Mapping the Research Landscape of Monotherapy and Combination Therapy in Hypothyroidism Patients with Residual Symptoms: A scoping Review

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Summary

Background

Hypothyroidism is a form thyroid disease that was first noted 1950. Hypothyroidism is one of the most common thyroid gland disorders. It affects up to 5% of the general population, with an additional 5% undiagnosed. It is defined by inadequate thyroid hormone production required by the body. Hypothyroidism has a variety of causes and symptoms. The standard treatment is levothyroxine T4, but some patients with sufficient treatment to normalize thyroid hormone levels still experience residual symptoms. Appropriate treatment necessitates a precise diagnosis and is influenced by coexisting medical conditions. Much research and clinical attention has been addressed to combination therapy with the addition of triiodothyronine (T3) to standard treatment for this group of people the last 2 decades.

Purpose

The purpose of this scoping review is to map the state of research about Monotherapy and combination therapy in Hypothyroidism patients with residual symptoms.

Methodology

This is a scoping review and we have searched PubMed and Scopus from January 2013 to January 2023 to include in this article. The including criteria was the last 10 years, English language, monotherapy (T4), and combination therapy(T4+T3).

Results

The search yielded 392 results in PubMed, and 167 results in Scopus, after screening, ten articles fulfilled the criteria and were used in this scoping review. A review of the ten studies provided four common themes related to the topic and the research questions. The first theme from the studies is the efficacy of T4+T3 combination therapy. Another theme is the prevalence and symptoms of residual hypothyroidism. Another dominant theme in the studies was the optimal dose and duration of T3 supplementation. The fourth theme in the scoping review was abnormal thyroid hormone metabolism in patients treated with levothyroxine. This scoping review highlights the diverse findings across the included articles, indicating a need for more consensus in the literature regarding monotherapy versus combination therapy.

Conclusion

This scoping review gives insights into T3 supplementation in patients with residual symptoms of hypothyroidism after levothyroxine treatment. It shows that a T4+T3 combination therapy may improve symptom intensity, quality of life and thyroid hormone level in some people with residual hypothyroidism symptoms. The analysis findings indicate that T4+T3 combination therapy could be a viable treatment option for people with residual symptoms and highlight the need for additional research in this area to enable better management of patients with hypothyroidism.

Keywords

Hypothyroidism; T4 monotherapy; T4+T3 combination therapy; Prevalence; Persistent symptoms

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Background

Hypothyroidism is a common endocrine condition in which the thyroid gland produces too little of the hormone thyroxine. It affects women five times more than men (1). It affects up to 0.3 % to 5% of the general population, with an additional 5% undiagnosed (2, 3). According to Wiersinga et al. (2012) (4), an illness that destroys the thyroid gland was found to be the most common cause of hypothyroidism, followed by post-thyroidectomy and radioactive iodine treatment. Hypothyroidism is often asymptomatic in its early stages but may progress to cause significant morbidity and reduced quality of life. The first case of hypothyroidism was reported in 1850 (5). The development of an efficient treatment took place in less than 50 years. Appropriate treatment necessitates a precise diagnosis and is influenced by coexisting medical conditions (6). In areas without iodine, autoimmune thyroiditis became a common cause of hypothyroidism many years later (5). Administration of synthetic thyroid hormone, typically in the form of Levothyroxine (T4), is the conventional treatment for hypothyroidism. The purpose of treatment is to relieve hypothyroidism-related symptoms and return the body's thyroid hormone levels to normal.

Levothyroxine dosage is based on several variables, including the patient's age, weight, and degree of hypothyroidism (7). The conventional course of treatment involves starting with a low dose and progressively increasing until the blood levels of thyroid hormone are within the normal range. To make sure the patient is getting the right dosage of levothyroxine, thyroid hormone levels must be regularly monitored. For example, if the patient suffers changes in weight or other medical conditions, adjustments to the dose may be required over time. However, this standard treatment may lead to several residual symptoms that include fatigue, joint pains, weight gain, depression, constipation, muscle weakness, and brain fog (4).

Supplementary treatment for patients with residual treatment has been tested in research studies and in clinical practice. T3 has been proposed as an appropriate supplementary treatment for patients with residual symptoms after normalized thyroid hormone levels. T3 has been examined in an extensive and extended observational study conducted over 17 years from 1997 to 2014 in the UK (7). It is, however, unclear when supplementary treatment should be introduced or in what dosage. Increased knowledge about the prevalence of this sub-group of patients with hypothyroidism and the mechanisms involved as well as treatment guidelines should be beneficial for primary care practitioners.

Purpose

The aim of this scoping review is to survey the state of the available knowledge and evidence for mono- and combination therapy in patients with hypothyroidism particularly those with residual symptoms despite levothyroxine treatment.

Research Questions

This study is guided by the following PICO (see Methodology) and research questions to find important data related to this topic.

- What is the prevalence of residual symptoms in levothyroxine-treated hypothyroidism patients.
- What is the optimal dose and duration of T3 supplementation for improving symptom severity and life quality in levothyroxine-treated hypothyroidism patients having residual symptoms?
- How does T3 supplementation affect thyroid hormone levels, symptom intensity and quality of life in levothyroxine-treated hypothyroidism patients having residual symptoms compared to the single therapy in managing the condition?

Methodology

Study design

The study employed a scoping review design methodology, which allowed for a comprehensive overview of the current state of knowledge and research gaps concerning the effect of T3 on levothyroxine-treated hypothyroidism patients with residual symptoms. The review process followed established guidelines, including the framework developed by Hilary Arksey & Lisa O'Malley 2005 (8) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (9).

The study was conducted in five stages, starting with the identification of research questions, followed by the identification of relevant studies. The studies were selected based on the inclusion criteria. The data charting and collating stage involved the collection of information on the prevalence of residual symptoms, effects on symptoms and thyroid

hormone levels, mechanisms, dosage, side-effects, benefits, and risks associated with supplementary T3 treatment. Finally, the results were summarized and reported.

Selection

The following inclusion and exclusion criteria and PICO (Table 1) were used to guide the literature search.

Inclusion criteria: Studies examining supplementary treatment with T3 for patients with residual symptoms after T4 treatment for patients with hypothyroidism. Combination therapy T4+T3. Peer-reviewed articles.

Exclusion criteria: Not published in English. Articles published before 2013. No exclusion criteria based on study design were used. Articles not addressing combination therapy (T4+T3).

The timeframe was chosen due to the rapid pace of advancement in this field and the need to manage a large corpus of literature within a limited timeframe.

Table 1. PICO

PICO Component	Description
Population	Patients with residual symptoms of hypothyroidism after treatment with T4
Intervention	Supplementary treatment with T3
Comparison	Monotherapy with T4
Outcomes	Prevalence of residual symptoms, effects on symptoms and thyroid hormone levels, mechanisms, dosage, side-effects, benefits, risks

Data Collection and Analysis

The search process was conducted in two databases, PubMed and Scopus, on February 7, 2023.

The following search string was used in both databases:

(("laevothyroxine"[All Fields] OR "thyroxine"[MeSH Terms] OR "thyroxine"[All Fields] OR "levothyroxine"[All Fields] OR "levothyroxin"[All Fields]) AND ("residual"[All Fields] OR "residuals"[All Fields] OR ("resist"[All Fields] OR "resistance"[All Fields] OR "resistances"[All Fields] OR "resistant"[All Fields] OR "resistants"[All Fields] OR "resisted"[All Fields] OR "resistence"[All Fields] OR "resistences"[All Fields] OR "resistent"[All Fields] OR "resistibility"[All Fields] OR "resisting"[All Fields] OR "resistive"[All Fields] OR "resistively"[All Fields] OR "resistivities"[All Fields] OR "resistivity"[All Fields] OR "resists"[All Fields])) AND ("triiodothyronin"[All Fields] OR "triiodothyronine"[MeSH Terms] OR "triiodothyronine"[All Fields] OR "triiodothyronines"[All Fields] OR ("triiodothyronine"[MeSH Terms] OR "triiodothyronine"[All Fields] OR "liothyronine"[All Fields]) OR "T3"[All Fields])) AND (y_10[Filter])

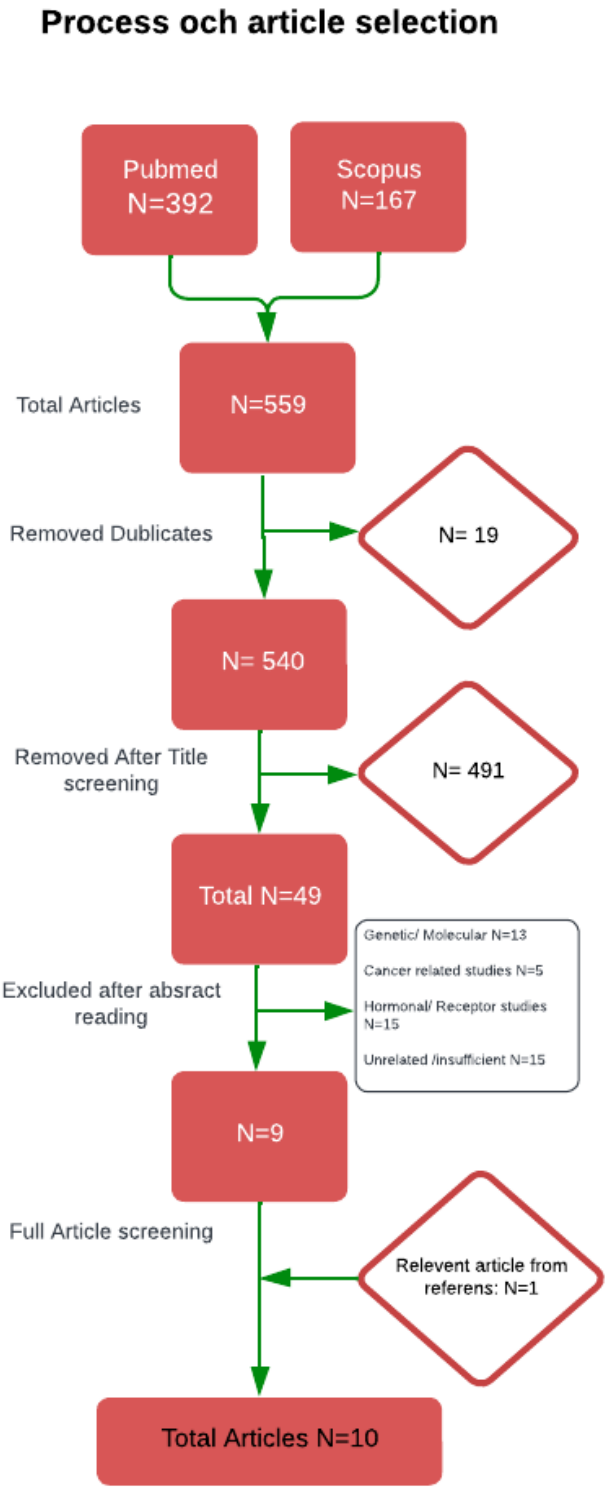
Ethics in the included in studies

Ethical review was not necessary for this scoping review, given the nature of scoping studies, which seek to map and synthesize existing literature comprehensively. All the included original studies had ethical approval.

Results

The literature search was conducted, resulting in ten articles relevant to the study aim. The search yielded 392 results in PubMed and 167 results in Scopus with the same search string. After transferring the entire set of articles from both databases and removing the duplicates entries 19 articles, a total of 540 articles remained. Afterward the articles were reviewed based of their title using inclusion and exclusion criteria and 481 were excluded. We assessed the abstract of remaining 59 articles, an additional 50 were eliminated based on the inclusion and exclusion criteria. One additional relevant paper was found through the references of the remaining nine papers. Ten articles were included in the scoping review (Figure 1).

The included articles and their results are described in Table 2.



Figur:1 Process and article selection

Table 2: Study characteristics

Authors	Study design	Participant NR	Date	Result summary
Bjerkreim et al.	RCS	69	2022	The study showed that combination therapy was effective in improving clinical signs and symptoms of hypothyroidism. Used a non-blinded randomized crossover study over 12 weeks. No differences in blood pressure or resting heart rate between the two treatment groups, no cardiovascular adverse effects were recorded.
Cruz-Loya et al.	Personalized stimulation tool	15	2022	Explored the optimized dosage of T4 and a combination of T3 and T4 in hypothyroid patients with different BMIs. Developed p-THYROSIM, a personalized simulation program. The p-THYROSIM model was used to predict optimum dosing, with daily T3 doses of 5 to 7.5 µg of T3 combined with 62.5-100 µg of LT4 for women or 75-125 µg of T4 for men.
Ettleson, M. D., & Bianco, A. C.	Narrative Review	469	2020	Examined why some patients using T4 therapy alone were symptomatic, aiming to explain why some patients experienced T4 failure. Emphasized the importance of individualized treatment and close monitoring of thyroid function. Patients with specific genetic and/or immunologic makeup might experience persistent symptoms of hypothyroidism with impaired cognition and tiredness.
Freeman et al.	Comparative study	575	2019	Compared thyroid symptoms in patients receiving stable thyroid therapy for six months to patients without hypothyroidism. The intervention group had 302 patients, while the control group had 273. The average total hypothyroid symptom scale (HSS) scores were much higher in the treatment group than in the control group.
Shakir et al.	Randomized double blinded study	90	2021	The primary and secondary outcome measures, such as thyroid function tests, weight, and total cholesterol, did not show any significant differences between the treatments. Residual symptom cognitive and metabolic impairments, thyroid-specific symptoms, and visual memory impairment.
Heald et al.	A double-blind, randomized, controlled trial	54	2020	The trial showed that patients preferred liothyronine plus levothyroxine to levothyroxine alone, but there were no differences in secondary outcomes. No adverse events were reported with any of the treatments, and both were tolerated equally well.

Lan et al.	systematic review and meta-analysis	883	2022	According to the meta-analysis, combination therapy did not improve the mental health of hypothyroid patients. The subgroup analysis showed that the scales used, gender, ratio of T3-T4 administration, or times of T3 administrations had no effect on the psychological health results.
Tariq et al.	Retrospective observational Study	100	2018	The study showed that there were conflicting results from the meta-analysis of combination therapy, and that T4 monotherapy was more effective than both synthetic T4/T3 therapy and natural desiccated thyroid extract therapy in terms of improving clinical signs and symptoms of hypothyroidism.
Wiersinga	population-based case control study	Not specified	2021	An increase in the prevalence of treated hypothyroidism and its treatment with T4 and T4+T3, it also explores the nature and pathophysiology of persistent symptoms despite normal TSH levels and proposes the use of T4+T3 therapy as a possible treatment option. The prevalence of treated hypothyroidism is positively associated with female sex, white ethnicity, and obesity.
Gottwald et al.	Narrative review	Not specified	2021	Levothyroxine and triiodothyronine combination therapy's effects on general health, mood, fatigue, psychological and neurocognitive symptoms, quality of life, and other factors were examined in 48 studies. Survey of 363 physicians found 98% support for LT4 monotherapy.

The study by Bjerkreim et al. (10) investigated the impacts of T3 and T4 on the quality of life of hypothyroid patients that had earlier reported residual symptoms with monotherapy. Bjerkreim et al. (10) showed that after 12 weeks of T3 monotherapy, patients reported significant improvements in 12 of the 13 domains of the ThyPRO questionnaire. T4 monotherapy, on the other hand, had only modest impacts in two of these areas. The non-blinded randomized crossover study was carried out in 12 weeks, with participants involved in either monotherapy or combination therapy.

The study by Cruz-Loya et al. (11) investigated the optimized dosage of T4 and a combination of T3 and T4 in hypothyroid patients with different BMIs and found that personalized dosing can improve hormone level regulation and reduce symptoms for hypothyroid patients. However, the authors also noted that the optimal T4 + T3 ratio might

vary depending on the patient's BMI and gender the study used Personalized Mechanistic Model for thyroid regulation dynamics.

The study by Ettleson & Bianco (12) investigated why some patients using T4 therapy alone were symptomatic. The study aimed to explain why some patients experienced T4 failure. Patients with hypothyroidism whose symptoms or metabolic problems continue after serum thyrotropin normalization may benefit from T4 and T3 medication through reduction of residual symptoms.

The study by Freeman et al. (13) mainly compared thyroid symptoms using the hypothyroid symptom scale (HSS) in patients receiving stable thyroid therapy for six months to patients without hypothyroidism. The study was carried out over six months. The results indicated that individuals receiving levothyroxine therapy exhibited more persistent thyroid symptoms, as indicated by higher mean total HSS scores than those given a placebo. The study concluded that while T4 monotherapy is effective in most patients it also highlights the necessity of monitoring patients undergoing T4 treatment for ongoing symptoms.

A review by Shakir et al. (14) of the current hypothyroidism management guidelines assessed T3 as a prodrug in combination with T4 as monotherapy. According to this study, levothyroxine medication reduced arterial stiffness in people with subclinical hypothyroidism, but no significant differences were found between mono-and combination therapies regarding all outcomes such as thyroid function tests, weight, and total cholesterol.

The study by Heald et al. (15) researched on managing symptomatically unresponsive patients to T4 therapy. The researchers assessed the most effective therapy for the symptoms and showed that patients preferred combination therapy and tolerated both treatments well with no adverse events in either group. However, there were no significant differences between the groups regarding residual symptoms.

The study is an article by Lan et al. (16) a meta-analysis bases on 18 articles (883 patients) compared a combination of T4 and T3 versus T4 monotherapy to improve the psychological health of hypothyroid patients. They found no differences between groups regarding of gender, dosage, and timing of treatment. The study also showed that tablet formulation is critical for T4 absorption and bioavailability. Tablet excipients, manufacturing

procedures, and storage conditions were discovered to impact the quality and stability of LT4 tablets.

Tariq et al. (17) conducted a retrospective observational study on 100 people of 2400 patients receiving T4 monotherapy to compare the efficacy of T4 monotherapy with synthetic T3+T4 or desiccated thyroid extract (DTE) combination therapy for a mean duration of 27 months. The study found that serum T3, T4 plus T3 (synthetic therapy), or DTE (natural therapy) were superior to T4 alone in life quality improvement for some patients with hypothyroidism and did not have adverse effects or increase cardiac mortality. The study also revealed that long-term combination therapy for hypothyroidism can improve quality of life without causing side effects. While combination therapy was associated with lower serum thyrotropin level.

The article by Wiersinga (18)is a population-based case control study on the complexity and unresponsiveness of T4+T3 Combination Therapy and how the combination therapy has gained popularity the last 2 decades. They found that the prevalence of residual symptoms in levothyroxine-treated hypothyroidism patients having normal serum thyrotrophin (TSH) levels was approximately 5-10%. The authors also suggested using T4 plus T3 combination therapy may be considered in patients with persistent symptoms despite optimal levothyroxine therapy. Most common symptoms Fatigue (80% to 90%), weight management (70% to 75%), memory (60%to 80%) and mood (40% to 50%).

The narrative review by Gottwald (19) investigated the effects of combination therapy in randomized clinical trials. Non-physiological T3 dosages were used in several RCTs that failed to demonstrate the superiority of combination therapy. They claim that patients with hypothyroidism differ greatly regarding residual thyroid function, ideal thyroid homeostasis, and polymorphisms in deiodinase, an enzyme that activates and deactivates circulating thyroid hormones. As a result, these RCTs were not able to demonstrate the benefits of combination therapy benefits in specific hypothyroid phenotypes.

The analysis of the ten articles identified four major themes related to the topic and the research questions (Table 3). Seven of the ten articles examined the use of combination therapy of T4 and T3 in the management of residual symptoms. In addition to supporting the use of T3 in the management of residual symptoms, all the included articles listed the

benefits, risks, and factors that are related to the use of T3 in the management of residual symptoms in hypothyroidism therapy.

THEME Table

Table 3

Themes	Articles
Prevalence and Symptoms of Residual Hypothyroidism	Bjerkreim et al. (2022), Tariq et al. (2018), Freeman et al. (2019), Wiersinga (2021)
Abnormal Thyroid Hormone Metabolism in Levothyroxine-treated Patients	Cruz-Loya et al. (2022), Gottwald-Hostalek and Kahaly (2021), Freeman et al. (2019), Ettleson and Bianco (2020), Shakir et al. (2021), Wiersinga (2021)
Efficacy of T4+T3 combination therapy	Bjerkreim et al. (2022), Cruz-Loya et al. (2022), Gottwald-Hostalek and Kahaly (2021), Tariq et al. (2018), Ettleson and Bianco (2020), Heald et al. (2019), Wiersinga (2021)
Optimal Dose and Duration of T3 Supplementation	Gottwald-Hostalek and Kahaly (2021), Tariq et al. (2018), Freeman et al. (2019), Ettleson and Bianco (2020), Heald et al. (2019), Wiersinga (2021), Cruz-Loya et al. (2022)

Prevalence and symptoms of residual hypothyroidism: Bjerkreim et al. Tariq et al. Freeman et al. and Wiersinga all describe residual symptoms after normalizing hormone levels with T4. These symptoms are the same as for untreated hypothyroidism: fatigue, weight gain, Cold intolerance, cognitive impairment, muscle stiffness, puffiness, dizziness (10, 13, 17, 18). These studies all estimate a prevalence of residual symptoms to be between 5% to 10% of all patients treated for hypothyroidism.

Abnormal Thyroid Hormone Metabolism in Levothyroxine-treated Patients: Cruz-loya et al. Gottwald -Hostalek and Kahaly, Freeman et al., Ettleson and Bianco, Shakir et al. and Wiersinga discuss the reasons for residual symptoms in some T4-treated patients (11, 12, 13, 14, 18, 19). They hypothesize that these patients metabolize thyroid hormone differently from other patients with hypothyroidism.

Efficacy of T4+T3 combination therapy: Bjerkreim et al., Cruz-loya et al., Gottwald-Hostalek and Kahaly, Tariq et al., Ettleson and Bianco, Heald et al. and Wiersinga examine the result of combination therapy and compare to monotherapy for patients with residual symptoms (table 4) (10, 11, 12, 15, 17, 18, 19). Thyroid hormone levels are improved and stabilized with T4 treatment, and the residual symptoms are improved overall by combining with T3 treatment.

Table 4: Summary of symptoms when T4 is used alone and when both T3 and T4 are used in the therapy.

Symptom	Levothyroxine Only	Levothyroxine + T3
Fatigue	High	Improved
Weight gain	No changes	Improved
Depression	No changes	Improved
Joint pain	No changes	Improved
Constipation	No changes	Improved
Muscle weakness	No changes	Improved
Brain fog	No changes	Improved

Optimal Dose and Duration of T3 Supplementation: Gottwald-Hostalek and Kahaly, Tariq et al., Freeman et al., Ettleson and Bianco, Heald et al., Wiersinga and Cruz-Loya et al. all study dosage and duration of T3 supplementary treatment (11, 12, 13, 15, 17, 18, 19). In summary, their results do not point out an optimal treatment plan and their recommendations point to individualizing both dosage and duration for optimal effect on residual symptoms.

Discussion

The evidence regarding the clinical benefits of T3 supplementation in levothyroxine-treated hypothyroidism patients with residual symptoms is limited and inconclusive. The review of the evidence indicates knowledge gaps about mono-combination therapy for managing hypothyroidism. It is clear in the studies that there are controversies on whether to use single or multiple therapies to manage this condition. There are many considerable debates when it comes to treatment of hypothyroidism regarding whether monotherapy T4 is adequate or if adding T3 would improve the treatment results (10, 17). Common residual symptoms after T4 treatment such as fatigue, weight gain, depression and join pain are found in approximately 5% to 10% of all patients with hypothyroidism. This is thought to be cause by an abnormal metabolism of thyroid hormone in this group of patients. In general supplementation with T3 seems to improve residual symptoms but the dosage and duration of T3 treatment need to be individualized for optimal results.

The research questions posed in this scoping review were designed to guide the investigation and address the gaps in knowledge in this area and resulted in four themes.

The first theme concerns the prevalence of residual symptoms in levothyroxine-treated hypothyroidism patients and identification of the most common symptoms experienced by these patients 5% to 10% (13, 19). This information was critical to understanding the extent of the problem. The high prevalence of hypothyroidism 0.3 % to 5% globally and 0.2% to 5.3% in Europe, and the high proportion with residual symptoms (5%-10%) indicate that this area of knowledge has considerable impact on primary care. The prevalence for each of overt and mild undiagnosed hypothyroidism in nine European countries was estimated to be approximately 5% by a meta-analysis (3). Primary care physicians need to be well-informed about the emerging evidence for supplementary T3 treatment to manage this large group of patients. Residual symptoms such as fatigue, weight

gain, and mood changes are commonly reported by patients with stable thyroid hormone levels (18). This indicates that managing hypothyroidism effectively is more complex than simply maintaining normal TSH levels and that there is a need to pay closer attention to patient-reported outcomes and symptoms (10, 18).

According to study by Luca Chiovato (2) the prevalence of residual symptoms in treated hypothyroid patients can be due to various reasons, such as individual set-points, the coexistence of other autoimmune diseases, and failure to properly convert T4 to T3 with a low T3/T4 ratio on levothyroxine monotherapy. Some patients may still experience persistent symptoms despite controlling TSH levels with levothyroxine. Guidelines recommend against routine combination therapy, but it may be considered as an experimental approach in certain circumstances. The 2012 European Thyroid Association recommends combination therapy only for patients with ongoing symptoms despite good adherence to T4 therapy and a normal serum TSH range for longer than 6 months (4).The Italian Society of Endocrinology and the Italian Thyroid Association also endorse this recommendation in 2016 (20).

The second theme concerns the abnormal metabolism of thyroid hormone in patients with hypothyroidism. Insight into the mechanisms underlying the observed improvement in symptoms and quality of life is essential to adequate management. The role abnormal thyroid hormone metabolism in patients treated with levothyroxine is a vital point that emerged in analyzed articles. According to some of the included studies (12, 14, 18), some patients might have an abnormal conversion of T4 to T3. Gottwald et al. (19) highlight the difficulties of levothyroxine monotherapy in restoring physiological tissue T3, which has inspired research on T3 combination therapy. These findings further substantiate the need for a more personalized approach to hypothyroidism treatment, as individual differences in thyroid hormone metabolism may play a critical role in treatment outcomes. According to the study by Luca Chiovato (2), residual symptoms in treated hypothyroid patients can be due to various reasons, such as individual set-points, the coexistence of other autoimmune diseases, and failure to properly convert T4 to T3 with a low T3/T4 ratio on levothyroxine monotherapy.

The third theme focused on the effect of T3 supplementation on thyroid hormone levels, residual symptom intensity and quality of life in levothyroxine-treated hypothyroidism patients having residual symptoms. Several studies highlight potential benefits of T4+T3 combination therapy, notably in those patients' persistent symptoms despite T4 monotherapy

(17). Bjerkreim et al. (10) showed that after 12 weeks of T3 monotherapy, patients reported significant improvements in 12 of the 13 domains of the ThyPRO questionnaire. Furthermore, more than 92% of patients reported feeling "excellent, very good, or good" with either T3 monotherapy or T4+T3 combination therapy compared to T4 monotherapy (17). On the other hand, some studies found no significant differences between the effect of monotherapy T4 versus combination therapy (T4+T3) (14). This controversy makes it difficult to give general management guidelines. Insufficient evidence is available to determine whether certain patients might benefit from a more individual treatment plan that includes T3(10, 11, 12, 15, 17, 18, 19).

A systematic review by Eyal Kraut et al. (21) illustrated and identified 13 guidelines; two were intended for the pediatric population. Of the remaining guidelines that addressed combination therapy, nine concluded T4 alone should be the standard treatment and that there is insufficient evidence to recommend combination therapy. Only the 2012 ETA and 2014 ATA recommended combination therapy opposite to what guidelines recommends on unique situations and experimental treatment. Guidelines recommend against routine combination therapy, but it may be considered as an experimental approach in certain circumstances. The 2012 European Thyroid Association recommends combination therapy only for patients with ongoing symptoms despite good adherence to T4 therapy and a normal serum TSH range for longer than 6 months (4).The Italian Society of Endocrinology and the Italian Thyroid Association also endorsed this recommendation in 2016 (20).

The last theme concerned the optimal dose and duration of T3 supplementation for improving symptoms severity and life quality in levothyroxine-treated hypothyroidism patients with residual symptoms. This information would be useful for clinicians in determining the most effective treatment options for these patients and for improving patient outcomes. The study by Cruz-loya et al. (11) found that personalized dosing can improve hormone level regulation and reduce symptoms for hypothyroidism patients. The authors examined how gender and obesity affect thyroid dynamics control in these patients over time and noted that the optimal T4+T3 ratio might vary depending on the patients BMI and gender. Several different studies highlight the importance of individualized therapy in hypothyroid patients by examining pharmacokinetic differences and tablet and bioavailability. However, more research is needed in this area to determine the best practice for implementing T3 supplementation (13, 17, 19)

The optimal dosage seems to vary based on age and the characteristics of the residual symptoms. In an older study by Appelhof et al. (21) 141 patients between age 18-70 with primary hypothyroidism with adequate T4 treatment in the last 6 months were included. The study found that patients preferred combined therapy because of mood, fatigue, and neurocognitive function changes. No significant differences were found between the measurement taken at baseline and a measurement taken at later among the treatment group which further boosts evidence that is provided by Bjerkreim and Tariq (10, 17) by suggesting that T4+T3 combination therapy may be an effective treatment option for hypothyroidism.

By examining the research questions and developing different themes in relation to this topic of monotherapy and combination therapies in managing hypothyroidism and residual symptoms, this scoping review adds to what was already known about the effectiveness of T3 supplementation in improving symptom severity, quality of life, and thyroid hormone levels in levothyroxine-treated hypothyroidism patients having residual symptoms and interprets this knowledge in a primary care context.

Strengths and Weaknesses

One strength of this scoping review is that it included recent articles that have recent information about the use of standard treatment and the addition of T3 in the management of residual symptoms since this is an emerging field of interest with considerable research being performed the last few years. Another strength of this review lies in the study design. One of the advantages of scoping review is that it allows for the inclusion of a wide range of study designs which provide a more comprehensive understanding of a research topic. Selection of the studies that were used in the research was made from reliable databases, which increases the probability that most relevant literature has been found.

A limitation of the review is that there was a limited analysis. No analysis of the quality of the included studies was performed.

Conclusion

The Scoping Review suggests that T4+T3 combination therapy may improve symptom severity, quality of life, and thyroid hormone levels in patients having residual symptoms of hypothyroidism. Residual symptoms of hypothyroidism need to be better understood to optimize personalized medicine approaches. The optimal dose and duration of T3 supplementation remain unclear, but during persistent symptoms, the management should also focus on other causes, with T4+T3 normalizing tissue and brain T3 content rather than T4 alone. Abnormal thyroid hormone metabolism is a common issue faced by levothyroxine-treated patients, and future clinical trials are needed to answer the remaining questions about the role of LT4+T3 combination therapy in treating hypothyroidism.

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