# Maintaining Healthy BMI Reduces GERD and Subsequent Acid Suppressing Medication Side Effects Including *C. Difficile* Infections

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## Introduction

Over the past two decades both the incidence and severity of *Clostridium difficile* infections (CDI) have steadily increased. CDI symptoms range from mild (watery diarrhea 2-3 times per day or more, abdominal cramping and tenderness) to severe (watery diarrhea up to 10-15 times a day with pus or blood, severe abdominal symptoms, fever, dehydration and possible kidney failure). Some cases may require hospitalization and may even result in death.[1] The Centers for Disease Control and Prevention (CDC) estimates there were 500,000 CDI cases in the United States in 2011 with 29,000 deaths within 30 days of initial diagnosis.[2]

*C. difficile* is now considered the most common microbial cause of healthcare-associated infections in U.S. hospitals. The economic burden of CDI is tremendous as well, totaling up to $4.8 billion each year in excess health care costs for acute care facilities alone.[3] Identifying risk factors has become an important component to understanding and quelling the rapid rise in incidence and severity of CDI; known risk factors include:

- Chronic antibiotic use
- Use of proton pump inhibitors (PPI)
- Nasogastric tube use
- Advanced age
- Multiple comorbid conditions
- Obesity
- Diabetes mellitus [4]

This review will more deeply explore two particular risk factors, PPI use and obesity.

## Proton Pump Inhibitor Use, GERD, Elevated BMI and Increased CDI Risk

Proton pump inhibitors (PPIs) are a group of drugs used to inhibit the secretion of stomach acid by the gastric parietal cells. These medications irreversibly block the hydrogen/potassium (H+/K+) ATPase, the enzyme responsible for acid production. Common examples of PPIs include Omeprazole, Esomeprazole, and Pantoprazole.

The most common use of PPIs is for gastroesophageal reflux disease (GERD), dyspepsia, reflux esophagitis and peptic ulcer disease. Recommended use is short-term; typically 2-12 weeks. However, this is often not adhered to and can result in patients continuing to take PPIs for extended periods of time and subsequently presenting with symptoms linked to reduced gastric acid levels. The long-term and in many cases, chronic, use of PPIs without reassessment or 'deprescribing' can lead to a host of negative outcomes including not just an increased risk of primary CDI but an increased rate of CDI *recurrence* as well. [5]

Research has indicated that gastric acid suppression through use of PPIs may increase the risk for primary CDI. One of the various mechanisms of CDI has to do with the lowering of the gastric acid levels which would normally neutralize ingested *C. difficile* and its spores. Reduced gastric acidity in the presence of PPI use allows for the passage of these infectious agents to reach the lower GI tract where infection can occur. It is also hypothesized that the change in gastric acid levels leads to a downstream alteration on the gut microbiome profile further lowering host defense mechanisms against CDI. [6, 8]

The strength of this positive association prompted the FDA to issue a Drug Safety Communication in 2012 stating that, "the use of stomach acid drugs known as proton pump inhibitors (PPIs) may be associated with an increased risk of Clostridium difficile–associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve." The FDA reviewed a total of 28 observational studies in 26 publications and noted that 23 studies

showed a higher risk of CDI or disease associated with PPI exposure, compared to no PPI exposure, ranging from 1.4 – 2.75 times higher in the exposed population. [7]

In a meta-analysis of 16 studies comprised of 7703 patients and published by Tariq et al in *JAMA* in 2017, the use of gastric acid suppressants including PPIs and histamine H2 receptor blockers, was positively associated with a significantly increased risk of recurrent CDI at 22.1% compared with 17.3% in patients who were not taking gastric acid suppression prescriptions. The study concluded that it may be reasonable to stop gastric acid suppressants in patients with CDI and that recurrent CDI and health care costs could be reduced by prudent prescribing and limiting unnecessary use of acid suppressant medications. [8]

While avoiding or 'deprescribing' gastric acid suppressants may be beneficial in reducing risk of CDI, the downside associated with unmanaged GERD and excessive gastric acid exposure must also be brought into the equation. Safe and alternative methods to reduce risks should be considered, particularly in the management of GERD as PPI treatment is the first line pharmaceutical approach to GERD and accounts for over 50% of the costs of prescriptions for *all digestive diseases.* [9]

Gastric acid suppression prescriptions, however, are not necessarily the most targeted therapy for GERD as studies have indicated a strong association between rates of GERD incidence and BMI levels in both men and women [10, 11]

The relationship between GERD and BMI has been found to extend across all categories of BMI and in a 2006 *NEJM* review of over 12,000 women from the Nurses' Health Study cohort, the association was not significantly altered after controlling for smoking, alcohol consumption, use of medications that decrease pressure at the lower esophageal sphincter, diabetes, and dietary habits – many factors which are often discussed as being linked to an increased risk of GERD. [10]

Ongoing research continues to validate the results regarding the link between elevated BMI and GERD. A study, conducted by Festi, D et al in 2009 and published in the *World Journal of Gastroenterology*, found sufficient evidence to support the relationship between being obese/overweight and GERD frequency with further evidence that weight loss through diet or surgery can induce a significant improvement in GERD symptoms. The researchers noted possible mechanisms for the association between obesity and increased GERD incidence including: increased intragastric pressure, gastroesophageal pressure gradient, slower esophageal acid clearance and several other possible underlying mechanisms related to both elevated BMI and GERD. [12]

Once a mainly Western cultural problem, GERD has now become a worldwide concern with data from 28 studies looking at global burden of GERD with estimates of prevalence at:

- 18.1–27.8% in North America,
- 8.8–25.9% in Europe,
- 2.5–7.8% in East Asia,
- 8.7–33.1% in the Middle East,
- 11.6% in Australia, and
- 23.0% in South America.

Just as alarming is the fact that GERD prevalence is approximately 50% higher in studies conducted in the USA, Europe and Asia *after 1995* than compared to those carried out before 1995. That sharp increase in prevalence may be indicative of overuse or may be associated with gastric symptoms common to increased BMI. This paper published in *Gut* in 2014 by Boeckxstaens G, et al reiterated the association between GERD and elevated BMI while also suggesting that GERD and abnormal gastric acid production may, in fact, not be causal. [13]

If this is the case, then treating GERD with PPIs may not only be unhelpful but potentially also set the stage for a host of negative downstream side effects as well as increasing risk of side effects from reduced gastric acid levels-- such as increased risk for CDI.

It is becoming increasingly apparent that elevated BMI increases the risk of symptoms of GERD whereas weight loss decreases this risk.[13] Accordingly, PPIs may not be the best approach to manage GERD at all. In fact, a review from *Digestive Diseases and Sciences* looked at the parallel trends in rising obesity and

rising GERD related disorders and concluded 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 and that avoiding weight gain in the first place is associated with a lower risk of GERD. [14]

Connecting the research dots suggests that elevated BMI is strongly associated with increased GERD prevalence and when GERD is (potentially incorrectly) treated with medications such as PPIs there is a resultant lowering of host defense mechanisms potentially leading to increased risk for both primary and recurrent CDI.

## Further Associations: Elevated BMI and CDI

Previously published research has indicated that patients with CDI have a statistically greater body mass index (BMI) than matched control groups.[15] This relationship was reinforced in a recent article published in *Alimentary Pharmacology and Therapeutics.* Lead researcher, R. Mulki from Einstein Medical Center of Philadelphia, found that:

1. Patients with a BMI of 35 kg/m2 or greater had a 1.7 fold higher risk of severe CDI compared to those with a BMI of 20-35 kg/m/2
2. BMI of greater than 35 kg/m2 is an independent predictor of severe CDI as was the presence of diabetes mellitus
3. In patients with community- onset C. diff, a BMI of greater than 35 kg/m2 was associated with a 1.96-fold increase in risk of severe C. diff compared to those with a BMI of 20 to 35 kg/m2
4. In patients with hospital-onset C. diff, a BMI of greater than 35 kg/m2 was associated with a 1.48 greater rate of severe C. diff compared to those with lower BMIs [4]

Although the exact mechanisms are not fully understood it is hypothesized that one of the reasons obesity (BMI over 30 kg/m2) is related to an increased risk for CDI is due to an underlying imbalance in gut flora that contributes to both obesity and CDI. This imbalance, namely the loss of diversity and altered levels in microbiota composition including a reduction of *Bacteroidetes* and a proliferation of *Firmicutes* was seen in individuals with increased risk of CDI, obesity and type 2 diabetes (T2D).

The similarity of imbalances in these chronic conditions reinforces the finding that both obesity and T2D are independent predictors of severe CDI potentially due in part to imbalances in the human gut microbiota. [16, 17, 18]

## Discussion and Summary

In summary, elevated BMI is associated with increased incidence of GERD and is hypothesized to occur due to a variety of different mechanisms. GERD, a common complaint in Western cultures, is most commonly treated with acid suppressing medications such as PPIs. A parallel rise has been seen between rising BMI levels and GERD diagnoses with a subsequent surge in PPI prescriptions. In a similar pattern, the rates of CDI have also increased leading to rising economic burden and negative health outcomes.

Positive associations have been found between rising obesity/BMI levels and CDI rates as well and recent studies point to changes in the human microbiome as a potential mechanism for increased rates of CDI, in addition to the obvious increase in CDI prevalence associated with the use of PPIs for GERD, a common occurrence in those with elevated BMI.

## Therapeutic lifestyle approaches

A predictable decrease in GERD rates should be seen with a reduction in BMI levels in the population and, if we were to hypothesize additional benefits, a reduction in PPI prescriptions and a resultant decrease in CDI rates, mainly due to a normalization of gastric acid levels which typically provide defense against *C. difficile* and spores.

If we were to further extrapolate data reviewed in this article we might also conclude that a reduction in BMI may alter the gut microbiome to a more favorable ratio of *Bacteroidetes* and *Firmicutes* leading to a less favorable growth

medium for *C. difficile* bacteria and possibly provide support in those with type 2 diabetes as well.

Healthcare providers should individualize each client's personalized data to include optimizing BMI and support to balance gut flora diversity and quantity to enhance ideal microbiota function. This might be done through nutritional and dietary supplement recommendations.

Weight loss, high fiber diet, low processed carbohydrate consumption, maintenance dosing of probiotics from fermented or supplemental sources, and reducing inflammation will help to provide a reduction in risk factors associated with CDI.

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[2] Centers for Disease Control and Prevention: https://www.cdc.gov/hai/organisms/cdiff/cdiff_infect.html (accessed 4/24/2017)

[3] Centers for Disease Control and Prevention: https://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html (accessed 4/24/2017)

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