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Does Obesity Influence the Risk of *Clostridium difficile* Infection among Patients with Ulcerative Colitis?

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Abstract

Background—Patients with ulcerative colitis (UC) are at an increased risk for *C. difficile* infection (CDI) compared with the general population. Recent data suggests that obesity also increases the risk of CDI.

Aims—To examine whether obesity influences the risk of CDI among patients with UC.

Study—We conducted a retrospective cross-sectional study of UC patients seen in gastroenterology clinic between January 1, 2014 and December 31, 2015. Records were reviewed for patients with diagnosis of UC prior to 2014, and first diagnosis of CDI between 1/1/14 to 12/31/15. Body mass index (BMI) defined underweight (BMI<18.5), normal weight (18.5 BMI<25), overweight (25 BMI<30), and obese (BMI ≥ 30). Age-adjusted and multivariate logistic regression was performed including gender, tobacco use, UC disease duration, medication exposure, and vitamin D deficiency.

Results—Of the 636 patients with UC, 114 (18%) were obese, 232 (36%) overweight, 274 (43%) normal weight, and 16 (2.5%) underweight. Nineteen patients (3.0%) developed CDI during the study period. CDI risk was not associated with BMI (OR 0.90, 95% CI 0.79-1.02). Compared to normal weight patients, risk of CDI was not influenced by obesity (multivariate OR 0.63, 95% CI 0.15-2.58), or being overweight (multivariate OR 0.33, 95% CI 0.08-1.30) or

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underweight (multivariate OR 2.98, 95% CI 0.45-19.83). CDI was associated with ever use of TNF therapy (multivariate OR 6.09, 95% CI 2.07-17.93) but not vedolizumab (multivariate OR 0.76, 95% CI 0.08-7.36).

Conclusions—Obesity does not appear to be associated with risk of *C. difficile* infection among patients with UC.

Keywords

ulcerative colitis; *Clostridium difficile*; obesity

INTRODUCTION

Clostridium difficile is the leading cause of nosocomial diarrhea in the United States, with increasing incidence in the community setting. *C. difficile* infection (CDI), particularly with a hypervirulent strain (B1/NAP1/027), can result in significant morbidity and mortality¹. Risk factors for CDI include increasing age, hospitalization, antibiotic use, proton pump inhibitor use, recent surgery, and comorbidities such as inflammatory bowel disease, diabetes or chronic kidney disease². Inflammatory bowel disease (IBD), including both Crohn's disease and ulcerative colitis (UC), is independently associated with a 2-3 fold increased risk of CDI compared with the general population, with higher rates of flare and colectomy resulting from infection³. Therefore, there remains an important need to identify risk factors for the development of CDI in this population.

Recent data also suggests that obesity may be an independent risk factor for the development of CDI. A retrospective case-control study examining hospitalized patients with CDI found an elevated mean body mass index (BMI) of 33.6 (SD 4.3) vs 28.9 (SD 5.4) associated with CDI compared to non-CDI controls, respectively⁴. Mulki *et al.*⁵ recently also demonstrated a 1.7-fold increased risk of severe CDI among hospitalized patients with a BMI >35 kg/m² compared to normal and overweight individuals (BMI 20-35 kg/m²). However, in a cross-sectional study of hospitalized patients with CDI and non-CDI controls, no significant difference was observed between median BMI or at various BMI categories, suggesting obesity may not impact CDI risk across all populations⁶.

Obesity is also becoming more common among patients with IBD, associated with increase in fat mass due to steroids and physical inactivity⁷, inadequate nutrition⁷, and drug-induced remission⁸. Increases in BMI are associated with higher rates of loss of response to infliximab^{9,10}. With respect to *C. difficile* infection, among patients with pouchitis and underlying IBD, obesity increased the risk of CDI (OR 5.5, 95% CI 1.4-21.4) in a large cross-sectional study of 3566 patients with pouchitis¹¹. The propensity towards CDI in patients with IBD or obesity may be attributable to alterations of the gut microbiome. *C. difficile* is an anaerobic Gram-positive, spore-forming bacillus microorganism belonging to the *Firmicutes* family. An increased *Firmicutes/Bacteroidetes* ratio has been identified among patients with IBD¹² as well as patients with obesity¹³, and is associated with the development of CDI¹⁴.

With similar underlying dysbiosis contributing to CDI risk in UC and obesity, the aim of our study was to examine whether obesity in the setting of UC increases the risk of CDI.

MATERIALS AND METHODS

Study Design and Patient Population

We performed a retrospective, cross-sectional study utilizing electronic medical records (EMR), available after 2010, of unique patients with ulcerative colitis (UC) seen between January 1, 2014 and December 31, 2015 at the Scripps Clinic Division of Gastroenterology. Patients with UC were identified using the International Classification of Diseases, Ninth Revision (ICD-9) codes (556.X). The diagnosis of UC was confirmed based on chart review for standard clinical, endoscopic, and histopathologic criteria¹⁵, and diagnosis was required to precede at-risk study period of January 1, 2014 and December 31, 2015 during which diagnoses of CDI were ascertained. Patients were excluded from the study if they were less than 18 years of age, had diagnosis of CDI prior to the study period, or underwent colectomy prior to the study period.

Definition of Outcome

The primary outcome of this study is the development of *Clostridium difficile* infection (CDI).

Variable Definitions and Data Record

CDI was identified initially using ICD-9 (008.45), and confirmed through manual chart review of provider notes and documentation of positive testing for CDI (*C. difficile* toxin B PCR, or combined *C. difficile* antigen/toxin assay that relies on glutamate dehydrogenase to detect antigen and enzyme immunoassay for toxin; test performed based on provider order). Data recorded included demographic information, UC history (year of onset, year of diagnosis, hospitalizations), tobacco use, prescription information (including treatment for UC, as well as exposure to proton pump inhibitors (PPI), systemic steroids or antibiotics within 3 months of CDI diagnosis), medical comorbidities, previous hospitalizations (within 6 months of CDI), previous IBD-related or other abdominal surgeries, most recent colonoscopy prior to CDI diagnosis (including Mayo endoscopic subscore), and clinical course of CDI (including UC flare).

Using height and weight (at date of last follow-up visit with gastroenterologist between 2014 and 2015) from the EMR, we calculated body mass index (BMI) to classify patients as underweight (BMI < 18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), obese (BMI ≥ 30).

Statistical Analysis

In the cross-sectional study we examined patients with UC with at least one follow-up visit with a gastroenterologist between 1/1/2014 to 12/31/2015. As a cross-sectional study, we looked at risk of a diagnosis of CDI during this study period. Unpaired t-test, chi-squared analysis, ANOVA, and Fisher's exact tests for between group comparisons. Conditional logistic regression was used to calculate odds ratios for the cross-sectional study, and

presented as age-adjusted analyses. In the age-adjusted analyses, exposure to TNF was the only variable significantly associated with development of CDI, and therefore was included in a limited multivariate logistic regression model including age and gender. An additional multivariate conditional logistic regression model of clinically relevant variables including age, gender, tobacco use, UC disease duration, medication exposure, and vitamin D deficiency was performed to evaluate for potential confounders, and did not affect statistical efficiency. Multivariate linear regression was used to evaluate BMI and CDI risk. All analyses were performed using StataMP 13 (STATA Corp., College Station, TX). Continuous variables are reported as means with SDs. Categorical variables are reported as counts and percentages. All analyses used 2-sided statistical tests.

Ethics Board Approval

The study protocol was approved by the Scripps Institutional Review Board.

RESULTS

The final study cohort included 636 patients with ulcerative colitis (48% male; mean age 54 $\pm$ 17 years) (Table 1). Average disease duration of UC was 15.2 years (SD 12.5). When classified according to BMI, 114 (18%) were obese, 232 (36%) overweight, 274 (43%) normal weight, and 16 (2.5%) underweight.

Among the 636 patients with UC examined for this study, 19 (3.0%) patients developed CDI during the follow-up period. There were no statistically significant differences in baseline characteristics between UC patients with and without CDI (Table 2).

The majority of CDI cases (n=17, 89%) were community-acquired CDI, and the remaining two were hospital-acquired cases. With respect to medication exposure in the 3 months preceding CDI diagnosis, 5 patients with UC (26%) had received antibiotics, 2 (11%) received systemic steroids (steroid use was within 1 month of CDI diagnosis for both cases), and 3 (16%) were on PPI therapy. Six patients (32%) were hospitalized within the preceding 6 months of CDI diagnosis. Three patients (16%) had a history of diabetes mellitus. At the time of CDI diagnosis, five patients with UC (26%) were on anti-TNF α therapy (two patients in combination with thiopurine), and 1 (5%) patient on tofacitinib. Six patients (32%) developed UC flare attributed to CDI. Among the 6 patients with CDI-associated UC flares, 3 patients required hospitalization, with one ultimately requiring total colectomy and another requiring anti-TNF α for rescue therapy. The 3 patients managed as outpatients resolved their flare with concomitant vancomycin and corticosteroid treatment.

Risk of CDI by BMI category

Based on BMI, patients with UC were classified as underweight, normal, overweight, or obese (Tables 1&2). Compared to normal weight patients, risk of CDI was not influenced by obesity (age-adjusted OR 0.55, 95% CI 0.15-2.05, limited multivariate OR 0.59, 95% CI 0.15-2.31, multivariate OR 0.63, 95% CI 0.15-2.58) (Table 3). Being overweight or underweight, compared to normal BMI, also did not appear to influence risk of CDI (Table 3). There was no significant association of CDI risk across BMI categories (p=0.08). In the age-adjusted analyses, exposure to TNF was the only variable significantly associated with

development of CDI (OR 6.02, 95% CI 2.20-14.46), and therefore was included in a limited multivariate logistic regression model including age and gender. Ever use of TNF therapy remained associated with CDI in both the limited multivariate regression model (OR 5.76, 95% CI 2.07-16.00) and full multivariate regression model (OR 6.09, 95% CI 2.07-17.93). In contrast, no association of vedolizumab was observed with CDI (age-adjusted OR 2.40, 95% CI 0.30-19.53, multivariate OR 0.76, 95% CI 0.08-7.36).

Because of the small number of patients with CDI, we also ran the model using BMI as a linear variable. Changes in BMI were associated with risk of CDI on univariate analyses (age-adjusted OR 0.87, 95% CI 0.77-0.99) but not multivariate analyses (OR 0.90, 95% CI 0.79-1.02).

DISCUSSION

Obesity does not appear to influence the risk of CDI among patients with UC. Our study represents the first study examining the association of obesity and CDI in patients with UC. Several studies have demonstrated an increased risk of CDI among patients with IBD, including ulcerative colitis^{3,16}. A few studies have also demonstrated an association between obesity and CDI^{4,5}. Thus, it was interesting to observe that obesity did not increase the risk of CDI among patients with UC compared to other BMI categories.

Our study did not demonstrate an association with obesity and CDI in UC patients, but did identify on both age-adjusted and multivariate analyses an increased risk for CDI in UC patients with ever exposure to anti-TNF therapy. Disease severity and immunosuppression are considered significant risk factors for the development of CDI in IBD. Corticosteroids have an approximately 2-3 fold increased risk for CDI in IBD¹⁷. Whether the risk of CDI is increased among patients with IBD exposed to anti-TNF therapy is unclear, and this may be a consequence of disease severity rather than the therapy itself. In a retrospective cohort study of 503 patients with recurrent CDI, biologic therapy, and in particular, infliximab, was associated with recurrent CDI¹⁸. It must also be noted that vedolizumab utilization was low in our cohort, likely due to its approval during our study period (at-risk study timeframe from January 1, 2014 to December 31, 2015; vedolizumab approval from Food and Drug Administration in May 2014). Thus, our study is limited in its ability to assess for association of CDI and anti-integrin therapy.

Alterations of the gut microbiome composition and abundance, or dysbiosis, play a vital role in the risk of CDI in the general population, and is evidenced by the successful use of fecal microbiota transplantation for the treatment of CDI. Dysbiosis in inflammatory bowel disease is manifested as alterations in the diversity and composition of the gut microbiome, with decreases in the proportions of *Bacteroidetes* and increases in *Firmicutes*, *Proteobacteria* and *Actinobacteria* among patients with IBD¹². An increased *Firmicutes* to *Bacteroidetes* ratio in the gut microbiome has also been demonstrated in independent cohorts of patients with obesity and CDI. The results of our study would suggest that coexisting UC and obesity do not synergistically increase the risk of CDI, but perhaps the underlying resulting dysbiosis associated with these conditions results in the increased risk of CDI seen independently in these conditions.

Strengths of our study include a large sample size and a well-defined population. We identified a 3% prevalence of CDI among UC patients, whether diagnosed as community-acquired or hospital-acquired CDI, and this is lower or comparable to rates described for other IBD cohorts^{16,19}. The prevalence of CDI among obese vs. normal patients was 2.8% and 4.2%, respectively, and based on our sample size we cannot rule out the possibility of a type 2 error. Limitations of our study include its cross-sectional design, which reduced our ability to identify risk factors for CDI in relation to its incidence. As a retrospective study relying on an electronic medical record, it is possible that not all cases of CDI were captured among our patient cohort, particularly if they were seen by providers not utilizing our health record system for data capture. However, our prevalence estimates would suggest that rates of CDI capture were mostly complete.

In conclusion, our study suggests that obesity does not appear to influence the risk of CDI among patients with UC. Ultimately, there are several factors that contribute to a patient's risk for developing CDI. Exposure to TNF therapy appears to be associated with CDI, but this may be attributable to underlying IBD severity as well as prior or concomitant exposure to antibiotics, corticosteroids, and immunosuppressants. Further study is warranted with respect to other factors that may play a role in CDI in UC patients, as CDI remains a significant burden in the IBD population.

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References

1. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. 2013; 108:478–98. quiz 99. [PubMed: 23439232]
2. Bloomfield LE, Riley TV. Epidemiology and Risk Factors for Community-Associated Clostridium difficile Infection: A Narrative Review. *Infect Dis Ther*. 2016; 5:231–51. [PubMed: 27370914]
3. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007; 5:345–51. [PubMed: 17368234]
4. Bishara J, Farah R, Mograbi J, et al. Obesity as a risk factor for Clostridium difficile infection. *Clin Infect Dis*. 2013; 57:489–93. [PubMed: 23645850]
5. Mulki R, Baumann AJ, Alnabelsi T, et al. Body mass index greater than 35 is associated with severe Clostridium difficile infection. *Aliment Pharmacol Ther*. 2017; 45:75–81. [PubMed: 27790736]
6. Punni E, Pula JL, Asslo F, Baddoura W, DeBari VA. Is obesity a risk factor for Clostridium difficile infection? *Obes Res Clin Pract*. 2015; 9:50–4. [PubMed: 25660175]
7. Sousa Guerreiro C, Cravo M, Costa AR, et al. A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. *Am J Gastroenterol*. 2007; 102:2551–6. [PubMed: 17680845]
8. Haas L, Chevalier R, Major BT, Enders F, Kumar S, Tung J. Biologic Agents Are Associated with Excessive Weight Gain in Children with Inflammatory Bowel Disease. *Dig Dis Sci*. 2017; 62:3110–6. [PubMed: 28895012]
9. Scaldaferri F, D'Ambrosio D, Holleran G, et al. Body mass index influences infliximab post-infusion levels and correlates with prospective loss of response to the drug in a cohort of inflammatory bowel disease patients under maintenance therapy with Infliximab. *PLoS One*. 2017; 12:e0186575. [PubMed: 29073159]

10. Guerbau L, Gerard R, Duveau N, et al. Patients with Crohn's Disease with High Body Mass Index Present More Frequent and Rapid Loss of Response to Infliximab. *Inflamm Bowel Dis*. 2017; 23:1853–9. [PubMed: 28837519]
11. Kistangari G, Lopez R, Shen B. Frequency and Risk Factors of Clostridium difficile Infection in Hospitalized Patients With Pouchitis: A Population-based Study. *Inflamm Bowel Dis*. 2017; 23:661–71. [PubMed: 28296825]
12. Manichanh C, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. *Nat Rev Gastroenterol Hepatol*. 2012; 9:599–608. [PubMed: 22907164]
13. Manges AR, Labbe A, Loo VG, et al. Comparative metagenomic study of alterations to the intestinal microbiota and risk of nosocomial Clostridium difficile-associated disease. *J Infect Dis*. 2010; 202:1877–84. [PubMed: 21050115]
14. Hopkins MJ, Macfarlane GT. Changes in predominant bacterial populations in human faeces with age and with Clostridium difficile infection. *J Med Microbiol*. 2002; 51:448–54. [PubMed: 11990498]
15. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of G. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010; 105:501–23. quiz 24. [PubMed: 20068560]
16. Khanna S, Shin A, Kelly CP. Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol*. 2017; 15:166–74. [PubMed: 28093134]
17. Schneeweiss S, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Aliment Pharmacol Ther*. 2009; 30:253–64. [PubMed: 19438424]
18. Razik R, Rumman A, Bahreini Z, McGeer A, Nguyen GC. Recurrence of Clostridium difficile Infection in Patients with Inflammatory Bowel Disease: The RECIDIVISM Study. *Am J Gastroenterol*. 2016; 111:1141–6. [PubMed: 27215924]
19. Vindigni SM, Broussard EK, Surawicz CM. Alteration of the intestinal microbiome: fecal microbiota transplant and probiotics for Clostridium difficile and beyond. *Expert Rev Gastroenterol Hepatol*. 2013; 7:615–28. [PubMed: 24070153]

Table 1

Baseline Characteristics of Study Cohort

Ulcerative Colitis (n=636)	
Age (yrs), mean (SD)	53.6 (16.6)
Female, n (%)	328 (52)
UC Location, n (%)	
Pancolitis	318 (51)
Left side	170 (27)
Rectum	140 (22)
Disease duration, yrs (SD)	15.2 (13)
Tobacco use, n (%)	
Current	27 (4)
Former	175 (28)
Never	420 (66)
Unknown	14 (2)
BMI Category, n (%)	
Underweight	16 (3)
Normal	274 (43)
Overweight	232 (36)
Obese	114 (18)
Biologic exposure, n (%)	
Anti-TNF therapy	101 (16)
Vedolizumab	18 (3)

Table 2 Baseline Characteristics for Patients with UC, with and without *C. difficile* Infection

	UC with CDI (n= 19)	UC without CDI (n = 582)	p-value
Age (yrs), mean (SD)	58.2 (23.8)	32.4 (16.3)	0.21
UC Location, n (%)			0.43
Pancolitis	13 (68)	283 (49)	
Left side	3 (16)	158 (27)	
Rectum	3 (16)	134 (23)	
Gender, n (%)			0.31
Female	12 (53)	298 (51)	
Male	7 (37)	284 (49)	
Disease duration, yrs (SD)	16.2 (15)	15.3 (13)	0.75
Tobacco use, n (%)			0.58
Current	0 (0)	25 (4.3)	
Former	4 (21)	157 (27)	
Never	15 (79)	386 (66)	
Unknown	0 (0)	14 (2.4)	
BMI Category, n (%)			0.06
Underweight	2 (11)	14 (2)	
Normal	11 (58)	250 (43)	
Overweight	3 (16)	215 (37)	
Obese	3 (16)	103 (18)	
Biologic exposure, n (%)			
Anti-TNF therapy	8 (42)	11 (58)	0.001
Vedolizumab	1 (5)	18 (95)	0.41

Abbreviations: CDI, *C. difficile* infection

Table 3

Risk of *C. difficile* Infection by BMI Category

	Age-adjusted OR	95% CI	Limited Multivariate OR*	95% CI	Multivariate OR**	95% CI
Obese vs. Normal	0.55	0.15 - 2.05	0.59	0.15 - 2.31	0.63	0.15 - 2.58
Overweight vs. Normal	0.28	0.08 - 1.03	0.28	0.07 - 1.07	0.33	0.08 - 1.30
Underweight vs. Normal	3.61	0.70 - 18.51	2.47	0.41 - 14.70	2.98	0.45 - 19.83
Overweight and Obese vs. Normal	0.37	0.13 - 1.04	0.37	0.13 - 1.07	0.43	0.15 - 1.29
Obese vs. Overweight and Normal	0.90	0.25 - 3.20	0.96	0.26 - 3.49	1.04	0.28 - 3.85

* Limited Multivariate odds ratio (OR) adjusted for age, gender and ever exposure to anti-TNF therapy.

** Multivariate OR adjusted for gender, age, tobacco use, UC disease duration, ever exposure to anti-TNF therapy, ever exposure to vedolizumab