BMC Pharmacology and Toxicology

RESEARCH

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Thyroid hormone changes after tumor necrosis factor inhibitor therapy in euthyroid patients with rheumatic diseases

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Abstract

Background/aim Tumor necrosis factor-alpha (TNF-α) plays a central role in chronic inflammatory diseases. Anti-TNF agents are widely used in rheumatological conditions; however, their association with thyroid hormone parameters in patients without pre-existing thyroid disease remains incompletely understood. This study aimed to evaluate changes in thyroid hormone profiles during anti-TNF therapy in euthyroid patients with rheumatic diseases.

Methods In this retrospective study, 98 patients diagnosed with rheumatoid arthritis, ankylosing spondylitis, or Behçet's disease without known thyroid disease were evaluated. Thyroid function tests, including thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4), anti-thyroid peroxidase (anti-TPO) antibodies, inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and metabolic parameters were assessed at baseline and after 3 and 6 months of anti-TNF therapy.

Results Anti-TNF therapy was associated with significant reductions in inflammatory markers (CRP and ESR, $p < 0.01$). A modest decrease in fasting glucose levels and an increase in high-density lipoprotein cholesterol (HDL-C) were observed during follow-up ($p = 0.024$ and $p = 0.044$, respectively). TSH and fT4 levels remained stable over time, whereas a gradual increase in fT3 levels was observed ($p < 0.01$). No significant changes were detected in anti-TPO antibody levels.

Conclusions Among euthyroid patients with rheumatic diseases, predominantly rheumatoid arthritis and ankylosing spondylitis, anti-TNF therapy was associated with stable thyroid function parameters. The observed increase in fT3 levels may reflect reduced inflammatory burden rather than direct thyroidal effects. These findings support the thyroid safety of anti-TNF agents while highlighting potential links between inflammation control and peripheral thyroid hormone conversion.

Keywords Anti-TNF, Biological treatment, Rheumatological disease, Thyroid autoantibodies, Thyroid functions

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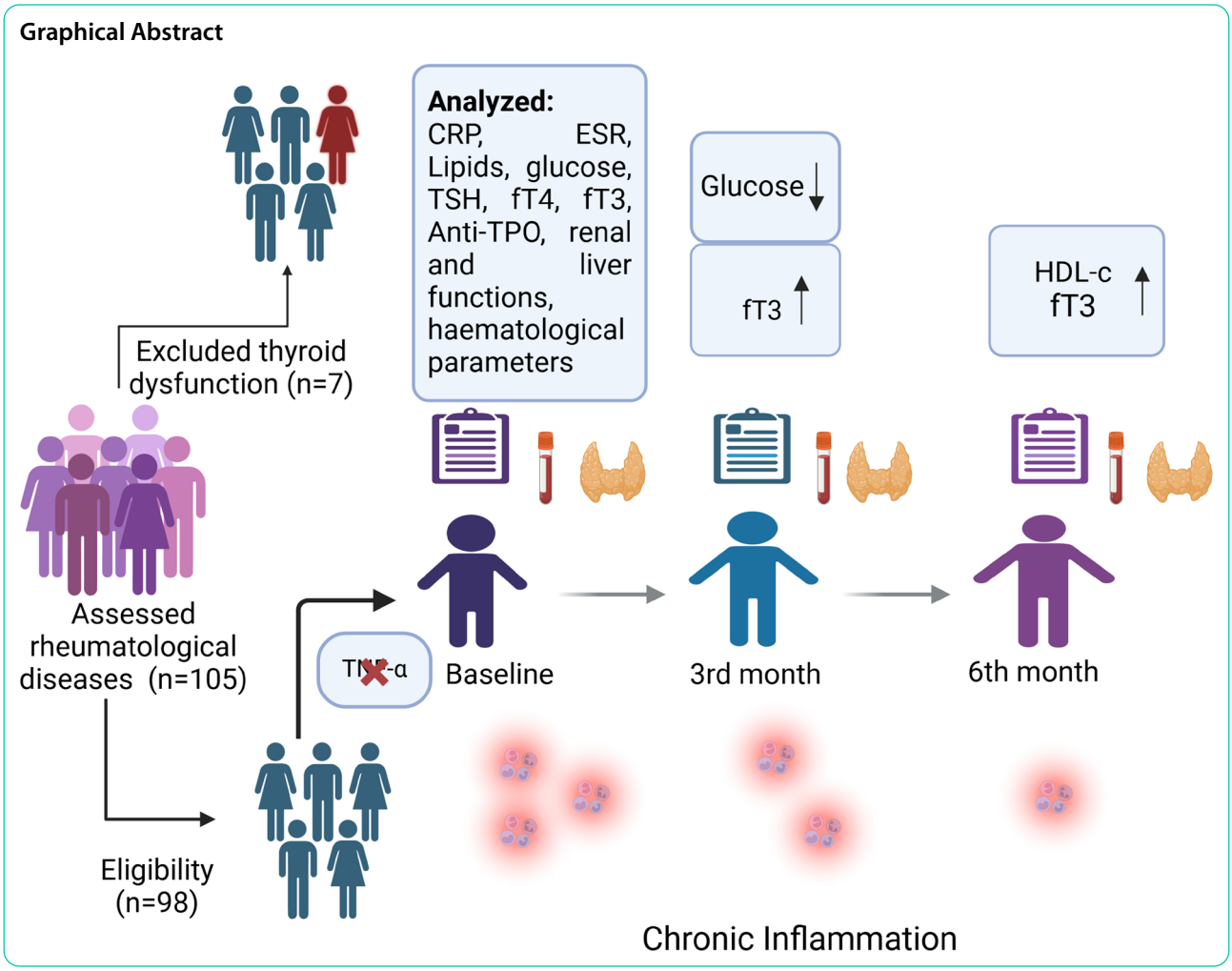

Introduction

Tumor necrosis factor-alpha (TNF-α) constitutes a pro-inflammatory cytokine that is integral in the modulation of the inflammatory response [1]. The synthesis of TNF-α is significantly elevated in numerous chronic autoimmune rheumatic disorders, notably including rheumatoid arthritis (RA), ankylosing spondylitis (AS), Behcet's disease (BD), and Familial Mediterranean Fever (FMF), leading to tissue destruction and systemic inflammation [2]. In circumstances where disease-modifying antirheumatic drugs (DMARDs), which have been utilized in the management of rheumatic conditions, prove ineffective or are contraindicated, a variety of biological therapeutics known as anti-TNF agents have been formulated to attenuate the inflammatory response associated with these diseases [2, 3]. Anti-TNF agents are extensively employed in contemporary therapeutic regimens for autoimmune diseases and have demonstrated superior efficacy compared to DMARDs, particularly those utilized in the treatment of rheumatic disorders [2].

Recent investigations have underscored the correlation between inflammatory processes and autoimmune phenomena, while also suggesting the potential interactions between TNF-α and thyroid physiological functions [4–7]. Inflammatory cytokines, including TNF-α, may alter hypothalamic–pituitary–thyroid axis activity and deiodinase-mediated thyroid hormone metabolism in the context of systemic inflammation [8]. Thyroid pathologies frequently manifest in conjunction with autoimmune mechanisms, with entities such as Hashimoto's thyroiditis and Graves' disease originating from autoimmune etiology [9, 10]. The immunomodulatory effects of TNF-α on thyroid cells and the effects of anti-TNF therapies on thyroid functions have not been fully elucidated [11]. Considering the increasing use of these agents, understanding their effects on thyroid functions is of great importance [12]. Nevertheless, the existing literature presents inconsistencies, with several studies indicating that anti-TNF therapies might induce alterations in thyroid autoantibody concentrations and subsequently affect thyroid functionality [8, 12, 13]. Within the existing

literature, while certain studies propose that anti-TNF therapy could confer benefits in autoimmune thyroid conditions (notably Graves' ophthalmopathy), a limited number of case reports suggest the emergence of adverse outcomes such as subacute thyroiditis or granulomatous thyroiditis, thereby indicating that thyroid autoimmunity may be provoked by these therapeutic agents [11, 14–22]. This scenario highlights that anti-TNF therapies may yield divergent outcomes concerning thyroid functionality and autoimmunity, with a definitive effect yet to be established.

Given the disparate findings in the existing literature regarding the influence of anti-TNF agent therapy on thyroid function, our objective was to investigate the potential effects and safety profile of anti-TNF treatments on thyroid physiology in patients devoid of prior thyroid pathology, who were also not undergoing antithyroid pharmacotherapy or thyroid hormone replacement. Consequently, we sought to elucidate the early and mid-term ramifications of these agents in individuals exhibiting normative thyroid functionality. To achieve this, we assessed the impact of the anti-TNF agents etanercept, golimumab, adalimumab, infliximab, and certolizumab pegol on thyroid function parameters and autoantibody concentrations over a specified duration in patients diagnosed with RA, AS, or BD, all of whom had no antecedent thyroid disorders. The principal aim of this investigation is to ascertain the effects of anti-TNF therapies on the levels of thyroid hormones. The outcomes of this research may significantly enhance the comprehension of the interplay between inflammatory processes and thyroid hormone metabolism, thereby facilitating the formulation of more informed therapeutic approaches in clinical settings.

Methods

Study design and ethical approval

This retrospective study was conducted to evaluate the association between anti-TNF therapy and thyroid hormone parameters in adult patients aged 18–75 years diagnosed with RA, AS, or Behçet's disease. All participants were followed at the Rheumatology Outpatient Clinic of a tertiary university medical center between 01 January 2022 and 31 January 2024.

Ethical approval for the study was obtained from the Recep Tayyip Erdogan University Non-Invasive Clinical Research Ethics Committee (Approval Date: 08.02.2024; Approval Number: 2024/35). The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

Given the retrospective design of the study and the use of anonymized data derived from existing medical records, the requirement for written informed consent specific to this study was waived by the local ethics committee. All relevant clinical and laboratory data were collected retrospectively from the hospital's electronic medical records and archived files. To ensure confidentiality, each patient was assigned a unique identification number, and all data were fully anonymized prior to analysis.

In routine clinical practice at our institution, all patients provide written informed consent prior to initiating biologic therapies, and comprehensive screening is performed for tuberculosis, viral hepatitis, human immunodeficiency virus (HIV) infection, active infections, and malignancies before treatment.

Study participants

The CONSORT flow diagram pertaining to the current study is illustrated in Fig. 1. The inclusion and exclusion criteria for study participants are shown in Table 1. Out of the 105 patients subjected to initial evaluation, 7 (comprising 1 hyperthyroid and 6 hypothyroid individuals) were excluded from the study due to the identification of thyroid dysfunction. Consequently, a total of 98 patients were incorporated into the study. Among these, 39 patients have a diagnosis of RA, 46 were diagnosed with AS, and 13 were identified with Behçet's disease. All diagnoses were validated by a single rheumatologist in accordance with the internationally recognized criteria specific to each respective condition (Behçet's disease according to the guidelines set forth by the International Behçet's Disease Study Group (ICBD) [23], the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria for RA [24], and the AS diagnosis adhered to the Assessment in Spondylarthritis International Society (ASAS) criteria) [25]. Each patient commenced treatment in alignment with the pertinent clinical strategy. Treatment determinations were made by the rheumatologist, considering the patient's clinical presentation, comorbid conditions, and prevailing rheumatological treatment protocols. Additional treatments considered necessary as standard practice (for instance, supplementary DMARDs such as low-dose methotrexate or sulfasalazine) could be arranged alongside anti-TNF treatment; however, any supplementary interventions that might impact thyroid function (including thyroid hormone replacement therapy, antithyroid medications, amiodarone, lithium, iodine-containing contrast agents, etc.) were expressly excluded from this study protocol.

Data collection and laboratory methods

Data were collected retrospectively from medical records between 01 January 2022 and 31 January 2024. The authors accessed the research data for analysis and interpretation between February 2024 and April 2024. Demographic information (such as age, gender, body mass index, the presence of comorbidities, duration of illness,

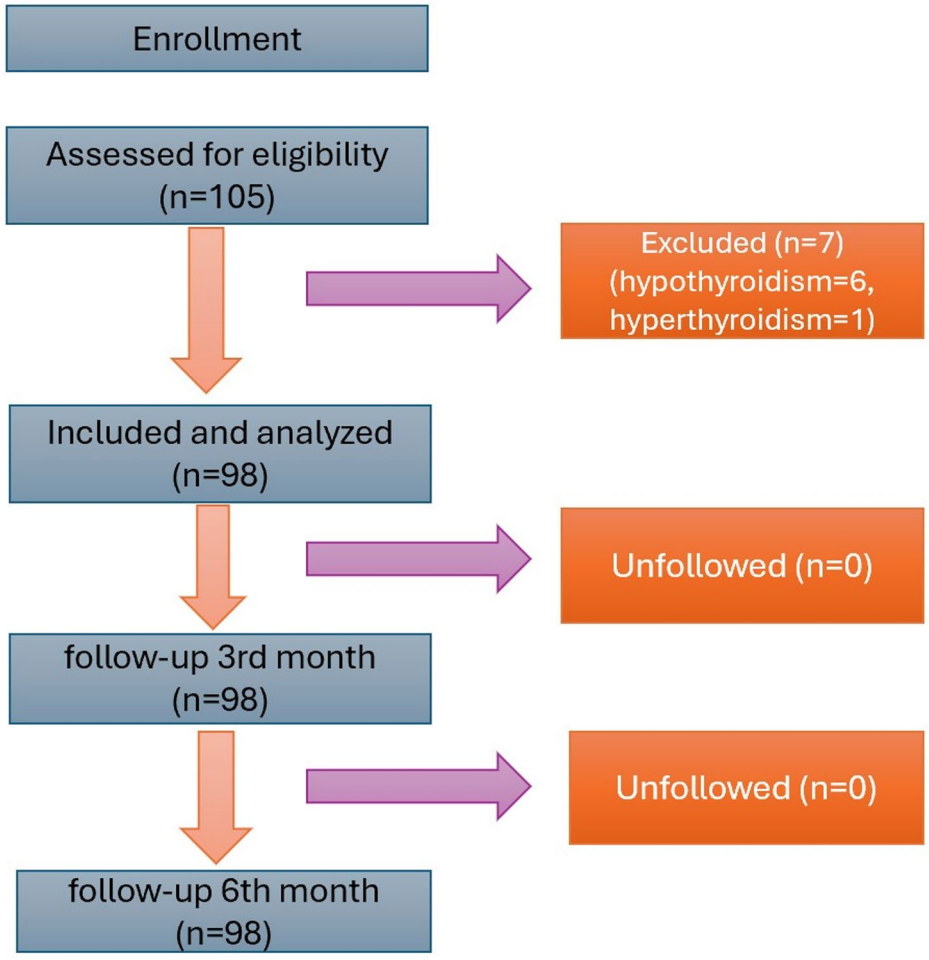

Fig. 1 CONSORT Flow diagram

Table 1 The inclusion and exclusion criteria for study participants

Inclusion Criteria	Exclusion Criteria
• Individuals must be aged between 18 and 75 years	• Prior administration of anti-TNF agents
• A confirmed diagnosis of rheumatoid arthritis (RA), ankylosing spondylitis (AS), or Behçet's disease must be established in accordance with pertinent international diagnostic and screening guidelines	• Participants with known or newly diagnosed thyroid dysfunction, specifically hyperthyroidism or hypothyroidism,
• Participants must have recently commenced at least one of the anti-TNF biologic therapies (including etanercept, golimumab, adalimumab, infliximab, or certolizumab pegol)	• Individuals currently receiving antithyroid medications or thyroid hormone replacement therapy for any purpose, or any treatments that may influence thyroid function, such as amiodarone or lithium
• Baseline thyroid function assessments (comprising TSH, fT3, and fT4 levels) must fall within normal physiological ranges, with no documented history of thyroid pathology present	• Pregnancy and/or lactation
• A minimum follow-up duration of six months	• Individuals below the age of 18 or above the age of 75

and utilized medications) pertaining to the patients was meticulously documented during the initial consultation. Hematological and biochemical assessments (including complete blood count, liver and renal function tests, and lipid profile) alongside thyroid function tests—namely thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4)—as well as measurement of anti-thyroid peroxidase antibodies (anti-TPO Ab), which are commonly detected in patients with autoimmune hypothyroidism [26], were conducted prior to the initiation of treatment and subsequently at the third and sixth months of the therapeutic regimen. All venous blood specimens from the participants were collected between the hours of 08:00 and 09:00 in

the morning, adhering to a fasting protocol for a minimum of 8–10 h. The quantification of TSH, fT3, and fT4, were executed utilizing the standard chemiluminescence immunoassay technique within the confines of the hospital laboratory. Anti-TPO concentrations were determined by a competitive chemiluminescent immunoassay (ADVIA Centaur® anti-TPO assay; Siemens Healthineers) performed on the ADVIA Centaur XP platform. Results were reported in U/mL. Based on the manufacturer-defined reference criteria, values exceeding 60 U/mL were classified as anti-TPO positive. The hematological and biochemical evaluations were carried out using fully automated analytical instruments. During each follow-up consultation, patients were systematically interrogated regarding any potential adverse effects or the need for additional pharmacological interventions, which were duly recorded.

Statistical analysis

The statistical analysis was applied by using IBM SPSS version 24.0 (SPSS Corp., Chicago, Illinois, USA). The distribution of continuous variables was assessed by the Shapiro-Wilk test. Since normality was not consistently confirmed across all three time points, non-parametric methods were applied. Changes over time were evaluated using the Friedman test for repeated measures, followed by post hoc pairwise comparisons with the Wilcoxon signed-rank test. Differences between therapy groups and between disease groups were tested using the Mann-Whitney U test. Continuous data are presented as median (25th -75th percentile), while categorical variables are presented as relative frequencies. The results were regarded as statistically significant for $P < 0.05$.

Table 2 Demographic and clinical characteristics of the study participants

Parameter	Baseline value*
N	98
Age, years	52 (39–62)
Gender (men/women), %	47.9/52.1
BMI, kg/m2	28.78 (25.38–32.41)
Smoking, %	17.5
Type of rheumatic disease, %	
Rheumatoid arthritis	39.8
Ankylosing spondylitis	46.9
Behçet's Disease	13.3
Disease duration, years	9 (6–15)
Comorbidities, %	
Diabetes	11.2
CAD	9.2
Hypertension	48.0
Hyperlipidaemia	11.2
Therapy, %	
NSAID	16.4
Salazopryn	8.0
Leflunomide	9.1
Methotrexate	15.7
Methylprednisolone (maximum 5 mg/day)	10.9
Azathioprine	1.8
Colchicine	0.7

* Continuous variables are presented as median (25th -75th percentile) and categorical variables are presented as relative frequencies

Abbreviations: Body Mass Index, BMI; Coronary Artery Disease, CAD; Non-Steroidal Anti-Inflammatory Drug, NSAID

Results

Baseline data on demographic and clinical characteristics of 98 patients included in the study are shown in Table 2.

Regarding biological therapy, 30 patients (30.6%) were treated by etanercept, 17 patients (17.3%) by golimumab, 38 patients (38.8%) by adalimumab, 9 patients (9.2%) by infliximab, and 4 patients certolizumab pegol (4.1%).

The findings derived from laboratory analyses elucidating the inflammatory and cardiometabolic profiles of the patients assessed prior to the initiation of anti-TNF therapy, as well as at the third and sixth months of treatment, are presented in Table 3. Consistent with expectations, the administration of anti-TNF agents is associated with considerable reductions in inflammatory biomarkers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) ($p = 0.012$, $p < 0.001$, respectively). Furthermore, the intervention with anti-TNF agents yields a notable decline in plasma fasting glucose concentrations over time ($p = 0.024$), concomitantly resulting in an elevation of high-density lipoprotein cholesterol (HDL-C) levels observed at the third month ($p = 0.044$).

The results of the laboratory analyses delineating the hepatic, renal, and thyroid functional status of the subjects assessed prior to the initiation of anti-TNF therapy, as well as at the third and sixth months of treatment, are systematically outlined in Table 4. Consistent with anticipated outcomes, the administration of anti-TNF agents resulted in a statistically significant elevation in serum albumin concentrations ($p < 0.01$). Nevertheless, a discernible decline in renal function was observed over the course of treatment. Furthermore, a statistically significant augmentation in fT3 levels was noted across all participants over time ($p < 0.01$). During biological therapy, the proportion of anti-TPO Ab–positive patients remained largely unchanged over time. At baseline, 11 patients (11.2%) had anti-TPO levels above the laboratory reference threshold (>60 IU/mL). This proportion was 10 patients (10.2%) at both the third and sixth months of follow-up, indicating overall stability in thyroid autoantibody prevalence during treatment.

Due to the relatively small number of patients with Behçet's disease, disease-specific longitudinal analyses were primarily performed for the RA and AS subgroups and are presented in Table 5. In the RA group, median

Table 3 Inflammatory and cardiometabolic biomarkers at baseline and during treatment

Parameter	Baseline	After 3 months	After 6 months	*P*
Inflammatory biomarkers				
CRP, mg/L	8.55 (3.19-16.00)	5.00 ** (2.24–8.90)	5.20 ** (2.18–9.45)	0.012
ESR, mm/h	18 (10–30)	12 *** (6–20)	10 *** (4–19)	< 0.001
Ferritin, ng/mL	49 (23–76)	45 (16–69)	48 (18–74)	0.373
Leukocytes, x103/µL	8070 (6570–9600)	7260 * (6180–8930)	7180 *** (6050–8370)	0.020
Neutrophils, x103/µL	5030 (3480–6070)	4180 * (3250–5290)	4120 *** (3100–5050)	< 0.01
Lymphocytes, x103/µL	2220 (1850–2700)	2350 (1860–2780)	2260 (1890–2880)	0.036
Monocytes, x103/µL	550 (418–650)	500 (410–623)	470 (380–563)	0.136
Cardiometabolic biomarkers				
Glucose, mg/dL	96 (88–106)	91 (84–105)	91 * (84–100)	0.024
HbA1c, %	5.7 (5.3–6.1)	5.7 (5.3–6.2)	5.7 (5.4-6.0)	0.830
TC, mg/dL	204 (175–241)	216 (177–245)	210 (185–236)	0.521
TG, mg/dL	130 (84–176)	113 (87–177)	129 (93–172)	0.743
LDL-C, mg/dL	125 (105–153)	135 (107–166)	129 (107–150)	0.429
HDL-C, mg/dL	50 (41–63)	52 * (42–64)	52 (40–63)	0.044

Data are presented as median (25th -75th percentile) and compared by Friedman test

Significant difference from baseline by Wilcoxon's paired test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Abbreviations: C-Reactive Protein, CRP; Erythrocyte Sedimentation Rate, ESR; Glycated Hemoglobin, HBA1C; Total Cholesterol, TC; Triglyceride, TG; Low-Density Lipoprotein Cholesterol, LDL-C; High-Density Lipoprotein Cholesterol, HDL-C

thyroid-stimulating hormone (TSH) levels were 1.26 (0.59–2.65) µIU/mL at baseline, 1.28 (0.76–2.33) µIU/mL at 3 months, and 1.37 (0.74–2.26) µIU/mL at 6 months. Corresponding TSH values in the AS group were 1.33 (0.84–2.05), 1.58 (0.99–2.43), and 1.47 (0.93–2.17) µIU/mL, respectively. Free thyroxine (fT4) concentrations remained stable in both groups throughout follow-up. In contrast, free triiodothyronine (fT3) levels demonstrated a progressive increase in the AS group, rising from 3.22 (2.64–3.58) ng/mL at baseline to 3.31 (3.04–3.68) ng/mL at 3 months and 3.40 (3.12–3.81) ng/mL at 6 months. In the RA group, fT3 levels showed a modest upward trend from 3.03 (2.56–3.58) ng/mL at baseline to 3.17 (2.52–3.45) ng/mL at 3 months and 3.22 (2.83–3.50) ng/mL at 6 months.

Anti-thyroid peroxidase antibody (anti-TPO Ab) levels did not exhibit marked changes over time in either subgroup. In patients with RA, median anti-TPO values were 29.9 (28.0–52.0) IU/mL at baseline, 31.7 (28.0–43.1) IU/mL at 3 months, and 28.0 (29.7–47.0) IU/mL at 6 months. In the AS group, corresponding values were 29.6 (28.0–40.6), 28.7 (28.0–36.2), and 31.8 (28.0–41.5) IU/mL, respectively. Overall, no consistent increasing pattern in thyroid autoantibody levels was observed during the six-month treatment period.

Independent analyses according to the administered biological agent were performed for etanercept, golimumab, and adalimumab (Table 6), excluding infliximab and certolizumab pegol due to limited sample size. TSH and fT4 concentrations remained generally stable over the six-month follow-up across all treatment groups.

fT3 levels showed a gradual increase in all three groups; however, a statistically significant elevation at the sixth month was observed only in patients receiving adalimumab, in whom median fT3 values increased from 2.88 (2.50–3.45) ng/mL at baseline to 3.34 (3.01–3.62) ng/mL at six months. In contrast, changes in fT3 levels in the etanercept and golimumab groups did not reach statistical significance.

With respect to thyroid autoimmunity, anti-TPO Ab concentrations remained relatively stable throughout the treatment period in all three biologic therapy groups. No consistent increasing pattern in anti-TPO levels was observed during follow-up.

Table 4 Parameters of liver, kidney and thyroid function at baseline and during treatment

Parameter	Baseline	After 3 months	After 6 months	*P*
Liver function parameters				
Total protein, g/dL	7.5 (7.2–7.8)	7.6 (7.3–7.9)	7.4 (7.1–7.9)	0.445
Albumin, g/dL	4.2 (3.9–4.4)	4.3 ** (4.1–4.6)	4.3 ** (4.1–4.6)	< 0.01
AST, U/L	20 (15–26)	20 (17–27)	20 (17–26)	0.087
ALT, U/L	19 (14–29)	22 (14–31)	21 (14–28)	0.087
GGT, U/L	20 (16–26)	20 (17–28)	23 (17–31)	0.077
ALP, U/L	87 (69–97)	82 (71–96)	87 (66–99)	0.491
LDH, U/L	176 (141–206)	184 (165–222)	191 (157–220)	0.658
Kidney function parameters				
Urea, mg/dL	27 (22–36)	28 (23–36)	29 (24–36)	0.191
Creatinine, mg/dL	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.8 ** (0.6–0.9)	0.034
GFR, mL/min/1.73 m2	102 (92–115)	100 *** (86–111)	98 *** (88–108)	< 0.01
Uric acid, mg/dL	5.0 (4.0–6.0)	5.3 * (4.3–6.1)	5.1 * (4.6-6.0)	0.023
Thyroid function parameters				
TSH, µIU/mL	1.24 (0.76–2.33)	1.36 (0.86–2.36)	1.39 (0.86–2.17)	0.494
fT4, ng/dL	1.19 (1.01–1.38)	1.15 1.02–1.34	1.20 1.01–1.32	0.948
fT3, pg/mL	3.19 (2.57–3.57)	3.24 * (2.84–3.56)	3.37 ** (3.02–3.72)	< 0.01
Anti-TPO-Ab, IU/mL	29.9 (28.0-41.2)	28.7 (28.0-36.5)	31.5 (28.0-42.9)	0.192

Data are presented as median (25th -75th percentile) and compared by Friedman test

Significant difference from baseline by Wilcoxon's paired test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Abbreviations: Aspartate Aminotransferase, AST; Alanine Aminotransferase, ALT; Gamma-Glutamyl Transferase, GGT; Alkaline Phosphatase, ALP; Lactate Dehydrogenase, LDH; Thyroid-Stimulating Hormone, TSH; free Thyroxine, fT4; free Triiodothyronine, fT3; anti-thyroperoxidase antibody, Anti-TPO Ab

Discussion

This study evaluated changes in inflammatory markers, metabolic parameters, renal indices, hematological profiles, and thyroid function tests in patients with rheumatoid arthritis, ankylosing spondylitis, and Behçet's disease who received anti-TNF therapy for six months. Specifically, laboratory parameters measured prior to treatment initiation were compared with values obtained at the third and sixth months of therapy in euthyroid individuals without known thyroid disease. The primary objective was to determine whether anti-TNF therapy was associated with meaningful changes in thyroid hormone profiles, while also exploring its potential impact on systemic inflammation and related metabolic and biochemical parameters. Our findings indicate that anti-TNF treatment was associated with effective suppression of inflammatory activity, favorable metabolic changes, and overall biochemical stability of thyroid function during follow-up.

Consistent with previous studies, anti-TNF therapy resulted in significant reductions in CRP and ESR levels, accompanied by increased serum albumin concentrations, reflecting improved inflammatory control [27–29]. Extensive clinical evidence supports the efficacy of TNF inhibition in reducing inflammatory burden and improving disease activity in chronic immune-mediated disorders, and our results align with this established body of literature. Beyond inflammatory suppression, we observed improvements in selected cardiometabolic parameters, including reductions in fasting plasma glucose and increases in HDL-c. These findings are concordant with prior reports demonstrating partial metabolic recovery following TNF-α blockade [27, 28, 30–34]. Chronic inflammatory states, particularly rheumatoid

Table 5 Parameters of thyroid function at baseline and during treatment with respect to underlying rheumatic disease

Parameter	Type of rheumatic disease	Baseline	After 3 months	After 6 months	*P*
TSH, µIU/mL	Rheumatoid arthritis	1.26 (0.59–2.65)	1.28 (0.76–2.33)	1.37 (0.74–2.26)	0.910
	Ankylosing Spondylitis	1.33 (0.84–2.05)	1.58 (0.99–2.43)	1.47 (0.93–2.17)	0.422
fT4, ng/mL	Rheumatoid arthritis	1,14 (0.97–1.36)	1.11 (1.00-1.40)	1.09 (1.00-1.30)	0.510
	Ankylosing Spondylitis	1.24 (1.06–1.41)	1.19 (1.02–1.32)	1.20 1.04–1.32	0.541
fT3, ng/mL	Rheumatoid arthritis	3.03 (2.56–3.58)	3.17 (2.52–3.45)	3.22 (2.83–3.50)	0.249
	Ankylosing Spondylitis	3.22 (2.64–3.58)	3.31 *, # (3.04–3.68)	3.40 * (3.12–3.81)	< 0.01
Anti-TPO-Ab, IU/mL	Rheumatoid arthritis	29.9 (28.0–52.0)	31.7 (28.0-43.1)	28.0 (29.7–47.0)	0.633
	Ankylosing Spondylitis	29.6 (28.0-40.6)	28.7 (28.0-36.2)	31.8 (28.0-41.5)	0.290

Data are presented as median (25th -75th percentile) and compared by Friedman test. Rheumatoid arthritis: $N=39$; Ankylosing Spondylitis: $N=46$. * Significantly different from baseline ($P<0.05$ by Wilcoxon's paired test). # Significantly different from group with rheumatoid arthritis by Mann-Whitney U test ($P<0.05$). Abbreviations: Thyroid-Stimulating Hormone, TSH; free Thyroxine, fT4; free Triiodothyronine, fT3; Anti-thyroperoxidase antibody, Anti-TPO Ab

Table 6 Parameters of thyroid function at baseline and during treatment with respect to received biological therapy

Parameter	Biological therapy	Baseline	After 3 months	After 6 months	*P*
TSH, µIU/mL	Etanercept	1.56 (0.58–2.48)	1.66 (0.92–2.31)	1.51 (0.97–2.46)	0.941
	Golimumab	1.24 (0.96–3.45)	2.15 (1.13–3.06)	1.21 (0.69–2.64)	0.056
	Adalimumab	1.23 (0.70–2.06)	1.04 # (0.80–2.12)	1.38 (0.74-2.00)	0.337
fT4, ng/mL	Etanercept	1.16 (1.03–1.37)	1.12 (1.02–1.33)	1.24 (0.99–1.37)	0.712
	Golimumab	1.19 (1.01–1.41)	1.24 (0.94–1.41)	1.20 1.00-1.26	0.955
	Adalimumab	1.24 (1.00-1.36)	1.10 (1.00-1.24)	1.14 1.00-1.27	0.186
fT3, ng/mL	Etanercept	3.12 (2.57–3.55)	3.24 (2.58–3.56)	3.27 (3.00-3.50)	0.381
	Golimumab	3.31 (2.90–3.72)	3.32 (3.13–3.93)	3.37 (3.13–3.97)	0.120
	Adalimumab	2.88 (2.50–3.45)	3.07 (2.59–3.44)	3.34 * (3.01–3.62)	0.011
Anti-TPO-Ab, IU/mL	Etanercept	29.2 (28.0-57.1)	28.7 (28.0-39.9)	32.6 (28.0–49.0)	0.424
	Golimumab	28.2 (28.0-37.3)	28.6 (28.0-36.1)	32.2 (28.0-40.7)	0.487
	Adalimumab	29.9 (28.0-41.2)	28.2 (28.0–36.0)	29.6 (28.0-41.1)	0.485

Data are presented as median (25th -75th percentile) and compared by Friedman test. Etanercept: $N=30$; Golimumab: $N=17$; Adalimumab: $N=38$

* Significantly different from baseline ($P<0.05$ by Wilcoxon's paired test)

Significantly different from group treated by golimumab ($P<0.05$ by Mann-Whitney U test)

Abbreviations: Thyroid-Stimulating Hormone, TSH; free Thyroxine, fT4; free Triiodothyronine, fT3; anti-thyroperoxidase antibody, Anti-TPO Ab

arthritis, are associated with increased cardiometabolic risk, largely mediated by elevated TNF-α levels [27, 30, 35]. TNF-α interferes with insulin receptor signaling, promotes insulin resistance, and may adversely affect pancreatic beta-cell function [36]. By inhibiting TNF-α, biologic therapy may contribute to improved insulin sensitivity through restoration of insulin receptor phosphorylation and enhanced peripheral glucose utilization [37–39]. Additionally, reduced systemic inflammation may improve adipokine regulation and endothelial function, further supporting metabolic homeostasis [37, 40]. Clinical observations, including reports of improved

glycemic control or delayed diabetes progression after anti-TNF initiation, further support these mechanisms [36, 41].

Improvements in HDL-c observed in our study may similarly reflect reduced inflammatory burden. During chronic inflammation, HDL particles lose their anti-atherogenic properties under the influence of pro-inflammatory cytokines such as TNF-α [28, 30]. TNF-α inhibition may therefore contribute not only to quantitative increases in HDL-c but also to qualitative restoration of HDL functionality. Furthermore, improved disease control may increase physical activity and nutritional status, indirectly contributing to favorable metabolic changes. In some cases, tapering or discontinuation of glucocorticoids after initiation of biologic therapy may also have positively influenced glucose and lipid parameters [27]. Collectively, these findings reinforce the concept that controlling chronic inflammation plays a central role in reducing cardiometabolic risk in rheumatic diseases [27, 31, 32].

With respect to renal parameters, we observed modest increases in serum creatinine and uric acid levels, accompanied by a progressive but clinically mild decline in estimated glomerular filtration rate (eGFR). Although the magnitude of change remained within acceptable clinical limits, this finding warrants careful interpretation. Similar modest changes in renal indices have been reported in patients receiving anti-TNF therapy [42]. In a prospective cohort of ankylosing spondylitis patients, minor eGFR reductions were observed but were not directly attributable to anti-TNF agents after adjustment for confounders [42]. While improved physical activity and potential increases in muscle mass following better disease control could contribute to higher creatinine levels, this explanation remains speculative. Importantly, rare cases of immune-mediated renal complications, including various forms of glomerulonephritis, have been described in association with anti-TNF therapy [45, 46], suggesting that renal function changes during biologic treatment may reflect multifactorial mechanisms. Concomitant medications frequently used in rheumatic diseases—particularly nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate—may further influence renal hemodynamics and creatinine metabolism [43]. Although no clinically overt renal adverse events were documented in our cohort, periodic monitoring of renal function during anti-TNF therapy appears prudent, especially in patients receiving nephroactive medications.

Hematologically, anti-TNF therapy was associated with reduced neutrophil counts and relatively increased lymphocyte levels, findings that likely reflect normalization of inflammatory cell distribution under effective cytokine suppression [31]. Discontinuation or dose reduction of glucocorticoids in some patients may also have contributed to these changes.

Regarding thyroid function, TSH and fT4 levels remained stable, whereas a modest but statistically significant increase in fT3 levels was observed. Anti-TPO antibody levels remained largely unchanged overall, consistent with previous studies [8, 13, 17]. The observed increase in fT3 may be interpreted in the context of inflammation-related alterations in peripheral thyroid hormone metabolism. Chronic inflammatory states are frequently associated with features resembling non-thyroidal illness syndrome, characterized by reduced peripheral conversion of T4 to T3 without primary thyroid dysfunction [44–47]. Pro-inflammatory cytokines, including TNF-α and interleukin-6 (IL-6), have been shown to suppress type 1 and type 2 deiodinase activity, thereby reducing T3 generation [46]. Consequently, TNF-α inhibition may partially restore deiodinase activity and increase circulating fT3 levels as systemic inflammation declines [48].

Notably, subgroup analysis revealed that the increase in fT3 was primarily driven by patients with ankylosing spondylitis, whereas individuals with rheumatoid arthritis exhibited only a non-significant upward trend. This pattern likely reflects disease-specific immunopathological differences rather than statistical inconsistency. Ankylosing spondylitis is predominantly characterized by innate immune activation and interleukin-17 (IL-17) and interleukin-23 (IL-23) axis–mediated inflammation, whereas rheumatoid arthritis involves a more complex adaptive immune response with prominent B-cell activation and autoantibody production [49–53]. These divergent inflammatory profiles may differentially influence peripheral thyroid hormone metabolism following TNF-α blockade. The more pronounced fT3 response observed in ankylosing spondylitis may therefore reflect stronger cytokine-driven modulation of deiodinase activity in this disease context.

Nevertheless, alternative explanations should be considered. Stable fT4 levels suggest unchanged thyroidal hormone secretion, indicating that the fT3 increase is likely to reflect peripheral metabolic modulation rather than direct thyroid stimulation. Changes in thyroid hormone–binding proteins during systemic inflammation and its resolution may influence measured free hormone fractions [54, 55]. Additionally, given the modest magnitude of change, regression to the mean cannot be entirely excluded. Taken together, these considerations suggest that the observed fT3 elevation represents a multifactorial phenomenon related to systemic inflammatory modulation rather than a direct thyroid-specific effect of anti-TNF therapy.

Although no statistically significant change in anti-TPO antibody levels was observed across the overall cohort,

exploratory analyses according to biologic agent did not reveal a consistent or clinically meaningful pattern of change during follow-up. Due to the very small absolute number of anti-TPO–positive patients within each subgroup, percentage-based fluctuations may appear more pronounced than the actual numerical changes. Median anti-TPO concentrations remained broadly stable in patients receiving etanercept, golimumab, and adalimumab over the six-month period.

Given the relatively small number of anti-TPO–positive individuals and the limited sample size within each treatment subgroup, subtle differences in thyroid autoantibody dynamics cannot be excluded. TNF inhibitors differ in molecular structure and mechanism of action, with monoclonal antibodies exerting sustained cytokine neutralization, whereas receptor fusion proteins primarily act as soluble TNF scavengers [56]. Previous reports have described heterogeneous effects of anti-TNF therapy on autoantibody profiles in various autoimmune conditions [11, 13, 56]. However, in the present study, no clear agent-specific signal suggesting induction or exacerbation of thyroid autoimmunity was identified. Larger, adequately powered longitudinal studies are required to clarify whether differential immunological effects of individual TNF inhibitors influence thyroid autoantibody dynamics.

In our study, the baseline prevalence of anti-TPO antibody positivity was approximately 11%, a rate comparable to those reported in population-based studies of the general adult population (11.9%) [57]. Although the literature is heterogeneous, several studies have suggested that autoimmune inflammatory rheumatic diseases may be associated with increased frequencies of thyroid autoantibodies compared with population controls [5, 58–63]. However, in the present study, patients with previously diagnosed thyroid disease or those receiving thyroid-specific treatment were excluded at baseline. This exclusion strategy may have reduced the likelihood of detecting an increased burden of thyroid autoimmunity and may partly explain why the observed prevalence was similar to that reported in the general population.

Importantly, anti-TPO positivity remained stable throughout the six-month follow-up, with 11 patients at baseline and 10 patients at both the third and sixth months exceeding the positivity threshold, and no meaningful change in prevalence during anti-TNF therapy. This finding suggests that, in euthyroid individuals without known thyroid disease, TNF-α blockade was not associated with the emergence or progression of biochemical thyroid autoimmunity over the study period. Nevertheless, the relatively modest sample size should be considered when interpreting these results, as subtle differences in autoimmune thyroid prevalence may not be detectable in smaller cohorts.

To our knowledge, this study provides additional real-world data on thyroid hormone changes during anti-TNF therapy in euthyroid patients with different rheumatic diseases. However, results should be interpreted in light of several limitations. First, the retrospective design and single-center setting limit causal inference. Second, thyroid ultrasonography was not performed during follow-up. Biochemical stability does not exclude structural thyroid alterations, and imaging could have provided additional information regarding thyroid volume, echogenicity, or early autoimmune changes—particularly relevant in light of the baseline anti-TPO positivity rate of approximately 11%. Therefore, our conclusions regarding thyroid safety are confined to biochemical parameters over six months and should not be interpreted as evidence of structural neutrality. Third, the unequal distribution of biologic agents limited agent-specific comparisons, particularly for infliximab and certolizumab pegol. Fourth, the small number of patients with Behçet's disease restricted disease-specific analysis, and findings should primarily be interpreted in the context of rheumatoid arthritis and ankylosing spondylitis. Fifth, concomitant use of methotrexate, NSAIDs, and corticosteroids may have acted as confounders, and stratified analyses were not feasible without substantially reducing statistical power. Finally, post-hoc comparisons were reported using nominal p-values without formal correction for multiple testing. Although this approach was chosen to minimize false-negative findings in an exploratory setting, the potential for type I error should be considered when interpreting the results.

In summary, in inflammatory rheumatic diseases such as rheumatoid arthritis and ankylosing spondylitis, anti-TNF therapy was associated with effective suppression of systemic inflammation, favorable metabolic changes, and overall biochemical stability of thyroid function in euthyroid individuals. The modest increase observed in fT3 levels likely reflects partial normalization of inflammation-related alterations in peripheral thyroid hormone metabolism rather than direct stimulation of thyroidal hormone secretion. No clear evidence of worsening thyroid autoimmunity emerged during the six-month follow-up. Prospective, multicenter studies with larger and more balanced cohorts, extended follow-up, integrated thyroid imaging, and comprehensive immunological assessment are needed to more clearly define the long-term endocrine consequences of TNF-α blockade in rheumatic diseases.

Conclusion

The findings of the present study indicate that tumor necrosis factor inhibitor therapy in euthyroid patients with rheumatic diseases is associated with modest improvements in selected cardiometabolic parameters,

including fasting glucose and HDL cholesterol levels, while overall thyroid function remained biochemically stable during the six-month follow-up period. The observed increase in fT3 levels may reflect inflammation-related changes in peripheral thyroid hormone metabolism rather than a direct thyroidal effect of biologic therapy.

These findings should be interpreted in light of several limitations, including the absence of thyroid ultrasonographic evaluation, the heterogeneous distribution of biologic agents, potential confounding effects of concomitant medications, and the relatively short duration of follow-up. In addition, the small number of patients treated with certain anti-TNF agents limited agent-specific comparisons.

Despite these limitations, the study provides clinically relevant evidence supporting the short-term biochemical thyroid safety of tumor necrosis factor inhibitor therapy in euthyroid individuals with rheumatic diseases. Future prospective studies incorporating longer follow-up, balanced representation of biologic agents, structural thyroid assessment, and detailed evaluation of renal and metabolic outcomes are needed to better elucidate the long-term endocrine and systemic effects of biologic therapy.

Acknowledgements
The authors from the University of Belgrade-Faculty of Pharmacy are financially supported by the Ministry of Science, Technological Development and Innovation, Republic of Serbia (contract No: 451-03-33/2026-03/200161 and No: 451-03-34/2026-03/200161).

Author contributions
FM contributed to the study of conception and design. Material preparation and data collection were performed by FM, BK and OC. Statistical analysis was performed by JV and AK. The first draft of the manuscript was written by FM and BK. All the authors have read and approved the final version of the manuscript.

Funding
None.

Data availability
All data generated or analyzed during this study are included in this article. The data will be available upon reasonable request (contact persons: filizmercantepe@hotmail.com).

Declarations

Ethical approval
This study was approved by the Recep Tayyip Erdogan University Non-Invasive Clinical Research Ethics Committee (Approval Date: 08.02.2024; Approval Number: 2024/35) and was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study and the use of anonymized data obtained from existing medical records, the requirement for written informed consent was waived by the ethics committee.

Generative AI and AI-assisted technologies in the writing process
Artificial intelligence-assisted technologies were utilized solely to enhance the readability and academic language of this manuscript during the writing process. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

Competing interests
The authors declare no competing interests.

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Received: 10 January 2026 / Accepted: 30 March 2026
Published online: 04 April 2026

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