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Chapter

Gastroesophageal Reflux Disease and Obesity

I Dewa Nyoman Wibawa and Ni Wayan Wina Dharmesti

Abstract

The global rise of gastroesophageal reflux disease (GERD) prevalence makes it one of the most common diagnoses performed in a daily practice. Obesity significantly contribute to GERD development, accordingly, it has accounted for the increasing cases of GERD. Obesity can disrupt the esophagogastric junction integrity, which promote the development of GERD and its complication. The frequency of GERD symptoms and its mucosal complications also found more often in obesity. The parallel increase of both condition has initiated numerous studies to determine the most beneficial therapeutic options in managing this challenging condition. Current available therapy for GERD in obesity including weight reduction, pharmacotherapy, and surgery.

Keywords: GERD, obesity, erosive esophagitis, treatment

1. Introduction

Occasional reflux of gastric content into the esophagus is a physiological phenomenon, until it presents with symptoms and/or mucosal complication, which defines the condition of GERD [1]. GERD is one of the most common diagnoses performed in a daily practice [2]. Clinically, GERD may manifest with cardinal symptoms of heartburn and regurgitation. Other symptoms are classified as esophageal (e.g., dysphagia, chest pain) and extraesophageal (atypical) symptoms [3]. GERD encompassed several subgroups, based on endoscopy and histopathological findings, such as erosive esophagitis, Barrett's esophagus, and nonerosive reflux disease (NERD) [3].

Recent evidence showed a rising prevalence of GERD and it was estimated 1.03 billion individuals are suffering from GERD globally [4, 5]. GERD has also become more prevalent nowadays in a previously uncommon region, such as Asia Pacific [6]. Excessive body weight is one of the multiple conditions that contribute to this escalation in GERD cases [7]. Yamasaki *et al*. in their study discovered a characteristic finding of GERD patients were primarily obese or severely obese [7]. Many of previous studies showed a common finding of reflux symptoms in patients with obesity, indicated an association between GERD and obesity [8]. The risk of both reflux symptoms and mucosal injury related to GERD is found to be increased in obesity [9]. Metabolic syndrome also appears to play a role in the development of GERD, since it independently increased the probability of NERD progression into erosive esophagitis [10]. Given the background of growing burden in both conditions, the following

sections will discuss the pathophysiology and available therapeutic modalities for GERD in obese individuals.

2. GERD in obesity

Obesity has reached an epidemic proportion globally [11]. This condition is diagnosed when the measured body mass index (BMI) is ≥30 kg/m^2 and further classified into three group based on its severity levels: class I (BMI 30.0–34.9), class II (BMI 35.0–39.9), and class III (BMI ≥40.0) [11]. Epidemiological study have shown that obesity is a major risk factor for GERD and, consequently, has accounted for the increasing prevalence of GERD, worldwide [12]. Study by Hampel *et al.* showed overweight and obesity fulfill a number criteria for a causal relationship with GERD [9]. Previous studies also discovered the influence of BMI on GERD was not affected by nutritional intake [13–15].

Study by Murray *et al*. showed that subjects with obesity reported more frequent heartburn compared to the subjects with normal weight (OR 2.91) and this obese subjects also showed significant association with severe heartburn (OR 1.19) [13]. A dose–response relationship between frequency of heartburn or regurgitation and high BMI was observed by El-Serag *et al*. [16]. This study also found subjects with mucosal erosion were more often to be overweight or obese, compared to subjects without erosion [16].

2.1 Pathophysiology of GERD in obesity

Since obesity has contributed largely to the increased of GERD prevalence, there has been a substantial attention to explore the possible mechanisms of GERD development in obesity [17]. The essential pathology in the development of GERD is excessive acid and bile salt exposure on the gastric mucosa [3]. This abnormal exposure may lead to distressing symptoms of GERD when the number of reflux events is enormous, the period of mucosal exposure to gastric content is prolonged, there is concomitant defect in mucosal integrity, or hypersensitivity to refluxate [3]. The integrity of the esophagogastric junction (EGJ), both structural and functional, is an important antireflux barrier [3]. Major mechanisms of EGJ incompetence that discovered in GERD are anatomical derangement of the EGJ including hiatal hernia, decreased pressure of lower esophageal sphincter (LES), and transient lower esophageal sphincter relaxation (TLESR). Delayed gastric emptying and prolonged esophageal clearance time has been found in subsets of patients as mechanism that may exacerbate GERD [3].

Several factors that could increase acid exposure time on the esophagus was found more often in patients with obesity than in individuals with normal weight [12]. The development of GERD in obese individuals was previously thought to be mainly structural, owing to the weight of abdominal fat that increase intra-abdominal pressure, thereby increased the likelihood reflux occurrence. Recent evidence also suggest that obesity may alter the physiologic function of lower esophageal sphincter (decreased LES pressure, increased frequency of transient LES relaxation), and/or gastroesophageal motility (delayed esophageal clearing time, impaired gastric emptying) [9, 13].

The development of a hiatal hernia is the main factor that disrupts the integrity of the EGJ in patients with excess body weight [9]. The prevalence of hiatal hernia is

significantly higher in subjects with obesity than in subjects with a normal BMI [18]. The physiological explanation for the interplay between obesity, risk for hiatal hernia, and subsequent development of GERD was thoroughly explored in a manometry study conducted by Pandolfino *et al* [19]. Their study discovered an altered pressure morphology within and across the EGJ in obese subjects that would augment the movement of acid and bile salts toward the esophagus. Obesity caused greater axial separation between the LES and the diaphragm, that ultimately lead to the development of hiatal hernia [19]. This proximal displacement of the LES creates a lower basal pressure of LES, diminishes the increment in LES pressure that occurs during straining, and increases transient LES relaxation (TLESR) frequency during gastric distention with gas [20, 21]. Transient LES relaxation seems to be the most important mechanism responsible for reflux [22]. Overweight and obese patients showed a significantly higher TLESR rate during the post-prandial period as compared to subjects with normal BMI [23]. It also appeared that both BMI and waist circumference have a dose-effect relationship with TLESR [23].

Central obesity also play a part in the pathogenesis of GERD [18]. Current data suggest that central obesity causes an increase in intra-gastric pressure, which subsequently increased esophageal exposure to gastric content and impaired esophageal acid clearance [24, 25]. Moreover, the visceral fat is a metabolically active organ that produces interleukin-6 and tumor necrosis factor-α, that may have impact on LES. Recent data also suggest that insulin resistance, a consequence of visceral obesity, may be an important contributing factor [26]. Studies also found that abdominal obesity may change the secretion of adipokines such as adiponectin and leptin that has been regarded as the key factor for the development of esophageal neoplasia in the setting of obesity [12, 17]. Adipokine has anti-inflammatory and immunomodulatory properties and may stimulate apoptosis [27]. Obesity decrease the secretion of adiponectin and this was associated with increased risk of BE [28]. Leptin has been shown to have mitogenic properties, that later study found it may induce proliferation of esophageal cancer [29]. Kendall *et al*. found the risk of BE were higher in subjects with high level of serum leptin (OR 4.6) [30]. All of the proposed mechanisms that promotes the development of GERD in obesity is summarized in **Figure 1**.

The traditional theory of refluxed gastric content has caused direct injury to the esophageal mucosa, as discussed above, is challenged by the findings of recent studies in rats and human that found the exposure of esophageal mucosa to gastric content did not cause a direct acid injury in the esophagus [31, 32]. Instead, it stimulated the esophageal mucosa to secrete cytokines that induce proliferative changes in epithelial cells and attract the T lymphocyte and other pro-inflammatory cells that eventually caused mucosal damage [31, 32]. Hypoxia-inducible factor-2α (HIF-2α) is a transcription factor that is involved in the mediation of some inflammatory response [33] and appear to be the key mediator that initiate the cytokine-mediated mucosal injury [34]. The exposure gastric juice to esophageal epithelial cells leads to the production of reactive oxygen species, a key substance to stabilize HIF-2α in the setting of GERD [35, 36]. This stabilized HIF-2α will accumulate in the nucleus and stimulate the secretion of inflammatory cytokines that lead to the establishment of GERD [34]. This new paradigm in GERD pathogenesis, however, has not been studied in term of its possible role in GERD with obesity. Nonetheless, this undisclosed association between cytokine-mediated mucosal injury and obesity in the pathogenesis of GERD may serve as an opportunity for researches in the future.

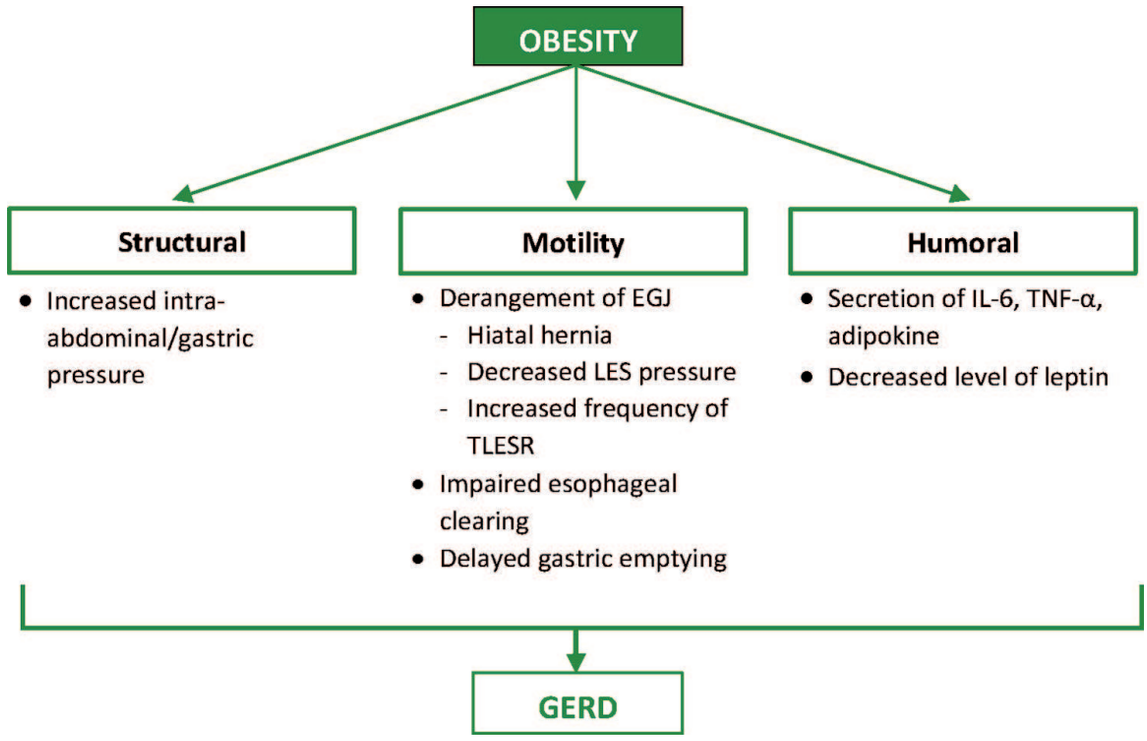

Figure 1.
Pathophysiology of GERD in obesity. EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; LES, lower esophageal sphincter; TLESR, transient lower esophageal sphincter relaxation.

3. Management

Management of GERD requires more than one approach, which considered the symptom severity, endoscopic findings, and possible physiological abnormalities [36]. Treatment modalities includes lifestyle modification, pharmacologic therapy, and surgery [36]. The growing attention to the reflux problems in patients with obesity has prompted a numerous studies to obtain the most beneficial therapeutic options [18]. In the following section, recent evidences that support the beneficial effect of particular treatment options in GERD patients with obesity will be discussed.

3.1 Weight reduction

Lifestyle modification is the recommended first step in the treatment of GERD. However, the only measures that have been shown to be beneficial on the part of obese patient is weight loss [37]. Weight loss is strongly recommended in overweight or obese GERD patients to improve the reflux symptoms [6, 36]. A prospective cohort study has found that in GERD subjects with overweight and obesity, weight reduction was significantly decreased the overall prevalence of GERD with significant improvement in overall symptoms scoring, compared to baseline [38]. The result of this study also showed a substantial reduction in overall GERD scores only observed among subjects who loss body weight ≥5% from baseline. Study conducted by de Bortoli *et al*. found that group of GERD patients who had weight reduction was showing not only a higher rate of symptoms improvement, but also managed to reduce the dosage of proton pump inhibitor (PPI), compared to group without weight reduction [39].

This study also recommend all patients with GERD to achieve a minimum 10% weight loss from baseline in order to hasten the efficacy of PPI to relieve GERD symptom [39]. The result of the above studies is supported by the finding of dose-dependent relationship between reduction in body weight and improvement of GERD symptoms [40]. Study conducted by Park *et al* found weight reduction was significantly associated with improvement of GERD symptom, but showed no association with improvement in erosive esophagitis [41].

3.2 Pharmacotherapy

PPI are the mainstay medical treatment for GERD, it is initially given as active-phase therapy, with continuous use to improve and heal the mucosal erosion, then follows by on-demand therapy phase for maintenance [6, 36]. However, there are still scarce yet inconsistent data available regarding the influence of obesity to the response of PPI treatment for GERD patients. Peura *et al.* conducted a study that found the efficacy of PPI therapy on the reduction in heartburn symptoms frequency and severity was similar across BMI categories, in both NERD and erosive esophagitis patients [42].However, when the therapeutic target of the initial phase of PPI therapy is based on the sustained symptomatic response (SSR, *i.e.* free from reflux symptoms for the last 7 days), Sheu *et al.* found a lower SSR rates in the overweight and obese groups, compared to control group [43]. During maintenance therapy, the mean number of PPI tablets used was significantly higher in the overweight and obese groups than in the control group [43]. This findings was further studied by Chen *et al.* to determine whether double-dose PPI can elevate the SSR rate for overweight or obese patients [44]. They also checked whether different genotypes of CYP2C19 would affect the SSR rates. This study found a higher rates of SSR in the double-dose PPI group than in the standard group. Treatment with double-dosed PPI also improved the cumulative rates of SSR in the extensive metabolizer group [44].

Pharmacotherapy in obesity is indicated in patients with obesity-associated complications that have failed to achieve a healthy weight by implementing a low-calorie diet and regular exercise [45]. Less coverage of antiobesity drugs by insurance and their high cost has limits patients' choices. In addition, until the present time there is no available data that describe the impact of using antiobesity to achieve weight loss in patients with GERD.

3.3 Surgery

Antireflux surgery is an alternative for long-term treatment of GERD patients with severe reflux esophagitis (LA grade C or D), large hiatal hernias, and/or persistent distressing GERD symptoms [36]. Laparoscopic antireflux surgery (Nissen fundoplication, Toupet fundoplication) has been viewed as an alternative to lifelong PPI treatment in GERD [18]. The efficacy and safety of this procedure in patient with obesity, however is still controversial [46, 47]. Therefore bariatric surgery (Roux-en-Y gastric bypass) is being more considered recently as a procedure of choice for GERD in patient with morbid obesity [18]. Bariatric surgery was able to achieve substantial weight reduction and lower abdominal-thoracic pressure gradient [18]. Many studies have shown consistent improvement in both reflux symptoms and mucosal complication of GERD following a bariatric procedure in obese patients [18]. Nonetheless, it must be highlighted that all patients, require a lifelong and multidisciplinary follow up care after bariatric surgery [18].

Laparoscopic sleeve gastrectomy (LSG) is another approach of bariatric procedure that has gained more attention, owing to less technical complexity as compare to laparoscopic Roux-en-Y gastric bypass (LRYGB), it showed lower incidence of postoperative complication, and leads to substantial weight loss [48]. The impact of LSG on GERD, however is still inconsistent in regards to the control of pre-existing reflux, development of *de novo* GERD after procedure, and several studies suggested that LSG is a refluxogenic procedure [49–51]. Another study showed that the main technical issues that determine the occurrence of postoperative GERD are relative narrowing of the sleeve and hiatal hernia [52]. Ultimately, the baseline severity of reflux symptoms and mucosal injury is the key determinants of patient's feasibility to surgery [51]. Erosive esophagitis is considered as a relative contraindication to the surgery by the joint statement of ASMBS, SAGES, and ASGE [53]. Recently, the available management options for GERD after LSG include pharmacotherapy with PPI or repair with laparoscopic Roux-en-Y gastric bypass [52]. These available options should be openly discussed with the patients [51].

4. Conclusions

Obesity is a major risk factor of GERD and has accounted for the rising GERD case, worldwide. The fundamental mechanisms in the development of GERD were found more frequently in patients with obesity. Accordingly, the frequency of reflux symptoms and mucosal complications of GERD were also higher in obese patients. Current available treatment options has highlight the benefit of weight loss in GERD patients with obesity, not only to improve the symptoms but also to enhance the response to GERD pharmacotherapy. Role of antiobesity pharmacotherapy is still limited in GERD patients. Those patients who failed the conservative medical therapy may be considered for surgical procedure to achieve weight reduction and improvement of GERD symptoms. The baseline reflux symptoms severity and mucosal injury are key factors in determining which patients that will benefit from surgery. The possible postoperative complication and available management options should be openly discussed with patients.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. The American Journal of Gastroenterology. 2006;**101**(8):1900-1920. DOI: 10.1111/j.1572-0241.2006.00630.x

[2] Katzka DA, Pandolfino JE, Kahrilas PJ. Phenotypes of gastroesophageal reflux diseases: Where Rome, Lyon, and Montreal meet. Clinical Gastroenterology and Hepatology. 2020;**18**:767-776. DOI: 10.1016/j.cgh.2019.07.015

[3] Roman S, Pandolfino JE, Kahrilas PJ. Gastroesophageal reflux disease. In: Podolsky DK, Camilleri M, Fitz JG, Kalloo AN, Shanahan F, Wang TC, editors. Yamada's Textbook of Gastroenterology. Sixth ed. Oxford: John Wiley & Sons; 2016. pp. 906-928

[4] Boulton KHA, Dettmar PW. A narrative review of the prevalence of gastroesophageal reflux disease (GERD). Annals of Esophagus. 2022;**5**:7. DOI: 10.21037/aoe-20-80

[5] Nirwan JS, Hasan SS, Babar ZUD, Conway BR, Ghori MU. Global prevalence and risk factors of gastro-esophageal reflux disease (GORD): Systematic review with meta-analysis. Scientific Reports. 2020;**10**:5814. DOI: 10.1038/s41598-020-62795-1

[6] Goh KL, Lee YY, Leelakusolvong S, Makmun D, Maneerattanaporn M, Quach DT, et al. Consensus statement and recommendations on the management of mild-to-moderate gastroesophageal reflux disease in the southeast Asian region. JGH Open. 2021;**5**:855-863. DOI: 10.1002/jgh3.12602

[7] Yamasaki T, Hemond C, Eisa M, Ganocy S, Fass R. The changing epidemiology of GERD: Are patients getting younger. Journal of Neurogastroenterology and Motility. 2018;**24**(4):559-569. DOI: 10.5056/jnm18140

[8] El-Serag H. The association between obesity and GERD: A review of the epidemiological evidence. Digestive Diseases and Sciences. 2008;**53**(9):2307-2312. DOI: 10.1007/s10620-008-0413-9

[9] Hampel H, Abraham NS, El-Serag HB. Meta-analysis: Obesity and the risk for gastroesophageal reflux disease and its complications. Annals of Internal Medicine. 2005;**143**:199-211. DOI: 10.7326/0003-4819-143-3-200508020-00006

[10] Hershcovici T, Fass R. Nonerosive reflux disease (NERD)-an update. Journal of Neurogastroenterology and Motility. 2010;**16**(1):8-21. DOI: 10.5056/jnm.2010.16.18

[11] Haththotuwa RN, Wijeyaratne CN, Senarath U. Worldwide epidemic of obesity. In: Mahmood TA, Chervenak FA, Arulkumaran S, editors. Obesity and Obstetrics Second ed. Amsterdam: Elsevier; 2020. pp. 3-8. DOI: 10.1016/C201-8-0-02230-6

[12] Chang P, Friedenberg F. Obesity & GERD. Gastroenterology Clinics of North America. 2014;**43**(1):161-173. DOI: 10.1016/j.gtc.2013.11.009

[13] Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, et al. Relationship between body mass index and gastro-esophageal reflux symptoms: The Bristol Helicobacter project. International Journal of Epidemiology. 2003;**32**:645-650. DOI: 10.1093/ije/dyg108

[14] Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. Journal of the American Medical Association. 2003;**290**:66-72. DOI: 10.1001/jama.290.1.66

[15] Nandurkar S, Locke GR 3rd, Fett S, Zinsmeister AR, Cameron AJ, Talley AJ. Relationship between body mass index, diet, exercise, and gastro-esophageal reflux symptoms in community. Alimentary Pharmacology & Therapeutics. 2004;**20**:497-505. DOI: 10.1111/j.1365-2036.2004.02156.x

[16] El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. The American Journal of Gastroenterology. 2005;**100**(6):1243-1250. DOI: 10.1111/j.1572-0241.2005.41703.x

[17] Emerenziani S, Rescio MP, Guarino MPL, Cicala M. Gastro-esophageal reflux disease and obesity, where is the link? World Journal of Gastroenterology. 2013;**19**(39):6536-6539. DOI: 10.3748/wjg.v19.i39.6536

[18] Thalheimer A, Bueter M. Excess of body weight and gastroesophageal reflux disease. Visceral Medicine. 2021;**37**:267-272. DOI: 10.1159/000516050

[19] Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ. Obesity: A challenge to esophagogastric junction integrity. Gastroenterology. 2006;**130**:639-649. DOI: 10.1053/j.gastro.2005.12.016

[20] Mattioli S, D'Ovidio F, Pilotti V, Di Simone MP, Lugaresi M, Bassi F, et al. Hiatus hernia and intrathoracic migration of the esophagogastric junction in gastroesophageal reflux disease. Digestive Diseases and Sciences. 2003;**48**:1823-1831. DOI: 10.1023/A:1025471801571

[21] Kahrilas P, Shi G, Manka M, Joehll R. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distention in reflux patients with hiatal hernia. Gastroenterology. 2000;**118**:688-695. DOI: 10.1016/S0016-5085(00)70138-7

[22] Sifrim D, Holloway R. Transient lower esophageal sphincter relaxations: How many or how harmful? The American Journal of Gastroenterology. 2001;**96**:2529-2532. DOI: 10.1111/j.1572-0241.2001.04095

[23] Wu JC, Mui LM, Cheung CM, Chan Y, Sung JJ. Obesity is associated with increased transient lower esophageal sphincter relaxation. Gastroenterology. 2007;**132**:883-889. DOI: 10.1053/j.gastro.2006.12.032

[24] Derakhsan MH, Robertson EV, Fletcher J, Jones GR, Lee YY, Wirz AA, et al. Mechanism of association between BMI and dysfunction of the gastro-esophageal barrier in patients with normal endoscopy. Gut. 2012;**61**(3):337-343. DOI: 10.1136/gutjnl-2011-300633

[25] Ringhofer C, Lengliner J, Riegler M, Kristo I, Kainz A, Schoppmann SF. Waist to hip ratio is a better predictor of esophageal acid exposure than body mass index. Neurogastroenterology and Motility. 2017;**29**(7):e13033. DOI: 10.1111/nmo.13033

[26] Hsu CS, Wang PC, Chen JH. Increasing insulin resistance is associated with increased severity and prevalence of gastro-esophageal reflux disease. Alimentary Pharmacology & Therapeutics. 2011;**34**:994-1004. DOI: 10.1111/j.1365-2036.2011.04817.x

[27] Kelesidis I, Kelesidis T, Mantzoros CS. Adiponectin and cancer: A systematic review. British Journal of Cancer. 2006;**94**(9):1221-1225. DOI: 10.1038/sj.bjc.6603051

[28] Rubenstein JH, Kao JY, Madanick RD, Zhang M, Wang M, Spacek MB, et al. Association of adiponectin multimers with Barrett's oesophagus. Gut. 2009;**58**(12):1583-1589. DOI: 10.1136%2Fgut.2008.171553

[29] Ogunwobi O, Mutungi G, Beales IL. Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cyclooxygenase-2-dependent, prostaglandin-E2-mediated transactivation of the epidermal growth factor receptor and c-Jun NH2-terminal kinase activation. Endocrinology. 2006;**147**(9):4505-4516. DOI: 10.1210/en.2006-0224

[30] Kendall BJ, Macdonald GA, Hayward NK, Prins JB, Brown I, Walker N, et al. Leptin and the risk of Barrett's oesophagus. Gut. 2008;**57**(4):448-454. DOI: 10.1136/gut.2007.131243

[31] Souza RF, Huo X, Mittal V, Schuler CM, Carmack SW, Zhang HY, et al. Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury. Gastroenterology. 2009;**137**:1776-1784. DOI: 10.1053/j.gastro.2009.07.055

[32] Dunbar KB, Agoston AT, Odze RD, Huo X, Pham TH, Cipher DJ, et al. Association of acute gastroesophageal reflux disease with esophageal histologic changes. Journal of the American Medical Association. 2016;**315**:2104-2112. DOI: 10.1001/jama.2016.5657

[33] Taylor CT. Interdependent roles for hypoxia inducible factor and nuclear factor-kappaB in hypoxic inflammation. The Journal of Physiology. 2008;**586**:4055-4059. DOI: 10.1113/jphysiol.2008.157669

[34] Souza RF, Bayeh L, Spechler SJ, Tambar UK, Bruick RK. A new paradigm for GERD pathogenesis: Not acid injury, but cytokine-mediated inflammation driven by HIF-2α: A potential role for targeting HIF-2α to prevent and treat reflux esophagitis. Current Opinion in Pharmacology. 2017;**37**:93-99. DOI: 10.1016/j.coph.2017.10.004

[35] Feagins LA, Zhang HY, Zhang X, Hormi-Carver K, Thomas T, Terada LS, et al. Mechanisms of oxidant production in esophageal squamous cell and Barrett's cell lines. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2008;**294**:G411-G417. DOI: 10.1152/ajpgi.00373.207

[36] Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. The American Journal of Gastroenterology. 2022;**117**:27-56. DOI: 10.14309/ajg.0000000000001538

[37] Eherer A. Management of gastroesophageal reflux disease: Lifestyle modification and alternative approaches. Digestive Diseases. 2014;**32**:149-151. DOI: 10.1159%2F000357181

[38] Singh M, Lee J, Gupta N, Gaddam S, Smith BK, Wani SB, et al. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: A prospective interventional trial. Obesity (Silver Spring). 2013;**21**(2):284-290. DOI: 10.1002/oby.20279

[39] De Bortoli N, Guidi G, Martinucci I, Savarino E, Imam H, Bertani L, et al. Voluntary and controlled weight loss

can reduce symptoms and protom pump inhibitor use and dosage in patients with gastroesophageal reflux disease: A comparative study. Diseases of the Esophagus. 2014;**29**(2):197-204. DOI: 10.1111/dote.12319

[40] Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Weight loss and reduction in gastroesophageal reflux. A prospective population-based cohort study: The HUNT study. The American Journal of Gastroenterology. 2013;**108**:376-382. DOI: 10.1038/ajg.2012.466

[41] Park SK, Lee T, Yang HJ, Park JH, Sohn CI, Ryu S, et al. Weight loss and waist reduction is associated with improvement in gastroesophageal disease reflux symptoms: A longitudinal study of 15295 subjects undergoing health checkups. Neurogastroenterology and Motility. 2016;**29**(5):1-7. DOI: 10.1111/nmo.13009

[42] Peura DA, Pilmer B, Hunt B, Mody R, Perez MC. The effects of increasing body mass index on heartburn severity, frequency and response to treatment with dexlansoprazole or lansoprazole. Alimentary Pharmacology & Therapeutics. 2013;**37**:810-818. DOI: 10.1111/apt.12270

[43] Sheu BS, Cheng HC, Chang WL, Chen WY, Kao AW. The impact of body mass index on the application of on-demand therapy for Los Angeles grades A and B reflux esophagitis. The American Journal of Gastroenterology. 2007;**102**:2387-2394. DOI: 10.1111/j.1572-0241.2007.01468.x

[44] Chen WY, Chang WL, Tsai YC, Cheng HC, Lu CC, Sheu BS. Double-dosed pantoprazole accelerates the sustained symptomatic response in overweight ang obese patients with reflux esophagitis in Los Angeles grade a and B. The American Journal of Gastroenterology. 2010;**105**(5):1046-1052. DOI: 10.138/ajg.2009.632

[45] Apovian CM, Aronne LJ, Bessenen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: An endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism. 2015;**100**(2):342-362. DOI: 10.1210/jc.2014-3415

[46] Tekin K, Toydemir T, Yerdel MA. Is laparoscopic antireflux surgery safe and effective in obese patients? Surgical Endoscopy. 2012;**26**(1):86-95. DOI: 10.1007/s00464-011-1832-9

[47] Morgenthal CB, Lin E, Shane MD, Hunter JG, Smith CD. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. Surgical Endoscopy. 2007;**21**(11):1978-1984. DOI: 10.1007/s00464-007-9490-7

[48] Gadiot RP, Biter LU, van Mil S, Zengerink HF, Apers J, Mannaerts GH. Long-term results of laparoscopic sleeve gastrectomy for morbid obesity: 5 to 8-year results. Obesity Surgery. 2017;**27**:59-63. DOI: 10.1007/s11695-016-2235-8

[49] Oor JE, Roks DJ, Ünlü Ç, Hazebroek EJ. Laparoscopic sleeve gastrectomy and gastroesophageal reflux disease: A systematic review and meta-analysis. American Journal of Surgery. 2016;**211**:250-267. DOI: 10.1016/j.amjsurg.2015.05.031

[50] Mion F, Tolone S, Garros A, Savarino E, Pelascini E, Robert M, et al. High-resolution impedance manometry after sleeve gastrectomy: Increased intragastric pressure and reflux are frequent events. Obesity Surgery. 2016;**26**(10):2449-2456. DOI: 10.1007/s11695-016-2127-y

[51] Daher HB, Shahara AI. Gastroesophageal reflux disease, obesity, and laparoscopic sleeve gastrectomy: The burning questions. World Journal of Gastroenterology. 2019;**25**(33):4805-4813. DOI: 10.3748/wjg.v25.i33.4805

[52] Rebecchi F, Allaix ME, Patti MG, Schlottmann F, Morino M. Gastroesophageal reflux disease and morbid obesity: To sleeve or not to sleeve? World Journal of Gastroenterology. 2017;**23**(13):2269-2275. DOI: 10.3748/wjg.v23.i13.2269

[53] Evans JA, Muthusamy VR, Acosta RD, Bruining DH, Chandrasekhara V, Chathadi KV, et al. ASGE standards of practice committee. The role of endoscopy in the bariatric surgery patient. Surgery for Obesity and Related Diseases. 2015;**11**:507-517. DOI: 10.1016/j.soard.2015.02.2015

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