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AN UPDATE ON HYPOTHYROIDISM

Abstract: Objective: Several important pieces of evidence have surfaced in the past five years that endocrinologists need to be aware of, as they are likely to help in the management of patients with hypothyroidism. The aim of this review was to highlight the most clinically relevant recent advances that impact on patient care.

Methods: Narrative review based on the literature on management of hypothyroidism and the author's interpretation of the evidence.

Results: The source of symptoms in people with subclinical hypothyroidism in most cases is unlikely to be due to this biochemical disturbance. Selenium supplementation in patients with Hashimoto's thyroiditis do not alleviate persistent symptoms. Endocrinologists may be tempted to offer total thyroidectomy to patients with persistent symptoms as suggested by a recent study, however methodological limitations render it inconclusive and the risks of surgical complications do not justify such a drastic intervention. Recent evidence does not support the notion that deiodinase polymorphisms may be responsible for persistent symptoms in patients treated with levothyroxine. Combination treatment with levothyroxine and liothyronine continues to be debated, despite that ample evidence amassed over the past 30 years has shown no superiority over levothyroxine monotherapy. Guidelines on hypothyroidism, although useful on many aspects of management of hypothyroidism, have generated confusing messages about combination therapy.

Conclusion: Patient dissatisfaction with the treatment of hypothyroidism is a common, but highly complex and multifactorial phenomenon that is often frequently handled inappropriately by health professionals.

Keywords: Hypothyroidism, update, symptoms, combination treatment

INTRODUCTION

If one were to browse through the standard medical textbooks from 40 years ago, hypothyroidism would feature as one of the best understood, most studied endocrine

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conditions. The strong impression from reading the relevant chapters would be that the pathophysiology is well understood, diagnostic tests are robust and treatment is easy, effective, cheap and can be monitored accurately by reliable biochemical analyses. Yet, as we enter the second quarter of the 21st century debates and controversy about managing patients with hypothyroidism have never been as intense and passionate, both among experts and patients [1-3]. Much of this discourse is centred around patients who appear to be clinically and biochemically adequately replaced with thyroid hormones, yet complain of persistent symptoms and are dissatisfied with their treatment and care [4].

In this review several relevant questions about hypothyroidism are considered, in the light of recent published evidence.

SYMPTOMS IN PATIENTS WITH UNTREATED SUBCLINICAL HYPOTHYROIDISM

The majority of patients currently treated with thyroid hormones in the developed world have subclinical hypothyroidism at the time of diagnosis [5]. Indeed a significant proportion have no biochemical evidence of hypothyroidism at the time of initiation of thyroid hormone treatment [6-8]. It seems that unnecessary testing for thyroid dysfunction and inappropriate initiation of thyroid hormone treatment is largely driven by distressing symptoms [3,9-11]. Although the benefits of treatment of subclinical hypothyroidism remain unclear, some international guidelines recommend that symptomatic patients should be considered suitable candidates for levothyroxine (LT4) therapy [12-14]. Whether subclinical hypothyroidism indeed causes symptoms has been contentious and several previous studies have yielded conflicting results and have been subject to methodological drawbacks, not least small sample sizes [15]. A study therefore with sufficient numbers of subjects and robust methodology has been keenly awaited. Such a study was conducted and reported by in 2021 [16]. The authors performed a community based study and identified a large number of previously undiagnosed people with subclinical hypothyroidism. Most individuals with subclinical hypothyroidism had a serum TSH of less than 10 mU/L. They were assessed for symptoms and compared with a euthyroid control group. Symptoms compatible with hypothyroidism (such as fatigue) were common, but occurred with similar frequency in both groups. The study is consistent with what we already knew about the low likelihood ratios of all hypothyroid symptoms [17], but went much further in demonstrating that the presence of symptoms is a very poor discriminator in aiding decision-making about treating subclinical hypothyroidism. Furthermore, it strongly suggests that when patients present with symptoms and are found to have mild subclinical hypothyroidism, it is more than likely that their symptoms have an aetiology other than thyroid dysfunction.

SELENIUM SUPPLEMENTATION FOR HASHIMOTO'S THYROIDITIS

The quest for uncovering a physical cause for persistence in symptoms of patients with Hashimoto's thyroiditis has dominated research in hypothyroidism for 30 years, focusing mainly of combination treatment [2,4]. Selenium deficiency has been suggested as another culprit [18] and many patients with Hashimoto's thyroiditis are currently taking selenium supplements in the hope that their unexplained symptoms will abate. There is some physiological rationale for this hypothesis given that deiodinases that convert T4 to T3 are selenoproteins [19]. Small, methodologically challenged studies have supported the notion for a role of selenium on patient reported outcomes [18]. But the question, until recently remained unanswered. A large randomised placebo-controlled study carried out in Denmark was published recently and addressed the role of selenium in Hashimoto's thyroiditis [20]. While selenium supplements had a modest lowering effect on thyroid peroxidase antibodies (TPOAb), no significant effect was found on quality of life. This study puts to rest the case for selenium supplementation in Hashimoto's thyroiditis, in areas where selenium deficiency is not endemic. Given that excessive selenium supplementation carries its own risks,[18] this strategy should be avoided.

TOTAL THYROIDECTOMY FOR HASHIMOTO'S THYROIDITIS

A related hypothesis linked to selenium supplements, is that persistent symptoms (such as fatigue) in treated patients with Hashimoto's thyroiditis may arise due to the underlying inflammation associated with the autoimmune process [2]. Removal of the thyroid is known to reduce thyroid autoantibodies [21], so a randomised controlled study was set up in Norway to test this hypothesis [22]. Patients with Hashimoto's thyroiditis on LT4 treatment achieving normal serum TSH, who complained of persistent symptoms were randomised to total thyroidectomy or no surgical treatment. A large number of patients was recruited and completed the study. After 18 months of follow-up those patients who underwent total thyroidectomy had a dramatic reduction in serum TPOAb compared to controls. In addition thyroidectomised patients reported significantly improved quality of life. However, as anticipated a significant minority of thyroidectomised patients (4.1-5.5%) developed hypoparathyroidism and voice change. The results of this study are interesting, however its principal weakness is the absence of a placebo and the non-blinded nature of its design, which of course for practical reasons is difficult if not impossible to justify when the intervention is surgical. One needs to keep in mind that several of the randomised double-blind placebo controlled trials comparing LT4 treatment against combination LT4+liothyronine (LT3) treatment also demonstrated impressive improvements in quality of life in the control groups [23], so

the effect of placebo in trials of interventions in hypothyroidism where the principal outcome is quality of life or symptoms, appears to be powerful. It is the author's strong view therefore that clinicians need to be extremely cautious in embracing this therapeutic approach in the absence of additional, more convincing evidence, or the principle of *primum non nocere* may be being violated.

DEIODINASE POLYMORPHISMS AND PERSISTENT SYMPTOMS IN PATIENTS TREATED WITH LT4

Deiodinases are responsible for peripheral conversion of T4 to T3 and are central to thyroid homeostasis [19]. Polymorphisms in the DIO1 and DIO2 genes are relatively common and some have been implicated in impaired peripheral conversion of T4 to T3 [24]. This in turn has been proposed as the cause, or at least a contributor to impaired wellbeing in some LT4 treated patients and has been used as an argument for use of combination LT4+LT3 treatment [2,25]. A few small studies have generated some supportive evidence, albeit weak due to poor methodology [26,27]. In 2025 a Danish group used data from the UK biobank to test this hypothesis [28]. In this large study hypothyroid patients with polymorphisms of DIO1 and DIO2 and a polymorphism in the MCT10 gene were compared to matched hypothyroid controls without the polymorphisms. The data categorically showed no differences in the prevalence of persistent symptoms. This landmark study provides a strong argument against the hypothesis that DIO polymorphisms are important contributors to persistent symptoms in treated hypothyroid patients. The relevance of this study in the management of patients with hypothyroidism is illustrated by the fact that misinformation about the relevance of these polymorphisms is abundant and patients are encouraged by some patient organisations to waste their resources in pursuing such tests via self referral to private laboratories (https://thyroiduk.org/the-basics/deiodinase-2-genetic-test/).

THE LATEST ON COMBINATION THERAPY

Over the past several years attempts have been made to produce a formulation of LT3 that produces a physiological serum profile. The rapid and wide oscillations in serum free T3 (FT3) concentrations associated with the currently available formulations of T3 [29] are generally seen as undesirable for long term use. This limitation is considered by some authors as a plausible contributor to the negative results of several randomised controlled studies aimed to demonstrate superiority of combination treatment over levothyroxine alone [30]. In 2025 an Iranian group published evidence for a new LT3 formulation that resulted in what appeared to be physiological serum levels of FT3 [31]. However, no data were provided on patient reported outcomes. Whether

"slow T3" formulations will prove to be a worthwhile advance in therapeutics is yet to be determined.

In the past year one further randomised controlled trial comparing combination treatment with LT4 alone was published [32], showing no advantage of combination LT4+LT3 treatment. Thus the total number of such studies now adds up to 21, accompanied by several meta-analyses/systematic reviews, which lead to the conclusion that combination LT4+LT3 treatment offers no benefit in terms of patient quality of life or symptoms [33-40] (Table 1). Yet, T3 enthusiasts have recently published a meta-analysis of 11 randomised controlled studies showing that patient preference swung at 52% in favour of combination treatment, while 24% apiece were indifferent

Table 1
Characteristics and summary of patient reported outcomes of systematic reviews and meta-analyses comparing levothyroxine with combined levothyroxine and liothyronine treatment

REFERENCE	YEAR OF PUBLICATION	TYPE OF ANALYSIS	NUMBER OF STUDIES INCLUDED	NUMBER OF PATRICIPANTS	SUMMARY OF FINDINGS FOR PATIENT REPORTED OUTCOMES
Grozinsky-Glasberg S, et al.[33]	2006	Meta-analysis	11	1216	No effect on: bodily pain, depression, anxiety, fatigue, quality of life
Joffe RT, et al. [34]	2007	Meta-analysis	9	551	No effect on measures of psychiatric symptoms. No effect on patient preference
Ma C, et al. [35]	2009	Systematic review	10	~1200	No effect on well-being, cognitive function, quality of life
Akirov A, et al. [36]	2019	Systematic review and meta-analysis	7	348	No effect on preference
Millan-Alanis JM, et al. [37]	2021	Systematic review and meta-analysis	18	1563	No effect on: clinical status, quality of life, psychological distress, depressive symptoms, fatigue. Patient preference for combination treatment
Lan H, et al. [38]	2022	Systematic review and meta-analysis	18	883	No effect on: depression, fatigue, pain, anxiety, anger
Hidalgo J, et al. [39]	2024	Systematic review	3	157	No high-quality evidence supporting either intervention
Guglielmi R, et al. [40]	2025	Systematic review	10	1298	No effect on: fatigue, depression, somnolence, symptoms of hypothyroidism
de Lima Beltrao FE, et al. [41]	2025	Systematic review, meta-analysis, meta-regression, network meta-analysis	11	1135	Patient preference for combination treatment

of preferred LT4 alone [41]. These figures were used to argue in favour of combination LT4+LT3 treatment, however (as eloquently outlined by experts in an Endocrine Society discussion (https://www.youtube.com/watch?v=JTyYNQE7Fuc), they morph differently in the context of what clinicians face in their daily practice. Usually a patient who has been on LT4 is switched to combination LT4+LT3 treatment for a period of time and then is reviewed by the doctor so that a decision can be made for long-term treatment. The crucial question in this scenario is simple: "do you want to continue?" then the answer based on the above meta-analysis is 50-50, in other words same as tossing a coin. Be that as it may, the studies that included patient preference, in addition to quality of life and symptoms, reveal an important reality. That these patient reported outcomes do not shift in parallel to each other as one might assume. In this respect a recent study by a Danish group is particularly enlightening. Sixty-six patients with hypothyroidism and persistent symptoms were switched to combination LT4+LT3 treatment and followed up [42]. Twelve patients (18.2%) felt no benefit and reverted to LT4 monotherapy. The majority (n=54, 81.8%) felt subjectively better and continued on combination LT4+LT3 treatment long term. After a median follow-up of 5.6 years patients treated with combination LT4+LT3 therapy were assessed for quality of life and persistent symptoms. Quality of life was as good as a group of matched euthyroid controls. However, the same patients continued to experience "hypothyroid" symptoms which were comparable to a group of untreated clinically hypothyroid patients. These findings are intriguing and difficult to reconcile, but illustrate the fluidity and subjectivity of patient reported outcomes, their dependence on many other factors (Figure 1) and the need to understand better the significance and nuances of these parameters.

DO GUIDELINES HELP?

National and international guidelines on the management of hypothyroidism have been published, to help clinicians manage their patients. They include the American Thyroid Association (ATA) guideline, published in 2014 [43], the National Institute for Health and Care Excellence (NICE) guideline, published in 2019 and updated in 2023 [13], as well as European [44] and Italian guidelines [40] published in 2025. These are important documents with useful information and mostly appropriate interpretations of the available evidence. On the subject of persistent symptoms among treated patients who appear to be clinically and biochemically euthyroid, there are some notable anomalies. One of the recommendations of NICE is *"Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing, but avoid using doses that cause TSH suppression or thyrotoxicosis"* [13]. This is an intriguing statement given that two independent

randomised double blind placebo controlled trials have shown that symptoms and quality of life of patients is unaltered by attempts to "fine tune" the dose of LT4 [45,46]. The 2025 European Thyroid Association guideline on use of levothyroxine monotherapy in hypothyroidism [44] has avoided this misinterpretation of the evidence and recommended that *"Levothyroxine in patients with primary hypothyroidism should be adjusted to aim for a serum TSH level within the population reference interval. Once the target TSH is achieved, complicated regimens and minute adjustments of LT4 dose to improve quality of life or modulate body weight are not useful and not advised"*. This recommendation was signposted as "strong" with "high quality" of supportive evidence (ØØØØ).

In relation to the use of combination LT4+LT3 treatment for patients with persistent symptoms the ATA guideline [43] issued a rather cryptic recommendation: *"For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone (in the absence of an allergy to levothyroxine constituents or an abnormal serum thyrotopin), there is currently insufficient evidence to support the routine use of a trial of a combination of levothyroxine and liothyronine therapy outside a formal clinical trial or N-of-1 trial…"*. Unsurprisingly, this has been interpreted by clinicians as either an endorsement of the use of combination treatment, or a warning against it. NICE have recapitulated the ATA ambiguity by stating: *"Do not routinely offer liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine, because there is not enough evidence that it offers benefits over levothyroxine monotherapy, and its long-term adverse effects are uncertain*" [13]. At a meeting of the Italian Association of Endocrinologists in 2024, the author asked an audience of some 400 endocrinologists to indicate what they understood by the above NICE recommendation. The outcome was nothing short of a revelation. The key word was "routinely" in the context of the use of combination LT4+LT3 treatment, which was interpreted thus: 56% voted for "only use in exceptional circumstances, eg myxoedema coma", 19% voted for "can use it just once per patient", 15% voted for "use if patient requests it", and 10% voted for "should never use LT4+LT3".

The 2025 Italian guidelines [40] have considered all the available evidence to date on the use of combination LT4+LT3 treatment, including desiccated thyroid extract and formulated the following recommendation: *"The panel recommends monotherapy with LT4 in comparison to combined therapy with LT4+LT3*", signposting this recommendation as "very low quality" evidence and "strong, in favor of the intervention". Yet, in the conclusions section the guideline states *"The indication remains, regardless of costs, for the use of LT3 in addition to LT4 for the small minority of patients who, after the attainment of biochemical euthyroidism with*

LT4 alone, do not achieve subjective clinical compensation in terms of perception of psycho-physical well-being". It appears therefore that recommendations by existing

guidelines on the use of combination LT4+LT3 treatment are reflections not so much of objective evaluation of the available evidence, but rather attempts to reconcile differing interpretations and interests among stakeholders.

INSIGHTS FROM PATIENT AND PHYSICIAN SURVEYS

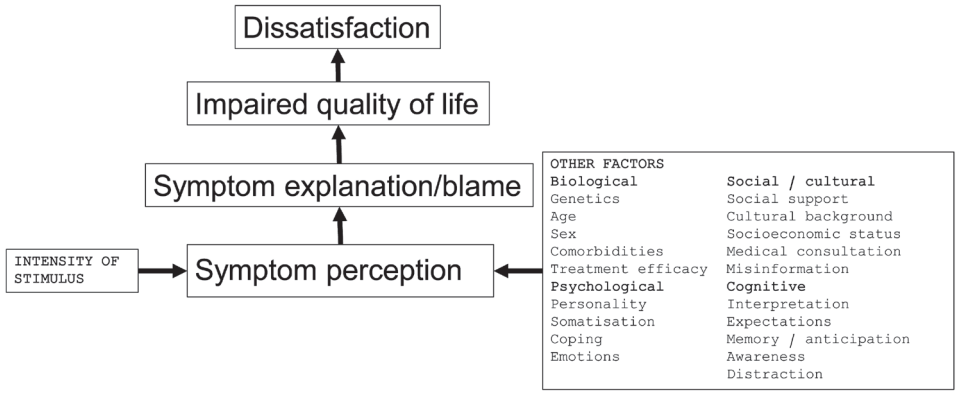
A large patient survey with 3915 respondents from 68 countries has recently revealed some interesting information about patient perspectives. Several patient reported outcomes were explored including persistent symptoms, quality of life, patient treatment preferences and dissatisfaction with treatment and care. Dissatisfaction with treatment and care was very common and expressed by 63.3% of respondents [47]. Dissatisfaction was not associated with type of treatment for hypothyroidism (LT4 alone, combination treatment of LT4+LT3, LT3 alone or desiccated thyroid extract). Strong associations were found between dissatisfaction and lack of trust in doctors, country of residence, somatisation, personality type and misinformation [10,47-49]. Another large recent survey of European thyroid experts showed that although the majority (61-77.1%) of respondents attributed persistent symptoms to comorbidities, psychological factors and unrealistic patient expectations, 40% chose to use combination LT4+LT3 treatment for such patients [50]. This therapeutic choice was much commoner in countries with high gross national product per capita compared to poorer countries. Furthermore, 7.5% of physicians (especially private practitioners) stated that they would use thyroid hormone treatment for euthyroid patients presenting with unexplained fatigue [51]. This highly contentious practice varied widely across different countries (between 1.1% in Switzerland and 29.3% in Serbia). A further interesting finding was that thyroid experts were more likely to treat hypothyroid patients with persistent symptoms with combination LT4+LT3 treatment, rather than themselves if they suffered the same predicament (28.0% vs 16.3%)[52], revealing a concerning tendency to medicalise patients presenting with psychosocial complaints.

THE GENESIS OF PATIENT DISSATISFACTION

That so many patients diagnosed and treated for hypothyroidism are dissatisfied with their treatment and care, should not cause surprise. We only need to consider that according to one US based study 30.5% of patients treated with LT4 had normal serum TSH before commencing treatment, while 61% only had subclinical hypothyroidism[6]. Such patients who presumably are prescribed LT4 in the hope that their "hypothyroid" symptoms will abate, realistically have little chance of improving and are therefore likely to become dissatisfied. Our current understanding of how symptoms

are perceived has led to the hypothesis (backed by a body of evidence) that numerous factors, other than the stimulus that leads to the symptom, modulate the appreciation of symptom intensity[53] (Figure 1). Symptoms can be amplified or dampened down by the brain. Patients then interpret their experience in a way that makes sense to them. Quality of life is impacted by these processes, which shapes the level of satisfaction expressed. This notion is central to understanding and managing patients with persistent symptoms and applicable in the care of patients with hypothyroidism.

Figure 1
Proposed scheme for generation of dissatisfaction.



MANAGEMENT OF PERSISTENT SYMPTOMS IN HYPOTHYROIDISM

Persistent, and often unexplained symptoms are common in many specialties.[54] Such patients need to be investigated for exclusion of underlying organic diseases, recognised as having medically unexplained symptoms and managed appropriately with help from health professionals who are specifically trained for the purpose.[4] Instead of this approach, it seems that in real life thyroid experts often choose combination LT4+LT3 treatment to address unexplained persistent symptoms for their hypothyroid patients.[50]

CONCLUSIONS

Recent evidence has clarified several important areas in the management of hypothyroidism. Selenium supplements in patients with Hashimoto's thyroiditis are of no value in the absence of selenium deficiency. We should not expect symptom improvement with treatment of mild subclinical hypothyroidism. The role of deiodinase

polymorphisms in mediating persistent symptoms is unclear and genetic testing for these markers is unjustified. The efficacy of total thyroidectomy in alleviating persistent symptoms is inconclusive and currently not justified. The case for combination LT4+LT3 treatment for hypothyroid patients with persistent symptoms continues to be made by some experts despite ample evidence showing no superiority over LT4 monotherapy. The possibility that some hypothyroid patients truly benefit form combination LT4+LT3 treatment is not negated by the numerous negative randomised controlled studies. However, the evidence suggests that the effect size of any benefit on patient reported outcomes is either extremely small, or responsive patients are exceptionally rare. What is clear, is that persistent symptoms among patients with treated hypothyroidism is a complex and multifactorial phenomenon. Thyroid experts need to broaden their therapeutic approach beyond offering combination LT4+LT3 treatment.

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