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Relationship between Hypothyroidism Management and Patient Quality of Life: A Systematic Review

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Abstract

Background: Levothyroxine (LT4) therapy is highly effective for biochemical correction of hypothyroidism, yet many patients report persistent symptoms and reduced health-related quality of life (HRQoL) despite achieving target thyroid-stimulating hormone (TSH) levels. Whether alternative management strategies meaningfully improve HRQoL remains clinically important. ***Aim*:** To systematically review and qualitatively synthesize evidence on the relationship between hypothyroidism management approaches and patient quality of life. ***Methods:*** A systematic review was performed following PRISMA principles. Eligible studies were primary clinical studies evaluating adults with hypothyroidism or subclinical hypothyroidism in which HRQoL was measured and related to a management approach, treatment strategy, formulation, or biochemical response. Nine studies met eligibility and were synthesized qualitatively due to heterogeneity in populations, interventions, comparators, and HRQoL instruments. ***Results:*** Evidence from large randomized trials in older adults with subclinical hypothyroidism showed no clinically meaningful HRQoL benefit from LT4 compared with placebo or usual care. In primary hypothyroidism, switching from LT4 tablets to liquid LT4 was consistently associated with improved patient-reported QoL in selected cohorts, often without major changes in thyroid biochemistry. Trials of LT4/LT3 combination therapy generally did not demonstrate consistent HRQoL superiority over LT4 alone, although some studies reported patient preference or selective domain improvements. Observational studies and surveys repeatedly documented impaired HRQoL among LT4-treated patients compared with controls, and HRQoL was frequently weakly correlated or not correlated with TSH/FT4 within the reference range. ***Conclusion:*** Quality of life in treated hypothyroidism is influenced by more than biochemical normalization alone. LT4 treatment in older adults with subclinical hypothyroidism does not appear to improve HRQoL, while liquid LT4 may improve HRQoL in selected, dissatisfied, or absorption-challenged patients. Combination therapy remains an inconsistent strategy for HRQoL improvement. Future research should prioritize patient-centered outcomes, identify phenotypes of persistent symptoms, and test targeted management pathways using validated thyroid-specific HRQoL instruments.

Keyword: Hypothyroidism, Levothyroxine (LT4), Health-Related Quality of Life (HRQoL), Thyroid-Stimulating Hormone (TSH), Patient-Reported Outcomes (PROs).

BACKGROUND

Hypothyroidism is a common endocrine disorder managed predominantly with levothyroxine replacement, aiming to restore euthyroidism and alleviate symptoms. Although most patients achieve biochemical control, a clinically important subset reports persistent fatigue, cognitive complaints, mood symptoms, and impaired daily functioning while taking LT4, even when TSH is within the reference range. This discrepancy has intensified interest in whether management factors beyond "TSH normalization" influence HRQoL, including dose targets, treatment of subclinical hypothyroidism, alternative formulations such as liquid LT4, and the use of combination LT4/LT3 therapy. Patient-reported outcome measures such as

ThyPRO and generic instruments such as SF-36 have revealed that residual symptom burden may persist despite apparently adequate replacement, highlighting the need to understand which management approaches measurably improve patients lived experience. Large pragmatic trials in older adults with subclinical hypothyroidism further challenge assumptions that biochemical correction necessarily translates into symptomatic and HRQoL gains, emphasizing the importance of tailoring treatment decisions to outcomes that matter to patients (Stott *et al*., 2017; Mooijaart *et al*., 2019). At the same time, evolving evidence suggests that formulation and administration timing can influence treatment satisfaction and potentially HRQoL, particularly in patients with adherence difficulties or conditions affecting absorption (Guglielmi *et al*., 2018; Bornikowska *et al*., 2021).

Study Aim

The aim of this systematic review was to synthesize clinical evidence on the relationship between hypothyroidism management and patient quality of life, focusing on how treatment strategies, formulations, and treatment contexts (including subclinical hypothyroidism) influence HRQoL outcomes.

METHODOLOGY

A systematic literature review approach was applied using PRISMA-aligned methods. The eligibility framework focused on adult participants with primary hypothyroidism or subclinical hypothyroidism in whom management was defined as a therapeutic strategy or treatment context, and in whom quality of life was assessed using validated generic or thyroid-specific instruments. Studies were eligible if they reported HRQoL outcomes in relation to a management approach such as initiation of LT4 for subclinical hypothyroidism, switching LT4 formulation, achieving euthyroidism under LT4 therapy, or using LT4/LT3 combination therapy. Both randomized and observational designs were eligible to reflect real-world management questions, provided the report contained primary data and clear HRQoL assessment. Studies focusing exclusively on pediatric populations, pregnancy, thyroid cancer survivorship without hypothyroidism management focus, or lacking validated HRQoL measures were excluded.

The search strategy conceptually targeted three domains: hypothyroidism, management or therapy (including LT4, LT3, combination therapy, formulation changes), and quality of life outcomes. The final included set comprised nine primary studies representing randomized controlled trials, crossover trials, and observational or survey-based analyses. Because included studies differed substantially in population characteristics (subclinical vs overt hypothyroidism; older adults vs mixed ages), intervention types (placebo-controlled initiation trials vs formulation switching vs combination therapy), and HRQoL instruments, meta-analysis was not undertaken and a qualitative synthesis was performed.

RESULTS

Nine eligible studies were included and synthesized across four management-relevant domains: LT4 treatment for subclinical hypothyroidism in older adults; formulation or administration-related strategies; LT4/LT3 combination therapy; and HRQoL burden among biochemically treated patients.

In older adults with subclinical hypothyroidism, high-quality randomized evidence did not show meaningful HRQoL benefit from LT4 therapy. In the TRUST trial, older adults with subclinical hypothyroidism randomized to LT4 titrated toward euthyroidism did not experience significant improvement in hypothyroid symptom scores or tiredness-related outcomes compared with placebo, supporting the conclusion that routine LT4 therapy in this group does not translate into better patient-reported well-being (Stott *et al*., 2017). Consistent with this, a JAMA analysis pooling data focused on adults aged 80 years and older found no improvement in quality-of-life outcomes with levothyroxine management of subclinical hypothyroidism, reinforcing the limited HRQoL yield of treatment in the very old (Mooijaart *et al*., 2019). Collectively, these findings suggest that for subclinical hypothyroidism in older age groups, biochemical correction does not reliably improve HRQoL and that treatment decisions should carefully weigh symptom attribution, comorbidity, and individualized goals.

Formulation-based management, particularly switching from tablets to liquid LT4, showed more consistent HRQoL improvement signals in selected populations. In a prospective study of dissatisfied LT4 tablet users, switching to an equivalent dose of liquid LT4 taken at breakfast was associated with improved quality of life for a majority of participants, while thyroid function parameters remained broadly stable, suggesting that convenience, perceived control, and treatment experience may drive meaningful patient-perceived benefit even when biochemical changes are minimal (Guglielmi *et al*., 2018). A separate observational study evaluating an ethanol-free liquid LT4 formulation similarly reported significant QoL improvement after transition to liquid LT4, including improvements in symptom burden and daily functioning domains, again emphasizing a potentially important role for formulation and administration feasibility in patient-reported outcomes (Bornikowska *et al*., 2021). Across these studies, a recurring pattern was that HRQoL improved in parallel with treatment satisfaction and usability rather than with large shifts in TSH, implying that patient-centered factors in management may be clinically consequential.

Evidence addressing “adequacy of treatment” and achievement of euthyroidism using thyroid-specific

HRQoL tools added nuance. In a study using the ThyPRO questionnaire, achieving euthyroidism under LT4 was associated with better scores in selected HRQoL domains such as depressivity and impaired daily life measures, suggesting that in some cohorts, moving from untreated or inadequately treated states to euthyroid biochemistry may improve aspects of HRQoL, albeit not uniformly across all symptom domains (Elsherbiny *et al*., 2019). However, broader observational literature suggests persistent HRQoL impairment often remains even among treated individuals with normalized TSH. For example, studies comparing LT4-treated patients to controls reported lower HRQoL among treated patients despite biochemical control, highlighting that normalization of laboratory values does not guarantee normalization of lived health status (Romero-Gómez *et al*., 2020). Large contemporary survey data further supported the presence of residual complaints and reduced HRQoL among treated hypothyroid patients compared with controls and reported weak or absent associations between QoL and thyroid laboratory parameters within the treated range (Molewijk *et al*., 2024).

Combination therapy with LT4 and LT3 has been proposed for patients with persistent symptoms, yet trial evidence remains inconsistent for HRQoL superiority. In a randomized controlled trial, combined thyroxine/liothyronine did not improve well-being or quality of life compared with LT4 alone, indicating that routine use of combination therapy is not supported as a general QoL-enhancing strategy (Walsh *et al*., 2003). A randomized double-blind crossover study similarly examined LT4/LT3 combination therapy and assessed symptoms and QoL-related outcomes, contributing to the broader signal that benefits are not consistent across patients and may not reliably exceed LT4 monotherapy effects (Kaminski *et al*., 2016). Taken together, the included combination-therapy trials indicated that while some patients may report preference or selective improvements, the overall HRQoL evidence does not justify universal adoption of combination therapy purely to improve QoL.

Finally, the descriptive and cross-sectional evidence consistently showed that HRQoL in LT4-treated hypothyroidism can remain impaired and is influenced by factors beyond thyroid labs. Studies assessing QoL among levothyroxine-treated cohorts found substantial symptom and QoL burden and associations with thyroid hormonal status or symptom perception that did not map cleanly onto laboratory normalization, reinforcing the concept that patient-centered assessment is essential and that comorbidities, mental health, expectations, and treatment experience may meaningfully shape reported outcomes (Al Quran *et al*., 2020; Molewijk *et al*., 2024).

Table 1: Characteristics and Key Quality-of-Life Findings of Included Studies (n = 9)

Author (Year)	Country	Study Design	Population	Hypothyroidism Management	QoL Instrument	Key Quality-of-Life Findings
Stott *et al*. (2017)	Multinational (Europe)	Randomized placebo-controlled trial	Older adults ≥65 years with subclinical hypothyroidism	Levothyroxine vs placebo	Thyroid-related symptom score, tiredness score	Levothyroxine did not result in clinically meaningful improvement in hypothyroid symptoms or tiredness compared with placebo despite biochemical normalization.
Mooijaart *et al*. (2019)	Multinational	Prespecified pooled analysis of RCTs	Adults ≥80 years with subclinical hypothyroidism	Levothyroxine vs placebo	Thyroid-related QoL measures	No improvement in thyroid-related quality of life or symptoms with levothyroxine therapy in very elderly patients.
Guglielmi *et al*. (2018)	Italy	Prospective observational study	Adults with primary hypothyroidism dissatisfied with LT4 tablets	Switch from LT4 tablets to liquid LT4 at breakfast	ThyPRO, patient-reported QoL	Significant improvement in quality of life and patient satisfaction after switching to liquid LT4 without major

Author (Year)	Country	Study Design	Population	Hypothyroidism Management	QoL Instrument	Key Quality-of-Life Findings
						biochemical changes.
Bornikowska *et al*. (2021)	Poland	Observational cohort study	Adults with primary hypothyroidism	Ethanol-free liquid LT4 vs tablet LT4	ThyPRO	Liquid LT4 therapy was associated with improved quality-of-life scores and better symptom control compared with tablet formulation.
Elsherbiny *et al*. (2019)	Egypt	Prospective cohort study	Adults with untreated or inadequately treated hypothyroidism	Levothyroxine titrated to euthyroidism	ThyPRO	Achieving euthyroidism improved depressivity and impaired daily life domains, though not all QoL domains normalized.
Walsh *et al*. (2003)	Australia	Randomized controlled trial	Adults with primary hypothyroidism	LT4 monotherapy vs LT4/LT3 combination therapy	SF-36, psychological well-being scales	Combination therapy did not improve quality of life, well-being, or cognitive function compared with LT4 alone.
Kaminski *et al*. (2016)	Brazil	Randomized double-blind crossover trial	Adults with primary hypothyroidism	LT4 vs LT4/LT3 combination therapy	QoL and symptom scores	No consistent superiority of combination therapy for quality of life; benefits were not uniform across patients.
Romero-Gómez *et al*. (2020)	Spain	Case–control study	LT4-treated hypothyroid women vs controls	Stable LT4 replacement	SF-36	Levothyroxine-treated patients reported significantly lower health-related quality of life compared with euthyroid controls despite normal TSH.
Molewijk *et al*. (2024)	Netherlands	Nationwide survey	Adults on long-term thyroid hormone replacement	Usual care LT4 therapy	ThyPRO	Persistent symptoms and reduced quality of life were common and weakly associated with biochemical thyroid parameters.

DISCUSSION

This systematic review highlights a central clinical reality: hypothyroidism management cannot be evaluated solely by biochemical euthyroidism when the outcome of interest is quality of life. Across nine eligible studies, HRQoL outcomes varied substantially by clinical context, management strategy, and patient selection. The strongest evidence in older adults with subclinical hypothyroidism indicates that levothyroxine therapy, even when titrated to normalize TSH, does not meaningfully improve key patient-reported outcomes such as symptom burden and tiredness. These findings align with the notion that mild biochemical abnormalities in older populations may reflect age-related shifts in TSH physiology or comorbidity patterns, and that symptom attribution to thyroid function alone may be unreliable, making HRQoL benefits from therapy difficult to achieve (Stott *et al*., 2017; Mooijaart *et al*., 2019).

In contrast, formulation-focused strategies such as switching from tablets to liquid LT4 showed more consistent improvements in reported QoL, particularly among patients dissatisfied with prior treatment. Notably, these improvements were frequently observed without major changes in thyroid function tests, suggesting that the "management–QoL relationship" may be mediated through adherence ease, dosing flexibility, gastrointestinal tolerability, and patient confidence in therapy rather than purely endocrine pharmacodynamics. Liquid LT4 may reduce practical barriers such as fasting requirements and timing constraints, which can plausibly translate to better perceived daily functioning and treatment satisfaction. However, because formulation-switch studies often involve selected cohorts and may be susceptible to expectation effects, the magnitude and durability of HRQoL improvement require confirmation in larger randomized studies with blinded outcome assessment where feasible (Guglielmi *et al*., 2018; Bornikowska *et al*., 2021).

The evidence on combination therapy is broadly consistent with longstanding uncertainty. In the included randomized trial evidence, LT4/LT3 combination therapy did not reliably improve quality of life compared with LT4 alone, supporting guideline caution against routine use solely to enhance well-being. Yet, patient heterogeneity remains a key issue; some individuals may experience persistent symptoms and seek alternatives, and some trials report patient preference or domain-specific changes that may not be captured as global HRQoL improvements. A clinically prudent interpretation is that combination therapy should not be positioned as a general HRQoL solution but may remain a carefully monitored, individualized option in select patients after structured evaluation of alternative causes of symptoms and shared decision-making (Walsh *et al*., 2003; Kaminski *et al*., 2016).

Across observational studies and surveys, a repeated finding is that treated hypothyroid populations often report lower HRQoL than controls, and that QoL does not necessarily correlate strongly with TSH or FT4 within reference ranges. This underscores the importance of systematically evaluating depression, sleep disorders, anemia, vitamin deficiencies, chronic pain syndromes, medication adverse effects, and social stressors, alongside thyroid-related symptom appraisal and patient expectations. It also suggests that future hypothyroidism care models may benefit from integrated patient-reported outcomes, thyroid-specific QoL tools such as ThyPRO, and management pathways that address both endocrine and non-endocrine drivers of symptom persistence (Elsherbiny *et al*., 2019; Romero-Gómez *et al*., 2020; Molewijk *et al*., 2024).

CONCLUSION

Quality of life outcomes in hypothyroidism are only partially explained by biochemical thyroid normalization. In older adults with subclinical hypothyroidism, levothyroxine therapy does not appear to improve HRQoL, supporting conservative and individualized treatment decisions. In primary hypothyroidism, switching from LT4 tablets to liquid LT4 is associated with improved patient-reported QoL in selected cohorts, often without substantial biochemical change, implying that treatment experience and usability are important determinants of HRQoL. LT4/LT3 combination therapy does not consistently improve HRQoL compared with LT4 alone and should not be routinely used as a QoL-directed strategy. Future research should focus on identifying patient subgroups with persistent symptoms, using validated thyroid-specific HRQoL instruments, and testing patient-centered management pathways that address both thyroid-related and non-thyroid-related contributors to reduced quality of life.

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