Anti-Tumor Necrosis Factor Treatment does not decrease the Risk of Type 2 Diabetes in Patients with Inflammatory Bowel Disease

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Anti-Tumor Necrosis Factor Treatment Does Not Decrease the Risk of Type 2 Diabetes in Patients With Inflammatory Bowel Disease

Patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are at increased risk of type 2 diabetes (T2D).[1,2] The proinflammatory cytokine tumor necrosis factor α (TNF-α) plays a central role in the inflammatory process of IBD, and anti-TNF-α therapy is commonly used in the treatment of IBD. Because anti-TNF therapy is suggested to improve insulin sensitivity,[3] we hypothesized that treatment with anti-TNF therapy decreases the risk of T2D in patients with IBD.

We conducted a nationwide population-based cohort study of all adult patients diagnosed with IBD in Demark during the period 1977–2018. All individuals were followed from cohort entry (January 1, 2005) or date of IBD diagnosis, whichever occurred last, and until the date of first T2D diagnosis, emigration, death, or end of study (December 31, 2018), whichever occurred first. IBD was defined as registrations with UC or CD in the Danish National Patient Register (DNPR). Cases with T2D were identified based on registrations with T2D in the DNPR or the filling of prescriptions of glucose-lowering drugs based on data in the Register of Medicinal Product Statistics. Information on anti-TNF treatment was retrieved from the DNPR and the Register of Medicinal Product Statistics. IBD patients were categorized as exposed from the date of first anti-TNF therapy if they received TNF antagonists that is approved for treatment of IBD in Denmark (infliximab, adalimumab, and golimumab).

Patients with a diagnosis of T2D or with exposure to anti-TNF therapy prior to study entry were excluded. At date of initiation of anti-TNF therapy, we matched anti-TNF–exposed patients with anti-TNF–naïve patients in 2 steps. First, we made exact matching on sex, IBD subtype, and IBD duration. Next, for each anti-TNF–exposed patient, we selected matches from the first step in a 1:3 ratio using propensity scores (Supplementary Material). Matches that initiated anti-TNF treatment during follow-up were censored at the date of first exposure.

Incidence rates and hazard ratios (HRs) with 95% confidence intervals (CIs) of T2D were calculated in anti-TNF–exposed vs anti-TNF–unexposed patients using Cox proportional hazards models. The analyses were also stratified by type of IBD, age, sex, and calendar year of study entry. Because corticosteroids are an independent risk factor for T2D,[4] we stratified the analysis according to exposure to oral corticosteroid treatment during follow-up as a time-varying variable. In a sensitivity analysis, anti-TNF exposure was lagged by 6 months to account for latency and diagnostic delays.

We identified 62,060 adult patients with IBD alive and residing in Denmark at study entry. Prior to study entry, we excluded 401 (0.6%) patients due to previous exposure to any anti-TNF therapy (infliximab, adalimumab, golimumab, etanercept, and certolizumab pegol), 6163 (10.0%) with a history of T2D, and 1715 (3.2%) with extremes propensity scores, leaving 53,781 patients in the study cohort. A total of 6947 (12.9%) IBD patients were exposed to anti-TNF therapy. After matching on propensity score in a ratio of 1:3, 4044 exposed and 12,132 unexposed IBD patients were included in the analysis (Supplementary Table 1). The mean duration of anti-TNF therapy exposure was 22.5 $\pm$ 24.6 months. At study entry, 56.2 % of the anti-TNF–naïve patients received mesalamine, 41.1% received intestinal corticosteroids, 27.8% received oral corticosteroids, and 10.7% received azathioprine (Supplementary Table 1).

During 128,183 person-years of follow-up, 94 (2.3%) anti-TNF exposed and 504 (4.2%) anti-TNF–naïve IBD patients developed T2D. The incidence of T2D was 4.8 per 1000 person-years in IBD patients exposed to anti-TNF therapy and 4.6 per 1000 person-years in IBD patients unexposed to anti-TNF therapy, yielding a HR for T2D of 1.08 (95% CI, 0.86–1.35). This was consistent in CD and UC, in men and women and in different groups of age at diagnosis, calendar year of study entry, and with 6-month lag of exposure (Table 1). When stratifying the analysis by exposure to corticosteroids, we found that among users of corticosteroids, patients exposed to anti-TNF therapy had a lower risk of T2D compared with anti-TNF unexposed patients, although not statistically significant (HR, 0.79; 95% CI, 0.41–1.49).

In conclusion, in this nationwide cohort study, using thorough adjustment for potential confounders, we found no altered risk of T2D among IBD patients exposed to anti-TNF therapy compared with unexposed patients.

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In Western countries, the IBD population is ageing, implying that these patients, in addition to their IBD, will face various age-related diseases, including cardiometabolic diseases. Therefore, clinicians need to address the prevention and treatment of cardiometabolic diseases in this patient group who is already at increased risk of these diseases due to their IBD.[5] Current evidence suggests that in patients with IBD, systemic inflammation is a more dominant driver of cardiovascular diseases than traditional risk factors such as hypertension and hyperlipidaemia.[6] Therefore, efficient treatment of intestinal and consequently systemic inflammation would be expected to decrease the risk of cardiometabolic diseases. However, the present study does not support a marked protective effect of anti-TNF therapy on the risk of T2D in patients with IBD. This contrasts with data from 2 previous studies. In a small study, anti-TNF therapy had favorable effects on insulin and C-peptide levels, and insulin sensitivity (Homeostatic Model Assessment for Insulin Resistance) in nonobese, nondiabetic patients with IBD.[7] Also, in a prospective study of patients with CD who initiated treatment with anti-TNF therapies, lower levels of fasting glucose and glycated hemoglobin were reported in those who responded to the treatment.[8]

A prominent strength of our study is its nationwide nature allowing inclusion of patients with IBD from a country with free and easy access to healthcare, thus minimizing selection bias. Another important strength is our assessment of the outcome, T2D, which was based on an algorithm taking both hospital contacts and medications into account, hence minimizing any misclassification. In the present study, we also used a propensity score matched design to balance all measured confounders between the treatment groups.[9] However, some limitations of our study must be acknowledged. Although we included information on sex, age, IBD subtype, calendar period, surgeries, and comorbidities in the

Table 1. Incident T2D Among Patients With IBD Exposed to Anti-TNF Therapy Compared With 3 Propensity Score–Matched Unexposed Patients

	Anti-TNF Therapy Exposed			Anti-TNF Therapy Unexposed				
Value	PY	T2D Cases	IR/1000 PY	PY	T2D Cases	IR/1000 PY	HR (95% CI)	*P* for Interaction
All	19,467	94	4.8	108,716	504	4.6	1.08 (0.86-1.35)	
Sex								
Female	10,152	48	4.7	56,771	204	3.6	1.38 (1.00-1.91)	.05
Male	9315	46	4.9	51,945	300	5.8	0.88 (0.64-1.21)	
Age at IBD diagnosis								
17-40 y	10,436	21	2.0	59,780	106	1.8	1.21 (0.75-1.95)	.55
41-65 y	8118	59	7.3	44,607	344	7.7	0.94 (0.71-1.25)	
>65 y	912	14	15.3	4328	54	12.5	1.23 (0.68-2.22)	
IBD subtype								
CD	6419	31	4.8	34,199	146	4.3	1.27 (0.85-1.88)	.35
UC	13,048	63	4.8	74,517	358	4.8	1.01 (0.77-1.33)	
Year of IBD diagnosis								
<2005	10,254	46	4.5	59,872	286	4.8	0.93 (0.67-1.27)	.20
2005-2019	9213	48	5.2	48,844	218	4.5	1.25 (0.91-1.71)	
Current corticosteroid use								
No	17,398	81	4.7	103,970	429	4.1	1.07 (0.84-1.37)	.37
Yes	2069	13	6.3	4746	35	7.4	0.79 (0.41-1.49)	
6 mo lag								
	17,509	81	4.6	101,824	474	4.7	1.02 (0.80-1.29)	

Patients were matched on sex, IBD subtype, and IBD duration and on propensity score. The following variables were included in the propensity score: sex, age at IBD diagnosis, IBD subtype (CD or UC), period of IBD diagnosis, region of Denmark, IBD-related surgeries, comorbidities, and medications.
CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IR, incidence rate; PY, person-years; T2D, type 2 diabetes; TNF, tumor necrosis factor; UC, ulcerative colitis.

propensity score and further conducted a stratified analysis taking corticosteroids into account, we did not have information on other potential confounders such as body mass index, diet, and smoking. Also, we cannot completely exclude residual confounding by disease severity implying that the anti-TNF–exposed individuals may have more active disease compared with anti-TNF–unexposed individuals, which conceptually could increase future risk of T2D, thereby blunting any beneficial impacts of anti-TNF therapy.

Future studies of the effect of anti-inflammatory agents in the prevention of cardiometabolic diseases and their long-term effects on disease course and their safety profiles are warranted. To that end, our study based on real-life observational data adds to the current evidence, but larger, well-powered studies are warranted.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.12.011.

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Conflicts of Interest
The authors disclose no conflicts.

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Supplementary Material

Propensity Score

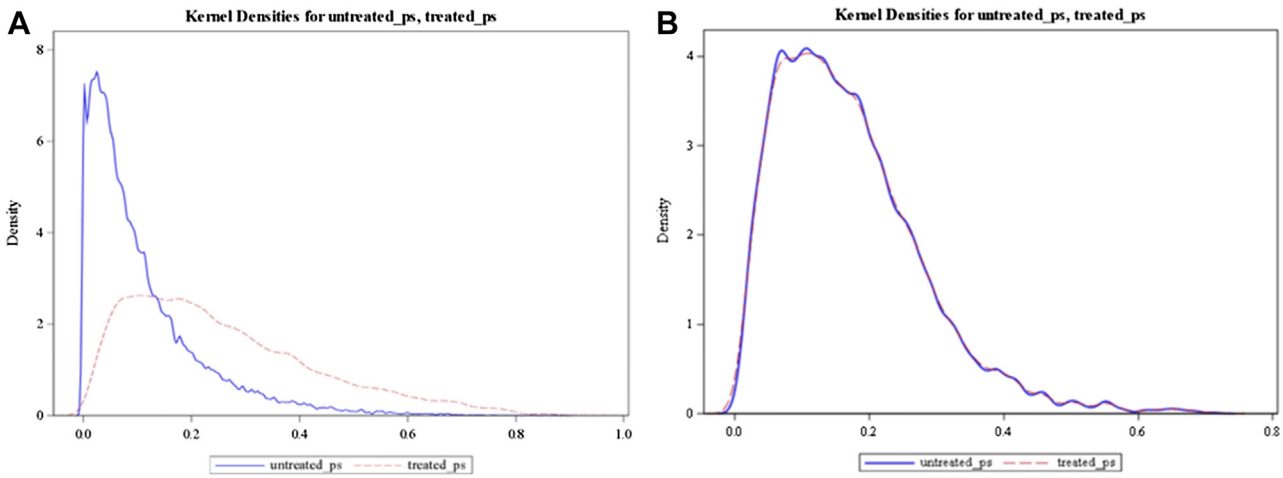
We identified 62,060 inflammatory bowel disease (IBD) patients alive in the period 2005–2018. IBD patients were categorized as exposed to anti-tumor necrosis factor (TNF) therapy if they received TNF antagonists that is approved for treatment of IBD in Denmark (infliximab, adalimumab, and golimumab). After exclusion of 401 patients exposed to any anti-TNF therapy (infliximab, adalimumab, golimumab, etanercept, and certolizumab pegol), 6163 patients with a history of type 2 diabetes, and 1715 patients with extreme propensity scores (<0.002 or >0.888), 53,781 patients were included. Among these, 6947 (12.9%) were exposed to anti-TNF treatment.

We used a 2-step approach to make the study population more homogenous. To reduce the number of potential matches, we first used exact matching on sex, IBD subtype, and IBD duration. To control for confounding by indication, we used propensity scores, that is, the conditional probability of exposure to TNF antagonists given the observed covariates. Multivariable logistic regression was used to estimate the propensity score based on the following covariates: sex, age at IBD diagnosis (categorical with 1-year intervals), IBD subtype (Crohn's disease or ulcerative colitis), period of IBD diagnosis (categorical with 1-year intervals), region of Denmark (5 regions), IBD-related surgeries (any vs none), comorbidities that may be considered as a contraindication or caution for TNF antagonists (any vs none for cardiovascular disease, pulmonary disease, renal disease, liver disease, cancer, rheumatoid disease, other intestinal disease, infections), and medication used within last year (any vs none for cardiovascular, dermatological, urological, muscular, antiinfection, eyes and ear, antiallergic, neuro/psychological, hormonal, and contraceptive). Even though sex, IBD subtype, and IBD duration were used in the exact matching, we included these variables in calculating the probability of treatment with anti-TNF to ensure that the propensity score also matched on these variables. We included sex in the propensity score to account for potential sex-differential manifestations of the disease that can affect treatment choices. IBD subtype was an essential factor because more patients with Crohn's disease than ulcerative colitis receive anti-TNF therapy in Denmark. IBD duration was included because this variable may reflect the age at diagnosis and whether the IBD patient is incident or prevalent at the start to follow-up. In debuting patients, not having any IBD-related hospitalizations or clinic visits before start to follow-up did not reflect low disease severity and, thereby, the probability of anti-TNF treatment. Therefore, these covariates were not included in the final propensity score.

When we matched 1 exposed to 3 unexposed patients with the nearest-neighbor matching with width 0.025, we identified 4044 exposed with 3 matches each. The overlap in propensity score distribution by treatment groups is presented for the full cohort (Supplementary Figure 1*A*) and the 1:3 matched cohort (Supplementary Figure 1*B*). Notice that the x-axis and y-axis vary in the 2 figures.

Oral Corticosteroid Treatment as a Time-Varying Covariate

Redeemed prescriptions of oral corticosteroids (Anatomic Therapeutic Classification code H02AB) during follow-up were identified. End of exposure was estimated based on information about dispensed date and defined daily dose. Overlap between exposure periods was collapsed.



Supplementary Figure 1. (*A*) Propensity score distribution in the full cohort. (*B*) Propensity score distribution in the 1:3 matched study population.

Supplementary Table 1. Patient Characteristics of the Study Cohort Grouped by Exposure to Anti-TNF Therapy

	Cohort Matched 1:3 on Propensity Score[a]			
	Anti-TNF Exposed (n = 4044)		Anti-TNF Unexposed (n = 12,132)	
Patient Characteristics	n	%	n	%
Sex				
Female	2038	50.4	6114	50.4
Male	2006	49.6	6018	49.6
Type of IBD				
CD	1355	33.5	4065	33.5
UC	2689	66.5	8067	66.5
Age at entry				
17–40 y	2284	56.5	7104	58.6
41–64 y	1515	37.5	4425	36.5
>64 y	245	6.1	603	5.0
Year at first IBD diagnosis				
<2005	1504	37.2	4757	39.2
2005–2019	2540	62.8	7375	60.8
IBD duration				
<1 y	2649	65.5	7047	65.5
1–10 y	866	21.4	2598	21.4
>10 y	529	13.1	1587	13.1
IBD-related surgery				
0	2583	63.9	7984	65.8
1	411	10.2	1505	12.5
>1	1050	26.0	2643	21.8
No. of hospital admissions with IBD				
0	2664	63.4	9648	79.5
1	756	18.7	1481	12.2
>1	724	17.9	1003	8.3
No. of outpatient visits with IBD				
0	1158	28.6	4289	35.4
1	111	2.7	970	8.0
>1	2775	68.6	6873	56.7
Comorbidities				
Cardiovascular disease[b]	152	3.8	420	3.5
Pulmonary disease[c]	106	2.6	283	2.3
Renal disease[d]	21	0.5	61	0.5
Liver disease[e]	43	1.1	117	1.0
Cancer[f]	69	1.7	165	1.4
Rheumatoid disease[g]	72	1.8	167	1.4
Other intestinal disease[h]	92	2.3	214	1.8
Infections[i]	369	9.1	928	7.6

Supplementary Table 1. Continued

	Cohort Matched 1:3 on Propensity Score[a]			
	Anti-TNF Exposed (n = 4044)		Anti-TNF Unexposed (n = 12,132)	
Patient Characteristics	n	%	n	%
Medication				
Mesalamine	2664	65.9	6824	56.2
Intestinal corticosteroids	2448	60.5	4986	41.1
Oral corticosteroids	1391	34.4	3370	27.8
Azathioprine	857	21.2	1297	10.7

CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis.
[a]Matched on sex, IBD type, IBD duration, and propensity score. The following variables were included in the propensity score: sex, age at IBD diagnosis, IBD subtype (CD or UC), period of IBD diagnosis, region of Denmark, IBD-related surgeries, comorbidities, and medications.
[b]Vascular disease in the brain, hypertensive heart disease, ischemic heart disease, diseases of the endocardium and valves, or cardiac arrest.
[c]Pulmonary heart disease, chronic lower respiratory diseases, lung diseases due to external agents, or interstitial pulmonary diseases.
[d]Hypertensive renal disease, glomerular diseases, renal failure, or kidney transplantation.
[e]Chronic viral hepatitis, liver disease, or esophageal varices.
[f]All cancers except malignant neoplasms.
[g]Systemic connective tissue disorders or ankylosing spondylitis.
[h]Abscess or fistulas.
[i]Serious infections.