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Gastro-esophageal reflux disease and obesity, where is the link?

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Core tip: This topic is aimed to explore the potential mechanisms responsible for the association between gastro-esophageal reflux disease (GERD) and obesity, that remain to be fully elucidated. Despite numerous evidence that show an increased risk of GERD symptom and/or complication in obese patients, the interplay between GERD and obesity is not clear. Based on the literature we have tried to summarize the evidence concerning the role of obesity in the GERD pathogenesis to better understand the possible role of weight loss as a therapeutic approach for this disease.

Abstract

The confluence between the increased prevalence of gastro-esophageal reflux disease (GERD) and of obesity has generated great interest in the association between these two conditions. Several studies have addressed the potential relationship between GERD and obesity, but the exact mechanism by which obesity causes reflux disease still remains to be clearly defined. A commonly suggested pathogenetic pathway is the increased abdominal pressure which relaxes the lower esophageal sphincter, thus exposing the esophageal mucosal to gastric content. Apart from the mechanical pressure, visceral fat is metabolically active and it has been strongly associated with serum levels of adipocytokines including interleukin-6 and tumor necrosis factor α , which may play a role in GERD or consequent carcinogenesis. This summary is aimed to explore the potential mechanisms responsible for the association between GERD and obesity, and to better understand the possible role of weight loss as a therapeutic approach for GERD.

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INTRODUCTION

Gastro-esophageal reflux disease (GERD), with symptoms demonstrated to impair quality of life (QoL), appears to show important variation in its prevalence. When defined as at least weekly heartburn and/or acid regurgitation, the prevalence in the Western world generally ranges between 10% and 20% whereas in Asia the prevalence is reported to be less than 5%^[1]. Longitudinal studies have addressed several risk factors for GERD, and indeed obesity is indicated as a potential risk factor^[2]. Interestingly, obesity, typically defined as a body mass index (BMI) of > 30 , has risen to epidemic levels in several regions of North America, Europe and Asia^[3]. The confluence between the increased prevalence of GERD, in

Table 1 Proposed mechanisms by which abdominal obesity causes reflux

Mechanical factors	Increased intra-gastric and gastro-esophageal pressure gradient Increased risk of Hiatal Hernia Increased sensitivity to distension-induced TLESR Decreased lower esophageal sphincter pressure
Humoral factors	Increased level of adipocytokines including interleukin 6 and tumor necrosis factor α
Motility disorders	Delayed gastric emptying rate and delayed esophageal clearing time

TLESR: Transient lower esophageal sphincter relaxation.

terms of symptoms, erosive esophagitis, Barrett's esophagus (BE), esophageal adenocarcinoma and of obesity has generated great interest in the association between these two conditions and the potential mechanisms responsible for this association.

Several studies have focused on the potential relationship between GERD and obesity and results emerging from those investigations have shown that obesity is associated with an increased risk of both GERD symptoms and complication *i.e.*, erosive esophagitis, BE and esophageal adenocarcinoma as compared to individuals with a normal BMI^[4]. There was also some degree of a dose-dependent relationship between BMI and these GERD-related disorders and, moreover, a recent large cohort focusing on adult females reported a possible dose-response increase in the risk of GERD with a higher BMI even if within the normal range^[5].

PATHOGENESIS

Even if several mechanisms by which obesity causes reflux disease have been proposed (Table 1). The pathogenetic pathway commonly suggested is the increased abdominal pressure which relaxes the lower esophageal sphincter (LES), thus exposing the esophageal mucosal to the gastric content^[6,7]. Results of 24-h pH-monitoring studies have shown that obesity is associated with a significant increase in the number of reflux episodes, as well as long-lasting reflux episodes and the time with pH < 4, especially in the post-prandial period^[8]. This finding has been confirmed, in a more recent study, also by means of pH-impedance monitoring: not only the acid reflux but also the number of non acid reflux episodes increased significantly as BMI increased^[9]. A recent study aimed to assess the pressure morphology and function of the esophago-gastric junction, by using the high resolution manometry methodology, reported that due to obesity the gastro-esophageal pressure gradients are altered in a way that would promote the retrograde flow of gastric content into the esophagus. Both the intra-gastric pressure and the gastro-esophageal pressure gradient were clearly correlated with both the BMI and waist circumference but, when these were simultaneously analysed in a regression model, the waist circumference was found to be independently associated with the different pressure

gradients, whereas the relationship between BMI and pressure became non-significant or considerably reduced. In addition to abnormal pressure gradients, high-resolution manometry also revealed that obesity was associated with hiatus hernia (HH). There was a significant correlation between BMI, waist circumference and axial separation of the intrinsic LES and crural diaphragm, and it was postulated that this was a manifestation of pressure stress due to the increased intra-gastric pressure^[10]. In agreement with this finding, in a retrospective case-control study assessing BMI in relation to esophagitis and HH, it was found that obesity is strongly associated with the combined occurrence of esophagitis and HH^[11]. It is widely recognized that HH has several pathophysiological implications in the pathogenesis of GERD: increased incidence of strain-induced reflux, reduced LES pressure, impaired esophageal acid clearance and increased sensitivity to distension-induced transient lower esophageal sphincter relaxation (TLESR)^[12]. Among mechanisms responsible of reflux TLESR seems to play the most important role^[13]. The reflux pattern after a standard meal, has been recently evaluated in obese and overweight patients by using a combined 2 h post-prandial esophageal manometry and pH monitoring^[14]. The results of this study have shown that, during the post-prandial period, both the obese and overweight patients presented a substantial increase in the rate of TLESRs and in the proportion of TLESRs with acid reflux as compared to individuals with a normal BMI. Both BMI and waist circumference showed a significant positive correlation with TLESRs and there was a dose-effect relationship. Therefore, it would appear that a higher post-prandial intra-gastric pressure causes a more intense stimulation both on the stretch and tension mechanoreceptors in the proximal stomach, which leads to more postprandial TLESRs.

ABDOMINAL OBESITY

Abdominal or visceral fat (VAT) is strongly different in respect to peripheral or subcutaneous fat (SCAT). For example, VAT is more metabolically active, is characterized by a higher number of immune and inflammatory cells, and is more insulin-resistant thus leading to an higher overall mortality in respect to SCAT^[15].

Abdominal obesity can better explain some of the epidemiological features of BE and esophageal adenocarcinoma. The distribution of body fat tends to be more visceral than truncal in high-risk groups for BE^[16]. A recent study has shown that the abdominal diameter measured as the waist circumference is a risk factor for BE independently of BMI, while the association between BMI and BE disappeared after adjustment of the abdominal diameter^[17]. These studies indicate that abdominal fat is the key factor linking obesity and BE. Apart from the mechanical pressure, visceral fat is metabolically active, and has been clearly associated with serum levels of adipo-cytokines including interleukin 6 and tumor ne-

crosis factor α , which may play a role in GERD and/or consequent carcinogenesis^[18]. In fact, in a very recent study, a large amount of visceral abdominal fat in respect to subcutaneous fat was found to be associated with a significant increase in the risk of BE^[19].

OUTCOME

Considering the dose-response relationship between obesity and occurrence of GERD and/or the resulting complications, an inverse relationship between weight loss and GERD symptoms would be expected. The prevalence of GERD symptoms in overweight and obese subjects as well as impact of weight loss on GERD symptoms has been assessed in a recent prospective study^[20]. Weight loss strategies included dietary modifications, increased physical activity as well as behavioral changes. The results coming from the study showed that weight loss led to a significant improvement in GERD symptoms, thus establishing weight loss as an important modification of life style in the treatment of GERD. Moreover, weight loss over a 6-mo period, was associated with a reduction in GERD symptoms in 81% of the patients and with complete resolution in 65% of the patients. This finding provides support for recommending weight-loss in the primary treatment of overweight reflux patients, however this clinically important finding has unfortunately not been described so far. Further investigations on the long-term effect of weight loss on reflux occurrence and on the reduction in reflux symptoms are needed before any definitive conclusions can be drawn regarding eventual beneficial effects of weight loss.

CONCLUSION

Obesity appears to be involved not only in the development of GERD symptoms but, also in the occurrence of GERD complication such as erosive esophagitis, Barrett's esophagus and esophageal adenocarcinoma.

Despite considerable evidence confirming the important role of increased esophago-gastric pressure gradient, and of production of inflammatory mediators by abdominal adipose tissue in the pathogenesis of GERD, the interplay between obesity and GERD is still not clear. Moreover, weight loss seems to reduce GERD symptoms but further studies are warranted to better understand the exact mechanism by which obesity causes reflux disease in order to identify and establish new therapeutic approaches.

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