



Impact of Anti-TNF therapy on Thyroid Function in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

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ABSTRACT

Background: Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic autoimmune inflammatory disorders in which TNF- α plays a key role. Anti-TNF agents are widely used in the management of these diseases. Since TNF- α is also involved in the pathogenesis of autoimmune thyroid disease (AITD), this study aimed to assess whether anti-TNF therapy influences thyroid function.

Methods: This prospective study included 50 RA and 51 AS patients aged 18–85 years. Patients received either conventional treatment (DMARDs and NSAIDs/sulfasalazine) or anti-TNF agents. Serum TSH, free T4, and anti-TPO levels were measured at baseline and after 6 months. Thyroid dysfunction and AITD prevalence were compared between two treatment groups.

Results: In the RA group, subclinical hyperthyroidism was observed in both arms; In the anti-TNF group, one patient had hypothyroidism and another had subclinical hypothyroidism. Improvement in subclinical hyperthyroidism was seen in one patient in the DMARD arm, while improvement occurred in the patient with hypothyroidism and in one patient with subclinical hyperthyroidism in the anti-TNF arm ($p > 0.05$). In the AS group, central hyperthyroidism developed in one patient receiving conventional treatment. In anti-TNF group one patient with subclinical hypothyroidism improved to normal values, while another developed central hypothyroidism. Anti-TPO positivity was 18% in the conventional group and 3.4% in the anti-TNF group ($p > 0.05$). A significant TSH change was observed only in the RA-DMARD group ($p < 0.05$); While no significant changes in free T4 were detected in any group.

Conclusion: Anti-TNF therapy showed no significant effect on thyroid function or autoimmune thyroid disease in patients with RA and AS during the six-month follow-up.

Keywords: Rheumatoid arthritis; Ankylosing spondylitis; Autoimmune thyroid diseases; Thyroid dysfunction; TNF α ; Anti TNF- α treatment

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INTRODUCTION

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic autoimmune rheumatic diseases characterized by persistent inflammation. Their pathogenesis involves a complex interplay of genetic, environmental and immunological factors. Clinically, they are characterized by inflammatory arthritis and immunosuppressive therapies are widely employed to control disease activity and prevent joint damage (1-3).

The main treatment options for rheumatoid arthritis and ankylosing spondylitis include nonsteroidal anti-inflammatory drugs, corticosteroids (NSAIDs), conventional disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor-alpha (TNF- α) inhibitors, and other biological agents (4, 5). Although conventional therapies such as DMARDs are effective for many patients with RA and AS, disease activity remains inadequately controlled in a substantial proportion of cases. For patients with inadequate response to conventional treatment, targeted therapeutic strategies directed against key inflammatory cytokines have been developed. In particular, tumor necrosis factor-alpha (TNF- α) inhibitors have demonstrated significant clinical efficacy and have been shown to slow or prevent radiographic progression of structural joint damage (6).

The role of TNF- α in the pathophysiology of RA and AS is well established. In patients with AS, biopsy specimens from the sacroiliac joint have demonstrated increased infiltration of inflammatory cells, including T lymphocytes and monocytes (2). In patients with RA, elevated levels of TNF- α levels have been detected in synovial fluid, and experimental studies have shown that TNF- α promotes the production of other inflammatory cytokines. Inhibition of TNF- α has been shown to effectively reduce synovial inflammation (7).

The frequent association of autoimmune thyroiditis (AIT) with systemic rheumatic

diseases, including ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome has been documented in numerous studies (8-11). This comorbidity may be attributed to elevated systemic levels of TNF- α levels, which serves as a key mediator in immune-mediated inflammation. While experimental models suggest that TNF- α inhibition can lead to regression of inflammatory infiltration and fibrosis in thyroid tissue, the clinical impact of anti-TNF- α agents on thyroid function and hormone regulation remains to be fully elucidated (12).

This uncertainty is particularly relevant, as recent studies have demonstrated elevated TNF- α levels in patients with autoimmune thyroiditis, supporting the hypothesis that TNF- α contributes to disease pathogenesis by inducing the expression of multiple pro-inflammatory mediators in thyroid cells (13). Therefore, clarifying the effects of anti-TNF- α therapies on thyroid function is of considerable clinical significance.

The aim of this study was to evaluate the prevalence of autoimmune thyroid disease and thyroid dysfunction in patients with RA and AS, and to assess the effects of anti-TNF agents on thyroid function in these patients.

MATERIALS AND METHODS

This study was conducted at the Rheumatology Outpatient Clinic of the Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Yüzüncü Yıl University, between October 2022 and July 2023 and included patients diagnosed with rheumatoid arthritis and ankylosing spondylitis. The study cohort comprised 60 patients with RA, diagnosed according to the 2010 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria and 60 patients with AS classified using the ASAS (Assessment of Spondyloarthritis International Society) criteria. However,

several patients from both groups became unreachable during the study period, and were lost to follow-up. Additionally, one patient died while the study was ongoing.

In this prospective study, patients with RA and AS were stratified into two subgroups. Within the RA cohort, Group 1 comprised patients receiving conventional synthetic DMARD therapy, while Group 2 included those treated with anti-TNF agents. In the AS cohort, Group 1 included patients receiving NSAID and/or sulfasalazine and Group 2 consisted of patients treated with anti-TNF therapy.

Thyroid function tests were performed in both the RA and AS groups at baseline (day 0) and again at the sixth month of treatment and the results were compared. Throughout the follow-up period, patients were monitored for the development of thyroid dysfunction. In addition, anti-thyroid peroxidase antibody (anti-TPO) antibody levels were measured to evaluate the presence and prevalence of autoimmune thyroiditis.

In the RA cohort, 26 patients in Group 1 and 24 patients in Group 2 completed the study. In the AS cohort, the final analysis included 22 patients in Group 1 and 29 patients in Group 2, due to losses to follow-up and one patient death. Patients who were lost to follow-up were excluded from the analysis.

In both the RA and AS groups, patient ages ranged from 18 to 85 years. Differences in age or sex differences were not considered in the analyses.

Serum fT4 (normal range: 0.70–1.48 ng/mL), TSH (0.35–4.94 μ IU/mL), and anti-TPO antibodies (values >5.61 U/mL considered positive for autoimmune thyroid disease) were measured. Biochemical improvement was defined as the normalization of thyroid-related parameters, including TSH and free T4. Thyroid function status was categorized as follows:

1. Euthyroid: TSH and fT4 within their respective reference ranges.

2. Hypothyroidism: TSH >4.94 μ IU/ml accompanied by fT4 <0.70 ng/ml.

3. Hyperthyroidism: TSH <0.35 μ IU/ml accompanied fT4 >1.48 ng/ml. Patients with TSH <0.35 μ IU/ml and normal fT4 were classified as having subclinical hyperthyroidism, while those with TSH >4.94 μ IU/ml and normal fT4 were classified as having subclinical hypothyroidism. Patients with normal TSH and fT4 >1.48 ng/ml were categorized as having central hyperthyroidism, and those with normal TSH and fT4 <0.70 ng/ml were categorized as having central hypothyroidism.

Descriptive statistics for continuous variables were reported as mean, standard deviation, and minimum–maximum, while categorical variables were expressed as frequencies and percentages. Between-group comparisons were conducted using the Mann–Whitney U test, and within-group comparisons were assessed using the Wilcoxon test. The chi-square test was used to analyze associations between categorical variables. A *p* value <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 22.

The study was approved by the Ethics Committee of Van Yüzüncü Yıl University, Faculty of Medicine. Written informed consent was obtained from all participants after providing both oral and written information, in accordance with the principles of the Declaration of Helsinki.

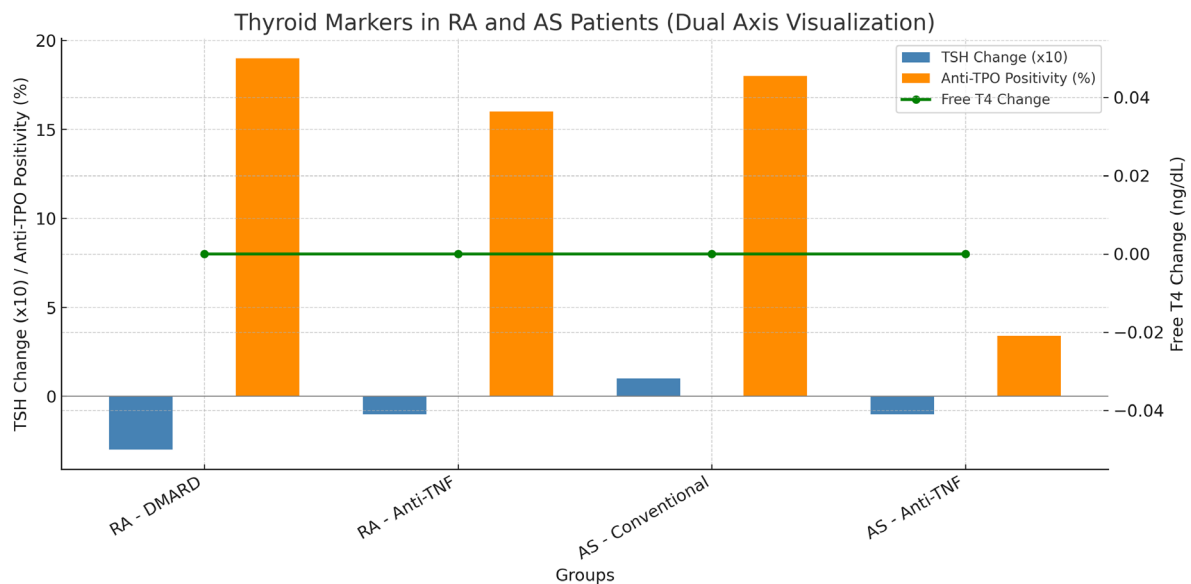
RESULTS

A total of 101 patients were included in the study, and distributed as follows: 27 patients in the RA–DMARD group, 23 patients in the RA–anti-TNF group, 26 patients in the AS–conventional therapy group, and 25 patients in the AS–anti-TNF group. The patients' demographic characteristics, thyroid function parameters and the anti-TNF agents used are summarized in Table 1.

Thyroid function tests and Anti-TPO antibody levels were assessed at baseline and after six months of treatment (Fig. 1).

Table 1. Demographic characteristics, Thyroid function parameters, and Medication profiles of the study population

	RA				AS			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Age	59.50	57.67	37.23	40.24				
Sex (F/M)	22/4	20/4	10/12	5/24				
RF+	17	19	-	-				
CCP+	14	17	-	-				
	Week-0	Month6	Week0	Month6	Week0	Month6	Week0	Month6
Anti-TPO+ Count	5	6	4	4	4	4	1	1
Anti-TPO+ Mean	22.17	21.25	10.37	6.11	64.48	61.81	17.91	13.06
TSH	1.53	1.85	2.44	1.78	1.59	1.68	1.35	1.26
fT4	1.03	1.02	1.09	1.08	1.03	1.09	1.02	1.07
Anti-TNF Agens								
Adalimumab			9	37.5%			13	44.8%
Etanercept			5	20.8%			7	24.1%
Golimumab			3	12.5%			3	10.3%
Infliximab			-	0%			4	13.8%
Certolizumab			7	29.1%			2	6.8%

**Fig. 1.** Changes in TSH, Free T4 and anti-TPO From Baseline to 6-Month Follow-Up

In the RA–DMARD group, a statistically significant decrease in TSH levels was observed after six months ($p=0.042$), while no significant change was detected in free T4 levels. In the RA–anti-TNF group, four patients exhibited thyroid dysfunction at baseline (one with hypothyroidism, one with subclinical hypothyroidism, and two with subclinical hyperthyroidism); three of these patients showed improvement after six months. However, overall, no statistically significant changes were observed in TSH

or free T4 levels overall ($p>0.05$).

In the AS–Conventional therapy group, no thyroid dysfunction was detected at baseline. After six months, central hyperthyroidism was observed in one patient. In the AS–anti-TNF group, one patient with subclinical hypothyroidism showed improvement; however, another patient, developed new-onset central hypothyroidism during follow-up. Overall, no statistically significant changes in hormone levels were observed in this group.

Table 2. Changes in thyroid Function parameters in patients with RA and AS during 6-Month Follow-up period

Group	Baseline Thyroid Dysfunction, n	Thyroid Dysfunction at 6-Month, n	Anti-TPO positivity%	Anti-TPO positivity at 6 Months, %	Change in TSH (<i>p</i> value)	Change in Free T4 (<i>p</i> value)
RA - DMARD	2 (Subclinical Hyperthyroidism)	1 patient Improved, no new cases reported	19%	19%	<0.05	>0.05
RA - Anti-TNF	4 (1 overt hypothyroidism, 1 subclinical hypothyroidism, 2 subclinical hyperthyroidism)	3 patients Improved, no new cases reported	16%	16%	>0.05	>0.05
AS - Conventional	0	1 new cases of Central Hyperthyroidism)	18%	18%	>0.05	>0.05
AS - Anti-TNF	1 (Subclinical Hypothyroidism)	1 baseline case Improved, 1 New case of Central Hypothyroidism	3.4%	3.4%	>0.05	>0.05

In the RA–DMARD group, 19% of patients were anti-TPO positive at both baseline and six months. In the RA–Anti-TNF group, 16% were positive, with no change after treatment. In the AS–Conventional therapy group, remained 18% positive throughout the study, while in the AS–Anti-TNF group, 3.4% were anti-TPO positive, showing no change over the study period (Table 2).

Regarding mean anti-TPO values, in Group 1 (RA–DMARD), baseline and at six-months levels were 22.17 ± 71.61 and 21.25 ± 31.56 U/mL, respectively, with no significant difference over time. Similarly, in group 2 (RA–anti-TNF), baseline and six-month anti-TPO levels were 10.37 ± 31.56 and 6.11 ± 13.13 U/mL, respectively, also showing no statistically significant change during follow-up.

Overall, anti-TNF therapy did not result in significant deterioration or improvement in thyroid function. Conventional therapy (DMARDs) was associated with a statistically significant change in TSH levels only in RA patients. In the RA–DMARD group (Group 1), the mean TSH level increased from 1.53 ± 0.80 to 1.85 ± 0.96 during the follow-

up period ($p=0.042$). Isolated cases of new-onset thyroid dysfunction were observed in both the AS–anti-TNF and AS–Conventional therapy groups.

DISCUSSION

The aim of this study was to evaluate the prevalence of autoimmune thyroid disease and thyroid dysfunction in patients with RA and AS, and to assess the impact of anti-TNF therapy on thyroid function in these patient populations.

As reported in the current literature, the incidence of autoimmune thyroiditis is higher among individuals with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease, compared with the general population (8, 9, 10, 14). Therefore, clarifying whether anti-TNF- α agents, widely used in the management of autoimmune and inflammatory disorders, influence the development or resolution of thyroid dysfunction-particularly autoimmune thyroiditis (AIT)-is of considerable clinical importance.

TNF- α is also recognized as an important factor in the pathogenesis of thyroid diseases, including autoimmune thyroiditis (12). Several studies have reported that TNF- α protein and TNF- α mRNA levels in thyroid tissue are significantly higher in individuals with AIT and other thyroid disorders compared with those without thyroid disease. Lymphocytes infiltrating the thyroid gland represent a major source of TNF- α , and production by thyroid epithelial cells themselves has also been documented (15, 16).

Additionally, TNF- α inhibits thyroglobulin production, reduces TSH-stimulated iodine uptake by thyroid cells (17), and decreases type 2 deiodinase activity, thereby reducing the peripheral conversion of T4 to T3 and diminishing the autocrine production of triiodothyronine (18, 19). By influencing the hypothalamic-pituitary-thyroid axis, TNF- α also suppresses TRH release, which subsequently leads to reduced TSH production (20).

Considering the involvement of TNF- α in the etiopathogenesis of thyroid dysfunction, anti-TNF- α therapy has been hypothesized to exert a protective or potentially therapeutic effect on the development of AIT (21).

Although the effects of anti-TNF therapy on thyroid dysfunction in RA remain unclear, both improvement in thyroid function and worsening of thyroid abnormalities have been reported in RA patients receiving anti-TNF treatment (12, 22-26). In our study, subclinical hyperthyroidism was detected in two RA patients receiving conventional therapy. After six months of follow-up, thyroid function normalized in one patient, whereas the abnormality persisted in the other. In the anti-TNF group, hypothyroidism was identified in one patient, subclinical hypothyroidism in one patient, and subclinical hyperthyroidism in two patients. At the six-month follow-up, thyroid function normalized in the patient with hypothyroidism and in one patient with subclinical hyperthyroidism, whereas subclinical hypothyroidism and subclinical hyperthyroidism persisted in the

remaining patients.

The leading hypothesis for newly developed thyroid dysfunction is that it may result from immunogenic responses to anti-TNF agents. In our RA cohort, however, no new-onset thyroid dysfunction was observed in either the DMARD or anti-TNF groups, precluding any firm conclusions regarding immunogenicity. Although improvements in thyroid dysfunction were noted in both groups, the absence of a statistically significant association between these changes and anti-TNF therapy does not support a beneficial effect of anti-TNF agents on thyroid function.

Anti-TPO positivity is present in approximately 10% of the general population across different cohorts (27). In our study, anti-TPO positivity was detected in 19% of RA patients receiving DMARDs and in 16% of those receiving anti-TNF therapy, with no statistically significant difference between the groups. Furthermore, no significant change in anti-TPO status was observed over the six-month follow-up period. These findings indicate that anti-TNF therapy does not appear to exert a substantial effect on anti-TPO levels in RA patients. When existing studies are considered collectively, the heterogeneity of reported outcomes further underscores the difficulty of drawing definitive conclusions regarding this relationship.

Regarding TSH changes, an increase was observed in Group 1, whereas a decrease was noted in Group 2. After six months of follow-up, the rise in TSH in Group 1 reached statistical significance. In contrast, the decline in TSH in the anti-TNF group did not achieve statistical significance. This lack of significance may be attributable to a markedly elevated baseline TSH value in a single patient within the anti-TNF group, which likely influenced the overall group comparison.

The effect of anti-TNF therapy on thyroid function in AS remains uncertain. Only a limited number of studies have explored this topic, and most have focused on autoimmune thyroid involvement and anti-TPO measurements rather than detailed thyroid

function outcomes. In a retrospective study by Tarhan et al. involving 108 AS patients, subclinical hyperthyroidism was identified in three patients and subclinical hypothyroidism in two patients, all of whom were in the non-anti-TNF group (11). In our study, no thyroid dysfunction was present at baseline in the non-anti-TNF group; however, central hyperthyroidism emerged in one patient after six months of follow-up. In the anti-TNF group, subclinical hypothyroidism was present in one patient at baseline, with biochemical improvement observed after six months.

When evaluating Anti-TPO positivity in AS patients, reported prevalence rates vary considerably across studies. In 1994, Bianchi et al. reported increased anti-TPO positivity in patients with RA and psoriatic arthritis compared with the general population, but found no significant difference in AS patients

(28). In contrast, a 2013 study by Emmungil et al. reported an anti-TPO positivity rate of 13.8% in AS patients compared with 2.5% in controls, indicating a significantly higher prevalence in the AS group (29). Similarly, Tarhan et al., in a retrospective study of 108 AS patients, reported a high anti-TPO positivity rate of 29%, with significantly lower rates observed among patients receiving anti-TNF therapy (11). In our study, anti-TPO positivity was 18% in the conventional treatment group and 3.4% in the anti-TNF group, with no statistically significant difference between the two groups. Although the difference did not reach statistical significance, the lower rate of anti-TPO positivity in the anti-TNF group, aligns with the findings of Tarhan et al. Potential explanations for this trend include the relatively small sample size and the wide variability inherent to anti-TPO measurements.

Table 3. Reported effects of anti-TNF- α therapy on thyroid function and autoimmune thyroid disease (AITD): summary of published studies (Year)

	Population / Disease	Anti-TNF Agent(s)	Effect on Thyroid / AITD	Notes
Caramaschi et al. (2006)	RA, n=54	Infliximab, Etanercept	Mixed (antibody seroconversion in both directions)	Different effects depending on subgroup
Elkayam et al. (2005)	RA, n=26	Infliximab	Neutral	ATPO remained negative
Raterman et al. (2011)	RA, pilot study	Adalimumab	Positive	Improved thyroid function in hypothyroid patients
Tarhan et al. (2013)	AS, n=108	Etanercept, Infliximab, Adalimumab	Positive	Retrospective study, 6 months follow-up
Paschou et al. (2018)	IBD (Crohn's/UC), n=41	Infliximab, Adalimumab	Neutral	FT4 decreased slightly, others unchanged
Van Lieshout et al. (2008)	RA, case	Adalimumab	Negative	Graves' disease developed
Allanore et al. (2001)	RA, case	Etanercept	Negative	Transient hyperthyroidism
Cerniglia & Judson (2013)	Sarcoidosis, case	Infliximab	Negative	Hypothyroidism
Pascart et al. (2014)	Mixed rheumatic diseases	Etanercept, Adalimumab, Infliximab	Variable	Case series and review
Tunçekin et al. (2023)	RA & AS, n \approx 100 (Van cohort)	Infliximab, Adalimumab, Etanercept, Golimumab	Neutral (no significant change in TSH, fT4, Anti-TPO after 6 months)	Only isolated cases of dysfunction observed

When evaluating changes in TSH and free T4 levels, no statistically significant difference were found between the two groups. Similarly, within-group comparisons from baseline to the six-month follow-up demonstrated no significant changes in TSH or free T4 levels.

A review of the existing literature indicates that thyroid dysfunction—particularly autoimmune thyroid disease—frequently coexists with RA and AS. However, whether this association is directly related to TNF- α activity remains uncertain. Furthermore, it is still debated whether autoimmune thyroid disorders observed during anti-TNF therapy in RA and AS patients represent coincidental findings, paradoxical reactions or manifestations of immunogenicity (26).

In 2020, Furtak et al. published a review addressing whether anti-TNF therapy increases the risk of thyroid disease or exerts a protective effect against its development. They categorized available studies according to whether anti-TNF treatment demonstrated negative, positive or neutral effects on thyroid disease (30) (Table 3). Research on biological anti-TNF- α agents dates back to the 1990s; however, despite the relatively long follow-up periods reported in many studies, it remains unclear whether anti-TNF- α therapy influences the development or regression of autoimmune thyroid disease.

In our study, the evaluation was primarily based on biochemical parameters; consequently, patients were not systematically assessed from a clinical standpoint, and no structured documentation of clinical symptoms was not performed. Notably, anti-TPO positivity—the principal biochemical marker of autoimmune thyroid disease—was markedly elevated in one patient. The patient was referred to the appropriate specialty clinic for further evaluation to exclude the possibility of thyroid lymphoma.

The limitations of this study include the small sample size, the relatively short follow-up period and the absence of a formal power analysis.

CONCLUSION

In this study, the short-term effects of anti-TNF therapy on thyroid function were evaluated in patients with RA and AS. Our findings demonstrated that anti-TNF agents did not induce significant changes in TSH levels, free T4 concentrations or anti-TPO antibody positivity over a six-month follow-up period. These results suggest that no clinically relevant short-term endocrine adverse effects on thyroid function were observed with anti-TNF therapies.

However, the occurrence of isolated cases of thyroid dysfunction underscores the need for ongoing clinical vigilance, particularly in patients at increased risk of autoimmune thyroid diseases. Regular monitoring of thyroid function tests can facilitate the early detection of subclinical thyroid dysfunction and enable timely management in patients receiving anti-TNF therapy.

To better elucidate the relationship between autoimmune and inflammatory diseases such as RA and AS and the development of other autoimmune conditions, well-designed controlled studies with larger patient populations, longer follow-up durations and preferably multicenter designs are warranted.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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