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Non-thyroidal illness syndrome in cardiology: insights into pathogenesis, diagnosis, and treatment approaches

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Abstract

Euthyroid sick syndrome (ESS), also known as non-thyroidal illness syndrome (NTIS), is characterized by abnormal thyroid function test results in patients without intrinsic thyroid disease, often observed in critically diseased patients. This review evaluates the current understanding of ESS in daily cardiology practice, including its pathogenesis, diagnostic criteria, and therapeutic approaches, with a focus on ICU patients. Recent advances in research on the role of inflammatory cytokines and the impact of thyroid hormone replacement therapy are also discussed. A total of 1,346 records were found (432 in MEDLINE, 586 in Web of Science, and 328 in Scopus), and 142 duplicates were removed. All titles with an abstract were reviewed, and 89 qualified for a full review of eligibility. Eight articles met the inclusion criteria and were qualitatively summarized in this review. with a PRISMA flowchart illustrating the selection process. This systematic review underscores the importance of recognizing ESS in cardiology practice, as its management may impact cardiovascular outcomes.

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Introduction

Euthyroid sick syndrome is frequently observed in critically ill patients, particularly those with cardiovascular diseases. This syndrome manifests as abnormalities in thyroid function tests, specifically low triiodothyronine (T3) and thyroxine (T4) levels, although normal or low thyroid-stimulating hormone (TSH) levels. ESS has been associated with poor prognosis in cardiac patients, making it a crucial issue in cardiology practice [1]. Although ESS is well-documented in various systemic illnesses, including infections, trauma, and sepsis, its impact on cardiovascular outcomes and the benefits of thyroid hormone replacement therapy (THRT) remain controversial.

Our review aims to explore the pathophysiology of ESS, its diagnostic criteria, the role of inflammatory cytokines, and potential for therapeutic interventions. We also examine the recent research advances that may shape future guidelines for managing ESS in patients with cardiovascular disease and other critical conditions, such as sepsis, trauma, renal failure, and chronic liver disease.

Materials and methods

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search was performed using MEDLINE, Web of Science, and Scopus databases, covering studies between 2005 and 2024, however some earlier works were analyzed for historical perspective. The review focused on studies exploring euthyroid sick syndrome in cardiology practice, including diagnosis, pathogenesis, and treatment options. Non-cardiac conditions, such as sepsis, chronic kidney disease, and trauma, were also considered to highlight the broad incidence of ESS.

The search terms included: "euthyroid sick syndrome," "non-thyroidal illness syndrome," "cardiovascular disease," "thyroid function," "thyroid hormone replacement therapy," "cytokines," "sepsis," "renal failure," and "liver disease." Inclusion criteria were original research articles, systematic reviews, meta-analyses, and clinical trials in English, investigating ESS in cardiovascular settings and other systemic diseases. Studies not directly related to the thyroid system or involving patients with intrinsic thyroid disorders were excluded.

Selection process: a total of 1,346 records (432 in MEDLINE, 586 in Web of Science, and 328 in Scopus) were found, and 142 duplicates were removed. All titles and abstracts were reviewed for relevance, leading to 89 studies qualifying for full-text evaluation. Ultimately, eight articles met the inclusion criteria and were qualitatively summarized in this review focusing on ESS in cardiology and related systemic conditions.

Results

1. Diagnosis Criteria

Euthyroid sick syndrome (ESS), or non-thyroidal illness syndrome (NTIS), is diagnosed primarily through thyroid function tests, which typically reveal low serum levels of triiodothyronine alongside normal or reduced levels of thyroxine and thyroid-stimulating hormone [1]. Diagnosis necessitates excluding intrinsic thyroid disease, which can often mimic ESS. Clinically, the evaluation of ESS is critical, particularly among patients with acute cardiovascular conditions like acute heart failure and myocardial infarction, as they frequently exhibit alterations in thyroid hormone levels [2,3]. The correlation between the presence of ESS and poor clinical outcomes is well documented, making timely diagnosis and management imperative [4]. Studies indicate that nearly 70% of patients presenting with acute coronary syndromes exhibit thyroid function abnormalities characteristic of ESS, with lower T3 levels associated with increased mortality rates [5,6].

2. Thyroid Function Test Results

Thyroid function tests in patients with ESS typically demonstrate a distinct pattern: low total and free T3 levels, normal or low T4 levels, and normal or slightly low TSH levels. As the illness progresses, T4 levels may decline, while TSH remains normal or low [7]. These changes are hypothesized to reflect the adaptive response to severe illness, diverting energy away from thyroid hormone production to support vital organ function. Studies have demonstrated that lower T3 levels are particularly prevalent in patients with heart failure, myocardial infarction, and septic shock, correlating with higher mortality rates [8, 9]. In non-cardiac critical illnesses like chronic kidney disease and trauma, the pattern of low T3 syndrome is similar and also predicts worse outcomes [10, 11].

3. Pathogenesis

The pathogenesis of ESS is complex and involves multiple mechanisms, including altered deiodinase activity, changes in thyroid hormone transport proteins, and dysregulation of the hypothalamic-pituitary-thyroid (HPT) axis. In critically ill patients, reduced activity of type 1 deiodinase results in decreased peripheral conversion of T4 to T3, leading to low serum T3 levels [12]. Concurrently, type 3 deiodinase activity is increased, further degrading T3 and exacerbating low T3 syndrome [13]. This adaptive response is thought to conserve energy during periods of critical illness, although it might contribute to the deterioration of organ function, especially in the cardiovascular system.

4. Role of Inflammatory Cytokines

Inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), play a crucial role in the development of ESS. These cytokines inhibit deiodinase activity, reducing the bioavailability of thyroid hormones at the tissue level [14]. Studies have demonstrated a strong correlation between elevated cytokine levels and the severity of thyroid dysfunction in critically ill patients, particularly in those with cardiovascular disease and sepsis [15]. For example, in a cohort of patients with heart failure, those exhibiting low T3 levels were found to have a twofold increase in mortality risk compared to those with normal thyroid function [16]. This correlation emphasizes the importance of integrating cytokine assessments into the clinical evaluation of patients with ESS, particularly in critical care settings.

In conditions such as chronic kidney disease and liver cirrhosis, elevated cytokine levels similarly exacerbate thyroid dysfunction, revealing the extensive influence of systemic inflammation on thyroid hormone metabolism [17, 18]. Understanding these molecular mechanisms is crucial for developing targeted therapeutic interventions aimed at modulating cytokine activity and restoring normal thyroid function in critically ill patients.

Table I. Summary om key findings

	Key Findings
Definition	ESS, also known as non-thyroidal illness syndrome (NTIS), involves abnormal thyroid hormone levels in critically ill patients without intrinsic thyroid disease.
Pathogenesis	ESS results from changes in thyroid hormone metabolism, primarily due to the influence of inflammatory cytokines like IL-6 and TNF-α, inhibiting the conversion of T4 to T3, resulting in altered deiodinase activity, and increased T3 degradation.
Diagnostic Criteria	Low T3, normal or low T4, normal or slightly reduced TSH levels; ESS is common in heart failure, myocardial infarction, and sepsis; often correlating with poor outcomes.
Thyroid Function Test Results	Low T3, normal or low T4, normal or low TSH; while rT3 may be elevated in severe cases.
Inflammatory Cytokines Role	IL-6, TNF-α, IFN-γ inhibit deiodinase activity; cytokine levels correlate with severity of ESS.
Treatment with Thyroid Hormone Replacement Therapy	THRT benefits are debated; it may help selected subgroups but lacks consistent mortality benefit. Recognizing ESS in cardiology is critical as low T3 is an independent predictor of poor prognosis. Decisions regarding THRT need to be individualized.
Research Advances	New biomarkers, cytokine-targeted therapies, and selective hormone analogs show promise in ESS management.

Discussion

The role of thyroid hormone replacement therapy (THRT) in ESS remains controversial with research yielding mixed results regarding its efficacy and safety. Some studies suggest that THRT may improve outcomes in critically ill patients, particularly those with cardiovascular disease and persistent low T3 syndrome [19]. However, other trials have found no significant mortality benefit from THRT in ESS patients and caution against its use due to potential adverse effects, such as increased myocardial oxygen demand, which can exacerbate cardiac ischemia [20, 21]. The variability in study outcomes has prompted further inquiry into the specific patient populations that might benefit from THRT. A meta-analysis of randomized controlled trials found that THRT may benefit select subgroups, such as those with severe heart failure or chronic low T3 syndrome, but routine use in critically ill patients remains unsupported by robust evidence [22]. Non-cardiac conditions like sepsis and renal failure exhibit similar variability in response to THRT, further

complicating its clinical application [23, 24]. The inconsistent findings across different studies necessitate a nuanced understanding of the physiological responses to THRT and the potential for adverse effects in critically ill populations.

Recent advancements in research have shed light on the molecular mechanisms underlying ESS and the potential for targeted therapies. Advances in understanding the role of inflammatory cytokines and the regulation of deiodinase activity have opened new avenues for therapeutic intervention. For instance, therapies that inhibit IL-6 or TNF-α may have the potential to restore normal thyroid hormone levels in patients experiencing ESS. Additionally, novel biomarkers, such as reverse T3 (rT3) and thyroid hormone-binding proteins, may improve the diagnosis and prognosis of ESS in cardiology patients and those with systemic illnesses like sepsis and chronic liver disease [25]. Emerging data also suggest that modulation of the HPT axis through selective hormone analogs may offer a more tailored approach to managing ESS, particularly in patients with heart failure or acute coronary syndromes.

ESS is a common but often overlooked condition in cardiology practice, particularly in critically ill patients. The syndrome's pathogenesis is complex and multifactorial, involving altered thyroid hormone metabolism, cytokine-mediated inflammation, and adaptive changes in the HPT axis. Non-cardiac conditions, such as sepsis, trauma, and renal failure, share similar thyroid function abnormalities, underscoring the broad relevance of ESS in critical care settings. Although THRT remains controversial, recent advances in understanding the molecular mechanisms of ESS may pave the way for more targeted therapeutic approaches in the future.

Thus, ESS presents a significant clinical challenge within cardiology, particularly in critically ill patients. Its pathogenesis involves complex interactions between altered thyroid hormone metabolism, inflammatory cytokines, and the adaptive responses of the HPT axis. While the role of THRT remains contentious, ongoing research into the molecular underpinnings of ESS may lead to innovative treatment strategies that improve patient outcomes.

Conclusions.

Euthyroid sick syndrome presents a significant clinical challenge in cardiology practice and across various critical care settings. While current evidence suggests that ESS is an adaptive response to illness, its association with poor outcomes in cardiovascular and non-cardiovascular patients necessitates further research into its pathogenesis and treatment. The role of THRT remains unclear, and future studies should aim to clarify its potential benefits in specific patient populations. Advances in biomarkers and targeted therapies may provide new insights into managing ESS, ultimately improving outcomes for critically ill patients.

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