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Original Article

GLP-1 Analog Use is Associated With Improved Disease Course in Inflammatory Bowel Disease: A Report from the Epi-IIRN

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Abstract

Background and Aims: The growing use of glucagon-like peptide 1 (GLP-1) analogs for type 2 diabetes mellitus (DM2) and obesity necessitates studies about their use in patients with inflammatory bowel diseases (IBD).

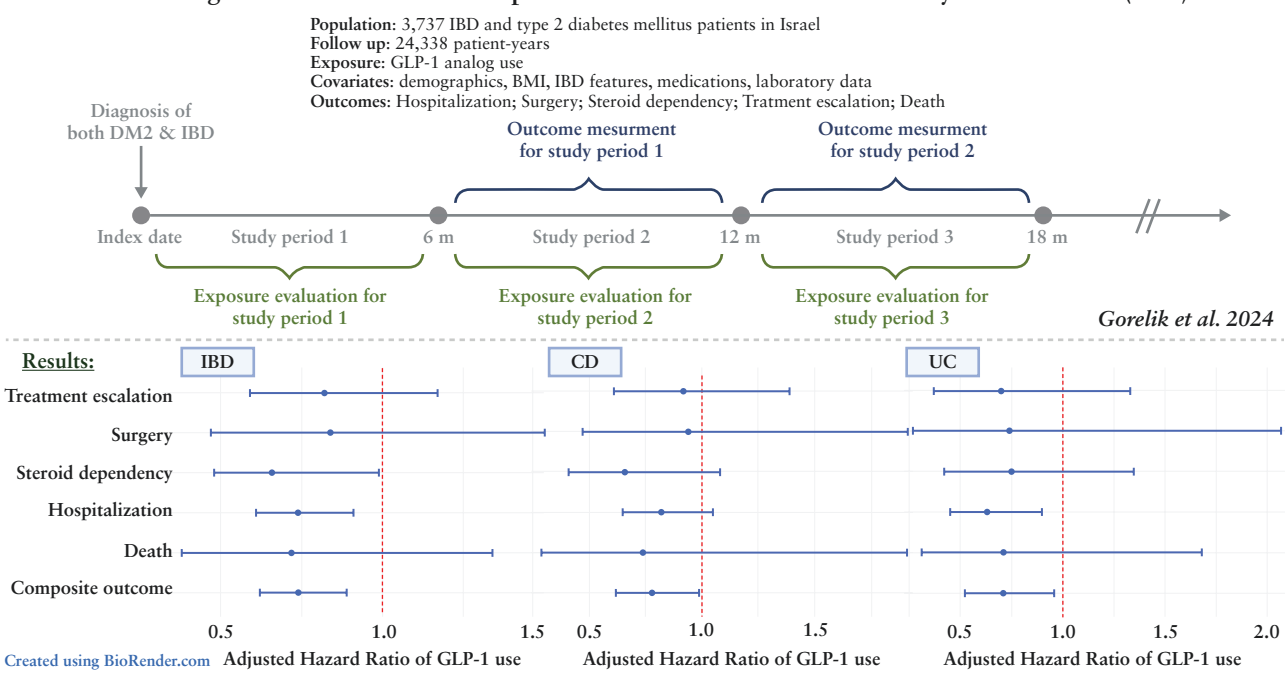
Methods: Data on patients with DM2 were retrieved from an Israeli nationwide cohort of patients with IBD (epi-IIRN), recording GLP-1 analog exposure for at least 6 months. The primary outcome was poor disease outcomes (ie, composite of steroid dependence, initiation of advanced IBD therapy, hospitalization, surgery, or death). Cox proportional hazard models with time-varying covariables were used to assess the impact of GLP-1 use on outcomes during follow-up.

Results: We included 3737 patients (24 338 patient-years) with IBD and DM2 [50.4% ulcerative colitis (UC)], of whom 633 were treated with GLP-1 analogs. Accounting for demographics IBD/DM2 related variables, medication use, and laboratory measurements, GLP-1 analog use was associated with reduced composite outcome in the full cohort (adjusted hazard ratio [aHR] 0.74, 95% confidence interval [CI] 0.62-0.89) and in each subtype [UC (aHR 0.71, 95% CI 0.52-0.96) and Crohn's disease (aHR 0.78, 95% CI 0.62-0.99)]. Similar trends were seen in multivariate analyses of each individual outcome, although only hospitalization was significant (aHR 0.74, 95% CI 0.61-0.91). The protective effect of GLP-1 analogs was seen in patients with obesity (aHR 0.61, 95% CI 0.50-0.77), but not in non-obese (aHR 0.94, 95% CI 0.67-1.31).

Conclusions: GLP-1 analogs are associated with improved outcomes in IBD, specifically in patients with obesity. The mechanisms of these effects require further investigation as well as their role in patients without DM2.

Key Words: GLP-1 analog; Inflammatory bowel disease; Obesity; Type 2 diabetes mellitus

Graphical Abstract



1. Introduction

The co-occurrence of inflammatory bowel disease (IBD) and components of the metabolic syndrome, such as obesity and insulin resistance, has been rising,[1–3] posing treatment challenges. The clinical use of gastro-mimetic hormone analogs has revolutionized diabetes care and obesity management in recent years. Glucagon-like peptide 1 (GLP-1) analogs, known for their potent incretin effect after a meal, regulate postprandial glucose levels by stimulating insulin secretion from pancreatic beta-cells.[4] Additionally, they target multiple pathways to increase satiety and reduce hunger, thereby promoting weight loss. This endogenous gut hormone has a crucial role in intestinal physiology, including regulating intestinal motility and promoting intestinal health.[5] Given these roles and common gastrointestinal side effects, GLP-1 analogs were suspected to influence the course of intestinal diseases such as IBD. The association between GLP-1 analog use and IBD-related outcomes in patients with diabetes mellitus type 2 (DM2) was examined in 2 population-based studies. A Danish study reported a lower rate of poor IBD outcomes among patients who started GLP-1 analogs/dipeptidyl peptidase-4 (DPP-4) inhibitors,[6] while this association was not found in a US database study, although lower surgery rates were reported.[7] These studies have methodological limitations and in light of the growing use of GLP-1 analogs, there is a need for more data on their effect on IBD disease course. We aim to investigate the association between GLP-1 analog use and IBD outcomes in the epi-IIRN, an Israeli nationwide cohort of patients with IBD with validated medication dispensation data and IBD outcomes.

2. Methods

2.1. Study population

We retrieved data on all patients with IBD and DM2 from the nationwide epidemiological Israeli IBD research nucleus (epi-IIRN) cohort, which includes all patients with IBD in Israel from 2005 through June 2021. Data were gathered for the epi-IIRN from the 4 Israeli Health Maintenance Organizations (HMOs), covering 98% of the population. The IBD case-ascertainment algorithm, which utilizes a combination of IBD-related diagnoses and medication purchases, and its validation, were previously detailed.[8] DM2 diagnosis was made in patients who fulfilled at least 2 prescriptions of non-insulin glucose-lowering medications or 2 separate International Classification of Diseases (ICD)-9 diagnoses of DM2 (medication names and ICD-9 codes are listed in Supplementary material). The status and value of outcomes and variables were assessed at 6-month intervals ('study periods' from this point onwards) for each patient beginning with the index date. The index date was defined as the first date where both DM2 and IBD diagnoses were confirmed ('index date' from this point onwards). This study was approved by the institutional review board of Shaare Zedek Medical Center where the database resides (0134-17-SZMC).

2.2. Outcomes and exposures

The primary outcome was poor IBD-related outcomes defined as a composite of steroid dependency, IBD treatment escalation, IBD-related hospitalization, abdominal/perianal surgery, or death. Steroid dependency was defined as at least 4 dispensations of systemic corticosteroids within 1 year, or a consecutive treatment duration of at least 90 days. Treatment escalation was defined as an initiation of a biologic or small molecule therapy, not used in a previous study period, or a switch to a different class. IBD-related hospitalization was considered if longer than 1 day and had an IBD-related diagnosis at discharge. Diagnosis codes, medications, and surgery codes are provided in Supplementary material. Each of the outcomes that constitute the composite outcome was individually evaluated also as a secondary outcome. Analyses

were performed for all patients with IBD (full cohort) and for ulcerative colitis (UC) and Crohn's disease (CD) separately.

The main exposure variable of interest was GLP-1 analog use, defined as at least 1 treatment dispensation in the study period. The covariates used in the models were age at index date, age at IBD diagnosis, body mass index (BMI), IBD subtype (for the models of all patients with IBD), previous surgery, perianal disease, hemoglobin and HbA1c levels, use of a biologic or small molecule therapy for IBD, sulfonylureas, biguanides, DPP-4 inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors, and insulin. Exposures to non-GLP-1 analog medications were considered positive for a study period if a dispensation occurred at least once. Measured variables (ie, BMI and laboratory tests) were recorded for each study period if they occurred during this time. If more than 1 result occurred, the latest was used. For each study period, an outcome was considered positive if it occurred in the next study period (see graphical abstract).

2.3. Statistical analyses

Baseline variables were presented as proportions, medians, and interquartile ranges (IQR). To address missing values in numerical variables, we performed K-nearest neighbor imputation for each patient with the mean of the 5 nearest values within close time intervals. Variables with a missing rate of more than 25% were not used. Event rates were calculated per 1000 patient years, and 95% confidence intervals (CIs) for the event rate were estimated using a Poisson distribution approach. To estimate the risk of the outcomes and GLP-1 analog use we utilized multivariable Cox proportional hazards models with time-varying covariables and the Prentice-Williams-Petersen approach. The Prentice-Williams-Petersen model allows to stratify the baseline hazard of recurring events, with the assumption that the occurrence of each event in a patient is not independent of previous events, as previous steroid dependency, hospitalization, and surgery are risk factors for additional events. The gap time calculation was used to account for time intervals between subsequent events. All Cox models were performed both as univariable, with GLP-1 analog use as the sole variable, and multivariable models adjusted for the variables listed above. Since death is not a recurring event, we utilized a standard Cox proportional hazards model with time-varying covariates to estimate the effect of GLP-1 analogs on death.

Association and possible mediation of patient weight on the effect of GLP-1 analogs was assessed by a Wald test with an interaction term between GLP-1 analogs and BMI. Also, since the association might not be linear, we performed subgroup analyses of patients with obesity defined as BMI ≥30 and non-obese (BMI < 30). The patients were grouped based on the first BMI that was measured for each patient during follow-up. To assess the validity of the division of patients based on the first measured BMI, we performed a mixed effects model to assess the within-subject BMI variability over periods of time. The BMI was defined as the dependent outcome, the time period as the fixed effect covariate, and the patient ID was defined as the random effect.

We performed several sensitivity analyses. Firstly, a complete case analysis was performed in which all continuous covariates were removed from the models. Second, all models were assessed with non-imputed values of continuous variables, and, lastly, the exposure, outcomes, and covariates were used in standard Cox proportional hazards models with time-varying covariates to assess whether calculating risks to the first event, rather than recurring events, has an effect on results. Lastly, we assessed the cumulative exposure to GLP-1 analogs during follow-up. For each patient, the cumulative exposure increased by 1 for every prior follow-up period in which the patient was exposed to GLP-1 analogs. Additionally, any exposure before the start of follow-up (index date) also increased the variable by 1.

Statistical significance was determined when p-values were lower than 0.05. Analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

3. Results

3.1. Study population

The cohort included 3737 patients with IBD and DM2 with a total follow-up of 24 338 patient-years and a median follow-up of 6 years per patient (interquartile range [IQR] 2.8-9.7). There were 1883 (50.4%) UC patients with a total follow-up of 12 587 patient-years and a median follow-up of 6.3 years (IQR 3.0-9.9) and 1854 CD patients with a total follow-up of 11 750 patient-years and a median follow-up of 5.7 years (IQR 2.7-9.5 years). At the index date, patients who used GLP-1 analogs tended to be younger and had a higher BMI, HbA1c, and insulin use in both UC and CD (Table 1).

3.2. GLP-1 analog use is associated with reduced risk of poor disease outcomes

The rate of the composite outcome was 316 events per 1000 patient-years (95% CI 309-323). Hospitalization, surgery, steroid dependency, and an escalation of therapy occurred at rates of 174 (95% CI 169-179), 14 (95% CI 12-15), 136 (95% CI 132-141), and 37 (95% CI 34-39) per 1000 patient-years, respectively. A total of 491 patients (13.1%) died during follow-up [event rate 19 per 1000 patient-years (95% CI 18-21)]. The rates of all events were higher in CD patients (Supplementary Table S1).

In univariable survival analysis, GLP-1 analog was associated with a reduced risk of composite adverse disease outcomes in the full cohort (hazard ratio [HR] 0.79, 95% CI 0.66-0.96), and in patients with UC (HR 0.73, 95% CI 0.54-0.98), while in patients with CD, a non-significant trend was seen (HR 0.86, 95% CI 0.66-1.08). In multivariable analyses GLP-1 analog use was significantly associated with a reduced risk of the composite outcome in the full cohort (adjusted HR [aHR] 0.74, 95% CI 0.62-0.89), in patients with UC (aHR 0.71, 95% CI 0.52-0.96), and CD (aHR 0.78, 95% CI 0.62-0.99). Among the secondary outcomes, GLP-1 analog use was associated with a reduced risk of hospitalization in the full cohort and in patients with UC, but not with CD (aHR 0.74, 95% CI 0.61-0.91; aHR 0.63, 95% CI 0.45-0.9; aHR 0.82, 95% CI 0.65-1.05, respectively; Table 2 and Supplementary Table S2). A reduced risk of hospitalization was seen in the full cohort and in UC patients (aHR 0.74, 95% CI 0.61-0.91; and aHR 0.63, 95% CI 0.45-0.90). For all other secondary outcomes, no significant associations were seen between GLP-1 analog use and the risk of the outcome (Table 2). A subgroup analysis excluding patients who were exposed to GLP-1 analogs at the beginning of follow-up (n = 3568), demonstrated a similar protective effect of GLP-1 analogs

Table 1 Baseline characteristics at index date[a] of patients who ever used GLP-1 analogs versus never-users according to IBD subtype.

	Full cohort		Ulcerative colitis		Crohn's disease	
	Non-GLP-1 analog users (*n* = 3104)	GLP-1 analog users (*n* = 633)	Non-GLP-1 analog users (*n* = 1584)	GLP-1 analog users (*n* = 299)	Non-GLP-1 analog users (*n* = 1520)	GLP-1 analog users (*n* = 334)
Age at index date in years, median [IQR]	62 [52, 70]	56 [47, 62]	62 [53, 70]	56 [48, 63]	62 [52, 70]	55 [46, 62]
Age at IBD diagnosis in years, median [IQR]	60 [50, 68]	54 [45, 62]	60 [51, 68]	55 [47, 62]	60 [49, 68]	55 [46, 62]
Male sex, *n* (%)	1664 (53.6)	306 (48.3)	926 (58.5)	158 (52.8)	738 (48.6)	148 (44.3)
BMI at index date, kg/m^2, median [IQR]	28 [25, 32]	32 [29, 36]	28 [25, 32]	31 [29, 35]	28 [25, 32]	33 [29, 37]
Perianal disease at index date, *n* (%)			—	—	111 (7.3)	38 (11.4)
Previous surgery, *n* (%)	171 (5.5)	23 (3.6)	61 (3.9)	7 (2.3)	110 (7.2)	16 (4.8)
Previous hospitalization, *n* (%)	1577 (50.8)	292 (46.1)	750 (47.3)	118 (39.5)	827 (54.4)	172 (52.1)
Previous advanced therapy use, *n* (%)	239 (7.7)	66 (10.4)	69 (4.4)	10 (3.3)	170 (11.2)	56 (16.8)
Steroids in last 5 years, *n* (%)	745 (24.0)	142 (22.4)	370 (23.4)	56 (18.7)	375 (24.7)	86 (25.7)
Laboratory at index date[b]						
HbA1c, %, median [IQR]	6.5 [6.1, 7.15]	7.2 [6.3, 8.2]	6.6 [6.2, 7.2]	7.3 [6.4, 8.5]	6.5 [6.1, 7.1]	7.0 [6.2, 8.1]
Platelets,[a]10^9/L, median [IQR]	259 [213, 317]	270 [230, 320]	251 [209, 308]	266 [223, 313]	270 [217, 328]	276 [238, 328]
Leukocytes,[a]10^9/L, median [IQR]	7.7 [6.3, 9.2]	7.9 [6.5, 9.7]	7.6 [6.2, 9.0]	7.7 [6.3, 9.3]	7.8 [6.4, 9.4]	8.2 [6.7, 10.0]
Hemoglobin, g/dL, median [IQR]	13.1 [12, 14.2]	13.2 [12.1, 14.3]	13.3 [12.2, 14.2]	13.3 [12.2, 14.6]	12.8 [11.8, 14.0]	13.1 [12.1, 14.2]
CRP, mg/dL, median [IQR]	0.8 [0.3, 2.1]	0.9 [0.4, 2.1]	0.6 [0.2, 1.7]	0.6 [0.3, 1.7]	0.9 [0.3, 2.7]	1.1 [0.5, 2.6]
Albumin, g/dL, median [IQR]	4.1 [3.8, 4.3]	4.1 [3.9, 4.3]	4.1 [3.9, 4.4]	4.2 [4.0, 4.4]	4.1 [3.8, 4.3]	4.1 [3.9, 4.3]
Fecal calprotectin, µg/mg, median [IQR]	166 [70, 385]	116 [62, 319]	163 [64, 513]	117 [63, 343]	167 [70, 360]	112 [61, 318]
Medication use at index date						
DPP-4 inhibitors, *n* (%)	311 (10)	94 (14.8)	158 (10.0)	50 (16.7)	153 (10.1)	44 (13.2)
Insulin, *n* (%)	287 (9.2)	163 (25.8)	153 (9.7)	87 (29.1)	134 (8.8)	76 (22.8)
Biguanides, *n* (%)	1,513 (48.7)	333 (52.6)	781 (49.3)	162 (48.5)	732 (48.2)	171 (57.2)
Sulfonylureas, *n* (%)	241 (7.8)	91 (14.4)	122 (7.7)	47 (15.7)	119 (7.8)	44 (13.2)
SGLT2 inhibitors, *n* (%)	110 (3.5)	38 (6.0)	60 (3.8)	16 (5.4)	50 (3.3)	22 (6.6)
Systemic steroids, *n* (%)	418 (13.5)	68 (10.7)	221 (14.0)	28 (9.4)	197 (13.0)	40 (12.0)
Infliximab, *n* (%)	62 (2)	10 (1.6)	23 (1.5)	0 (0.0)	39 (2.6)	10 (3.0)
Adalimumab, *n* (%)	69 (2.2)	19 (3.0)	5 (0.3)	1 (0.3)	64 (4.2)	18 (5.4)
Ustekinumab, *n* (%)	5 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	5 (0.3)	2 (0.6)
Vedolizumab, *n* (%)	32 (1.0)	13 (2.1)	17 (1.1)	4 (1.3)	15 (1.0)	9 (2.7)
Tofacitinib, *n* (%)	7 (0.2)	0 (0.0)	5 (0.3)	0 (0.0)	2 (0.1)	0 (0.0)
Thiopurines, *n* (%)	203 (6.5)	45 (7.1)	68 (4.3)	15 (5.0)	135 (8.9)	30 (9.0)
Methotrexate, *n* (%)	42 (1.4)	14 (2.2)	68 (4.3)	15 (5.0)	27 (1.8)	10 (3.0)
5-ASA, *n* (%)	1676 (54.0)	337 (53.2)	1068 (67.4)	204 (68.2)	608 (40.0)	133 (39.8)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium/glucose cotransporter 2.
[a]Index date was defined as the first date where both diabetes mellitus and inflammatory bowel disease diagnoses were confirmed.
[b]Missing data rate: BMI: 23.1%; HbA1c: 16.8%; Hemoglobin, leukocytes and platelets: 16.0%; Albumin: 36.5%; and Fecal calprotectin: 88.5%.

with a reduced risk of the composite outcome (aHR 0.77, 95% CI 0.61-0.96).

Sensitivity analyses with models that included complete cases or non-imputed data, and a standard Cox proportional hazards model that assesses risks of first event occurrence, all demonstrated that GLP-1 analog use was associated with a reduced risk of the composite outcome (Supplementary Table S3).

3.3. The association between GLP-1 analog use with poor IBD outcomes is differential between obese and non-obese patients

Next, we aimed to estimate whether GLP-1 analog use and its association with poor IBD outcomes is mediated by weight, due to the drug's major effect on weight. The Wald test did not demonstrate a significant effect of the interaction term between GLP-1 analog use and BMI. Since the mediation can possibly be non-linear, we further evaluated the effect of GLP-1 analog use in subgroups of patients with obesity (BMI ≥ 30), or non-obese (BMI < 30). The mixed effects model demonstrated that the average intercept of BMI is 29.6 and on average it changes to –0.04 between subsequent study periods within patients, suggesting minimal variation in BMI. In patients with obesity, GLP-1 analog use was associated with a substantial reduction in risk of composite outcomes in the full cohort and in patients with UC and CD separately (aHR 0.61, 95% CI 0.50-0.77; aHR 0.63, 95% CI 0.48-0.89; aHR 0.60, 95% CI 0.45-0.79, respectively), not seen in non-obese patients (Table 3).

In the full cohort, a significant association between the use of various non-insulin DM2 medications with a reduced risk of the composite outcome was seen, which was weaker than the effect seen for GLP-1 analogs. The differences in effect sizes were even more notable in the analysis of patients with obesity, where only GLP-1 analogs were significantly associated with a reduced risk of the composite outcome, not seen in non-obese patients (Supplementary Table S4). Lastly, when analyzed as the primary exposure, cumulative GLP-1 analogs exposure was significantly associated with a reduced risk of the composite outcome (aHR 0.96, 95% CI 0.93-0.99 per additional exposure period).

4. Discussion

The results of this study suggest that GLP-1 analogs are associated with reduced hazard for poor disease outcomes in patients with IBD and concomitant DM2. While there is limited data on the use of GLP-1 analogs in patients with IBD, our observation is in line with previous studies. In a nationwide study of patients with IBD with DM2 from Denmark, a lower risk of IBD-related outcomes among patients treated with GLP-1-based therapies compared with other anti-diabetics was observed.[6] It is worth noting that this study lacked information on patients' BMI and HbA1c values. Additionally, the authors grouped GLP-1 analogs and DPP-4 inhibitors, precluding a definite conclusion regarding the sole effect of GLP-1 analogs on IBD outcomes. A recent US claims database study reported that surgery was lower among GLP-1 analog initiators in both patients with CD and UC compared with patients who initiated other anti-DM2 medication, although other IBD disease outcomes were not impacted.[7] Importantly, they report no safety signal in patients with IBD. Of note, this database relies on synthetic data to protect patient confidentiality and uses aggregate counts and statistical summaries. In our subgroup analysis, the reduced rate of poor outcomes was seen in both UC and CD. Some of the strengths of our study include longitudinal analysis which accounts for multiple and recurring events, and that the database relies on medication dispensation and not claims.

The prevalence of obesity in patients with IBD is on the rise, currently ranging from 15% to 40%,[9] with an increasing prevalence of metabolic comorbidities.[10] Several studies suggested that patients with IBD with overweight/obesity are more likely to have active disease,[11] higher risk of relapse,[12] shorter time to surgery,[13] and are more prone to postoperative

Table 2 Adjusted hazard ratios with 95% confidence intervals for the composite and secondary outcomes of GLP-1 analog use in the full cohort and subgroup analyses[a].

	All IBD (*n* = 3737)	Ulcerative colitis (*n* = 1883)	Crohn's disease (*n* = 1854)
Composite outcome	**0.74 (0.62, 0.89)**	**0.71 (0.52, 0.96)**	**0.78 (0.62, 0.99)**
Hospitalization	**0.74 (0.61, 0.91)**	**0.63 (0.45, 0.90)**	0.82 (0.65, 1.05)
Surgery	0.84 (0.47, 1.50)	0.74 (0.27, 2.07)	0.94 (0.47, 1.91)
Steroid dependency	**0.66 (0.48, 0.99)**	0.75 (0.42, 1.35)	0.66 (0.41, 1.08)
Treatment escalation	0.82 (0.59, 1.17)	0.70 (0.37, 1.33)	0.92 (0.61, 1.39)
Death[b]	0.72 (0.38, 1.34)	0.71 (0.31, 1.68)	0.74 (0.29, 1.91)

Abbreviations: GLP-1, glucagon-like peptide 1; IBD, inflammatory bowel disease. Significant findings are in bold.
[a]All models were adjusted for patient age, sex, body mass index, HbA1c, hemoglobin, previous surgery, perianal disease, age at IBD diagnosis, use of biologic therapy or small molecules, sulfonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, sodium/glucose cotransporter 2 inhibitors, and insulin. In the full cohort, the IBD subtype was also included in the model.
[b]Hazard ratios for death were calculated with a standard Cox proportional hazards model with time-varying covariates.

Table 3 The aHR and 95% CI of GLP-1 analog use with the composite outcome in full cohort and in UC and CD patients in obese and non-obese patients.

	All IBD	Ulcerative colitis	Crohn's disease
BMI ≥ 30	**0.61 (0.50, 0.77), (*n* = 1475)**	**0.63 (0.48, 0.89), (*n* = 720)**	**0.60 (0.45, 0.79), (*n* = 755)**
BMI < 30	0.94 (0.67, 1.31), (*n* = 2120)	0.77 (0.37, 1.61), (*n* = 1084)	1.05 (0.73, 1.52), (*n* = 1036)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CD, Crohn's disease; GLP-1, glucagon-like peptide 1; IBD, inflammatory bowel disease; UC, ulceritive colitis. Significant findings are in bold.
[a]All models were adjusted for patient age, sex, body mass index, HbA1c level, hemoglobin, previous surgery, perianal disease (only in CD), age at IBD diagnosis, use of biologic therapy or small molecules, sulfonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, sodium/glucose cotransporter 2 inhibitors, and insulin. In the full cohort, the IBD subtype was also included in the model.

complications.[14–16] Therefore, obesity in patients with IBD should be addressed. The introduction of GLP-1 analogs to the obesity field has revolutionized the approach to weight loss and is estimated to be utilized by millions.[17] In patients with IBD and obesity, 2 recent small-scale retrospective cohorts reported that semaglutide led to similar weight loss compared to non-IBD patients.[18,19] Our sub-analysis suggests that GLP-1 analog use is associated with improved IBD disease course specifically in patients with obesity.

Obesity and central adiposity are associated with increased inflammation, as measured by elevated C-reactive protein levels.[20–22] Central adiposity is associated with lower response to IBD therapy and increased pro-inflammatory cytokines, suggesting a potential role for abdominal fat in the inflammatory process.[23] Recent evidence suggests that GLP-1 analogs carry anti-inflammatory properties that can potentially affect IBD disease activity.[24] In animal models, administration of GLP-1 analogs can improve colitis[25] and improve intestinal barrier function,[26] further suggesting a direct effect on the inflammatory process. In humans, improvement in UCs and ankylosing spondylitis was seen in an obese patient who started liraglutide for weight loss.[27] Whether the effect of GLP-1 analogs is independent of the weight loss needs to be determined. Since dietary patterns were found to be associated with IBD development and exacerbation, one potential explanation for the positive effect that GLP-1 analogs have on the disease course is related to a change in dietary patterns (ie, reduced intake of ultra-processed foods).[28] As the role of GLP-1 analogs unveiled for other obesity-associated indications,[29,30] obesity-associated IBD might be another potential target for this potent therapy.

This study has some limitations. First, although the epi-IIRN has been shown to be a robust database, with validated data from a nationwide cohort over 15 years and highly reliable medication and laboratory data,[8] features such as disease location and endoscopic findings are lacking. Second, parameters that affect the choice of an anti-diabetic agent and are also associated with morbidity and mortality such as cardiovascular disease and its severity, chronic kidney disease, and additional complications of diabetes are not well characterized. Of note, our cohort is relatively older, and further research is needed to support these results in younger individuals. The age distribution in our cohort precluded further subgroup analyses and should be considered when interpreting the results of this study. Third, our dataset uses medication-dispensing data, which does not ensure patients' medication adherence. However, studies have shown there is a relatively good correlation between pharmacy dispensing and medication adherence.[31,32] Fourth, during the study period, GLP-1 analogs were prescribed for glucose control and not indicated for weight loss. However, our subgroup analysis in patients with obesity suggests the relevancy of our findings for this indication as well. Fifth, data on biomarkers in the study periods was commonly missing which precluded reliable imputation and therefore was not reported or incorporated into the survival models. Lastly, we show association and not causality, and our results may not be generalizable to other countries, as population-specific unmeasured environmental and genetic factors possibly influenced our findings. However, our results are similar to other datasets from other geographic locations, validating the findings.

In conclusion, our results show that the use of GLP-1 analogs is associated with improved IBD disease course and might have beneficial effects on patients with IBD with DM2 and obesity. Further prospective studies should examine the effect of GLP-1 analog use administered for weight loss in patients with IBD with obesity without DM2 and search for mechanisms of action.

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Conflict of Interest

None for all authors. All authors approved the final version of the article, including the authorship list.

Author Contributions

YG, DT, and HBY designed the study; RL, DS, YLW, ABT, EM, GZ, ID, and DT constructed the database; YG performed the analyses; YG, IG, and HBY wrote the manuscript; RL, GZ, ID, and DT critically reviewed the manuscript.

Data Availability

Data may be accessed upon reasonable request.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

References

1. Nic Suibhne T, Raftery TC, McMahon O, Walsh C, O'Morain C, O'Sullivan M. High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. *J Crohns Colitis* 2013;**7**:e241–8.
2. Johnson AM, Harmsen WS, Aniwan S, Tremaine WJ, Abu Dayyeh BK, Loftus EV. Prevalence and impact of obesity on disease-specific outcomes in a population-based cohort of patients with ulcerative colitis. *J Crohns Colitis* 2021;**15**:1816–23.
3. Jess T, Jensen BW, Andersson M, Villumsen M, Allin KH. Inflammatory bowel diseases increase risk of type 2 diabetes in a nationwide cohort study. *Clin Gastroenterol Hepatol* 2020;**18**:881–8.e1.
4. Hunt JE, Holst JJ, Jeppesen PB, Kissow H. GLP-1 and intestinal diseases. *Biomedicines* 2021;**9**:383.
5. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev* 2007;**87**:1409–39.
6. Villumsen M, Schelde AB, Jimenez-Solem E, Jess T, Allin KH. GLP-1 based therapies and disease course of inflammatory bowel disease. *EClinicalMedicine* 2021;**37**:100979.
7. Desai A, Petrov J, Hashash JG, *et al*. Use of glucagon-like peptide-1 receptor agonists for type 2 diabetes mellitus and outcomes of inflammatory bowel disease. *Aliment Pharmacol Ther* 2024;**60**:620–32. doi:10.1111/apt.18138
8. Friedman MY, Leventer-Roberts M, Rosenblum J, *et al*. Development and validation of novel algorithms to identify patients with inflammatory bowel diseases in Israel: an epi-IIRN group study. *Clin Epidemiol* 2018;**10**:671–81.
9. 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;**14**:110–21.
10. Elangovan A, Shah R, Ali SMJ, Katz J, Cooper GS. High burden of obesity and low rates of weight loss pharmacotherapy in

inflammatory bowel disease: 10-year trend. *Crohns Colitis 360* 2023;**5**:otad007.
11. Jain A, Nguyen NH, Proudfoot JA, *et al*. Impact of obesity on disease activity and Patient-Reported Outcomes Measurement Information System (PROMIS) in inflammatory bowel diseases. *Am J Gastroenterol* 2019;**114**:630–9.
12. Greuter T, Porchet F, Braga-Neto MB, *et al*. Impact of obesity on disease activity and disease outcome in inflammatory bowel disease: results from the Swiss inflammatory bowel disease cohort. *United European Gastroenterol J* 2020;**8**:1196–207.
13. Hass DJ, Brensinger CM, Lewis JD, Lichtenstein GR. The impact of increased body mass index on the clinical course of Crohn's disease. *Clin Gastroenterol Hepatol* 2006;**4**:482–8.
14. Causey MW, Johnson EK, Miller S, Martin M, Maykel J, Steele SR. The impact of obesity on outcomes following major surgery for Crohn's disease: an American College of Surgeons National Surgical Quality Improvement Program assessment. *Dis Colon Rectum* 2011;**54**:1488–95.
15. Ding Z, Wu XR, Remer EM, *et al*. Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. *Colorectal Dis* 2016;**18**:163–72.
16. Jiang K, Chen B, Lou D, *et al*. Systematic review and meta-analysis: association between obesity/overweight and surgical complications in IBD. *Int J Colorectal Dis* 2022;**37**:1485–96.
17. GLP1 agonists set to become the best-selling drugs in 2024, says GlobalData. 2024. https://www.globaldata.com/media/pharma/glp1-agonists-set-to-become-the-best-selling-drugs-in-2024-says-globaldata/ Accessed July 4, 2024.
18. Ramos Belinchón C, Martínez-Lozano H, Serrano Moreno C, *et al*. Effectiveness and safety of GLP-1 agonist in obese patients with inflammatory bowel disease. *Rev Esp Enferm Dig* 2024;**116**:478–483. doi:10.17235/reed.2024.10305/2024
19. Desai A, Khataniar H, Hashash JG, Farraye FA, Regueiro M, Kochhar GS. Effectiveness and safety of semaglutide for weight loss in patients with inflammatory bowel disease and obesity. *Inflamm Bowel Dis* 2024:izae090. doi:10.1093/ibd/izae090
20. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. *Am J Cardiol* 2010;**106**:56–61.
21. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obes Rev* 2013;**14**:232–44.
22. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017;**13**:851–63.
23. Yarur AJ, Bruss A, Moosreiner A, *et al*. Higher intra-abdominal visceral adipose tissue mass is associated with lower rates of clinical and endoscopic remission in patients with inflammatory bowel diseases initiating biologic therapy: results of the constellation study. *Gastroenterology* 2023;**165**:963–75.e5.
24. Mehdi SF, Pusapati S, Anwar MS, *et al*. Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. *Front Immunol* 2023;**14**:1148209.
25. Wang W, Zhang C, Zhang H, Li L, Fan T, Jin Z. The alleviating effect and mechanism of GLP-1 on ulcerative colitis. *Aging (Albany NY)* 2023;**15**:8044–60.
26. Bang-Berthelsen CH, Holm TL, Pyke C, *et al*. GLP-1 induces barrier protective expression in Brunner's glands and regulates colonic inflammation. *Inflamm Bowel Dis* 2016;**22**:2078–97.
27. Lourie J. A novel use of liraglutide: induction of partial remission in ulcerative colitis and ankylosing spondylitis. *Clin Med Rev Case Rep* 2019;**6**:281.
28. Narula N, Chang NH, Mohammad D, *et al*. Food processing and risk of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2023;**21**:2483–95.e1.
29. Lincoff AM, Brown-Frandsen K, Colhoun HM, *et al*.; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389**:2221–32.
30. Malhotra A, Grunstein RR, Fietze I, *et al*. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N Engl J Med* 2024;**391**:1193–205. doi:10.1056/NEJMoa2404881
31. Sodihardjo-Yuen F, van Dijk L, Wensing M, De Smet PA, Teichert M. Use of pharmacy dispensing data to measure adherence and identify nonadherence with oral hypoglycemic agents. *Eur J Clin Pharmacol* 2017;**73**:205–13.
32. Fontanet CP, Choudhry NK, Isaac T, *et al*. Comparison of measures of medication adherence from pharmacy dispensing and insurer claims data. *Health Serv Res* 2022;**57**:524–36.