Diagnosi e Cura delle Tireopatie
Padova, 25 Febbraio 2013

La Terapia dell'Ipotiroidismo

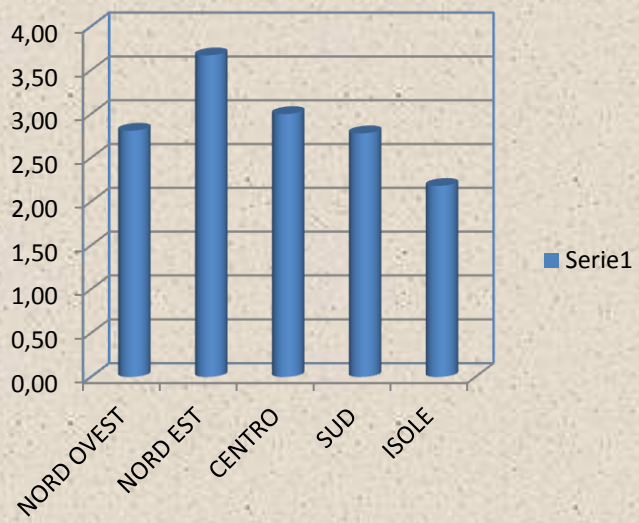
Enrico Papini
UOC Endocrinologia e Malattie Metaboliche
Ospedale Regina Apostolorum

S. Campo et al 2013

HS= Base dati: 952.144 soggetti

Distribuzione geografica ipotiroidismo primario

2,96%

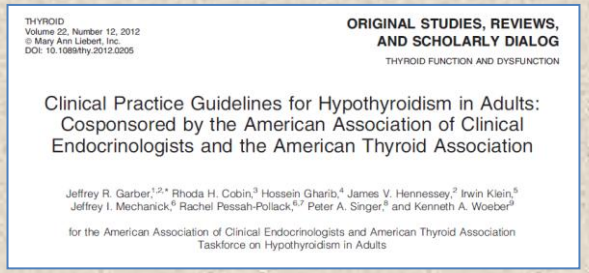


Prevalenza stimata di Ipotiroidismo in Italia:

3,71%

Rapporto F:M 4,8

- 70,5% con un dosaggio di TSH ultimi 15 mesi
- **63% con una prescrizione di ormoni tiroidei ultimo anno**



THYROID
Volume 22, Number 12, 2012
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DOI: 10.1089/thy.2012.0205

ORIGINAL STUDIES, REVIEWS, AND SCHOLARLY DIALOG
THYROID FUNCTION AND DYSFUNCTION

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

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

Terapia sostitutiva: Levotiroxina (L-T4)

- **RECOMMENDATION 22.1**

  Patients with hypothyroidism should be treated with L-thyroxine monotherapy. **Grade A, BEL 1**

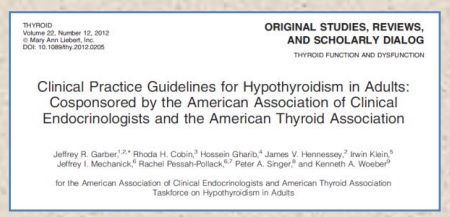
  SEE: *L-thyroxine treatment of hypothyroidism*

- **RECOMMENDATION 22.2**

  The evidence does not support using L-thyroxine and L-triiodothyronine combinations to treat hypothyroidism. **Grade B, BEL 1**

Farmacocinetica della L-T_4

Biodisponibilità orale	60-80% ~
Concentrazione sierica	Picco a 2-4 h
Legame alle proteine plasmatiche	99.97%
Metabolismo	Desiodazione (>>) Deaminazione e coniugazione
Escrezione (20%~)	Feci (>>) e urine
Emivita	7 gg ~ (190 ore)
Steady state	6-8 sett



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Evitare gli ormoni estrattivi e la L-T3

- **RECOMMENDATION 22.3**

  L-thyroxine and L-triiodothyronine combinations should not be administered to pregnant women or those planning pregnancy. **Grade B, BEL 3**

- **RECOMMENDATION 22.4**

  There is no evidence to support using desiccated thyroid hormone in preference to 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**

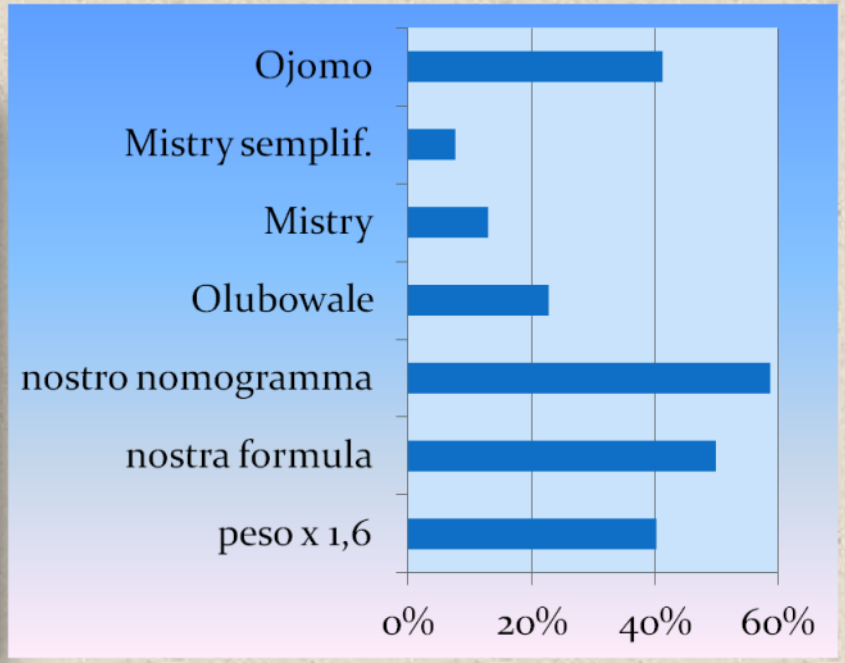
Come assumere la LT4?

A digiuno, 30 – 60 minuti prima di colazione (o bedtime 4 ore dopo il pasto).

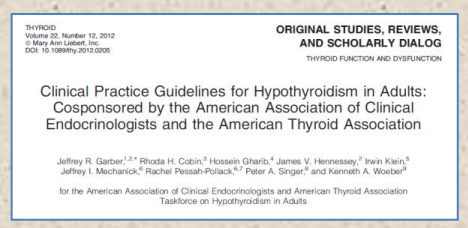
- **RECOMMENDATION 23**
  L-thyroxine should be taken with water consistently 30–60 minutes before breakfast or at bedtime 4 hours after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption. **Grade B, BEL 2**

Per iniziare: quale dosaggio?

Età	BMI <23	BMI 23-28	BMI >28
<40	1,8	1,7	1,6
40-55	1,7	1,6	1,5
>55	1,6	1,5	1,4



Cortesia di Salvatore Corsello, UCSC



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Quale target terapeutico?

TSH nei limiti della norma (non gravide).

- **RECOMMENDATION 17**

  In patients with hypothyroidism who are not pregnant, 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. **Grade B, BEL 2**

Quale Monitoraggio?

TSH: ogni 4 – 8 settimane fino al target terapeutico.
Dopo la stabilizzazione: ogni 6 – 12 mesi

- **RECOMMENDATION 13**

  Patients being treated for established hypothyroidism should have serum TSH measurements done at 4–8 weeks after initiating treatment or after a change in dose. Once an adequate replacement dose has been determined, periodic TSH measurements should be done after 6 months and then at 12-month intervals, or more frequently if the clinical situation dictates otherwise. **Grade B, BEL 2**

  SEE: *L-thyroxine treatment of hypothyroidism*

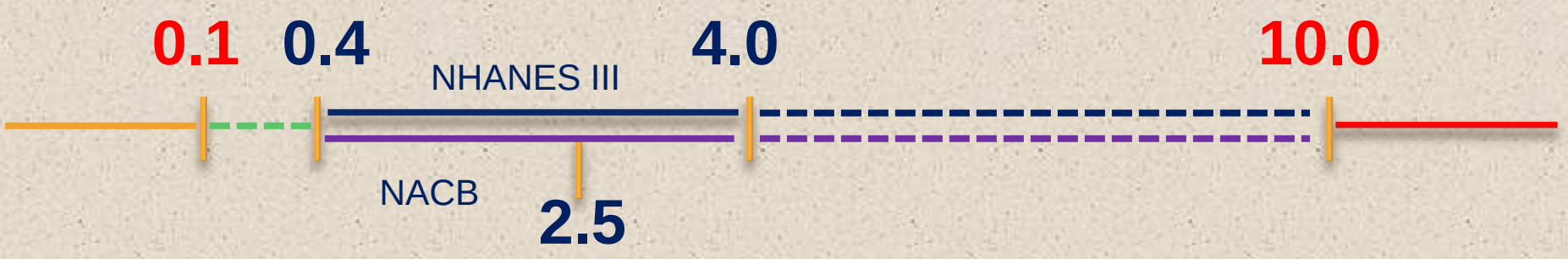
Il problema dell'Ipotiroidismo subclinico

Subclinical hypothyroidism

Trattamento raccomandato

TSH mUI/L

Trattamento raccomandato



SPECIAL FEATURE

Editorial

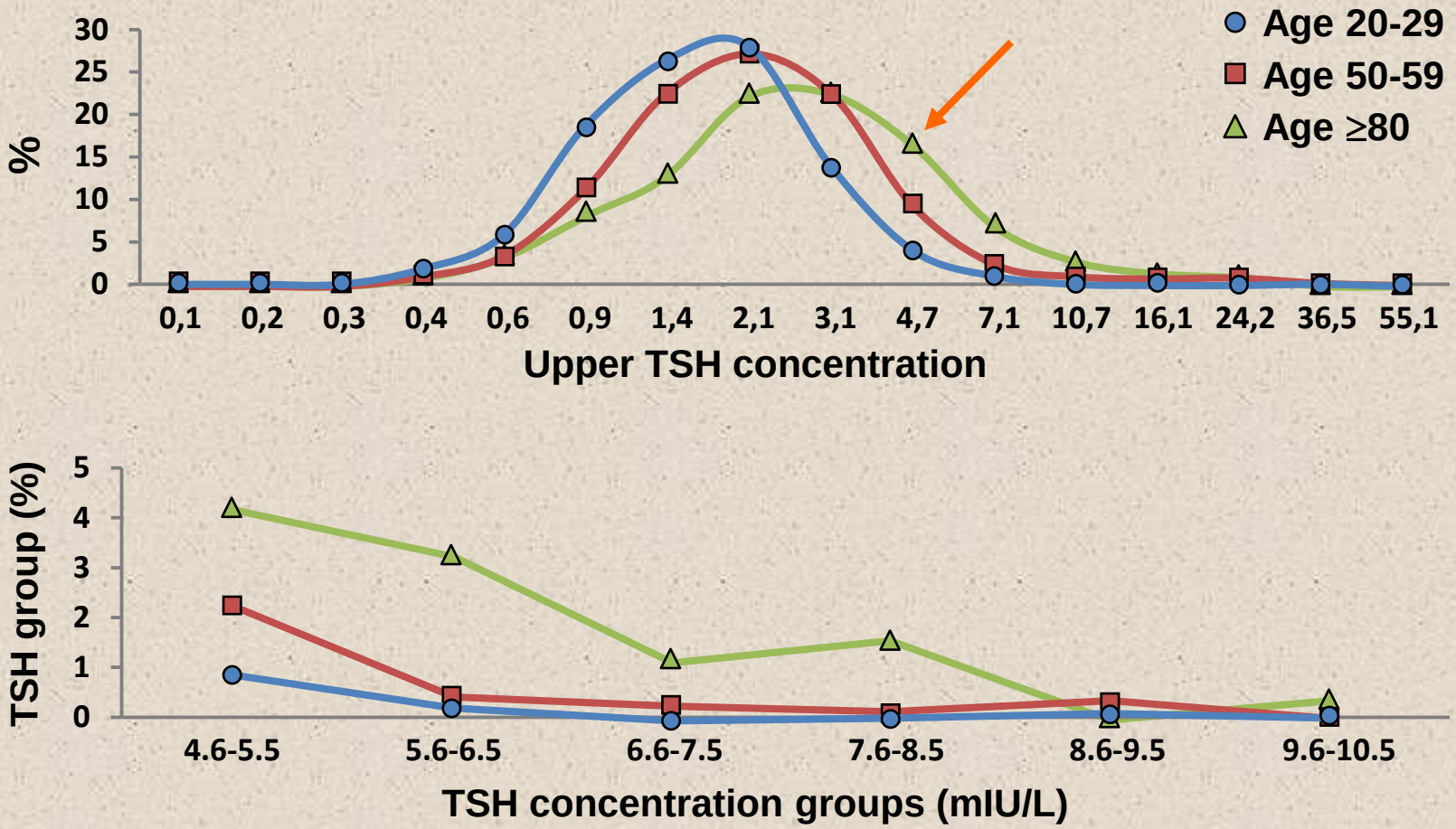
J Clin Endocrinol Metab, September 2013, 98(9):3584–3587

The Normal TSH Reference Range: What Has Changed in the Last Decade?

Bernadette Biondi

Department of Clinical Medicine and Surgery, University of Naples Federico II, 80131 Naples, Italy

Serum TSH and Age



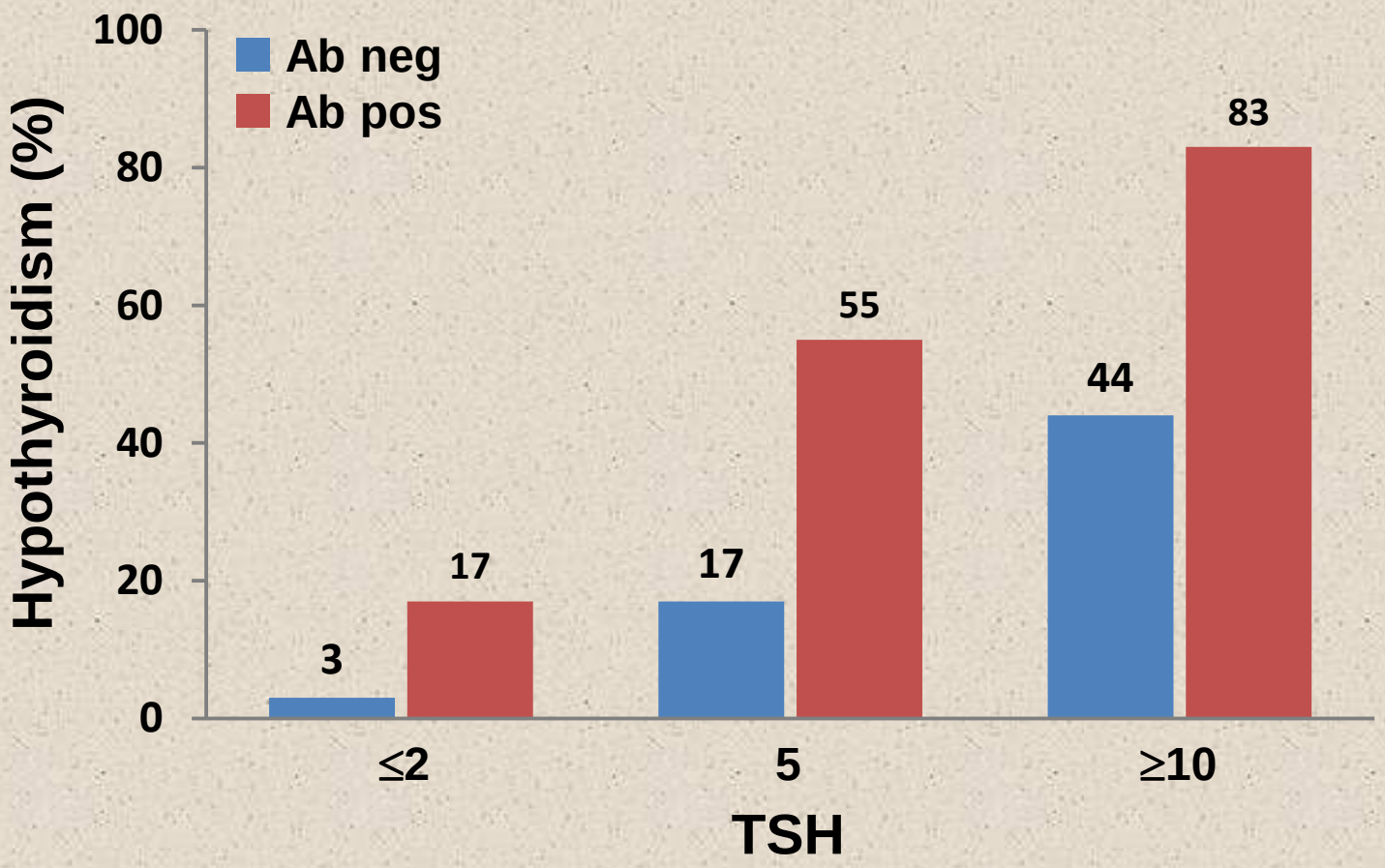
JCEM 92:4575, 2007

Subclinical Hypothyroidism

Against LT4 treatment

- Impact on CV morbidity and mortality: unclear, especially in elderly
- Data on improved symptoms: equivocal
- Improved cognitive outcomes: unproven
- Possible complications of overtreatment

Risk of Overt Hypothyroidism in a 60-Year-Old Woman with SCHypo



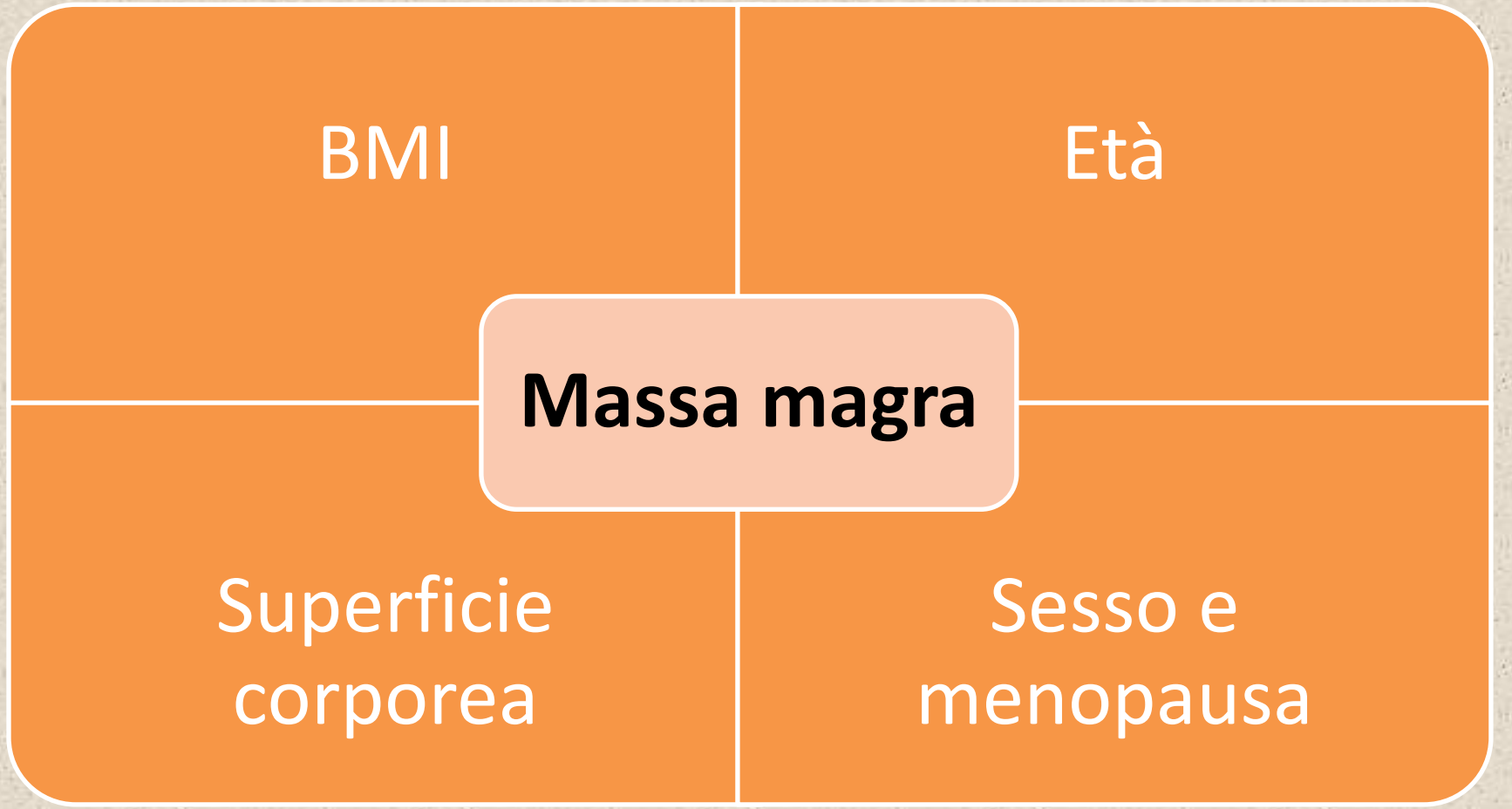
Vanderpump M et al, 2003

Subclinical Hypothyroidism

Recommendation 16

- Treatment of TSH levels **5-10** mIU/L should be considered in patients with symptoms of hypothyroidism, positive TPOAb or atherosclerotic CV disease.

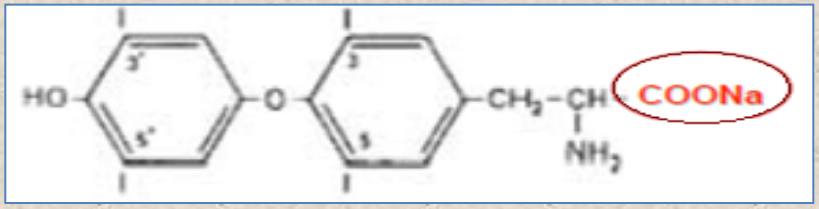
Fabbisogno di L-Tiroxina: in media 1.6 mcg/Kg/dì ma varia in funzione di:

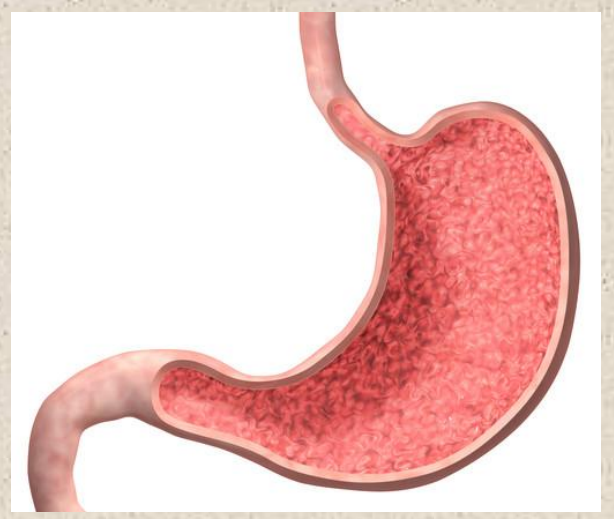


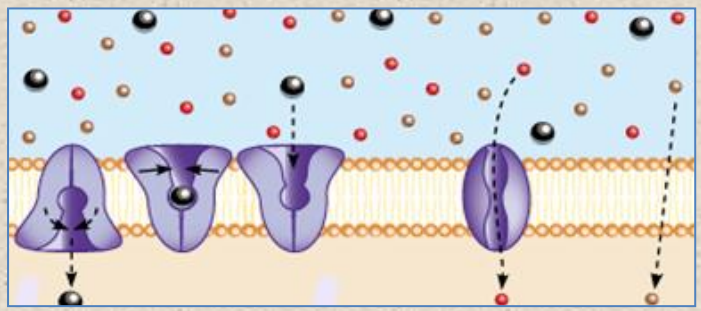
Santini F et al, J Clin Endocrinol Metab 2005

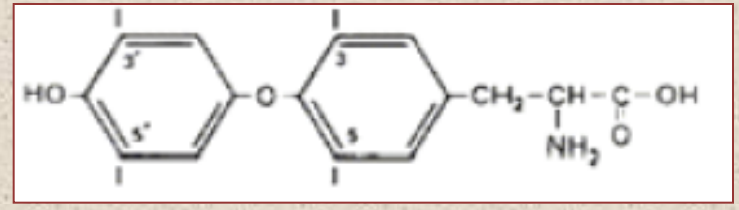
Assorbimento della L-T4

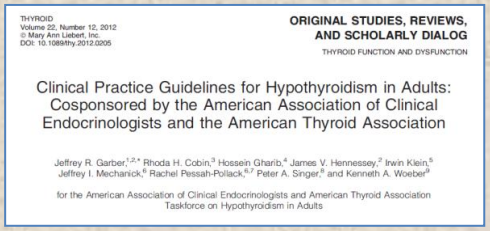
- pH gastrico acido determinante per dissoluzione compresse e solubilità del farmaco.
- FT4: picco sierico a 1-2 ore con plateau a 3-4 ore.
- Assorbimento: digiuno (45%) e 1 tratto dell'ileo (34%).











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Dosaggio iniziale: funzione dell'età e dello stato generale della persona

- **RECOMMENDATION 22.7.1**

  When initiating therapy in young healthy adults with overt hypothyroidism, beginning treatment with full replacement doses should be considered. **Grade B, BEL 2**

  SEE: *L-thyroxine treatment of hypothyroidism*

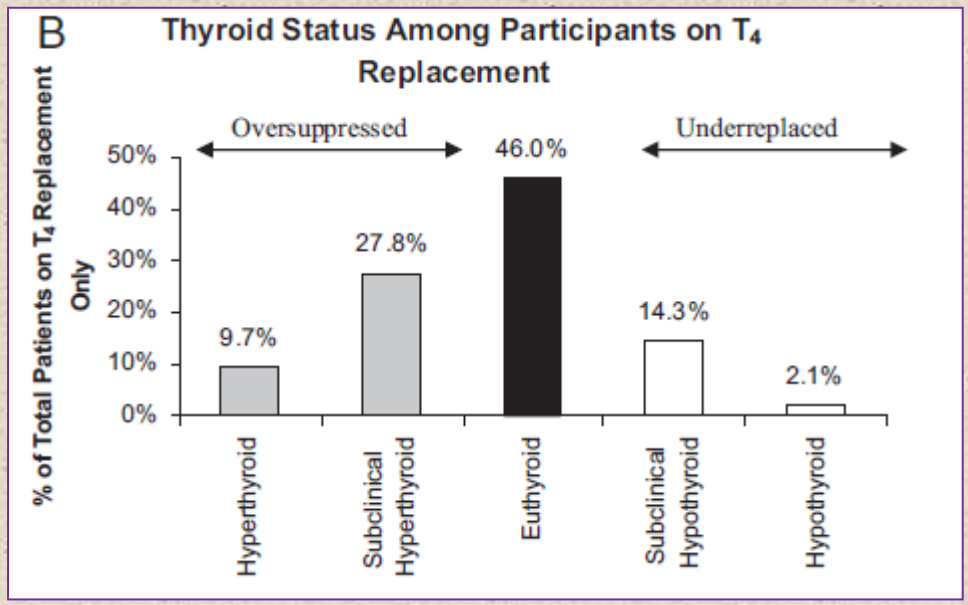
- **RECOMMENDATION 22.7.2**

  When initiating therapy in patients older than 50–60 years with overt hypothyroidism, without evidence of coronary heart disease, an L-thyroxine dose of 50 μg daily should be considered. **Grade D, BEL 4**

  SEE: *L-thyroxine treatment of hypothyroidism*

MONITORAGGIO TERAPIA SOSTITUTIVA: ANZIANI O COMORBIDITA'

"One size does not fit all"



Somwaru LL et al, J Clin Endocrinol Metab 2009

Farmaci e alimenti interferenti

TABLE 10. AGENTS AND CONDITIONS HAVING AN IMPACT ON L-THYROXINE THERAPY AND INTERPRETATION OF THYROID TESTS

10.1. Interference with absorption

Bile acid sequestrants (cholestyramine, colestipol, colesevelam) Sucralfate Cation exchange resins (Kayexelate) Oral bisphosphonates Proton pump inhibitors Raloxifene[a] Multivitamins (containing ferrous sulfate or calcium carbonate) Ferrous sulfate Phosphate binders (sevelamer, aluminum hydroxide)	Calcium salts (carbonate, citrate, acetate) Chromium picolinate Charcoal Orlistat[b] Ciprofloxacin H2 receptor antagonists[a] Malabsorption syndromes • Celiac disease • Jejunoileal bypass surgery • Cirrhosis (biliary) • Achlorhydria	Diet • Ingestion with a meal • Grapefruit juice[a] • Espresso coffee • High fiber diet • Soybean formula (infants) • Soy

Pasto (di qualunque tipo) ma anche fibre, ananas, soia e caffè.
E poi: multivitamici, ferro, calcio, bifosfonati, sucralfato.

Il problema degli inibitori di pompa (PPI)

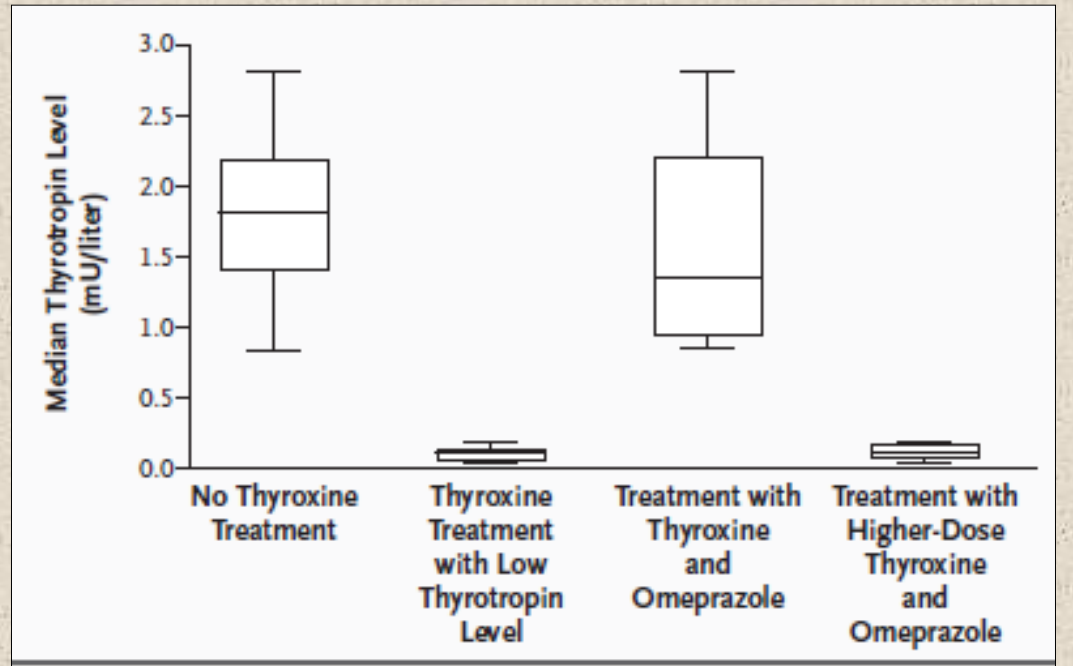
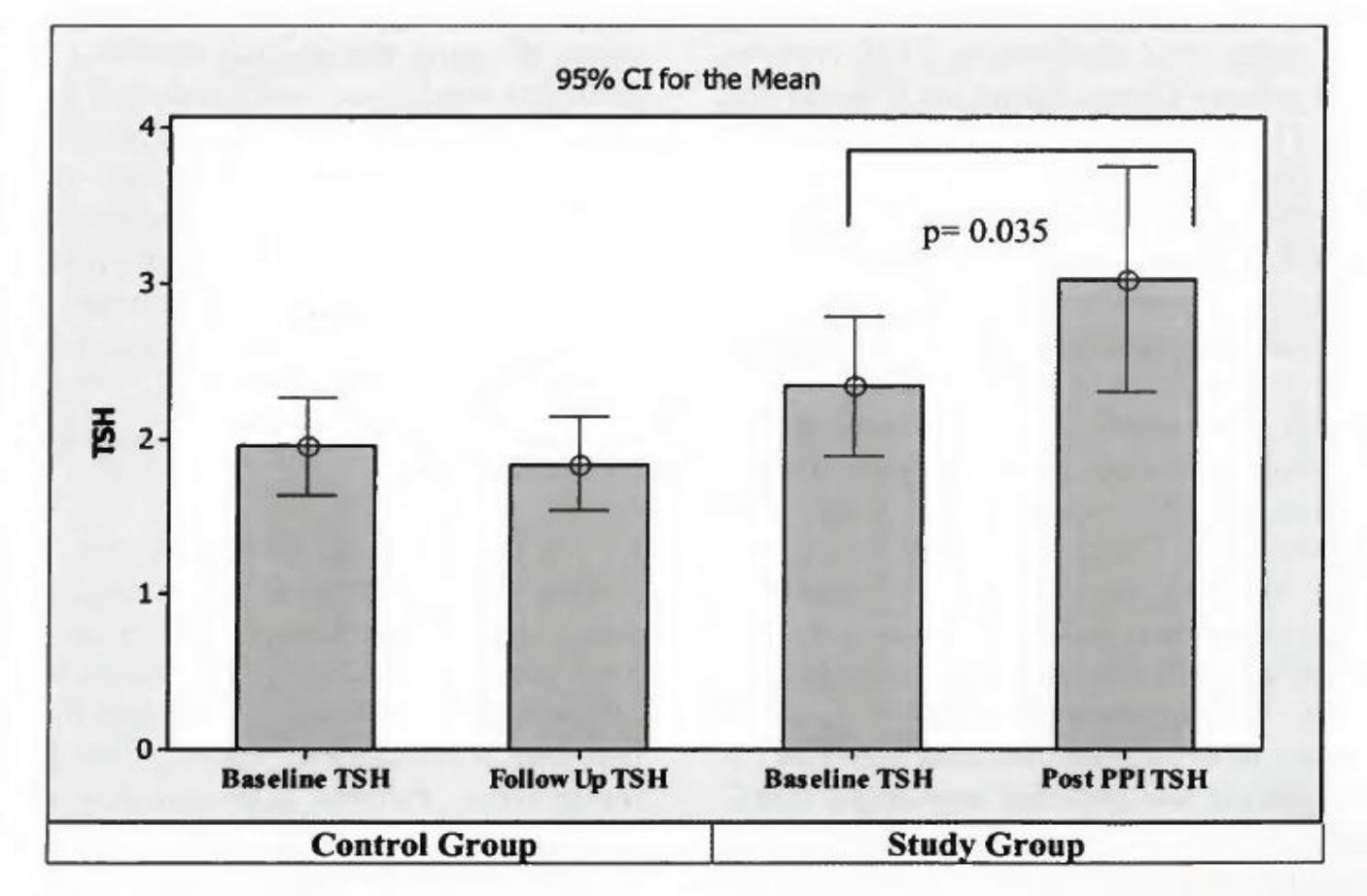


Figure 2. Effect of Long-Term Omeprazole Treatment on Thyrotropin Levels in 10 Patients Simultaneously Treated with Thyroxine.

Centanni M, N Engl J Med 2006; Sachmechi I, Endocr Pract 2007

- Circa il 50% dei pazienti in terapia con L--T_4 assume anche PPI
- Nel 58% dei pazienti che assumono contemporaneamente i 2 farmaci è necessario modificare il dosaggio di L-T_4 e controllare ripetutamente il TSH.

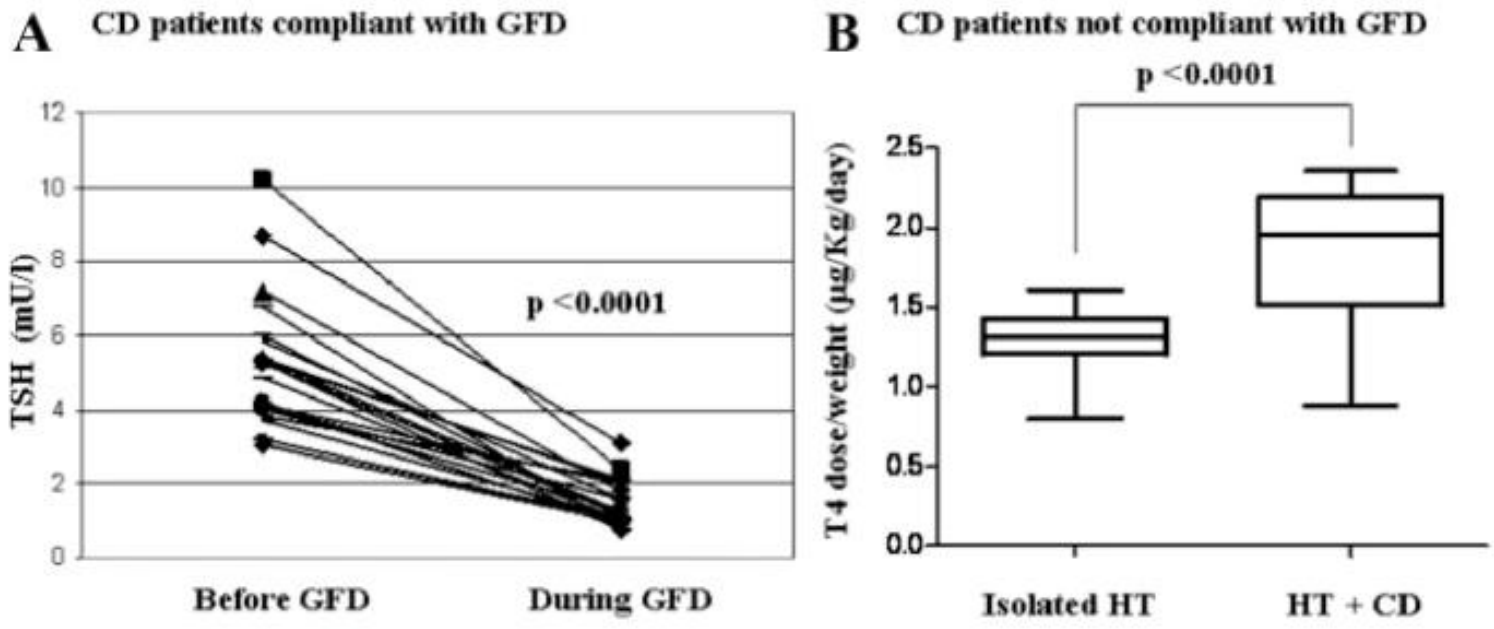
Medea G, Congresso SIMG 2012



Il livello medio di TSH aumenta dopo 2-6 mesi di terapia con IPP.
Il 19% dei pazienti ha richiesto un aggiustamento della dose di L-T4 dopo l'inizio degli IPP; l'incremento medio è stato del 35%.

Intolleranza al Glutine

Figura 1. Morbo celiaco e assorbimento della tiroxina



Fonte: Virili *et al.*, 2012 [8].

Lactose Intolerance Revealed by Severe Resistance to Treatment with Levothyroxine

Manuel Muñoz-Torres, Mariela Varsavsky, and Guillermo Alonso

THYROID
Volume 16, Number 11, 2006

Prevalenza: caucasici 7-20%, nativi americani 80-95%.

Difetti quantitativi o qualitativi dell'enzima lattasi.

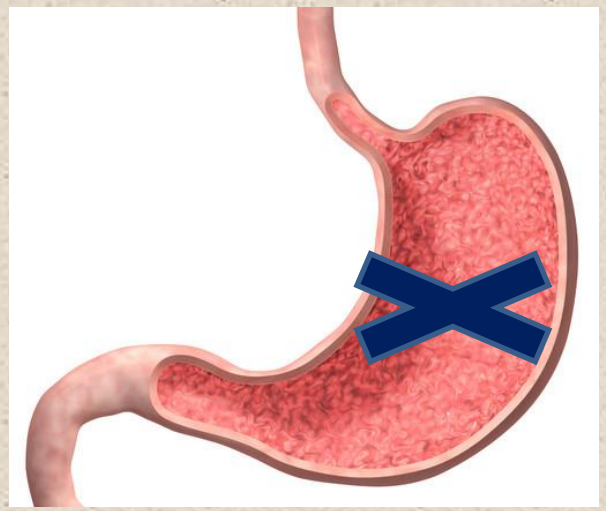
Causa di resistenza al trattamento con LT4: infrequente.

Dieta priva di lattosio: risoluzione del problema.

Disponibili formulazioni di LT4 prive di lattosio.

L-T4: Formulazione solida vs liquida

Solide: compresse
Liquide: soluzione orale in gtt e flacone monodose; capsule molli



- ✓Aumentato pH gastrico
- ✓Interferenze alimentari, caffè
- ✓Compliance ridotta (“ho fretta”)
- ✓Difficoltà della deglutizione.

La formulazione liquida raggiunge la Cmax circa 30 minuti prima della solida.

Walter-Sack I et al, Clin Pharmacokinet 2004
Pabla D et al, Eur J Pharm Biopharm 2009
Ducharme MP, ICE-ECE 2012
Benvenga S, ICE-ECE 2012

Pharmacokinetics and Potential Advantages of a New Oral Solution of Levothyroxine vs. other Available Dosage Forms

Authors C. S. Yue[1], C. Scarsi[2], M. P. Ducharme[1]

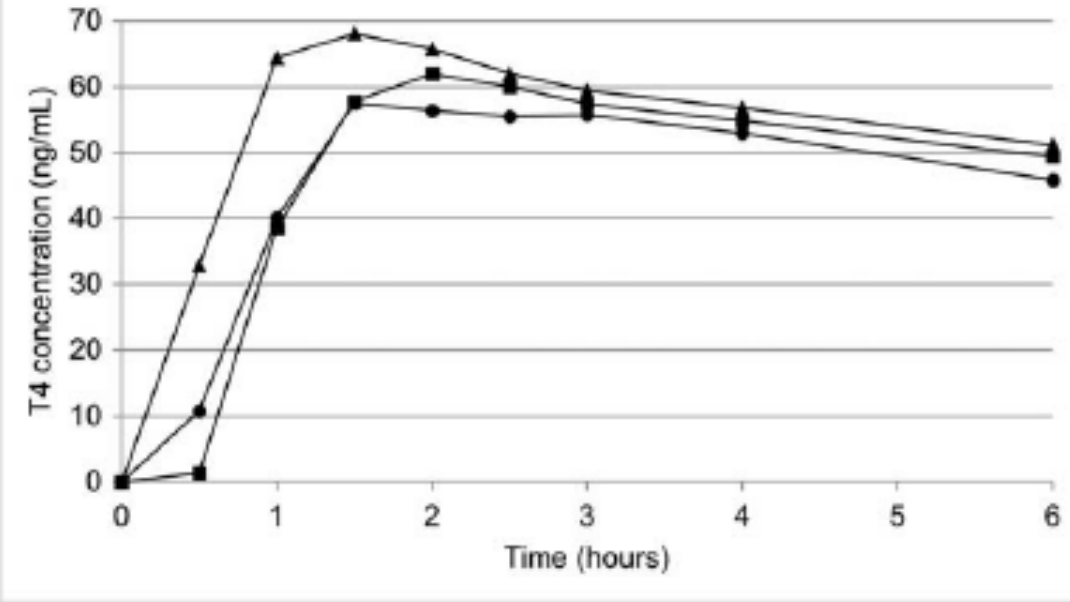


Fig. 2 Mean Levothyroxine Profiles by Formulation for 6 h Immediately Post-Dose. Triangles, squares and circles represent mean concentrations for solution, capsules and tablets respectively.

Eur J Endocrinol. 2013 Nov 22;170(1):95-9.. Print 2014.

Oral liquid levothyroxine treatment at breakfast: a mistake?

Cappelli C, Pirola I, Gandossi E, Formenti A, Castellano M.

All the patients on liquid l-T4 treatment were contacted by phone to ask them whether they took l-T4 at breakfast. We identified 54 patients who were submitted to TSH, fT4, and fT3 evaluation, with the indication that the same dosage of l-T4 be consumed 30 min before breakfast

NO SIGNIFICANT DIFFERENCE IN THYROID HORMONE CONCENTRATIONS was observed in patients when they consumed L-T4 at breakfast or when they consumed it 30 minuutes before breakfast for 3 and 6 months (TSH: 2.5±1.1 vs 2.5±1.1 and 2.4±1.1 mIU/l respectively, fT4: 12.4±2.4 vs 12.5±2.4 and 12.3±2.1 pg/ml respectively, and fT3: 3.4±0.6 vs 3.4±0.6 and 3.3±0.5 pg/ml respectively.

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

Drug-Induced Abnormal TSH

Drug	Hypo-/hyper-	Mechanism
Bexarotene	Y/N	Central
Lithium	Y/?Y	Autoimmune
Amiodarone	Y/Y	Iodine
Interferon	Y/Y	Autoimmune
Sunitinib	Y/N	?

Drug-Induced Abnormal TSH

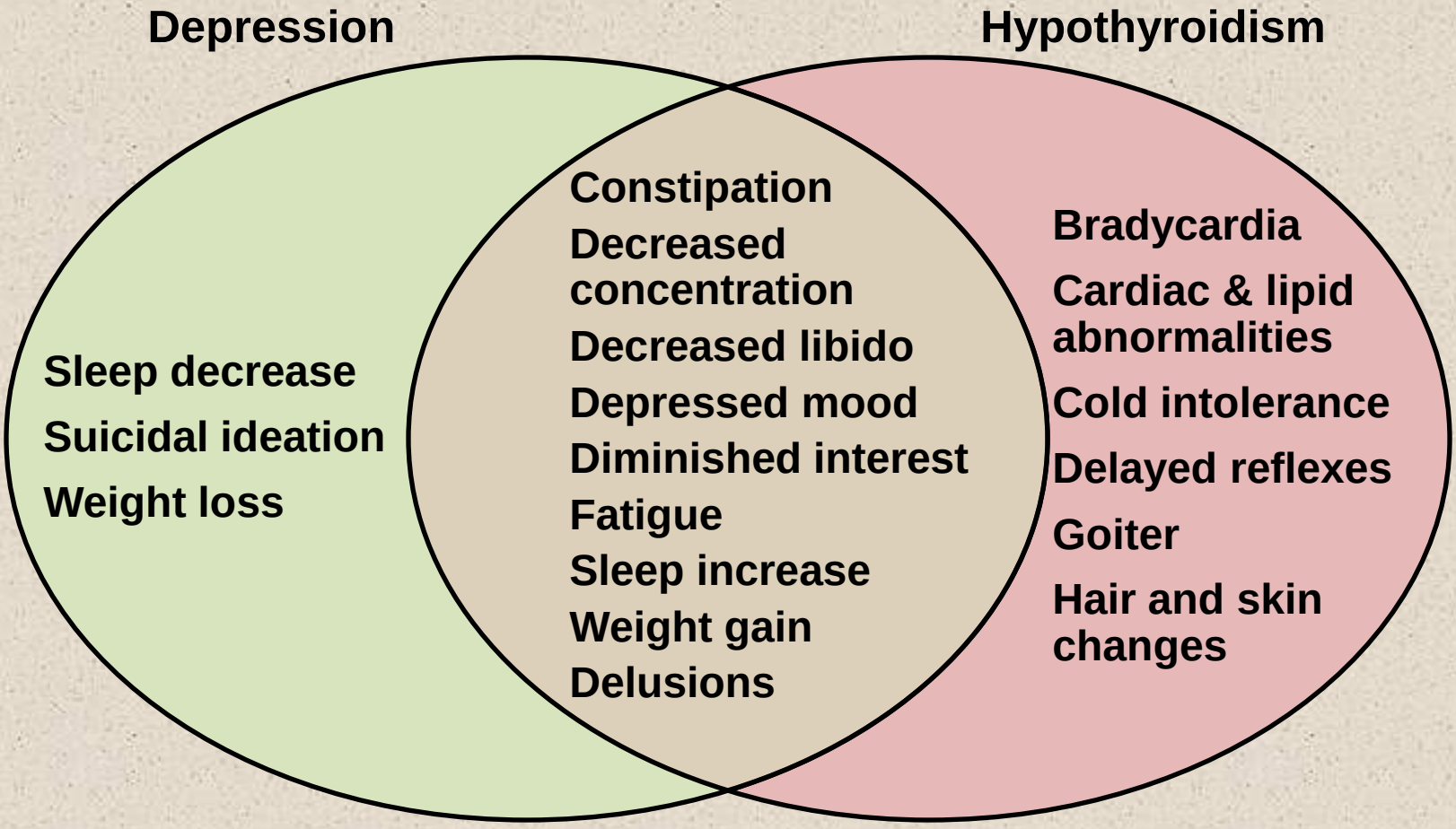
↑ TSH due to ↑ T4 metabolism:

- Dilantin
- Phenobarbital
- Rifampin
- Tegretol

Perchè alcuni pazienti continuano a lamentarsi nonostante normali livelli di TSH?

- Cause extratiroidee
- Dose di T4 inadeguata
- Necessità di combinazione T4 / T3

Common Features of Hypothyroidism and Depression



Nemeroff CB: J Clin Psychiatry 50 (Suppl:13-20), 1989

Quando consultare l'Endocrinologo?

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.

Federazione Italiana Endocrinologia, Diabetologia, Andrologia, Metabolismo e Obesità

Commissione Attività Cliniche

PROCEDURE PER L'INQUADRAMENTO E LA GESTIONE AMBULATORIALE DELLA PATOLOGIA TIROIDEA

Obiettivi specifici

1. riduzione delle richieste inappropriate di visita e diagnostica di laboratorio
2. riduzione delle liste di attesa per patologia tiroidea
3. riduzione delle visite endocrinologiche urgenti inappropriate
4. modello "hub and spoke" e creazione di un protocollo operativo comune.

Strumenti di lavoro

1. condivisione dei criteri per la gestione clinica della patologia tiroidea con MMG, endocrinologi e ODP
2. realizzazione di eventi formativi
3. rilevazione dei cambiamenti in un periodo di applicazione sperimentale.