The Relationship Between Obesity and Functional Gastrointestinal Disorders: Causation, Association, or Neither?

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Abstract: It is possible that functional gastrointestinal disorders (FGIDs) and obesity have more in common than merely sharing high population prevalence. Epidemiologic data indicate that obesity is associated with chronic gastrointestinal complaints, many of which overlap with FGIDs such as irritable bowel syndrome or dyspepsia. This raises the possibility that obesity and FGIDs may be mechanistically linked. In this paper, we review and summarize the literature linking obesity and FGIDs, comment on the clinical relevancy of existing data, and suggest next steps for future research in this field.

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Obesity is overwhelmingly prevalent in the United States. As of the 2004 National Health and Nutrition Examination Survey,[1] 1 in 3 Americans had a body mass index (BMI) exceeding 30 kg/m^2, and the obesity epidemic shows no signs of abating. Functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS) and functional dyspepsia are also extremely prevalent. Population-based data indicate that 5–10% of the US population suffers from IBS, the most common FGID.[2-5] It is possible that FGIDs and obesity have more in common than merely high population prevalence rates. Epidemiologic data indicate that obesity is associated with a wide range of chronic gastrointestinal (GI) complaints, many of which overlap with FGIDs such as IBS or dyspepsia.[6-11] This association raises the possibility that obesity and FGIDs may be mechanistically linked and that studying this relationship might provide insights into the pathophysiology of several FGIDs. However, data linking obesity and FGIDs are inconsistent, suggesting that any epidemiologic associations may simply be spurious—a case of "true, true, and unrelated." This article reviews data linking obesity and FGIDs and summarizes the evolving theories regarding the possible mechanisms linking these common conditions. The article ends with recommendations on how this information might impact the practicing gastroenterologist, both now and in the future.

Evaluating the Possibility of an Association Between Obesity and Functional Gastrointestinal Disorders

Before considering the potential mechanisms linking obesity with FGIDs, it is important to first establish whether there is even an epidemiologic link between these common conditions. If obesity and FGIDs were found to reliably track together, this would support the hypothesis that these conditions are potentially linked and would warrant further investigation to understand why they might be associated with one another.

Although it is well established that obesity is associated with gastroesophageal reflux disease (GERD),[6,11,12] it remains less clear whether obesity is a risk factor for common FGIDs, including IBS and dyspepsia. There have been several studies measuring the association between obesity and various chronic bowel complaints.[6-11] In some cases, the relationship between obesity and specific syndromes appears to be strong, whereas in other cases, the link is tenuous. This section will review key studies that have investigated the relationship between obesity, FGIDs, and related GI symptoms.

Published studies have had inconsistent conclusions. As an example of a recent negative study, van Oijen and colleagues studied 1,023 consecutive patients referred for outpatient endoscopy in a university-based hospital in The Netherlands.[6] Subjects completed a validated bowel symptom questionnaire to evaluate the presence and severity of various GI symptoms, including dyspepsia and IBS-related symptoms (lower abdominal pain, bloating, diarrhea, and constipation). After performing logistic regression analysis adjusted for a range of confounders, the authors found no relationship between BMI and FGID symptoms. In contrast, as might be expected, there was a positive relationship between acid reflux symptoms and BMI. The authors concluded that BMI alone may not predict the occurrence of dyspepsia or IBS-type symptoms, but BMI may be linked to acid reflux disease. It should be noted that this study is limited, as the patient population was highly selected (patients who were undergoing endoscopy) and because the definitions of IBS and dyspepsia did not meet strict criteria such as those proposed by the Rome III Committee on FGIDs. Nevertheless, this study is notable for its large sample size and careful statistical approach. This large and well-designed study tends to cast doubt on the link between obesity and common FGIDs.

In a large population-based survey of over 1,900 subjects in Olmsted County, Minnesota, Delgado-Aros and colleagues studied the relationship between BMI and a range of upper and lower GI symptoms.[7] After performing logistic regression analysis to adjust for potential confounding variables, the authors found no statistically significant association between obesity and lower abdominal pain, constipation, or nausea. However, there was a significant association between obesity and upper abdominal pain, bloating, and diarrhea. This study is notable for its large sample size and use of a randomly selected, community-based sample. This study tends to support the study conducted by van Oijen and colleagues, in that it found no significant relationship with abdominal pain or constipation, which are the hallmark features of IBS. Nevertheless, the study did reveal strong relationships between obesity and various symptoms of dyspepsia, including upper abdominal pain and bloating. As with the previous study, analysis of the study conducted by Delgado-Aros and coworkers did not employ validated definitions of FGIDs and instead relied upon self-reported bowel symptoms. Nevertheless, self-reported symptoms are still clinically relevant, making these data important even if they do not reflect traditionally acknowledged symptom complexes such as Rome-positive IBS or dyspepsia.

Talley and colleagues performed two additional population-based studies investigating the connection between BMI and bowel symptoms.[8,9] The first study administered a validated bowel symptom questionnaire to a random sample of community-based subjects in Australia.[8] Similar to the Olmsted County survey, this study revealed a positive correlation between increased BMI and diarrhea, but it failed to show a relationship between BMI and bloating, lower abdominal pain, or constipation. The second study conducted by Talley and associates was a survey of a birth cohort of 26-year-old New Zealanders.[9] Using an abbreviated version of the bowel symptom questionnaire, the investigators found a significant relationship between obesity and a range of bowel symptoms, including abdominal pain, nausea, and diarrhea. However, this study also categorized patients with IBS (using Manning criteria) and found no association between obesity and IBS. The study is limited, however, because all the subjects were only 26 years of age.

Adding further debate to the association between obesity and FGIDs is a novel study conducted by Svedberg and coworkers, who performed two separate case-control studies to investigate the relationship between obesity and IBS.[10] The authors compared the prevalence of obesity in a group of patients with IBS versus a control group of unrelated non-IBS subjects. Obese patients were 2.6 times more likely to have IBS compared to nonobese subjects (odds ratio, 2.6; 95% confidence interval, 1.0–6.4). The authors then went a step further by performing a case-control study among monozygotic twins discordant for IBS (ie, sets of twins in whom one twin had IBS, but the other did not). This analysis attempted to control for genetic factors. In contrast to their nontwin case-control study, the authors found no significant relationship between obesity and IBS in the

Table 1. Studies Measuring the Relationship Between Obesity and Chronic Gastrointestinal Symptoms

	Lower abdominal/IBS symptoms				*Upper abdominal/dyspepsia symptoms*		
Study	**Lower abdominal pain**	**Constipation**	**Diarrhea**	**IBS**	**Upper abdominal pain**	**Bloating**	**Nausea**
van Oijen MG, et al.[6]	–	–	–	Not tested	–	–	–
Delgado-Aros S, et al.[7]	–	–	+	Not tested	+	+	–
Talley NJ, et al.[8]	–	–	+	Not tested	–	–	Not tested
Talley NJ, et al.[9]	+	Not tested	+	–	+	Not tested	+
Svedberg P, et al.[10] Nontwin study	Not tested	Not tested	Not tested	+	Not tested	Not tested	Not tested
Svedberg P, et al.[10] Twin study	Not tested	Not tested	Not tested	–	Not tested	Not tested	Not tested
Aro P, et al.[11]	–	Not tested	+	–	–	Not tested	Not tested

Symptoms are grouped into lower abdominal/irritable bowel syndrome (IBS) symptoms or upper abdominal/dyspepsia symptoms. The most consistent relationship across studies is between obesity and diarrhea. The relationship between obesity and other symptoms is highly inconsistent between studies. Details regarding individual studies are discussed in the text.

discordant twin analysis. However, it is possible that the lack of association is merely a reflection of inadequate variation in BMI within sets of twins, as twins tend to have similar physical characteristics (eg, BMI) because of high correlations within each set. Thus, the lack of a relationship between obesity and IBS within the discordant sets of twins may merely be an anomaly of inadequate intratwin variations in BMI.

In another Swedish study, Aro and colleagues measured the relationship between chronic GI complaints, including IBS, and obesity among patients undergoing endoscopy.[11] Unlike the study conducted by van Oijen and associates, these patients were randomly selected from the general Swedish population and were asked to undergo endoscopy as part of the study protocol. The patients did not otherwise have specific indications for endoscopy. Therefore, the cohort was more representative of the general population compared to the group in the previously described study by van Oijen and coworkers. Although the study was primarily designed to measure the relationship between obesity and GERD, as measured by symptoms and endoscopic findings of erosive esophagitis, the investigators also reported data on epigastric pain, diarrhea, and IBS. After adjusting for demographic characteristics and excluding subjects found to have esophagitis or peptic ulcer disease on endoscopy, the authors found that only diarrhea remained significantly associated with obesity. This study is notable for its population-based approach and exclusion of patients with objective evidence of organic foregut disease.

Table 1 summarizes the studies examining the link between obesity, FGIDs, and related GI symptoms. The most consistent relationship is between obesity and diarrhea. In contrast, none of the studies found a statistically significant relationship between obesity and constipation. This finding may appear to be surprising, as constipation has been historically linked with sedentary lifestyles. However, constipation is certainly a multifactorial disease, and lifestyle modifications likely have only a minor impact on its symptoms. In addition, with the exception of one study,[9] there is very little evidence linking obesity to lower abdominal pain and inconsistent evidence that obesity is related to IBS. The relationship between obesity and foregut symptoms such as epigastric pain, bloating, and nausea appears to be slightly more robust, yet it is still inconsistent. Overall, the weight of the evidence indicates that obesity may be a strong and consistent predictor of diarrhea, as well as an inconsistent predictor of other GI complaints, particularly of the foregut. Importantly, the link between obesity and foregut symptoms diminishes

after adjusting for patients with endoscopically evident disease, suggesting that much of the relationship is driven by acid peptic disorders, rather than true FGIDs.

Obesity as the Cause of Functional Gastrointestinal Disorders and Chronic Gastrointestinal Symptoms

The relationship between obesity, FGIDs, and related GI symptoms is sufficiently strong to at least raise the possibility that they are mechanistically linked. Therefore, it should be examined how obesity could lead to chronic GI symptoms or vice versa.

Epidemiologic data most strongly link obesity with diarrhea, and there are several potential explanations for this relationship. Aro and coworkers hypothesize that obese patients are more likely to ingest excess amounts of poorly absorbed sugars, which in turn can promote osmotic diarrhea.[11] In particular, fructose corn syrup is now highly prevalent in Western diets, particularly in the United States, and obese patients are likely to consume more fructose than nonobese controls. This finding alone might explain part of the relationship between obesity and diarrhea. The existing epidemiologic studies have not controlled specific dietary variables such as ingestion of poorly absorbed sugars, making it impossible to judge whether the observed relationships may be muted, or altogether disappear, if the analyses were repeated after adjusting for fructose consumption.

Although never formally studied, it is also possible that the use of proton pump inhibitors (PPIs) might confound the relationship between obesity and FGID symptoms, as follows: obese patients are more likely than control patients to have GERD; GERD patients are much more likely to receive PPI therapy than patients without GERD; and PPI therapy may promote varying forms of bacterial overgrowth by eliminating gastric acid, which in turn can promote abdominal pain, bloating, diarrhea, constipation, and dyspepsia-related symptoms. In fact, between 5–10% of PPI users have one or more GI symptoms as a result of their therapy. Although this theory invokes several steps, each step is tenable, as it is now well established that obesity is a risk factor for GERD. In addition, there is no question that GERD leads to PPI use in many patients. Furthermore, it has long been established that PPI therapy can alter gastric, duodenal, and intestinal bacterial profiles. For example, Thorens and colleagues randomized 47 patients with peptic ulcer to receive 4 weeks of cimetidine versus omeprazole and then obtained cultured duodenal juice during follow-up endoscopy.[13] The authors found a higher incidence of bacterial overgrowth in the omeprazole arm (53% vs 17%). This finding was duplicated by Fried and coworkers, who further demonstrated that PPI-related bacterial overgrowth was due to both oral and colonic-type bacteria, not merely oral flora alone.[14] Theisen and colleagues found that suppression of gastric acid with omeprazole led to a high prevalence of bacterial overgrowth that in turn led to a markedly increased concentration of unconjugated bile acids.[15] Moreover, Lewis and associates documented that omeprazole-related bacterial overgrowth was associated with shorter intestinal transit times.[16] These studies suggest that PPI-related bacterial overgrowth could potentially lead to IBS symptoms such as diarrhea as a result of an increased osmotic load from bile acids coupled with more rapid intestinal transit. Of note, the studies linking obesity to diarrhea have not been adjusted for and have not reported PPI exposure in the cases versus the controls. Future studies should account for this variable, given its high prevalence in obese patients and its association with FGID-type symptoms. Even if the PPI effect is relatively rare in terms of causing clinically important symptoms, it would only take a minor imbalance between cases and controls to yield statistically significant results when amplified by a large sample size.

There have been several other proposed mechanisms explaining the imbalances in other GI symptoms beyond diarrhea. In particular, binge eating is common in obese patients and may contribute to increased GI symptoms, as these patients often eat to the point of abdominal discomfort. Crowell and colleagues surveyed both obese and normal-weight women on their eating behaviors and frequency of GI symptoms and found a positive association between BMI and the size of binge meals in obese patients with binge-eating disorder.[17] Obese patients were also found to have a larger percentage of calorie intake from fat than normal-weight controls, which may lead to delayed gastric emptying, which in turn may cause abdominal bloating, nausea, and vomiting. The authors also found a significant association among binge eating, obesity, and IBS symptoms.

Numerous studies have documented altered gastric physiology in the obese, including variations in gastric capacity and the gastric emptying rate. These variations are relevant because they may contribute to the increase in foregut symptoms reported in obese subjects. Nevertheless, the results are inconsistent between studies, possibly due to the varied tools used to measure these parameters (eg, gastric balloon, ultrasound, computed tomography).[18] Gastric balloon studies have found significantly larger gastric volumes in obese subjects than nonobese subjects, whereas studies employing imaging modalities to estimate gastric capacity did not find a significant difference.[19-23] Gastric emptying has also been studied using various techniques, with scintigraphy considered to be the gold standard. This line of inquiry is based upon the hypothesis

that delayed gastric emptying might precipitate foregut symptoms. Thus, studies have sought to compare gastric transit in obese versus nonobese subjects. Interestingly, several studies have shown increased gastric emptying of solids in obese patients compared to nonobese subjects.[24,25] Other studies have shown no significant change in gastric emptying in subjects of varying BMI.[26-28] This contrasts with a small study published by Jackson and coworkers in which 19 obese women were found to have significantly delayed gastric emptying when compared to 19 lean women.[29] Increased gastric emptying may decrease satiety, leading to more frequent meals, which may lead to or perpetuate weight gain. However, this is unlikely to contribute to functional GI symptoms. In short, gastric physiology studies may generate more questions than answers regarding the relationship between obesity and foregut symptoms.

Alterations in GI neuropeptide function in obesity have also been an area of great interest that may have implications in FGIDs. GI neuropeptides such as cholecystokinin, leptin, peptide YY, and glucagons-like peptides 1 and 2 are intricately involved in the regulation of satiety, eating behaviors, and GI motility.[30] It has been hypothesized that even a minor alteration in the highly regulated interplay between neural, hormonal, and muscular function of the GI tract could contribute to the development of obesity by altering motility and eating behaviors. Ghrelin, a novel endogenous natural ligand for the growth hormone secretagogue receptor that is mainly released from gastric fundic mucosa, has been shown to induce adiposity and weight gain.[31] Ghrelin is structurally categorized as a motilin-like peptide that potentiates phase III–like gastric contractions, increases gastric acid secretions, and increases gastric emptying. Serum concentrations of ghrelin have been found to increase during fasting and immediately prior to meal initiation and, conversely, fall postprandially.[31] Based upon this evidence, it is thought that ghrelin plays a role in hunger and satiety and, in the broader sense, regulation of energy homeostasis.

Normal-weight individuals have been shown to have higher ghrelin levels than their obese counterparts.[32] Cummings and associates and Hansen and coworkers have both shown that plasma ghrelin levels increase after diet-induced weight loss in obese individuals.[33,34] There have also been studies suggesting that weight loss improves symptoms of FGID, which will be presented below. Extrapolating from these data, perhaps weight loss may contribute to decreased FGID symptoms through an increase in plasma ghrelin levels, which improves gastric motility and emptying and decreases caloric intake in obese individuals for improved energy homeostasis. There have not been any studies published to date directly investigating this hypothesis. Although two studies from Japan have found fasting ghrelin levels to be higher in women with functional dyspepsia, neither the cases nor the controls were obese.[35,36] Further studies are needed to clarify the neurohormonal connection between obesity and FGID.

The Effect of Weight Loss on Functional Gastrointestinal Disorders and Related Symptoms

The epidemiologic evidence linking obesity with FGIDs and GI symptoms is inconsistent, and there are numerous supporting hypotheses. However, any doubt regarding this relationship could be settled through proof-of-principle studies demonstrating that weight loss can abate or reverse the FGID-related symptoms; after all, if the relationship between obesity and GI symptoms were a causal link and not merely an association, one would expect weight change to be positively associated with GI symptom reporting.

Unfortunately, the available data for tracking changes in weight to changes in symptom reporting are relatively sparse and inconsistent. Research efforts thus far have mainly concentrated on weight changes and their effects on GERD symptoms, with several studies demonstrating that a decrease in BMI does improve GERD, albeit with somewhat inconsistent results between studies.[37-40] However, it is unclear if this is also true for FGID symptoms. Cremonini and colleagues used survey data from a large prospective natural history study of upper and lower GI symptoms in a population-based sample from Olmsted County, Minnesota.[41] The investigators measured the longitudinal relationship between body weight changes and upper GI symptoms. A random sampling of local residents was mailed either the GERD symptoms questionnaire or the bowel disease questionnaire and was followed-up with the same questionnaire roughly one decade after completion of the initial survey (median follow-up, 10.5 years). The authors focused on dyspepsia syndromes, including pain-predominant and dysmotility-predominant dyspepsia. The study revealed that weight gain over the study period, as defined by a 10-pound increase over time, was modestly associated with developing dysmotility-predominant dyspepsia (eg, bloating, early satiety). In contrast, weight loss did not correlate with a loss of baseline dyspepsia symptoms. However, the study is limited by the unknown temporal relationship between weight loss and the reported changes in symptoms, as the changes may have dissipated over time due to other psychosocial factors not

surveyed in this study. Nevertheless, the study is notable for providing longitudinal data and a glimpse into causation, not merely cross-sectional association.

Additional data are provided by studies measuring the impact of bariatric surgery for treatment of morbid obesity. Two small studies have shown improvement in GI symptoms in patients following laparoscopic bariatric surgery.[42,43] Poves and colleagues surveyed 100 morbidly obese individuals (mean BMI, 47 kg/m^2) who were surgical candidates for laparoscopic Roux-en-Y gastric bypass, as well as 100 nonobese control patients using the Gastrointestinal Quality-of-Life Index (GIQLI).[42] These results were compared to GIQLI data from 100 participants who had undergone gastric bypass a mean of 17.2 months prior, with a mean preoperative BMI of 47.2 kg/m^2 and a mean postoperative BMI of 30.2 kg/m^2. Although the control and gastric bypass groups had comparable GIQLI scores with no statistically significant difference, the scores of morbidly obese patients were significantly lower. Unfortunately, there was no breakdown of data by specific digestive symptoms. A smaller study by Foster and associates addressed this issue by surveying 43 morbidly obese patients preoperatively and then 6 months after gastric bypass.[43] The authors measured the relationship between BMI changes and individual FGID-related symptoms, including abdominal distension, urgency, constipation, and diarrhea. Forty-three subjects completed the questionnaire preoperatively. Compared to normal-weight controls, obese subjects were more likely to report abdominal pain and IBS symptoms. When the same questionnaire was re-administered 6 months postoperatively, with a response rate of 81%, the preoperative BMI of 47.8 kg/m^2 decreased to a postoperative BMI of 31.6 kg/m^2. A significant improvement was noted in abdominal distention, urgency, diarrhea, and constipation. The authors postulated that altered eating habits resulting from the surgery may have improved the symptoms. They further surmised that improvements in psychological factors, including enhanced body image, may have been partially responsible for the decrease in GI symptoms. Whether the decrease is due to these changes or neurohormonal alterations from the surgical procedure is debatable.

Implications for Current Practice

Although obesity is clearly linked to GERD, its relationship with FGIDs and related GI symptoms remains tenuous. Obesity has an epidemiologic association with diarrhea, in particular, but it has inconsistent associations with other foregut symptoms (eg, nausea, bloating, upper abdominal pain) and hindgut symptoms (eg, constipation, lower abdominal pain). Moreover, it remains unclear whether these associations, however tenuous, imply causations. The available data indicate that weight loss may modestly improve both upper and lower abdominal GI symptoms, thus suggesting a potential causal link.

Obesity is a major risk factor for a range of serious medical conditions, including cardiovascular disease, pancreatitis, and liver disease, among many other conditions. All medical practitioners, including gastroenterologists, must remain aggressive about addressing and treating obesity in their patients. Although it may be premature to claim that weight loss can alleviate the symptoms of FGIDs, it is unlikely that weight loss will exacerbate these symptoms. Given the strength of the available evidence, it seems reasonable to tell patients that weight loss may modestly improve GERD and other symptoms, particularly diarrhea, and that this benefit is one of many that weight loss can provide. Although the pathophysiology linking obesity to FGID-related symptoms is evolving, patients may benefit from a high-level understanding that weight loss may improve a range of abnormal eating behaviors, positively improve GI hormone levels, and potentially help regulate GI motility. Finally, physicians should always remain wary of PPI use that is not otherwise indicated and should discontinue PPIs in patients with chronic GI complaints who may not otherwise benefit from the antisecretory properties of these medicines.

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