V Corso Aggiornamento Ame in Endocrinologia Clinica

UNIVERSITA’ DEGLI STUDI DI MESSINA
DIP. DI MEDICINA CLINICA E SPERIMENTALE

Master di Endocrinologia dell’Infanzia, dell’Adolescenza e della Donna

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IPOTIROIDISMO SUBCLINICO-
Accusa.
Perché, chi e quando trattare
Ricerca su PubMed (al 15.03.2014)

<table>
<thead>
<tr>
<th>Stringa</th>
<th>Numero di articoli su PubMed</th>
<th>Numero di articoli su Google</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical hypothyroidism</td>
<td>2.514</td>
<td>332.000</td>
</tr>
<tr>
<td>Therapy of subclinical hypothyroidism</td>
<td>1.212</td>
<td>318.000</td>
</tr>
</tbody>
</table>
Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association

THYROID
Volume 22, Number 12, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2012.0205

Pages 1200-1235

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for the American Association of Clinical Endocrinologists and American Thyroid Association Task force on Hypothyroidism in Adults

THYROID
Volume 22, Number 12, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2012.2212.ed

EDITORIALS AND COMMENTARY

Diagnosis and Treatment of Hypothyroidism: Rules, Longstanding Exceptions, and the Emerging Entity of Thyroid Hormone Receptor Alpha Resistance

Charles H. Emerson
Question: How should patients with hypothyroidism be treated and monitored?

• **Recommendation 22.1** - Patients with hypothyroidism should be treated with L-thyroxine monotherapy [Grade A, BEL 1].

• **Recommendation 22.2** - The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism [Grade B, BEL 2]. This recommendation was downgraded to Grade B because of still-unresolved issues raised by studies that report that some patients prefer and some patient subgroups may benefit from a combination of L-thyroxine and L-triiodothyronine.

• **Recommendation 22.3** - L-thyroxine and L-triiodothyronine combinations should not be administered to pregnant women or those planning pregnancy. [Grade B, BEL 1]. This recommendation was upgraded to Grade B because of potential for harm.

• **Recommendation 22.4** - There is no evidence to support using desiccated thyroid hormone in preference of L-thyroxine monotherapy in the treatment of hypothyroidism and therefore desiccated thyroid hormone should not be used for the treatment of hypothyroidism. [Grade D, BEL 4]


**Recommendations:**

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

• It is recommended that L-T4 monotherapy remains the standard treatment of hypothyroidism (1/+ ++).
<table>
<thead>
<tr>
<th>Item</th>
<th>Text (with reference number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dosage of L-T4</td>
<td>With little residual thyroid function, therapy requires approximately 1.6 μg/kg of L-thyroxine daily (155,156). Patients who are athyreotic (after total thyroidectomy and/or radioiodine therapy) (157) and those with central hypothyroidism may require higher doses (158), while patients with subclinical hypothyroidism (159–162) or after treatment for Graves' disease (163) may require less. In the case of central hypothyroidism, estimates of dosage based on 1.6 μg/kg L-thyroxine daily and assessment of free $T_4$, not TSH, should guide therapy.</td>
</tr>
<tr>
<td>Dose adjustments</td>
<td>Dose adjustments are guided by serum TSH determinations 4–8 weeks (156,170) following initiation of therapy, dosage adjustments, or change in the L-thyroxine preparation (139,171). While TSH levels may decline within a month of initiating therapy with doses of L-thyroxine such as 50 or 75 μg, making adjustments with smaller doses may require 8 weeks or longer before TSH levels begin to plateau (170,172). Increment changes of 12.5–25 μg/d are initially made, but even smaller changes may be necessary to achieve goal TSH levels.</td>
</tr>
<tr>
<td>Question</td>
<td>Guidelines Recommendation [and recommendation number]</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td><strong>Which patients</strong> with TSH levels above a given laboratory’s reference range should be considered for treatment with L-T4?**</td>
<td>Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine. [14.2]</td>
</tr>
<tr>
<td>In patients with hypothyroidism being treated with L-thyroxine, what should the target TSH ranges be?</td>
<td>... the target range should be the normal range of a third generation TSH assay. If an upper limit of normal for a third generation TSH assay is not available, in iodine-sufficient areas an upper limit of normal of 4.12 mIU/L should be considered and if a lower limit of normal is not available, 0.45 mIU/L should be considered. [17]</td>
</tr>
<tr>
<td>In patients with hypothyroidism being treated with L-thyroxine who are pregnant, what should the target TSH ranges be?</td>
<td>In patients with hypothyroidism who are pregnant, the target range for TSH should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges are not available in the laboratory, the following upper-normal reference ranges are recommended: first trimester, 2.5 mIU/L; second trimester, 3.0 mIU/L; and third trimester, 3.5 mIU/L. [18]</td>
</tr>
</tbody>
</table>

**When to treat hypothyroidism**

Although there is general agreement that patients with primary hypothyroidism with TSH levels above 10 mU/L should be treated (106, 115-117), which patients with TSH levels of 4.5-10 mU/L will benefit is less certain (118, 119).

A substantial number of studies have been done on patients with TSH levels between 2.5 and 4.5, indicating beneficial response in atherosclerosis risk factors such as atherogenic lipids (120-123), impaired endothelial function (124, 125), and intima media thickness (126). However, there are virtually no clinical outcome data to support treating patients with subclinical hypothyroidism with TSH levels between 2.5 and 4.5 mU/L.

The possible exception to this statement is pregnancy because the rate of pregnancy loss, including spontaneous miscarriage before 20 weeks gestation and stillbirths after 20 weeks, have been reported to be increased in anti-thyroid antibody-negative women with TSH values between 2.5 and 5.0 (127).

**L-thyroxine treatment of hypothyroidism**

Dose adjustments are guided by serum TSH determinations 4–8 weeks (156,170) following initiation of therapy, dosage adjustments, or change in the L-thyroxine preparation (139,171). While TSH levels may decline within a month of initiating therapy with doses of L-thyroxine such as 50 or 75 μg, making adjustments with smaller doses may require 8 weeks or longer before TSH levels begin to plateau (170,172). Increment changes of 12.5–25 μg/d are initially made, but even smaller changes may be necessary to achieve goal TSH levels.
Patients with serum TSH concentrations of 3–4.5 mU/L

Patients with serum TSH concentrations in this range can have increased rates of progression to overt hypothyroidism, therefore they should be monitored with periodic thyroid function tests, especially if they have positive antithyroid peroxidase antibodies.

During pregnancy, serum TSH concentrations of more than 2.5 mU/L during the first trimester and of 3.1–3.5 mU/L during the second trimester are probably indicative of mild hypothyroidism.

Pregnant women should be treated if they have TSH concentrations at the upper limit of the normal range for women who are not pregnant (132,133).

Women in a euthyroid state who have autoimmune thyroiditis in early gestation should be monitored during pregnancy for raised serum TSH concentrations during pregnancy (132,133). Alternatively, such women could be treated with thyroid hormone, because findings of a prospective randomised trial showed a decrease in miscarriage rates with treatment (134).
• Patients with mild subclinical hypothyroidism, with serum TSH concentrations of 5–9 mU/L

• Subclinical hypothyroidism might be associated with greater cardiovascular risk in young and middle-aged people than in people older than 65 years (7) and therefore treatment is probably most justifiable in this age-group. Furthermore, patients aged 61–80 years might not benefit because small increases in serum TSH (eg, TSH concentrations of 5–8 mU/L) are not indicative of true thyroid hormone deficiency in many cases (84). Last, raised serum TSH concentrations might be associated with decreased mortality in people older than 85 years (44).

• Patients with new onset of symptoms (5), depression, goitre, positive antithyroid antibody tests, or cardiovascular risk factors (eg, hypertension, hypercholesterolaemia, insulin resistance or diabetes, or isolated diastolic dysfunction) might also benefit from treatment. If levothyroxine replacement has a beneficial effect, treatment should be continued and serum TSH concentrations should be assessed every 6–12 months to ensure that they remain within the normal range. Patients can progress to overt hypothyroidism, therefore increases in levothyroxine might be needed during follow-up. In the absence of clear-cut beneficial effects, replacement therapy should be stopped, and serum TSH concentrations should be assessed at yearly intervals. Available evidence (44,84) suggests that the benefit of treatment might be reduced in patients older than 65 years with serum TSH concentrations of 4·5–10 mU/L; if levothyroxine treatment is started, low doses (25–50 μg/day) should be used in patients with known coronary artery disease.

• Treatment of mild subclinical hypothyroidism is not recommended in elderly (older than 75 years) and very elderly (older than 80 years) patients because, aside from an increased risk of congestive heart failure in patients with serum TSH concentrations of more than 7–10 mU/L, there is no evidence that these patients are symptomatic, and levothyroxine treatment does not improve cognitive function or quality of life.
• Patients with subclinical hypothyroidism with serum TSH concentrations of 10 mU/L or higher.

• Patients with high TSH concentrations have a significantly increased risk of progression to overt hypothyroidism, might be more frequently symptomatic, and might have an increased likelihood of cardiovascular disease.

• Treatment with levothyroxine is recommended in these patients. Replacement therapy should be individualised in elderly and very elderly patients with serum TSH concentrations of more than 10 mU/L. Low doses of levothyroxine are often adequate to normalise serum TSH concentrations in elderly patients. The target TSH serum concentration might be higher in individuals older than 70 years than in younger patients, to mimic physiological values (e.g., 4–7 mU/L).

• Over-treatment with levothyroxine should be avoided because of the adverse cardiovascular and skeletal consequences of iatrogenic hyperthyroidism in elderly people. (8)

• Nonostante l’assenza di linee guida specifiche, nel corso degli ultimi anni sono stati pubblicati alcuni studi pediatrici significativi sulla storia naturale dell’ipotiroidismo subclinico in bambini e adolescenti. In una recente review, Monzani et al. hanno raccolto con criteri molto rigorosi i possibili effetti del trattamento ormonale sostitutivo [3]. Sono stati selezionati 9 studi, per un totale di 4.018 bambini esaminati, i cui risultati vengono in parte riportati nelle Tabelle 1 e 2. Nonostante gli studi siano eterogenei per eziologia dell’ipotiroidismo subclinico (autoimmune e non autoimmune), numero ed età dei pazienti esaminati e range di livelli di TSH, l’informazione che ne deriva è abbastanza chiara.

Nell’ipotiroidismo subclinico non su base autoimmune [Tabella 1] la progressione verso l’ipotiroidismo franco è molto bassa (0-13%) e una percentuale non indifferente di casi, a volte superiore al 50%, ha un’evoluzione verso l’eutiroïdismo. Quindi, bisogna pensare alla possibilità che si tratti di forme transitorie di ipotiroidismo subclinico e monitorizzare la situazione.

• Dati simili sono emersi anche dagli studi fatti sull’ipotiroidismo su base autoimmune [Tabella 2] dovuto alla tiroidite cronica linfocitaria. In questo caso l’evoluzione verso l’ipotiroidismo clinico è leggermente maggiore (5,5-39%), ma non elevatissima; invece, in una percentuale non indifferente di casi, si assiste a un’evoluzione verso l’eutiroïdismo (21,9-41%). Anche nella tiroidite cronica linfocitaria, quindi, l’atteggiamento prevalente deve essere quello di monitoraggio.
La storia naturale della tiroidite cronica linfocitaria ci dice che il 28% dei bambini va incontro a remissione, il 34% diventa ipotiroido clinico e il 28% resta ipotiroido subclinico, nel follow-up da 3 a 5 anni [1].

La storia naturale della tiroidite autoimmune è stata esaminata anche nello studio prospettico effettuato da Radetti et al. [5] su 160 bambini (età media di 9 anni) affetti da tiroidite cronica autoimmune. I risultati di questo studio indicano che il 65% dei soggetti che erano eutiroidei alla prima osservazione restava eutiroideo a distanza di 5 anni, il 25% diventava ipotiroido clinico e il 9,5% evolva verso l’ipotiroidismo subclinico. Tra i 55 bambini con ipotiroidismo subclinico alla prima osservazione, il 29% dei bambini andava incontro a remissione, il 42% diventava ipotiroido clinico e il 29% restava ipotiroido subclinico, nel follow-up a 5 anni. Quindi, poiché l’ipotiroidismo subclinico della tiroidite cron. linf. può essere reversibile anche a distanza di alcuni anni, si rende indispensabile eseguire il follow-up.

Al momento, c’è un’ indicazione generale a trattare bambini con valori di TSH >10 mU/L poiché i dati della letteratura sono concordi nell’ affermare che questa situazione nell’ adulto è associata a un maggior rischio di progressione verso l’ ipotiroidismo clinico, le malattie cardiovascolari, le dislipidemie e la depressione. Resta invece controverso l’ atteggiamento nelle forme con TSH tra 5 e 10 mU/L.

In conclusione, pensiamo che siano necessari in futuro studi randomizzati controllati sugli effetti della terapia sulla sfera neuropsichica, sulla funzione cardiaca, sul profilo lipidico e sulla mineralizzazione ossea.