THE ROLE OF THYROID FUNCTIONAL DISORDERS IN AUTOIMMUNE PROCESSES AND THEIR ASSOCIATION WITH THE DEVELOPMENT OF RHEUMATOID POLYARTHRITIS

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Abstract: *A systematic analysis of the epidemiological association, immunopathogenetic mechanisms, clinical-diagnostic "overlap points", therapeutic interactions, and prognostic impact between thyroid functional disorders/autoimmune thyroid diseases and rheumatoid arthritis (rheumatoid polyarthritis) based on contemporary primary literature and official clinical guidelines. Meta-analyses, cohort/observational studies, Mendelian randomization investigations published during 2010–2026, as well as official recommendations in rheumatology and thyroidology (ACR/EULAR/ATA/ETA and regional protocols) were selected, and an integrative logical model and diagnostic algorithm for clinical practice were developed.*

Keywords: *rheumatoid arthritis; rheumatoid polyarthritis; autoimmune thyroid disease; Hashimoto's thyroiditis; Graves' disease; hypothyroidism; subclinical hypothyroidism; hyperthyroidism; anti-TPO; anti-Tg; TRAb; ACPA; RF; Th17/Treg; TNF-α; IL-6; IL-17; deiodinase; comorbidity; treatment interaction.*

Relevance: RA is a chronic autoimmune disease associated with a high global disability burden, with approximately 17.6 million people living with RA worldwide in 2020 and a projected increase to 31.7 million by 2050. The global prevalence of Hashimoto's thyroiditis in the adult population is estimated at approximately 7.5%, with significant regional variation. Thyroid autoantibodies are also frequently detected in the general population (e.g., historical NHANES analyses report TPOAb positivity at approximately 13%). Against this background, the co-occurrence of RA and thyroid autoimmunity in the same patient should not be considered a "rare exception" but rather a frequently encountered comorbid condition in clinical practice.

The second layer of relevance concerns clinical consequences: evidence suggests that thyroid dysfunction may distort RA activity assessment, exacerbate fatigue and pain syndromes, and jointly increase cardiovascular risk. Thirdly, if safety-monitoring issues (absorption, hematological toxicity, laboratory test interpretation) between RA therapy (DMARDs, biologic agents, glucocorticoids) and thyroid therapy (levothyroxine, antithyroid drugs) are not properly managed, iatrogenic risk may increase.

Main Body: Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory arthritis characterized by symmetric synovitis, autoantibody production (RF, ACPA), and, over time, bone-cartilage erosion; early detection and active suppression of inflammation reduce structural damage and disability. The term "rheumatoid polyarthritis" is largely a

historical/clinico-traditional designation, reflecting the polyarticular onset and typical course of RA; modern classification favors RA terminology.

Thyroid functional disorders are typically distinguished by laboratory phenotypes: hypothyroidism (TSH↑, FT4↓), subclinical hypothyroidism (TSH↑, FT4 normal), hyperthyroidism/thyrotoxicosis (TSH↓ and FT4/FT3↑), and subclinical hyperthyroidism (TSH↓, FT4 normal). One of the most common causes of these functional disorders is autoimmune thyroid diseases (AITD), primarily Hashimoto's thyroiditis (often leading to hypothyroidism) and Graves' disease (the classic cause of hyperthyroidism).

The conceptual framework explaining the association between RA and AITD is the "common immune regulatory defect + organ-specific targets" model: on one hand, genetic/epigenetic predisposition and environmental triggers (e.g., smoking) lead to breakdown of autoimmune tolerance; on the other hand, the specific autoantigens of each organ (citrullinated proteins vs. thyroid peroxidase/thyroglobulin/TSH-receptor) determine the clinical phenotype of the immune response. Therefore, viewing the RA–thyroid association not merely as "comorbidity statistics" but as "immune network dynamics" guides diagnostic and therapeutic strategies more precisely.

According to a systematic assessment based on GBD 2021 analysis, the global burden of RA in 2020 was approximately 17.6 million patients, with an age-standardized prevalence of 208.8/100,000 (≈0.21%), and significantly higher prevalence in women (F:M ≈2.45). Prevalence estimates may vary depending on diagnostic criteria used, registry quality, and "disease severity distribution" models; thus, RA is often cited in the range of 0.5–1% in clinical practice, although global modeling results may yield lower figures.

The global prevalence of Hashimoto's thyroiditis in adults is estimated at the meta-analysis level to be approximately 7.5% (95% CI 5.7–9.6), with considerable variation according to economic status and geographic region. The subpopulation within the AITD spectrum that has not progressed to "clinical hypothyroidism/hyperthyroidism" and presents only with autoantibody positivity may be even larger; for example, some population analyses note TPOAb/TgAb positivity occurring in double-digit percentages.

The most comprehensive integrative evidence regarding the association between RA and thyroid dysfunction comes from a meta-analysis encompassing 29 studies, demonstrating an increased risk of thyroid dysfunction in individuals with RA: overall thyroid dysfunction OR≈2.25; subclinical hypothyroidism OR≈2.18; subclinical hyperthyroidism OR≈2.13; hyperthyroidism OR≈1.65. However, these ORs do not directly represent "disease prevalence"; real prevalence may range widely from 10–40% depending on the population, as reported in various cross-sectional studies. For instance, in a cohort/cross-sectional study of women, thyroid dysfunction was observed in nearly 40% of the RA group compared to approximately 8% in controls. Furthermore, a population-based cohort demonstrated increased incidence of hypothyroidism in individuals with RA (aHR≈1.67).

A significant meta-analysis on thyroid autoimmunity (antibodies) indicates higher positivity rates of anti-TPO and anti-Tg in RA (anti-TPO OR≈2.33; anti-Tg OR≈3.17). This finding reinforces the "increased occurrence" of AITD in RA through another immunological marker, while also reminding us of the possibility of geographic/genetic heterogeneity (association stronger in some regions, weaker in others).

A result that appears paradoxical at first glance but is logical from an immunomodulation perspective: Swedish registry data showed that the incidence of AITD treated with thyroxine following an RA diagnosis was lower compared to the general population (HR≈0.81), and even lower in those receiving bDMARDs (HR≈0.54). This suggests a "dynamic model" wherein (i) AITD comorbidity is frequent before RA diagnosis, and (ii) after RA diagnosis, active inflammation control reduces new episodes of AITD.

Table 1

Epidemiological Indicators and Evidence of Association

Indicator	Estimated Level/Effect	Notes
Global RA prevalence (2020)	17.6 million; 208.8/100,000	Higher in women; projected ≈31.7 million in 2050
Global Hashimoto's thyroiditis prevalence (adults)	≈7.5%	Sensitive to region/diagnostic method
TPOAb positivity in general population (NHANES)	≈13%	Presence of autoantibodies ≠ dysfunction
RA → risk of thyroid dysfunction	OR≈2.25	Subtypes: subclinical hypo OR≈2.18; subclinical hyper OR≈2.13; hyper OR≈1.65
RA → thyroid autoantibodies	anti-TPO OR≈2.33; anti-Tg OR≈3.17	Thyroid autoimmunity more common in RA
RA → hypothyroidism incidence	aHR≈1.67	Stronger in women and elderly
AITD incidence after RA diagnosis	HR≈0.81; bDMARD HR≈0.54	Hypothesis of "preventive effect" during treatment

The immunological "core" of the association between RA and AITD is the breakdown of tolerance and the deviation of adaptive immune response toward a pathological direction. In RA, B-cell responses associated with citrullinated autoantigens and ACPA, as well as neutrophil NETosis processes, may amplify the autoimmune cycle. In AITD, lymphocytic infiltration of thyroid tissue, autoantibodies such as anti-TPO/anti-Tg/TRAb, and Th17/Treg imbalance play crucial roles.

Although the full role of genetic factors is multi-locus and population-sensitive, immune "checkpoint" and signal transduction pathways (T-cell activation, co-stimulation, transcription factors) may represent a common platform for RA and AITD. For example, comprehensive reviews exist on the association of the PTPN22 variant with multiple autoimmune phenotypes and its impact on T/B cell signaling. The CTLA-4 pathway (a mechanism that reduces T-cell activation) has been shown at the meta-analysis level to have genetic associations with RA, and CTLA-4 may also be linked to AITD. The STAT4 rs7574865 polymorphism has been

studied for both autoimmune thyroid diseases (AITD) and RA in various populations (results are population-sensitive).

These genes are not "disease-guaranteeing" markers, but biologically logical chains can be constructed through them: breakdown of immune tolerance, enhancement of Th1/Th17 polarization, facilitation of B-cell autoantibody production.

In AITD pathogenesis, the IL-17/IL-23 axis and disruption of the Th17/Treg balance are described as a "critical checkpoint"; IL-17 signaling may increase mediators (e.g., IL-6 and adhesion molecules) that amplify thyroid inflammation. In RA, TNF-α and IL-6 are central cytokines of inflammation, and their elevated levels correlate with numerous clinical and laboratory parameters.

From an endocrine standpoint, cytokines such as IL-6 and TNF may influence thyroid hormone metabolism and the "set-point" of the hypothalamic-pituitary-thyroid (HPT) axis: IL-6 has been shown to inhibit the activation of thyroxine (T4) to T3 and enhance inactive pathways — one of the mechanisms of non-thyroidal illness syndrome (NTIS). Therefore, in chronic inflammatory conditions like RA, decreased FT3 (classic NTIS) is theoretically and practically relevant, but this condition must be distinguished from "classic thyroid dysfunction".

There are attempts to explain RA pathogenesis not only as "systemic" but also in terms of "local tissue endocrinology". The presence of thyroid hormone transporters/receptors and deiodinases has been demonstrated in synovial fibroblasts and synovial tissue; DIO2- and DIO3-positive cells are more abundant in RA, which may enhance degradative pathways of T4/T3 and reduce local bioactive T3 bioavailability. Authors also discuss that TNF may regulate this local network, and IL-6 can decrease T3 and increase rT3 in humans. This model is useful for explaining the metabolic and immune "microenvironment" of RA: inflammation → decreased local hormone activity → immune/tissue response "recalibrated" → possible reinforcement of the inflammatory cycle (direct clinical evidence for this is limited here, but the biological basis exists).

The classic clinical picture of RA — symmetric joint swelling and pain, morning stiffness, involvement of small joints (MCP, PIP), and long-term structural changes; the 2010 ACR/EULAR classification is specifically aimed at identifying early and persistent synovitis. EULAR guidelines regard early control, timely initiation of DMARDs, and treat-to-target strategies as factors improving clinical outcomes.

Thyroid dysfunction presents with multisystem symptoms: in hypothyroidism — fatigue, cold sensitivity, weight gain, bradycardia, dry skin, cognitive slowing; in hyperthyroidism — weight loss, tachycardia, tremor, heat intolerance, nervousness, and insomnia. In Hashimoto's process, hormones may remain normal for extended periods, with only antibodies elevated; in such cases, treatment is often not required, and TSH monitoring is important.

"Clinical overlap" between RA and thyroid dysfunction poses greater problems in the following areas:

First, symptom overlap: fatigue, depressive background, muscle pain, and general "somatic complaints" may be related to RA activity, a fibromyalgia component, or thyroid dysfunction. Review evidence suggests that fibromyalgia and chronic diffuse pain syndromes may be more common in combined RA + AITD cases.

Second, joint symptoms: "hypothyroid arthropathy" (myalgia, joint stiffness, sometimes effusion), carpal tunnel syndrome, and muscle weakness can occur in hypothyroidism; this may mimic the onset of RA or lead to an erroneous conclusion of "increased activity" in a patient with established RA.

Third, disease activity assessment: some cross-sectional studies have shown higher DAS28 and pain VAS scores in patients with RA + hypothyroidism. These results are heterogeneous but warrant clinical caution. Meanwhile, positive correlations between thyroid autoantibodies and RA autoantibodies (ACPA) have been noted in female RA cohorts (e.g., correlation between ACPA and TPOAb).

In the co-management of RA and thyroid dysfunction, diagnostics have two objectives: (1) reliably confirming/excluding each disease according to its own "core criteria"; (2) correctly interpreting laboratory tests amidst confounders such as inflammation, drug effects, and NTIS.

The 2010 ACR/EULAR classification criteria classify "definite RA" based on "synovitis in at least one joint" + absence of alternative diagnosis + a score ≥6/10 across four domains (number/site of involved joints; serology — RF and/or ACPA; acute phase reactants — CRP/ESR; symptom duration). Among serological markers, ACPA (anti-CCP) often has high specificity and may correlate with prognosis (erosive course); RF is sensitive but less specific.

Regarding imaging, EULAR recommendations advocate evidence-based use of X-ray (structural damage), ultrasound/MRI (early synovitis, erosion, and inflammation) in diagnosis, prognosis, and monitoring.

In the diagnosis of thyroid dysfunction, TSH is one of the most sensitive "screening tests"; primary hypothyroidism is confirmed by TSH↑ and FT4↓, while subclinical hypothyroidism is considered when TSH↑ and FT4 are normal. Regarding subclinical hypothyroidism, ETA recommendations discuss strategies such as differing clinical approaches based on TSH levels (e.g., 4–10 vs. >10 mIU/L), retesting TSH/FT4 at 2–3 month intervals, and assessing anti-TPO. (Note: individual interpretation considering laboratory reference ranges and population characteristics is necessary.)

Diagnosis of Hashimoto's thyroiditis often relies on clinical context + anti-TPO/anti-Tg + ultrasound features; large series have shown that elevated anti-TPO is very frequently encountered in Hashimoto's. Official patient guidelines emphasize that in euthyroid, antibody-positive states, hormone therapy is not mandatory; TSH monitoring is sufficient, and repeating antibody titers is usually unnecessary.

In distinguishing Graves' disease from other causes of thyrotoxicosis, TRAb, radioiodine uptake (RAIU), and clinical context are important.

In chronic inflammation (RA) or severe systemic illnesses, NTIS (euthyroid sick syndrome) may lead to decreased FT3 and atypical combinations of TSH/FT4; it is noted that administering "thyroid hormone" in such situations is often unnecessary and may even be harmful. Additionally, glucocorticoids, NSAIDs (particularly high-dose salicylates), heparin, and other drugs can complicate interpretation of thyroid function tests. This necessitates consideration, especially during glucocorticoid use in RA patients, that decreased TSH or T3 may reflect drug/NTIS effects rather than "underlying thyroid disease".

Table 2

Thyroid Phenotypes, Autoantibodies, and Associated Clinical Risks with RA

Thyroid Status	Typical Lab Profile	Typical Autoantibodies	Association with RA (Evidence Type)	Practical Notes
Hashimoto's (euthyroid)	TSH normal; FT4 normal	anti-TPO↑, anti-Tg±	Thyroid autoantibodies more common in RA (OR)	LT4 usually not needed; TSH monitoring
Subclinical hypothyroidism	TSH↑; FT4 normal	anti-TPO+ in many cases	Risk of subclinical hypothyroidism in RA ≈2× (OR≈2.18)	Retest TSH; treatment more justified if TSH >10
Manifest hypothyroidism	TSH↑; FT4↓	anti-TPO often +	Increased incidence of hypothyroidism in RA (aHR≈1.67)	LT4 substitution; comorbid CVD/risk assessment important
Graves' (manifest hyperthyroidism)	TSH↓; FT4/FT3↑	TRAb+	MR: GD → may slightly increase RA risk	Confirm etiology; control thyrotoxicosis essential
Subclinical hyperthyroidism	TSH↓; FT4 normal	TRAb±	Subclinical hyper OR≈2.13 in RA	Consider cardiac rhythm and bone metabolism context; individual decision

The following algorithm is constructed on a "risk-based testing" model, proposed as a practical guide consistent with ACR/EULAR and ATA/ETA thyroid principles, but not replacing a direct universal screening standard for RA–thyroid comorbidity.

Table 3

Diagnostic Algorithm "Minimal Panel" and Extended Panel

Step	Minimal (frequent in practice)	Extended (if indicated)	Evidence/Notes
RA screening/confirmation	Clinical synovitis; ESR/CRP; RF and ACPA	Ultrasound/MRI; X-ray; other arthritis markers	ACR/EULAR 2010; EULAR imaging recommendation
Thyroid screening	TSH + FT4	FT3; anti-TPO/anti-Tg; TRAb; ultrasound; RAIU	TSH sensitive; etiology determined by TRAb/RAIU

Step	Minimal (frequent in practice)	Extended (if indicated)	Evidence/Notes
Confounders	Medication list; glucocorticoid/NSAID	NTIS probability; retesting; clinical context	Drugs and NTIS distort TFT

Treatment and Management

The core principle in management — controlling both diseases according to their respective guidelines, while anticipating that therapy for one condition may interfere with the laboratory/clinical picture of the other.

RA Therapy: Treat-to-Target and DMARD Strategy

Modern management of RA is based on the treat-to-target (T2T) concept: disease activity is frequently assessed using validated instruments, and therapy is adjusted to achieve the goal (remission or low disease activity). The 2021 American College of Rheumatology recommendations articulate the essence of the T2T approach and principles for optimizing DMARDs. The 2022 European League Against Rheumatism update reiterates strategic rules such as starting with csDMARDs (often methotrexate), escalating to bDMARDs/tsDMARDs if necessary, and tapering DMARDs (but not completely discontinuing) during stable remission.

From the perspective of thyroid comorbidity, RA therapy has two potential "beneficial consequences": (1) reduction of inflammation may ameliorate NTIS-like metabolic changes; (2) certain immunomodulators may positively influence markers of thyroid autoimmunity. For example, decreased TSH and reduced TPOAb have been reported in some hypothyroid RA patients during anti-TNF therapy with adalimumab. Furthermore, reviews suggest that biologic antirheumatic agents more often show neutral or positive trends rather than exacerbating thyroid autoimmunity.

However, these "benefits" are not sufficiently standardized to alter clinical decisions: the choice of RA therapy is primarily based on RA activity, prognostic markers, and safety profile; thyroid issues are managed in parallel.

The American Thyroid Association recommends levothyroxine as the primary treatment for hypothyroidism; the goal is to achieve euthyroidism and maintain TSH within the normal range. Multiple factors affect levothyroxine absorption: calcium carbonate, proton pump inhibitors, bile acid sequestrants (cholestyramine, etc.), iron preparations, aluminum antacids, sucralfate, and others may reduce LT4 absorption; clinical practice requires temporal separation and dose adjustment.

It is noted that in Hashimoto's thyroiditis with elevated antibodies but normal TSH/FT4, hormone therapy is not required; periodic TSH monitoring is sufficient, and repeating antibody titers is usually unnecessary. Regional (Russian-language) clinical guidelines also emphasize that AIT diagnosis should not be based solely on "palpation or gland size", but on a combination of "major signs" (primary hypothyroidism + antibodies/ultrasound features); follow-up of antibody dynamics has no prognostic value, and treatment primarily consists of substitution.

The ATA 2016 guidelines for thyrotoxicosis regard establishing the "correct etiology" as the foundation of treatment: in Graves' hyperthyroidism, radioiodine, antithyroid drugs, or surgery options are selected based on patient context and preferences. Antithyroid drugs (methimazole/propylthiouracil) can cause rare but life-threatening agranulocytosis; contemporary reviews estimate agranulocytosis incidence typically in the 0.2–0.5% range and emphasize the necessity of patient education to immediately discontinue the drug and consult a physician if fever/pharyngitis symptoms occur.

This point becomes even more critical when intersecting with RA: csDMARDs used in RA therapy (methotrexate, leflunomide, sulfasalazine) also require hematological monitoring; therefore, in combinations of antithyroid drugs + DMARDs, the laboratory monitoring schedule should be synchronized for early detection of leukopenia/neutropenia risk.

Table 4

Thyroid Medications and RA Medications: Interactions and Monitoring

Combination/Situation	Problem	Practical Solution
Levothyroxine + calcium/iron/PPI/cholestyramine	↓ LT4 absorption, possible TSH↑	Separate administration times; dose adjustment based on TSH
Glucocorticoids (in RA)	Transient TSH↓; T3↓; TFT interpretation difficult	Rely on clinical picture + TSH/FT4; consider NTIS/drug effect
NSAIDs (high-dose salicylates)	Altered T4/T3 binding; artifacts in FT4 measurements	Rely more on TSH; clinical context
Antithyroid drugs + csDMARDs (MTX/LEF/SSZ)	Risk of agranulocytosis/neutropenia; infection risk	CBC monitoring; immediate workup for fever/pharyngitis
Anti-TNF (adalimumab) in RA	Trend towards ↓ TPOAb, ↓ TSH in some patients	Do not interpret as "treating thyroid"; reassess TFT based on clinical need
bDMARDs and AITD incidence	Decreased AITD incidence after RA diagnosis (registry evidence)	Continue thyroid monitoring; potential benefit of "immune surveillance" considered

Conclusion: The association between RA and thyroid functional disorders is highly likely to be real and clinically significant: meta-analyses demonstrate increased prevalence of thyroid dysfunction and thyroid autoantibodies in RA. Population cohorts indicate an increased incidence of hypothyroidism in individuals with RA, and some registries suggest that AITD incidence may decrease after RA diagnosis (especially in bDMARD recipients), suggesting possible secondary benefits of "aggressive inflammation suppression" across the autoimmune spectrum. Mendelian randomization results indicate complexity and sometimes

contradictory causal directions; therefore, in clinical practice, targeted testing based on symptoms, risk profile, and drug exposure (TSH/FT4 ± autoantibodies; RA markers) is more logical than universal screening.

From an immunopathogenetic perspective, Th17/Treg imbalance and the cytokine network (TNF-α, IL-6, IL-17), as well as local tissue endocrinology (deiodinase network in synovium), provide a conceptual framework explaining the RA–thyroid intersection; these mechanisms may pave the way for future biomarker and therapeutic strategies.

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