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COMMENT

Combined LT3 and LT4 therapy for precision medicine: easier with TTCombo system

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Abstract

Hypothyroidism is typically treated with levothyroxine monotherapy. However, despite normalized serum thyroid-stimulating hormone levels, 5–10% of patients continue to experience persistent symptoms, raising concerns about the adequacy of thyroxine monotherapy. Combination therapy with levothyroxine and liothyronine has been proposed as an alternative, but it presents practical challenges, including dosing complexity, the short half-life of triiodothyronine, increased monitoring requirements, and potential adverse effects. Moreover, there is no clear consensus within the medical community regarding the superiority of combination therapy over levothyroxine monotherapy, although some studies indicate potential benefits in specific patient populations. Genetic factors, such as polymorphisms in the DIO2 gene, may influence individual responses to therapy, further complicating treatment. To address the limitations of combination therapy, we propose a novel approach: TTCombo. This digital health technology delivers personalized doses of levothyroxine and liothyronine, improving treatment adherence and optimizing outcomes. By providing individualized, physiologically tailored hormone replacement, TTCombo has the potential to revolutionize hypothyroidism management and enhance patient quality of life.

Keywords Hypothyroidism · Combined therapy · Levothyroxine · Triiodothyronine · Precision medicine

Introduction

Thyroid hormones, thyroxine (T4) and triiodothyronine (T3), play a critical role in regulating metabolism, growth, and development in humans [1]. T4 is produced by the thyroid gland, while T3 is mainly derived from the conversion of T4 in peripheral target tissues. These two hormones work together to maintain physiological homeostasis and metabolic equilibrium [2].

In hypothyroidism, an insufficient amount of circulating thyroid hormones disrupts this delicate balance. While thyroxine has been mistakenly regarded as merely a prohormone that acts through its conversion to T3, both hormones have distinct but complementary intrinsic activities. Therefore, T4 monotherapy, primarily using levothyroxine (LT4), is the standard treatment for hypothyroidism [3]. However, approximately 5–10% of patients continue to experience persistent symptoms even when serum thyrotropin (TSH) levels are normalized [4, 5]. This phenomenon raises questions about the adequacy of T4 monotherapy in meeting the full spectrum of thyroid hormone needs in these individuals.

The use of combination therapy with both T4 (levothyroxine) and T3 (liothyronine) for treating hypothyroidism presents several practical difficulties that can complicate patient management. Here are the key challenges associated with this approach:

- **Dosing complexity**: The optimal ratio of T4 to T3 in combination therapy is not universally established, leading to variability in treatment regimens. Recommendations suggest a starting ratio between 13:1 and 20:1 (T4:T3) by weight [6–8]; however, commercially available preparations often deviate from these ratios, complicating dosing adjustments and potentially leading to suboptimal therapeutic outcomes

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- **Short half-life of T3**: T3 has a much shorter half-life (approximately 1 day) compared to T4 (about 7 days). This requires multiple daily doses of T3 to maintain stable serum levels, which can be inconvenient for patients and may lead to adherence issues. In contrast, T4 can be administered once daily [9, 10];
- **Monitoring requirements**: Combination therapy requires close monitoring of serum TSH, free T4, and free T3 levels to ensure that hormonal balance is achieved and maintained [4]. This necessitates more frequent follow-up visits and laboratory tests, placing additional burdens on both healthcare providers and patients;
- **Risk of adverse effects**: The introduction of T3 can increase the risk of hyperthyroid symptoms, such as palpitations, anxiety, and weight loss. Long-term use of T3 has also been associated with potential risks, including atrial fibrillation and decreased bone density, particularly in older patients [11]. These risks necessitate careful patient selection and ongoing assessment of side effects.
- **Lack of consensus**: There is ongoing debate within the medical community regarding the efficacy of T4 + T3 combination therapy compared to T4 monotherapy.

In summary, while T4 + T3 combination therapy may offer benefits for some hypothyroid patients, it presents practical difficulties related to dosing, monitoring, potential adverse effects, and the need for careful patient management. Therefore, it is a complex option that requires thorough consideration and expertise.

The management of hypothyroidism, particularly in individuals lacking a thyroid gland, necessitates a personalized equilibrium of tissue levels of T4 (thyroxine) and T3 (triiodothyronine) to achieve optimal metabolic balance. Each patient may require a unique ratio of these hormones to address their specific physiological needs [3, 12–14], as thyroid hormones play a critical role in regulating metabolism, energy levels, and overall health. In the absence of a thyroid gland, patients rely entirely on exogenous hormone replacement therapy.

Hypothyroidism treatment, between doubts and certainties

Hypothyroidism treatment has long been anchored in the use of oral levothyroxine (LT4), which is endorsed by the American Thyroid Association (ATA) Guidelines as the standard therapy for all forms of hypothyroidism. These guidelines explicitly recommend against the routine use of combination therapy with LT4 and liothyronine, even for patients who report persistent symptoms while on LT4 monotherapy [3]. In addition, a recent trial by Brigante et al. did not show any advantages of combined LT4 and LT3 therapy for patients who already disliked the LT4 + LT3 therapy and found the regimen too complex [15]. However, a recent Consensus Document by the ATA itself, the European Thyroid Association (ETA), and the British Thyroid Association (BTA) suggests a shift in perspective, proposing that future clinical guidelines may incorporate levothyroxine/liothyronine combination therapy [4]. This recommendation is predicated on evidence indicating that LT4 treatment does not fully replicate the serum thyroid hormone profiles observed in individuals with normal thyroid function [4]. A notable concern is that a significant number of patients receiving LT4 report symptoms associated with hypothyroidism - such as memory impairment, weight gain, fatigue, depression, and diminished quality of life - despite undergoing normal values of TSH levels [16–18]. Research indicates that in up to 15% of athyreotic individuals on LT4 therapy, serum T3 or free T3 (fT3) levels may fall within the lower half or even below the normal range [12–14]. Investigations into this phenomenon have identified potential genetic factors, including mutations or single nucleotide polymorphisms (SNPs) in genes responsible for thyroid hormone signaling which may influence the effectiveness of LT4 treatment [19]. In athyreotic individuals, both circulating and intracellular T3 levels are critically dependent on the activity of type 1 (D1) and type 2 (D2) deiodinases [20]. The DIO2 gene encodes human D2, and a specific SNP, Thr92Ala (rs225014), is prevalent in the general population, with the $DIO2^{Ala/Ala}$ homozygous variant occurring in approximately 12.9% to 14.9% of individuals [21]. Given the role of DIO2 in regulating local thyroid hormone levels, the association between the Thr92Ala-DIO2 polymorphism and altered responses to thyroid hormone replacement therapy in hypothyroid patients is intriguing [22, 23]. However, the clinical implications of this mutation regarding the benefit of combination therapy remain uncertain [4].

While most studies have not demonstrated a clear advantage of T4/T3 combination therapy over T4 alone [24], some research has indicated improvements in mood, quality of life, and neurocognitive function [25–28], among certain patient populations [21–24]. Additionally, crossover studies reveal that nearly half of the patients preferred the combination therapy approach [25, 26, 29, 30]. A recent meta-analysis further suggests that a higher proportion of patient preferred combined therapy, although adverse events and reaction were comparable to those experienced by on LT4 alone [31]. On the other hand, a very recent randomized controlled trial showed no significant change in quality of life after six months of combination therapy twice daily [15].

Levothyroxine and liothyronine combination therapy

According to the American Thyroid Association (ATA) Guidelines, the appropriate daily dosage of LT4 for

athyreotic patients should be calculated based on body weight [3]. Achieving an optimal daily dose of thyroid hormones, along with the ability to make precise adjustments, is essential for maintaining stability of TSH levels and minimizing the risk of iatrogenic hyperthyroidism or inadequately compensated hypothyroidism [32, 33].

In a healthy individual, the intact thyroid gland produces 85–100 µg of T4 and 5–6.5 µg of T3 daily. Additionally, type 1 and type 2 deiodinases convert T4 into T3, contributing another 26.5 µg of T3 each day [6]. In athyreotic patients, however, the thyroidal production of T3 is missing and if the patient carries the DIO2Ala/Ala polymorphism, the peripheral conversion of LT4 to LT3 may also be impaired [34]. Therefore, to approximate a "physiological state," thyroid hormone replacement therapy should ideally be administered in a ratio of 14:1 for LT4 to LT3. Modeling studies have attempted to estimate the appropriate dosages of levothyroxine and liothyronine required to restore physiological levels of fT4 and fT3 [6, 7]. These studies suggest that liothyronine can be substituted for levothyroxine at a ratio of 1:3 [8]. For instance, Van Tassell et al. estimated that for a 72.5 kg athyreotic patient, a regimen of 92.5 mcg LT4 combined with 3.25 mcg LT3 taken twice daily would yield relatively stable serum T3 levels [6]. If this approach is validated it would ensure that patients receive the right medication at the correct dosage and timing, tailored to their specific needs.

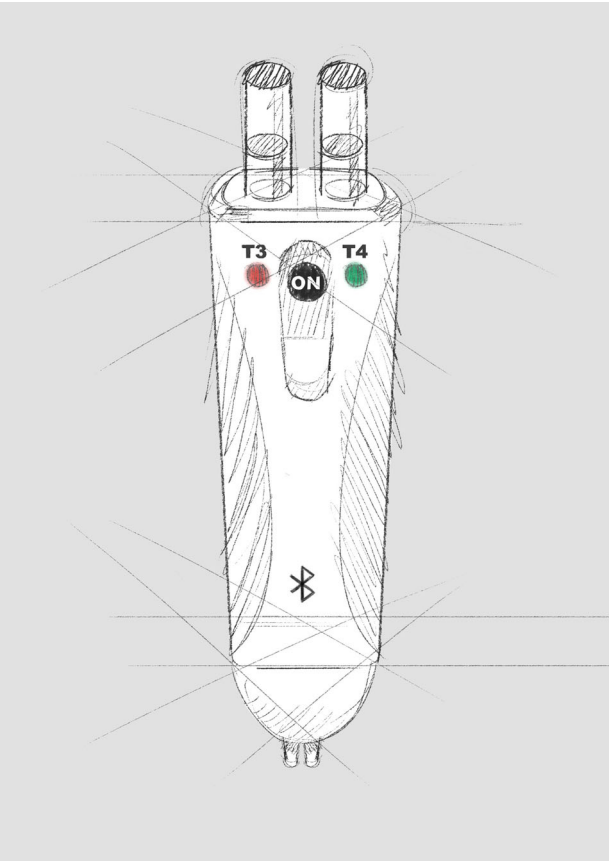

Fig. 1 Graphical aspect of TTCombo

How can we overcome these limitations we have outlined in administering T4 and T3 in combination?

To overcome the limitations associated with administering T4 and T3 in combination therapy for hypothyroidism, we can draw inspiration from advancements in diabetology, where innovative technologies have significantly improved insulin administration and patient adherence. This model suggests that a similar approach could be applied to thyroid hormone therapy, leading to the development of a device that personalizes and optimizes the combined use of T4 and T3, particularly for patients who require enhanced thyroid function replacement therapy.

Therefore, in this viewpoint, we will illustrate a proof of concept for a device that has this potential, namely TTCombo (Thyroxine, Triiodothyronine Combination Therapy) (Fig. 1).

TTcombo is a digital health technology capable of delivering the right amount of oral levothyroxine and liothyronine at the right time daily, ameliorating the treatment of hypothyroidism worldwide. It is easy to think that a compact, portable, automated digital device capable of administering the right dosage of liothyronine and levothyroxine to restore physiological levels of circulating thyroid hormones could have many beneficial effects. TTCombo is a device designed to hold vials of liothyronine and levothyroxine. The device includes software capable of separately regulating the delivery of the two medications, ensuring the oral administration of the combined therapy in the morning and liothyronine alone in the evening. The delivery mode, dosage, and levothyroxine/liothyronine ratio are stabilized based on an algorithm that incorporates pilot studies and the patient's clinical characteristics to enable personalized therapy. Furthermore, such a device could not only improve compliance due to its simplicity and convenience, but also allows an interplay between patient and physician who can remotely adjust the therapy. TTCombo could be a window open to the future for a personalized treatment with thyroid hormones even more closed to physiological requirements.

Key features of TTCombo include:

- **Personalized dosing:** the device can administer T4 and T3 according to various predetermined ratio profiles tailored to individual patient needs, such as age, comorbidities, and body mass index (BMI). Physicians can select and modify these profiles based on ongoing assessments of the patient's condition;

- **Enhanced treatment outcomes:** by facilitating individualized dosing adjustments, TTCombo has the potential to improve thyroid hormone profile and enhance overall treatment outcomes for patients with hypothyroidism;
- **Improved patient adherence:** the user-friendly design of TTCombo aims to simplify the administration process (e.g. by simply pushing a "button") potentially increasing patient adherence to therapy.

Cost issue

The present viewpoint does not take into account, at this time, the issue of research and development costs for the device. Nevertheless, an undeniable benefit is the eco-sustainability of the TTCombo system, which consequently leads to cost reduction. In fact, bulky packaging is no longer necessary, and large amounts of paper and plastic are no longer wasted, as each vial lasts about one month.

Furtheromore, it seems that combination therapy may require greater dose adjustments, and therefore higher monitoring costs, during the first six weeks of therapy, which then decrease. Additionally, moderate adherence to combination therapy has been reported in 67% of patients [15]. This could be due to the complexity of the therapeutic regimen (i.e., three different vials daily). It is indeed reasonable to think that the use of a single device that delivers pre-set therapeutic doses would increase compliance with therapy, resulting in reduced therapy monitoring costs. The game between costs and profits is still wide open.

In conclusion, while current therapies for hypothyroidism have their limitations, the development of innovative devices like TTCombo could provide a more effective and personalized solution, ultimately potentially improving the quality of life for patients requiring thyroid hormone replacement therapy. Continuous research and technological advancements are essential to meet the evolving needs of this patient.

Data availability

No datasets were generated or analysed during the current study.

Author contributions CC and SI conceptualized, reviewed and edited the manuscript, EG wrote the original manuscript

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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