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-

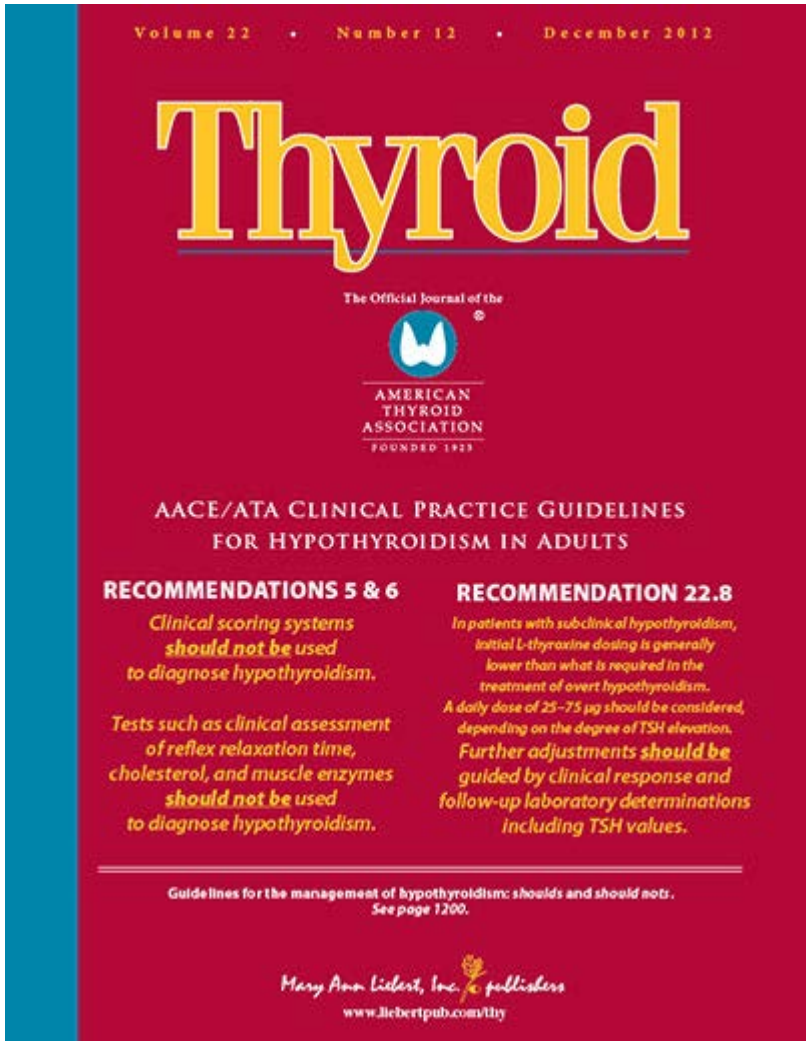
Accusa.

Perché, chi e quando trattare

Ricerca su PubMed (al 15.03.2014)

Stringa	Numero di articoli su PubMed	Numero di articoli su Google
Subclinical hypothyroidism	2.514	332.000
Therapy of subclinical hypothyroidism	1.212	318.000

Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association



THYROID
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ORIGINAL STUDIES, REVIEWS, AND SCHOLARLY DIALOG

THYROID FUNCTION AND DYSFUNCTION

Pages 1200-1235

Jeffrey R. Garber,[1,2,*] Rhoda H. Cobin,[3] Hossein Gharib,[4] James V. Hennessey,[2] Irwin Klein,[5] Jeffrey I. Mechanick,[6] Rachel Pessah-Pollack,[6,7] Peter A. Singer,[8] and Kenneth A. Woeber[9]

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

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EDITORIALS AND COMMENTARY

EDITORIAL

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

Charles H. Emerson

Garber JR et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association *Thyroid 22: 1200-1235, 2012*

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]

Wiersinga WM et al. ETA2012 Guidelines: The use of L-T4+L-T3 in the treatment of hypothyroidism. *Eur Thyroid J 1: 55-71, 2012*

Recommendations:

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

•I t is recommended that L-T4 monotherapy remains the standard treatment of hypothyroidism (1/+ ++).

Garber JR et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. ***Thyroid 22: 1200-1235, 2012.***

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

Item	Text (with reference number)
Daily dosage of L-T4	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.
Dose adjustments	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.

Garber JR et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. ***Thyroid 22: 1200-1235, 2012.***

Question	Guidelines Recommendation [and recommendation number]
Which patients with TSH levels above a given laboratory's reference range should be considered for treatment with L-T4 ?	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]
In patients with hypothyroidism being treated with L-thyroxine, what should the target TSH ranges be?	… 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]
In patients with hypothyroidism being treated with L-thyroxine who are pregnant, what should the target TSH ranges be?	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]

Garber JR et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid 22: 1200-1235, 2012.*

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

Item	Text (with reference number)
When to treat hypothyroidism	Although there is general agreeement 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 betwee 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.

DS Cooper, B Biondi. Subclinical thyroid disease. *Lancet* 2012; 379: 1142–54

- **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).

DS Cooper, B Biondi. Subclinical thyroid disease. *Lancet* 2012; 379: 1142–54

- **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**.

DS Cooper, B Biondi. Subclinical thyroid disease. *Lancet* 2012; 379: 1142–54

- **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** (**eg, 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)

A. Cassio. Storia naturale dell'ipotiroidismo subclinico ed effetti della terapia in età pediatrica: aspetti generali. ***In: 1° Forum di Endocrinologia della Fondazione IBSA (Baveno-Stresa, 10-12 Maggio 2013) dedicato a : IPOTIROIDISMO SUBCLINICO Il trattamento terapeutico nel bambino, nella donna e nell'adulto.***

- 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'eutiroidismo**. 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'eutiroidismo (21,9-41%).** Anche nella **tiroidite cronica linfocitaria**, quindi, **l'atteggiamento prevalente deve essere quello di monitoraggio**.

M Tonacchera. **Ipotiroidismo subclinico nell'adolescenza.** ***In: 1° Forum di Endocrinologia della Fondazione IBSA (Baveno-Stresa, 10-12 Maggio 2013) dedicato a : IPOTIROIDISMO SUBCLINICO Il trattamento terapeutico nel bambino, nella donna e nell'adulto***

- La **storia naturale** della **tiroidite cronica linfocitaria** ci dice che il **28%** dei bambini va incontro a **remissione**, il **34% diventa ipotiroideo clinico** e il **28% resta ipotiroideo 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 ipotiroideo clinico e il **9,5% evolveva 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 ipotiroideo clinico** e il **29% restava ipotiroideo 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**.

1 Rallison ML, Dobyns BM, Meikle AW, Bishop M, Lyon JL, Stevens W. Natural history of thyroid abnormalities: prevalence, incidence, and regression of thyroid diseases in adolescents and young adults. *Am J Med 1991 Oct;91(4):363-70*.
5 Radetti G, Gottardi E, Bona G, Corrias A, Salardi S, Loche S; Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ ISPED). The natural history of euthyroid Hashimoto's thyroiditis in children. *J Pediatr 2006 Dec;149(6):827-32*.

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- 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.**


Thank you!
MERCI
Thanks
Grazie
danke
Arigatou


ARMY