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The Association Between Obesity and GERD: A Review of the Epidemiological Evidence

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Abstract

The current epidemics of obesity and gastroesophageal reflux disease (GERD)–related disorders, including symptoms, esophageal erosions, Barrett’s esophagus (BE), and esophageal adenocarcinoma, have generated much interest in studying the association between these two conditions. Results of multiple case-control and cohort studies indicate that obesity satisfies several criteria for a causal association with GERD and some of its complications, including a generally consistent association with GERD symptoms, erosive esophagitis, and esophageal adenocarcinoma. An increase in GERD symptoms has been shown to occur in individuals who gain weight but continue to have a body mass index (BMI) in the normal range, contributing to the epidemiological evidence for a possible dose-response relationship between increasing BMI and increasing GERD. However, data are less clear on the relationship between BE and obesity, with more recent investigations showing little association. However, when considered separately, abdominal obesity seems to explain a considerable part of the association with GERD, including BE. Overall, epidemiological data show that maintaining a normal BMI may reduce the likelihood of developing GERD and its potential complications.

Introduction: Secular Trends

Obesity, typically defined as a body mass index (BMI) of >30 , has risen to epidemic proportions in the United States and several regions in Europe and Asia. Data from 2 US NHANES surveys show that, among adults aged 20–74 years, the prevalence of obesity increased from 15.0% in 1976–1980 to 32.9% in 2003–2004.^{1,2} Although other factors, such as genetic disposition, may be contributors, in general, increased food intake and decreased physical activity have been cited as the primary causes for the observed trends. The prevalence of gastroesophageal reflux disease (GERD) and related disorders also has been steadily increasing in the United States, Western Europe, and Scandinavian countries.³ [Dent 2005/p 711/Table 1; p 713/col 2/¶ 4] The increasing incidence is most remarkable for esophageal adenocarcinoma,⁴ [Pohl 2005/p 145/col 1/¶ 6] but has been reported for GERD symptoms⁵ and Barrett’s esophagus (BE) as well.^{6,7} [Conio 2001/p 308/col 1/¶ 5] Esophageal adenocarcinoma incidence in the United States, for example, increased 6-fold between 1975 and 2001.⁵ Similar increases have been observed in the United Kingdom, the Scandinavian countries, and Australia.⁸ The reasons for this rise in GERD and its complications have not been clearly identified, and many studies have investigated whether the increase in the prevalence of obesity and GERD are related. Overall, there seems to be quite a good amount of evidence of a modest association between BMI, particularly in the obese range, and GERD symptoms. Although the data are not as strong, the trend appears to be similar for an association with erosive esophagitis. Data show a more

pronounced association between esophageal adenocarcinoma and obesity. However the data are more conflicting for BE and obesity. This article reviews the results of a recent comprehensive meta-analysis of the available epidemiological data linking obesity with GERD and its complications, as well as discusses additional studies investigating this relationship. The question of whether an increase in obesity prevalence accounts for the increased incidence of GERD, particularly of its complications, is also explored.

Association Between Obesity and GERD: A Meta-Analysis

Hampel et al conducted a systematic review and meta-analysis of epidemiological studies that examined the association between obesity and several GERD-related disorders, including GERD symptoms, esophageal erosions, and esophageal adenocarcinoma.⁹ [Hampel 2005/p 199–200/abstract and col 2/¶3] As of 2005, our group identified 23 relevant studies: 9 for GERD symptoms, 7 for erosive esophagitis, and 7 for esophageal adenocarcinoma. The following inclusion criteria had to be fulfilled: 1) cross-sectional, case-control, or cohort study that permitted assessment of a causal association between overweight or obesity and esophageal disease; 2) clear definition of obesity as defined by BMI in (kg/m²) or height-to-weight ratio; and 3) a well-defined outcome of interest that included GERD symptoms rated using validated symptom scores, esophageal erosions confirmed by endoscopy, and esophageal adenocarcinoma validated by pathology review. We excluded case reports and case series, studies with fewer than 50 case subjects, and studies that failed to report risk estimates.

Obesity and GERD Symptoms

All 9 studies that we identified were cross-sectional examinations of GERD symptoms in randomly selected samples of the general population. [Hampel 2005/p 201–202/col 2/¶2] These studies were mostly conducted in countries of North America or Western Europe. [Hampel 2005/p 200/Table 1] The association between obesity and GERD symptoms was examined in high-quality studies using validated questionnaires in randomly selected samples of the general population; however, the strength of the association is rather modest and 3 studies^{10–12} [Andersen 1991/p 10/col 1/¶1; Lagergren 2000/p 28/col 1/¶1; Wu 2003/p 946/col 2/¶1] showed no significant association. The effect of weight gain examined in a study by Nilsson et al found that a gain greater than 3.5 BMI units was associated with an approximately 3-fold increase in the risk of developing new reflux symptoms.¹³ [Nilsson 2003/p 70/col 1/¶1] Adjustment for potential confounders was included, albeit variably, in these studies. In general, adjustment for race, NSAID intake, cigarette smoking, *Helicobacter pylori* status, socioeconomic status, or physical activity did not change the significance or direction of the observed associations.

Of note, a recent large cohort study in women conducted after our meta-analysis confirmed these overall findings and also reported a possible dose-response increase in the risk of GERD even in the normal range of BMI.¹⁴ [Jacobson 2006/p 2340/abstract] This study surveyed 10,545 female participants in the Nurses' Health Study about the frequency, severity, and duration of GERD symptoms and used logistic regression analysis to investigate the relationship between survey responses and BMI. As participant BMI increased, the odds ratios for frequency of symptoms increased significantly ($P < 0.001$). Similar to the findings of Nilsson et al,¹³ [Nilsson 2003/p 70/col 1/¶1] this study also showed that, even in women with BMIs in the normal range, weight gain corresponding to an increase of more than 3.5 kg/m² in BMI increased the risk of GERD frequency compared with women with no weight changes.¹⁴ [Jacobson 2006/p 2340/abstract]

Obesity and Erosive Esophagitis

In the meta-analysis, we identified 7 studies (4 case-control,^{15–18}[Nilsson 2002/p626/abstract; Stene-Larsen 1988/p 427/abstract; Wilson 1999/p 2840/abstract; Labenz 2004/p 1652/abstract] 2 cross-sectional,^{19, 20}[Chang 1997/p 668/abstract; Furukawa 1999/p 441/abstract] and 1 cohort²¹[Ruhl 1999/p 424/abstract] investigating the relationship between obesity and erosive esophagitis that fulfilled the inclusion and exclusion criteria. Six out of these 7 studies, including 1 cohort study,²¹[Ruhl 1999/p 424/abstract] showed a significant positive association with obesity; while only 1 study, which was conducted in Japan, showed no significant association.²⁰[see figure 2 in ref ⁸ Hampel 2005/p 203] (Figure 1) The studies on esophageal erosions are mostly from clinic-based studies and are, therefore, susceptible to ascertainment bias. Furthermore, it is difficult to adjust for the use of antisecretory medications and their possible masking effects on erosive esophagitis. Nevertheless, the findings from these studies support an association between obesity and increased risk of erosive esophagitis.

Obesity and Esophageal Adenocarcinoma

We identified 7 case-control studies that examined the association between BMI and esophageal adenocarcinoma.^{22–28} Four of these studies examined esophageal adenocarcinoma separate from that of the gastric cardia,^{22,25,26,28} 1 study that excluded cancers of the cardia,²⁷ and 2 studies that combined the esophagus and gastric cardia.^{23,24} The pooled adjusted odds ratios were 1.52 (95% CI: 1.15–2.0) for overweight and 2.78 (1.85–4.16) for obesity (Figure 2). These estimates were pooled from all studies except that of Zhang et al, which combined the estimates for both esophageal and gastric cardia cancers. Five of these 7 studies showed a significant positive association between BMI and esophageal adenocarcinoma and 2 showed no significant association (Figure 2). Although not conducted uniformly in all studies, adjustments for age, sex, race, smoking, alcohol consumption, caloric intake, history of reflux symptoms, or education level did not alter the significance or direction of associations.

For esophageal adenocarcinoma, the association with obesity is most pronounced and comes from population-based case-control studies. However, recall bias is a major problem in cancer studies. For example, if patients with cancer were concerned that their eating habits and BMI may have caused their disease process, they were more likely to overestimate their historical weight compared to noncancer controls. However, several cancer studies had a control group of either squamous cell cancer of the esophagus or distal gastric adenocarcinoma, and BMI was found to have either no association or a significant negative association with these cancer controls,^{22,26} [Vaughn 1995/p 85/abstract; Lagergren 1999/p 883/abstract] thus arguing against recall bias. Several studies examined adenocarcinoma of the gastric cardia and reported a modest and less consistent association with obesity.

In summary, this meta-analysis indicated that obesity was associated with a significant 1.5- to 2-fold increase in the risk of GERD symptoms and erosive esophagitis, and a 2- to 2.5-fold increase in the risk of esophageal adenocarcinoma as compared to individuals with normal BMI. Subsequent meta-analyses confirmed these findings in a larger number of studies from the United States and highlight the heterogeneous results from Europe, with individual studies demonstrating both positive associations and no association.^{29,30} [Corley 2006/p 2624/col 1–2/¶ 2–3; Kubo 2006/p 872/abstract]

The Conflicting Data Concerning Barrett's Esophagus and Obesity

At the time of conducting our meta-analysis, there were no analytic studies of obesity and BE that satisfied our inclusion criteria. However, during the past 2 years, several published studies have examined the association between obesity and BE with mixed results that include showing a significant risk increase with high BMI,^{31,32} [El-Serag 2005/p 2154/col 1/¶ 2; Stein 2005/

p1005/abstract] a significant increase with high BMI only in the presence of GERD symptoms,³³ [Smith 2005/p 2485/col 1/¶ 1] or no association.³⁴ [Gerson 2007/p 1079/abstract]

More recently, a case-control study within the Kaiser Permanente Northern California population compared 320 persons with a new BE diagnosis, 316 subjects with GERD without BE, and 317 population controls.³⁵ [Corley 2007/p 34/abstract] In that study, there was an association between BE and a larger abdominal circumference compared with population controls and a trend for association compared with GERD patients. There was no association demonstrated between BE and BMI. Adjustment for GERD only partially attenuated the association between BE and circumference, thus suggesting a limited role for GERD. However, the modest correlation between esophageal acid exposure, as measured by 24-hour pH metry, and the presence of GERD symptoms³⁶ [Klauser 1990/p 206/col 1/¶ 3] may help clarify the apparently limited role of GERD symptoms in explaining the association between obesity and BE or esophageal adenocarcinoma found in epidemiological studies.³⁵

Given the strong evidence of an association between increasing BMI and the risk of GERD symptoms as well as esophageal adenocarcinoma, the lack of an independent association between BMI and BE might seem surprising. However, with the exception of the BE studies, the studies in our meta-analysis did not include other body measures; and, therefore, did not adjust their results for abdominal diameter. Two recent large case-control studies have shown that abdominal diameter (but not BMI) is an independent risk factor of BE.^{35,37} [Corley, Gastro 2007/p 34/abstract; Edelstein 2007/p 17/¶ 2]

Does Obesity Explain the Epidemiological Features of GERD-Related Disorders?

Before drawing conclusions from trends linking obesity and GERD, we must consider other epidemiological factors. The relative importance of obesity as a possible cause of GERD must be assessed in terms of explaining the gender- and race/ethnicity-related differences in the distribution of GERD. GERD symptoms seem to be equally prevalent between men and women (or slightly more common in women) and between Caucasians and other racial/ethnic groups. Esophagitis is more common among men and Caucasians,^{38,39} [El-Serag 2004/p 1696/col 1/¶ 1] BE is much more common in men and Caucasians,⁴⁰ [Falk 2005/p 1093/col 2/¶ 2] and esophageal adenocarcinoma is dominated by men and Caucasians.⁴¹

Both obesity and GERD are increasing in parallel, and it is plausible that this could account for an increase in GERD symptom prevalence. However, it is likely that the increase in obesity prevalence occurring over the past 15 years or so^{1,42} [Flegal 2002/p 1724/Table 1; Ogden 2002/p 1730/col 3/¶ 2] would explain the increase in esophageal adenocarcinoma incidence, which has been rising over perhaps the past 20 years⁵ [El-Serag 2007/p23/col 1/¶ 3]—given the probable long latency period required before prolonged GERD leads to esophageal adenocarcinoma.

Abdominal Obesity

Simple obesity does not explain gender or ethnic predilections because the prevalence of obesity is also increasing rapidly in demographic groups at relatively low risk of BE and esophageal adenocarcinoma (eg, women and African Americans). However, abdominal obesity explains 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, including Caucasians (compared with African Americans)⁴³ and men (compared with women). [Weinsier 2001/p 635/col 2/¶ 2] A recent study reported a consistent association between abdominal diameter (independent of BMI) and GERD symptoms in Caucasians, but not in

African Americans or Asians⁴⁴ [Corley, Gut 2007/p 756/abstract] (Figure 3). These findings, combined with the increased prevalence of abdominal obesity in men, suggest that increased obesity may disproportionately increase GERD in Caucasians and men. Two other recent studies have shown abdominal diameter measured as waist circumference to be a risk factor of BE independent of BMI, and the association between BMI and BE disappeared after adjustment of abdominal diameter.^{35,37} [Corley, Gastro 2007/p 23/abstract; Edelstein 2007/p 17/¶ 2] Abdominal obesity may also be a marker of visceral obesity that promotes GERD-related disorders via humoral mechanisms. Our group conducted a case-control study in patients who underwent endoscopy at a single large VA medical center. We compared 36 patients with documented BE who had an abdominal computed tomography (CT) scan within 1 year of the endoscopy with 93 control patients without BE who also had an abdominal CT scan.³¹ [El-Serag 2005/p 2151/abstract; p 2154/col 2/¶ 2] The surface areas of visceral adipose tissue calculated from CT scan images at the level of intervertebral disc between L4 and L5 was approximately 1.5-fold greater in the BE cases than controls, whereas differences in subcutaneous adipose tissue were less pronounced. Visceral fat has been strongly associated with increased release of several proinflammatory cytokines (eg, tumor necrosis factor- α), as well as with lower serum levels of adiponectin, which has an anti-apoptotic and antiproliferative effect, thus in aggregate increasing the inflammation and hence the malignant transformation in patients with GERD.

Effect of Diet and Physical Activity

Individuals who are obese have exercise and eating habits that markedly differ from those of individuals of normal weight. It is possible that the effects of obesity on GERD-related symptoms and complications could be confounded by the dietary intake and physical activity of these individuals. It has also been postulated that consumption of fatty foods, rather than obesity itself, is responsible for GERD.⁴⁵ [Castell 1996/p626/col 1/¶ 1] Unfortunately, the role of physical activity has not been adequately examined. Moreover, although some studies are suggestive, no consistent association has been found between dietary fat and GERD or esophageal adenocarcinoma. Studies that examined total caloric intake, found the effect of BMI to be independent of dietary intake of fiber, fruits and vegetables, or other macronutrients or micronutrients.^{22, 25, 46} For example, studies that examined GERD adjusted for alcohol or coffee consumption^{13, 47–49} [Nilsson 2003/p 67/col 2/¶ 3; Diaz-Rubio 2003/p 100/Table 2; Locke 1999/p644/Table 2; Murray 2003/p 647/col 2/¶ 3] or other dietary factors, such as dietary fiber¹³ [Nilsson 2003/p 67/col 2/¶ 3] or total energy intake,¹¹ [Lagergren 2000/p 29/col 1/¶ 5] reported no significant changes in the odds ratios. The uncertainty about the relevant exposure period in the life of patients with GERD-related disorders, coupled with difficulty in accurate measurement of dietary intake especially during remote times, has contributed to the difficulty in conducting and interpreting dietary studies.

Mechanistic Clues From Epidemiological Studies

The epidemiological trends observed in studies of obesity and GERD have led to speculation about the possible mechanical changes in the upper GI tract that may account for the associations. Obese individuals may experience extrinsic gastric compression by surrounding adipose tissue, leading to an increase in intragastric pressures and subsequent relaxation of the lower esophageal sphincter, as well as increased pressure stress and anatomic disruption of the gastroesophageal junction. The anatomic disruption of the gastroesophageal junction may result in the formation of a hiatal hernia. The support for this supposition is weak in epidemiological studies. One study found obesity to be significantly associated with esophagitis¹⁷ [Wilson 1999/p 2840/abstract] only in the presence of hiatal hernia. Similarly, Stene-Larsen et al¹⁶ [Stene-Larsen 1988/p 427/abstract; p 430/col 2/¶ 1] found that 68% of patients with esophagitis had concomitant hiatal hernia and that obesity was significantly

associated with both conditions, and El-Serag et al⁵⁰[El-Serag 2002/p 899/abstract] found that obesity was a risk factor for severe esophagitis independent of hiatal hernia. In the studies described above, the criteria for identifying and measuring hiatal hernia may not have been used correctly or uniformly.

Lastly, 2 studies suggested that the association of obesity and GERD might be mediated by the effect of circulating estrogen.^{13,15} [Nilsson 2003/p 66/abstract; Nilsson 2002/p 628/col 1/¶ 1] The first study reported a significant association between obesity and esophagitis in women and that the use of estrogen in overweight postmenopausal women appeared to potentiate this effect. The second study, in a large population-based cohort, found that obese women had a higher risk of GERD symptoms compared with obese men, and the risk was highest among premenopausal women and postmenopausal women on estrogen therapy. However, several other studies have found that the increased risk of acid-related esophageal disease among overweight and obese persons was neither confounded nor modified by gender. The estrogen hypothesis does not explain the gender- or race-related differences in GERD.

In summary, this review suggests that obesity is associated with a significant 1.5- to 2-fold increase in the risk of GERD symptoms and erosive esophagitis, and a 2- to 2.5-fold increase in the risk of esophageal adenocarcinoma as compared to individuals with normal BMI. A causal association between obesity and GERD-related disorders is suggested by the parallel secular trends, the significant association in most cross-sectional and case-control studies, the compatible temporal association in cohort studies, and the suggestive dose-response relationship. An accurate interpretation of the epidemiological data is that avoiding weight gain in the first place is associated with a lower risk of GERD. The outcomes of treating obesity are discussed elsewhere in this supplement.

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Figure 1.

Data from a meta-analysis shows the adjusted odds ratios from cross-sectional and case-control studies examining the association between overweight or obesity (body mass index ≥ 25 kg/m²) and erosive esophagitis. There is a significant overall risk association with increased BMI and erosive esophagitis. (Hampel et al, Ann Intern Med 2005)

Figure 2.

Data from a meta-analysis shows the adjusted odds ratios from case-control studies examining the association between overweight (body mass index ≥ 25 kg/m²) and adenocarcinoma of the esophagus (top) and the association between obesity (body mass index > 30 kg/m²) and esophageal adenocarcinoma (bottom). There is a consistent and significant association between overweight/obesity and esophageal adenocarcinoma. (Hampel et al, Ann Intern Med 2005)

Figure 3.

The dose-response association between abdominal diameter and the risk of GERD symptoms. Increased abdominal diameter (adjusted for BMI) was a consistent independent risk factor for GER-symptoms in whites. (modified from Corely et al, Gut 2007)