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Original Article

Impact of anti-tumor necrosis factor treatment on lipid profiles in Korean patients with ankylosing spondylitis

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Objective: To investigate the effects of anti-tumor necrosis factor (TNF) treatment on lipid profiles and identify risk factors for an increase in total cholesterol (TC) after the anti-TNF treatment in ankylosing spondylitis (AS) patients.

Methods: This retrospective cohort study analyzed AS patients who received the first-line anti-TNF treatment. Patients with at least nine months of follow-up were included; those who were under 18 years or on any lipid-lowering agent were excluded. A linear mixed model was used to assess the impact of anti-TNF inhibitors on disease activity and lipid profile (TC, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides [TG]). Univariable and multivariable linear regression were used to identify risk factors for an increase in TC after 3 months of anti-TNF treatment.

Results: A total of 315 AS patients were enrolled (78.1% male, median age 32.0 [26.0~41.0]). TC, HDL, and TG levels significantly increased particularly within the first 3 months of anti-TNF treatment, while LDL level did not show significant changes. Changes in inflammatory markers and lipid particles (TC, LDL, TG) were correlated over time, but HDL showed no significant correlation. Older age, higher baseline erythrocyte sedimentation rate, and lower baseline LDL level were related to an increase in TC after 3 months of the anti-TNF treatment.

Conclusion: In AS patients, anti-TNF treatment has been found to increase lipid particles, potentially due to its anti-inflammatory effects. Future research should explore the underlying mechanism and the clinical implications of dyslipidemia, particularly the occurrence of cardiovascular events, following anti-TNF treatment in AS patients.

Keywords: Ankylosing spondylitis, Tumor necrosis factor inhibitors, Dyslipidemias, Inflammation

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease which can be effectively treated with anti-tumor necrosis factor (TNF) agents to alleviate symptoms and inflammation [1,2]. The inflammatory nature of rheumatic disease is a well-known risk factor of cardiovascular disease (CVD) [3]. Accumulated data has shown elevated cardiovascular morbidity and mortality in patients with AS. A previous meta-analysis up to January 2014 found that patients with AS have an increased risk of CVD. The incidence of myocardial infarction in AS patients was 5.3% (1.6%~11.0%), showing a significant increase

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compared to the control group (odds ratio [OR]=1.60, 95% confidence interval [CI]: 1.32~1.93). The incidence of stroke in AS patients was 3.6% (1.5%~6.5%), also showing a significant increase (OR=1.50, 95% CI: 1.39~1.62) over the control group [4]. And a recent meta-analysis comprising 40 studies also indicates a higher risk of ischemic heart disease and stroke in patients with axial-spondyloarthritis (ax-SpA) (OR: 1.51, 95% CI: 1.21~1.87 and OR: 1.30, 95% CI: 1.04~1.62, respectively) [5].

Dyslipidemia, a major risk factor of CVD, is characterized by an elevation of serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL), or triglycerides (TG) and reduced serum high-density lipoprotein cholesterol (HDL) concentration [6]. Since dyslipidemia is modifiable, monitoring of dyslipidemia should be emphasized along with identification of other factors that can affect the lipid profile. Therefore, several efforts have been made to identify the effect of anti-TNF inhibitor on lipid profiles, but the results were conflicting [7]. Moreover, extant studies on changes in the lipid profile after anti-TNF treatment in Korean patients with AS are limited [8]. Considering that the risk of CVD and dyslipidemia varies depending on race/ethnicity, a study specifically on Korean patients with AS is warranted. Hence, the object of this study was to investigate the effect of anti-TNF treatment on the lipid profile in Korean patients with AS. Factors associated with changes of lipid particles after anti-TNF treatment were also identified.

MATERIALS AND METHODS

Study population

We carried out a retrospective cohort study on patients with AS who received the first-line anti-TNF treatment according to availability of lipid profile between January 2010 and December 2020 in a rheumatology clinic at a tertiary referral hospital in Seoul, South Korea. All patients met the diagnostic criteria for AS defined by the 1984 modified New York criteria [9]. Patients under the age of 18 years, patients treated with any lipid lowering agent, or patients having less than nine months of follow-up information were excluded. This study was approved by the institutional review board (IRB) of Hanyang University Hospital (IRB file no. HYUH 2019-09-016). The need for informed consent was waived for this retrospective study.

Data collection

We obtained demographic and AS-related clinical information, including and the type of anti-TNF agent used and human leukocyte antigen-B27 positivity. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), as well as by the serum concentration of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Baseline and follow-up lipid profile data, including TC, LDL, HDL, and TG, were obtained at 3 months, 9 months, 15 months, and 21 months after initiating anti-TNF treatment. Dyslipidemia was defined as TC ≥240 mg/dL or one or more of the followings: LDL ≥160 mg/dL, TG ≥200 mg/dL, or HDL <40 mg/dL according to the definition per the Korean Society of Lipid and Atherosclerosis Korean guideline for the management of dyslipidemia 4th edition. Radiographs taken within 2 years of the baseline were evaluated using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

Statistical analysis

Continuous data with normal distribution were presented as

Table 1. Baseline demographics and characteristics of enrolled patients

Variable	Values (n=315)
Male	246 (78.1)
Age (yr)	32.0 (26.0~41.0)
HLA-B27 positivity (n=300)	267 (84.8)
Baseline mSASSS (n=300)	14.0 (9.1~22.0)
Initial BASDAI (n=282)	7.4 (6.4~8.5)
CRP (mg/dL) (n=313)	1.6 (0.5~3.9)
ESR (mm/h) (n=313)	41.0 (16.0~73.0)
Dyslipidemia	58 (18.4)
Lipid profile	
Total cholesterol (mg/dL)	174.6 (151.4~197.0)
LDL, mg/dL (n=125)	108.9±29.0
HDL, mg/dL (n=119)	49.0±13.7
TG, mg/dL (n=134)	93.5 (67.0~148.0)
Use of anti-TNF agents	
Adalimumab	123 (39.0)
Golimumab	80 (25.4)
Etanercept	62 (19.7)
Infliximab	50 (15.9)

Values are presented a number (%), median (Interquartile range), or mean±standard deviation. HLA: human leukocyte antigen, mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, TNF: tumor necrosis factor.

mean with standard deviations while non-normal distributed data were reported as median (interquartile range). And categorical data were represented as frequencies and percentages.

The effects of anti-TNF inhibitors on disease activity (BASDAI, ESR, and CRP) and lipid profile (TC, LDL, HDL, and TG) were assessed at five time points (baseline, 3 months, 9 months, 15 months, and 21 months). Differences in measurements between baseline and other time points were analyzed using a linear mixed model, and post-hoc tests with Bonferroni correction were applied if statistically significant differences were observed. The Spearman test was used to evaluate the correlation between changes in CRP and ESR levels and lipid particles from the baseline since the values were not normally distributed.

Univariable and multivariable linear regression analyses were performed to identify predictors for significant changes in TC (TC at 3 months to baseline TC). The multivariable linear analysis retained sex, age, and the type of anti-TNF agent; variables with a p-value ≤0.1 in the univariable analyses were included in the multivariable linear regression. To avoid multicollinearity, LDL was selected instead of TC. ESR and CRP were both considered as pivotal variables of substantial interest. Consequently, distinct multivariable models were developed for ESR and CRP to comprehensively address their significance.

Data analysis was performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was achieved at a p-value less than 0.05.

RESULTS

Demographics and clinical characteristics of enrolled patients

A total of 315 patients were included in the study. Most of the patients were male (78.1%), and the median age at baseline was 32.0 years (26.0~41.0 years). Baseline mSASSS was 14.0 units (9.1~22.0 units). Initial values for BASDAI, CRP, and ESR were 7.4 units (6.4~8.5 units), 1.6 mg/dL (0.5~3.9 mg/dL), and 41.0 mm/h (16.0~73.0 mm/h), respectively. A total of 58 patients (18.4%) could be classified as having dyslipidemia. Baseline measurements for TC, LDL, HDL, and TG were 174.6 mg/dL (151.4~197.0 mg/dL), 108.9±29.0 mg/dL, 49.0±13.7 mg/dL, and 93.5 mg/dL (67.0~148.0 mg/dL), respectively. The anti-TNF agents used were adalimumab (39.0%), golimumab (25.4%), etanercept (19.7%), and infliximab (15.9%). Table 1 provides an overview of the demographic and clinical characteristics of the enrolled patients.

Effects of anti-TNF agents on disease activity and lipid profile

Table 2 presents the impact of anti-TNF treatment on disease activity and lipid profile. A linear mixed model was used to assess differences in these factors over a 21-months follow-up

Table 2. Changes in disease activity and lipid profiles after anti-TNF treatment

	0 month		3 months		9 months		15 months		21 months		p-value	Significant time pair*
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD		
BASDAI (unit)	282	7.4±1.4	281	3.3±1.4	277	2.7±1.4	257	2.4±1.4	233	2.2±1.3	<0.0001	0 vs. (3, 9, 15, 21)
CRP (mg/dL)	313	3.0±3.5	311	0.5±1.4	313	0.4±1.0	243	0.4±0.9	212	0.3±0.7	<0.0001	0 vs. (3, 9, 15, 21)
ESR (mm/h)	313	46.4±35.9	310	10.0±16.7	311	9.4±15.1	243	9.7±13.4	210	10.3±14.6	<0.0001	0 vs. (3, 9, 15, 21)
TC (mg/dL)	315	177.2±36.1	312	194.7±37.7	311	192.6±38.6	246	193.5±36.4	212	195.5±37.3	<0.0001	0 vs. (3, 9, 15, 21)
LDL (mg/dL)	125	108.9±29.0	137	110.9±30.7	170	114.3±29.3	161	118.3±27.1	149	118.0±28.7	0.136	
HDL (mg/dL)	119	49.0±13.7	131	53.1±18.5	160	53.1±17.0	154	52.4±19.3	137	49.1±18.6	0.033	
TG (mg/dL)	134	123.3±84.8	159	155.7±120.5	188	146.0±106.9	167	149.8±113.8	152	178.5±171.6	<0.0001	0 vs. (3, 21)

SD: standard deviation, TNF: tumor necrosis factor, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride.
*Post-hoc tests are used with Bonferroni correction.

period. The results revealed a significant decrease in BASDAI scores and levels of CRP and ESR following anti-TNF treatment.

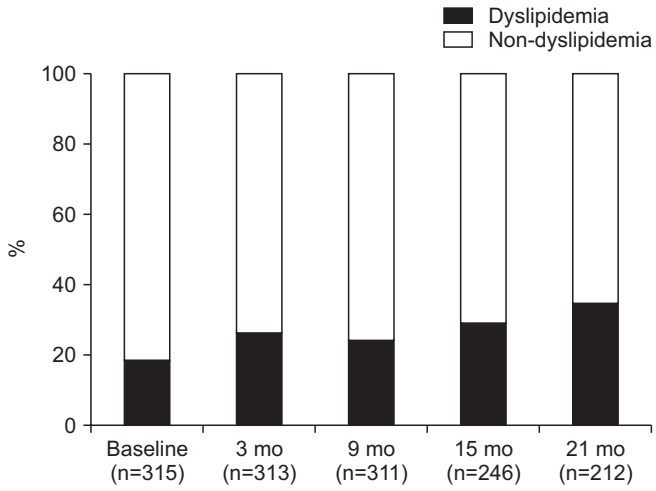

Figure 1. Changes in proportion of dyslipidemia patients following anti-tumor necrosis factor treatment.

Regarding lipid profile, there were significant increases in TC, TG, and HDL levels over the course of treatment, particularly within the first 3 months ($p<0.0001$, $p<0.0001$, $p=0.033$, respectively). However, there were no significant changes in LDL level following anti-TNF treatment. Furthermore, it appears that the proportion of patients with dyslipidemia, as defined by the Korean guideline for the management of dyslipidemia, increased over the follow-up duration (Figure 1).

Correlation between changes in CRP and ESR levels and lipid profile

Figure 2 illustrates the changes in CRP levels and lipid profiles over time following anti-TNF treatment. Similar patterns were observed in the graphs depicting ESR level and lipid particles (data not shown). There was a negative correlation between changes in CRP and ESR levels and TC from 3 months to 21 months, while changes in LDL and TG showed a negative cor-

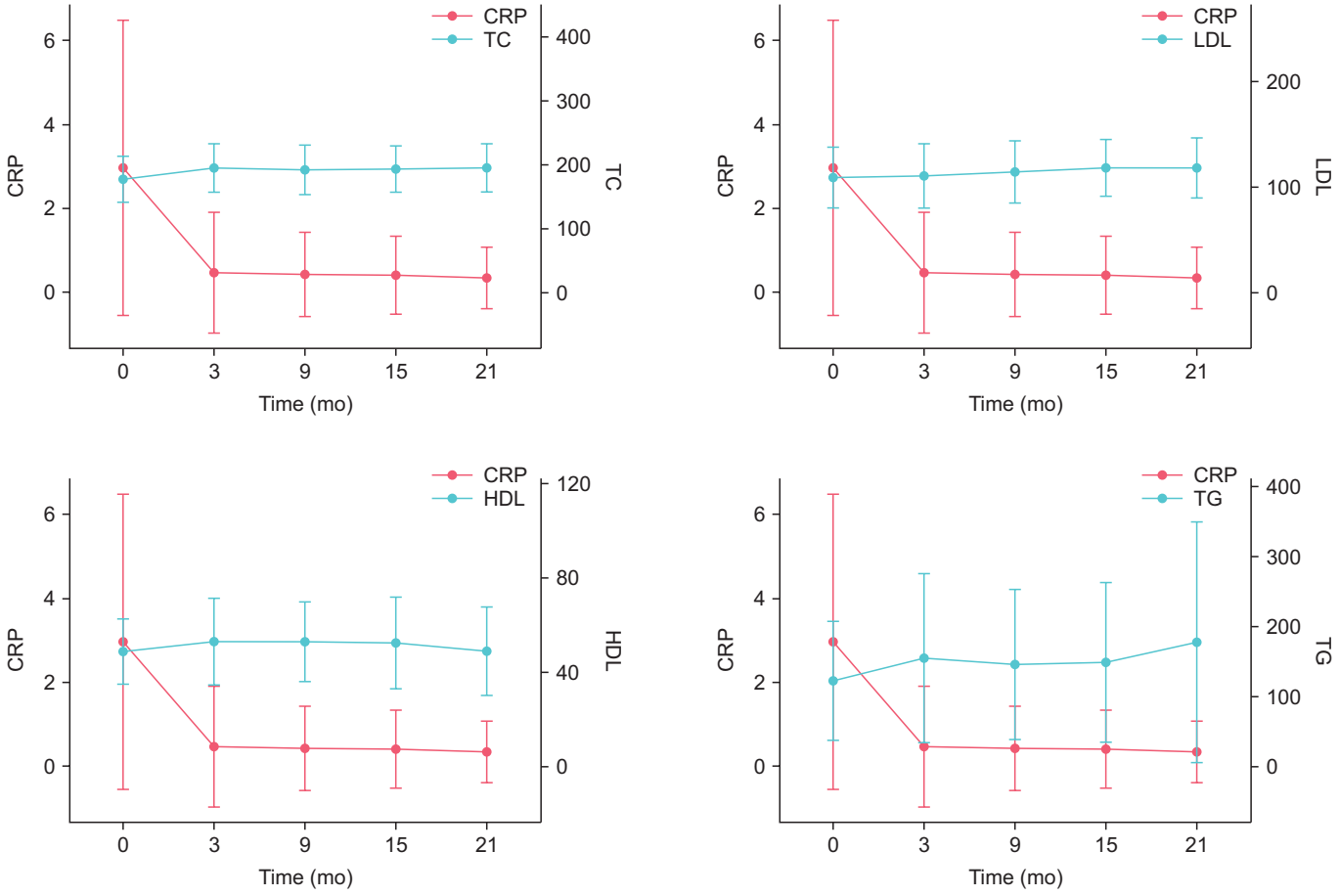

Figure 2. Changes in CRP and lipid particles after anti-tumor necrosis factor treatment. CRP: C-reactive protein, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride.

Table 3. Correlation between changes in CRP and ESR levels and lipid profile over time

	CRP				ESR			
	Δ3 months	Δ9 months	Δ15 months	Δ21 months	Δ3 months	Δ9 months	Δ15 months	Δ21 months
TC	−0.392‡	−0.431‡	−0.416‡	−0.400‡	−0.402‡	−0.420‡	−0.417‡	−0.429‡
LDL	−0.308*	−0.387†	−0.354†	−0.174	−0.333†	−0.404†	−0.410†	−0.210
HDL	−0.096	−0.194	−0.021	−0.056	−0.227	−0.200	−0.122	−0.245
TG	−0.374†	−0.322*	−0.509‡	−0.191	−0.308*	−0.304*	−0.361†	−0.091

Δ, Decrease of respective variable from baseline value. CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride. *p<0.05; †p<0.01; ‡p<0.001.

Table 4. Risk factors for increased total cholesterol after anti-TNF treatment

	Univariable		Multivariable			
	Estimate	p-value	CRP model (n=122)		ESR model (n=122)	
			Estimate	p-value	Estimate	p-value
Male (Ref. Female)	1.785	0.661	2.116	0.722	4.822	0.417
Age (yr)	0.122	0.436	0.742	0.002	0.720	0.002
Baseline mSASSS	−0.028	0.806				
Initial BASDAI	−0.424	0.735				
CRP (mg/dL)	2.405	<0.0001	1.190	0.093		
ESR (mm/h)	0.244	<0.0001			0.159	0.033
LDL (mg/dL)	−0.348	<0.0001	−0.322	0.001	−0.324	0.001
HDL (mg/dL)	−0.032	0.877				
TG (mg/dL)	−0.089	0.003	−0.047	0.203	−0.041	0.258
Use of anti–TNF agents						
Adalimumab	Reference		Reference		Reference	
Golimumab	−0.154	0.971	10.735	0.139	10.073	0.162
Etanercept	−10.423	0.024	−3.959	0.512	−4.489	0.453
Infliximab	−2.047	0.680	−3.616	0.686	−4.925	0.577

TNF: tumor necrosis factor, mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride.

relation from 3 months to 15 months. However, no significant correlation was observed between changes in CRP and ESR levels and HDL (Table 3).

Risk factors for elevation of total cholesterol after anti-TNF treatment

In order to identify risk factors for an increase in TC after 3 months of anti-TNF treatment, we performed univariable and multivariable linear regression analyses. In the univariable analysis, it was observed that higher baseline CRP (estimate 2.405, p<0.0001) and ESR (estimate 0.244, p<0.0001) levels were significantly associated with an increase in TC. Conversely, lower baseline LDL (estimate -0.348, p<0.0001) and TG (estimate -0.089, p=0.003) levels were associated with an increase in TC. And the use of etanercept was found to be related to a reduced likelihood of experiencing an increase in TC when compared to the use of adalimumab (estimate -10.423, p=0.024).

In multivariable model 1, which included CRP instead of ESR, older age (estimate 0.742, p=0.002) and lower baseline LDL level (estimate -0.322, p=0.001) remained significant factors associated with an increase in TC. In multivariable model 2, which included ESR instead of CRP, older age (estimate 0.720, p=0.002), higher baseline ESR (estimate 0.159, p=0.033), and lower baseline LDL level (estimate -0.324, p=0.001) were found to be associated with increased TC (Table 4).

DISCUSSION

In this retrospective cohort study, we examined the impact of anti-TNF treatment on lipid profiles and identified the risk fac-

tors associated with an increase in TC following the treatment. TC, HDL, and TG levels significantly increased particularly within the first 3 months of anti-TNF treatment, while LDL level did not change significantly. Changes in CRP and ESR levels and lipid profiles (TC, TG, and LDL) showed strong correlations over time, but changes in HDL did not exhibit significant correlation. Furthermore, we identified older age, higher baseline ESR, and lower baseline LDL levels as risk factors associated with an increase in TC after 3 months of anti-TNF treatment.

Various studies have investigated the impact of anti-TNF treatment on lipid profiles. Although few studies have reported findings consistent with ours, showing increases in TC, HDL, and TG levels after anti-TNF treatment but no significant changes in LDL [10,11], the majority of studies have shown largely inconsistent results: In our study, similar to some other studies, we observed that anti-TNF treatment resulted in a significant increase in TC [7,10-20]. Other studies did not find such an effect [21-24]. Additionally, the impact on TG levels varied across studies, with some showing an elevation [7,10,16,17,21], and others reporting no change [12,14,18,22,23]. The effects on LDL and HDL were also inconclusive. Some studies demonstrated an increase in LDL [15,17,19,20] while others did not find a significant change [10-12,16,18,21,22,24]. Similarly, HDL levels were found to increase in some studies [10-15,17-20], but not in others [7,16,21-24]. And It is noteworthy that the majority of these studies have primarily focused on RA.

Recently, Min et al. assessed the influence of anti-TNF treatment on lipid profiles and the atherogenic index of plasma (AIP) in a study involving ax-SpA patients (132 anti-TNF users and 106 non-users) [8]. Over a 2-year follow-up period, they also reported that TC levels showed a slight increase over the 2-year follow-up in the anti-TNF user group. However, other lipid parameters and AIP remained stable. These disparities with our study's findings could potentially be attributed to variations in patient populations and sample sizes.

The mechanism underlying the elevation of lipid particles following anti-TNF treatment remains unclear and is believed to be a complex process. One possible explanation is related to the resolution of inflammation. Chronic inflammation is known to alter lipid metabolism, impair lipoprotein function, and reverse cholesterol transport pathway [25]. As inflammation subsides, there may be metabolic changes that occur, leading to alterations in lipid metabolism and subsequent increases in lipid levels. Our study findings may support this hypothesis: anti-TNF treatment has been demonstrated to effectively reduce inflammation, and we observed correlations between changes in disease activity and changes in lipid particles. Furthermore, we identified a higher baseline ESR as a risk factor for an increase in TC following anti-TNF treatment. Similarly, a previous study of 230 patients with AS who received anti-TNF agents showed increased TC, LDL, and HDL levels. These lipid changes were only significant in patients whose CRP levels decreased below 10 mg/L, indicating that lipid alterations are dependent on inflammation reduction rather than being specific to the anti-TNF treatment [20]. However, further research is needed to fully comprehend the mechanisms involved in this process.

It is important to note that we did not consider the clinical implications of dyslipidemia in terms of CVD episodes, as our focus was solely on changes in lipid profiles. Interestingly, we observed no increase in LDL levels in our study. LDL is recognized as a major atherogenic lipoprotein and has traditionally been the primary target of cholesterol-lowering treatments. Furthermore, we observed an increase in HDL levels, which is known for its cardioprotective effects [26]. These findings might support that anti-TNF treatment does not appear to increase cardiovascular risk and may even have beneficial effects. A meta-analysis study showed that the use of anti-TNF is associated with a reduced risk of myocardial infarction and stroke in patients with RA [27]. However, in the case of AS, the available data is limited and conflicting. A previous study involving 5,046 patients with SpA demonstrated a reduced risk of major adverse cardiovascular events and cerebrovascular events with the use of anti-TNF agents [28]. However, a recent study of 450 patients with ax-SpA reported contrasting results, suggesting that the administration of anti-TNF treatment is not directly linked to a reduction in the CVD risk. Anti-TNF treatment may effectively control inflammation in the anti-TNF agent exposed group, leading to a reduction in cardiovascular risk. However, the analysis shows that controlling inflammation, rather than anti-TNF treatment itself, is more pivotal in reducing the risk of CVD [29]. Therefore, further studies evaluating changes in lipid profiles and CVD risk in anti-TNF users should focus on disease activity and inflammation, as well as traditional cardiovascular risk factors such as smoking and non-steroidal anti-inflammatory drug use.

The present study has some limitation. First, comorbidities such as hypertension, diabetes mellitus, obesity and other related factors known to alter lipid profile, including physical activity, were not considered. Second, there might be a selection bias

since we excluded patients treated with lipid-lowering agents. Third, our study solely concentrated on alterations in lipid profiles. However, it's worth noting that there are other markers of plasma atherogenicity, such as AIP [30]. Firth, the Ankylosing Spondylitis Disease Activity Score (ASDAS) which is a more disease-specific and objective disease activity index than ESR and CRP levels, could not be utilized in our study [31]. Another limitation of our study is the relatively short follow-up duration, highlighting the importance of conducting further studies with longer observation periods. This is particularly relevant as some studies have reported delayed alterations in HDL levels following anti-TNF treatment. For example, Wijbrandts et al. [22] found a significant increase in HDL levels after 16 weeks of adalimumab treatment, but by the end of the 52-week study, the levels had returned to baseline. Nevertheless, we believe that our study provides valuable foundational data, considering the limitations in previous research accounting impact of anti-TNF treatment on lipid profile in AS patients, particularly for the Korean population. Furthermore, we tried to identify the risk factors associated with an increase of TC following anti-TNF treatment which has received limited attention in prior studies.

CONCLUSION

In conclusion, anti-TNF treatment has been found to increase lipid particles in AS patients, likely due to its anti-inflammatory effects. Future research should focus on exploring the clinical importance of such alteration in lipid particles after anti-TNF treatment, particularly relationship with cardiovascular events, while taking into account the role of inflammation.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Concept and design: I.K., B.N., and T.H.K. Administrative, technical, or material support: S.L., J.H.S., T.H.K. Acquisition, analysis, or interpretation of data: All authors. Statistical analysis: I.K., B.N., N.C., Drafting of the manuscript: I.K., B.N. Supervision: T.H.K. All authors were involved in drafting and revising the manuscript critically for important intellectual content and final approval of the version to be published.

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