Original Article

Impact of obesity on disease activity and disease outcome in inflammatory bowel disease: Results from the Swiss inflammatory bowel disease cohort

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Abstract

Objective: The purpose of this study was to investigate the impact of obesity on disease activity and disease outcome in patients with inflammatory bowel disease.

Patients and methods: The impact of obesity on inflammatory bowel disease disease activity and outcome was retrospectively assessed in 3075 patients enrolled in the prospective nation-wide Swiss inflammatory bowel disease cohort between July 2006 and September 2018. Baseline characteristics, disease activity and disease course in 325 obese inflammatory bowel disease patients (body mass index $\geq$30 kg/m^2) were compared to 1725 normal weight inflammatory bowel disease individuals (body mass index 18.5-24.9).

Results: Among 3075 patients in the prospective Swiss inflammatory bowel disease cohort, 325 patients (10.6%) were obese, namely, 194 Crohn's disease patients, 131 ulcerative colitis, and inflammatory bowel disease-unclassified patients. Disease activity scores were elevated in obese Crohn's disease (Crohn's Disease Activity Index 33 vs 20, $p = 0.001$), but not ulcerative colitis patients. Obese Crohn's disease, but not ulcerative colitis patients were less likely to be in remission based on a Crohn's Disease Activity Index less than 100 and a calprotectin less than 100 ug/g. In a multivariate regression model, obesity was negatively associated with disease remission in Crohn's disease (odds ratio 0.610, 95% confidence interval 0.402–0.926, $p = 0.020$), but not ulcerative colitis. Increased soft stool frequency was observed in both obese Crohn's disease and ulcerative colitis patients. Adjusted Cox regression models revealed increased risk of complicated disease course in obese Crohn's disease patients (hazard ratio 1.197, 95% confidence interval 1.046–1.370, $p = 0.009$). No association between obesity and disease progression, index treatment failure was seen neither in Crohn's disease nor ulcerative colitis.

Conclusion: Obesity is associated with decreased rates of disease remission and increased risk of complicated disease course in Crohn's disease over a six-year follow-up period. No effects were seen on disease progression and index treatment failure neither in Crohn's disease nor ulcerative colitis.

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Key Summary

What is known

- Prevalence of obesity, defined as a body mass index (BMI) of $\geq$30 kg/m^2, has dramatically increased over the past 25 years and reached epidemic proportions.
- Obesity is common among patients with inflammatory bowel disease (IBD).
- Data on the impact of a BMI of $\geq$30 kg/m^2 on IBD disease outcome have been conflicting.

What is new

In our nationwide Swiss IBD cohort:

- Obesity rate in IBD patients was 11%.
- Obese Crohn's disease (CD), but not ulcerative colitis (UC) patients showed increased disease activity scores compared to normal weight individuals.
- Adjusted Cox regression models revealed increased risk of a complicated disease course in obese CD patients over a six-year follow-up period.
- No association between obesity and disease progression, index treatment failure was seen neither in CD nor UC.

Introduction

Inflammatory bowel disease (IBD), with its two subtypes of Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract that can result in malabsorption syndrome.[1] However, in IBD clinical practice both overweight and obese patients are frequently encountered.[2]

Prevalence of being overweight, defined as a body mass index (BMI) of $\geq$25 kg/m^2, and obesity (BMI $\geq$30 kg/m^2) has dramatically increased over the past 25 years and reached epidemic proportions.[3] It is estimated that 2.1 billion people suffer from overweight and 600 m suffer from obesity worldwide.[4] Paralleling growing rates of obesity, prevalence and incidence of IBD have been increasing over the past years.[5–7] In IBD, rates of obesity also appear to be on the rise.[8,9] In the USA, it is currently estimated that 15–40% of IBD patients are obese.[2] It is currently not entirely clear whether increasing obesity rates are causally linked with higher IBD rates. At least, premorbid obesity has been recently associated with the development of CD, but not UC.[10] Obesity-associated dysbiosis might be a contributing factor.[2] Obesity has further been demonstrated to increase the risk of autoimmune disorders, such as rheumatoid arthritis, psoriasis and psoriatic arthritis.[11,12] In terms of mechanism, mesenteric fat has been shown to be an important source of C-reactive protein (CRP) triggering local inflammation and bacterial translocation in CD.[13]

Despite these mechanistic insights, data on the impact of obesity on disease activity and course in IBD patients have been conflicting.[2] It is known from other autoimmune disorders, that obesity can negatively affect disease activity and result in worse outcomes.[14,15] Obesity *per se* represents a chronic, low-grade inflammatory state and might perpetuate the release of pro-inflammatory cytokines.[15] It has been further shown that obesity is associated with inadequate response to anti-tumour necrosis factor (anti-TNF) treatment in several immune-mediated diseases.[16] However, in CD obesity has not been consistently associated with increased prevalence of IBD-related complications, while in UC a cohort of 202 patients did not reveal an association between obesity and disease severity.[2,17,18] To date it is not known if weight reduction should be uniformly recommended in IBD practice, and whether a decrease of BMI has a positive impact on future disease course. Contrary to

expectations, weight loss might even negatively affect IBD; in a case series from Mayo Clinic higher incidence rates of *de novo* IBD cases after bariatric surgery were observed, although it has yet to be determined whether this is a direct effect of weight loss or rather a consequence of changes in the microbiome post-surgically.[19]

In light of these uncertainties, we used prospectively collected data from the nation-wide Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) to investigate the impact of obesity on disease activity and disease course in patients with IBD.

Methods

Study design

This study was a retrospective analysis of prospectively obtained data from the SIBDCS. Enrolment into the SIBDCS started in 2006 with patient recruitment from all regions across Switzerland. All patients had been previously diagnosed with IBD according to international guidelines.[20,21] The SIBDCS is funded by the Swiss National Science Foundation (SNSF). Institutional review board (IRB) approval has been obtained from the local ethics committee of each participating centre (IRB approval number EK-1316, approved on 5 February 2007). All patients had provided written informed consent prior to inclusion into the SIBDCS.[22]

Study population and data collection

Inclusion criteria for the SIBDCS have been published elsewhere.[22] Patients included in the SIBDCS undergo structured assessment of disease activity at baseline and during annual follow-up visits. Detailed questionnaires are completed by both the patient and the respective IBD physician. For the purpose of this study, we included normal weight and obese IBD patients. The following inclusion criteria were applied: (a) diagnosis of UC or CD; (b) enrolment into the SIBDCS between 2006–2018; (c) available data on weight and BMI at enrolment and during follow-up. Data were collected up to 6 September 2018. For the longitudinal analyses of the development of complications, we excluded patients with complications (see definitions) at baseline, and at least one annual follow-up visit was required.

Definitions and outcome measures

Normal weight was defined as a BMI of 18.5–24.9 kg/m^2, and for the definition of obesity the threshold of $\geq$30 kg/m^2 was used. The following parameters were assessed: (a) clinical disease activity measured by the Crohn's Disease Activity Index (CDAI) for CD[23] and the modified Truelove Witts Activity Index (MTWAI)

for UC;[24,25] (b) disease location at diagnosis, enrolment and follow-up according to the Montreal classification (L1–L4 in CD and E1–E3 in UC);[26] (c) disease behaviour in CD according to the Montreal classification (B1–B3);[26] (d) quality of life measured by the IBDQ and the SF-36 questionnaire;[27,28] (e) biological disease activity measured by CRP and faecal calprotectin; and (f) presence of extraintestinal manifestations (EIMs). The following EIMs were reported and analysed: arthritis/inflammatory arthralgia, pyoderma gangrenosum, erythema nodosum, aphthous stomatitis/oral ulcers, axial spondylarthropathy, uveitis/iritis and primary sclerosing cholangitis.

To assess whether or not obesity affects disease course, we looked at three different outcomes as follows:

Disease progression:
- CD: progression from inflammatory (B1) to penetrating/fibrostenotic phenotype (B2, B3).
- UC: more proximal extension (E1 to E2/E3, E2 to E3).

Disease complications:
- CD: development of fistula (perianal, non-perianal, any fistula), development of strictures (intestinal stenosis), surgery (intestinal resection, fistula and abscess surgery) and hospitalization.
- UC: surgery (intestinal resection) and hospitalization.

Index treatment failure:
- Need for new anti-TNF.

Statistical analyses

All statistical analyses were performed with the statistical package program STATA (version 13.1, College Station, Texas, USA). Data distribution was analysed using Normal-QQ-Plots. Quantitative data are presented as (a) mean and standard deviation (SD) for normally data; and (b) median and interquartile range (IQR) in the case of a non-normal distribution. Categorical data are summarised as percentage of the total group. Quantitative data were compared using Student's *t*-test for normally distributed data and using Wilcoxon rank-sum test for non-normally distributed data. Categorical data were compared using the chi-square test. For assessment of development of complications, Kaplan-Meier curves and Cox proportional hazard models were computed. Cox proportional hazard models were adjusted (multivariate) for baseline disease modifiers (sex, age at diagnosis, smoking at baseline and steroid treatment at baseline) to generate an adjusted hazard ratio (HR), the Bonferroni method was applied in order to avoid random significance generation where applicable.

For the purpose of this study, a *p*-value of <0.05 was considered statistically significant.

Results

Patient characterization

Characteristics of the patients considered for the purposes of these analyses are shown in Table 1. Of the total 3075 patients enrolled in the SIBDCS (median BMI of 23.9 kg/m^2, IQR 21.3–26.7, range 13.7–56.8), we identified 325 patients (10.6%) with an obese BMI of $\geq$30 kg/m^2 (median BMI of 32.9 kg/m^2, IQR 31.1–35.3, range 30.0–56.8). Of those 325 patients, 194 were diagnosed with CD (59.7%) and 131 with UC/IBD

unclassified (IBD-U) (40.3%). Their median age at IBD diagnosis was 32 years (IQR 24–43) with a disease duration of 13 years (IQR 7–21). Eighty-four patients were current smokers (25.9%). Median follow-up within the IBD cohort was 6.0 years (IQR 3.6–9.0). Compared to normal weight patients, obese CD and UC patients were older at diagnosis and study enrolment (age at diagnosis 31 years vs 25 years, $p < 0.001$ for CD patients and 34 years vs 29 years, $p < 0.001$ for UC patients). Among obese UC patients, more male patients were observed when compared to normal weight individuals (60.3 vs 47.2%, $p = 0.006$). Obese CD patients were less likely to be treated with steroids (39.7 vs 48.6%, $p = 0.023$). There were no further differences between obese and normal weight patients

Table 1. Patient demographics and disease characteristics in all patients and stratified by inflammatory bowel disease (IBD) subtype.

	All patients			Crohn's disease			Ulcerative colitis/IBD-U		
BMI category	Normal	Obese	*p*	Normal	Obese	*p*	Normal	Obese	*p*
Number of patients	1725	325		977	194		748	131	
Gender									
Male	778 (45.1)	164 (50.5)		425 (43.5)	85 (43.8)		353 (47.2)	79 (60.3)	
Female	947 (54.9)	161 (49.5)	0.075	552 (56.5)	109 (56.2)	0.936	395 (52.8)	52 (39.7)	**0.006**
Diagnosis									
CD	977 (56.6)	194 (59.7)							
UC	709 (41.1)	123 (37.9)							
IBD-U	39 (2.3)	8 (2.5)	0.546						
Age at diagnosis	26, 20–35	32, 24–43		25, 19–34	31, 23–42		29, 21–37	34, 26–43	
(median, IQR, range)	1–82	10–78	**<0.001**	1–81	10–78	**<0.001**	7–82	12–73	**<0.001**
Age at enrolment	37, 27–49	45, 36–56		37, 26–50	44, 35–56		38, 29–47	46, 36–55	
(median, IQR, range)	17–85	18–85	**<0.001**	17–85	18–65	**<0.001**	17–84	18–81	**<0.001**
Disease duration	12, 6–50	13, 7–21		12, 6–21	13, 7–22		11, 6–18	13, 7–20	
(median, IQR, range)	0–59	0–49	0.079	0–57	0–47	0.405	0–59	0–49	0.102
Previous treatment									
5-ASA	1274 (73.9)	245 (75.4)	0.564	570 (58.3)	118 (60.8)	0.521	704 (94.1)	127 (97.0)	0.294
Steroids	1447 (83.9)	265 (81.5)	0.296	843 (86.3)	164 (84.5)	0.522	604 (80.8)	101 (77.1)	0.334
Immunomodulators	1244 (72.2)	249 (76.6)	0.094	796 (81.5)	162 (83.5)	0.503	448 (59.9)	87 (66.4)	0.158
CNI	104 (6.0)	17 (5.2)	0.575	20 (2.1)	4 (2.1)	1.000	84 (11.2)	13 (9.9)	0.660
Anti-TNF	845 (49.0)	169 (52.0)	0.319	590 (60.4)	123 (63.4)	0.432	255 (34.1)	46 (35.1)	0.820
Current treatment									
5-ASA	818 (47.4)	154 (47.4)	0.991	237 (24.3)	52 (26.8)	0.452	581 (77.7)	102 (77.9)	0.962
Steroids	828 (48.0)	139 (42.8)	0.083	475 (48.6)	77 (39.7)	**0.023**	353 (47.2)	62 (47.3)	0.977
Immunomodulators	872 (50.6)	185 (56.9)	**0.035**	552 (56.5)	123 (63.4)	0.076	320 (42.8)	62 (47.3)	0.333
CNI	39 (2.3)	9 (2.8)	0.578	3 (0.3)	1 (0.5)	0.516	36 (4.8)	8 (6.1)	0.531
Anti-TNF	717 (41.6)	142 (43.7)	0.476	519 (53.1)	105 (54.1)	0.798	198 (26.5)	37 (28.2)	0.672
History of surgery									
No	1139 (66.0)	215 (66.2)		486 (49.7)	106 (54.6)		665 (88.9)	113 (86.3)	
Yes	586 (34.0)	110 (33.8)	0.965	491 (50.3)	88 (45.4)	0.213	83 (11.1)	18 (13.7)	0.381
Smoking status									
Non-smoker	1288 (74.7)	239 (73.5)		654 (66.9)	129 (66.5)		634 (84.8)	110 (84.0)	
Smoker	428 (24.8)	84 (25.9)		320 (32.8)	63 (32.5)		108 (14.4)	21 (16.0)	
Unknown	9 (0.5)	2 (0.6)	0.773	3 (0.3)	2 (1.0)	0.339	6 (0.8)	0 (0.0)	0.683

5-ASA: aminosalicylates; anti-TNF: anti-tumour necrosis factor; BI: body mass index; CD: Crohn's disease; CNI: calcineurin inhibitor; IBD-U: IBD unclassified; IQR: interquartile range; UC: ulcerative colitis.

with regards to disease duration, past and current anti-TNF and/or immunomodulatory treatment, surgical history and smoking status, neither in CD nor UC patients.

Disease activity

Disease behaviour was comparable between obese and normal weight CD patients. However, obese CD patients were less likely to have isolated ileal disease L1 (14.4 vs 24.3%, $p = 0.003$). Despite lower rates of stenosis (33 vs 43.1%, $p = 0.009$), obese CD patients had higher CDAI scores (median 33 vs 20, $p = 0.001$) and CRP levels (5 vs 3 mg/l, $p < 0.001$) compared to normal weight individuals. In fact, obese CD patients were less likely to be in remission based on a CDAI of < 100 (94.7% vs 97.8%, $p = 0.017$) and a faecal calprotectin of < 100 ug/g (25.6% vs 46.4%, $p = 0.015$), but not based on a faecal calprotectin of < 250 ug/g. Frequency of soft stools was also increased (8 vs 4 per week, $p = 0.001$). Obese CD patients reported higher prevalence of EIMs (63.4 vs 54.4%, $p = 0.020$), particularly arthritis/arthralgia (57.2 vs 46.2%; $p = 0.005$) and axial spondylarthropathy (9.8 vs 5.7%, $p = 0.035$. For details see Table 2. As the impact of obesity on disease activity at baseline might be confounded by numerous factors, particularly IBD medication, disease duration, smoking and age, we performed a multivariate logistic regression (dependent variable CDAI < 100). In this model, obesity remained significantly associated with disease activity. As indicated by an odds ratio (OR) < 1, a BMI of ≥ 30 kg/m^2 was an independent negative predictor for presence of disease remission (OR 0.610, 95% CI 0.402–0.926, $p = 0.020$). For details see Supplementary Material Table 1.

No difference in terms of disease location and extent was seen between obese and normal weight UC patients. We observed differences in the number of bowel movements ($p = 0.021$) and CRP levels (4 vs 2 mg/l, $p = 0.008$) between obese and normal weight UC patients, but not in terms of clinical activity score (MTWAI), number of bloody stools, faecal calprotectin and presence of any EIMs (Table 3). Remission rates were not different between the two groups based on a MTWAI of < 3 (63.1 vs 63.4%, $p = 0.944$) and a faecal calprotectin of < 100 ug/g (48.1 vs 53.2%, $p = 0.630$). Using the same multivariate logistic regression model as in CD, obesity status did not predict disease remission (defined as MTWAI < 3) after correction for confounding factors (Supplementary Material Table 2).

Quality of life

Quality of life was affected in obese CD and UC patients, although to a lesser extent in the latter group. IBDQ systemic and social scores (23 vs 26, $p = 0.001$, 31 vs 34, $p = 0.005$) as well as SF-36 physical score (47 vs 51, $p < 0.001$) were decreased in obese compared to normal weight CD patients. We observed no difference in terms of use of medical resources and absence from work in the past 3 months between obese and normal weight patients, neither in CD nor UC (Tables 2 and 3).

Disease outcome

To investigate the impact of obesity on disease course, we analysed the follow-up of all obese patients – stratified by IBD subtype – and compared them to normal weight individuals. There was no difference with regards to the length of the total follow-up between the two groups (6.0 vs 5.9 years).

In CD, obesity was negatively associated with disease progression (HR 0.804, 95% CI 0.662–0.977, $p = 0.029$). However, in the adjusted model (corrected for sex, age at diagnosis, smoking at baseline and steroid treatment at baseline), there was no difference between obese and non-obese CD patients (HR 0.926 (95% CI: 0.759–1.129, $p = 0.445$). In the univariate model, there was no significant association between obesity and development of disease complications. However, when adjusting for above mentioned modifiers, obese patients were more likely to develop complicated disease in the follow-up period (HR 1.197, 95% CI 1.046–1.370, $p = 0.009$). While there was an association between obesity and index treatment failure in the univariate analysis (HR 0.864, 95% CI 0.769–0.970, $p = 0.014$), this association was no longer significant after adjusting for confounding factors (HR 0.954, 95% CI 0.848–1.076, $p = 0.439$) nor multivariate analysis.

In UC patients, we did not detect significant association of obesity with disease progression (HR 0.936, 95% CI 0.722–1.215, $p = 0.620$), disease complications (HR 1.136, 95% CI 0.864–1.494, $p = 0.362$) nor index treatment failure (HR 0.966, 95% CI 0.804–1.161, $p = 0.712$). However, in the adjusted model, obese patients showed a clear trend towards higher rates of complicated disease (HR 1.315, 95% CI 0.997–1.735, $p = 0.052$). For details see Figure 1 (Kaplan-Meier curves and unadjusted/adjusted HR).

Discussion

Obesity is common among patients with IBD. Data on the impact of a BMI of ≥ 30 kg/m^2 on IBD disease outcome have been conflicting.[2] We investigated the

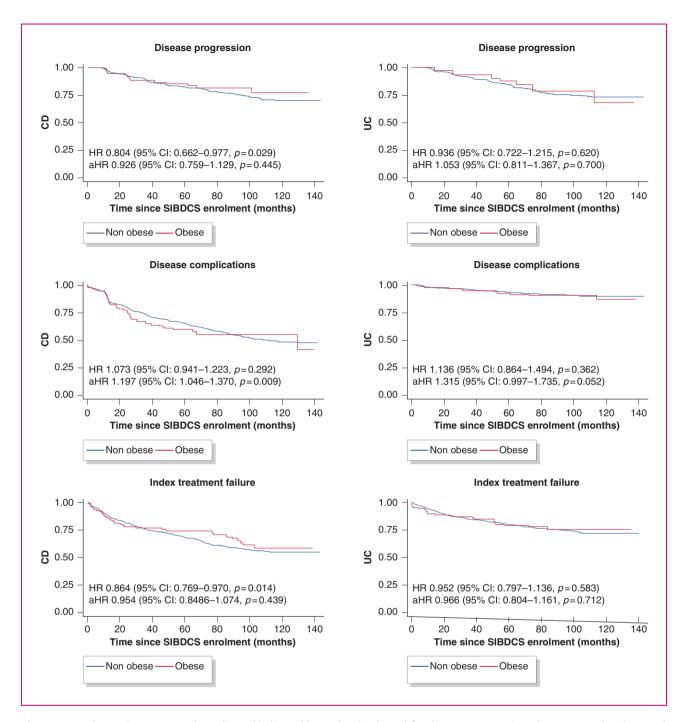**Table 2.** Disease activity and quality of life in Crohn's disease.

BMI category	Normal (*n* = 977)	Obese (*n* = 194)	*p*
Fistulas			
Perianal	237 (24.3)	50 (25.8)	0.654
Any	323 (33.1)	65 (33.5)	0.904
Abscess			
No	744 (76.2)	148 (76.3)	
Yes	233 (23.8)	46 (23.7)	0.967
Intestinal stenosis			
No	556 (56.9)	130 (67.0)	
Yes	421 (43.1)	64 (33.0)	**0.009**
Behaviour			
B1 (inflammatory)	364 (37.3)	87 (44.9)	
B1p (B1 + perianal disease)	144 (14.7)	31 (16.0)	
B2 (stricturing)	200 (20.5)	28 (14.4)	
B2p (B2 + perianal disease)	124 (12.7)	20 (10.3)	
B3 (penetrating)	72 (7.4)	11 (5.7)	
B3p (B3 + perianal disease)	73 (4.5)	17 (8.8)	0.195
EIM			
Arthritis	451 (46.2)	111 (57.2)	**0.005**
Uveitis/iritis	104 (10.6)	27 (13.9)	0.187
PG	12 (1.2)	2 (1.0)	1.000
EN	67 (6.9)	19 (9.8)	0.174
Oral ulcers	141 (14.4)	25 (12.9)	0.573
AS	56 (5.7)	19 (9.8)	**0.035**
PSC	8 (0.8)	1 (0.5)	1.000
Any	531 (54.4)	123 (63.4)	**0.020**
CDAI score	20, 6–53	33, 6–69	
(median, IQR, range)	0–345	0–280	**0.001**
Number of soft stools	4, 0–14	8, 0–25	
(median, IQR, range)	0–140	0–100	**0.001**
Disease location at diagnosis			
L1 (ileal)	237 (24.3)	28 (14.4)	
L2 (colonic)	195 (20.0)	45 (23.2)	
L3 (ileo-colonic)	449 (46.0)	88 (45.4)	
L4 (upper GI only)	10 (1.0)	1 (0.5)	
Unknown/Unclear	86 (8.8)	32 (16.5)	**0.002**
CRP in mg/l	3, 1–7	5, 3–12	
(median, IQR, range)	0–155	0–245	**<0.001**
Faecal calprotectin in ug/g	105, 32–293	139, 61–296	
(median, IQR, range)	0–3500	15–1835	0.467
IBDQ Bowel score	59, 51–65	57, 49–63	
(median, IQR, range)	22–70	30–70	0.071
IBDQ Systemic score	26, 21–30	23, 19–28	
(median, IQR, range)	7–35	9–35	**0.001**
IBDQ Emotional score	68, 57–75	66, 56–76	
(median, IQR, range)	14–84	28–84	0.922
IBDQ Social score	34, 28–35	31, 26–35	
(median, IQR, range)	6–35	7–35	**0.005**
IBDQ Total score	185, 159–202	177, 150–198	
(median, IQR, range)	66–224	78–223	0.091
SF36 Physical score	51, 44–56	47, 36–53	
(median, IQR, range)	16–72	13–67	**<0.001**
SF36 Mental score	47, 38–54	48, 38–55	
(median, IQR, range)	10–66	18–66	0.285
Medical resources consumption (in last 3 months)			
Hospitalization	71 (14.7)	21 (21.0)	0.114
Outpatient visit	164 (33.7)	28 (28.3)	0.297
Work absence (in last 3 months)			
No	315 (86.5)	45 (80.4)	
Yes	49 (13.5)	11 (19.6)	0.218

AS: axial spondylarthropathy; BMI: body mass index; CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; EIM: extraintestinal manifestation; EN: erythema nodosum; GI: gastro-intestinal; IQR: interquartile range; PG: pyoderma gangrenosum; PSC: primary sclerosing cholangitis.

Table 3. Disease activity and quality of life in ulcerative colitis.

BMI category	Normal (*n* = 748)	Obese (*n* = 131)	*p*
EIM			
Arthritis	250 (33.4)	56 (42.8)	**0.039**
Uveitis/iritis	46 (6.2)	10 (7.6)	0.521
PG	9 (1.2)	3 (2.3)	0.402
EN	29 (3.9)	4 (3.1)	0.806
Oral ulcers	47 (6.3)	5 (3.8)	0.270
AS	18 (2.4)	6 (4.6)	0.159
PSC	41 (5.5)	1 (0.8)	**0.014**
Any	325 (43.5)	59 (45.0)	0.735
MTWAI score	2, 0–4	2, 1–4	
(median, IQR, range)	0–17	0–16	0.136
Total number of bowel movement/day			
1–2	438 (60.8)	59 (45.7)	
3–4	133 (18.5)	35 (27.1)	
5–6	75 (10.4)	15 (11.6)	
7–9	38 (5.3)	9 (7.0)	
10+	36 (5.0)	11 (8.5)	**0.021**
Bloody stools			
None	514 (71.2)	94 (72.9)	
Occasionally with BM	142 (19.7)	25 (19.4)	
>50% of BM	38 (5.3)	8 (6.2)	
With every BM	28 (3.9)	2 (1.6)	0.627
Disease location at diagnosis			
Pancolitis	273 (36.5)	57 (43.5)	
Left-sided colitis	234 (31.3)	32 (24.4)	
Proctitis	147 (19.7)	28 (21.4)	
Unknown/unclear	94 (12.6)	14 (10.7)	0.298
CRP in mg/l	2, 1–5	4, 1–6	
(median, IQR, range)	0–130	0–71	**0.008**
Faecal calprotectin in ug/g	83, 30–495	102, 58–260	
(median, IQR, range)	1–3450	9–1043	0.683
IBDQ Bowel score	61, 52–66	60, 53–65	
(median, IQR, range)	16–70	16–70	0.357
IBDQ Systemic score	27, 22–30	23, 19–29	
(median, IQR, range)	5–35	6–35	**<0.001**
IBDQ Emotional score	70, 60–76	67, 59–75	
(median, IQR, range)	12–84	51–84	0.371
IBDQ Social score	34, 30–35	33, 28–35	
(median, IQR, range)	5–35	6–35	0.227
IBDQ Total score	190, 165–205	184, 162–201	
(median, IQR, range)	44–224	62–224	0.086
SF36 Physical score	53, 46–57	50, 39–56	
(median, IQR, range)	16–68	17–65	**0.002**
SF36 Mental score	49, 41–54	48, 39–54	
(median, IQR, range)	15–62	15–61	0.381
Medical resources consumption (in last 3 months)			
Hospitalization	42 (10.3)	9 (12.9)	0.517
Outpatient visit	109 (26.6)	23 (32.4)	0.311
Work absence (in last 3 months)			
No	304 (94.1)	42 (91.3)	
Yes	19 (5.9)	4 (8.7)	0.509

AS: axial spondylarthropathy; BM: bowel movement; BMI: body mass index; CRP: C–reactive protein; EIM: extraintestinal manifestation; EN: erythema nodosum; IQR: interquartile range; MTWAI: modified Truelove Witts Activity Index; PG: pyoderma gangrenosum; PSC: primary sclerosing cholangitis.

Figure 1. Kaplan-Meier curves and unadjusted/adjusted hazard ratios (aHRs) for disease progression, disease complications and index treatment failure in obese vs non-obese patients, stratified by inflammatory bowel disease (IBD) subtype. Normal body mass index (BMI) is reference (hazard ratio (HR) = 1). CD: Crohn's disease; CI: confidence interval; SIBDCS: Swiss Inflammatory Bowel Disease Cohort Study; UC: ulcerative colitis.

impact of obesity on IBD disease activity and disease outcome in a large Swiss cohort with a follow-up of 6 years. Our main findings are as follows: (a) obesity rate in patients enrolled into the SIBDCS was 11%; (b) obese CD, but not UC patients showed increased

disease activity scores compared to normal weight individuals; (c) in a multivariate logistic regression model, obesity was negatively associated with disease remission in CD patients; and (d) obese CD patients were more likely to develop disease complications, while no

association between obesity and disease progression or index treatment failure was seen, neither in CD nor UC.

Obesity has been associated with increased disease activity and worse clinical outcomes in other autoimmune diseases, such as rheumatoid arthritis and psoriatic arthritis, which might be attributed to obesity being considered a low chronic inflammatory state associated with the increased release of proinflammatory cytokines.[14,15] In IBD, data have been less consistent. Some studies reported an association between obesity and penetrating CD as well as higher prevalence of colonic involvement, while others did not.[17,18,29–31] In UC, a lower prevalence of pancolitis has been reported in obese patients in one study; as such, no clear association between obesity and UC activity has been established to date.[2,18] A recent and comprehensive analysis of patient-reported data in more than 7000 IBD patients suggests increased risk of persistent disease activity or relapse in both CD and UC patients.[32] Whilst we observed no differences with regards to disease behaviour (B1–B3 in CD) and extent (E1–E3 in UC) between obese and normal weight patients in our cohort, we found that obese CD, but not UC patients, showed increased disease activity scores compared to normal weight patients. The daily soft stool frequency was increased from a median of four times per day in normal weight patients to eight times per day in obese CD patients. In our estimation, this is a clinically meaningful difference. The finding of higher disease activity in obese CD patients is particularly noteworthy, as BMI is an integral component of the CDAI score, in which a high BMI actually lowers the score by a maximum of 10 points.[23] If BMI was to be excluded, these differences would have been even more striking. Based on CDAI and faecal calprotectin (< 100 ug/g), obese CD patients were less likely to be in disease remission compared to normal weight controls. Negative association between obesity and clinical remission remained significant in a multivariate logistic regression model. However, there was no difference between obese and non-obese patients with regards to remission rates when using higher faecal calprotectin cut-off values (such as 250 ug/g).[33] Although we observed no differences in MTWAI between obese and normal weight UC patients, higher stool frequency in obese patients compared to normal weight UC patients could be interpreted as an indication for increased UC activity – if calprotectin and CRP data were not available. An association between soft stools and obesity has been previously shown in a non-IBD population.[34] As endoscopic disease activity was not systematically collected and assessed in the Swiss IBD cohort, it is not possible to differentiate between mild ongoing disease activity

and complete disease remission. Possible explanations for an increased stool frequency in the context of the latter might be higher rates of bile acid malabsorption, faster colonic transit or irritable bowel syndrome (as a result from dysbiosis).[35–37] Taken together, the difference in disease activity between obese and non-obese IBD patients might not be as large as seen in other autoimmune diseases. Nonetheless, the significant impact of obesity on quality of life and increased stool frequency in both obese UC and CD patients should urge treating physicians to take weight into account when managing IBD patients.

So far, data on the impact of obesity on disease outcome in IBD have been conflicting.[2] While some studies reported decreased rates of IBD surgery, hospitalizations and initiation of anti-TNF treatment, others demonstrated increased risk for surgery, severe hospitalizations and longer hospital stays in obese patients when compared to normal weight patients.[2,29,38] In other studies, no differences in disease outcomes between obese and normal weight patients were observed.[39,40] The recent and comprehensive analysis from Jain and colleagues revealed an independent and dose-dependent association between obesity and risk of disease relapse in CD and UC.[32] In our study, we show that obese CD patients were indeed more likely to develop disease complications compared to non-obese patients. Although the *p*-value did not reach statistical significance, obese UC patients appear to have a worse outcome with regards to the development of complications, too. In contrast, we did not detect any association between obesity and disease progression or index treatment failure, neither in CD nor UC.

Our study has several strengths. The availability of a relatively large number of patients (>3000 patients within the cohort, 325 with an obese BMI) and a long follow-up period (6 years) make our cohort data more robust and our findings more reliable than those reported in previous studies. In addition, stringent inclusion and exclusion criteria combined with data collection in a prospective manner and close (annual) follow-up minimised the drawbacks of a retrospective data analysis. Furthermore, we analysed both patient- and physician-reported outcomes. Finally, our outcome analyses have been adjusted for several disease modifiers and therefore make the findings more reliable.

Nevertheless, our study has also some limitations. Due to the nature of the SIBDCS data collection, it was not possible to assess efficacy of anti-TNF treatment in obese patients compared to normal weight individuals. This type of analysis would be of particular interest given previous findings of rapid anti-TNF clearance and low trough levels in obese patients.[2,41]

Given that the SIBDCS is not a population-based study, obesity prevalence estimations were not possible, and patients with a more complicated disease course recruited at tertiary referral centres might be overrepresented. Thus, our findings cannot be applied one to one to a general IBD population. Index treatment failure was defined as need for new anti-TNF despite the availability of newer biologics. However, the latter have been introduced in Switzerland only very recently. A further limitation is the lack of endoscopic data. Finally – although data was prospectively collected – we report on a retrospective analysis.

In conclusion, in our study obesity was associated with increased disease activity and decreased quality of life, particularly in CD. We further observed – in a multivariate Cox proportional hazard model – a significant association between obesity and development of disease complications in CD. However, obesity does not appear to have an impact on disease progression or index treatment failure. Weight changes might be beneficial, but cannot be uniformly recommended based on the current data. Additional analyses of large population-based datasets are merited to further study the relationship between obesity and IBD disease course.

Declaration of conflicting interests

The author(s) declare that they have no conflict of interests to report.

Ethics approval

Institutional review board (IRB) approval has been obtained from the local ethics committee of each participating centre (IRB approval number EK-1316, approved on 5 February 2007).

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