Обзоры литературы

Новый взгляд на старую дилемму: лечение гипотиреоза при помощи комбинированной терапии L-тироксином и L-трийодтиронином

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В данном обзоре приведена информация о последних исследованиях в области комбинированного лечения гипотиреоза L-тироксином и L-трийодтиронином. Несмотря на то что были опубликованы достоверные данные об эффективности комбинированной терапии T_3 и T_4 у крыс после тиреоидэктомии, последние исследования и метаанализы не указывают на значимое преимущество комбинированной терапии по сравнению с монотерапией T_4. Более того, у пациентов, получающих комбинированную терапию, чаще развиваются побочные эффекты, такие как тахикардия, нервозность и общая слабость. Тем не менее по сравнению с комбинированной терапией L-T_4+L-T_3 при монотерапии T_4 обычно наблюдается сниженный уровень свободного T_3 и повышенный уровень свободного T_4 сыворотки крови, при этом отношение св.T_3/св.T_4 ближе к показателям, характерным для здорового человека. Согласно рекомендациям ETA и ATA, на сегодняшний день монотерапия T_4 считается первоочередной в лечении гипотиреоза. Тем не менее во многих случаях рекомендации не соблюдаются, и пациенты принимают высушенные экстракты щитовидной железы или разнообразные "препараты" T_3 доступные в интернете. Недавно было выявлено, что однонуклеотидный полиморфизм (ОНП) генов дейодиназы 1-го (Д1) и 2-го (Д2) типов, а также гена фосфодиэстеразы 8В ассоциирован со снижением уровня свободного T_3 и дисфункцией щитовидной железы. Данные наблюдения подчеркивают необходимость в дальнейших исследованиях эффективности применения готовых комбинированных препаратов, а также в разработке долгожданных формул L-T_3 с отсроченным действием или низкодозированных (капсулы или таблетки по 5 мкг) препаратов L-T_3 с целью облегчения подбора правильной дозы при комбинированной терапии с препаратами L-T_4 в контексте персонализированного подхода к лечению. Последние данные о возможном влиянии ОНП генов дейодиназ или белков-переносчиков тиреоидных гормонов на концентрацию свободного T_3 в тканях открывают путь к генотипированию пациентов с тиреоидэктомией в анамнезе, предъявляющих характерные жалобы и имеющих низкое отношение св.T_3/св.T_4.

Ключевые слова: *L-тироксин, L-трийодтиронин, гипотиреоз, однонуклеотидный полиморфизм, Thr92Ala, отношение св.T_3 /св.T_4.*

New aspects of an old dilemma: treatment of hypothyroidism with L-thyroxine combined with L-triiodothyronine

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The current review summarizes the most recent developments in the field of combined treatment with LT4+LT3 in hypothyroidism. Though it was well established for the past 20 years that T3 combined with T4 was best able to achieve euthyroidism in hypothyroidectomized rats, several recent studies and meta-analyses did not demonstrate any increased benefit of combined treatment as compared with T4 monotherapy. Moreover, patients under combination treatment are more prone to experience adverse effects, such as tachycardia, nervousness and fatigue. Conversely, T4 monotherapy usually leads to lower FT3 and higher serum FT4 levels as compared to the LT4+LT3 regimen thus resulting in a FT3:FT4 ratio closer to that of healthy subjects. Today, T4 monotherapy constitutes first-line treatment of hypothyroidism according to both the ETA and ATA Guidelines. However, in many cases the guidelines are not followed, with patients often taking compounded desiccated thyroid hormones or various T3 preparations available on the web. Recently, single nucleotide polymorphisms (SNPs) in the deiodinase type 1 (DIO1) and type 2 (DIO2) genes and in the phosphodiesterase 8B gene have been associated with T3 decrease and thyroid dysfunction. The above observations point to the necessity for more research into the application of customized treatment as well as to the need for the long-awaited LT3-retard formulations or low-dose (about 5μg/tablet/capsule) LT3 preparations to be appropriately dosed with LT4 in the context of a personalized treatment strategy. The recent finding that SNPs in DIOs or in thyroid hormone transporter genes may affect serum T3 in tissues opens up the way to the genotyping of those thyroidectomized patients who complain of symptoms and have a lower FT3:FT4 ratio.

Key words: *L-thyroxine, L-triiodothyronine, hypothyroidism, single nucleotide polymorphisms (SNPs), Thr92Ala, FT3:FT4 ratio.*

Introduction

Hypothyroidism is a common endocrine disease characterized by an array of symptoms, the frequency and intensity of which vary according to the grades of the disease [1, 2]. Few or no symptoms are present in minimal disease, whereas considerably more symptoms are reported in moderate and overt hypothyroidism [3].

According to the American and European Guidelines, L-thyroxine (LT4) is the first-line treatment for hypothyroidism, as it generates more consistently physiological concentrations of 3,5,3'-triiodothyronine (T3) [4, 5]. Full replacement is usually achieved with about 1.6 μg/Kg/BW of LT4, though individual variations are higher. The treatment is generally well tolerated and improves the symptoms and signs of hypothyroidism in the vast majority of treated patients. However, a number of patients, approximately 10%, report that their symptoms persist, this appreciably impacting their quality of life (QOL) even though biochemical euthyroidism has been achieved [6]. In these cases the combined treatment of LT4 together with L-triiodothyronine (LT3) might be an option, albeit the results of most of the studies conducted using the combination treatment failed to demonstrate any increased benefit when compared with monotherapy.

The aim of this short review is to update our current knowledge by briefly describing some of the most recent studies using combination therapy in patients with residual symptoms and to recap the outcome of this treatment in relation to potential predictors and monitoring.

Physiology and pathophysiology of the HPT axis

The production of thyroid hormones (TH) T4 and T3, the two pillars of human metabolism, are regulated externally by a negative feedback mechanism between serum T4, T3 and thyroid-stimulating hormone (TSH) and internally by the intrathyroid availability of iodine. Thus, the biosynthesis of TH begins with the sequential steps of iodine metabolism: active iodide transport into the thyroid, iodide oxidation and subsequent iodination of tyrosyl residues of thyroglobulin (Tg) [7]. In an iodine deficient state, the decreased synthesis of TH leads to a reduction in plasma T4, rapidly activating secretion of the hypothalamic thyrotropin-releasing hormone (TRH) and TSH, the latter stimulating the thyroid to grow and restore TH synthesis and secretion [8]. Given that the *TSHB* and *TRH* genes are negatively regulated by T3 (and not by T4), it is essential that T4 be converted to T3 in order to maintain the negative feedback mechanism. It is well known that the peripheral conversion of T4 to T3 is mediated by type 1 deiodinase (D1) and occurs mainly in the liver, kidney and muscles. Type 2 deiodinase (D2), which converts T4 to T3 in the brain, is co-expressed with TSH in pituitary cells, in astrocytes in the mediobasal hypothalamus, in astrocytes located in thyroid hormone-sensitive regions of the brain, such as the cerebral cortex and hippocampus, and also in tanycytes, specialized ependymal cells lining the floor and infralateral wall of the 3rd ventricle [10, 11]. Therefore, a constant production of brain T3, an essential component for the normal activity of the hypothalamic-pituitary-thyroid (HPT) axis, requires well synchronized activity of astrocytes and tanycytes to locally generate T3. It is further hypothesized that variability in the sensitivity of cells to D2 activity and/or to thyroid hormone signaling might occur causing a state of tissue hypothyroidism which is not reflected by the normal levels of TSH [12] and that may partially explain the residual symptoms experienced by some patients. The fundamental knowledge that T3 is derived in humans by conversion of T4, even in the absence of the thyroid gland as was shown in experiments in rats, originally promoted monotherapy with LT4, to achieve a steady-state serum T3 level, as first-line treatment of hypothyroidism [13].

The clinical studies

There is however the other side of the coin. Crucially, LT4 monotherapy in hypothyroidism often results in a higher T3:T4 ratio, as serum T3 is in the lower reference range, or even lower, and FT4 is relatively high, while TSH is adequately suppressed. Meanwhile, the long-term effects of the higher T3:T4 ratio are not clear, neither is it known whether they contribute to the generation and persistence of symptoms in certain patients. Thus, combination treatment of LT4+LT3 represented an endeavor to concurrently achieve clinical and biochemical euthyroidism [14]. However, the findings that the addition of T3, even by 10-12.5 μg/day, to T4, the latter reduced by 50 μg, is liable to result in overtreatment thus inducing serious side effects, notably cardiac arrhythmia [4], tachycardia, nervousness, sleep disturbances, sweating and discomfort, have seriously restricted wide application of this treatment modality. The ETA has moreover stated "the evidence base to advocate this treatment modality is very limited and therefore LT4+LT3 combination therapy should be considered solely as an experimental treatment modality" (5). The above developments are mainly based on the fact that several LT4+LT3 therapy studies could not collectively provide solid grounds for this kind of treatment since numerous inconsistencies and discrepancies were observed (5). Moreover, though favorable effects were observed on serum lipids with combination LT4+LT3 treatment, a higher activation of bone resorption demonstrated yet another important limitation of the treatment [15].

There is also the matter of non or inadequate adherence to combination therapy as well as the use of compounded versions of thyroid hormone. In a recent

Danish study performed via a questionnaire on trends in the use of LT4+LT3 combination therapy, 84% of the 293 patients reported a beneficial treatment effect, 44% of the responders received their prescriptions from general practitioners, 50% received desiccated thyroid and 28% reported that they adjust their dose themselves [16]. These numbers indicate that the European Guidelines on LT4+LT3 combination therapy are not universally followed, at least in Denmark, and also that the media may influence the prescription pattern [16]. Also noteworthy is a case of iatrogenic hypothyroidism resulting from compounded thyroid hormone (T4/T3) therapy when the thyroid replacement was changed from 175 μg LT4 to 57/13.5 μg compounded LT4+LT3 daily, this leading to high TSH and enlargement of the pituitary. Resolution of the abnormalities was achieved with reintroduction of LT4 treatment [17]. Reports of this kind clearly substantiate the recommendations of the ETA and ATA Guidelines against routine prescription of compounded thyroid hormone. In another recent cross-sectional study investigating the association between thyroid function tests (TFTs) and QoL in patients with differentiated thyroid cancer on LT4 monotherapy, no association between TFTs including T4+T3 and 3.5-T2/T3 ratios and QoL was found by multiple linear regression analyses [18]. The data do not suggest that a change in LT4 dose can improve such symptoms as fatigue or wellbeing in hypothyroid patients which are likely due to low T3 levels [18].

In a computer simulation study, pharmacokinetic and physiological human data were validated and compared in three clinical models: combined LT4+L/T3 vs LT4-only treatment, parenteral LT4 administration and central hypothyroidism [19]. In thyroidectomized patients, combined LT4+LT3 therapy or LT4-only replacement normalized plasma T3 via administration of 145 μg LT4/day or 165 μg LT4 day, respectively. The combined LT4+LT3 dosing needed to normalize both plasma and tissue T3 levels was 105 μg LT4 + 9 μg T3 per day, while plasma T4 and TSH remained normal. It was thus observed that combined LT4+LT3 treatment-simulated standard LT4-only therapy was sufficient to renormalize average tissue T3 levels and maintain TSH and T4 plasma levels within the normal range, indicating adequacy and efficiency of standard LT4-only treatment, which appears to be the optimal choice [19].

There is debate among specialists not only as to the risks and benefits of combination therapy but also regarding which is the most appropriate thyroid functioning test [20]. Indicatively, repeated measurements of serum T3 at baseline or during LT4+LT3 therapy could not predict a positive response to this treatment modality.

It is known that LT4 administration reduces whole-body D2-dependent T4 conversion to T3, though the effect of LT4 on D2 activity in the hypothalamus is minor [21]. An in vitro analysis into D2 ubiquitination prompted by diverse tissue extracts led to moderately lower D2 ubiquitination in the hypothalamus: this suggested that, unlike other D2 expressing tissues, the hypothalamus is genetically determined to possess higher sensitivity to T4 [21]. A number of experimental studies have shown that tissue-specific differences in D2 ubiquitination might well comprise an inherent property of the TRH/TSH feedback mechanism. In addition, studies in thyroidectomized rats have revealed that a constant delivery of LT4 and LT3 alone is capable of entirely normalizing T3-dependent metabolic markers along with gene expression profiles [13].

Genetic variance

Individual differences in response to therapy may also be related to single nucleotide polymorphisms (SNPs) in the DIO2 gene, which encodes the deiodinase 2 enzyme regulating the conversion of T4 to T3 in the brain and in other tissues. In this line of evidence, it was shown that SNPs of the DIO2 Thr92Thr gene (Thr92Ala and Ala92Ala) may be responsible for reduced serum as well as intracellular T3 in thyroidectomized patients on replacement treatment with levothyroxine [22]. The most studied variant is rs225014 (Thr92Ala), which had no effects on serum TSH, FT4 or T3 [13, 22], though it has, importantly, been linked to diabetes, hypertension and the risk of osteoarthritis [23]. In addition, these two SNPs in DIO2, Thr92Ala (rs225014) and rs225015, were associated with impaired baseline measures of psychological wellbeing, although another study did not find any improvement to combined LT4+LT3 treatment, thus offering some evidence in favor of a personalized treatment approach to hypothyroidism in athyreotic patients [24, 25].

The three-generation LifeLines Cohort Study including genome-wide genetic data of 12,625 participants found that the Ala/Ala genotype of the D2-Thr92Ala SNP was present in 11.3% of LT4 users and in 10.7% of the general population [26]. It is noteworthy that the highest quartiles of FT3 and the FT3/FT4 ratio may predict a 49% and 67% higher prevalence of metabolic syndrome (MetS) in men and a 62% and 80% higher prevalence in women [26].

Besides its association with QoL in millions of patients with hypothyroidism, Thr92Ala-D2, a common SNP, exhibits a strong susceptibility to ubiquitination and proteasomal degradation, which is regulated within the D2 molecule [27]. By accumulating in the Golgi, Ala92-D2 may, following oxidative stress, disrupt basic cellular functions, increase pre-apoptosis and cause disease [27].

Another study was recently conducted aiming to demonstrate that the presence of SNPs in the D2 Thr92Thr gene (Thr92Ala and Ala92Ala) result in decreased serum and intracellular T3 [28]. Indeed, an analysis of the D2

gene in 102 thyroidectomized patients who were on levothyroxine replacement and who carried the Thr92Ala or Ala92Ala isoforms of D2 substantiated this hypothesis, thus pointing to the need for the personalized treatment of hypothyroidism in athyreotic patients [28]. More specifically, of the 102 patients, 37 (37.3%) were homozygous wild-type (Thr/Thr), 52 (51%) were heterozygous (Thr/Ala), while 13 (12.7%) were homozygous mutants (Ala/Ala) at the 92 position. Post surgery, mean FT4 levels were seen to be significantly elevated as compared to pre-surgery values in the homozygous Thr/Thr and in the Ala/Thr, however not in the Ala/Ala group. Finally, assessments of the effect of clearance of the D2 protein in myocytes demonstrated that the D2-Ala protein had a longer half-life and was also more stable than the D2-Thr protein; also determined was the fact transfected D2 brought about dose-dependent apoptosis, this indicating that excess intracellular T3 could be lethal [28, 29].

It is also of note that the C-allele of a particular SNP in DIO1 (rs2235544) is associated with increased DIO1 activity, resulting in slightly higher FT3 and lower FT4 [30]. Furthermore, in T4-treated hypothyroid patients, the FT3/FT4 ratio is higher in subjects who are homozygote for this SNP as compared to the wild type (0.19 vs 0.17), albeit it has not been related to persistent symptoms [30]. However, it should be emphasized that most of these associations are independent of serum thyroid hormone levels, which highlights the importance of local regulation of thyroid hormones in tissues [30]. Though D2 accounts for about 70% of circulating serum T3 in humans, common genetic variants in DIO2 have not been linked to serum iodothyronines [31].

Recently, another SNP was identified which is associated with TSH levels, namely the rs4704397 SNP in the phosphodiesterase 8B (PDE8B) gene [32]. A large number of subjects (8938) of the Tromsø Study who were without thyroid disease or thyroid medication were successfully genotyped for rs4704397. Among these, subjects harboring the minor homozygote genotype (A:A) showed a median serum TSH level that was 0.29 mIU/L higher, as well as a significantly increased risk of myocardial infarction, as compared to those with the major homozygote genotype (G:G).

Epicrisis

Among those patients who, despite being on monotherapy, present low-normal baseline T3, the optimal approach for the assessment of their candidacy for combined treatment is to undergo genomic sequencing as well as to be enlisted in prospective and randomized investigations. In this context, it is recommended that the FT3/FT4 ratio be close to the physiological ratio of FT3/FT4 i.e. 1:14-1:15 (Fig 1) and additionally that serum T3 together with TSH be regularly monitored.

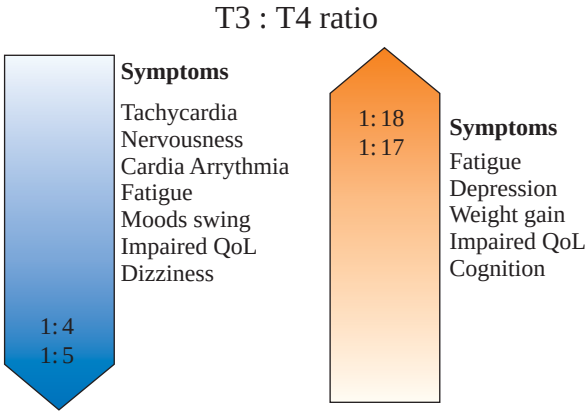

Figure 1. The ratio of T4:T3, physiological at 14:1–15:1, is a good parameter for evaluation of treatment either with LT4 monotherapy or with combination treatment with LT4+LT3. A ratio higher or lower than the physiological ratio is often accompanied by an increasing array of symptoms.

In the near future, genetic screening will enable better characterization of the biology of individuals with DIOs mutations thereby achieving more accurate detection of those patients who are in need of combined LT4+LT3 treatment. Furthermore, more numerous options and the availability of low-dose and highly absorbable T3 compounds will further contribute to the individual tailoring of treatment of hypothyroidism. In addition, the genotyping of thyroidectomized patients who complain of hypothyroid symptoms and have a relatively low FT3/FT4 ratio will also facilitate identification of those requiring combined LT4+LT3 treatment and will simultaneously optimize the use of technology in customized thyroidology.

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