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Role of Obesity in Barrett's Esophagus and Cancer

Liam Murray, MD^{a,*}, Yvonne Romero, MD^b

KEYWORDS

- Reflux esophagitis • Barrett's esophagus
- Esophageal adenocarcinoma • Obesity • Adiposity

The incidence of esophageal adenocarcinoma (EAC) has increased dramatically in the western world over the last 30 years,¹ and although the trends in the diagnosis of Barrett's esophagus (BE) are more difficult to interpret because of substantial increases in the use of endoscopy over this period and improvement in physician recognition,² it remains possible that there has been some increase in the incidence of BE and gastro-esophageal reflux disease (GERD) in recent years.³ The contemporaneous increase in obesity in the western world has focused interest on whether obesity is a risk factor for EAC and its precursors, whereas the failure of overall obesity to explain the basic patterns of EAC distribution (eg, the sex differences and differences between ethnic groups¹) has led to a focus on body fat distribution and abdominal obesity. Much interest has also been shown in the mechanisms whereby overweight or obesity may increase risk of this disease spectrum. This article reviews current evidence for the role that overweight/obesity and body fat distribution have in development of the esophagitis-metaplasia-dysplasia-adenocarcinoma sequence. Particular attention is paid to the stage at which adiposity may act to influence the risk of EAC, because this determines the importance of weight control and weight loss at each stage in the disease spectrum for the prevention of EAC.

IS ADIPOSITY A RISK FACTOR FOR REFLUX SYMPTOMS AND EROSION REFLUX ESOPHAGITIS, AND DO THE RELATIONSHIPS DIFFER FOR OVERALL AND ABDOMINAL OBESITY?

A large body of evidence has examined the relationship between adiposity and GERD symptoms (heartburn and acid regurgitation) and erosive esophagitis. In a meta-analysis of studies examining the association between body mass index (BMI) and reflux symptoms, Hampel and colleagues⁴ identified nine robust cross-sectional studies that

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included a total of 7373 subjects with symptoms and 55,603 without symptoms. All of the studies showed positive relationships between being overweight or obese and the presence of GERD symptoms; the pooled odds ratios (ORs) with 95% confidence intervals (95% CI) for overweight and obesity were 1.43 (1.16 to 1.78) and 1.94 (1.16 to 1.77), respectively. Only one of these studies reported findings separately for men and women, and relationships were somewhat stronger in women. The meta-analysis also included seven studies (4668 cases and 23,899 controls) that examined the association between BMI and erosive reflux esophagitis. All but one of these studies also showed positive associations; the pooled OR (95% CI) for overweight/obese (combined) was 1.76 (1.16 to 2.68), with stronger associations seen in obese men when compared with obese women. This meta-analysis showed that being overweight and obese, as measured by BMI, was associated with GERD symptoms and erosive esophagitis, but a higher BMI, even within the normal range, was also positively associated with GERD symptoms.⁵ More recent population-based studies have confirmed the association between being overweight or obese and GERD symptoms.^{6,7}

Few studies have examined the relationship between GERD symptoms and measures of adiposity other than BMI, which is a measure of overall adiposity and therefore provides no information on the distribution of body fat. Among 80,000 members of the Kaiser Permanente Health Plan in San Francisco and Oakland, California, Corley and colleagues⁸ showed that increased abdominal adiposity (measured by abdominal diameter) was associated with GERD symptoms even after adjustment for BMI (and other potential confounders) in whites but not in blacks or Asians. Adjusted ORs for the highest compared with lowest category of abdominal diameter were 1.85 (1.55 to 2.21), 0.95 (0.61 to 1.48), and 0.64 (0.18 to 2.30) for whites, blacks, and Asians respectively, with similar findings in white men and women. BMI was also associated with symptoms in this study; this association was attenuated somewhat by adjustment for abdominal diameter, suggesting that at least part of the relationship between BMI and GERD symptoms is mediated by abdominal obesity. In the Nurses' Health Study, a high waist-hip ratio (WHR) was also associated with GERD symptoms (OR [95% CI] for the highest quintile versus lowest quintile of WHR, 1.88 [1.45 to 2.45]), but in contrast to the Kaiser Permanente study, this association was blunted by adjustment for BMI.⁵

Two recently published studies performed in patients undergoing endoscopy in Korean medical centers have shown strong associations between abdominal adiposity and erosive reflux esophagitis. In one of these studies,⁹ the OR (95% CI) for esophagitis in subjects with abdominal obesity (defined as a waist circumference ≥ 80 cm in women and ≥ 90 cm in men) was 2.3 (1.6 to 3.1), and this relationship was independent of BMI. In the second study,¹⁰ the ORs for esophagitis in subjects with a WHR greater than 1 or 0.8 to 1 compared with less than 0.8 were 4.1 and 2.3, respectively. Although these results may not be generalizable to non-Asian populations, they provide evidence that abdominal obesity may be more important in the development of erosive esophagitis than overall obesity.

Strong evidence suggests that overall obesity is a risk factor for both GERD symptoms and erosive reflux esophagitis, with marginal evidence of a stronger association in men than women. Abdominal obesity has been shown to be a risk factor for GERD symptoms in whites, but this may not be true in blacks and Asians, and it is unclear whether abdominal obesity is a stronger risk factor for GERD than overall obesity. Recent evidence from Asian populations suggests that abdominal obesity rather than overall obesity increases esophagitis risk.

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DOES WEIGHT LOSS IN OBESE OR OVERWEIGHT PATIENTS IMPROVE SYMPTOMS OF GASTROESOPHAGEAL REFLUX DISEASE OR EROSIIVE ESOPHAGITIS OR PREVENT THE DEVELOPMENT OF BARRETT'S ESOPHAGUS?

Although there is a paucity of data with which to address this question and although not all studies are in agreement,¹¹ weight loss in obese or overweight patients appears to improve GERD symptoms,^{12,13} reduce acid reflux into the esophagus,¹⁴ and improve histologic and clinical esophagitis.¹⁵ Loss of visceral/abdominal fat may be particularly important in reducing reflux.¹⁴ The question of whether weight loss in patients with esophagitis will reduce the risk of developing BE has not yet been addressed.

IS ADIPOSITY A RISK FACTOR FOR BARRETT'S ESOPHAGUS, AND DO THE RELATIONSHIPS DIFFER FOR OVERALL AND ABDOMINAL OBESITY?

To date, few studies have examined the relationship between BMI and BE. In a small retrospective cross-sectional study of patients undergoing endoscopy within the Southern Arizona Veteran's Affairs Healthcare System,¹⁶ 65 patients with BE were compared with 385 patients without BE. Being overweight or obese was associated with the risk of BE; the ORs (95% CI) for overweight and obese patients compared with normal weight patients were 2.43 (1.12 to 5.31) and 2.46 (1.11 to 5.44), respectively. Bu and colleagues¹⁷ showed similar findings in another study of endoscopy patients; however, the control groups in these studies do not represent the normal population and may therefore generate misleading results. Cook and colleagues¹⁸ undertook a meta-analysis of studies comparing BMI in BE cases with population controls. Only three studies were identified,¹⁹⁻²¹ which gave a pooled OR (95% CI) per unit increase in BMI of 1.02 (1.01 to 1.04). This finding was a substantially more modest increase in risk than that seen in the descriptive cohort reports of endoscopy patients.

A recently published study has examined the relationships between overall and abdominal adiposity measured by WHR and BE risk.²² In this case-control study (which included 211 population controls), a high WHR was associated (after adjustment for confounders and BMI) with an substantially increased risk of BE, whether BE was defined as specialized intestinal metaplasia (SIM) positive (197 cases), SIM positive with a visible Barrett's segment (97 cases), or SIM positive with a visible long segment BE (54 cases). ORs (95% CI) for the three groups were 1.9 (1.1 to 3.2), 2.9 (1.5 to 5.7), and 4.1 (1.7 to 10.0), respectively. Corresponding ORs (95% CI) adjusted for confounders and WHR for overall obesity (defined as BMI ≥ 30) were 2.0 (1.1 to 3.5), 1.0 (0.5 to 2.0), and 1.2 (0.5 to 3.0), respectively. Abdominal adiposity was a strong risk factor for BE surviving adjustment for BMI, whereas, in contrast, the weaker association with BMI was attenuated by adjustment for the WHR ratio. Furthermore, the associations with WHR were strengthened rather than attenuated by adjustment for reflux symptoms, suggesting that central adiposity may exert its effect on BE risk by mechanisms that are independent of perception of reflux.

Similar results were obtained in a case-control study of 320 incident BE cases and 317 population controls undertaken within the Kaiser Permanente Northern California population.²³ In that study, abdominal circumference between 80 cm (32 inches) and 89 cm (35 inches) was related to BE risk; the OR (95% CI) adjusted for BMI was 2.24 (1.21 to 4.15). There was no increase in the risk of BE in cases with larger waist sizes ranging from 90 to greater than 130 cm, and there was no evidence of a dose-response curve (ie, the higher the waist circumference the higher the risk of BE). In contrast, adiposity as judged by BMI was not associated with the risk of BE. Abdominal circumference was associated with GERD symptoms, and some attenuation of

the association between waist circumference and BE was seen on adjustment for these symptoms; statistical significance was lost, but the OR (95% CI) remained elevated (1.78 [0.86 to 3.66]).

The findings of these two studies are supported by those of a small retrospective study of 36 BE patients and 93 controls (BE-negative endoscopy cases) in whom visceral and subcutaneous adipose tissue was measured from abdominal CT scans taken within 1 year of endoscopy. Visceral adipose tissue was 1.5 fold greater in cases than in controls (183 versus 115 cm², $P < .001$). Differences were also seen between cases and controls for subcutaneous adipose tissue, but these were less marked (248 versus 200 cm²), and in a multivariate model, visceral adipose tissue but not BMI was significantly associated with BE.

Data from these studies indicate that the distribution of body fat may be important in determining the risk of BE, suggesting that abdominal obesity appears to be a stronger risk factor than overall obesity. The data also indicate that at least part of the relationship between abdominal obesity and BE is mediated by mechanisms other than GERD symptoms.

IS THE INCREASED RISK OF BARRETT'S ESOPHAGUS IN OBESE OR OVERWEIGHT INDIVIDUALS INDEPENDENT OF THE INCREASE IN RISK OF ESOPHAGITIS?

Cook and colleagues¹⁸ have recently explored whether adiposity presents an additional risk for BE over and above that associated with GERD/GERD symptoms. A stronger association between BE and adiposity would indicate that adiposity could predict which GERD patients will develop BE. Consequently, screening and surveillance of overweight GERD patients might facilitate the early detection of BE, and weight reduction in such patients might reduce the risk of BE and possibly EAC. Cook explored this question by undertaking a meta-analysis of observational studies in which BE cases were compared with GERD controls (with or without confirmed esophagitis) or normal population controls. BMI was used as the proxy of adiposity in these studies. Although BMI was positively associated with BE when the comparison group was population controls, this was not true when BE cases were compared with GERD controls (no difference between studies with confirmed esophagitis controls and those in whom esophagitis was not confirmed). It was concluded that increasing adiposity presents no additional risk for BE beyond increasing the risk of GERD/GERD symptoms alone. A further study, which was not included in Cook's meta-analysis (published after the literature search), agreed with the findings of the meta-analysis. The BMI in 165 patients diagnosed with BE was not different from that in 586 patients with endoscopically proven esophagitis or gastroesophageal reflux proven by 24-hour pH monitoring.²⁴ The recent case-control study from the Kaiser Permanente Northern California population²³ also included a GERD symptom control group. In that study, although waist circumference and the waist/thigh ratio were associated with BE in a comparison with population controls, the relationship between BE and these measures of abdominal adiposity were weaker and not statistically significant when the comparison group was the GERD controls. It is possible that general or abdominal adiposity increases the risk of BE by principally increasing the risk of GERD/GERD symptoms.

IS ADIPOSITY A RISK FACTOR FOR ESOPHAGEAL ADENOCARCINOMA, AND DO THE RELATIONSHIPS DIFFER FOR OVERALL AND ABDOMINAL OBESITY?

Adiposity is a risk factor for EAC.^{19,25,26} Estimates of the degree of association between obesity and EAC differ between reports most likely because of differences

in study design. Sex and weight in youth had access to objective measures and were not a risk factor for

A meta-analysis showed an association (95% CI) for the two a slightly stronger association between AARP Diet and Health increased with increased and the (adjusted) (≥ 35) when compared. In a meta-analysis and the incidence was for EAC; it was

Corley and colleagues obesity (BMI) and Health Check-up (between 1965 and subsequently developed. A larger abdominal compared with low EAC risk; the OR (95% CI) (1.43 to 7.04). The strengthened on a symptoms. Abdominal or squamous cell carcinoma abdominal adiposity may increase symptoms. The recent incident cases of adenocarcinoma (combined) was associated with body mass index for a BMI of 30 or greater and the hazard ratio (2.04). The hazard ratio for electrical impedance

A study using the based study reviewed 1971 to 2000 with stratified an association in selected population provider in the same and weight measures. GERD was significantly associated with a BMI greater than 30 and EAC (OR [95% CI], 1.43 to 7.04), a small study.

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in study design. Some studies estimated obesity based on subject recall of their height and weight in youth or years prior to the diagnosis of cancer, whereas other studies had access to objective measurements collected in the past. In contrast, obesity is not a risk factor for squamous cell carcinoma of the esophagus.²⁵⁻²⁷

A meta-analysis of 14 observational studies (12 case-control and 2 cohort studies)²⁸ showed an association between being overweight or obese and EAC risk; pooled ORs (95% CI) for the two groups were 1.9 (1.5 to 2.4) and 2.4 (2.0 to 2.8), respectively, with a slightly stronger association in men than women. Abnet and colleagues²⁹ identified an association between BMI and EAC in a large cohort study. The risk of EAC in a NIH-AARP Diet and Health Study cohort (which included almost 500,000 participants) increased with increasing baseline BMI (based on self-reported height and weight), and the (adjusted) hazard ratio for participants with a BMI in the highest category (≥ 35) when compared with participants with a normal BMI was 2.27 (1.44 to 3.59). In a meta-analysis of prospective studies examining the association between BMI and the incidence of 20 different types of cancer, the strongest association in men was for EAC; it was the third strongest association in women.³⁰

Corley and colleagues²⁷ examined the associations between abdominal and overall obesity (BMI) and EAC risk in a nested case-control study within the Multiphasic Health Check-up cohort in Northern California. The abdominal diameter at baseline (between 1965 and 1969 inclusively) was compared between 101 participants who subsequently developed EAC and matched controls who did not develop this cancer. A larger abdominal diameter was associated with EAC; the OR (95% CI) for the highest compared with lowest quartile was 3.47 (1.29 to 9.33). BMI was also associated with EAC risk; the OR (95% CI) for a BMI of 30 or greater compared with normal was 3.17 (1.43 to 7.04). The relationship between abdominal diameter and EAC risk was strengthened on adjustment for BMI and was unaltered by adjustment for GERD symptoms. Abdominal diameter was not associated with cardiac adenocarcinoma or squamous cell carcinoma. These findings suggest that both overall adiposity and abdominal adiposity may independently increase the risk of EAC, and that abdominal adiposity may increase EAC risk by a mechanism unrelated to the induction of GERD symptoms. The results of this study are supported by a small study that examined 30 incident cases of adenocarcinoma of the gastric cardia and lower third of the esophagus (combined) within an Australian cohort study.³¹ This study showed a positive association with both BMI and abdominal circumference. The hazard ratio (95% CI) for a BMI of 30 or greater compared with a BMI of less than 25 was 3.7 (1.1 to 12.4) and the hazard ratio per 10 cm increase in abdominal circumference, 1.46 (1.05 to 2.04). The hazard ratio (95%) per 10 kg increase in fat-free mass (measured by bio-electrical impedance) was also increased in this study (2.06 [1.15 to 3.68]).

A study using the resources of the Rochester Epidemiology Project, a population-based study reviewing the records of all persons diagnosed with EAC (N = 29) from 1971 to 2000 with records dating back in some cases to their birth, did not demonstrate an association between BMI and EAC.³² Cases were matched with randomly selected population controls of like age (± 1 year) and sex who were seen by a local provider in the same year (± 1 year) that the case was diagnosed. Several height and weight measurements were available over each person's lifetime. A history of GERD was significantly associated with EAC (OR [95% CI], 5.5 [1.2 to 24.8]). Neither a BMI greater than 30 nor a maximal lifetime BMI greater than 30 were associated with EAC (OR [95% CI], 1.7 [0.4 to 7.0] and 1.3 [0.6 to 3.0]), respectively; however, this was a small study.

Overall, emerging data suggest that being overweight or obese is associated with an increased risk of EAC, and that abdominal adiposity is at least as important

a risk factor as is general adiposity. What is less clear is at what stage in the disease process adiposity acts to increase EAC risk. The association between obesity early in life and subsequent EAC risk^{19,25} together with the data suggesting that adiposity increases BE risk by principally increasing the risk of esophagitis¹⁸ suggest that adiposity may act early in the disease process. Most studies that have examined the relationship between obesity and EAC risk have shown it to be independent of reflux symptoms.^{19,22,25,27} Although this finding may reflect the insensitivity of symptom-based measures of assessing gastroesophageal reflux, obesity could also act to increase EAC risk by mechanisms that are unrelated to reflux, such as via insulin-like growth factors, and these mechanisms may operate later in the disease process. Alternatively, obesity-induced reflux may continue to occur during the later stages of the disease process (eg, after the development of the less acid-sensitive Barrett's epithelium) and be an important determinant of progression from BE to EAC.

Family studies also show obesity to be an important risk factor in BE and EAC. In a cohort study comparing the risk factors for EAC and adenocarcinoma of the gastric cardia in relatives with a family history of BE, EAC, or adenocarcinoma of the gastric cardia versus those who lacked this family history, after adjusting for confounders, obesity was associated with EAC and adenocarcinoma of the gastric cardia diagnosed at an early age (personal communication, A. Chak, March 2009). In another family study, first-degree relatives of BE or EAC probands were obese more often than endoscopy controls, although the results were not statistically significant; 44% of symptomatic relatives were obese versus 39% of symptomatic controls and 22% of asymptomatic relatives versus 19% of controls (personal communication, Y. Romero, March 2009). Aggregation of GERD symptoms in families^{33,34} could be due to shared or learned environmental behaviors such as diet, exercise, or lack thereof, or could be due to a genetic propensity for obesity or a susceptibility to esophageal damage in response to reflux. Although the role of family history in BE and EAC is actively under investigation, it appears that obesity has role in familial aggregation of GERD symptoms, BE, and EAC.

IS OBESITY ASSOCIATED WITH THE PROGRESSION FROM BARRETT'S ESOPHAGUS TO ESOPHAGEAL ADENOCARCINOMA, AND DOES THIS DIFFER FOR OVERALL AND ABDOMINAL OBESITY?

Studies that have compared measures of adiposity between EAC cases and BE controls can provide some insight into this question. One such study has been undertaken within the Netherlands.³⁵ In this hospital-based, case-control study, EAC cases were more likely than BE controls to have been overweight (BMI ≥ 25) at age 20 and 10 years before diagnosis; the adjusted ORs (95% CI) were 2.6 (1.2 to 5.5) and 1.8 (1.1 to 3.3), respectively. The stronger association at age 20 years than at 10 years before diagnosis also points to the importance of adiposity early in life, presumably before the development of BE. Data from the Irish FINBAR case-control study of EAC and BE showed that EAC cases were more likely to be overweight or obese 5 years before diagnosis than age- and sex-matched BE controls; ORs (95% CI) were 1.70 (1.03 to 2.79) and 3.32 (1.84 to 6.00), respectively (Murray L, unpublished data, 2008).

Further evidence of whether adiposity influences EAC risk in BE patients could be provided by examination of the intermediate stages in the progression to cancer (eg, dysplasia) or other markers for progression. One small study of 140 dysplasia-free BE patients has prospectively explored factors associated with the progression to low-grade dysplasia (mean follow-up period, 5.8 years).³⁶ Forty-four patients (31.4%) progressed to low-grade dysplasia and seven to high-grade dysplasia or

EAC. BMI was not as high-grade dysplasia detect associations in a cross-sectional study with the WHR is associated (eg, 4N and aneuploidy). The OR for aneuploidy was 1.2 to 15.6 and for a measure of general adiposity (95% CI) for aneuploidy in weight subjects (BMI ≥ 25) was 0.9 (0.3 to 2.3). These findings suggest that in determining future study, the participants included were markers of

There is a lack of a weight or obese increase in question is fundamental other biomarkers of damage,³⁹ or perhaps but this question can be multicenter) prospective studies taken at baseline grade dysplasia to be

CAN WEIGHT LOSS PREVENT PROGRESSION WITH BARRETT'S ESOPHAGUS?

Only one intervention part of a dietary intervention decreased fat intake in patients with Barrett's esophagus.⁴² This study randomized patients to a low-fat or usual diet. The intervention lasted 12 months and 2.5 kg of weight loss was seen between the two groups. Endoscopic markers of cellular atypia or percent total Ki67-positive cells in the 4N fraction did not change, but changes may not have been in the markers, or the process than those of alternative markers of progression with EAC or high-grade dysplasia. Weight loss in BE patients is difficult to understand and difficult to understand provided from large studies of progression from BE to EAC.

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EAC. BMI was not associated with the development of either low-grade dysplasia or high-grade dysplasia/EAC; however, this was a small study with limited power to detect associations between BMI and disease progression. Data from a cross-sectional study within the Seattle Barrett's Esophagus Project³⁷ have shown that the WHR is associated with a range of potential markers for progression to EAC (eg, 4N and aneuploidy on flow cytometry and 17p and 9p loss of heterozygosity). The OR for aneuploidy comparing the highest to lowest quartile of WHR was 4.3 (1.2 to 15.6) and for 17p loss of heterozygosity, 3.9 (1.3 to 11.4). In contrast, BMI, a measure of general adiposity, was not associated with these markers; the OR (95% CI) for aneuploidy, obese subjects (BMI ≥ 30) when compared with normal weight subjects (BMI < 25) was 0.9 (0.3 to 2.9) and for 17p loss of heterozygosity, 0.9 (0.3 to 2.3). These data suggest that abdominal adiposity may be more important in determining future EAC risk than overall adiposity, but this was not a prospective study, the participants were in general high-risk BE patients, and the outcomes examined were markers associated with progression to cancer rather than cancer itself.

There is a lack of appropriately designed studies to investigate whether being overweight or obese increases the risk of progression from BE to EAC. Nevertheless, this question is fundamental to the management of BE patients. Further studies examining other biomarkers of progression (eg, telomere length,³⁸ measures of oxidative DNA damage,³⁹ or perhaps DNA methylation patterns^{40,41}) as outcomes may be useful, but this question can only be adequately addressed by undertaking large (probably multicenter) prospective studies of BE patients with detailed anthropometric measurements taken at baseline and with sufficient length of follow-up to enable EAC or high-grade dysplasia to be examined as an outcome.

CAN WEIGHT LOSS PREVENT DISEASE PROGRESSION IN PATIENTS WITH BARRETT'S ESOPHAGUS?

Only one intervention study has investigated whether weight loss in BE patients, as part of a dietary intervention that included increased fruit and vegetable and decreased fat intake, affects biomarkers of cellular proliferation in Barrett's epithelium.⁴² This study randomized 93 patients to receive the diet/weight loss intervention or usual diet. The intervention group successfully lost weight (mean 3.6 kg loss at 18 months and 2.5 kg at 36 months); fruit and vegetable intake also increased. No difference was seen between the two groups in changes from baseline in the flow cytometric markers of cellular proliferation, percent Ki67-positive proliferating diploid G₁ cells, or percent total Ki67-positive proliferating cells, or in the presence of more than 6% of cells in the 4N fraction of the cell cycle. In this small study the dietary/weight loss changes may not have been of sufficient magnitude and duration to observe changes in the markers, or the intervention may have affected earlier stages in the neoplastic process than those assessed by the markers. Further trials of weight loss in BE with alternative markers of progression may help shed light on this area, but only large trials with EAC or high-grade dysplasia as the outcome can conclusively determine whether weight loss in BE patients can reduce cancer risk. Such studies may be so expensive and difficult to undertake that they will not be considered until reliable data are provided from large cohort studies documenting that obesity is associated with progression from BE to EAC.

An extremely small case series described the outcomes of five morbidly obese, long segment, biopsy-proven Barrett's esophagus patients who underwent Roux-en-Y gastrojejunostomy.⁴³ The BMI changed from 43 kg/m² to 33 kg/m², and all patients reported subjective improvement in reflux symptoms. Preoperatively, the mean BE

length was 6 ± 2 cm; two patients had low-grade dysplasia and one indeterminate dysplasia. At their postoperative surveillance endoscopy performed at least 1 year after surgery, the length of the BE segment had either decreased (in two patients) or completely disappeared (in two patients) for a mean length 2 ± 1 cm, and only one patient had dysplasia. In this small case series, Roux-en-Y gastrojejunostomy resulted in complete or partial regression of BE in four of five patients with improvement in reflux symptoms in all.

POTENTIAL MECHANISMS OF ACTION FOR RELATIONSHIP BETWEEN OBESITY AND BARRETT'S ESOPHAGUS/ESOPHAGEAL ADENOCARCINOMA (OR REFLUX DISEASE IN GENERAL)

Obesity may contribute to gastroesophageal reflux through several anatomic and physiologic mechanisms (eg, increased intra-abdominal pressure and development of hiatus hernia,⁴⁴ increased intragastric pressure and gastroesophageal sphincter gradient,⁴⁵ slower esophageal transit times,⁴⁶ and increased transient relaxations of the lower esophageal sphincter⁴⁷). Few studies have distinguished between overall obesity and abdominal obesity, but one recent study showed a similar, albeit weak, positive correlation between the BMI and waist circumference and intragastric pressure.⁴⁸ Clearly, promotion of gastroesophageal reflux is an important mechanism whereby overweight or obesity increases the risk of EAC or BE, but because at least part of the association between obesity and EAC appears to be independent of reflux, alternative mechanisms exist. A potential role for reflux-independent mechanisms is also likely given that obesity increases the risk of a variety of cancers unrelated to gastroesophageal reflux.

Adipose tissue is now regarded as the largest endocrine organ of the body. As well as being a major site for the metabolism of sex steroids and glucocorticoids, adipose tissue expresses and secretes a range of metabolically active factors (adipokines), including free fatty acids, interleukin (IL)-6, IL-8, tumor necrosis factor- α , leptin, adiponectin, plasminogen activator inhibitor-1, and resistin,⁴⁹ and visceral fat is more metabolically active than subcutaneous fat.⁵⁰ In general, these adipokines are proinflammatory, promote insulin resistance, and have a central role in the development of atherosclerosis. The induction of insulin resistance may also be important to cancer development. Chronically high insulin levels may promote proliferation and inhibit apoptosis via insulin receptors or alter the insulin-like growth factor (IGF) axis, resulting in reduced IGF-binding proteins (IGFBP) and higher levels of free IGF-1. Altered IGFBP-3 and IGF-1 levels have been associated with the development of several cancers, including breast, colorectal, and prostate cancer.⁵¹⁻⁵⁵ Gene expression studies in animals⁵⁶ and humans^{57,58} indicate a potential role for the IGF axis in the progression of BE to EAC, and a recently reported prospective study has shown an association between low IGFBP-3 levels and aneuploidy risk in BE patients.⁵⁹ Polymorphism of the IGFBP-3 gene was also associated with aneuploidy risk. These studies indicate that the IGF axis may have a role in mediating the association between obesity and EAC, and further investigation of this pathway is warranted.

Adiponectin, an important adipokine, is strongly inversely associated with central and overall obesity and with insulin resistance.⁶⁰ Low levels of adiponectin have been associated with breast,⁶¹ endometrial,^{62,63} colorectal,⁶⁴ and other cancers, and these associations appear to be largely independent of other obesity-related risk factors such as endogenous insulin concentration, IGF-binding proteins, or hormonal status.⁶⁰ Evidence is accumulating that adiponectin is an important regulator of cell proliferation; it can induce apoptosis, decrease the expression of cyclin

D1 and inhibit cell has anti-inflammatory kinases.⁶⁵ There are s of cancers in general, ponectin in relation found to be down- compared with no. The same group a protein Bax, a de a dose-dependent ponectin. A pilot ex levels in 51 BE patie that did not investi EAC. These finding prospective investi of BE to EAC are re

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D1 and inhibit cell-cycle progression, and inhibit growth factors.⁶⁰ Adiponectin also has anti-inflammatory effects, including the induction of anti-inflammatory cytokines.⁶⁵ There are several ways in which adiponectin may influence the development of cancers in general or EAC in particular. Few studies have examined the role of adiponectin in relation to the development of BE or EAC. Adiponectin receptors were found to be down-regulated in the Barrett's mucosa of 15 obese BE patients when compared with normal squamous esophageal mucosa from the same patients.⁶⁶ The same group also showed an increase in the expression of the pro-apoptotic protein Bax, a decrease in expression of the anti-apoptotic protein Bcl-2, and a dose-dependent increase in apoptosis after incubation of an EAC cell line with adiponectin. A pilot epidemiologic study showed no association between adiponectin levels in 51 BE patients when compared with 67 controls,⁶⁷ but this was a small study that did not investigate whether adiponectin has a role in the progression of BE to EAC. These findings need to be re-examined in other BE case-control studies, and prospective investigations of the role that adiponectin may have in the progression of BE to EAC are required.

Leptin is another adipokine secreted by adipocytes and gastric chief cells that may have a role in the development of BE and EAC. Circulating leptin levels are closely positively correlated with total body fat and are higher in women than men, even after allowing for differences in fat mass.⁶⁸ Leptin has been shown to stimulate cell proliferation and inhibit apoptosis in *in vitro* studies, including studies of EAC cell lines,^{69,70} and leptin receptors are expressed in the adult esophagus.⁷¹ Some epidemiologic studies show positive associations between leptin levels and breast, colorectal, and prostate cancer, although the data are somewhat inconsistent.⁷²⁻⁷⁴ A recent epidemiologic study has examined the relationship between serum leptin concentration and BE risk.⁶⁷ In this population-based, case-control study, leptin levels were strongly associated with the risk of BE in men but not women. In another study undertaken in an endoscopy population from a veteran's administration medical center in New York, gastric but not serum leptin levels were positively associated with BE. Further study of the relationship between leptin and BE/EAC is warranted.

Ghrelin is a peptide produced mainly in the fundus of the stomach that, among other functions, stimulates appetite.⁷⁵ Ghrelin levels are diminished in *Helicobacter pylori* infection,⁷⁶ and it has been proposed that ghrelin may be the link between the decline in *H. pylori* prevalence and the simultaneous increase in obesity and EAC seen in western populations in recent decades.⁷⁷ In this hypothesis, higher levels of ghrelin in subjects not infected with *H. pylori* are proposed to cause appetite stimulation, weight gain, and increased risk of EAC; however, ghrelin concentrations are lower in obese than nonobese subjects,⁷⁸ and ghrelin also stimulates upper gastrointestinal motility,⁷⁹ which may decrease gastroesophageal reflux. It also has profound anti-inflammatory effects⁸⁰ and has been shown to cause a decrease in TNF- α -induced COX-2 and IL-1 β expression in a BE cell line. It is biologically plausible that ghrelin may act to reduce EAC risk, and a prospective study undertaken within the Kaiser Permanente Health Plan supports a protective effect for high ghrelin levels against EAC. It is unlikely that ghrelin mediates the relationship between obesity and EAC risk.

SUMMARY

Evidence to date suggests that in whites and potentially Asians, obesity is associated with GERD symptoms, erosive reflux esophagitis, BE, and EAC in sporadic and familial cases. Obesity may impact the esophagitis-metaplasia-dysplasia-EAC sequence

early by increasing the risk of erosive esophagitis. There is some evidence that the effect of obesity at this stage in the sequence may differ between whites and nonwhites and between the sexes. More work is necessary to understand why historically more obese populations have a lower risk of BE and EAC.

Recent evidence points to a more important role for abdominal versus overall obesity in the development of esophagitis. Overall obesity is associated with a modest increase in the risk of BE, but this may be mediated by abdominal obesity. There is no clear evidence that overall or abdominal obesity increases the risk of BE beyond that which results from an increase in its precursor, esophagitis. Weight loss in patients with GERD symptoms or esophagitis reduces reflux, improves their symptoms, and may improve the clinical and histologic presentation of esophagitis. Weight control and weight loss should be advised for patients with GERD symptoms and erosive esophagitis, even though there is no evidence that weight loss can prevent the development of BE in such patients.

Being overweight or obese is unquestionably a risk factor for EAC in whites, and abdominal adiposity appears to be at least as important a risk factor as general adiposity. At least part of the obesity-related EAC risk is mediated through an increase in gastroesophageal reflux and subsequent esophagitis, but a body of evidence is accruing that reflux-independent mechanisms are also important, such as the development of insulin resistance, alteration of the IGF pathway, and the production of leptin, adiponectin, and inflammatory cytokines by adipose tissue, especially visceral adipose tissue. Further exploration of the importance of abdominal or visceral adiposity in EAC risk is warranted, as is further examination of the role of adipokines in the development of this risk.

Two fundamental questions that are of relevance to the management of all BE patients remain unanswered: (1) whether being overweight or obese increases the risk of EAC and (2) whether weight loss can reduce this risk. Large prospective studies of BE patients with detailed anthropometric and radiologic measurements of fat distribution taken at baseline, with inclusion of appropriate surrogate measures of progression and with sufficient length of follow-up to enable EAC or high-grade dysplasia to be examined as outcomes, are required. Randomized trials of weight loss in BE patients will also be necessary, but such studies cannot, at present, be justified on the basis of current evidence.

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Molecular and Genetic Cancer D

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KEYWORDS

- Barrett's esophagus
- Esophageal adenocarcinoma

One way in which organ cancer is through metaplasia, in which normal cells are replaced by metaplastic cells are transformation. Metaplasia, a chronic inflammation, is a result of the reflux-inflammation type cells, a condition that is a premalignant lesion for adenocarcinoma. It has risen at an alarming rate.

In the traditional pathogenesis of Barrett's esophagus, it is considered as occurring in the setting of chronic inflammation to adenocarcinoma. It remains the recommendation is with Barrett's esophagus is fraught with many problems, including the irreproducibility of dysplasia, indefinite, low-grade, a constellation of histological abnormalities that render the diagnosis of the genetic abnormality. Dysplasia is an even earlier stage.

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