Obesity as a Risk Factor for Clostridium difficile Infection

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Background. Obesity and Clostridium difficile infection (CDI) are both related to an increased Firmicutes/Bacteroidetes ratio in the intestinal microbiota. However, an association between obesity and CDI is unknown. We aimed to assess the association between obesity and CDI in hospitalized patients.

Methods. We conducted a retrospective case-control study. From January to December 2011, all consecutive patients hospitalized with CDI, in 2 internal medical departments in 2 hospitals, were included. Patients with CDI were compared to hospitalized patients without diarrhea, during the same period and in the same departments, and matched by age, sex, Charlson score, length of hospitalization, and antibiotic use during the last 3 months.

Results. Of the 6300 patients hospitalized, 178 were diagnosed with CDI. CDI prevalence was 2.8% (178/6300). Thirty patients were excluded from the study. The 148 cases with CDI were compared to 148 hospitalized controls. Mean body mass index (BMI) in the CDI group was 33.6 (SD, 4.3) versus 28.9 (SD, 5.4) in the control group (P = .001). The multivariable model of conditional logistic regression for matched pairs showed that a history of intra-abdominal surgery (odds ratio [OR] = 2.865; 95% confidence interval [CI], 1.26–6.52) and a high BMI value (OR = 1.196 per 1-unit increase in the BMI scale; 95% CI, 1.12–1.27) were the only variables found to be significantly associated with CDI.

Conclusions. Our findings suggest that obesity is associated with the risk of CDI. Further studies are needed to reveal the exact mechanisms underlying this association.

Keywords. Clostridium difficile; microbiota; Firmicutes; Bacteroidetes; BMI.

Clostridium difficile is the most common cause of infectious nosocomial diarrhea among adults in developed countries [1–4]. Clostridium difficile is a gram-positive anaerobic spore-forming bacterium and a member of the Clostridium genus, which is part of the Firmicutes phylum [5]. The incidence of C. difficile infection (CDI) is increasing and is associated with significant mortality, morbidity, increased length of hospital stay, and healthcare costs [6–8]. The most common risk factor for developing CDI identified in the literature is the use of antimicrobial agents [9–12]. Other risk factors have been described and include advanced age, hospitalization, severe comorbidities, exposure to cytotoxic chemotherapy, immunosuppressive therapy, and use of acid suppressive therapy, especially proton pump inhibitors (PPIs) [9, 11, 12].

CDI is believed to be causally related to perturbations in the intestinal microbiota [13]. Administration of antimicrobial agents is known to significantly disrupt intestinal microbiota [14], resulting in a lower intensity of the phylum Bacteroidetes and an abundance of the bacterial phyla Firmicutes, Proteobacteria, Actinobacteria, and Tenericutes, thus enabling C. difficile to colonize the intestines and cause infections [15, 16].

Recent evidence, primarily from investigations of animal models, suggests that gut microbiota affects nutrient acquisition and energy regulation. Its composition has also been shown to differ in lean versus obese
animals and humans. Initial findings have linked obesity with the decreased relative proportion of Bacteroidetes to Firmicutes [17]. Thus, we hypothesized that obese patients might be more susceptible to CDI than lean subjects. For this purpose, we conducted a case-control study to assess the association between obesity and CDI.

METHODS

Subjects and Study Design
A retrospective study was performed investigating whether obesity is associated with CDI in adult hospitalized patients. From January 2011 to December 2011, all consecutive patients with CDI, hospitalized in the Internal Medicine Department, Holy Family Hospital, Nazareth, and the Internal Medicine Department B, Ziv Hospital, Safed, Israel, were included. Patients were included only once in the analysis. We excluded patients who were ≤18 years old, pregnant, asymptomatic carriers of C. difficile, or who lacked sufficient data for calculating the Charlson comorbidity index score [18]. Data on demographic characteristics, underlying conditions, previous hospitalizations, abdominal surgery, drug and antibiotic therapy during the previous 90 days, and clinical and laboratory findings were collected. All data were obtained from patients’ electronic hospital and outpatient records.

The control group included patients who were not suffering from diarrhea and had been hospitalized during the same period and in the same department. The controls were matched (1:1) for age (±5 years), sex, comorbidity, length of stay (±2 days), and antibiotic use during the prior 3 months. The study was reviewed and approved by the local Ethics Committee of the Holy Family Hospital, Nazareth, and the Ziv Medical Center, Safed, Israel.

Definitions
Diarrhea was defined as the passage of 3 or more unformed stools for at least 2 consecutive days. CDI was defined as diarrhea not attributed to any other cause and associated with a positive stool test for C. difficile toxin A/B [9]. The decision to test for C. difficile was made by physicians uninvolved in the study. An enzyme immunoassay for C. difficile toxin A/B (TechLab, Inc, Blacksburg, Virginia) was used for toxin detection, performed according to the manufacturer’s instructions. Stool Tox A/B immunoassay was repeated in those patients with antibiotic-associated diarrhea with negative results from their first stool samples. Weight, height, and body mass index (BMI; weight [kg]/height2 [m2]), were recorded for each patient [19].

Statistical Analysis
Stata statistical software, version 12 (StatCorp, College Station, Texas) was utilized for data handling and analysis. Mean values, SDs, and P values were calculated. For testing differences between the CDI cases and the controls, χ2 tests were performed for the categorical variables, and Student t tests for the continuous variables. A P value of <.05 was set for concluding a significant effect in both univariable and multivariable analyses. A multivariable model of conditional logistic regression for matched pairs was performed to determine the association between risk factors and CDI. Only significant variables found in the univariable analysis were entered into the multivariable model.

RESULTS
Of the 6300 patients hospitalized in the 2 internal medicine departments, 178 were diagnosed with CDI. Thirty of the 178 (16.8%) were excluded from the study; 2 were pregnant, 9 were asymptomatic carriers of C. difficile, 9 were missing BMI data, and 10 were missing Charlson score data. One hundred forty-eight patients diagnosed with CDI with documented BMI were included in the study. In 27 of 148 (18.2%) cases, a repeat enzyme immunoassay for C. difficile toxin was performed. Prevalence of CDI in internal medicine department patients was 2.8% (178/6300) per year. Table 1 presents the characteristics of CDI patients and their control counterparts. A significantly higher mean BMI was found in CDI patients compared to controls (33.6 vs 28.9, respectively; P < .001). No significant differences were found between the CDI cases and controls in

Table 1. Demographic and Clinical Characteristics of Patients With Clostridium difficile Infection and Matched Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CDI Group (n = 148)</th>
<th>Control Group (n = 148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>64.6 (17.0)</td>
<td>64.2 (17.4)</td>
<td>.832</td>
</tr>
<tr>
<td>Male sex</td>
<td>71 (48.0)</td>
<td>71 (48.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Charlson score, mean (SD)</td>
<td>2.59 (1.96)</td>
<td>2.28 (1.79)</td>
<td>.156</td>
</tr>
<tr>
<td>Antibiotic use during the last 3 mo</td>
<td>76 (51.4)</td>
<td>73 (49.3)</td>
<td>.816</td>
</tr>
<tr>
<td>Length of stay, d, mean (SD)</td>
<td>8.1 (5.7)</td>
<td>8.3 (4.9)</td>
<td>.810</td>
</tr>
<tr>
<td>Proton pump inhibitor use</td>
<td>56 (37.8)</td>
<td>36 (24.3)</td>
<td>.017</td>
</tr>
<tr>
<td>BMI, kg/m2, mean (SD)</td>
<td>33.6 (4.3)</td>
<td>28.9 (5.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chemotherapy during the last 6 mo</td>
<td>6 (4.1)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>14 (9.5)</td>
<td>6 (4.1)</td>
<td>.10</td>
</tr>
<tr>
<td>History of intra-abdominal surgery</td>
<td>34 (23.0)</td>
<td>15 (10.1)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) unless otherwise specified. Abbreviations: BMI, body mass index; CDI, Clostridium difficile infection; SD, standard deviation.
This finding is notable, particularly due to the BMI’s “restriction-of-range” in our sample. Both groups were composed of above-average-BMI subjects. Low BMI values were underrepresented in our cohort. Despite this problem, we found that obesity was associated with CDI. Consequently, the estimated association between BMI and CDI is most probably an underestimation of the true association in the general population. Furthermore, when the BMI variable was taken out of a baseline model containing all the analyzed variables (not shown), the PPI variable (OR = 2.32; 95% confidence interval [CI], 1.24–4.36) and history of intra-abdominal surgery (OR = 2.65; 95% CI, 1.22–5.74) became highly significant. However, when the BMI variable was added, it captured a large portion of these 2 associations, consequently making the PPI variable insignificant (Table 2).

Emerging data have indicated an association between obesity and the risk of several nosocomial infections. Recent studies have shown obesity to be an independent predictor of nosocomial bacteremia in elderly patients [20] and septic shock [21], ventilator-associated pneumonia [21], and catheter-associated sepsis [22] in critically ill patients. Previous studies have indicated an interesting interaction between obesity and H1N1 influenza infection. Obesity has been shown to be associated with a higher risk of intensive care unit admission or death in patients with the 2009 influenza A (H1N1) pandemic infection [23].

The mechanisms underlying the association between obesity and infections are poorly established. Obesity-associated comorbidities such as type 2 diabetes, hypertension, atherosclerosis, obesity-related immune system dysregulation, decreased cell-mediated immune responses, and respiratory dysfunction have been proposed as possible mechanisms [24, 25].

The human gut hosts >100 trillion microorganisms encompassing thousands of species. In adults, Bacteroidetes and Firmicutes are the most prevalent phyla. Recently, Turnbaugh et al [17] described differences in the composition of intestinal microbiota of lean and obese mice, with obese mice having a higher proportion of intestinal Firmicutes. The microbiota of obese mice was rich in enzymes that break down otherwise indigestible dietary polysaccharides. Thus, Firmicutes in obese mice assist their hosts in harvesting calories from ingested food that could then be used as energy.

In another study, from the same group of investigators, Ley et al [26] studied a small number of obese humans, and found that obese subjects had lower numbers of Bacteroidetes and higher numbers of Firmicutes in their distal gut than did lean control subjects. Moreover, when obese individuals lost weight, the proportion of Firmicutes became similar to that in lean individuals.

Since these pioneering studies, significant associations have been found in other studies between the increase of some term of age, sex, antibiotic use during the last 3 months, length of stay, and average Charlson score. In addition, there were no significant differences between groups as to types of previous antibiotics (data not shown). However, compared to the control group, the use of PPIs was significantly more common in the CDI group than in the control group (37.8% vs 24.3%, respectively; \( P = .017 \)). In addition, the CDI group surpassed its control group in history of intra-abdominal surgery (23.0% vs 10.1%, respectively; \( P = .005 \)), and chemotherapy during the prior 6 months (4.1% vs 0%, respectively; \( P = .03 \)).

Table 2 presents the results of the multivariable analysis containing all the variables on which the CDI and control groups showed significant differences on univariable analysis (Table 1). An exception was the variable “chemotherapy during the last 6 months.” Due to a zero cell of this variable in the control group, we performed the multivariable model with and without the chemotherapy variable. The results obtained were appreciably the same, and thus we present this model without this variable.

This model illustrates that the variables predicting CDI (while the PPI and chemotherapy variables are controlled for) are BMI and a history of intra-abdominal surgery. A higher BMI value is associated with a higher chance for acquiring CDI. Moreover, the predictive value of BMI is relatively high. The pseudo-\( R^2 \) of the estimated model is equal to 0.30. Another (univariable) model was conducted, with BMI as the only explanatory variable. This model had a relatively high predictive power (odds ratio [OR] = 1.205; \( P < .001 \); pseudo-\( R^2 = 0.26 \)). Furthermore, a model containing all analyzed variables (Table 1), but omitting the BMI variable (model is not shown), had a pseudo-\( R^2 \) of only 0.16. On the basis of our results, it is expected that a difference of approximately 5 points on the BMI scale among a population similar to our sample (ie, with higher-than-average BMI values [BMI = 28.9]) doubles the chance of contracting CDI.

**DISCUSSION**

Our findings indicate that obesity is a significant and independent risk factor for CDI.

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**Table 2. Multivariable Analysis for Predictors of *Clostridium difficile* Infection**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m(^2)</td>
<td>1.196</td>
<td>1.12–1.27</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>1.497</td>
<td>.78–2.89</td>
<td>.229</td>
</tr>
<tr>
<td>History of intra-abdominal surgery</td>
<td>2.865</td>
<td>1.26–6.52</td>
<td>.012</td>
</tr>
<tr>
<td>No. of observations</td>
<td>296</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudo ( R^2 )</td>
<td>0.304</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval.
The association between obesity and subsequently the increased Firmicutes-to-Bacteroidetes ratio and CDI is plausible. The development of CDI is related to perturbations in the intestinal microbiota [13] and has shown that Bacteroidetes and *Bifidobacterium* play an important role in the mechanism of resistance to colonization by *C. difficile* [16]. Previous studies have shown lower concentrations of Bacteroidetes in the intestines of CDI patients [16] and higher intensities of Firmicutes and Proteobacteria in patients with CDI than in controls [15].

In conclusion, our findings indicate a strong association between obesity and CDI. This study, however, has limitations. First, because this is a retrospective study, some patients with CDI could have been overlooked, thus not included in the analysis. Second, some of our cases were of community onset; therefore, data on their previous hospitalizations and duration of prior antibiotic therapy were unavailable and were not adjusted for. Third, because of its low sensitivity, the use of toxin enzyme immunoassays for case definition could underestimate prevalence of the disease. Fourth, this study was based on a cohort from a single country and needs to be confirmed by additional prospective research involving other populations. Fifth, obesity is also related to major chronic diseases that may indirectly increase the risk of CDI, including diabetes, heart failure, stroke, asthma, gastroesophageal reflux, certain forms of cancer, and liver disease [30]. It is unclear whether any relationship between obesity and CDI risk may be due to obesity per se or explained by comorbidities induced by obesity. However, obesity was still associated with a higher risk of CDI in the multivariable model. Finally, the cross-sectional nature of our study does not allow us to draw conclusions regarding the causal relationship between CDI and obesity. For that to be shown, a longitudinal study using panel data should be carried out. Further restriction and prudent use of antibiotics in obese patients is recommended. Future studies should focus on the relationship between the increasing incidence of CDI and obesity in the United States and many Western countries [31]. The exact mechanisms underlying the association between obesity and CDI remain to be fully understood and further studies are warranted.

**Notes**

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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