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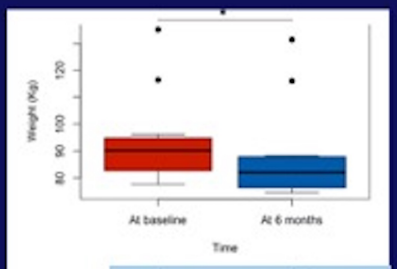
EFFECTIVENESS AND SAFETY OF GLP-1 AGONIST IN OBESE PATIENTS WITH INFLAMMATORY BOWEL DISEASE

IBD patients on GLP-1 agonists had a significant weight loss after 6 months therapy



Median percentage of change in body weight at 6 months (kg): -6.2 (-3.4 – (-8.5))

58.3% showed a 5% or more weight reduction at 6 months

	At 3 months	At 6 months
Weight loss ≥5%	33.3% (5/15)	58.3% (7/12)
Weight loss ≥10%	0% (0/15)	16.7% (2/12)

7/12 patients showed a weight reduction ≥ 5% and 2/12 ≥10%

There was no significant change in disease activity scores from baseline to 6 months

	At baseline	At 6 months	p-value
Harvey Score	3 (1-5)	4 (2.75-4.25)	0.388
Mayo Score	1.286 (0-1)	1.00 (1-2.23)	0.089
Fecal calprotectin, µg/g	40.9 (13.77-79.88)	32.7 (13.8-50.98)	0.376

No significant change was shown in the Harvey Score, Mayo Score, or fecal calprotectin.
Adverse events were mild. The most common were nausea (12.5%) and diarrhea (12.5%)

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Effectiveness and safety of GLP-1 agonist in obese patients with inflammatory bowel disease

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Abbreviations list: inflammatory bowel disease (IBD), glucagon-like peptide (GLP)-1 agonists, Crohn's disease (CD), ulcerative colitis (UC), Harvey-Bradshaw index (HBI), serious adverse events (SAEs).

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Abstract

Background: Obesity affects many patients with inflammatory bowel disease (IBD). Glucagon-like peptide (GLP)-1 agonists are a promising therapy for obese patients. However, there is a lack of evidence of the use of these drugs in IBD populations. We investigated the effectiveness and safety of GLP-1 agonists in a cohort of obese patients with IBD. **Methods**: We analyzed a retrospective series of cases of consecutive IBD patients who received GLP-1 agonists indicated for treating obesity between 2019 and 2021. The GLP-1 agonists included were semaglutide 1.0 mg or liraglutide 3.0 mg. The coprimary endpoints were the percentage of change in body weight from baseline to 6 months and a weight reduction of 5% or more at 6 months. In addition, we reviewed the safety profile of GLP-1 agonist therapy and its impact on the IBD course. **Results**: We included 16 obese patients with IBD (9 CD and 7 UC). The median body mass index at baseline was 35 (32-37). The percentage of change in body weight was -6.2% (-3.4-(-8.5)) at 6 months, and a 5% or more weight reduction was achieved in 58.3% (7/12) of patients at 6 months. The most common side effect was nausea (13.3%), and one patient withdrew for diarrhea. IBD activity score did not change significantly during follow-up. **Conclusion**: Our results showed that GLP-1 agonists were effective and had a good safety profile in IBD patients. Most adverse effects were mild, and the IBD activity had no significant changes.

Keywords: Inflammatory bowel disease. GLP-1 agonists. Obesity. Weight.

Key Summary: Obesity prevalence is increasing among patients with inflammatory bowel disease; Glucagon-like peptide (GLP)-1 agonists are commonly used for diabetes mellitus, and their indication for obesity has increased in the last few years. In this observational study, GLP-1 agonists were effective, in terms of body weight reduction, and safe in obese IBD patients.

Introduction

Obesity represents one of the most important conditions contributing to the overall burden of disease, including cardiovascular, neoplastic, and musculoskeletal disorders (1). Obesity prevalence is increasing among patients with inflammatory bowel disease (IBD), especially in developed countries – with a prevalence ranging from 15 to 40% (2–5) – and may have negative effects on its clinical course; obese patients have high circulating levels of proinflammatory adipokines and cytokines, such as tumor necrosis factor α, which may imply a worse course of IBD (6). Moreover, obesity could affect the response to medical treatment, partly by changes in the pharmacokinetics with increased distribution volume leading to lower drug levels (7,8). Extrapolation to other immune-mediated diseases, weight loss has been associated with improved disease activity and response to treatment (9,10). However, no similar studies have been published in IBD.

The therapeutic approach to obesity should be multidisciplinary, encompassing diet, physical exercise, medications, and even surgery. Glucagon-like peptide (GLP)-1 agonists are commonly used for diabetes mellitus, and their indication for obesity has increased in the last few years. GLP-1 agonists reduce weight through different mechanisms, including low appetite, early satiety, and visceral discomfort (11). Concerning the impact of GLP-1 agonists on IBD history, only one article showed a lower risk of hospital admissions and the need for steroids in IBD patients (12). More recently, a case-control study from Mayo Clinic showed similar effectiveness and safety of different anti-obesity medications – including GLP-1 agonists – after 12 months in IBD patients, compared to the general population (13).

In the present study, we aimed to evaluate the effectiveness and safety of GLP-1 agonists as a treatment for obesity in a cohort of patients with IBD.

Material and Methods

This study was conducted in a tertiary referral hospital in Madrid, Spain. We included a retrospective series of cases of consecutive obese patients with IBD who started with GLP-1 agonists between 2019 and 2021. The GLP-1 agonists prescribed were semaglutide 1.0 mg or liraglutide 3.0 mg. Patients with ulcerative colitis (UC) or

Crohn's disease (CD) were included in the study. Obesity was defined as a body-mass index (BMI) of ≥ 30. At baseline, before initiating the GLP-1 agonist, we registered demographics, comorbidities, Montreal's Classification (14), and therapies for IBD in the electronic chart. The study was approved by the Ethical Committee of Hospital Gregorio Marañón on January 23rd, 2023, and was performed in accordance with the Ethical Declaration of Helsinki of 1964.

The coprimary endpoint was the percentage of change in body weight from baseline to 6 months and a weight reduction of 5% or more at 6 months. The secondary endpoints included the percentage of change in body weight from baseline to 3 months and weight reduction of 10% or more at 6 months. We collected all the adverse events within 6 months of initiating the GLP-1 agonist therapy. The main variable of safety analysis was based on the occurrence of serious adverse events (SAEs) defined when the GLP-1 agonist therapy had to be withdrawn.

For IBD, inflammatory activity was established using fecal calprotectin and disease activity index: the Harvey-Bradshaw index (HBI) (15) for CD and the partial Mayo score for UC. Clinical response for CD was defined as a decrease in Harvey-Bradshaw score of 3 or more points from baseline. For UC, clinical response clinical response was considered as a decrease in partial Mayo score of 2 or more points from baseline. Another surrogate variable of inflammation was protein C-reactive (PCR). To assess GLP-1 agonists' effect on the course of IBD, we measured the change of disease activity variables from baseline to 6 months. Another surrogate variable of effectiveness was the need for IBD therapy escalation.

Categorical variables were summarized as the number of cases and percentages. Quantitative variables were expressed as median with interquartile range (IQR). We applied the Wilcoxon to compare repeated measurements of the same subjects at different time points. A p-value less than or equal to 0.05 was considered statistically significant. R was used for the analysis. All analysis was carried out using R software (version 4.1.0).

Results

We enrolled 16 patients in the study, 9 diagnosed with CD and 7 with UC. Table 1 showed clinical and demographic characteristics, and Table 2 depicted the baseline laboratory markers. The median basal weight was 90.2 kg (82-95), and the BMI was 35 (32-37). No patients had a previous history of medical or surgical treatment for obesity. The most frequent comorbidities were dyslipidemia (62.5%), followed by arterial hypertension (43.8%) and diabetes mellitus (25%). Most (87.5%) were on biologics, mainly infliximab and adalimumab. One patient was on tofacitinib. Four patients had immunomodulators, 2 in monotherapy, and 2 in combination therapy with a biologic. Most CD patients (66.7%) were in remission. Most UC patients (6/7) were in remission, and only 1 had moderate activity.

During the 6 months of our study period, 1 patient lost follow-up, and 3 patients had an early withdrawal, 2 for lack of effect, and 1 for side effects. 11 patients received liraglutide and 5 semaglutide. There were no significant changes in laboratory parameters between baseline and 6 months (Table 2). Within the diabetes mellitus subjects (n=4), the GLP-1 agonist reduced the glycated hemoglobin level by 0.3% after 6 months. The median percentage of change in body weight was -6.2 (IQR: -3.4-(-8.5)) at 6 months. A 5% or more weight reduction was in 58.3% (7/12) at 6 months. Moreover, the median percentage of change in body weight was -4.41% (IQR: -2.5-(-5,6)) at 3 months. We observed a weight reduction of 10% or more in 16.7% (2/12) at 6 months. The analysis was shown in Table 3 and Figure 1. Although the sample size was small, we performed a subanalysis comparing patients taking liraglutide and semaglutide. The median percentage of weight change of patients treated with liraglutide at 6 months was – 6,6(IQR: -5-(-9,4)) and -4,7(IQR: -3,2-(-7,6)) for those treated with semaglutide. A 5% or more weight reduction was in 71,4% (5/7) of patients treated with liraglutide and 40% (2/5) of patients treated with semaglutide at 6 months.

Overall, there was no significant change in disease activity score from baseline to 6 months. Data are shown in Table 3. During follow-up, 2 patients worsened. One had an

increased HBI score (6 to 8 points) with spontaneous drainage of a perianal abscess. This patient maintained the same therapy. The second patient had abdominal pain without an increase in the HBI score and received an isolated course of oral budesonide with a good clinical response. There was no need for intensification in patients receiving biologics. There was also no significant change in fecal calprotectin from baseline and at 6 months.

Overall, SAEs were reported in one patient who had diarrhea that led to therapy suspension. This patient had no elevated fecal calprotectin at baseline and either 6 months. The most common adverse events collected were nausea (12.5%) and diarrhea (12.5%). No deaths were recorded.

Discussion

In the present study, we showed that GLP-1 agonist treatment was effective with a weight reduction of 6.2% at 6 months and had a good safety profile in IBD patients. There are studies of GLP-1 agonists on obese patients without IBD. However, the evidence of these medications on IBD patients is scarce. One recent matched case-control study of 72 patients showed equal effectiveness of antiobesity drugs between IBD patients (n=36) and non-IBD controls (n=36). Particularly, the percent total body weight loss in the IBD group at 6 months (-5.4) and 12 months (-6.9) were in line with our results at 6 months (-6.2). In the subgroup analysis, IBD patients on liraglutide and semaglutide had a weight loss of -1.8% and -9.8% at 12 months, respectively (13). However, our data is not comparable due to the difference in time points follow-up. Studies in non-IBD population reported efficacy based on weight reduction (16–24). The SCALE clinical trial in obese patients treated with liraglutide estimated an 8% weight loss at 56 weeks, which aligns with our results. The STEP 1 trial with semaglutide showed a higher weight loss percentage of 14.9% at week 68 (24). In addition, the SCALE (23) and STEP 1(24) trials reported 63.2% and 86.4% weight reduction of 5% or more and 33% and 69.1% of weight loss of at least 10% from their baseline weight, respectively. In our study, 58.3% of the patients had a weight reduction of 5% or more at 6 months, and 16.7% had a weight loss of 10% or more.

Our results showed a lower rate of weight loss than those described. One explanation could be the small sample size of our study. In addition to this, our follow-up period was 6 months and not one year as in the other studies mentioned. In our study, the weight loss percentage at 3 months was 4.41%, and at 6 months, 6.2%, so an upward trend in this percentage could be expected in the following months.

Regarding safety, the most frequent adverse event in our series was nausea (13.3%). Only one patient had diarrhea associated with the treatment, which led to the GLP-1 therapy suspension. Commonly, GLP-1 agonists cause mild gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. In patients treated with liraglutide, nausea occurs in 25%, vomiting in 12.2%, and diarrhea in 11.6% (13,23,25,26). In patients treated with semaglutide, nausea has been reported between 11.4 and 20%, vomiting between 4 and 11.5%, and diarrhea between 4.5 and 11.3% (27–29). Most of these symptoms, with higher drug doses, appear transiently at the start of treatment and are associated with greater weight loss (25). The percentage of nausea reported in the published studies is consistent with our results. Another remarkable adverse event is the development of acute biliary events (23,30). In our cohort, no biliary episodes were reported; this may be explained by the limited follow-up time.

The clinical course of IBD patients treated with GLP-1 agonists indicated for obesity has not been systematically evaluated. Only the matched case-control study from the Mayo Clinic suggested no negative impact on IBD-related outcomes (13). Our results showed only 2 of 15 patients who worsened clinically; one of them needed oral budesonide. Both of them had mild activity at baseline. No patients required admission, surgery, intensification of the biologic, or systemic steroids. A Danish multicenter observational study analyzed the effect of therapies based on GLP-1 on the course of IBD in patients with type 2 diabetes mellitus (12). They included patients with IBD who were on GLP-1 agonists or DPP-4 inhibitors compared with other antidiabetics. They showed better outcomes with less need for oral steroids, TNFα inhibitors, IBD-related hospitalization, and surgery. This better course of IBD may be explained by reduced intestinal inflammation through the interaction between GLP-1 agonists with intestinal intraepithelial lymphocytes (31). Studies in mice suggested the benefit of GLP-1 agonists and DPP-4 inhibitors due to improved intestinal inflammation

(32,33). Bang-Bergensen et al. demonstrated reduced levels of colonic inflammation in a T-cell-driven adoptive transfer colitis mouse model treated with liraglutide (32). Anbazhagan et al. showed that GLP-1-SSM treatment reduced the expression of pro-inflammatory cytokine IL-1β, increased goblet cells, and preserved intestinal epithelial architecture in a colitis model (33).

Our study had several limitations. Firstly, the nature of a retrospective study. Secondly, the study had a small sample size, which may be explained due to the new indication of GLP-1 therapy for obesity. In addition, the limited follow-up time of 6 months may misdiagnose adverse events that appear in the long term. Along the same line, maintaining weight loss beyond 6 months has yet to be studied. However, this is the first study to focus on the effectiveness and safety of GLP-1 agonists and the course of IBD in obese patients with IBD. Future prospective studies are required to provide more data on the IBD population.

In conclusion, our study showed that GLP-1 agonists are effective and safe in obese patients with IBD. We estimated a 6.2% weight loss reduction at 6 months. Most adverse effects were mild, and the inflammatory activity had no significant changes.

Key point table

- Obesity prevalence is increasing among patients with inflammatory bowel disease; Glucagon-like peptide (GLP)-1 agonists are commonly used for diabetes mellitus, and their indication for obesity has increased in the last few years.
- In this observational study, GLP-1 agonists were effective, in terms of body weight reduction, and safe in obese IBD patients.

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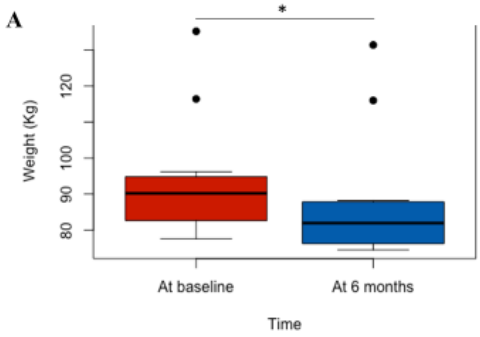
A



B

	At 3 months	At 6 months
Weight loss ≥5%	33.3% (5/15)	58.3% (7/12)
Weight loss ≥10%	0% (0/15)	16.7% (2/12)

Figure 1. A. Boxplot of weight loss in IBD patients with GLP-1 agonists. The central line in each box shows the median, the lower and upper limits of the box indicate the

interquartile range, the whiskers depict the minimum and maximum, and the outliers (black dots) of the weight values. IBD: inflammatory bowel disease. The graphics showed that IBD patients on GLP-1 agonists had significant weight loss after 6 months of therapy (p=0.002). * p-value was calculated using the Wilcoxon test. **B.** The table showed the weight loss percentage at 3 and 6 months of IBD patients receiving GLP-1 agonists.

Table 1. Demographic and clinical characteristics of the cohort at baseline.

	Obese patients with IBD (n=16)
Age (year)	50 (44-55)
Sex (women)	13 (81,3)
Active smoker	1 (6,3)
Diabetes mellitus	4 (25)
Arterial hypertension	7 (43,8)
Dyslipidemia	10 (62,5)
Chronic kidney disease	0 (0)
Chronic hepatopathy	4 (25)
Ischemic heart disease	1 (6,3)
Other autoinmune diseases	
IBD-associated arthritis	2 (12,5)
Axial spondyloarthritiS	1 (6,3)
Rheumatoid arthritis	2 (6,3)
Type of IBD	
CD	9 (56,3)
UC	7 (43,8)
Age at diagnosis of IBD	35 (30-40)
Duration of IBD (years)	12,5 (6,5-22)
Montreal Classification, **UC (n=7)**	
E1: Proctitis	0 (0)
E2: Left-sided	4 (57,1)
E3: Extensive UC	3 (42,9)
Montreal Classification, **CD (n= 9)**	
A1: ≤ 16 years	1 (11,1)
A2: 17-40 years	7 (77,8)
A3: > 40 years	1 (11,1)
L1: ileal	6 (66,7)
L2: colonic	3 (33,3)
L3: ileocolonic	0 (0)
+ L4: upper disease	0 (0)
B1: inflammatory	5 (55,6)
B2: stricturing	3 (33,3)
B3: penetrating	1 (11,1)
p: perianal disease	2 (22)
Immunomodulators	4 (25)
Biologic treatment:	14 (87,5)
Infliximab	6 (37,5)
Adalimumab	4 (25)

Numeric variables are expressed as the median and interquartile range (IQR). Categorical variables were summarized as the number of cases and percentages (%). IBD: inflammatory bowel disease; IQR: interquartile range; UC: ulcerative colitis; CD: Crohn's disease.

Table 2. Laboratory markers

	Obese patients with IBD at baseline (n=16)	**Obese patients with IBD at 6 months (n=12)**	**p-value**
Total cholesterol, mg/dL	193 (158-225)	148 (137-195)	0.10
LDL cholesterol, mg/dL	99 (84-141)	78 (58-126)	0.58
HDL cholesterol, mg/dL	54 (50,5-62,5)	42 (41-52)	0.20
Triglycerides, mg/dL	139 (97-197)	127 (103-200)	0.58
Glycemia, mg/dL	93 (89-119)	106 (77-145)	0.53
HbA1c, %	6,2 (5,5-7,8)	5,9 (5,3-7,58)	0.14
ALT, IU/L	29,5 (19-40)	23 (15-60)	0.67
AST, IU/L	22,5 (17-29)	17,5 (15,75-26,75)	0.92
Bilirubin, mg/dL	0,5 (0,4-0,7)	0,4 (0,3-0,5) (n=7)	0.59
GGT, IU/L	26,5 (17-49)	26 (21-34)	0.45
ALP, IU/L	72 (68-91)	83 (76-90)	0.67
Fecal calprotectin, µg/g	41 (14-80)	32,7 (13,8-50,98)	0.74
CRP, mg/dL	0,45 (0,4-0,78)	0 (0-1,5)	0.66
Creatinine, mg/dL	0,69 (0,65-0,84)	0,7 (0,6-0,95)	0.12

Numeric variables are expressed as the median and interquartile range (IQR). Categorical variables were summarized as the number of cases and percentages (%). IBD: inflammatory bowel disease; IQR: interquartile range; HbA1c: hemoglobin A1c; ALT: Alanine transaminase: AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; U/I: international units per liter. CRP: C reactive protein.

	At baseline	At 6 months	p-value*
Weight, Kg,	92.17 (83.42-94.60)	81.95 (76.62-87.67)	0.002
Harvey-Bradshaw Score (Crohn´s disease patients)	3 (1-5)	4 (2.75-4.25)	0.388
Partial Mayo Score (ulcerative colitis patients)	1.286 (0-1)	1.00 (1-2.23)	0.089
Fecal calprotectin, µg/g	40.9 (13.77-79.88)	32.7 (13.8-50.98)	0.376

Table 3. Comparison of weight, activity scores of IBD, and fecal calprotectin at baseline and after 6 months on GLP-1 agonists.

Numeric variables are expressed as the median and interquartile range (IQR). *p-value was calculated using the Wilcoxon test.