

Thyroid Hormone Replacement Therapy: More than Meets the Eye

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Editorial

The treatment of hypothyroidism with thyroid hormone replacement therapy has been the standard of care for over a century. Levothyroxine (LT4) is and has been the cornerstone of this treatment paradigm [1]. It can be taken either orally or intravenously, with the latter route used only in select circumstances. The long serum half-life permits daily as well as weekly administration. Several brand names exist in the market, as well as other alternative forms of thyroid hormone replacement (i.e. thyroid hormone extracts and preparations of liothyronine [T3]) [2]. Faced with an increasing demand for alternative therapy and medication regimens that foster greater compliance, physicians are often confronted with the dilemma of sticking to conventional dosing or trying a different treatment modality/regimen. Therefore, it is imperative that we understand the data behind compounds like liothyronine, once a week levothyroxine or desiccated thyroid extracts, for that matter. This will aid in clinical decision-making and help determine the true place of these compounds in practice algorithms.

It is a well-established fact that a small percentage of individuals do not feel at their optimal best on conventional levothyroxine therapy. One plausible explanation for this is the genetic variations/polymorphisms that occur in the thyroid hormone transporters and deiodinases. Analysis of family/twin data reveals that underlying genetics may cause serum thyroid functions tests to vary as much as 26-65%. For example, mutations in SECISBP2, a gene crucial to the synthesis of selenocysteine containing proteins (e.g. the deiodinases), have been identified in a small cohort. These individuals have mildly decreased serum T3 levels. Nonetheless, there is still no strong data to indicate that combination therapy with liothyronine and levothyroxine is superior to treatment with levothyroxine alone, in those with primary hypothyroidism [2].

Furthermore, even in patients on levothyroxine who feel unwell on monotherapy, there is a paucity of data supporting the routine trial of levothyroxine plus liothyronine. There was a suggestion from the European Thyroid Association (ETA) that combination therapy may be considered as an experiment in patients who have persistent complaints, despite thyrotropin (TSH) being in the normal range. This is on the premise that these individuals have received adequate support in dealing with the chronicity of their disease, and have had other possible autoimmune etiologies, of their symptoms, ruled out. Nevertheless, additional studies are needed targeting this subgroup of patients (e.g. those with normal TSH levels and low serum triiodothyronine, on levothyroxine monotherapy) to ascertain the true long-term risk/benefit ratio of dual therapy. Performing a genetic analysis to characterize a patient's type 2 deiodinase gene polymorphism, for example, is still at the research stage and should not be used in routine clinical practice. Lastly, short-term data indicates that three times a day dosing with liothyronine alone may

positively impact markers such as lipids and weight, but again there is no longitudinal data [2].

Another question that one might ponder upon is whether treatment with thyroid extracts is superior to treatment with levothyroxine monotherapy, in those with hypothyroidism. Until the late 1970s, desiccated thyroid extracts were the mainstay of thyroid hormone replacement. Despite a popular belief amongst some that this is a natural source of thyroid hormone, [3] all commercially available desiccated thyroid preparations come from pigs. The United States Pharmacopeia describes desiccated thyroid as "the cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by humans." The tablets, following measurement for T3 and T4 content, are formulated into doses that are expressed as grains. A 1 grain (65 mg) tablet contains 38 µg of T4, 9 µg of T3, protein-bound iodine, unmeasured quantities of diiodothyronine and moniodothyronine, calcitonin, and other inactive ingredients which given the compound stability [2].

Certain clinical concerns exist with the use of these compounds. Firstly, the T4 to T3 proportion in desiccated thyroid preparations is 4.2:1. This in turn leads to a supraphysiologic level of T3, as the human thyroid itself only produces T4 to T3 in a 14:1 ratio [2]. Secondly, since T3 has a short half life and levels continuously fluctuate over the course of the day, it is very difficult to monitor them [2,3] and titrate therapy accordingly.

The long term efficacy of the T4 to T3 ratio in porcine desiccated thyroid, as well as the effect of the remaining components of porcine thyroid that are mixed into the formulation, has not been assessed. Therefore, one cannot adequately comment on the risks and benefits of this therapy. Lastly, the use of this compound in pregnancy should definitely be contraindicated until more data is at hand on its maternal/fetal effects [2].

Off note, a large number of dietary supplements/nutraceuticals also lack the scientific backing needed to promote their use in the treatment of hypothyroidism. These include over-the-counter products marketed for "thyroid support," "thyroid health," or as a "thyroid supplement." Preparations like 3,5,3'-triiodothyroacetic acid (TRIAC or tiratricol), Asian ginseng, bladderwrack, capsaicin, echinacea, forskolin, L-tyrosine and selenium all fall into this category. 3 Further large scale studies with hard outcome data are needed to truly justify the use of these agents. Having said this, selenium seems to have gained momentum in the treatment of Graves' orbitopathy, as evidenced by a growing plethora of data [4,5].

Lastly, in countries like India, there has been a launch of once weekly preparations of levothyroxine and a fervent use of the same amongst some practitioners. Indeed, data from as far back as the late 1960s demonstrates the safety and efficacy of single doses of T4 [6,7]. However, the recommendations for the use of dosing regimen are very

specific and do not apply to the population at large. Strictly, the use of once a week levothyroxine should only be considered in those individuals where compliance to therapy is a major problem. Absorption testing can also be performed under supervised conditions to distinguish this from the impaired absorption of the drug. From a pharmacokinetic standpoint, we know that administering 7x the usual daily dose of levothyroxine results in supratherapeutic concentrations of T4. This lasts for about 24 hours, with the T3 levels actually remaining within reference parameters. Interestingly, once a week dosing leads to higher mean serum cholesterol, but similar levels of other markers of levothyroxine action (e.g. SHBG, osteocalcin, left ventricular ejection time, heart rate). Whilst this is reassuring, it is important to keep in mind that this data is not based on a large number of patients [8]. All in all, this mode of therapy should be reserved and only employed after all efforts to encourage compliance with daily therapy have been exhausted. Consideration can also be given to elderly patients who depend on a guardian or visiting nurse to give them their pills. Here, twice weekly therapy can also be implemented, as appropriate [2].

In conclusion, thyroid hormone replacement therapy should be encouraged with once a day levothyroxine, unless special circumstances warrant the use of the once a week preparation. Desiccated thyroid extract and other supplements/nutraceuticals should not be promoted as a substitute due to the lack of long-term data. Whether or not liothyronine should be used in combination with levothyroxine or as monotherapy, is still open to debate. The evolution of medicine has indeed brought with it a myriad of ways in which we can manage and treat our patients. Mediums like the internet have

revolutionized access to information. Regardless of whether they are based on sound scientific data or founded on myths floating in the community, increasing demands to deviate from conventional therapy pose a great challenge for all physicians. Only by understanding the evidence behind various treatment paradigms, will we be able to treat our patients in a safe, evidence-based and non-biased manner.

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