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Effects of anti-TNF-α treatment on lipid profile in inflammatory bowel disease

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MAIN POINTS

- This study evaluates the effect of anti-TNF treatment on lipid profile in pateints with IBD.
- No significant alterations were demonstrated in total cholesterol, LDL and triglyceride levels over 24 weeks. A significant increase in HDL levels was observed from baseline to 24 weeks.
- There are studies in the literature with conflicting results on this issue. Therefore, prospective studies with larger sample sizes, including long-term follow-up of patients and dietary factors, are warranted.

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ABSTRACT

Aim: Tumor necrosis factor-alpha (TNF-α) plays a significant role in the pathogenesis of inflammatory bowel disease (IBD) and is associated with atherosclerosis and dyslipidemia. Despite the established use of anti-TNF-α antagonists in the treatment of IBD, the impact of these drugs on lipid profiles remains unclear, with conflicting evidence in the literature. Our study aims to assess the effect of anti-TNF treatment on lipid profile in pateints with IBD.

Materials and Methods: Lipid profiles, including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and the atherogenic index, were measured in 103 patients (66 patients with CD, 37 with UC) at baseline and at 12 and 24 weeks of TNF-α inhibitor treatment, and the results were compared between the groups.

Results: No significant change in cholesterol levels was observed over the course of 24 weeks (p=0.349). However, a noteworthy increase in HDL levels was observed from baseline to 24 weeks (p=0.016). No significant alterations in LDL and triglyceride levels were noticed over 24 weeks. The atherogenic index demonstrated no significant changes over the treatment period (p=0.462).

Conclusion: Anti-TNF-α therapy, either with infliximab or adalimumab, among patients with IBD does not lead to a considerable alteration in lipid profiles after 3 and 6 months of treatment, with the exception of a significant increase in HDL.

Keywords: Inflammatory bowel diseases, Tumor necrosis factor-alpha, Dyslipidemia, Chronic inflammation, Atherosclerosis

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are two major forms of inflammatory bowel disease (IBD), the common feature of which is chronic inflammation of the gastrointestinal tract. Chronic inflammation is believed to contribute to the development of cardiovascular complications by contributing to all atherosclerotic processes [1]. Despite a systematic review assessing 11 studies concluding that IBD is not linked to elevated cardiovascular mortality [2, 3] and a meta-analysis results showing that mortality from cardiovascular disease was decreased [4], there were also studies indicating an increase in the risk of cardiovascular complications, even if not associated with an increase in mortality [3, 5-9]. Therefore, it is essential to evaluate and treat cardiovascular risk factors, including dyslipidemia, in patients with IBD.

Tumor necrosis factor-alpha (TNF-α) has been demonstrated to play a key role as a pleiotropic proinflammatory factor in the pathogenesis of IBD, and preclinical and clinical evidence supports the role of TNF-α in atherosclerosis and dyslipidemia [10-13]. For more than two decades, anti-TNF-α inhibitors have been the primary cornerstone in the treatment of IBDs. These drugs regulate the excessive immune response in the body, thereby reducing inflammation and helping control symptoms. As a strong modulator of inflammation, TNF-α inhibitors should be expected to improve lipid profiles in patients, but there are conflicting studies in the lit-

erature. The mechanisms by which anti-TNF treatment affects lipid profiles are not fully understood, but potential explanations include reduced inflammation, improved insulin sensitivity, modulation of adipokines, direct effects on lipid metabolism, and indirect effects through changes in disease activity [14-17].

Understanding the mechanisms by which these drugs might impact lipid metabolism is crucial. Therefore, the main goal of the current study was to evaluate the impact of TNF-α inhibitors on the lipid profiles of individuals diagnosed with IBD.

MATERIALS AND METHODS

This retrospective observational study aimed to evaluate the demographic characteristics of patients with inflammatory bowel disease (IBD) and assess the effects of anti-TNF-α treatment on lipid profiles. The study was conducted at Ankara City Hospital, Ankara, Turkey, from January 2020 to October 2023. Ethical approval of the research was obtained from the Institutional Review Committee (No: E1/4326/2023).

Study population

Subjects diagnosed with either CD or UC were eligible for inclusion. Participants were required to be currently undergoing treatment with anti-TNF-α medication, either adalimumab or infliximab. Patients with other chronic inflammatory conditions, contraindications to TNF-α inhibitors, treatment with anti-TNF-α inhibitors less than 6 months, history of any malignancy, younger than 18 years old, pregnant, or unwilling to participate were excluded from the study. In addition, subjects on antilipidemic agents were not included in the study.

Data collection

During the study, printed and electronic medical records were searched for data collection. Demographic data include age, sex, history of abdominal surgery, and body mass index (BMI). Regarding CD; disease duration, behavior, current treatment, and presence of perianal pathologies were recorded for each patient. In addition, regarding UC, extension of the disease was recorded. Patients undergoing anti-TNF-α inhibitor treatment were assessed for lipid profiles, including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and the atherogenic index at baseline (start of treatment), 12 weeks, and 24 weeks of the TNF-α inhibitor treatment.

Statistical analysis

Statistical analyses were carried out by using The Statistical Package for Social Sciences (SPSS, version 24.0) for Windows (IBM Corp.; Armonk, NY, USA). The Kolmogorov–Smirnov test was used to evaluate the normality of the continuous variable distribution. Normal distributed continuous variables were represented as mean ± standard deviation and were compared using the repeated measures ANOVA with a post hoc Bonferroni test. Non-normally distributed continuous variables were described as medians (minimum and maximum) and were compared using the Friedman test with the post hoc Wilcoxon test. Categorical variables are described as frequency (percentage). A p-value of <0.05 was set statistically significant. Bonferroni correction was applied to control for Type I error rate, and the adjusted significance level was set at p <0.017 for the three time point comparisons. Power analysis was performed using G*Power version 3.1 (Heinrich Heine Universität, Dusseldorf, Germany) using repeated measures F-tests. The predicted power is 0.96 with a 0.05 type 1 error.

RESULTS

The demographic characteristics of the study cohort, which consists of the CD and UC groups, are given in Table 1. In the CD group (n=66), patients exhibited a mean age of 41.0 ± 13.1 years, with a male predominance of 62.1%. The median disease duration was 68.0 months (range: 12.0 – 276.0), and the mean BMI was 23.7 ± 4.8. Notably, 51.5% of CD cases localized to the terminal ileum (L1), while the majority presented with inflammatory behavior (B1, 59.1%). Perianal disease was evident in 33.3%, and 47.1% had undergone prior major abdominal surgery. Adalimumab and infliximab were the predominant medications (62.1% and 37.9%, respectively. In the UC group (n=37), patients had a mean age of 44.9 ± 13.4 years, with 67.6% being male. The median disease duration was 84.0 months (range: 12.0-300.0), and the mean BMI was 23.7 ± 4.6. The majority of UC cases exhibited extensive disease (73.0%).

Table 2 demonstrates the impact of TNF-α inhibitor treatment on lipid profiles over 12 and 24 weeks. The results revealed no significant change cholesterol levels over the course of 24 weeks (p=0.349). However, a noteworthy increase in HDL levels was observed from baseline to 24 weeks (p=0.016). No significant alterations in LDL and triglyceride levels were noticed over 24 weeks. The atherogenic index demonstrated no significant changes over the treatment period (p=0.462). These findings suggest a substantial influence of TNF-α inhibitor treatment on HDL levels in our cohort of patients with IBD.

DISCUSSION

This study demonstrated that undergoing anti-TNF-α therapy, with adalimumab or infliximab, among patients with IBD does not lead to a considerable alteration in lipid profiles after 3 and 6 months of therapy, except a significant increase in HDL.

In the current literature, the effect of anti-TNF-α therapy on lipid profile is mostly studied in rheumatological diseases like systemic lupus erythematosus and rheumatoid arthritis, with inconsistent results. Our results regarding the increase

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Table 1. Demographic characteristics of all patients with IBD.

	Crohn (n=66)	Ulcerative colitis (n=37)
Age, years, mean ± SD	41.0 ± 13.1	44.9 ± 13.4
Sex (Male), n (%)	41 (62.1)	25 (67.6)
Disease duration, months, median (min-max)	68.0 (12.0 -- 276.0)	84.0 (12.0 - 300.0)
BMI, kg/m^2, mean ± SD	23.7 ± 4.8	23.7 ± 4.6
UC Extension, n (%)		
Left Sided		10 (27.0)
Extensive		27 (73.0)
CD localization, n (%)		
Ileal (L1)	34 (51.5)	
Colonic (L2)	8 (12.1)	
Ileo-colonic (L3)	24 (36.4)	
CD Behavior, n (%)		
Inflammatory disease (B1)	39 (59.1)	
Stenosing (B2)	11 (16.7)	
Penetrating (B3)	16 (24.2)	
P (Perianal disease), n (%)	22 (33.3)	
Prior major abdominal surgery, n (%)	31 (47.1)	0 (0.0)
Current medication, n (%)		
Adalimumab	41 (62.1)	23 (62.2)
Infliximab	25 (37.9)	14 (37.8)

BMI: body mass index, Montreal classification of Crohn's disease (CD); Disease location (L): L1 terminal ileum, L2 colon, L3 ileocolon; Disease behavior (B): B1 non stricturing non penetrating; B2 stricturing, B3 penetrating, UC: ulcerative colitis.

Table 2. Effects of anti-TNF-α inhibitor treatment on lipid profile.

	Baseline (1)	12 weeks (2)	24 weeks (3)	p value	p value (1-2)	p value (1-3)	p-value (2-3)
Total cholesterol (mg/dl)	162.98 ± 42.99	167.15 ± 43.26	165.57 ± 40.1	0.349	--	--	--
HDL (mg/dl)	42 (36-51)	45 (36-54)	45 (38-54)	**0.016**	0.137	0.003	0.120
LDL (mg/dl)	90.28 ± 35.56	90.39 ± 37.11	90.77 ± 35.89	0.976	--	--	--
Triglycerides (mg/dl)	128 (93-170)	132 (99-190)	134 (98-177)	0.648	--	--	--
Atherogenic index	0.1 ± 0.26	0.13 ± 0.27	0.11 ± 0.25	0.462	--	--	--

HDL: high-density lipoprotein, LDL: low-density lipoprotein.

in HDL levels are consistent with those of most of these studies [17-20]. However, data regarding the comparable effects of anti-TNF-α therapy in individuals with IBD are rather limited, and conflicting results are also present. For instance, in a study that included 128 patients with IBD who received infliximab or adalimumab, no significant changes in lipid profile were observed after 1 and 3 years of treatment [21]. Although our study had a shorter follow-up period than this study, we did not observe any changes except for HDL levels. In another systematic review, the use of anti-TNF-α agents showed no association with changes in total cholesterol following both induction and maintenance therapy, and no long-term alterations in HDL, LDL, or triglyceride levels were observed, but short-term changes in HDL, LDL, and triglyceride were observed in one study [22]. A different cohort consisting of 22 patients with IBD who received infliximab was prospectively monitored for 14 weeks. There was no alteration in triglyceride or LDL levels, but there were significant increases cholesterol and HDL levels compared with baseline [23]. In another prospective study involving 111 patients with CD treated with infliximab, it was noted that plasma levels of total cholesterol and HDL showed an increase during the first 3 months of treatment, followed by a relatively stable pattern thereafter [24]. When we compare the findings of these studies with our own study, we believe that an increase in HDL levels can be seen in the short-term follow-up, but long-term follow-up studies should also be emphasized. In contrast with the results of some studies with long follow-up periods, an outcome from the 3-year monitoring of 56 patients with IBD undergoing anti-TNF-α therapy revealed significant increases in the AI index, total cholesterol, and LDL levels, while HDL levels remained unaffected [25].

As evident from studies published in the literature have shown inconsistent findings regarding the correlation between anti-TNF-α therapy and lipid alterations in IBD. The lipid profiles seen in IBD are influenced by a complicated interplay of inflammatory cytokines, acute phase reactants, and severe inflammation or surgical intervention that disrupts intestinal integrity [26]. Moreover, medications such as statins or corticosteroids can affect lipid metabolism. Therefore, we

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are likely to attribute these inconsistencies across studies to factors such as sample size differences, varying study durations, and inadequate adjustment for covariates such as comorbidities, levels of inflammation control with treatment, disease severity, response to treatment, and other medications used.

Limitations

The major limitation of this study was its retrospective design. In addition, dietary factors that may affect lipid levels could not be evaluated. Lastly, this was a single-center study with a relatively small sample size. Therefore, multicenter prospective studies with larger sample sizes, including long-term follow-up of patients and dietary factors, are needed.

CONCLUSION

While some evidence suggests the potential benefits of TNF-α inhibitors on lipid profiles, further large-scale, longer-duration, and more uniform studies are needed to better understand their effects in different patient populations and to clarify the underlying mechanisms. Therefore, it is essential for health care providers to monitor lipid levels regularly in patients receiving TNF-α inhibitors and to individualize treatment based on their specific lipid profile and overall cardiovascular risk.

Ethics Committee Approval: The ethics committee approval for the study was obtained from Ankara City Hospital Clinical Research Ethics Committee (No: E1/4326/2023).

Informed Consent: Given the retrospective nature of the study, informed consent was not required from patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no competing interests to declare.

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