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Elevated helicobacter pylori prevalence in patients receiving TNF-α blocker therapy for inflammatory bowel disease

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Abstract

The aim of this retrospective study was to investigate the prevalence of Helicobacter pylori (H. pylori) in patients with ulcerative colitis or Crohn's disease who received TNF-α blocker therapy compared to a control group and to evaluate H. pylori as a potential side effect of TNF-α inhibitors in patients with dyspeptic complaints. This study included 140 patients aged 20-85 years. Among these patients, 70 were diagnosed with ulcerative colitis or Crohn's disease and prescribed TNF-α blockers assigned to the study group. The remaining 70 patients did not receive TNF-α blockers and were assigned to the control group. Patients' demographic data such as age and gender, biochemical laboratory parameters, dyspeptic diseases, drugs used and duration of usage were recorded. The quantity of H. pylori positivity was found as 45.7% in all patients. Of the 76 male patients, 39 (51.3%) were H. pylori (+), and 37 (48.7%) were H. pylori (-). Of the 64 female patients, 25 (39.1%) were H. pylori (+), and 39 (60.9%) were H. pylori (-). There was no statistically prominent disparity between the H. pylori (+) and H. pylori (-) patients regarding age and gender. The rate of H. pylori positivity was statistically meaningly lower in the study group compared to the control group (p=0.027). Our study suggests that TNF-α blockers may increase the risk of H. pylori infection in patients with ulcerative colitis or Crohn's disease and that H. pylori should be considered a potential side effect of TNF-α inhibitor therapy in these patients. Further research is needed to confirm these findings and investigate this association's underlying mechanisms. Clinicians should consider testing for H. pylori in patients receiving TNF-α inhibitors who develop dyspeptic symptoms.

Keywords: Ulcerative colitis, crohn's disease, TNF-α blockers, helicobacter pylori, dyspeptic diseases

Introduction

Inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease are chronic conditions affecting millions worldwide. These conditions can cause gastrointestinal symptoms, including abdominal pain, diarrhoea, and weight loss, and can significantly impact patients' quality of life [1-3]. TNF-α blockers have been developed as a new class of drugs to manage the symptoms of IBD symptoms by targeting the body's inflammatory response. While TNF-α blockers effectively reduce inflammation and improve clinical outcomes in IBD patients, their use is not without potential side effects [4, 5]. One such side effect is the increased risk of infection with *H. pylori*. *H. pylori* is a bacterium that can colonise the stomach lining and cause dyspeptic complaints, such as abdominal pain, bloating, and nausea [6-9]. The prevalence of *H. pylori* in IBD patients receiving TNF-α blocker therapy has not been well-studied [10-14]. Therefore, in this retrospective study, we aimed to investigate the effects of TNF-α blockers on the prevalence of *H. pylori* in patients with ulcerative colitis or Crohn's disease. Our findings may have important implications for using TNF-α blockers in IBD patients, particularly those who develop dyspeptic symptoms

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during treatment. In this introduction, we have provided background information on the prevalence and impact of IBD, introduced TNF-α blockers as a potential treatment option, and highlighted the possible side effect of *H. pylori* infection. We have also set the context for our study by explaining the gap in the literature and the importance of investigating this topic. By doing so, we aim to engage the reader and encourage them to continue reading the article.

Material and Methods

This study examined the data of patients using TNF-α blockers who applied to Giresun Training and Research Hospital General Surgery and Gastroenterology outpatient clinics with dyspeptic complaints between January 2021 and December 2022. The local ethics committee of our hospital approved the retrospective study protocol, and the study followed the ethical principles of the Declaration of Helsinki, revised in 2013.

This study included 140 patients aged 20-85 years who presented to our hospital with dyspeptic complaints, including pain or burning in the stomach, bloating, excessive belching or nausea after eating, an early feeling of satiety etc. Among these patients, 70 were diagnosed with ulcerative colitis or Crohn's disease and prescribed TNF-α blockers (infliximab, adalimumab, stelara and others) assigned to the study group. The remaining 70 patients did not receive TNF-α blockers and were assigned to the control group. Patients currently on antibiotics or with a history of receiving antibiotics over the past four weeks, pregnant and lactating women and patients with malignancies (e.g. gastric cancer) were excluded from the study.

Patients' demographic data such as age and gender, biochemical laboratory parameters, dyspeptic diseases, drugs used and duration of usage were recorded. The results were compared between the study and control groups.

Detection of H. Pylori Antibodies in the Study Group

The presence of *H. pylori* was investigated utilizing serological antibody concentrations. Accordingly, the enzyme-linked immunosorbent assay was based on quantitatively detecting *H. pylori* (IgG, IgA) antibodies in the serum of the patients in the study group using a commercially available kit (Human-Germany) according to the instructions of the manufacturer.

The principle of this test is based on binding specific antibodies (IgG, IgA) to *H. pylori*, if present, to examine the antigens of this bacteria installed on the inner surface of the ELISA test dish. Then the word is irrigated with a washing solution to remove the unbound substances. The plate is then incubated for 30 minutes after the end of the washing. The substrate (TMB) is added.

Statistical Analysis

Statistical analysis of the data obtained in this study was performed using the SPSS version 22.0 (SPSS for Windows, Statistical Package for the Social Sciences, IBM Corp., Armonk, NY). The normality of the variables was evaluated using the Shapiro-Wilk test. Continuous variables are expressed as mean ±standard, while categorical variables are given as frequency and percentage (n, %). The comparisons between the two groups were made using the Mann-Whitney U test, Chi-square test and Fisher's exact test. $p<0.05$ values were considered statistically significant.

Results

A total of 140 patients were included in the study, with 70 being in the study group and 70 in the control group. Of these patients, 76 (54.3%) were male, and 64 (45.7%) were female. All patients' mean age was 47.90±13.015 (20-85) years. The rate of *H. pylori* positivity was found as 47.1%.

No statistically significant difference was found between the two groups regarding age and gender. When biochemical parameters were examined, platelet count, eosinophil count and GGT were significantly higher (for all, $p<0.05$). At the same time, glucose, ALT, AST, ALP, Ca, P and ferritin were significantly lower in the study group compared to the control group (for all, $p<0.05$). The comparison of demographic features and biochemical parameters between the groups is given in Table 1.

Table 1. Comparison of demographic features and biochemical parameters between the study and control groups

Variables	Control Group (n=70) mean±SD	Study Group (n=70) mean±SD	U/χ^2	p*
Age (years)	48.20±10.45	47.60±15.23	2409	0.864
WBC	7.59±2.56	7.97±2.74	2699	0.299
HGB	13.06±1.89	12.36±2.45	2089	0.132
HTC	45.33±50.79	38.12±6.48	2199.5	0.296
MCV	97.40±93.14	83.56±8.52	2042.5	0.117
PLT	259.53±75.23	324.09±107.17	3350.5	**<0.001**
Neutrophils	4.62±2.38	4.95±2.6	2743.5	0.221
Lymphocytes	2.25±0.97	2.11±1.012	2129	0.181
Eosinophils	0.203±0.179	0.36±0.47	302.5	**0.017**
Creatinine	1.54±5.67	0.85±0.53	2430.5	0.935
Urea	31.20±13.18	28.03±12.94	1978	0.065
Glucose	110.68±55.53	97.81±18.49	1857.5	**0.014**
ALT	22.77±17.30	15.08±9.60	1446	**<0.001**
AST	22.03±14.44	17.79±9.20	1772	**0.007**
Protein	73.64±3.67	72.63±5.66	2146.5	0.206
Albumin	44.98±3.97	43.93±4.97	2172	0.246
GGT	28.74±30.82	29.27±86.86	1847	**0.012**
ALP	85.30±21.80	76.56±21.93	1851	**0.017**
Ca	9.57±0.69	9.45±0.511	1967	**0.044**
P	3.82±0.88	3.52±0.54	1802	**0.014**
CRP	12.28±29.99	16.73±33.73	2661	0.378
TSH	1.90±1.29	1.97±1.406	2516	0.783
Ferritin	90.94±172.96	79.29±156.39	1950	**0.037**
	n (%)	**n (%)**		
Gender				
Male	38 (50)	38 (50)	0.00	1.00
Female	32 (50)	32 (50)		

SD: Standard deviation; U: Mann-Whitney U test; χ^2: Chi-square test; *$p<0.05$

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Demographic features and biochemical parameters were also evaluated according to the presence of *H. pylori.* Accordingly, of the 76 male patients, 40 (52.6%) were *H. pylori (+)*, and 36 (44.4%) were *H. pylori (-).* Of the 64 female patients, 26 (40.6%) were *H. pylori (+)*, and 38 (59.4%) were *H. pylori (-)*. There was no statistically significant difference between the *H. pylori (+)* and *H. pylori (-)* patients regarding age and gender.

When biochemical parameters were examined, the mean MCV value was statistically significantly higher in the *H. pylori (+)* patients than in *H. pylori (-)* patients (p=0.001). Table 2 shows the comparison of demographic features and biochemical parameters between the *H. pylori (+)* and *H. pylori (-)* patients [Table 2].

Table 2. Comparison of demographic features and biochemical parameters according to H. Pylori positivity

Variables	H. Pylori (+) (n=66) mean±SD	H. Pylori (-) (n=74) mean±SD	U/χ^2	p*
Age (years)	47.94±12.57	47.88±13.34	2319	0.894
WBC	7.43±2.17	7.99±2.89	2482	0.546
HGB	12.99±2.27	12.551±2.17	1947.5	0.142
HTC	39.23±6.17	38.48±5.79	2037	0.279
MCV	87.44±5.11	83.44±8.19	1519.5	**0.001**
PLT	299.54±109.03	287.24±90.82	2195.5	0.690
Neutrophils	4.45±1.75	4.98±2.83	2451	0.482
Lymphocytes	2.23±1.01	2.16±0.98	2224	0.783
Eosinophils	0.36±0.54	0.2309±0.2	2062	0.330
Creatinine	0.89±0.60	0.83±0.64	1879	0.078
Urea	30.08±13.03	29.24±13.17	2097	0.410
Glucose	110.65±63.84	100.47±18.86	2106	0.432
ALT	18.44±10.79	22.61±37.10	2144.5	0.536
AST	17.98±5.21	20.99±14.77	2291.5	0.988
Protein	71.48±10.52	73.33±4.37	2348	0.796
Albumin	44.35±5.10	44.52±4.16	2169.5	0.609
GGT	19.58±8.56	34.58±81.30	2327.5	0.864
ALP	78.08±18.18	82.59±24.27	2528.5	0.246
Ca	9.56±0.57	9.48±0.63	2123,5	0.477
P	3.52±0.63	3.76±0.80	2485.5	0.205
CRP	12.08±27.10	15.94±34.47	2643.5	0.125
TSH	2.07±1.50	1.86±1.25	2156.5	0.571
Ferritin	70.59±144.79	93.70±175.18	2434.5	0.528
	n (%)	**n (%)**		
Gender				
Male	40 (52.6)	36 (47.4)	2.010	0.156
Female	26 (40.6)	38 (59.4)		

SD: Standard deviation; U: Mann-Whitney U test; χ^2:Chi-square test; *p<0.05

The rate of *H. pylori* positivity was statistically significantly higher in the study group than in the control group (p=0.042). H. pylori rates of the groups are shown in Figure 1.

When TNF-α blocker drugs used in 33 patients in the study group were evaluated with Fisher's Exact test, *H. pylori* positivity rate was found as 54.5% with infliximab, 66.7% with adalimumab, 37.5% with stelara and 58.8% with the other drugs. No statistically significant difference was found between the drugs in terms of the rate of *H. pylori* positivity (p=0.627). Table 3 shows *H. pylori* positivity according to ulcerative colitis and Crohn's disease. Accordingly, no significant difference was found between ulcerative colitis and Crohn's disease regarding *H. pylori* positivity (p>0.05).

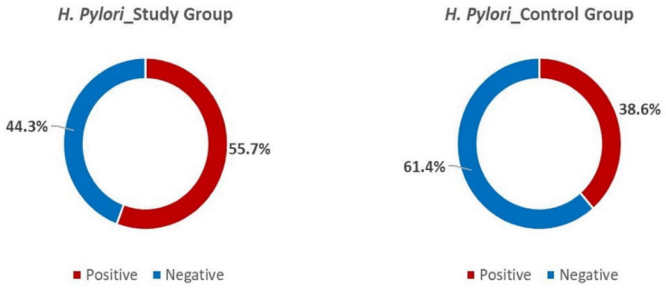

Figure 1. H. Pylori rates of the groups

Table 3. H. Pylori status according to diseases in the study group

	H. pylori		total	p
Disease	**positive**	**negative**		
Ulcerative colitis	30 (60%)	20 (40%)	50 (100%)	0.528
Crohn's disease	9 (45%)	11 (55%)	20(100%)	

Discussion

Our study has shown that the prevalence of *H. pylori* was significantly higher in IBD patients treated with TNF-α blockers compared to the control group. This finding suggests that TNF-α blockers may increase the risk of *H. pylori* infection in these patients, which should be considered when prescribing these drugs. One potential mechanism is that TNF-α plays a role in the immune response against *H. pylori* infection. TNF-α is involved in recruiting immune cells to the site of infection, promoting inflammation, and activating the immune system to fight against the bacterium. Inhibition of TNF-α by TNF-α blockers may weaken the immune response, allowing H. pylori to more easily colonize the stomach lining more [15, 16]. Another possible mechanism is that TNF-α blockers may affect the gastric environment, creating more favourable conditions for the survival and colonization of *H. pylori.* TNF-α has been shown to regulate the production of stomach acid and other factors in the gastric lining that can inhibit the growth of *H. pylori.* Inhibition of TNF α may alter the gastric environment, making it more conducive to the colonization of *H. pylori* [17-20]. Additionally, it has been suggested that TNF α blockers may alter the gut microbiota composition, which can indirectly affect *H. pylori* colonization. Disruption of the normal gut microbiota by TNF-α blockers may affect the balance of bacteria in the stomach and create conditions that favour the colonization of *H. pylori* [21-25]. It's important to note that the relationship between TNF-α blockers and *H. pylori* colonization is complex and likely involves multiple factors [26]. Further research is needed to elucidate the specific mechanisms by which TNF-α blockers may facilitate *H. pylori* colonization in patients with IBD and to better understand this association's

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clinical implications. It's always recommended to consult with a qualified healthcare professional for specific medical advice or information.

Dyspeptic symptoms are common in IBD patients, and our study suggests that *H. pylori* should be viewed as a potential cause of these symptoms in patients receiving TNF-α blockers. Clinicians should be aware of the increased risk of H. pylori infection in these patients and consider testing for *H. pylori* when patients develop dyspeptic symptoms during TNF-α blocker therapy.

Limitations

The main limitations of this study include the relatively small number of patients. In addition, although some biochemical parameters significantly differed between the groups with and without anti-TNF-α therapy (e.g. glucose, ALT, AST, ALP, Ca, P and ferritin), we could not analyse these results due to the small number of patients. These differences might be investigated in detail in more comprehensive studies. And we did not investigate the clinical outcomes of *H. pylori* infection in TNF-α blocker-treated patients. However, as a strength, this study is the first in the literature to show the effect of anti-TNF-α therapy on the presence of *H. pylori*.

Conclusion

This retrospective study showed that TNF-α blocker therapy is associated with a higher prevalence of *H. pylori* infection in patients with ulcerative colitis or Crohn's disease. Our findings have important clinical implications for managing these conditions, as *H. pylori* infection can cause dyspeptic complaints and may worsen the symptoms of IBD.

Given the potential side effects of TNF-α blockers, it is essential to monitor patients for dyspeptic symptoms and to test for *H. pylori* infection. Clinicians should consider the risk-benefit profile of TNF-α blocker therapy on a case-by-case basis, considering factors such as disease severity and other comorbidities.

Our study also highlights the need for further research to investigate the underlying mechanisms of the association between TNF-α blockers and *H. pylori* infection. This may include studies that examine the impact of TNF-α inhibition on the immune response to *H. pylori,* as well as studies that investigate the effects of other factors such as duration of therapy and patient demographics.

In conclusion, our study adds to the growing body of evidence on the potential side effects of TNF-α blockers in managing IBD. Our findings underscore the importance of monitoring patients for dyspeptic symptoms and testing for *H. pylori* infection and may inform clinical decision-making in driving these conditions.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The local ethics committee of Giresun University hospital approved the study protocol (Number of decision: KAEK-27).

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