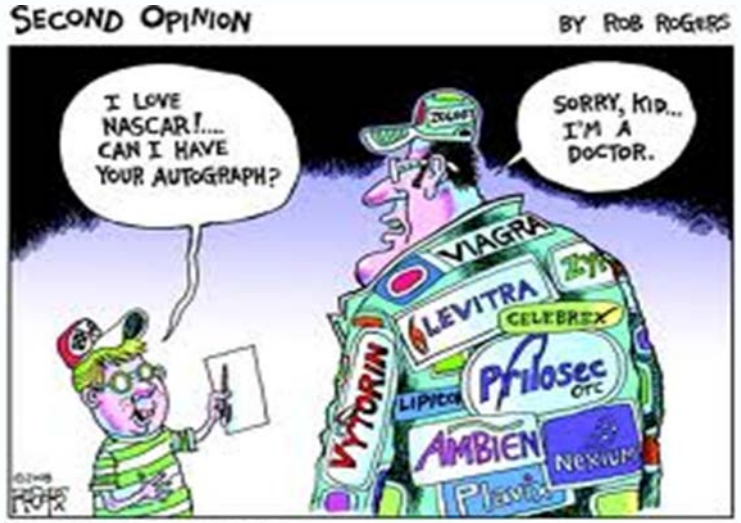
71° Congresso Nazionale

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

Salvatore Benvenga

Domus De Maria (CA)
5-10 ottobre 2015

CONFLITTO DI INTERESSI



S.B. ha ricevuto
sostegno per la ricerca
da parte di IBSA.

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*

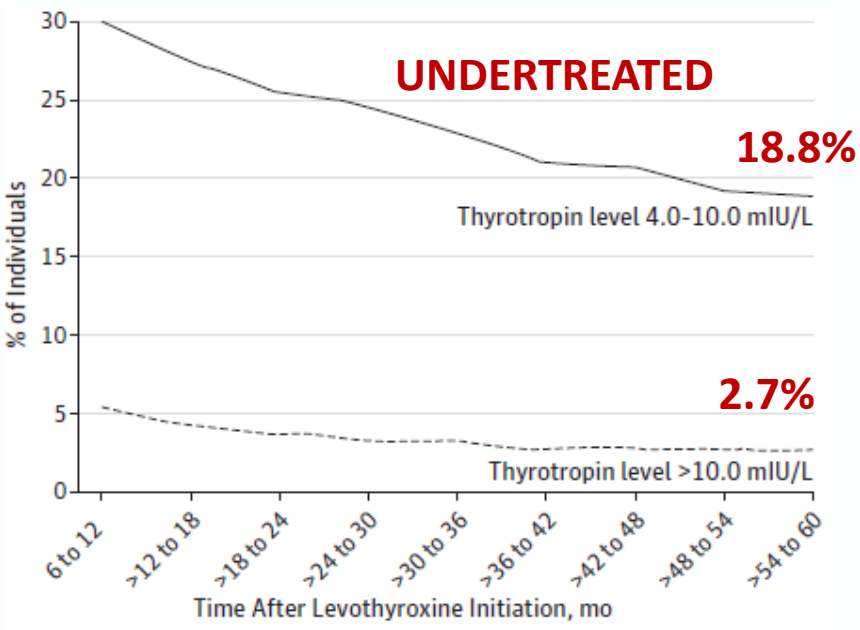
When to consult an endocrinologist

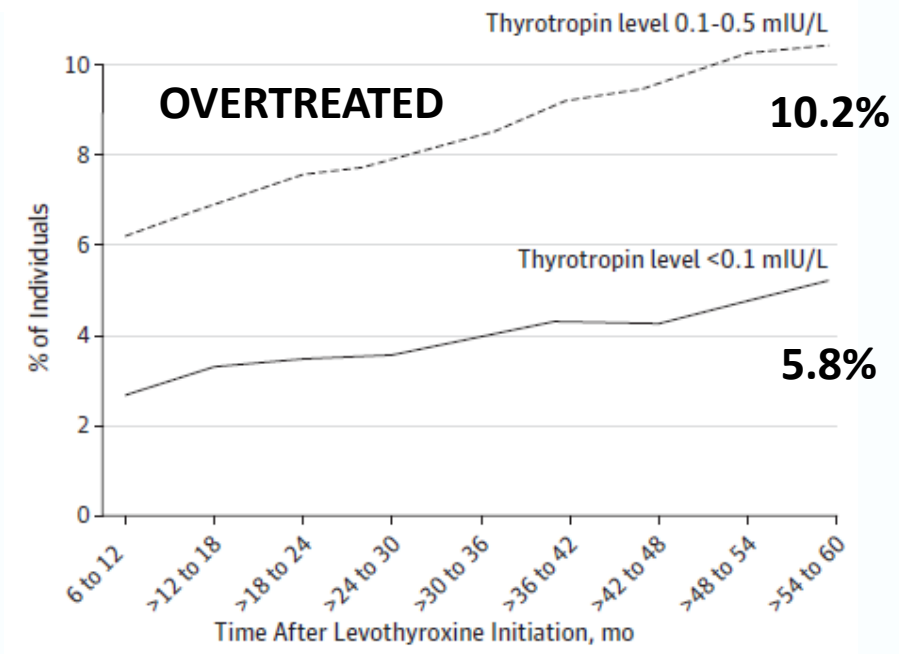
Although most physicians can diagnose and treat hypothyroidism, consultation with an endocrinologist is recommended in the following situations:

- 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.

PN Taylor, A Iqbal, C Minassian, A Sayers, MS Draman, R Greenwood, W Hamilton, O Okosieme, V Panicker, SL Thomas, C Dayan. **Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study**. *JAMA Intern Med. 2014; 174:32-9.*

Figure 3. Thyrotropin Levels After Initiation of Levothyroxine





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. ORME09F7LL

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

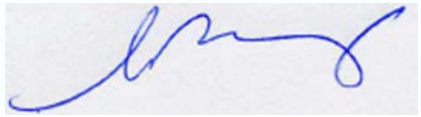
1.2 Tipologia della ricerca Sperimentale

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 MODALITA' DI ASSUNZIONE E DA BEVANDE, FARMACI/INTEGRATORI ALIMENTARI.

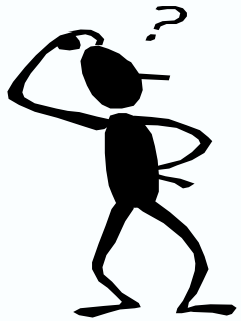
1.10.7 Personale extrauniversitario dipendente da altri Enti

nº	Cognome	Nome	Ente	Qualifica
1.	Alecci	Umberto	Azienda Sanitaria Provinciale (ASP) Messina	Medico Med Gen
2.	Inferrera	Santi	Azienda Sanitaria Provinciale (ASP) Messina	Medico Med Gen
3.	Marino	Sebastiano	Azienda Sanitaria Provinciale (ASP) Messina	Medico Med Gen

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.

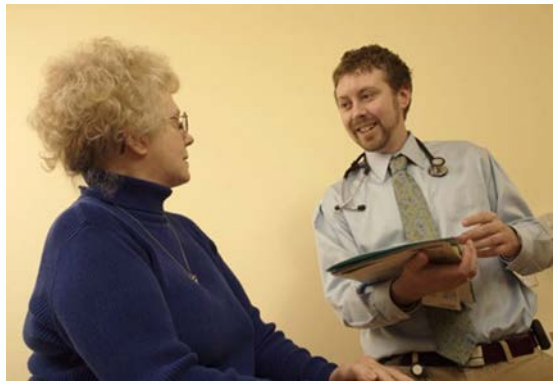
- Ma dove è scritto sul foglietto illustrativo ?
- Ho ricontrollato sulla scheda tecnica e sulla Guida all'Uso dei Farmaci, e l'interferenza di questo farmaco non c'è scritta !
- Neanche il collega che seguiva il caso prima di me lo sapeva !
- L'informatore scientifico non me ne ha parlato !
- Ma nel 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 "REFRATTARIETA' 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)**

Just ask ! (basta chiedere !)



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

INTERAZIONI FARMACOLOGICHE

Levotiroxina

Analgesici: concentrazioni plasmatiche falsamente ridotte di tiroxina con *fenilbutazone*

Antiaritmici: per l'uso con *amiodarone* ⇒ sezione 2.3.2

Antibatterici: *rifampicina* aumenta il metabolismo di levotiroxina (possono aumentare le richieste in corso di ipotiroidismo)

- Anticoagulanti: potenziamento dell'effetto di *acenocumarolo*, *fenindione* e *warfarin*

Antidepressivi: il produttore di *lofepramina* raccomanda di evitare levotiroxina

Antiepilettici: *carbamazepina*, *fenobarbital*, *fenitoina* e *primidone* aumentano il metabolismo di levotiroxina (possono aumentare le richieste in corso di ipotiroidismo)

Barbiturici e primidone ⇒ antiepilettici sopra

Betabloccanti: aumento del metabolismo di *propranololo* (riduzione dell'effetto)

Farmaci anti ulcera peptica: *sucralfato* riduce l'assorbimento di levotiroxina

Resine a scambio ionico: *colestiramina* riduce l'assorbimento di levotiroxina

Sherman SI et al. **Sucralfate causes malabsorption of l-thyroxine.**
Am J Med 96:531–35, 1994.

Northcutt RC et al. **The influence of cholestyramine on thyroxine absorption.**
JAMA 208:1857–61, 1969.

ED I SALI DI FERRO ??

Campbell NRC et al. **Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism.**
Ann Intern Med 117:1010–13, 1992

ED IL CARBONATO DI CALCIO ??

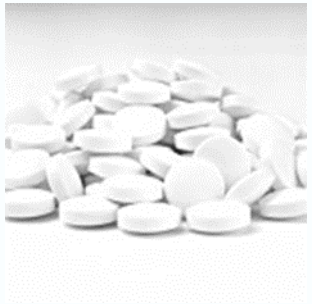
Schneyer CR. *JAMA 279: 750, 1998*
Singh N et al. *JAMA 283: 2822-25, 2000*

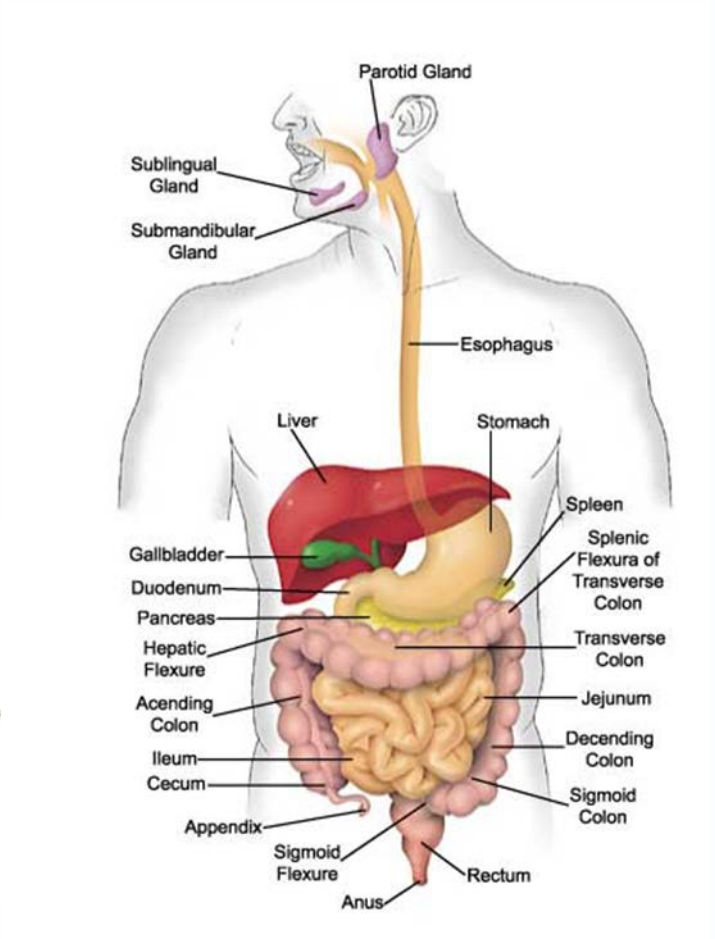
Cause farmacologiche di aumentata richiesta di L-T_4

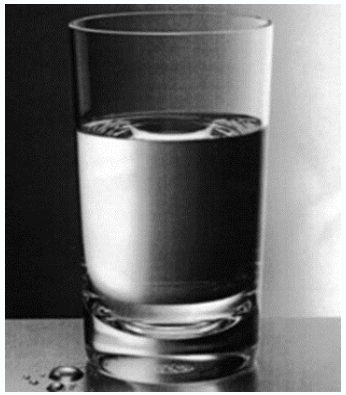
- Differenti **classi farmacologiche** possono influenzare la dose- efficacia di **L-T4** con diversi meccanismi

RIDUZIONE ACIDITA' GASTRICA	ADSORBIMENTO NEL LUME INTESTINALE	ACCELLERATO CATABOLISMO DELLA T4	↑ LEGAME ALLE PROTEINE PLASMATICHE
Inibitori Pompa Protonica	Solfato ferroso	Carbamazepina	Estrogeni
Sucralfato	Sequestranti degli acidi biliari	Fenitoina	Raloxifene
Idrossido di Alluminio	Resine a scambio ionico	Fenobarbitale	
Idrossido di Magnesio	Chelanti dei fosfati		
Calcio Carbonato			

VARIABILI IN GIOCO







L. Deiana, S. Marini, S. Mariotti. Ingestion of large amounts of papaya fruit and impaired effectiveness of levothyroxine therapy. *Endocr Pract 18: 98-100, 2012*

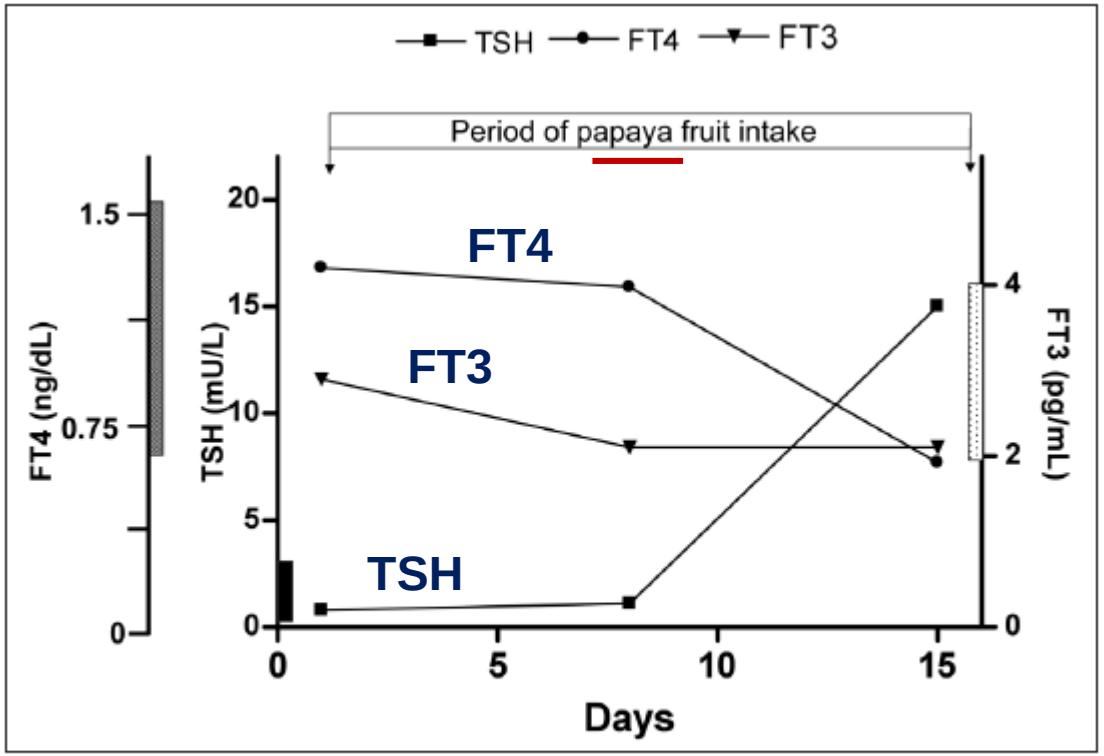
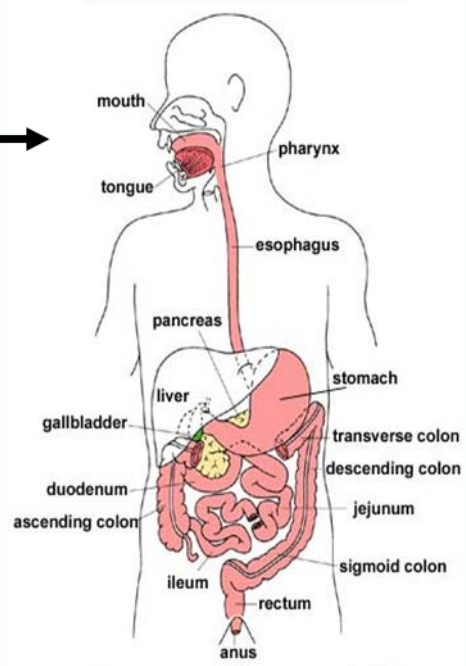


Fig. 1. Serum concentration of thyrotropin (TSH), free thyroxine (FT_4), and free triiodothyronine (FT_3) observed during 2 weeks of large daily intake of papaya fruit in a patient on long-term levothyroxine therapy (dosage, 1.6 mg/kg daily) after total thyroidectomy. Bars on the vertical axes represent normal ranges of TSH, FT_4, and FT_3.

WHERE L-THYROXINE TAKEN ORALLY IS ABSORBED *(Hays MT, 1994)*

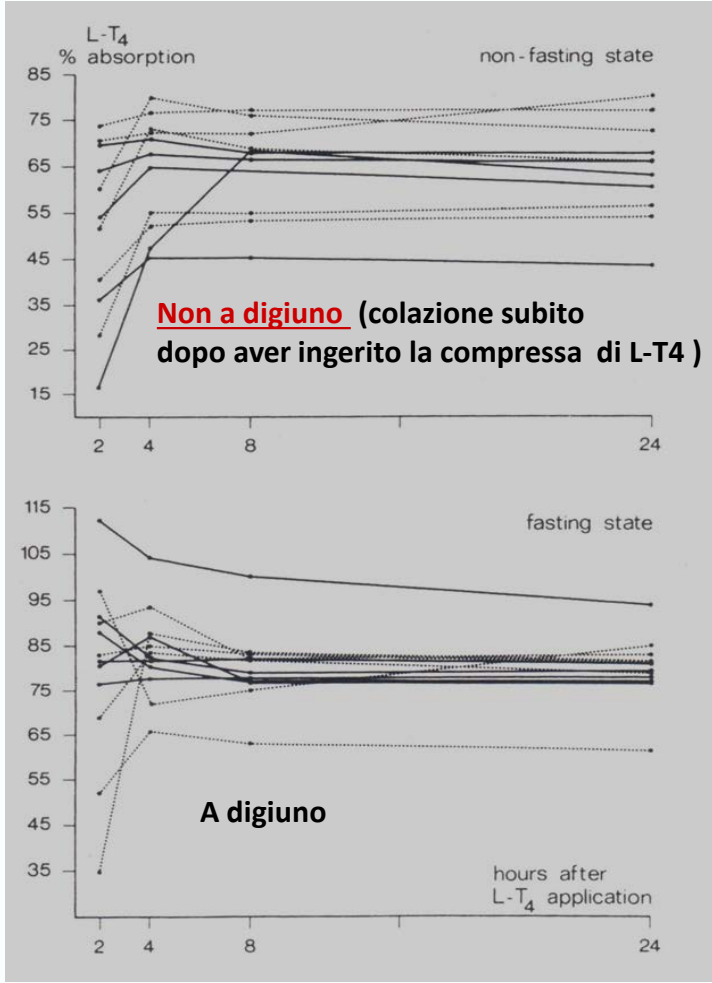


Duodeno: 21%

Digiuno: 45%

Ileo: 34%

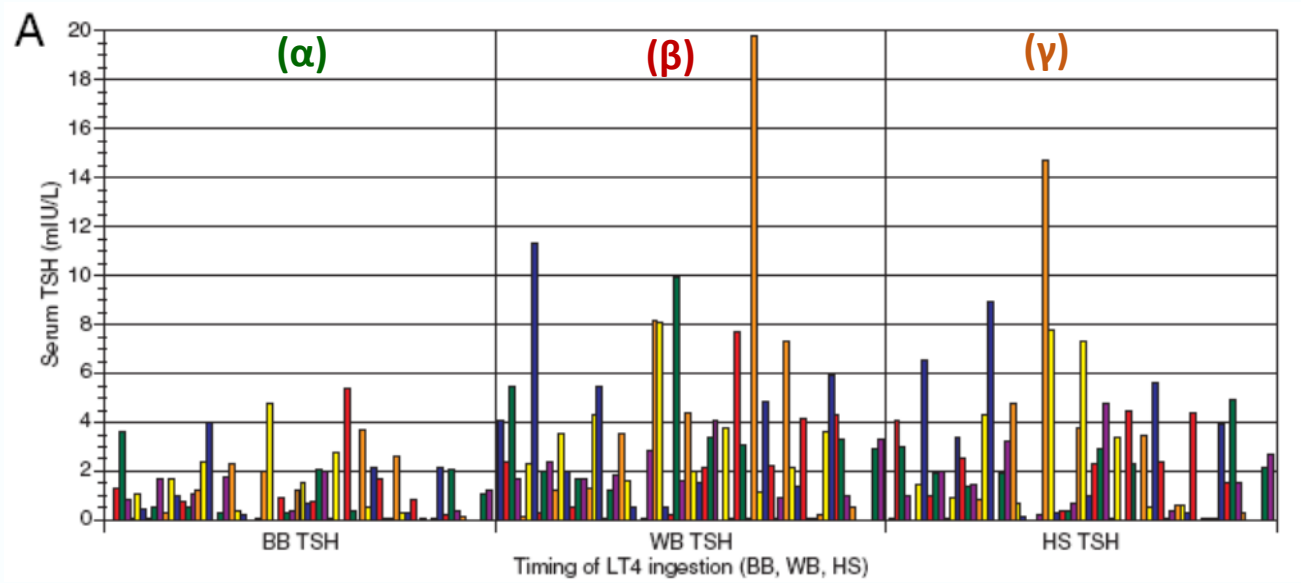
Wenzel KW, Kirschsieper HE.
Aspects of the absorption of oral L-thyroxine in normal man.
Metabolism 26: 1-8, 1977.



(α) Al mattino,
stomaco vuoto,
1 h prima di colazione.

(β) Al mattino, con
la colazione

(γ) La sera, 2 ore
dopo cena



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

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

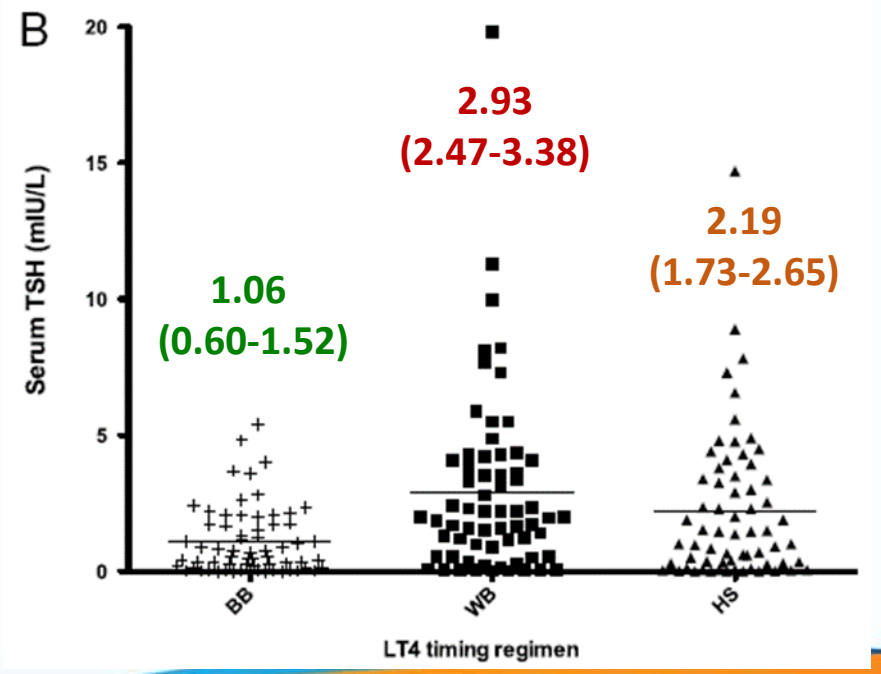
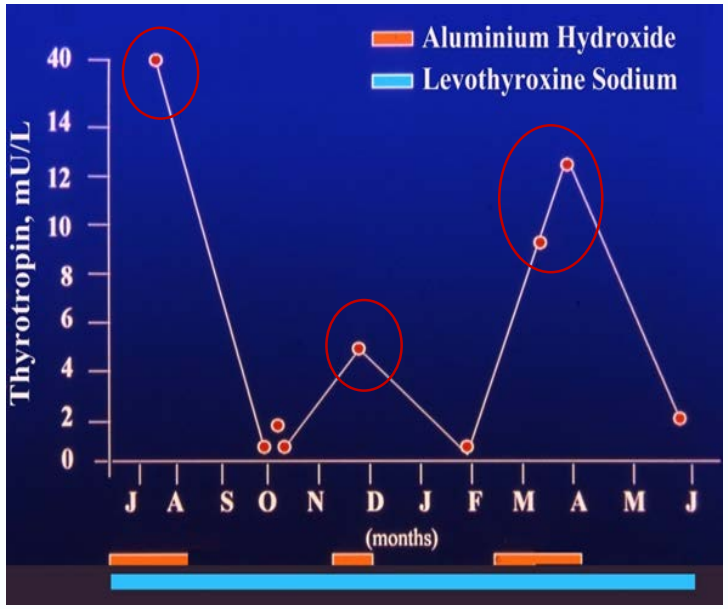
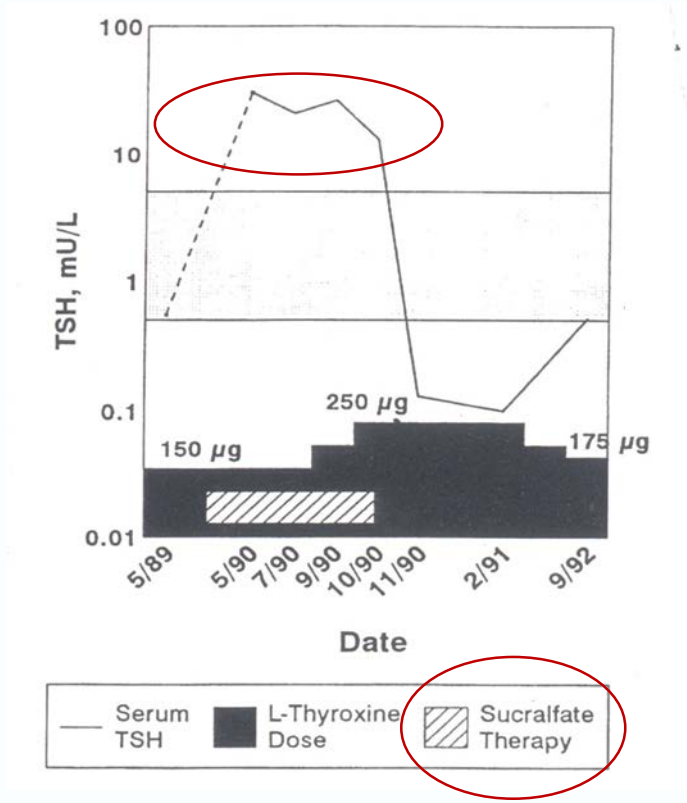


FIG. 1. A, Serum TSH concentrations of participants according to their LT_4 timing regimen (fasting, with breakfast, or at bedtime) for subjects who completed the study. Patients are displayed in the order and the *same color* in each of the three levothyroxine timings (each patient is not a unique color). B, Scatter plot showing TSH values during each LT_4 timing regimen for subjects who completed the study.



Sperber AD, Liel Y. Evidence for the interference on the intestinal absorption of levothyroxine sodium by aluminum hydroxide. *Arch Intern Med 152: 183-4, 1992*



Sherman SI et al.
Sucralfate causes malabsorption of L-thyroxine.
Am J Med 96:531-5,1994

Centanni M et al. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. *NEJM 354: 1787-1795, 2006*

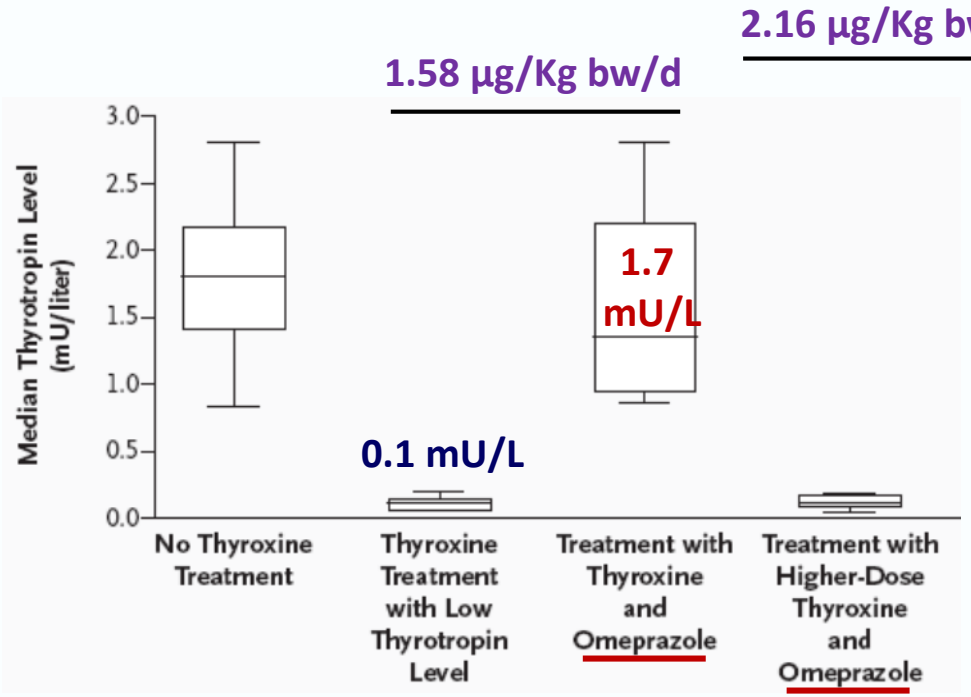


Fig. 2- Effect of long-term omeprazole treatment on serum Thyrotropin levels in 10 patients simulataneously treated with Thyroxine.

Sachmechi I et al. Effect of proton pump inhibitors on serum thyroid stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. *Endocr Pract 13:34, 345-349, 2007*

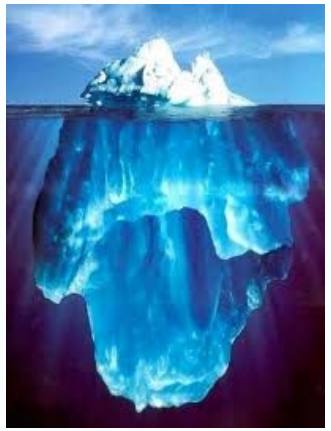
Significant ↑ of serum TSH over 6 months in hypothyroid subjects taking L-T4 and lansoprazole.

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%)

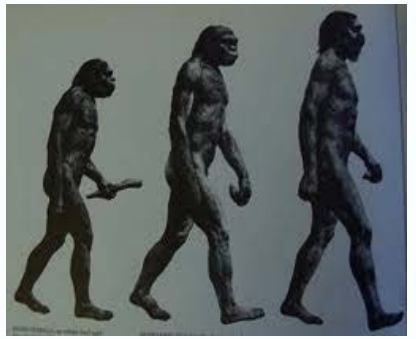
- **Pseudomalassorbimento : 1**
- **Assorbimento lento (ritardato) : 5**
- **Incongrua assunzione (DURANTE o DOPO colaz.): 3**
- **Interferenza da fibre alimentari: 1**
- **Interferenza da caffè: 4**
- **Interferenza da caffè + farmaco (inib. p. proton.): 1**
- **Interferenza monofarmacologica: 6, di 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 *.

		Costs (in Euro) for performing assays in the specified no. of patients §				
	Mean no. of assays	Number of patients				
		1	1,000	10,000	100,000	1 million
TSH (€ 16)	8	€ 128	€ 128,000	€ 1,280,000	€ 12,800,000	€ 128,000,000
FT4 (€ 16)	5	€ 80	€ 80,000	€ 800,000	€ 8,000,000	€ 80,000,000
FT3 (€ 16)	5	€ 80	€ 80,000	€ 800,000	€ 8,000,000	€ 80,000,000
TOTAL	18	€ 288	€ 288,000	€ 2,880,000	€ 28,800,000	€ 288,000,000

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



Comparison of formulas

Tablet #1	Tablet #2	Oral solution, drops	Soft gel capsules
lattosio monoidrato, amido di mais, gelatina, croscarmellosio sodico, magnesio stearato	fosfato di calcio bibasico, sodio carbossimetilamido, magnesio stearato, cellulosa microcristallina, talco, acido citrico, amido di mais	etanolo, glicerina	gelatina, glicerolo

ACCUMULATING LITERATURE on the **liquid formulation of L-T4**

- Brancato D, Scorsone A, Saura G, Ferrara L, Di Noto A, Aiello V, Fleres M, Provenzano V. Comparison of TSH Levels with **Liquid Formulation** Versus **Tablet Formulations** of Levothyroxine in the Treatment of Adult Hypothyroidism. *Endocr Pract. 2014 July, 20: 657-62*.
  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.

- Negro R, Valcavi R, Agrimi D, Toulis KA. Levothyroxine **Liquid Solution** Versus **Tablet** for Replacement Treatment in Hypothyroid Patients. *Endocr Pract. 2014 May 1:1-20. [Epub ahead of print]* –
  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**.

- Cappelli C, Pirola I, Gandossi E, Formenti A, Castellano M. **Oral liquid levothyroxine** treatment at **breakfast**: a mistake? *Eur J Endocrinol. 2013; 170: 95-9-*
  Conclusion- **Oral liquid L-T_4** formulations **could diminish the problem of L-T_4 malabsorption caused by coffee** when using traditional tablet formulations.

- Pirola I, Daffini L, Gandossi E, Lombardi D, Formenti A, Castellano M, Cappelli C. Comparison between **liquid** and **tablet** **levothyroxine formulations** in patients treated through **enteral feeding tube**. *J Endocrinol Invest. 2014 May 1.[Epub ahead of print]* –
  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.

- Ianiro G, Mangiola F, Di Renzo TA, Bibbò S, Franceschi F, Greco AV, Gasbarrini A. Levothyroxyne absorption in health and disease, and **new therapeutic perspective.** *Eur Rev Med Pharmacol Sci 2014; 18: 451-6*.
  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***

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

***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*)

L-T4		PPI	TSH (mU/L)
Dose	formulation	Pantoprazole	
700 µg/wk	tablet	NO	4.1 – 9.8
700 µg/wk	Liquid	NO	2.6
700 µg/wk	tablet	YES	16.5 , 18.9
700 µg/wk	Liquid	YES	3.0 , 3.3
800 µg/wk	tablet	NO	4.0
800 µg/wk	Liquid	NO	1.3 – 1.6
800 µg/wk	tablet	YES	6.3 , 7.8
800 µg/wk	Liquid	YES	1.3 – 1.9

Big difference

Small difference

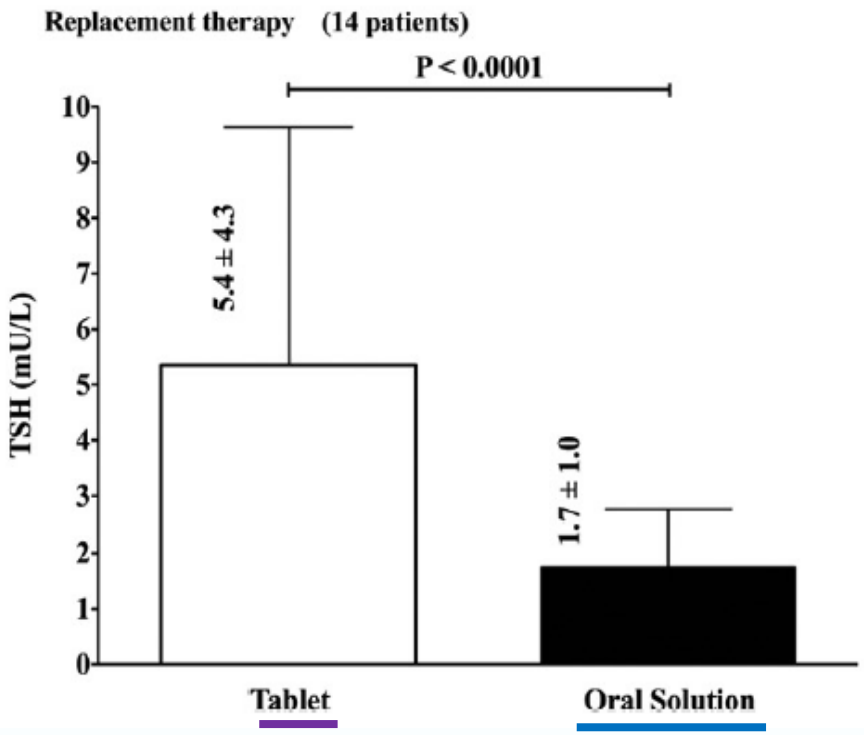
Big difference

Small difference

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*



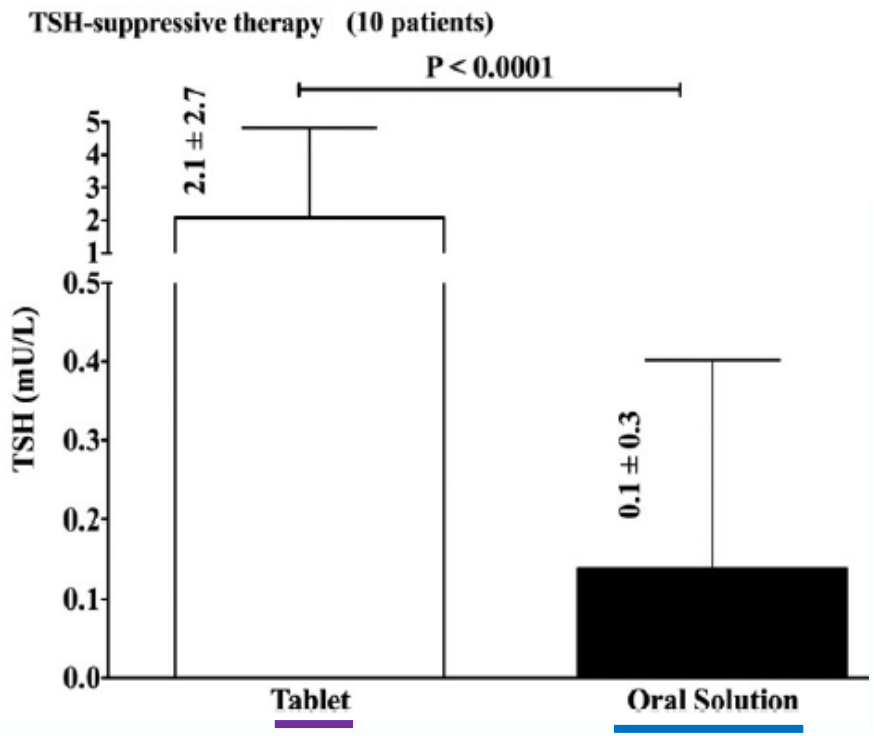


Figure 1. Serum TSH values (means SD) with LT4 therapy (□, **tablet LT4**; ▪, **oral solution**) while maintaining therapy with **PPIs**. The **switch** was **performed at the same daily dose.**

Vita R, Saraceno G, Trimarchi F, Benvenga S. Switching 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*

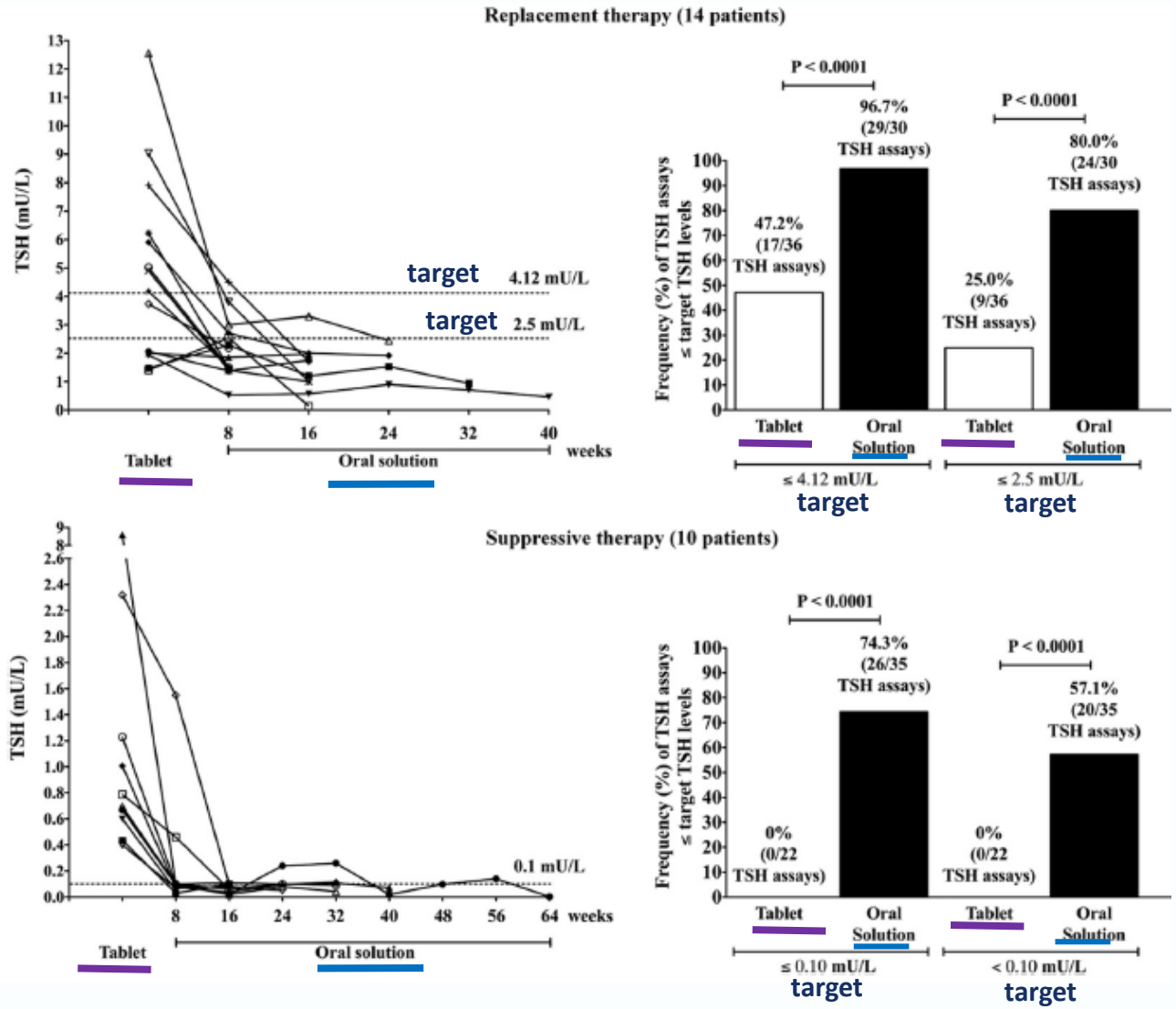
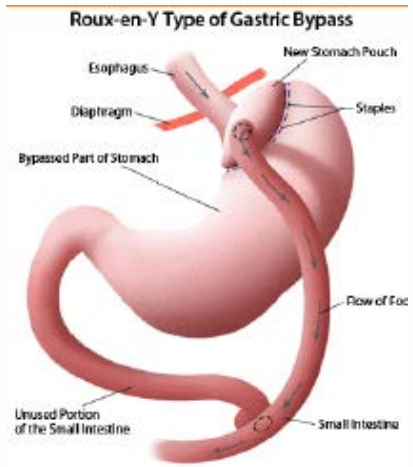


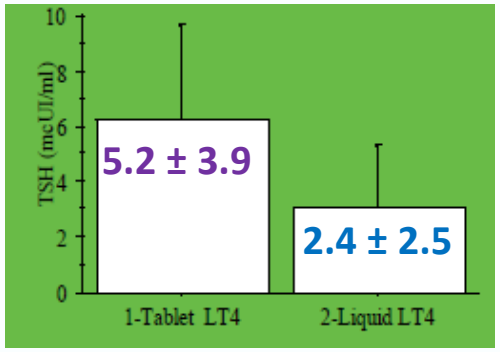
Figure 2. The **serum TSH** trend over time with the **tablet formulation** or the **oral solution** LT4 while maintaining therapy with **PPIs** in individual patients.

So that the figure is not too complicated, the illustrated TSH level with tablet LT4 is the individual mean level

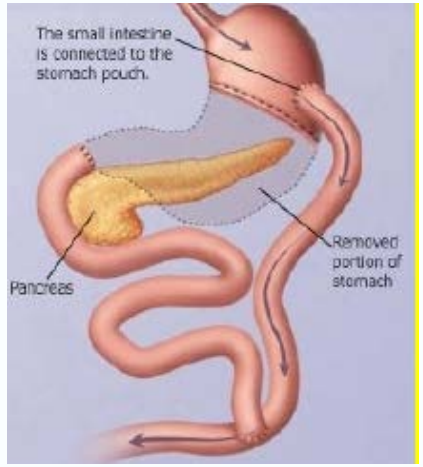
P. Fallahi, R. Vita, S. Camastra, I. Ruffilli, S. Benvenga, A. Antonelli, S. M. Ferrari

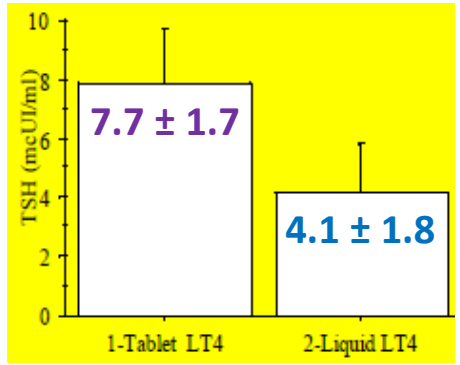
Serum TSH levels normalized in patients undergone to bariatric surgery after switching from Levo-thyroxine in tablet form to an oral liquid formulation. *Endocrine Society, San Diego, 2015*





tablet liquid





tablet liquid

Roux-en-Y gastric bypass

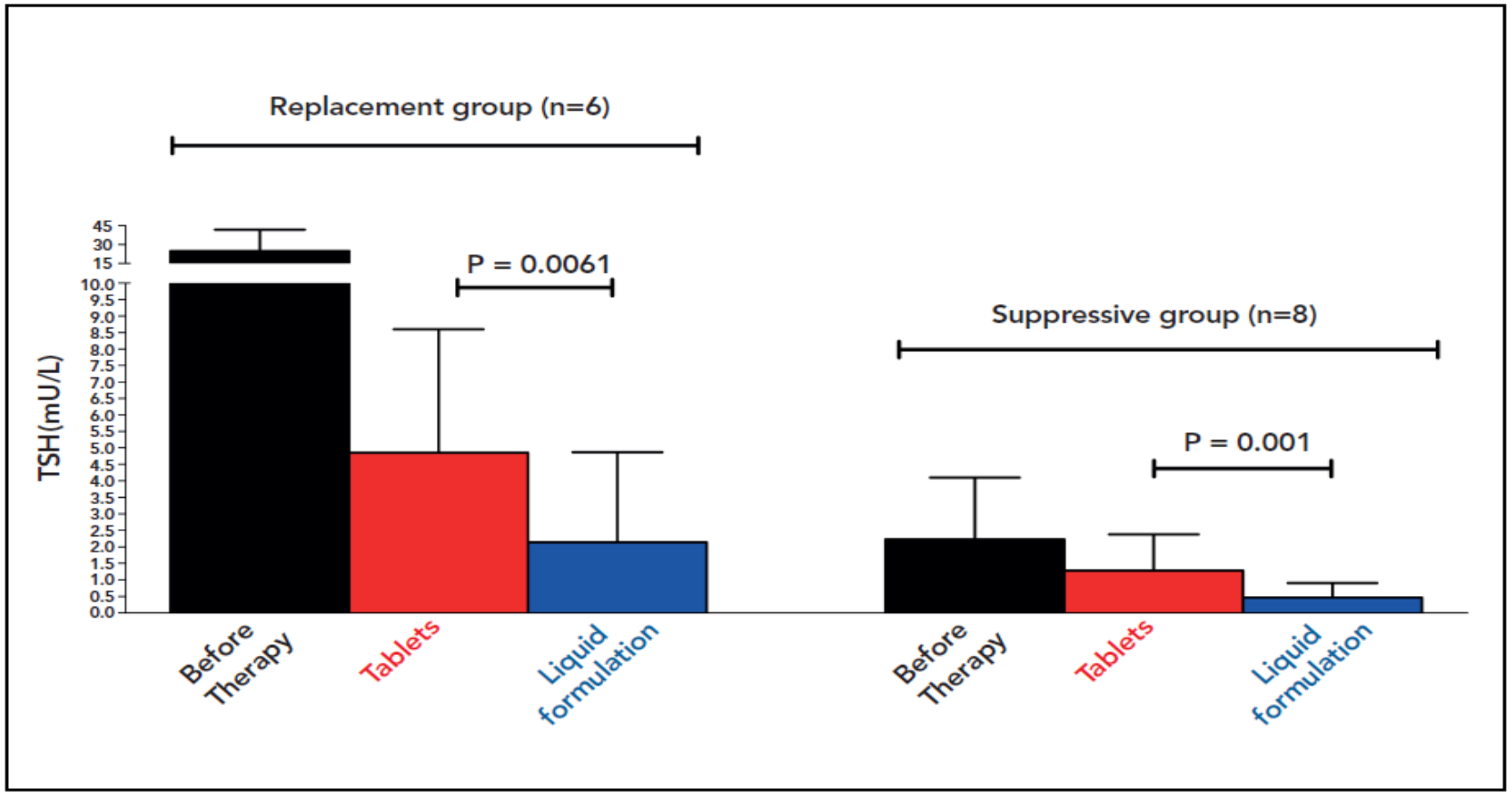
TSH levels of **7 patients** treated with **gastric bypass** were elevated after the operation (from 2 to 7 months later). After switching (with the same dosage, 30 minutes before breakfast) from **oral tablets** to a **liquid formulation**, TSH was significantly reduced. TSH was evaluated 1-3 months 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*

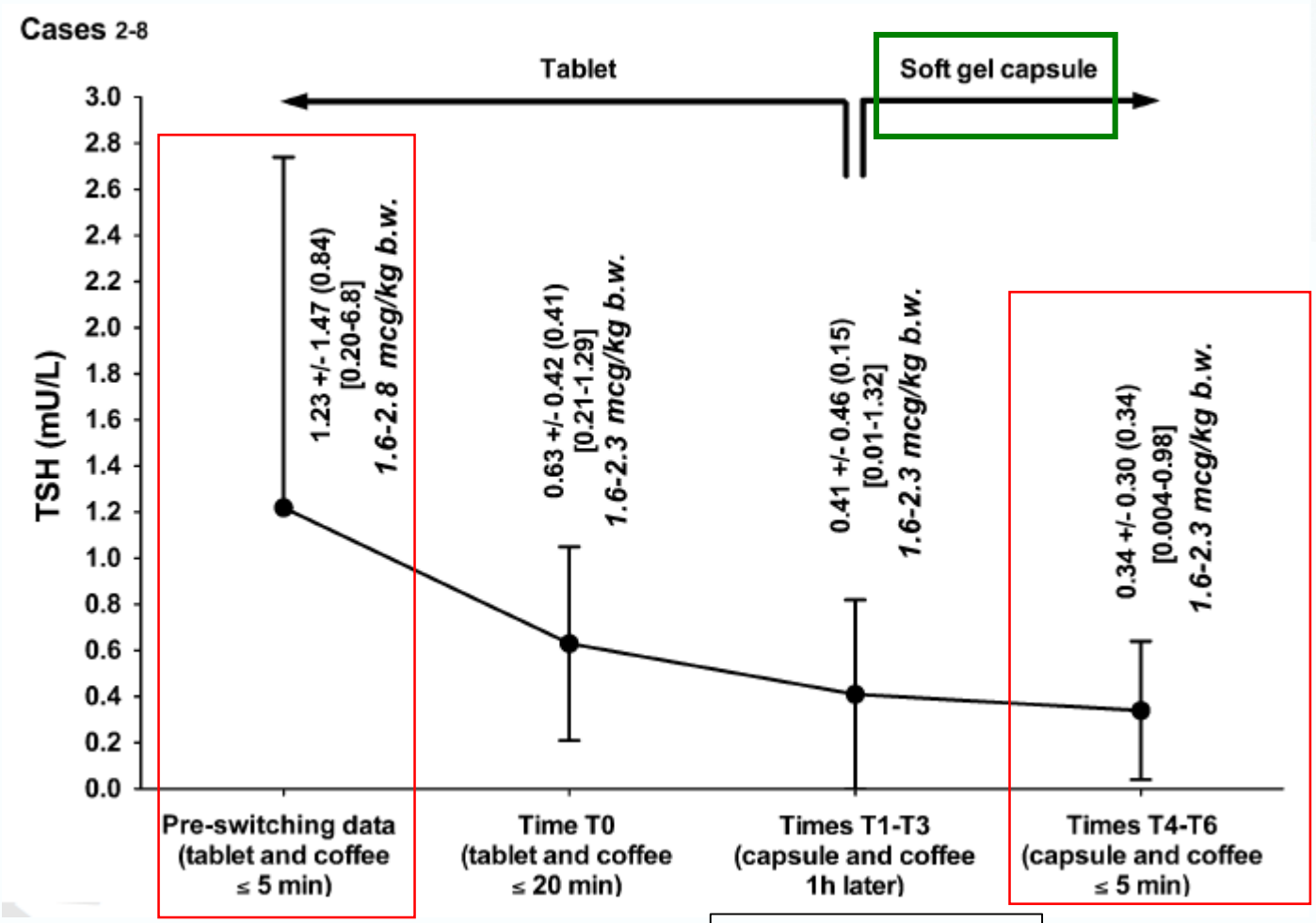
	tablet			Soft Gel capsule		tablet
mcg/day	100	125	150	125	100	100
TSH, mU/L	≥ 4.0	2.4	0.6	0.46 *vs.* 2.4	2.35 *vs.* ≥ 4.0	3.2 , 4.5

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)

	Tablet	Soft Gel Capsule
AUC0-4h	12710	16240 (+ 27.8%)
Cmax	73	108 (+ 48%)
Tmax	180	120 (60 min faster)

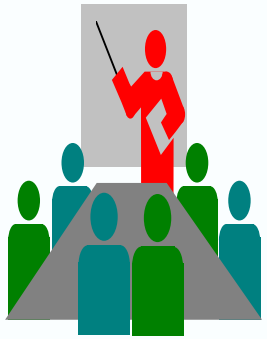
Vita R, Saraceno G, Trimarchi F, Benvenga S. A novel formulation of L-thyroxine (L-T4) reduces the problem of L-T4 malabsorption by coffee observed with traditional tablet formulations. *Endocrine 43: 154-160, 2013*



P= 0.00028

With tablets and coffee
1 h later
TSH was 0.28 ± 0.20

MESSAGGI DA PORTARE A CASA



- Le cp di L-T4 vanno assunte con acqua al mattino, 1 ora prima di colazione (o del solo caffé).
- 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 caffé, 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].

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.

Burch HB, Burman KD, Cooper DS, Hennessey JV. **A 2013 survey** of **clinical practice patterns** in the **management of primary hypothyroidism**. *J Clin Endocrinol Metab. 2014 Jun; 99(6):2077-85.*

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

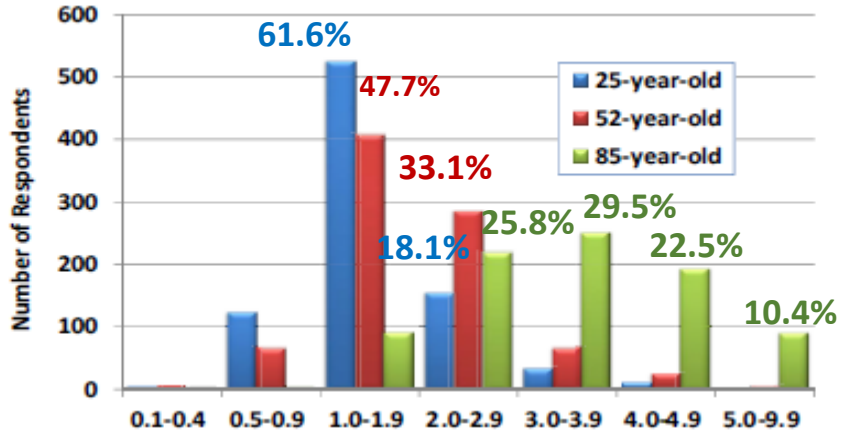
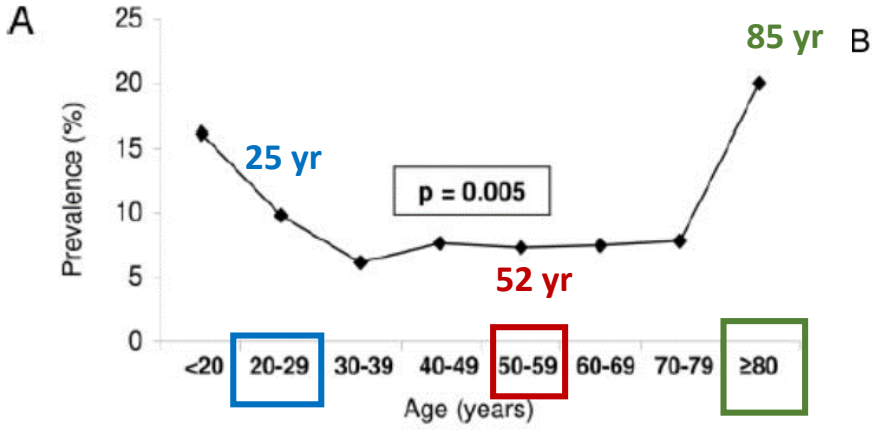
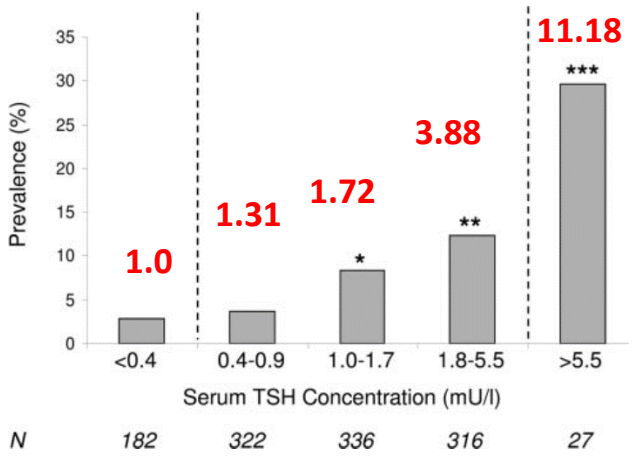


FIG. 1. A, Prevalence of malignancy in relation to patients' **age**.

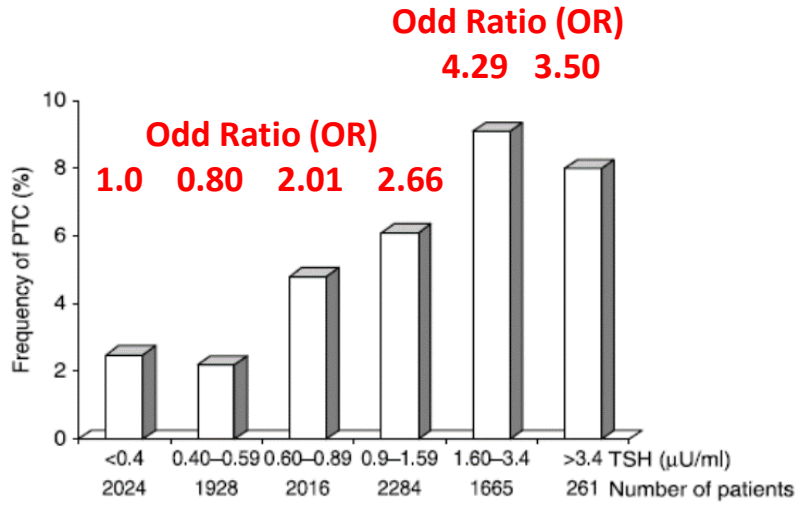


Boelaert K et al, JCEM 2006

Prevalence of DTC or PTC according to **serum TSH** concentrations



Boelaert K et al, JCEM 2006



Fiore et al, ERC 2009

Burch HB, Burman KD, Cooper DS, Hennessey JV. A 2013 **survey of clinical practice patterns** in **the management of primary hypothyroidism**. *J Clin Endocrinol Metab. 2014 Jun; 99(6):2077-85.*

Methods: Clinical members of **The Endocrine Society (TES), the ATA**, and the **AACE** were asked to take a web-based survey consisting of 30 questions dealing with **testing, treatment**, and modulating factors in the **management** of **primary hypothyroidism**.

Results: In total**, 880 respondents completed** the survey, including **618 members of TES, 582 AACE members**, and **208 ATA members. *North American*** respondents accounted for **67.6%, *Latin American* 9.7%, *European* 9.2%, *Asia and Oceania* 8.1%,** and ***Africa*** and ***Middle East 5.5%*** …

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)

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%).**

Burch HB, Burman KD, Cooper DS, Hennessey JV. **A 2013 survey** of **clinical practice patterns** in **the management of primary hypothyroidism** *J Clin Endocrinol Metab. 2014 Jun; 99(6):2077-85.*

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.**

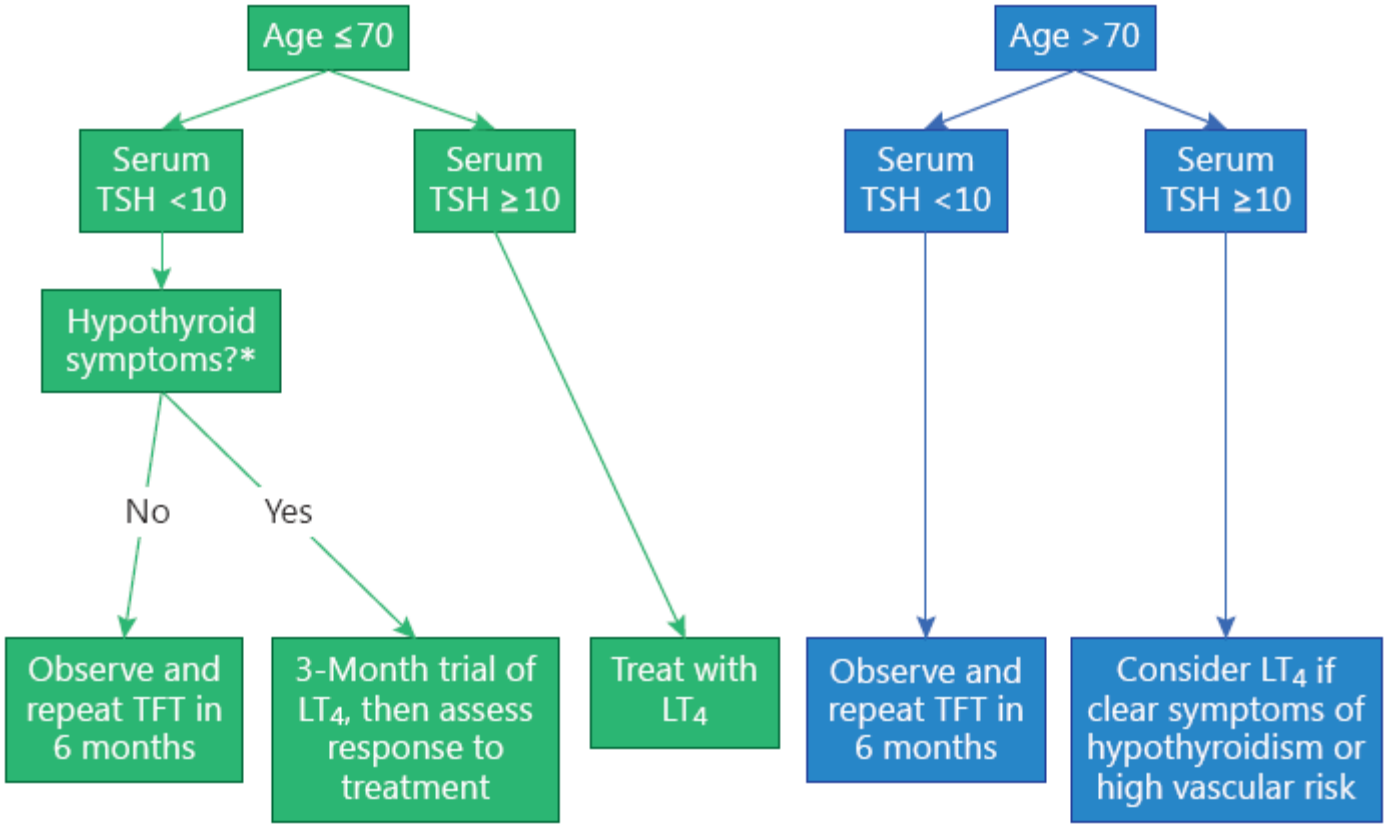
continued

2013 ETA Guideline: Management of Subclinical Hypothyroidism

Simon H.S. Pearce[a, b] Georg Brabant[c] Leonidas H. Duntas[d] Fabio Monzani[e] Robin P. Peeters[f] Salman Razvi[a, g] Jean-Louis Wemeau[h]

Eur Thyroid J 2013;2:215–228

Fig. 1. Suggested management algorithm. Initial management of persistent subclinical hypothyroidism in non-pregnant adults: persistent subclinical hypothyroidism describes patients with elevated serum TSH and within reference range serum FT 4 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**.



Pearce SHS et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism.
Eur Thyr J 2: 215-228, 2013.

- (1) There are two categories of SCH according to the elevation in serum TSH level: mildly increased **TSH levels 4.0–10.0 mU/lL**, 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

Pearce SHS et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism.
Eur Thyr J 2: 215-228, 2013.

- **(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 FT 4** should be **measured**. 3W
- **(11) L –T4 therapy of SCH is able to reduce the l**evels 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

Pearce SHS et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism.
Eur Thyr J 2: 215-228, 2013.

- **(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-T 3) or combined L –T4lL-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 ingest**ion. 2S

Pearce SHS et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism.
Eur Thyr J 2: 215-228, 2013.

- **(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

dr. *Giovanna Saraceno*
dr. *Roberto Vita*

prof. Francesco Trimarchi

ARGOMENTO

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