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ORIGINAL ARTICLE

High body mass index is not associated with increased treatment failure in infliximab treated pediatric patients with inflammatory bowel disease

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Abstract

Background and Aim: While weight gain during infliximab therapy in inflammatory bowel disease (IBD) is common, there has been limited research evaluating its impact on infliximab efficacy.

Methods: Primary aims of this study were to determine the frequency of excess weight gain (body mass index [BMI] > 25 kg/m^2) in children with IBD on maintenance infliximab and evaluate the impact on infliximab dosing, serum trough levels, and treatment failure. Secondary aims were to determine differences in weight gain, treatment characteristics, and clinical/biochemical variables between patients with therapeutic and subtherapeutic maintenance therapy trough levels. We performed a retrospective study of 253 pediatric IBD (75.1% Crohn's disease, 23.3% ulcerative colitis, 1.6% IBD-unclassified) patients on infliximab followed at BC Children's Hospital between January 2013 and January 2018.

Results: Median age at infliximab initiation was 13.9 years, median length of follow up was 56.9 months, and 55.7% were males; 10.3% of the cohort demonstrated excess weight gain (7.5% overweight, 2.8% obese). Average mg/kg dosing was not statistically different between groups (normal, overweight, and obese: 6.7, 6.4, and 6.7 mg/kg, respectively, $P = 0.52$). Median BMI of patients with therapeutic and subtherapeutic trough levels was similar at 19.9 kg/m^2 (interquartile range [IQR], 17.3–23.8) and 19.7 kg/m^2 (IQR, 17.4–21.9), respectively. BMI had no effect on secondary loss of response to infliximab, with no significant difference between normal and high BMI subgroups (13.4 vs. 16.7%, $P = 0.9$).

Conclusions: In a subgroup of pediatric IBD patients on maintenance infliximab, excess weight gain was not associated with higher weight-based dosing, lower serum trough levels, or increased risk of treatment failure.

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Introduction

Infliximab and other antitumor necrosis factor (TNF) agents have been used to induce and maintain remission in the pediatric inflammatory bowel disease (IBD) population.[1–4] Various factors may contribute to infliximab response, including disease severity, strictures, fistulas or abscess, serum albumin level, and body mass index (BMI).[3] Although it is clear that biologic therapy in children with IBD is associated with weight gain, the impact of elevated BMI on infliximab efficacy has been poorly studied.[5,6] Similarly, for adult IBD, studies of obesity's impact on response to biologics have been sparse and conflicting.

In a retrospective cohort study of adult ulcerative colitis (UC) patients on biologic therapy, each 1 kg/m^2 increase in BMI was associated with the risk of treatment failure (need for IBD-related surgery, hospitalization, or treatment modifications including dose escalation or addition of corticosteroid).[7] Furthermore, in a retrospective cohort study of adult IBD subjects in whom infliximab was initiated, increased BMI was associated with an earlier time to loss of response (LOR).[8] Conversely, a retrospective cohort analysis on over 300 Crohn's disease (CD) patients found that every unit of BMI increase (up to obese range) was associated with fewer flares and reduced LOR to infliximab.[9] Recently, the analyses of adult infliximab-treated IBD patients from four clinical trials (ACCENT-I, SONIC, ACT-1, and ACT-2) reported no association between obesity and achieving remission or clinical response.[10]

The aims of this retrospective pediatric cohort study were to characterize and determine the incidence of elevated BMI in children with IBD on maintenance infliximab and evaluate the impact of elevated BMI on infliximab dosing, serum trough levels, and LOR. Secondary aims were to determine the differences in weight gain, treatment characteristics, and clinical/biochemical variables between patients with therapeutic and subtherapeutic maintenance therapy trough levels. We hypothesized that increased BMI would be associated with lower maintenance infliximab trough levels and subsequent attempts at dose optimization, with increased risk of treatment failure.

Methods

Study design. We performed a retrospective study of pediatric IBD patients between 2 and 17 years of age who were followed at BC Children's Hospital and were stable on maintenance infliximab for a minimum of 6 months between January 2013 and January 2018 and who had a BMI recorded at infliximab initiation and at last follow up. Exclusion criteria included primary nonresponse, infliximab failure during the induction phase, and commencement of alternative therapy before maintenance with infliximab.

Patients were identified from the BC Children's Hospital GI Division IBD database. A single reviewer (Isaac Rodin) abstracted data through medical record review. Two reviewers (Kevan Jacobson, Justin Chan) validated the abstracted data. Data on patient demographics, age at diagnosis, therapies, and BMI at initiation of infliximab and at last follow up were extracted. Laboratory investigations, infliximab dose, dosing interval, physician global assessment (PGA), Pediatric Crohn's Disease Activity Index (PCDAI), and Pediatric Ulcerative Colitis Activity Index (PUCAI) were recorded at each infliximab infusion visit, and serum infliximab trough levels, where available, were recorded.

Weight was reported using three categories: normal BMI (18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI >30 kg/m^2). Based on published literature, a trough level ≥ 5 μg/mL during maintenance was considered therapeutic.[11] Secondary LOR was defined as losing response to infliximab (recurrence of moderate-to-severe disease based on PGA or a PCDAI or PUCAI >30), experiencing an infusion reaction, and requiring a drug change. Weight-based dosing refers to the practice of administering appropriate doses of infliximab based on the actual weight of the patient. Dose optimization was defined as an increase in weight-based dose or drug interval shortening to maintain clinical remission.

Statistical analysis. Continuous variables were reported as either medians with interquartile range (IQR) or mean ± SD or standard error depending on the data approximation to normal distribution, and discrete variables were reported as counts and proportions. Differences in infliximab treatment failure and mid-maintenance infliximab trough levels between high BMI and low BMI subgroups, and the relationship between BMI and dose optimization, were analyzed using a chi-squared test. Differences in treatment characteristics and clinical/biochemical variables between patients with sub- and therapeutic trough level recordings during maintenance infliximab therapy were analyzed using both chi-squared tests and two-sample *t* tests. Logistic multivariate regression analysis was used to determine the effect of concomitant therapy (immunomodulator [IM], antibiotics, and steroids) on end BMI and infliximab failure. Microsoft Excel version 16.0 and R Software (R Foundation for Statistical Computing, V 3.5.3, Vienna, Austria) were used for analyses, and $P < 0.05$ was considered statistically significant.

Ethical considerations. Ethical approval was obtained from the University of British Columbia Clinical Research Ethics Board and the British Columbia Children's and Women's Research Review Committee.

Results

Demographics. A total of 253 pediatric IBD patients on infliximab between January 2013 and January 2018 were identified and included (cohort details summarized in Table 1a).

Table 1 (a) Patient and treatment characteristics stratified by BMI at last follow up. (b) Patient and treatment characteristics of patients who moved from normal to elevated BMI

(a)

	Total cohort (n = 253)	Normal BMI (18.5–24.9 kg/m^2) (n = 217)	Overweight (25–29.9 kg/m^2) (n = 23)	Obese (>30 kg/m^2) (n = 13)
Patient characteristics				
IBD subtype, n (%)				
Crohn's disease	190 (75.1)	166 (76.5)	14 (60.9)	10 (76.9)
Ulcerative colitis	59 (23.3)	48 (22.1)	8 (34.8)	3 (23.1)
IBD-unclassified	4 (1.6)	3 (1.4)	1 (4.3)	0 (0)
Gender (males: females)	1.26	1.26	0.77	3.33
Disease duration, months, (median, IQR)	10.7 (IQR 2.1–30.9)	10.1 (2.1–29.4)	12.9 (1.8–40.4)	12.3 (0.2–28.8)
Age at IFX initiation, years (median, IQR)	13.8 (11.4–15.8)	13.7 (11.4–15.5)	15.2 (14.2–16.6)	14.0 (13.3–16.8)
Age at last IFX infusion, years (median, IQR)	16.7 (14.1–17.8)	16.4 (14.0–17.8)	17.6 (16.9–18.0)	17.2 (16.0–17.7)
BMI at IFX initiation (kg/m^2) (median, IQR)	17.3 (15.2–20.3)	14.7 (13.8–15.6)	22.6 (20.1–24.4)	25.0 (20.3–26.9)
BMI at last IFX infusion (kg/m^2) (median, IQR)	20.4 (17.9–23.1)	19.6 (17.5–21.6)	26.5 (25.9–27.4)	32.6 (31.3–33.0)
Treatment characteristics				
Length of time treated with IFX, months (median, IQR)	26.9 (12.9–41.7)	23.6 (12.9–42.4)	19.6 (13.6–37.7)	13.2 (10.9–44.4)
Average mean dose (mg, SE)	389.9 (9.9)	358.1 (8.7)	493.9 (29.7)	680.6 (53.1)*
Average dose (mg/kg, SE)	6.7 (0.13)	6.7 (0.20)	6.4 (1.8)	6.7 (2.4)
Average number of infusions per year (SE)	7.5 (0.28)	8.0 (0.32)	7.1 (0.35)	8.0 (0.83)
Infliximab LOR, n (%)	35 (13.8)	29 (13.4)	5 (21.7)	1 (7.7)
Infusion reaction, n (%)	10 (4.0)	8 (3.7)	2 (8.7)	0 (0)
Secondary LOR, n (%)	25 (9.8)	21 (9.7)	3 (8.7)	1 (7.7)

(b)

	Normal to elevated BMI (18–25 to >25 kg/m^2) (total n = 26)	Normal to overweight BMI (18–25 to 25–30 kg/m^2) (n = 19)	Normal to obese BMI (18–25 to >30 kg/m^2) (n = 7)
Patient characteristics			
IBD subtype, n (%)			
Crohn's disease	19 (73.1)	13 (68.4)	6 (66.7)
Ulcerative colitis	6 (23.1)	5 (26.3)	1 (14.3)
IBD-unclassified	1 (3.8)	1 (5.3)	0 (0)
Gender (males: females)	1.0	0.9	1.33
Age at IFX initiation, years (median, IQR)	13.3 (10.8–15.0)	13.3 (11.1–15.0)	12.7 (8.9–13.4)
Age at last IFX dose, years (median, IQR)	17.5 (15.8–17.9)	17.5 (15.6–17.9)	16.9 (15.3–17.6)
BMI at IFX initiation (kg/m^2) (median, IQR)	21.8 (19.4–24.7)	22.5 (19.9–23.6)	20.3 (18.3–24.9)
BMI at last IFX dose (kg/m^2) (median, IQR)	27.1 (26.1–31.1)	26.5 (25.7–27.1)	31.4 (31.1–41.0)
Treatment characteristics			
Average mean dose (mg, SE)	547.4 (36.6)	515.9 (42.6)	584.3 (57.8)
Average dose (mg/kg, SE)	7.9 (0.53)	8.1 (0.7)	7.7 (0.7)
Average number of infusions per year (SE)	9.3 (1.68)	9.3 (2.3)	7.4 (0.7)
Infliximab LOR, n (%)	4 (15.4)	4 (21.1)	0 (0)
Infusion reaction, n (%)	1 (3.8)	1 (5.3)	0 (0)
Secondary LOR, n (%)	3 (11.5)	3 (15.8)	0 (0)

*$P < 0.05$ (relative to normal BMI).

BMI, body mass index; IBD, inflammatory bowel disease; IFX, infliximab; IQR, interquartile range; LOR, loss of response; SE, standard error.

The cohort included 75.1% CD, 23.3% UC, and 1.6% IBD-unclassified patients and 141 (55.7%) males. In accordance with the Paris Classification of CD patients, 7.4% were classified with L1, 32.1% L2, and 61.5% L3 disease with L4a, L4b, and L4aL4b involvement in 48.9, 15.8, and 14.7%, respectively. With respect to disease behavior, 66.8% were classified with B1,

Table 2 Dose optimization of responders *versus* those who lost response stratified by BMI change

	BMI normal throughout (18–25 kg/m^2)	BMI normal to elevated (18–25 to >25 kg/m^2)	BMI elevated throughout (>25 kg/m^2)
Response			
Patient, *n* (% total cohort)	188 (74.3)	22 (8.7)	8 (3.2)
Dose optimization			
n, (% of total cohort)	52 (20.6)	3 (1.2)	1 (0.4)
Average final dose (mg/kg, SE)	8.2 (0.20)	7.7 (0.53)	7.8 (0.71)
Loss of response			
Patients, *n* (% total cohort)	29 (11.5)	4 (1.6)	2 (0.79)
Dose optimization			
n, (% of total cohort)	10 (4.0)	3 (1.2)	2 (0.79)
Average final dose (mg/kg, SE)	9.5 (0.76)	10.3 (0.14)	10.9 (0.38)

BMI, body mass index; SE, standard error.

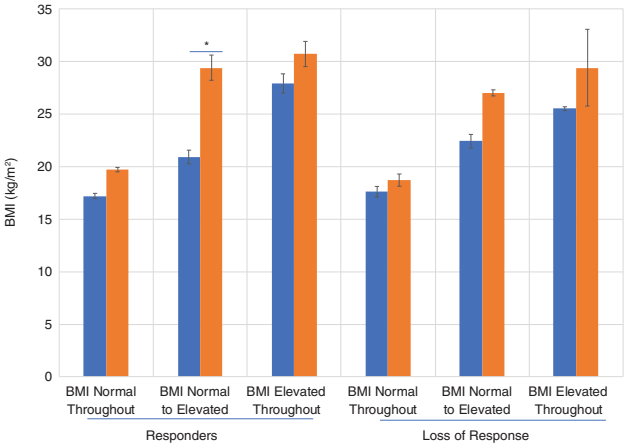

Figure 1 Body mass index (BMI) change from infliximab initiation to last follow up for responders and those who lost response compared to those who maintained a normal BMI, whose BMI remained elevated, and who moved from a normal to elevated BMI, $*P < 0.05$. (■), Before infliximab initiation; (■), last follow up.

13.7% B2, 4.2% B3, 15.5% B2/B3, and 45.3% had perianal disease. In inflammatory bowel disease - unclassified (UC/IBDU) patients, the frequency of E1, E2, E3, and E4 involvement was 0, 6.3, 27, and 66.7%, respectively, with 66.7% classified as disease severity S1. The median age at infliximab initiation was 13.8 years (IQR, 11.4–15.8), with no significant age difference between BMI groups (Table 1a). No significant difference in disease duration between groups at infliximab initiation was observed, with a median duration of disease of 10.7 months (IQR 2.1–30.9) and median length of follow up (on infliximab) of 26.9 months (IQR 12.9–41.7) (Table 1a).

Weight gain. At the last follow up, the median BMI of the cohort was 20.4 kg/m^2 (IQR 17.9–23.1) (Table 1a). In the overweight and obese groups, 17% (4/23) and 46% (6/13), respectively, had BMIs above the normal range at infliximab initiation, while 10.3% (26) of patients were reclassified from a normal to elevated BMI (7.5% in overweight and 2.8% in obese categories) (Table 1b). Notably, patients whose BMI increased from normal to elevated had a significantly higher BMI change than those whose BMI remained in the normal range throughout the study (8.1 and 2.4 kg/m^2, respectively, $P < 0.001$). In contrast, the average change in BMI of patients with an elevated BMI before infliximab initiation and at last follow up was similar to those with a normal BMI throughout the study (2.8 *vs* 2.4 kg/m^2, respectively).

Of the 218 (86%) children with response to infliximab, 188 (86.2%) had a normal BMI throughout the study, whereas 22 (10.1%) started with a normal BMI but had an elevated BMI at last follow up, and 8 (3.7%) had an elevated BMI before infliximab initiation and at last follow up (Table 2, Fig. 1). Similarly, in the 35 children who experienced secondary LOR and infliximab failure, 29 (82.9%) had a normal BMI throughout the study, while 4 (11.4%) with a normal BMI at infliximab start had an elevated BMI at last follow up, and 2 (5.7%) had an elevated BMI before infliximab initiation and at last follow up (Table 2, Fig. 1).

Concomitant therapy (IM, antibiotics, and/or corticosteroids) had no effect on BMI at the end of infliximab treatment (Table S1, Supporting information). Weight gain was dependent on disease subtype, with CD patients having a higher BMI change than UC/IBD-U patients between infliximab initiation and at last follow up (3.41 *vs* 1.48 kg/m^2, $P = 0.0015$). However, approximately the same proportion of patients with CD and UC/IBD-U had a normal BMI before infliximab initiation and at last follow up (87.4 *vs* 81.0%). Furthermore, the proportion of patients whose BMI increased from normal to elevated and those who had an elevated BMI throughout did not differ significantly for CD and UC/IBD-U patients (10 *vs* 11.1% and 2.6 *vs* 7.9% respectively). Notably, weight gain was not found to be dependent on the Paris Classification of patients in the cohort.

Infliximab dosing. As expected, patients in the overweight and obese categories had significantly higher average infliximab dosage than patients in the normal BMI category (493.9 and 680.6 mg *vs* 358.1 mg, respectively, $P < 0.001$) (Table 1). However, the average mg per kg dose and infusion number per year were not statistically different between groups (normal, overweight, and obese: 6.7, 6.4, and 6.7 mg/kg, respectively; $P = 0.52$ and 8.0, 7.1 and 8.0, $P = 0.52$ respectively) (Table 1a). When the cohort was further subdivided into those patients whose BMI increased from the normal to elevated range, the average mg per kg dose and infusion number per year were numerically higher at 7.9 mg/kg and 9.3 infusion/year compared to 6.7 mg/kg and 8.0 infusion/year for those with normal BMI throughout, respectively, although this failed to reach statistical significance ($P = 0.82$ and $P = 0.91$, Table 1b).

For responders, no significant difference in the frequency of infliximab dose optimization was observed between groups with 28.0, 13.6, and 12.5% of cases requiring dose optimization in the normal, normal to elevated, and elevated to elevated BMI groups, respectively (Table 2, $P = 0.43$). In addition, the mean final infliximab dose was similar between groups (8.2 mg/kg in the normal and 7.7 mg/kg and 7.8 mg/kg in the normal to

elevated and elevated to elevated BMI groups, respectively). Notably, for patients with LOR, dose optimization occurred more frequently in children with a normal BMI at infliximab initiation but had an elevated BMI at last follow up and in those who had an elevated BMI before infliximab initiation and at last follow up (75 and 100%, respectively) compared to children with a normal BMI throughout the study (34.5%), although the numbers were small, and these differences did not reach statistical significance (Table 2, $P = 0.16$).

For both responders and patients with LOR, dose optimization was independent of disease subtype. For responders, 26.3% of CD patients and 23.5% of UC/IBDU patients required dose optimization ($P = 0.30$). For those with LOR, 30.4% of CD patients and 41.7% of UC/IBDU patients required dose optimization ($P = 0.36$).

Trough levels. Infliximab trough levels were recorded in 169 (66.8%) patients during maintenance therapy (Table 3). The median duration from infliximab initiation to trough level was 18.6 months (IQR, 8.1–34.8), which did not differ significantly between BMI groups. Median infliximab trough concentrations did not differ significantly between BMI groups (Table 3) or by disease subtype (5.7 μg/mL CD *vs* 6.9 μg/mL UC/IBDU, $P = 0.74$). Subtherapeutic trough levels were recorded in 37.9% of patients. The median BMI of patients with therapeutic and subtherapeutic trough levels was similar at 19.9 kg/m^2 (IQR, 17.3–23.8) and 19.7 kg/m^2 (IQR, 17.4–21.9), respectively. Moreover, in patients with subtherapeutic trough levels, there were no significant differences in the number of patients between the three BMI categories, (Table 3). In addition, there was no significant difference in the proportion of patients with subtherapeutic trough levels when classified by disease subtype (CD and UC/IBD-U: 40.5 *vs* 31%, respectively, $P = 0.74$).

Infliximab loss of response. Of the 35 (13.8%) patients who lost response to infliximab, 25 experienced secondary LOR, and 10 had infusion reactions (Tables 1a and 2). BMI had no effect on infliximab failure, with no significant difference between normal and high BMI subgroups (13.4 *vs* 16.7%, respectively, $P = 0.9$). Furthermore, no statistically significant difference in infliximab failure rate was observed between subgroups, with 13.4% (29/217) in normal, 21.7% in overweight (5/23), and 7.6% (1/13) in obese BMI categories (Table 1a), or when further subdivided into those patients whose BMI increased from the normal to elevated range at 15.4% (Table 1b). Interestingly, corticosteroid use increased the odds of infliximab LOR by 53.5% ($P = 0.04$) when controlling for concomitant therapies.

Patient demographics and treatment characteristics between responders and those who lost response to infliximab were compared. No difference was observed between age, disease subtype, or BMI groups at last follow up (data not presented). Furthermore, there was no difference in treatment characteristics (final dose, infusions per year, and maintenance therapy trough concentrations) between groups.

Multivariate logistic regression analysis determined that none of the variables evaluated (gender, BMI at infliximab initiation and last follow up, disease subtype, maintenance therapy trough level, number of infliximab infusions per year, and final infliximab dose) were significant in predicting either dose optimization or LOR.

Characteristics between therapeutic and subtherapeutic trough levels. The median BMI of patients with therapeutic and subtherapeutic trough levels was similar at 19.9 kg/m^2 (IQR, 17.3–23.8) and 19.7 kg/m^2 (IQR, 17.4–21.9), respectively (Table S2). However, we observed a numerical difference in mean infliximab mg/kg dose associated with therapeutic compared to subtherapeutic trough concentrations (9.4 ± 0.25 *vs* 8.7 ± 0.38 mg/kg), although this failed to reach statistical significance (Table S2, $P = 0.054$). Notably, the mean dosing interval was significantly shorter in therapeutic than subtherapeutic trough level groups (5.2 ± 0.13 *vs* 6.4 ± 0.21 weeks, $P < 0.001$). As expected, significantly more patients with therapeutic trough levels had a C. reactive protein (CRP) <5 mg/L (84.8 *vs* 62.5%, $P = 0.012$), while no significant difference was found between erythrocyte sedimentation rate (ESR), PCDAI ($n = 123$), and PUCAI ($n = 45$) scores in patients with therapeutic and subtherapeutic trough levels (Table S2).

Discussion

In this single-center study on a well-characterized cohort of pediatric IBD patients on infliximab, we report that excess weight gain was not associated with higher weight-based mg/kg dosing, more frequent dose optimization, lower serum trough levels, or increased risk of treatment failure. Although dose optimization was more frequent in patients who eventually failed infliximab, this was not significantly more common in patients with excess weight gain, whether they responded to or failed infliximab therapy. Further to our secondary aims, therapeutic trough levels were associated with significantly shorter mean dosing intervals and significantly lower CRP levels than subtherapeutic trough levels, although no significant difference was found in infliximab dose, ESR, PCDAI, and PUCAI scores.

Our study adds to the body of evidence that infliximab use in children with IBD is associated with excess weight gain.[5,6] Appropriate weight gain is an important therapeutic goal and is likely due to a combination of factors, including a reduction in inflammatory burden and circulating inflammatory mediators and an increase in appetite and caloric intake. Mechanisms underlying excessive weight gain on anti-TNF therapy remain to be determined. Previous studies on rheumatoid arthritis patients have reported a lack of gain in muscle mass with anti-TNF therapy, suggesting that weight gain is due in part to an increase in fat mass, although these studies did not extend beyond 24 weeks.[12,13] Anti-TNF therapy may also contribute to an ongoing increase in appetite and weight gain through effects on ghrelin, leptin, and adiponectin, with the added potential confounding effect of genetic polymorphisms.[14–16]

Although obesity is recognized as a potential state of chronic low-grade inflammation,[17] it did not negatively impact CRP levels. Obesity has also been identified as a risk factor for increased clearance in population-based pharmacokinetic studies of anti-TNF agents; however, there was no significant difference in infliximab trough levels between patient groups in our study.[18–21]

Table 3 Patient characteristics and maintenance trough concentrations

	Total cohort (n = 169)	Normal BMI (18.5–24.9 kg/m^2) (n = 143)	Overweight (25–29.9 kg/m^2) (n = 18)	Obese (>30 kg/m^2) (n = 8)
Patient characteristics				
Gender (males: females)	0.92	0.91	0.64	3
BMI (kg/m^2) (median, IQR)	19.9 (17.3–23.1)	19.3 (17.1–21.4)	26.1 (25.4–27.6)	32.7 (31.4–37.5)
Infliximab characteristics				
Age at IFX Trough Level, y (median, IQR)	15.6 (13.2–17.0)	15.5 (13.1–16.9)	16.9 (15.5–17.4)	17.2 (15.7–17.5)
Length of time from IFX initiation to trough level, months (median, IQR)	18.6 (8.1–34.8)	17.7 (8.6–37.1)	24.3 (8.1–33.9)	9.8 (4.1–29.6)
Trough concentration (μg/mL) (median, IQR)	5.9 (3.9–10.3)	5.7 (3.9–9.6)	8.5 (5.7–11.0)	5.6 (4.8–12.8)
Patients with therapeutic trough concentrations (≥5 μg/mL), n (%)	105 (62.1)	85 (59.4)	14 (77.8)	6 (75)
Patients with subtherapeutic trough concentrations (<5 μg/mL), n (%)	64 (37.9)	58 (40.6)	4 (22.2)	2 (25)

BMI, body mass index; IFX, infliximab; IQR, interquartile range.

Responders with excess weight gain had significantly higher absolute infliximab dosing, although weight-based dosing was similar between groups (7.7 *vs* 8.2 mg/kg with excess weight gain *vs* normal BMI) and between CD and UC/IBD-U patients (7.6 mg/kg for CD and 8.8 mg/kg for UC/IBDU with excess weight gain *vs* 7.7 mg/kg for CD and for 8.4 mg/kg UC/IBDU with normal BMI). Furthermore, in keeping with the findings of Singh *et al*., our results suggest that obesity did not adversely influence infliximab efficacy when administered in a weight-based dosing regimen.[10] Notably, excess weight gain was not associated with a significant difference in the proportion of patients with subtherapeutic infliximab trough levels (23% in overweight/obese *vs* 40.6% in normal BMI cohorts) or in the proportion of patients with LOR (16.7% in overweight/obese *vs* 13.4% in normal BMI groups). Furthermore, in CD and UC/IBD-U patients with excess weight gain, no significant difference in the proportion of patients with subtherapeutic infliximab trough levels was noted compared to those with normal BMI (22.2% in overweight/obese CD and 20% in overweight UC/IBDU *vs* 43.4% in normal BMI CD and 30.8% in normal BMI UC/IBDU) or in the proportion of patients who failed infliximab (12.5% in overweight/obese CD and 25% in overweight/obese UC/IBDU *vs* 12.0% in normal BMI CD and 17.6% in overweight UC/IBDU). Similarly, Bhalme *et al*. reported no significant effect of BMI on LOR in adult CD patients on a weight-adjusted infliximab dosing regime, whereas in adult CD patients on adalimumab, an increased BMI was associated with an increased hazard of LOR (P = 0.045).[2] While Bond *et al*. found no relationship between BMI and infliximab trough levels, they also found no relationship with adalimumab.[22] Conversely, three studies involving 518 adult CD patients on infliximab reported that patients with a high BMI had more rapid and frequent LOR to infliximab.[8,9,23] It is possible that infliximab dosing was not adjusted appropriately and obese patients may not have received optimal weight-appropriate therapy. Seminerio *et al*. reported suboptimal infliximab dosing in obese patients with an average dose of approximately 4 mg/kg in class III obesity compared to 6.4 mg/kg in overweight patients and 7.9 mg/kg in patients with a normal BMI.[24] Through close monitoring, adjusting for key confounding variables, and adequate drug exposure, we are able to show that obesity may not be an important modifier in infliximab response in pediatric IBD patients.

Consistent with our findings, the recent publication from the ImproveCareNow registry reporting on a large retrospective pediatric CD cohort (n = 898, 87 overweight and 43 obese) noted that health-care visits, number of patients in corticosteroid-free remission, and use of medications were similar among obese and nonobese patients.[25] Moreover, in a meta-analysis of seven (two CD, five IBD) studies, obese patients were significantly less likely to undergo IBD-related surgery and hospitalization.[26] Conversely, in a large retrospective adult CD cohort (n = 2065, 3% obese)[27] and a pediatric IBD cohort (n = 100, 15% obese), a more severe clinical course was reported in obese patients.[28] Further studies are warranted to prospectively evaluate the impact of obesity on IBD course and drug responses.

Although our analysis did not demonstrate a correlation between corticosteroid use and weight gain, the adverse long-term metabolic effects of corticosteroids on muscle and fat composition and beneficial steroid-sparing effect of anti-TNF therapy warrants further study. Notably, corticosteroid use in our cohort increased the odds of infliximab failure. While the mechanisms responsible remain to be determined, it is possible that disease severity and potential steroid-induced alterations in immunological and biological responses played a role.

Our study has a number of strengths. Our cohort consists of a well-characterized, closely followed group of patients. Furthermore, compared to a number of earlier studies, we used stricter criteria for the classification of obesity. In addition, we incorporated a weight-based infliximab dosing regime and serum infliximab trough levels. However, there are several limitations inherent to our study. The data were collected in a retrospective manner; therefore, there was no standardized approach to recording patient data, although our IBD practice is largely standardized. Serum infliximab trough concentrations were not always performed in a routine manner as some patients had trough concentrations evaluated routinely and proactively, whereas other patients had trough concentrations taken based on a reactive strategy. Consequently, only maintenance therapy trough levels were recorded and compared. Despite this limitation, we were able to evaluate the relationship between BMI, trough levels, and clinical/biochemical markers of disease severity. In addition, only

treatment discontinuation was considered treatment failure. Another limitation is that infliximab dose change was initially based on weight/weight gain and not trough levels, limiting our ability to determine the impact of excess weight gain on infliximab trough concentrations. Finally, children gain weight naturally during growth that potentially confounds the relationship between infliximab and weight gain. This was addressed by multivariate analysis determining that neither age nor gender predicted dose optimization or response.

In conclusion, our study indicates that, in a cohort of pediatric IBD patients on infliximab maintenance therapy, 10.3% of the cohort demonstrated excess weight gain. This weight gain was not associated with higher weight-based mg/kg infliximab dosing, lower serum infliximab trough levels, or increased risk of treatment failure. It is currently unclear whether obesity in IBD patients influences the response to fixed-dose biologic agents. Prospective cohort studies are warranted to confirm these findings and to further study the impact of excess weight gain on response to biologic therapies.

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References

1 Eustace GJ, Melmed GY. Therapy for Crohn's disease: a review of recent developments. *Curr. Gastroenterol. Rep.* 2018; **2**: 19.
2 Bhalme M, Sharma A, Keld R, Willert R, Campbell S. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? *Eur. J. Gastroenterol. Hepatol.* 2013; **25**: 543–9.
3 De Bie CI, Escher JC, De Ridder L. Antitumor necrosis factor treatment for pediatric inflammatory bowel disease. *Inflamm. Bowel Dis.* 2012; **18**: 985–1002.
4 Shan J, Zhang J. Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: a systematic review and meta-analysis. *Joint Bone Spine*. 2018; **86**: 173–83.
5 Nakahigashi M, Yamamoto T. Increases in body mass index during infliximab therapy in patients with Crohn's disease: an open label prospective study. *Cytokine*. 2011; **56**: 531–5.
6 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**: 3110–16.
7 Kurnool S, Nguyen NH, Proudfoot J *et al*. High body mass index is associated with increased risk of treatment failure and surgery in biologic-treated patients with ulcerative colitis. *Aliment. Pharmacol. Ther.* 2018; **47**: 1472–9.
8 Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm. Bowel Dis.* 2013; **19**: 2118–24.
9 Brown P, Clark T, Dowson G *et al*. Relationship of body mass index to clinical outcomes after infliximab therapy in patients with Crohn's disease. *J. Crohns Colitis*. 2016; **10**: 1144–50.
10 Singh S, Proudfoot J, Xu R, Sandborn WJ. Obesity and response to infliximab in patients with inflammatory bowel diseases: pooled analysis of individual participant data from clinical trials. *Am. J. Gastroenterol.* 2018; **19**: 2118–24.
11 Vande Casteele N, Ferrante M, Van Assche G *et al*. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015; **148**: 1320–9.
12 Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. *Am. J. Clin. Nutr.* 2006; **84**: 1463–72.
13 Metsios GS, Stavropoulos-kalinoglou A, Douglas KMJ *et al*. Blockade of tumour necrosis factor-α in rheumatoid arthritis: effects on components of rheumatoid cachexia. *Rheumatology*. 2007; **6**: 445–51.
14 Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A *et al*. Anti-tumour necrosis factor therapy modulates ghrelin in patients with severe rheumatoid arthritis. *Ann. Rheum. Dis.* 2008; **67**: 1644–6.
15 Karagiozoglou-Lampoudi T, Trachana M, Agakidis C *et al*. Ghrelin levels in patients with juvenile idiopathic arthritis: relation to anti-tumor necrosis factor treatment and disease activity. *Metabolism*. 2011; **60**: 1359–62.
16 Chen C-Y, Tsai C-Y, Lee P-C, Lee S-D. Long-term etanercept therapy favors weight gain and ameliorates cachexia in rheumatoid arthritis patients: roles of gut hormones and leptin. *Curr. Pharm. Des.* 2013; **19**: 1956–64.
17 Singh S, Dulai PS, Zarrinpar A, Ramamoorthy S, Sandborn WJ. Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. *Nat. Rev. Gastroenterol. Hepatol.* 2017; **60**: 1359–62.
18 Dotan I, Ron Y, Yanai H *et al*. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm. Bowel Dis.* 2014; **20**: 2247–59.
19 Mostafa NM, Nader AM, Noertersheuser P, Okun M, Awni WM. Impact of immunogenicity on pharmacokinetics, efficacy and safety of adalimumab in adult patients with moderate to severe chronic plaque psoriasis. *J. Eur. Acad. Dermatology Venereol.* 2017; **31**: 490–7.
20 Passot C, Mulleman D, Bejan-Angoulvant T *et al*. The underlying inflammatory chronic disease influences infliximab pharmacokinetics. *MAbs*. 2016; **8**: 1407–16.
21 Wade JR, Parker G, Kosutic G *et al*. Population pharmacokinetic analysis of certolizumab pegol in patients with Crohn's disease. *J. Clin. Pharmacol.* 2015; **55**: 866–74.
22 Bond A, Asher R, Jackson R *et al*. Comparative analysis of the influence of clinical factors including BMI on adalimumab and infliximab trough levels. *Eur. J. Gastroenterol. Hepatol.* 2016; **28**: 271–6.
23 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.
24 Seminerio JL, Koutroubakis IE, Ramos-Rivers C *et al*. Impact of obesity on the management and clinical course of patients with inflammatory bowel disease. *Inflamm. Bowel Dis.* 2015; **21**: 2857–63.
25 Jain A, Bricker J, Kappelman MD, Dotson JL. Obesity does not affect early outcomes in children with newly diagnosed Crohn disease. *J. Pediatr. Gastroenterol. Nutr.* 2018; **67**: 622–5.

26 Hu Q, Ren J, Li G, Wu X, Li J. The impact of obesity on the clinical course of inflammatory bowel disease: a meta-analysis. *Med. Sci. Monit.* 2017; **23**: 2599–606.
27 Blain A, Cattan S, Beaugerie L, Carbonnel F, Gendre JP, Cosnes J. Crohn's disease clinical course and severity in obese patients. *Clin. Nutr.* 2002; **21**: 51–7.
28 Yerushalmy-Feler A, Ben-Tov A, Weintraub Y *et al*. High and low body mass index may predict severe disease course in children with inflammatory bowel disease. *Scand. J. Gastroenterol.* 2018; **53**: 708–13.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 Medications during time of infliximab.

Table S2 Clinical variables associated with maintenance infliximab trough concentrations.