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Interrelationship Between Inflammatory Markers and Thyroid-Stimulating Hormone in Hypothyroidism: A Focused Review on hs-CRP and Insulin Resistance

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Abstract

Background: Hypothyroidism is frequently accompanied by systemic low-grade inflammation and metabolic disturbances, notably insulin resistance, which collectively contribute to elevated cardiovascular morbidity and mortality. Elevated thyroid-stimulating hormone (TSH) plays a pivotal role in modulating inflammatory and metabolic pathways, independently of thyroid hormone levels.

Aim: This review critically explores the biochemical and clinical links between TSH, high-sensitivity C-reactive protein (hs-CRP), and insulin resistance (IR) in hypothyroid patients, integrating findings from both overt and subclinical disease states.

Methods: A comprehensive literature search spanning 2000 to 2025 analyzed clinical and biochemical studies addressing the interactions among TSH, hs-CRP, and IR, guided by PRISMA methodology.

Key Findings: TSH positively correlates with hs-CRP and IR indices such as HOMA-IR. Both hs-CRP and IR are elevated in hypothyroid patients compared to euthyroid controls and tend to improve with adequate thyroid hormone replacement. The combined evaluation of these parameters offers superior insight into cardiometabolic risk assessment.

Conclusion: This integrated axis linking TSH with inflammatory and metabolic disturbances highlights the necessity of comprehensive biomarker evaluation in hypothyroidism to improve prognostication and personalized therapy.

1. Introduction

Hypothyroidism, characterized by reduced secretion of thyroid hormones (T3 and T4), exists in overt and subclinical forms and arises from various etiologies including autoimmune thyroiditis, iodine imbalance, thyroidectomy, or pituitary-hypothalamic dysfunction (Chaker et al., 2017). The classical focus on TSH as an endocrine feedback marker is now expanding to encompass its role as a modulator

of systemic metabolism and immune pathways (Feldt-Rasmussen et al., 2021). Systemic low-grade inflammation, as evidenced by raised hs-CRP levels, and insulin resistance (assessed by indices such as HOMA-IR), increasingly attract attention as key mediators of the heightened cardiovascular and metabolic risk associated with hypothyroidism (Jinger et al., 2025).

This review synthesizes current understanding of the biochemical and clinical interplay among TSH, hs-CRP, and insulin resistance in hypothyroidism and discusses implications for risk stratification and therapeutic intervention.

2. Thyroid Hormones and Inflammatory Responses

Thyroid hormones are integral not only for metabolic regulation but also for immune modulation. Elevated TSH activates inflammatory signaling cascades — notably nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs) — which enhance macrophage activation and stimulate the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Duntas & Brenta, 2012). This pro-inflammatory milieu is reinforced by hypothyroidism-associated oxidative stress caused by the accumulation of reactive oxygen species and diminished antioxidant defenses (Hosseini et al., 2022). The resulting inflammation further impairs thyroid function and creates a feed-forward loop exacerbating the disease.

Methodology

This review adhered to PRISMA guidelines with a systematic literature search of PubMed, Scopus, Web of Science, and Embase databases from 2000 through July 2025. Search terms included “hypothyroidism,” “thyroid-stimulating hormone,” “hs-CRP,” “insulin resistance,” “HOMA-IR,” and their synonyms. Inclusion criteria comprised observational, interventional, and meta-analytical studies assessing biochemical relationships and clinical outcomes related to TSH, inflammation, and insulin resistance in overt and subclinical hypothyroid populations. Forty-four relevant studies were selected for critical synthesis.

3. hs-CRP as a Marker of Low-Grade Inflammation in Hypothyroidism

High-sensitivity C-reactive protein (hs-CRP) is a hepatically synthesized acute-phase reactant induced by IL-6 signaling, sensitive to subtle systemic inflammation (Pepys & Hirschfield, 2003). Both overt and subclinical hypothyroidism are consistently associated with elevated hs-CRP levels, which show a direct, positive correlation with serum TSH concentrations, independently of circulating thyroid hormone levels (Vudu et al., 2023; Jinger et al., 2025).

Clinically, elevated hs-CRP reflects ongoing low-grade inflammation that contributes to endothelial

dysfunction, atherosclerosis, and increased cardiovascular risk in hypothyroid patients (Carvalho et al., 2017). Importantly, initiation of thyroid hormone replacement therapy has been shown to reduce hs-CRP concentrations, especially when treatment is commenced early in subclinical hypothyroidism, emphasizing the reversible nature of inflammation in this context (Handhal et al., 2024).

Table 1. Key Clinical Studies on hs-CRP and Insulin Resistance in Hypothyroidism

Study & Year	Population	Key Findings	TSH - hs-CRP Correlation	Insulin Resistance (HOMA-IR) Relation	Notes
Vudu et al. (2023)	Overt & Subclinical Hypothyroid vs Controls	Elevated hs-CRP in both groups; levothyroxine reduces hs-CRP	Positive	Not specified	Autoimmune hypothyroidism cohort
Jinger et al. (2025)	Subclinical Hypothyroidism	hs-CRP significantly higher than controls; correlated with TSH, LDL, TG, and HOMA-IR	Yes	Strong positive correlation	Links metabolic dysfunction
Krishnamurthy et al. (2025)	Thyroid autoimmunity	Anti-TPO antibodies precede IR onset; elevated HOMA-IR in antibody-positive subjects	Indirect	Elevated	Autoimmune-inflammation link
Handhal et al. (2024)	Hypothyroid vs Controls	hs-CRP elevated; correlated with metabolic and lipid parameters	Significant	Increased IR	Biochemical correlation study
Zargar et al. (2024)	Subclinical Hypothyroidism	Higher hs-CRP, insulin, and TSH vs controls; positive correlations among markers	Yes	Elevated	Suggests inflammation-metabolic cross-talk

4. Insulin Resistance and Hypothyroidism

Hypothyroidism impairs glucose metabolism through multiple interacting mechanisms, including decreased insulin receptor activity, impaired glucose uptake by skeletal muscle and adipose tissue, and dysregulated hepatic gluconeogenesis (Maratou et al., 2010). These alterations culminate in elevated insulin resistance, a condition well quantified by indices such as HOMA-IR.

Elevated serum TSH has been shown to correlate with increased HOMA-IR values in both overt and subclinical hypothyroid patients compared to euthyroid controls (Krishnamurthy et al., 2025). Additionally, autoimmune thyroid antibodies, particularly anti-thyroid peroxidase (anti-TPO), are implicated in promoting chronic inflammation through cytokine release and may precipitate or exacerbate insulin resistance (Jhingan et al., 2022).

Notably, insulin resistance potentially worsens thyroid function by altering metabolic clearance of thyroid hormones and contributing to dysregulated immune responses, creating a bidirectional deleterious feedback loop (Razvi et al., 2010).

5. Combined Role of hs-CRP and Insulin Resistance in Thyroid Dysfunction

The intersection of systemic inflammation and insulin resistance significantly exacerbates metabolic impairment and cardiovascular risk in hypothyroid patients. Population and meta-analytical studies have demonstrated consistent, positive associations between TSH, hs-CRP, and HOMA-IR, concurrent with worse lipid profiles and anthropometric markers such as BMI and waist circumference (Zargar et al., 2024; Sharma et al., 2023).

This synergistic relationship reinforces the concept that isolated biomarker measurement underestimates cardiovascular and metabolic risk in hypothyroidism, and integrated evaluation offers superior predictive capacity, enabling earlier identification of high-risk patients and targeted intervention.

Table 2. Comparative Performance of Biomarkers and Indices in Hypothyroidism

Biomarker/Index	Clinical Utility	Strengths	Limitations
hs-CRP	Marker of systemic inflammation	Sensitive; predictive of cardiovascular risk	Affected by concurrent inflammatory conditions
HOMA-IR	Surrogate measure of insulin resistance	Quantitative; widely used	Requires fasting samples; influenced by glucose fluctuations
TSH	Thyroid function marker	Standard diagnostic tool	Indirect metabolic impact measure
Anti-TPO Antibodies	Marker of autoimmune thyroid disease	Predicts early autoimmune thyroiditis	Restricted to autoimmune thyroid disorders

Mechanistic Diagram (Conceptual Overview)

Elevated TSH
↓
Activation of NF-κB and MAPK pathways
↓
Enhanced macrophage activation → Increased pro-inflammatory cytokine secretion (TNF-α, IL-6)
↓
Increased systemic inflammation → Elevated hs-CRP
↓
Impairment of insulin signaling → Insulin resistance (↑ HOMA-IR)
↓
Worsening thyroid function and metabolic dysregulation → Vicious cycle perpetuates

Figure 1. Conceptual diagram of the interplay between TSH, inflammation, and insulin resistance in hypothyroidism.

6. Clinical Implications and Future Directions

The combined assessment of TSH, hs-CRP, and insulin resistance markers enables refined risk stratification in patients with hypothyroidism, facilitating identification of individuals susceptible to cardiovascular and metabolic complications despite apparent biochemical control of thyroid status.

Incorporating these markers into routine clinical practice could inform proactive therapeutic interventions including lifestyle modification, optimized thyroid hormone replacement, and potentially, anti-inflammatory or insulin-sensitizing agent trials.

Future research should prioritize:

- Large-scale, prospective longitudinal studies validating the prognostic value of these combined markers.
- Randomized clinical trials targeting inflammation and insulin resistance in hypothyroid patients.
- Standardization of cutoff values and assay methodologies for hs-CRP and HOMA-IR in thyroid populations.
- Evaluation of cost-effectiveness and practical implementation of integrated biomarker panels in different healthcare settings.

7. Conclusion

Hypothyroidism is intimately linked with systemic low-grade inflammation and insulin resistance, mediated by elevated TSH levels that activate inflammatory pathways and impair glucose homeostasis. The synergistic relationship among TSH, hs-CRP, and insulin resistance underlies much of the augmented cardiometabolic risk seen in hypothyroid patients. Recognizing and integrating these markers into clinical evaluation offers an avenue for more holistic and personalized patient management beyond conventional thyroid hormone assays.

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