Treatment of hypothyroidism: all that glitters is gold?

Anna Maria Formenti¹ · Gherardo Mazzioti² · Raffaele Giubbini³ · Andrea Giustina¹

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Levothyroxine (L-T4) is recommended worldwide for replacement therapy of hypothyroidism due to its efficacy in resolving the symptoms, long-term experience of its benefits, long serum half-life, and low cost. Since the isolation of L-T4 by Kendall in 1914 [1] and then the synthesis of T4 and its better absorbed sodium salt [2], it has become the therapy of choice, also due to the demonstration that about 80 % of biologically active tri-iodothyronine is derived from peripheral conversion of T4 [3].

The individually tailored dose of L-T4 therapy depends on different factors such as body weight, lean body mass, pregnancy status, degree of thyrotropin (TSH) elevation, age, comorbidities, etiology of hypothyroidism, and consequently amount of residual functional thyroid tissue. Therefore, thyroid hormone need may considerably vary among patients. As a matter of fact, although therapy is given correctly, over- as well as under-treatment may quite frequently be observed in clinical practice with relevant impact on different clinical outcomes. Indeed, complications of under-treatment are detrimental effects on the serum lipid profile [4], progression of atherosclerotic cardiovascular disease [5], and congestive heart failure [6].

Nowadays, evidence-based guidelines recommend 1 h interval between L-T4 tablet ingestion and breakfast to achieve the best therapeutic effects [7]. The absorption of an

orally daily administered dose of L-T4 is about 70–80 % under optimal fasting conditions [8]. Nevertheless, almost 50 % of treated patients show persistently abnormal thyroid functional tests 1 year after starting treatment [9]. This may be due, at least in part, as for many other chronic treatments [10], to compliance problems. Specifically, a subset of patients find difficult or even unfeasible, due for example to work requirements, to comply with the indication of assuming the tablet 1 h before breakfast. This often leads to disproportioned increase in doses of L-T4 and improper or expensive work-up [11].

Moreover, different pathologic conditions, such as atrophic and *Helicobacter Pylori*-related gastritis or celiac disease, could reduce the rate of absorption of L-T4 via modification of the gastric acid pH, that is essential for complete dissolution of the tablet [12, 13].

Furthermore, soy products and several drugs, such as calcium carbonate, bile acid sequestrants, proton pump inhibitors, and ferrous sulfate, may alter L-T4 absorption [7].

Trying to improve these pharmacokinetic drawbacks, recently new formulations of L-T4 have been introduced: soft gel capsules, containing T4 dissolved in glycerin, and the liquid formulation (only in a few countries). These preparations have been reported to reach the systemic circulation more quickly since gastric dissolution is not needed [14]. In a recent two-year prospective study involving hypothyroid patients without malabsorption or drug interference, Fallahi et al. reported higher effectiveness of liquid L-T4 formulation in normalizing TSH levels as compared to L-T4 tablets [15]. Indeed, the alcoholic component of the liquid formulation could play a crucial role favouring the direct absorption by the highly vascularized oral mucosa [16] and the L-T4 new formulations seem to offer the chance to overcome malabsorption determined by breakfast interference. In fact, it is known

✉ Andrea Giustina
a.giustina@libero.it

¹ Endocrine and Metabolic Disease Unit, Department of Molecular and Translational Medicine, University of Brescia, Viale Europa 11, 25123 Brescia, Italy

² Endocrine Unit, Department of Medicine, Carlo Poma Hospital, Mantua, Italy

³ Nuclear Medicine Unit, University of Brescia, Brescia, Italy

that simply the concomitant consumption of a cup of coffee may result in an altered absorption of L-T4 tablets [17], sequestering T4 within the intestinal lumen and also increasing gastro-intestinal temperature which is detrimental to the drug absorption. Such an effect was not observed with soft gel capsules of L-T4 which absorption was shown to be unaffected by the concurrent intake of coffee [18].

In this issue of the Journal, Morelli et al. [19] show that liquid formulation of L-T4 has the same advantages in terms of absorption already reported for the soft gel capsules. As a matter of fact, they have found no differences in thyroid functional test after 6 weeks administration of liquid L-T4 at breakfast or 10 or 30 min before breakfast with a cross-over design study [19]. The results of Morelli et al. are in agreement with another recent study reporting no interference of breakfast on absorption of oral L-T4 solution [20]. These findings are clinically relevant for three reasons: (a) if new formulations are better absorbed than L-T4 tablets, they may be of potential benefit also in several pathologic conditions of malabsorption; (b) they could ameliorate the patient compliance, thereby limiting the risk of under-treatment; and (c) unnecessary TSH tests may be avoided thus reducing the costs of hypothyroidism follow-up.

Interestingly, Morelli et al. [19] have found no differences in quality of life (QoL) of patients taking L-T4 at breakfast or 10 or even 30 min before breakfast. The meaning of this finding is not totally clear. On one hand, one can hypothesize that in the relatively small group of patients the traditional timing of administration was well accepted, as in general the more compliant patients are those that prevalently accept to participate in clinical trials. In fact, the normalization of TSH at study entry, when patients were taking the liquid formulation 30 min before breakfast, supports their effective compliance to the traditional therapeutic schedule. These findings do not exclude that particularly by avoiding L-T4 under-treatment, liquid L-T4 formulation may improve QoL in truly non-compliant patients. Finally, the use of questionnaires non-specific for hypothyroidism, may reduce their efficacy in collecting possible specific subtle changes, particularly in a relative short-term study [19]. In this regard, long-term prospective studies, involving a large number of subjects with different degrees of compliance to traditional treatment and tested with specific questionnaires [21], are needed to investigate the impact of novel L-T4 formulations on QoL. Furthermore, these future studies could clarify if the positive impact of these formulations on QoL may be due just to a more convenient administration schedule or to an improved outcome in terms of TSH normalization.

Possible controversies may arise from the practical use of liquid L-T4 in patients at risk or with risk of L-T4 overtreatment such as the elderly and secondary hypothyroid patients.

In fact, elderly patients are more susceptible to the adverse effects of thyroid hormone excess, like atrial fibrillation [22] and osteoporotic fractures [23, 24]. Therefore, careful titration of L-T4 dose, particularly when a formulation that ensures a better absorption is used, is needed to avoid iatrogenic thyrotoxicosis, especially in patients taking other medications in addition to L-T4 for a variety of co-morbidities [25].

Moreover, subtle iatrogenic thyrotoxicosis may often occur in patients treated for central hypothyroidism, due to absence of a reliable biochemical marker for positive treatment outcomes [26]. Indeed, serum TSH values are almost always undetectable at baseline in this clinical setting. Thus, potential overtreatment linked to increased absorption of L-T4 liquid formulations should be taken into account when managing hypopituitary patients. On the other hand, under-treatment of these patients may even take place, also due to the non-indicative role of TSH (in clinical practice low TSH could lead in some instances to lower inappropriately the dose of L-T4 in hypopituitary patients). Therefore, in this respect liquid formulation may find a role, with careful monitoring of circulating T4, also in secondary hypothyroidism.

Current guidelines for hypothyroidism treatment [7] do not give clear indications for using L-T4 liquid formulations as an alternative to traditional tablets, since, according to the authors, not enough literature has been so far produced concerning the potential advantages of this new formulation over traditional treatments. However, data recently published in different clinical settings [27] and in part commented in this Editorial, give in our opinion a reasonable basis for re-discussing the role of this new treatment option in future guidelines.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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