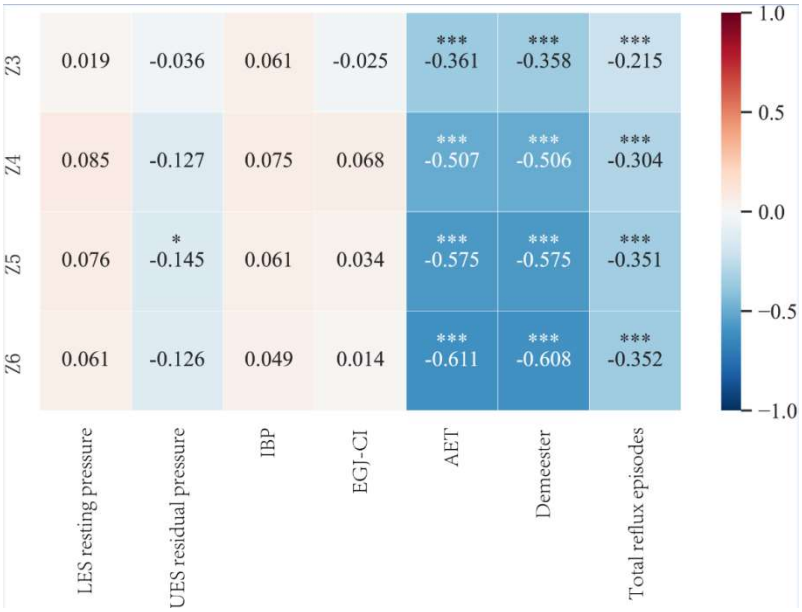

Table Chyba! Pouze hlavní dokument. **Comparison of esophageal parameters**

between the three body weight groups

		normal	overweight	obesity	P
	Age	55(40,64)	56(45,66)	53(38,65)	0.345
	Sex(Male)	91(35.69%)	58(44.96%)	104(45.81%)	0.052
	Height	165(160,172)	165(160,173)	168(160,175)	0.055
Endoscopy	RE%	32(12.5%)	17(13.2%)	47(20.7%)	***0.029***
	Barrett's esophagus%	9(3.5%)	7(5.4%)	16(7%)	
HREM	HH%	39(15.3%)	19(14.7%)	42(18.5%)	0.542
24h-pH	GERD%	43(16.86%)	28(21.71%)	87(38.33%)	***0.000***
MNBI	Z1	1737(1385,2237)	1804(1476,2125)	1888(1427,2278)	0.659
	Z2	1732(1313,2170)	1742.53±590.39	1698(1270,2073)	0.535
	Z3	1919(1457,2394)	1791.35±633.56	1632(1181,2176)	***0.001***
	Z4	2069.54±757.91	1942.61±742.27	1863(1203,2388)	***0.005***
	Z5	2055.13±740.48	1876.98±774.42	1778(1042,2320)	***0.000***
	Z6	1960.45±732.42	1658(1289.5,2188)	1613(951,2101)	***0.000***
	AET	0.8(0.2,2.5)	1.5(0.3,3.3)	2.6(1.1,5.9)	***0.000***
	DeMeester score	3.9(1.3,10.2)	5.6(1.5,12.95)	10.8(4.9,22.6)	***0.000***
	Total reflux episodes	20(10,38)	28 (13.5,40.5)	34(18,49)	***0.000***
LES	Resting pressure	13.3(8,18.6)	13.5(8.8,18.4)	16(10,22)	***0.000***
	Residual pressure	4.3(1.6,6.6)	3.5(1.55,6.05)	4(1.1,7.4)	0.475
	Length	3(2.4,3.61)	3.01±0.79	2.96(2.42,3.67)	0.832
UES	Resting pressure	30(21,39)	28(20,37)	30(21.6,41)	0.311
	Residual pressure	6.3(3.9,9.6)	8(4.9,10.3)	8.4(5.8,11)	***0.000***
	Length	3.5(2.87,3.95)	3.55(2.82,3.82)	3.5(2.76,4.04)	0.964
DL		7(6.28,7.88)	7.04(6.1,7.62)	6.84(6.12,7.55)	0.161
DCI		1394.5(797.1,2490.6)	1446.6(721.1,2485.55)	1593.8(943.9,2477.5)	0.119
IBP		7.1(4.1,11)	9.1(5.5,12.95)	10.3(6.6,14.6)	***0.000***
Number of peristaltic contractions		9(6,10)	9(5.5,10)	9(6,10)	0.655
EGJ-CI		37.9(23,55.4)	37.8(26.35,54.35)	46(27.9,69.3)	***0.000***

Table Chyba! Pouze hlavní dokument. **Correlation analysis and regression analysis of BMI and different indicators of esophageal functioning**

		BMI				
		r	P	β	OR (95%CI)	P
LES	Resting pressure	0.241	***0.000***	0.306	5.83 (3.44,8.23)	***0.000***
UES	Residual pressure	0.19	***0.000***	0.106	6.00 (4.54,7.46)	***0.009***
IBP		0.249	***0.000***	0.163	5.65 (3.45,7.85)	***0.000***
EGJ-CI		0.218	***0.000***	0.307	14.61 (6.91,22.31)	***0.000***
AET		0.286	***0.000***	0.155	0.41 (-1.2,2.01)	0.620
Demeester		0.285	***0.000***	0.166	1.46 (-4.09,7.02)	0.605
Total reflux episodes		0.184	***0.000***	0.076	24.14 (14.62,33.66)	0.000
MNBI	Z3	-0.142	***0.000***	-0.111	2134.56 (1915.77,2353.34)	***0.000***
	Z4	-0.126	***0.002***	-0.078	2183.94 (1948.45,2419.43)	***0.000***
	Z5	-0.173	***0.000***	-0.137	2306.76 (2067.58,2545.95)	***0.000***
	Z6	-0.207	***0.000***	-0.189	2318.72 (2087.74,2549.70)	***0.000***

Table Chyba! Pouze hlavní dokument. **Correlation analysis of esophageal coefficients and body weight**

		normal		overweight		obesity	
		r	P	r	P	r	P
LES	Resting pressure	0.098	0.119	0.071	0.421	***0.466***	***0.000***

UES	Residual pressure	-0.009	0.884	-0.058	0.516	0.041	0.536
IBP		0.106	0.09	-0.069	0.437	***0.243***	***0.000***
EGJ-CI		0.066	0.298	0.009	0.922	***0.435***	***0.000***
AET		0.055	0.382	0.43	0.63	0.042	0.532
Demeester		0.05	0.427	0.039	0.663	0.050	0.451
Total reflux episodes		-0.013	0.839	-0.006	0.948	-0.071	0.290
MNBI	Z3	-0.116	0.064	-0.063	0.479	0.121	0.068
	Z4	-0.112	0.074	-0.091	0.304	***0.133***	***0.046***
	Z5	-0.053	0.402	-0.065	0.463	0.057	0.396
	Z6	0.004	0.955	-0.082	0.354	-0.009	0.895

Table Chyba! Pouze hlavní dokument. **Comparison of differences in indicators between simple obesity and morbid obesity**

		OB n=186	MO n=41	P
LES	Resting pressure	14(9.75,20.55)	23.72±8.28	***0.000***
UES	Residual pressure	8.4(5.8,11.03)	8.27±3.3	0.607
IBP		9.6(6.35,14.53)	12.36±5.64	***0.035***
EGJ-CI		40.95(24.90,63.7)	75.57±25.97	***0.000***
AET		2.65(1.08,6.68)	2.6(1.1,4.65)	0.812
Demeester		10.5(4.83,23.4)	10.8(5.2,17.1)	0.881
Total reflux episodes		35(18.75,51)	32.83±22.07	0.244
MNBI	Z3	1603(1154.25,2183.5)	1743.68±563.30	0.674
	Z4	1803.5(10.81.5,2368)	2028.02±701.63	0.070
	Z5	1742(1041,2299.25)	1763.61±661.95	0.606
	Z6	1653(943.75,2135.75)	1487.66±627.89	0.395