Inquadramento del problema del malassorbimento intestinale della L-tiroxina. Implicazioni di risparmi per il Servizio Sanitario Nazionale.

Salvatore Benveniga
S.B. ha ricevuto sostegno per la ricerca da parte di IBSA.
When to consult an endocrinologist

Although most physicians can diagnose and treat hypothyroidism, consultation with an endocrinologist is recommended in the following situations:

- Children and infants
- Patients in whom it is difficult to render and maintain a euthyroid state
- Pregnancy
- Women planning conception
- Cardiac disease
- Presence of goiter, nodule, or other structural changes in the thyroid gland
- Presence of other endocrine disease such as adrenal and pituitary disorders
- Unusual constellation of thyroid function test results
- Unusual causes of hypothyroidism such as those induced by agents listed in Table 10.

From S. Benvenga. When thyroid hormone replacement is ineffective? *Curr Opin Endocrinol Diabetes Obes* 20: 467-77, 2013

«Approximately 20% of patients receiving L-T4 have TSH levels above the reference range and approximately 20% have TSH levels below that range [7]. In over 2000 L-T4 treated adult patients with primary hypothyroidism [9,10], 28.2% were undertreated (TSH > 4.0 mu/L), and 14.4% were overtreated (TSH <0.4 mU/L) [9].

Undertreated patients (including both subclinically and overtly hypothyroid patients) had a worse quality of life than adequately treated patients (TSH between 0.4 and 4.0 mU/L), regardless of their degree of undertreatment (subclinical or overt hypothyroidism) [10]«.
Università degli Studi di Messina
Programma di Ricerca "Ordinario" 2008/2009
(Bando Rettorale del 29/03/2010)
Prot. ORME097F7LL

1.1 Area Scientifico-Disciplinare su cui insiste il programma di ricerca 06 - Scienze mediche

1.2 Tipologia della ricerca Sperimentale

1.3 Titolo del Programma di Ricerca

EPIDEMIOLOGIA LOCALE DEL RIDOTTO ASSORBIMENTO INTESTINALE DELLA L-TIROXINA CAUSATO DA IMPROPRIA MODALITA’ DI ASSUNZIONE E DA BEVANDE, FARMACI/INTEGRATORI ALIMENTARI.

1.5 Responsabile Scientifico del programma di Ricerca

BENVENGA  Salvatore  Professore ordinario  MED/13

Firma .................................................................

Data 19/04/2010 09:59
1.3 Titolo del Programma di Ricerca

EPIDEMIOLOGIA LOCALE DEL RIDOTTO ASSORBIMENTO INTESTINALE DELLA L-TIROXINA CAUSATO DA IMPROPRIA MODALITÀ DI ASSUNZIONE E DA BEVANDE, FARMACI/INTEGRATORI ALIMENTARI.

1.10.7 Personale extrauniversitario dipendente da altri Enti

<table>
<thead>
<tr>
<th>n°</th>
<th>Cognome</th>
<th>Nome</th>
<th>Ente</th>
<th>Qualifica</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alecci</td>
<td>Umberto</td>
<td>Azienda Sanitaria Provinciale (ASP) Messina</td>
<td>Medico Med Gen</td>
</tr>
<tr>
<td>2</td>
<td>Inferrera</td>
<td>Santi</td>
<td>Azienda Sanitaria Provinciale (ASP) Messina</td>
<td>Medico Med Gen</td>
</tr>
<tr>
<td>3</td>
<td>Marino</td>
<td>Sebastiano</td>
<td>Azienda Sanitaria Provinciale (ASP) Messina</td>
<td>Medico Med Gen</td>
</tr>
</tbody>
</table>
ALCUNE REAZIONI, DA PARTE DEI MEDICI DI MED. GENERALE E DEGLI ENDOCRINOLOGI CHE MI INDIRIZZARONO I PAZIENTI, ALLA DIAGNOSI DI INCONGRUA MODALITA’ DI ASSUNZIONE DELLA L-T4 O DI INTERFERENZA ALIMENTARE/FARMACOLOGICA.

• Ma dove è scritto sul foglietto illustrativo?
• Ho ricontrollato sulla scheda tecnica e sulla Guida all’Uso dei Farmaci, e l’interferenza di questo farmaco non c’è scritta!
• Neanche il collega che seguiva il caso prima di me lo sapeva!
• L’informatore scientifico non me ne ha parlato!
• Ma nel foglietto illustrativo c’è scritto che la compressa va assunta “preferibilmente a digiuno”. “Preferibilmente” non significa “obbligatoriamente”.
• Nel bugiardino non c’è scritto quanto tempo prima della colazione bisogna assumere la compressa
INAPPROPRIATA GESTIONE DI UNA PAZIENTE INVIATAMI PER “REFRATTARIETÀ DEL TSH ALLA TERAPIA CON L-TIROXINA”

- **Ripetizione** dei dosaggi ormonali:
  - T3 e/o T4 = 16 volte
  - FT3 e FT4 = 19 volte
  - TSH = 34 volte (TRH test 5 volte)

- **Ripetizione** di indagini strumentali:
  - Scintigrafia tiroidea = 3 volte
  - Ecografia tiroidea = 3 volte
  - TAC sella turcica = 2 volte

*Just ask! (basta chiedere!)*


Ercole I, Sali DI FERRO ??


Ercole IL CARBONATO DI CALCIO ??

Schneyer CR. *JAMA* 279: 750, 1998

Cause farmacologiche di aumentata richiesta di L-T4

- Differenti **classi farmacologiche** possono influenzare la dose-efficacia di **L-T4** con diversi meccanismi

<table>
<thead>
<tr>
<th>RIDUZIONE ACIDITA' GASTRICA</th>
<th>ADSORBIMENTO NEL LUME INTESTINALE</th>
<th>ACCELERATO CATABOLISMO DELLA T4</th>
<th>↑ LEGAME ALLE PROTEINE PLASMATICHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inibitori Pompa Protonica</td>
<td>Solfato ferroso</td>
<td>Carbamazepina</td>
<td>Estrogeni</td>
</tr>
<tr>
<td>Sucralfato</td>
<td>Sequestranti degli acidi biliari</td>
<td>Fenitoina</td>
<td>Raloxifene</td>
</tr>
<tr>
<td>Idrossido di Alluminio</td>
<td>Resine a scambio ionico</td>
<td>Fenobarbitale</td>
<td></td>
</tr>
<tr>
<td>Idrossido di Magnesio</td>
<td>Chelanti dei fosfati</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcio Carbonato</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VARIABILI IN GIOCO

**Fig. 1.** Serum concentration of thyrotropin (TSH), free thyroxine (FT₄), and free triiodothyronine (FT₃) observed during 2 weeks of large daily intake of papaya fruit in a patient on long-term levothyroxine therapy (dosage, 1.6 mg/kg daily) after total thyroidectomy. Bars on the vertical axes represent normal ranges of TSH, FT₄, and FT₃.
WHERE L-THYROXINE TAKEN ORALLY IS ABSORBED (Hays MT, 1994)

Wenzel KW, Kirschsieper HE.
Aspects of the absorption of oral L-thyroxine in normal man.

Duodeno: 21%
Digiuno: 45%
Ileo: 34%
(α) Al mattino, stomaco vuoto, 1 h prima di colazione.

(β) Al mattino, con la colazione

(γ) La sera, 2 ore dopo cena

Statistica sul TSH
(α) P<0.001 vs. (β) e (γ)
(β) P= 0.026 vs. (γ)

Bach-Huynh T-G et al. Timing of levothyroxine administration affects serum thyrotropin concentration. *JCEM 94:3905-12, 2009*


Significant ↑ of serum TSH over 6 months in hypothyroid subjects taking L-T4 and lansoprazole.


Fig. 2- Effect of long-term omeprazole treatment on serum Thyrotropin levels in 10 patients simultaneously treated with Thyroxine.
Casi di “Malassorbimento” (n= 20) della L-T4 giunti alla osservazione in 12 mesi in ambulatorio *
(S. Benvenga. Curr Opin Endocrinol Diab Obes 20: 467-77, 2013)

* 20 su circa 210 nuovi pazienti in terapia con L-T4 osservati in quei 12 mesi= 9.5%.

Coinvolgimento di farmaci in 13 su 20 (65%)

- Pseudomalassorbimento : 1
- Assorbimento lento (ritardato) : 5
- Incongrua assunzione (DURANTE o DOPO colaz.): 3
- Interferenza da fibre alimentari: 1
- Interferenza da caffè: 4
- Interferenza da caffè + farmaco (inib. p. proton.): 1
- Interferenza monofarmacologica: 6, di cui
  - Sali di ferro : 1
  - Carbonato di calcio : 2
  - Inibitori pompa protonica : 3
- Interferenza plurifarmacologica: 2, di cui
  - Sali di ferro + inibit. pompa protonica: 1
  - Carbonato di calcio + inibit. pompa protonica: 1
- Patologie intestinali : 4, di cui
  - Celiachia: 3
  - Enterite di Crohn: 1
Average number of serum assays for TSH, FT4 or FT3 before observation in 13 outpatients observed for L-T4 malabsorption due to coffee and/or drugs, and related costs in the simulated number of patients *.

<table>
<thead>
<tr>
<th>Mean no. of assays</th>
<th>Number of patients</th>
<th>Costs (in Euro) for performing assays in the specified no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1,000</td>
</tr>
<tr>
<td>TSH (€ 16)</td>
<td>8</td>
<td>€ 128</td>
</tr>
<tr>
<td>FT4 (€ 16)</td>
<td>5</td>
<td>€ 80</td>
</tr>
<tr>
<td>FT3 (€ 16)</td>
<td>5</td>
<td>€ 80</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18</td>
<td>€ 288</td>
</tr>
</tbody>
</table>

* The 13 patients were observed over a 12-month period of time. Assays are those performed prior to our observation.
### Comparison of formulas

<table>
<thead>
<tr>
<th>Tablet #1</th>
<th>Tablet #2</th>
<th>Oral solution, drops</th>
<th>Soft gel capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>lattosio monoidrato, amido di mais, gelatina, croscarmellosio sodico, magnesio stearato</td>
<td>fosfato di calcio bibasico, sodio carbossimetilamido, magnesio stearato, cellulosa microcristallina, talco, acido citrico, amido di mais</td>
<td>etanolo, glicerina</td>
<td>gelatina, glicerolo</td>
</tr>
</tbody>
</table>
**ACCUMULATING LITERATURE** on the **liquid formulation of L-T4**

  **Conclusion.** Our study confirms that LT4-OS could have an increased absorption rate in comparison to LT4 tablets, especially when other factors interfering with LT4 absorption are present.

  **Conclusions.** The use of L-thyroxine liquid formulation compared to tablet resulted in a significantly higher number of hypothyroid patients who maintained the euthyroid state in a 12 months of follow up, and a reduced variability in TSH values.

  **Conclusion.** Oral liquid L-T₄ formulations could diminish the problem of L-T₄ malabsorption caused by coffee when using traditional tablet formulations.

  **Conclusions.** Our data showed that liquid L-T₄ formulation can be administered directly through feeding tube with no need for an empty stomach, with a significant improvement in therapy preparation and administration by nurses.

  **Conclusion.** The liquid formulation and the softgel formulation represent an innovative, effective and cheap therapeutic approach to hypothyroid patients with problems of impaired absorption of levothyroxine.
### Chronologic sequence in one patient (S Benvenga - personal observation, unpublished)

<table>
<thead>
<tr>
<th>TSH (mU/L)</th>
<th>formulation</th>
<th>L-T4 dose</th>
<th>PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>75</strong> *</td>
<td>tablet</td>
<td>525 µg/week (75 µg/d)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>9.8</strong></td>
<td>tablet</td>
<td>700 µg/week (100 µg/d)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>16.5, 18.9</strong></td>
<td>tablet</td>
<td>700 µg/week (100 µg/d)</td>
<td>YES</td>
</tr>
<tr>
<td><strong>4.1</strong></td>
<td>tablet</td>
<td>700 µg/week (100 µg/d)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>9.3 – 5.5</strong> (6.3, 7.8)</td>
<td>tablet</td>
<td>700 → 925 µg/week (800 µg/week)</td>
<td>YES</td>
</tr>
<tr>
<td><strong>0.04 ^ – 4.5 § (4.0)</strong></td>
<td>tablet</td>
<td>925 → 700 week (800 µg/week)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>2.6</strong></td>
<td>Liquid</td>
<td>700 wk (100 µg/d = 28 drops/d)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>3.0, 3.3</strong></td>
<td>Liquid</td>
<td>700 wk (100 µg/d = 28 drops/d)</td>
<td>YES</td>
</tr>
<tr>
<td><strong>1.7</strong></td>
<td>Liquid</td>
<td>800 wk (114.3 µg/d = 32 drops/d)</td>
<td>YES</td>
</tr>
<tr>
<td><strong>1.3 – 1.6</strong></td>
<td>Liquid</td>
<td>800 wk (114.3 µg/d = 32 drops/d)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>1.3 – 1.9</strong></td>
<td>Liquid</td>
<td>800 wk (114.3 µg/d = 32 drops/d)</td>
<td>YES</td>
</tr>
<tr>
<td><strong>1.4</strong></td>
<td>Liquid</td>
<td>800 wk (114.3 µg/d = 32 drops/d)</td>
<td>NO</td>
</tr>
</tbody>
</table>

*Pre-therapy. In view of this value, L-T4 therapy was started.

^ Clinically and biochemically hyperthyroid (TSH= 0.04 mU/L).

§ In view of this value (4.2 mU/L), switch of formulation was started.
Head-to-head comparison between tablet and liquid formulation [data rearranged from previous table] (S Benvenga - personal observation, unpublished)

<table>
<thead>
<tr>
<th>Dose (µg/wk)</th>
<th>Formulation</th>
<th>PPI</th>
<th>TSH (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>700</td>
<td>tablet</td>
<td>NO</td>
<td>4.1 – 9.8</td>
</tr>
<tr>
<td>700</td>
<td>Liquid</td>
<td>NO</td>
<td>2.6</td>
</tr>
<tr>
<td>700</td>
<td>tablet</td>
<td>YES</td>
<td>16.5, 18.9</td>
</tr>
<tr>
<td>700</td>
<td>Liquid</td>
<td>YES</td>
<td>3.0, 3.3</td>
</tr>
<tr>
<td>800</td>
<td>tablet</td>
<td>NO</td>
<td>4.0</td>
</tr>
<tr>
<td>800</td>
<td>Liquid</td>
<td>NO</td>
<td>1.3 – 1.6</td>
</tr>
<tr>
<td>800</td>
<td>tablet</td>
<td>YES</td>
<td>6.3, 7.8</td>
</tr>
<tr>
<td>800</td>
<td>Liquid</td>
<td>YES</td>
<td>1.3 – 1.9</td>
</tr>
</tbody>
</table>

Overall variation under 700 µg/wk: tablet = 4.6-fold (4.1 to 18.9 mU/L); Δ = 14.8 mU/L
Liquid = 1.3-fold (2.6 to 3.3 mU/L); Δ = 0.7 mU/L

Overall variation under 800 µg/wk: tablet = 2.0-fold (4.0 to 7.8 mU/L); Δ = 3.8 mU/L
Liquid = 1.3-fold (1.3 to 1.9 mU/L); Δ = 0.6 mU/L
Vita R, Saraceno G, Trimarchi F, Benvenga S. Levothyroxine From the Tablet to the Oral Solution Formulation Corrects the Impaired Absorption of Levothyroxine Induced by Proton-Pump Inhibitors. JCEM 99:4481-6, 2014

Figure 1. Serum TSH values (means SD) with LT4 therapy (□, tablet LT4; ●, oral solution) while maintaining therapy with PPIs. The switch was performed at the same daily dose.
Figure 2. The serum TSH trend over time with the tablet formulation or the oral solution LT4 while maintaining therapy with PPIs in individual patients.

So that the figure is not too complicated, the illustrated TSH level with tablet LT4 is the individual mean level.
Roux-en-Y gastric bypass
TSH levels of 7 patients treated with gastric bypass were elevated after the operation (from 2 to 7 months later). After switching (with the same dosage, 30 minutes before breakfast) from oral tablets to a liquid formulation, TSH was significantly reduced. TSH was evaluated 1-3 months after the switch: it significantly reduced from 5.2±3.9 to 2.4±2.5 µIU/ml, p<0.05

Biliary Pancreatic Roux-en-Y gastric bypass diversion
TSH levels of 3 patients treated with biliary pancreatic diversion were elevated after the operation (from 2 to 7 months later). After switching (with the same dosage, 30 minutes before breakfast) from oral tablets to a liquid formulation, TSH was significantly reduced. TSH was evaluated 1-3 months after the switch: it significantly reduced from 7.7±1.7 to 4.1±1.8 µIU/ml, p<0.05.
R Vita, G Saraceno, F Trimarchi, S Benvenga. In patients with no interference on the intestinal absorption of L-T4 caused by gastro-intestinal disorders or drugs, a liquid formulation of L-T4 permits to reach target TSH levels that were missed by the conventional tablet formulation. Annual Meeting of The European Thyroid Association (ETA) 2012, Pisa.

Fig. 1 – Comparison of TSH serum levels before therapy (black bar) and under L-T4 as tablets (red bar) or liquid formulation (blue bar) at the same daily dose. Blood was drawn after 5 months minimum of therapy with the liquid formulation.
R. Vita, S. Benvenga. Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in soft gel capsule. *Endocr Pract* 20: e38-41, 2014

<table>
<thead>
<tr>
<th>mcg/day</th>
<th>Tablet</th>
<th>Soft Gel capsule</th>
<th>Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td>125</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TSH, mU/L</th>
<th>Tablet</th>
<th>Soft Gel capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 4.0</td>
<td></td>
<td>0.46 vs. 2.4</td>
</tr>
<tr>
<td>2.4</td>
<td></td>
<td>2.35 vs. ≥ 4.0</td>
</tr>
<tr>
<td>0.6</td>
<td></td>
<td>3.2, 4.5</td>
</tr>
</tbody>
</table>

Serum TSH before starting L-T4 therapy: > 6.8 mU/L. **PPI = pantoprazol**

4 hour acute oral loading test (600 mcg L-T4, either tablet or capsule)

<table>
<thead>
<tr>
<th></th>
<th>Tablet</th>
<th>Soft Gel Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-4h</td>
<td>12710</td>
<td>16240 (+ 27.8%)</td>
</tr>
<tr>
<td>Cmax</td>
<td>73</td>
<td>108 (+ 48%)</td>
</tr>
<tr>
<td>Tmax</td>
<td>180</td>
<td>120 (60 min faster)</td>
</tr>
</tbody>
</table>

With tablets and coffee
1 h later
TSH was 0.28 ± 0.20
Le cp di L-T4 vanno assunte con acqua al mattino, 1 ora prima di colazione (o del solo caffè).

In alcuni pazienti, l’intervallo rispetto alla colazione deve essere superiore.

Alcuni farmaci interferiscono con l’assorbimento intestinale della L-T4.

Per vari pazienti, i tempi e/o le modalità di assunzione della L-T4, e/o tempi dell’assunzione di farmaci che interferiscono sull’assorbimento intestinale della L-T4 mal si conciliano con le loro abitudini di vita.

In Italia è già disponibile una formulazione liquida di L-T4 (soluzione in alcol etilico e glicerolo).

Ne abbiamo già testato l’efficacia (cioè resistenza all’interferenza) nei confronti degli inibitori di pompa protonica e del malassorbimento da causa ignota [per altri farmaci, per caffè, etc..., studi in corso].

In Italia è disponibile anche la formulazione come “capsula molle”.

Ne abbiamo già testato l’efficacia nei confronti del caffè e degli inibitori di pompa protonica [altri studi avviati].

### Discussed in the text, but do not appear in the list of recommendations

<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 T₄, 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>
</tr>
<tr>
<td>Which patients 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.
Prevalence of DTC or PTC according to serum TSH concentrations

Boelaert K et al, JCEM 2006

Boelaert K et al, JCEM 2006

Fiore et al, ERC 2009


Fig 2. Age-specific TSH targets among survey participants.

FIG. 1. A, Prevalence of malignancy in relation to patients’ age.

Prevalence of DTC or PTC according to serum TSH concentrations
Rate of correction
- Usual technique for correcting overt hypothyroidism:
  38.5% would gradually restore euthyroidism
  33.6% would select an empiric dose adjusted to achieve target levels,
  27.8% would start with a calculated full-replacement dose.

- Regional differences, with a greater use of a gradual approach outside of North America. Gradual approach would be used by:
  30.5% of North Americans
  46.8% of Middle East-Africans (P = .081)
  55.1% of Asia-Oceania respondents (P < .001)
  55.8% of Europeans (P < .001)
  60.5% of Latin Americans (60.5%, P < .001)

- For respondents preferring a gradual restoration of euthyroidism, most (61.1%) would increase in increments of 25 µg, followed by 50 µg (26.9%), and 12.5 µg (12.0%).

  The frequency of incremental increases was 6 weeks (35.7%), 4 weeks (23.0%), 2 weeks (20.5%), 8 weeks (18.0%), and 12 weeks (2.8%).

Preferred initial thyroid hormone preparation
• 99.2% would use L-T4, precisely:
  49.9% would use brand
  49.3% would use a generic
• 0.8% would use combined L-T4/L-T3
• 0% would use thyroid extracts

Regional differences for use of brand name L-T4
58.8% Europe
58.2% Asia-Oceania
58.0% Latin America
56.3% Middle East-Africa
37.9% North America (P < 0.001 vs all of the above)
Follow-up testing and dose adjustment

- Specific testing at the time of follow-up:
  TSH (98.7% of respondents),
  FT4 (59.9%),
  FT3 (7.8%), or total T3 (3.4%).

- Rechecking time of thyroid function tests after starting thyroid hormone therapy
  49.2% would recheck after 6 weeks,
  25.7% after 8 weeks,
  16.0% after 4 weeks,
  8.0% after 12 weeks,
  1.1% after 2 weeks

Long-term follow-up

- After achieving stable target TSH values, respondents were asked how often they would repeat thyroid laboratory testing.
  55.5% would obtain laboratory studies at 6-month intervals,
  34.0% at 12 months,
  9.3% at 3 months,
  1.2% at <3 months.
Initial management of persistent subclinical hypothyroidism in non-pregnant adults: persistent subclinical hypothyroidism describes patients with elevated serum TSH and within reference range serum FT4 on two occasions separated by at least 3 months. This algorithm is meant as a guide and clinicians are expected to use their discretion and judgement in interpreting the age threshold around 70 years.

* Depending on circumstances, individuals with goitre, dyslipidaemia, and diabetes may also be considered for treatment, along with those with planning pregnancy in the near future.

- (1) There are two categories of SCH according to the elevation in serum TSH level: mildly increased TSH levels 4.0–10.0 mU/L, and more severely increased TSH value (>10 mU/L). 2S
- (4) In younger SCH patients (<65 years; serum TSH <10 mU/L) with symptoms suggestive of hypothyroidism, a trial of L-thyroxine replacement therapy should be considered. 2W
- (5) There is limited evidence for improvement in mental function with LT-4 treatment of SCH in younger individuals. 3W
- (6) Following hemithyroidectomy, persistent SCH should be treated with L-T4 to normalise TSH levels. 2S
- (7) Patients with persistent SCH and diffuse or nodular goitre should be treated with L-T4 replacement with the aim of normalising serum TSH levels. 2W
- (8) There is no evidence for a favourable effect of L-T4 therapy on body weight in obese subjects with serum TSH levels <10 mU/L and normal FT4 concentrations. 3S

The quality of the literature concerning each aspect of the statement was graded as high (randomised controlled trial (RCT) evidence – level 1); moderate (intervention short of RCT or large observational studies – level 2), or low quality (case series, case reports, expert opinion – level 3) using modified GRADE criteria [4, 5].

The strength of each statement was classified as strong (S – a recommendation) or weak (W – a suggestion), depending upon the clinical significance and weight of opinion favouring the statement. Strong recommendations are clinically important best practice and will be applied to most patients in most circumstances, whereas weak statements should be considered by the clinician and will be applicable best practice only to certain patients or in certain circumstances.
• (9) In patients with type 1 diabetes mellitus, serum TSH should be monitored, once yearly. 3S

• (10) In patients with type 2 diabetes mellitus and an unexplained change in glycaemic control, serum TSH and FT4 should be measured. 3W

• (11) L-T4 therapy of SCH is able to reduce the levels of both total and LDL cholesterol, although normalisation of serum lipids is seldom achieved. 2S

• (12) The effect of L-T4 replacement on serum lipid concentrations is more pronounced in patients with pretreatment serum TSH value >10 mU/L. 1S

• (13) Even in the absence of symptoms, replacement therapy with L-T4 is recommended for younger patients (<65 years) with serum TSH >10 mU/L 2S

• (14) Age-specific reference ranges for serum TSH should be considered in order to establish a diagnosis of SCH in older people. 2S

• (15) The oldest old subjects (>80–85 years) with elevated serum TSH ≤ 10 mU/L should be carefully followed with a wait-and-see strategy, generally avoiding hormonal treatment. 3S
• (16) If the decision is to treat SCH, then oral L–T4 administered daily, is the treatment of choice. There is no evidence to support use of liothyronine (L-T3) or combined L–T4L–T3 in the treatment of SCH. 1S

• (17) For patients without cardiac disease, a weight-related dose of L–T4 should be used, approximating to 1.5 μg/kg/day (e.g. 75 or 100 μg/day for a woman, 100 or 125 μg for a man). 1S

• (18) For patients with cardiac disease and in the elderly, a small dose of L–T4 should be started, 25 or 50 μg daily. The dose of L–T4 should be increased by 25 μg/day every 14–21 days until a full replacement dose is reached. 3S

• (19) L–T4 should be taken on an empty stomach, either first thing in the morning, an hour before food, or at bedtime, 2 h or more after the last food. Medications causing interference with L–T4 absorption (calcium and iron salts, proton pump inhibitors, etc.) should be avoided, or taken 4 h or more after L–T4 ingestion. 2S
• (20) The serum TSH should be re-checked 2 months after starting L–T4 therapy, and dosage adjustments made accordingly. The aim for most adults should be to reach a stable serum TSH in the lower half of the reference range (0.4–2.5 mU/L). 2W

• (21) In the elderly, any treatment for SCH should be individualised, gradual and closely monitored. 2S

• (22) For older patients (>70–75 years), a higher treatment target for serum TSH (around 1–5 mU/L) is acceptable. 3W

• (23) For patients with mild SCH (serum TSH <10 mU/L) who have been started on L–T4 for symptoms attributed to SCH, response to treatment should be reviewed 3 or 4 months after a serum TSH within the reference range is reached. If there is no improvement in symptoms, L–T4 therapy should generally be stopped. 3W

• (24) If thyroid function has normalised following an initially abnormal serum TSH result, then no further testing is required in those who are asymptomatic, have negative thyroid autoantibodies or do not have goitre. 2S

• (25) In those who have persistent SCH but in whom treatment is not commenced, thyroid function should be tested 6 monthly for the first 2 years and then yearly thereafter. 2W

• (26) Once patients with SCH are commenced on L-T4 treatment, then serum TSH should be monitored at least annually thereafter. 2S
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