THE USE OF L-T4 + L-T3 IN THE TREATMENT OF HYPOTHYROIDISM.
AN ETA GUIDELINE 2012

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Background

Some L-T4 treated hypothyroid patients describe persistent symptoms although normal serum TSH levels are present.

The use of L-T4 + L-T3 combination therapy has been suggested to restore physiological levels of T4 and T3 in all tissues.

This treatment is controversial.

The ETA has nominated a Task-force to review the topic and formulate guidelines in this area. Taskforce members.
1. Is there an unmet need in L-T4 treated hypothyroid patients?

Three community-based studies

- From The U.K.: The proportion of caseness was higher in patients than in controls, in GHQ-12 (34% vs 26%, p=0.012). (Saravanan et al 2002)

- From The Netherlands: Patients showed poor performance in various domains of cognitive functioning compared with standard reference values (p=0.001). (Wekking et al 2005)

- From Norway: More females on L-T4 had high scores (HASD ≥8) for depression and anxiety than females not on L-T4: depression 18% vs 13% (p<0.001), anxiety 23% vs 19% (p<0.001). (Petersen et al 1990)

*However, the dimension and causality of the problem is not clear.*
Conclusions

In L-T4 treated hypothyroid patients with normal serum TSH values, psychological distress, impaired well-being and cognitive disturbances occur more often than in controls. (1/+OO)

Data suggests that 5-10% of patients have persistent symptoms which can be related to the disease and L-T4 therapy. (2/+OO)
2. Is there a biological rationale for persistent complaints in L-T4 treated hypothyroid patients?

Possible causes of persistent complaints in L-T4 treated hypothyroid patients.

• Non-specific causes: related to the chronic nature of the disease.

• Specific causes: related to thyroid disease and thyroid hormone replacement:

  1. Associated autoimmune diseases
  2. Thyroid autoimmunity
  3. Inadequacy of L-T4 dosage
  4. Inadequacy of L-T4 treatment modality

(2/+00)
3. *Is there evidence that L-T4 + L-T3 combination therapy serves the hypothyroid patient better than L-T4 monotherapy?*

**Historical background.**

- In the 1960s hypothyroidism was treated with tablets made from animal thyroid glands.

- In the 1970s industrially produced L-T4 became available. Deiodination of T4 to T3 was discovered, and therefore normal serum levels of T4 and T3 were achieved when giving L-T4 as monotherapy.

- Bunevicius, et al in 1999 described increased QOL in a study of a small patient group using a combination of L-T4+L-T3.
META-ANALYSIS OF RCTs.
(Grozinsky-Glasberg, 2006)

- Eleven clinical studies, in which 1216 adult hypothyroid patients on L-T4 treatment were randomized to receive T4 monotherapy or T4+T3 combination therapy.

- The meta-analysis found no difference in the effectiveness of combination versus monotherapy in any of the following factors: body pain, depression, anxiety, fatigue, quality of life, body weight.

The authors of the meta-analysis concluded:
“It is doubtful whether further trials evaluating combination therapy are needed because the chances that the accumulated evidence will change are low”.
Danish study – results.

- Serum TSH remained unaltered between the groups as intended.

- Significant differences were observed in 7 out of 11 QOL scores, indicating a positive effect related to the combination therapy.

- 49% preferred combination therapy.
- 15% preferred monotherapy.

(Nygaard et al. 2009)
Preference of patients in RCTs comparing L-T4 monotherapy with T4+T3 combination therapy in crossover or parallel study designs

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>n</th>
<th>PREF. T4</th>
<th>PREF. none</th>
<th>PREF. T4+T3</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Crossover studies</strong></td>
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<tr>
<td>Walsh 2003</td>
<td>100</td>
<td>46</td>
<td>18</td>
<td>36</td>
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<tr>
<td>Nygaard 2009</td>
<td>59</td>
<td>9</td>
<td>21</td>
<td>29</td>
<td>0.002</td>
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<tr>
<td>Bunevicius 1999</td>
<td>33</td>
<td>2</td>
<td>11</td>
<td>20</td>
<td>0.001</td>
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<tr>
<td>Escobar-Morreale 2005</td>
<td>26</td>
<td>2</td>
<td>6</td>
<td>18</td>
<td>0.015</td>
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<tr>
<td>Bunevicius 2002</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>228</td>
<td>61</td>
<td>58</td>
<td>109</td>
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<tr>
<td></td>
<td></td>
<td>(27%)</td>
<td>(25%)</td>
<td>(48%)</td>
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<td><strong>Parallel study</strong></td>
<td></td>
<td></td>
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<td>Appelhof 2005</td>
<td>140</td>
<td>14/48</td>
<td>-</td>
<td>43/92</td>
<td>0.024</td>
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<tr>
<td></td>
<td></td>
<td>(29%)</td>
<td></td>
<td>(47%)</td>
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Overall conclusions...

There is insufficient evidence that L-T4 + L-T3 combination therapy serves the hypothyroid patient better than L-T4 monotherapy (1/++0).

It is recommended that L-T4 monotherapy remains the standard treatment for hypothyroidism (1/+++).
4. Could it be that trials comparing L-T4 + L-T3 combination therapy and L-T4 monotherapy have not targeted the right population?

Limited data suggests that psychological well-being and preference for L-T4+ L-T3 combination therapy may be influenced by *polymorphisms* in thyroid hormone pathway genes, specifically in thyroid hormone transporters and deiodinases. (2/+00)
5. Which patients would qualify for L-T4 + L-T3 combination therapy?

• It is suggested that L-T4 + L-T3 combination therapy might be considered as an experimental approach for:
  – Compliant L-T4 treated hypothyroid patients.
  – Patients who have persistent complaints despite normalized TSH values.
  – Patients who have previously been given support to deal with the chronic nature of their disease.
  – Those in which associated autoimmune diseases have been ruled out. (2/+00 )

• It is suggested that combination therapy is discontinue, if no improvement is experienced, after three months. (2/++0)

• L-T4 +L-T3 combination therapy is not recommended for pregnant women and for patients with cardiac arrhythmias. (2/+00 )
6. What is the appropriate dosage of \( L-T4 + L-T3 \) combination therapy?

It is suggested that \( L-T4+ L-T3 \) combination treatment should be initiated in an \( L-T4/L-T3 \) dose ratio between 13:1 and 20:1 by weight. (2/+00)

Whereas \( L-T4 \) can be prescribed once daily, the \( L-T3 \) dose should be divided (if possible) into two daily doses (one before breakfast and one - the largest - before sleeping). (2/+00)
Methods for calculating L-T4 and L-T3 dosages for L-T4+ L-T3 combination therapy.

<table>
<thead>
<tr>
<th>T4 monotherapy</th>
<th>100 μg L-T4</th>
<th>150 μg L-T4</th>
<th>200 μg L-T4</th>
</tr>
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<tr>
<td>= dose x</td>
<td>= dose x</td>
<td>= dose x</td>
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**T4+T3 combination,**

| L-T3 dose y (y = x : 20) | 5  μg | 7.5  μg | 10  μg |
| L-T4 dose z (z = x – 3y) | 85  μg | 127.5  μg | 170  μg |
| L-T4 dose (round off)   | 87.5  μg | 125  μg | 175  μg |
| L-T4 : L-T3 dose ratio  | 17 : 1 | 17 : 1 | 17 : 1 |
7. Which preparations can be used in L-T4 + L-T3 combination therapy and how should their use be monitored?

- It is recommended to use separate L-T4 and L-T3 tablets in T4+T3 combination therapy. (1/+00)

- Thyroid function tests in blood samples withdrawn before morning medication has been taken, aiming at normal serum levels of TSH, FT4, FT3 and FT4/FT3 ratio. (1/++0)

- Combination of L-T4 and L-T3 should be reserved for use by accredited interns/endocrinologists. (2/++0)
My personal conclusions...

• We must **assist our patients** - to get the correct diagnosis.

• We must **assist our patients** - to not get lost on the Internet.

• A **minor group** of patients have a possible benefit from combination therapy.

• The **majority** of patients should still be treated with L-T4 monotherapy.