

# Thyroid Disorders

## Chapter 5

# Thyroid Hormone Replacement Therapy Options in the Treatment of Hypothyroidism

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## 1. Introduction

Disorders of the thyroid gland are one of the most common endocrine problems and hypothyroidism tends to affect a large proportion of the population. The prevalence of primary hypothyroidism in the UK is between 1-2% and is 10 times more common in females [1]. Management of hypothyroidism involves lifelong thyroid hormone replacement to alleviate the symptoms and improve long term adverse health outcomes associated with the disorder. Untreated, hypothyroidism can lead to adverse cardiovascular outcomes mediated by hypercholesterolemia, hypertension and worsening atherosclerosis. The goal of therapy in primary hypothyroidism is to maintain TSH levels within the population specific reference ranges and improving the symptoms.

Monotherapy with Levothyroxine (LT4) has been the mainstay for treatment since the 1970s when knowledge emerged that T3 levels were adequately restored with Levothyroxine therapy alone in post-thyroidectomy patients. This is from the discovery that 80% of circulating T3 levels was derived by peripheral conversion of T4 [2]. Since then, Levothyroxine has been used successfully as monotherapy for treatment of hypothyroidism. Ample evidence is now available to support its use and it is now widely recommended by most guidelines including the NICE guidelines, British Thyroid Association, European Thyroid Association and American Thyroid Association [1, 3-5].

## 2. Goals for Replacement Therapy

The goal of treatment with thyroid hormone replacement (Levothyroxine) is to normalize TSH levels as well as improve symptoms related to hypothyroidism. Symptoms of hypothyroidism can take longer to improve when compared to the time taken for biochemistry to normalize. Ninety percent of patients achieve adequate resolution of the symptoms of hypothyroidism with Levothyroxine therapy alone. The adequate recommended dose for Levothyroxine treatment is 1.6 to 1.7mcg/kg of body weight. In patients below 65 years of age with no significant cardiac disease, NICE guidelines (UK) now recommends high dose treatment initiation as this achieves quicker biochemical normalization of TSH levels. However, if patients have cardiovascular disease and over the age of 65 years, then it is recommended that patients are commenced on 25 to 50mcg of Levothyroxine, and the doses titrated at regular intervals to achieve target TSH levels. It is important to note that TSH reference ranges are population specific and can vary between different laboratories. Pregnancy specific TSH targets also exist and pregnancy is a unique scenario where TSH is often desired to be <2.5 mIU/L.

## 3. Additional/Alternative Therapies to Levothyroxine

Some patients despite being on adequate doses of Levothyroxine may continue to experience symptoms of hypothyroidism and this can often have a dramatic impact on their quality of life. It has been estimated that around 5-10% of patients may have ongoing symptoms of hypothyroidism despite being on adequate Levothyroxine doses. A body of evidence has started to emerge in addressing this particular issue which might be related to monotherapy and small RCTs have suggested an improvement in quality of life in patients taking combination Levothyroxine and Liothyronine (LT3) treatment [6].

There are other products available that have previously been used as forms of thyroid hormone replacement, all with varying efficacy. With over 100 years of knowledge about thyroid hormone replacement therapy, it is prudent that we build on the knowledge and data available. Below is a summary of products that have previously been used/currently available for use as an alternative to or in combination with Levothyroxine therapy [7].

### A: Desiccated Thyroid

Historically, this was the only product available in the early 20th century, and was very widely used. Desiccated thyroid was prepared by animal thyroid extracts containing both T4 and T3 in varying proportions. The recommended dose of desiccated thyroid was 2 grains which contained roughly 121mcg of T4 and 20 mcg of T3. We now understand that the T3 dose in desiccated thyroid far exceeds the required/recommended T3 dose and hence often lead to a sharp rise in serum T3 concentrations, rising to very high peak levels at 2 hours, often leading to significant symptoms of palpitations. Given the non-standardized preparation,

various forms of desiccated thyroid have varying pharmacokinetics and bioavailability.

Patients now have knowledge of available products owing to the wide range of information available on patient support websites and forums. Clinicians must be aware of natural desiccated thyroid extracts currently available on the market (although not licensed for use in the UK) such as Armour Thyroid, Nature-thyroid, WP Thyroid, NP Thyroid etc. These are derived from porcine thyroid extracts. Clinicians should warn patients of associated symptoms with the variable T3 doses of these products and the consequences of high serum T3 levels (arrhythmias and osteoporosis).

### **Studies using desiccated thyroid extract**

To our knowledge, only 1 RCT exists that investigated the effects of Desiccated Thyroid Extracts (DTE). Hoang et al. conducted a randomised, double-blind crossover study in 2013 comparing DTE with Levothyroxine in the treatment of Hypothyroidism.

The study involved 70 patients who were already stable on LT4 treatment for 6 months. Patients were then randomized to either DTE or LT4 for 16 weeks and then crossed over for the same duration. Data was collected looking at the biochemical and neurocognitive tests at the start of the study and again at each phase of the treatment period. Patients were given once daily dose of DTE and LT4. The mean levothyroxine dose during the study was 119.2mcg and the mean DTE dose was 80.6mg. Each grain (65mg) of DTE (as Armour® Thyroid) provided 38mcg levothyroxine and 9mcg liothyronine. The initial desiccated thyroid dose was based on the conversion: 1mg DTE = 1.667mcg levothyroxine. After 6 weeks of study medication, thyroid stimulating hormone (TSH) levels were checked and medication adjusted to maintain TSH between 0.5 and 3.0microIU/mL. Once the TSH was within range, medication was continued for at least another 12 weeks. Patients were then crossed over to the other treatment arm for 16 weeks, with TSH checked at 6 weeks as during the first treatment period.

This study found no statistically significant difference in the quality of life questionnaires. However, the team noted that 34% of patients preferred DTE as they had modest weight reduction during the DTE phase and noted some further improvement in symptoms and mental health without appreciable adverse effects. It is important to note that this is a small RCT with a relatively short duration of treatment and does not inform us about the long term effects of DTE [8].

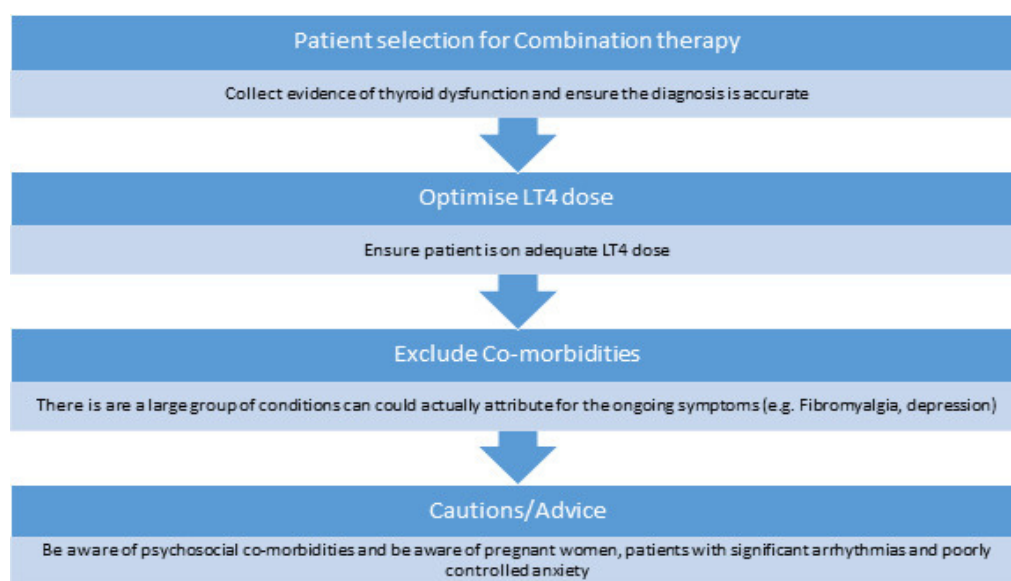
### **B: Liothyronine Sodium**

Synthetic L-T3 (Liothyronine sodium) has been available for use since the 1970s. It has a relatively short half-life in comparison to the more widely used LT4 requiring multiple daily doses. However, given its more superior GI tract absorption, the serum T3 levels can

peak very quickly, with patients reporting symptoms of palpitations as the levels rise. The only exceptional circumstance where LT3 may be of some benefit compared to LT4 is in cases of myxoedema coma or in thyroid cancer where patients are preparing for radioiodine ablation. However, there is now a growing body of evidence that supports the use of LT3 in combination with LT4 in a small subset of patients with Hypothyroidism, and this has been acknowledged by the European Thyroid Association and recent NICE guidance as well [3,5].

### C: Combination of Levothyroxine and Liothyronine therapy

The decision to commence Liothyronine therapy is something that requires careful consideration and prior to this, investigations need to be undertaken to ensure other endocrinopathies are excluded (adrenal insufficiency in particular) which could explain some the persistent symptoms reported by patients. After careful initial evaluation and thorough exclusions of other pathologies, a trial period of LT3 can be used in combination to their LT4 treatment in a select group of individuals. It should be made clear to patients, that this combination therapy needs to be used for a trial period initially, and that symptoms should be clearly evaluated after the 3 – 6 month trial period [5].



**Figure 1:** Selection criteria for combination therapy. Adapted from review by Dayan et al. [9].

### Studies using combination LT3 + LT4 treatment

Seven randomized controlled trials exist so far comparing combined LT4 and LT3 treatment with LT4 treatment alone. All trials were conducted in patients who were already established on LT4 treatment and were deemed to be stable on treatment.

The earliest RCT was conducted by Clyde et al. in 2003. This was a parallel design study, which included 46 participants. All patients were on treatment for hypothyroidism with LT4 for at least 6 months and had been on stable doses for minimum of 3 months. Seventy percent of patients were hypothyroid due to autoimmune thyroiditis. Group 1 patients were on combination therapy where 50 mcg of LT4 was deducted from the patient's usual dose and they

were commenced on 7.5mcg BD of LT3. The treatment was continued for 4 months in total and biochemical and quality of life surveys were conducted. The study found no statistically significant improvement in body weight, lipid profiles or hypothyroid symptoms measured on HRQOL questionnaire within the 2 groups [10].

Sawka et al. randomized 40 hypothyroid patients, with depressive symptoms in particular, on stable doses of LT4 already to receive either LT4 with placebo or a combination of LT3 and LT4 treatment. This was a double-blind study, which ran for 15 weeks. In the combination arm of the study, patients reduced their LT4 dose by 50% and added in LT3 at 12.5mcg BD. The doses were subsequently adjusted to keep TSH levels stable. The study found no statistically significant changes in self-reported mood and quality of life questionnaires in the placebo or combination therapy group. The authors therefore concluded that there was no major benefit in combination treatment based on their small study [11].

A group in Germany subsequently conducted a randomised, double-blinded, two-period, cross-over study in a small sample size of 23 patients. Here, Siegmund et al. examined effects on hormonal and metabolic effects as well as mood and quality of life questionnaires. The group found no significant difference between these groups. In fact, the mood was significantly impaired in by the combination in 8 patients within the group (Beck Depression Inventory scores of 8.51 vs 4.07,  $P 0.026$ ). The group also observed higher rates of subclinical hyperthyroidism associated with the combination therapy group and this directly affected well-being of the patients. This is likely due to the significant fluctuations in the LT3 doses achieving a steady state with its short half-life and rapid peak level rise. The combination dose results were similar to Sawka et al. group [12].

Both Sawka et al. and Siegmund et al. used combination therapy with a molar ratio of 14:1 with LT4 consisting 95% of the dose and 5% of the dose coming from LT3 dose.

Appelhof et al. conducted a double-blind, randomised controlled trial in 141 patients. They used 3 study groups: a group on LT4 alone, group with combination ratio of 5:1 and a final group with a combination ratio of 10:1. The study ran for 15 weeks and subjective preference was the primary outcome of the trial. Secondary endpoints assessed in this study were mood, fatigue, psychological symptoms and a set of neurocognitive tests. The dose ratios were 75mcg:15mcg of LT3 (5:1 ratio) and 75:7.5mcg (10:1) for example. The study results supported the notion that patients did prefer combination treatment (with weight reduction). However, the secondary outcomes did not show any differences between the groups. The study also noted that with the 5:1 ratio led to overtreatment and suppression of TSH levels (mean TSH levels were 0.07mU/L) [13].

One of the first randomised controlled trials in the UK was conducted by Saravanan et al. This was a large community-based double-blinded RCT that involved 697 patients. There



was partial substitution of LT4 by LT3 in this study design. Patients were given either 10mcg of LT3 or matched tablet of 50mcg of LT4. A marked placebo effect was noted by the investigators - however there was no difference in psychological well-being or quality of life within each of the groups. The team concluded that there perhaps may be a small subset of participants who noted benefit from combination therapy. However, the exact parameters could not be clearly identified. One of the major advantages of this group was the large sample size and the longer duration of observation (12 months) [14].

Nygaard et al. conducted randomised, double-blind, cross-over study with 59 patients over a 12 week period. Here the participants either received monotherapy with extra 50mcg of LT4 or a combination of LT4 with 20mcg of LT3. The initial phase of treatment ran for 12 weeks where then the participants crossed over to the treatment arm for another 12 weeks. This study had a positive result towards combination therapy and noted that combination therapy was superior to monotherapy in several aspects of QoL, depression and anxiety rating scales as well as patient's own preference [15].

Finally, Valizadeh et al. conducted a randomised controlled trial where patients either received monotherapy or a combination of LT4 and LT3 treatment. In the combination therapy group, 50mcg of patients LT4 dose was reduced and 6.25mcg of LT3 twice daily was added in followed by titration to 12.5mcg twice daily of LT3 as required. The study did not show any benefit of combination therapy in improving body weight, lipid profile or patients psychological well-being. The authors concluded that monotherapy with LT4 alone remains the main treatment of choice for patients with hypothyroidism [16].

Two out of the seven RCTs found there was a clinically important benefit of combined LT4 and LT3 for quality of life – social functioning and emotional health (Appelhoff et al. and Nygaard et al). It is important to note that majority of the RCTs conducted had small sample sizes and relatively short duration of observation concluding that long term effects of LT3 therapy remains unknown. However, a theme that has emerged from the combination therapy group is patient preference for treatment. Although the primary and secondary endpoints from all these RCTs did not yield positive results, the authors did comment on the fact that patients did prefer combination therapy and this led to some improvement in body weight and well-being.

With greater understanding of de-iodinase deficiencies, and patient access to genetic testing (via thyroid UK website), as clinicians, we do need to familiarize ourselves with using combination therapy (including initiation and titration dosing) should the need ever rise to initiate combination treatment on an individualized, trial-based basis.

#### **4. Liothyronine Sodium Dosing Regime**

Once a decision has been made to commence combined LT3 therapy, then dosing regimens need to be considered. A practical approach to dosing regimen may be starting patients on 5 – 20mcg of LT3 per day in split doses. Given the relatively short life of LT3, twice daily dosing is often required. One needs to consider starting on a low dose and titrating up and balancing the symptoms of palpitations related to the when T3 levels peak. Serum T3 levels peak 2-4 hours after dose administration and start to wear off after 12 hours of the dose. Given this, the optimal regime should consist of a twice daily LT3 dosing regimen. Having the 2nd dose 8 hours after the first dose administration may prevent the risk of insomnia and other symptoms related to T3 peaking around bedtime. The suggested best option for combination therapy would be to use a somewhat reduced LT4 dose and substituting with LT3 treatment. Some studies recommend a fixed substitution of 10mcg of LT3 for 50mcg of LT4. The main issues around the practicalities of dosing are related to limited LT3 formulations. Twenty microgram tablets is often the more widely (if not the only) available formulation of LT3. There is also no slow release LT3 preparation available on the market. Many patients thus would need to break the LT3 tablets to consume the desired dose [9].

#### **5. Monitoring Liothyronine Sodium Therapy**

Standard FT3 assays can be used to monitor the thyroid hormone levels and the aim is to maintain the TSH and T3 levels within the local population specific reference ranges. Ideally, the TSH, T3 and T4 levels should be measured 2-4 hours after LT3 dose administration to capture the peak T3 level. Maintaining TSH and FT3 within the reference range should ensure long term safety, as at present we have no long term data to inform about complications.

Patients should be indefinitely monitored for cardiovascular, psychological and bone adverse effects. The long term risks may include Atrial Fibrillation and osteoporosis, hence ECG, echocardiogram and bone densitometry may also need to be considered.

#### **6. Conclusions**

Levothyroxine remains the cornerstone of therapy for the vast majority of hypothyroid patients. One needs to be cautious in initiating LT3 or the combination of LT3 and LT4 treatment given the current evidence. Although not recommended as first line therapy for management of hypothyroidism, combination therapy with LT3 and LT4 may be beneficial in a small group of carefully selected individuals and there is some evidence supporting this. Although RCTs done so far have had small sample sizes and were of less duration, they do provide us with some useful insight into the potential benefits of combination therapy. With the recent availability of testing for possible genetic de-iodinase deficiency, we could start to see patients presenting to outpatient clinics with supporting evidence for consideration of combination therapy. In view

of this, further research is required into this emerging field and clinicians should at least be aware of the possibility of a trial of combination LT4 and LT3 therapy in the non-responsive hypothyroid patient.

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