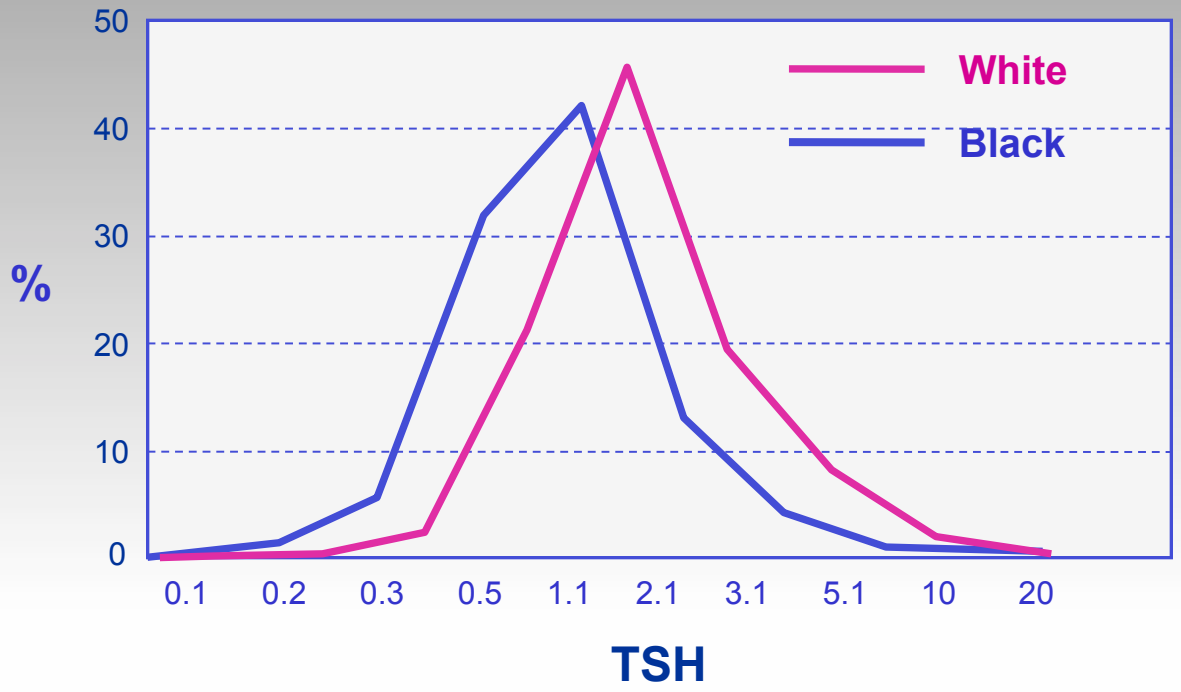
Ipotiroidismo Non Responsivo Alla Terapia Come Inquadrarlo

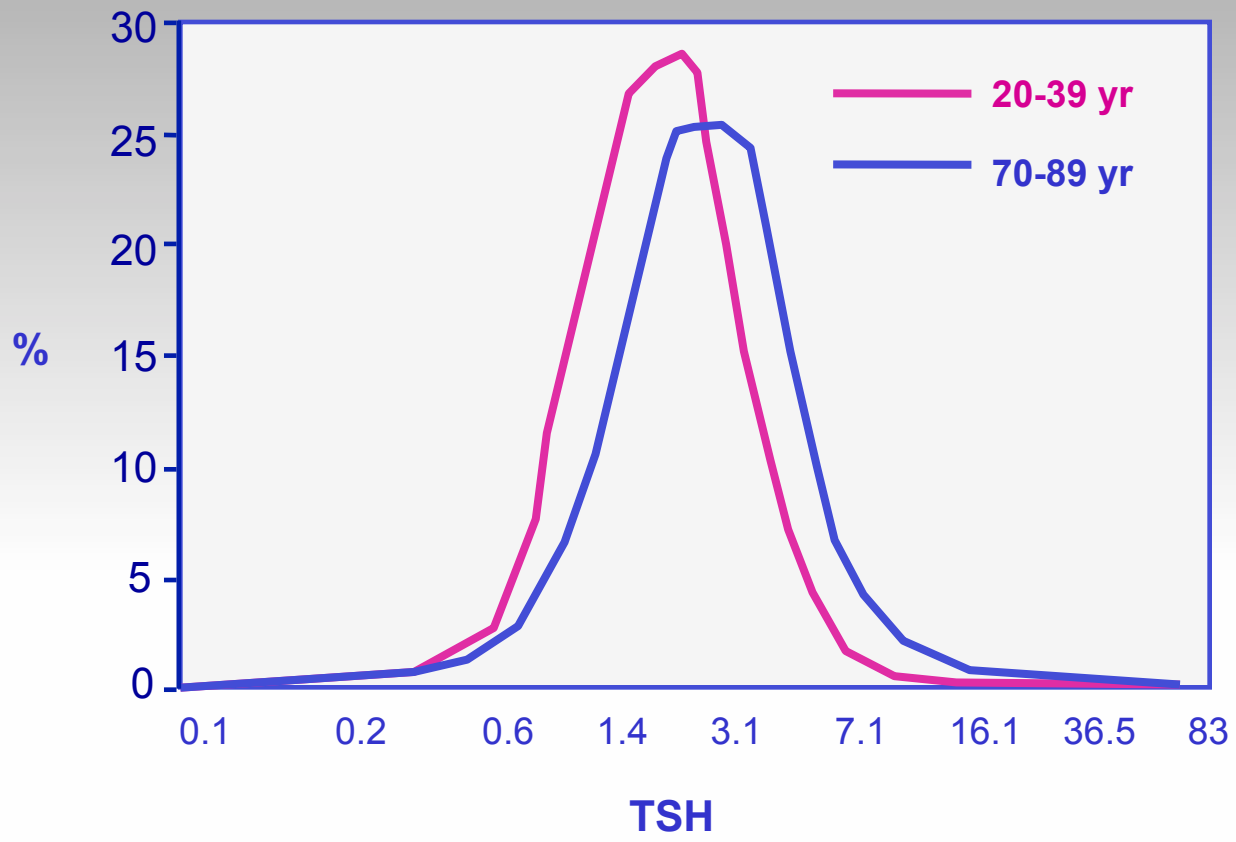
Dott. Roberto Negro
U.O. Endocrinologia
Lecce



Serum TSH distribution in U.S. reference population by ethnicity. (Population without thyroid disease, goiter, or taking thyroid medication and without risk factors that include pregnancy, taking estrogen, androgens, or lithium, and the presence of thyroid antibodies and biochemical evidence of hypothyroidism or hyperthyroidism.) The shift to the left among blacks is significantly different from whites and Mexican Americans ($P < 0.001$).

Hollowell J.G. et al., *J Clin Endocrinol Metab 2002*; 87: 489-499

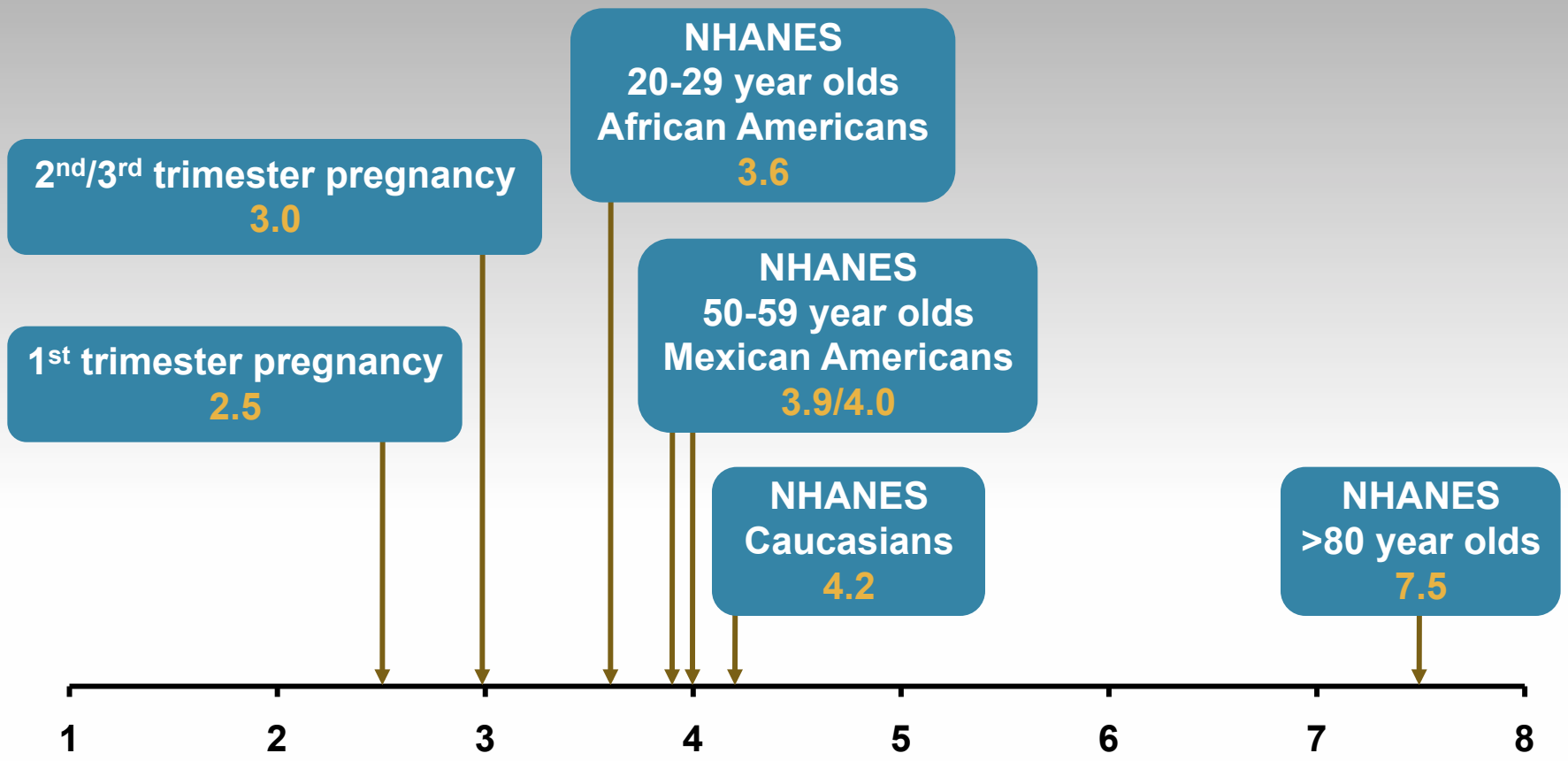
Shift in TSH Distribution to Higher Concentrations With Age



Shift in TSH distribution to higher concentrations with age.
Data from NHANES III (NH3) and NHANES 1999–2002 (NH 99_02) populations.

Surks M.I. et al., *J Clin Endocrinol Metab 2007*; 92: 4575

What is the Normal Upper TSH Limit (97.5%)?



Hollowell: *JCEM 2002*, 87: 4489
Abalovich et al: *JCEM 2007*, 92:S1
Surks: *JCEM 2007*, 92: 4575
Atzmon: *JCEM 2009*, 94: 1251

What is the Target of Treatment? What is "Normal" Serum TSH?

- An elusive and moving target
- Lab reference range (0.4-4.5 mIU/L)
- Factors influencing include age, ethnicity, I-intake and autoimmune disease
- Individual range is very narrow, 0.5 mIU/L overtime

Increased Levothyroxine Requirement

- Decreased intestinal absorption: cholestyramine, ferrous sulfate, sucralfate, calcium, aluminium hydroxide, dietary fiber or soy protein
- Reduced gastric acid secretion: H. Pylori infection, atrophic gastritis, PPI
- Malabsorption: coeliac disease, short bowel syndrome
- Estrogens
- Pregnancy
- Drugs acellerating Levothyroxine metabolism: rifampicin, phenobarbital, phenytoin, carbamazepine

AACE Guidelines 2006

Hypothyroidism ATA/AACE Guidelines

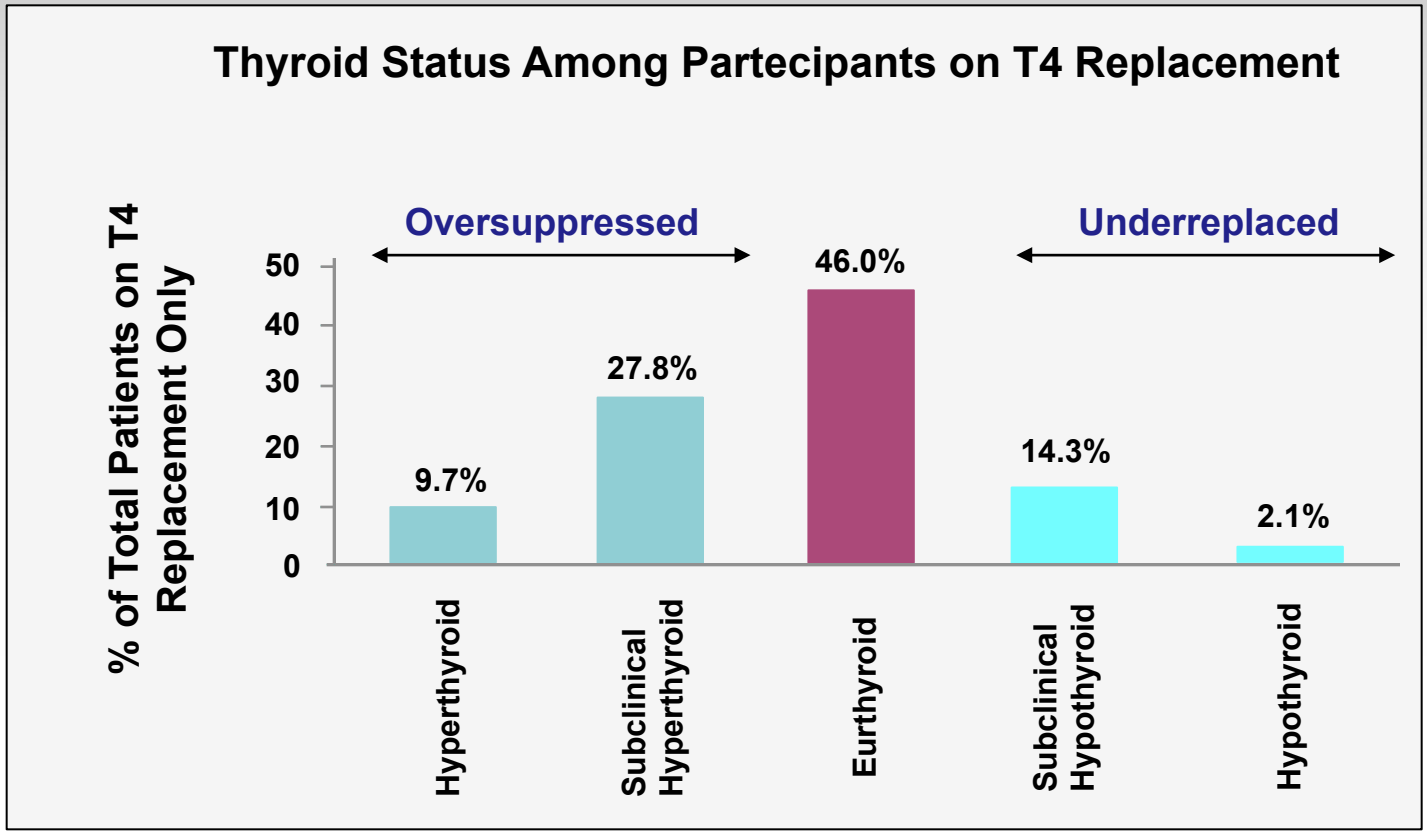
- Patients with hypothyroidism should be treated with L-thyroxine monotherapy.
- Replacement therapy requires approximately 1.6 µg/Kg of T4 daily.
- Patients being treated for established hypothyroidism should have serum TSH measurements done at 4-8 weeks after initiating treatment or after a change in dose.
- Once an adequate replacement dose has been determinated, periodic TSH measurements should be done after 6 months and then at 12 month intervals or more frequently if the clinical situation dictates otherwise.

ATA-AACE Guidelines 2012

Thyroid Hormone Over-Replacement and Under-Replacement in Elderly

3678 subjects aged 65 yr or older

Thyroid hormone users (n = 339)



Somwaru LL et al., *J Clin Endocrinol Metab 2009*; 94: 1342-1345

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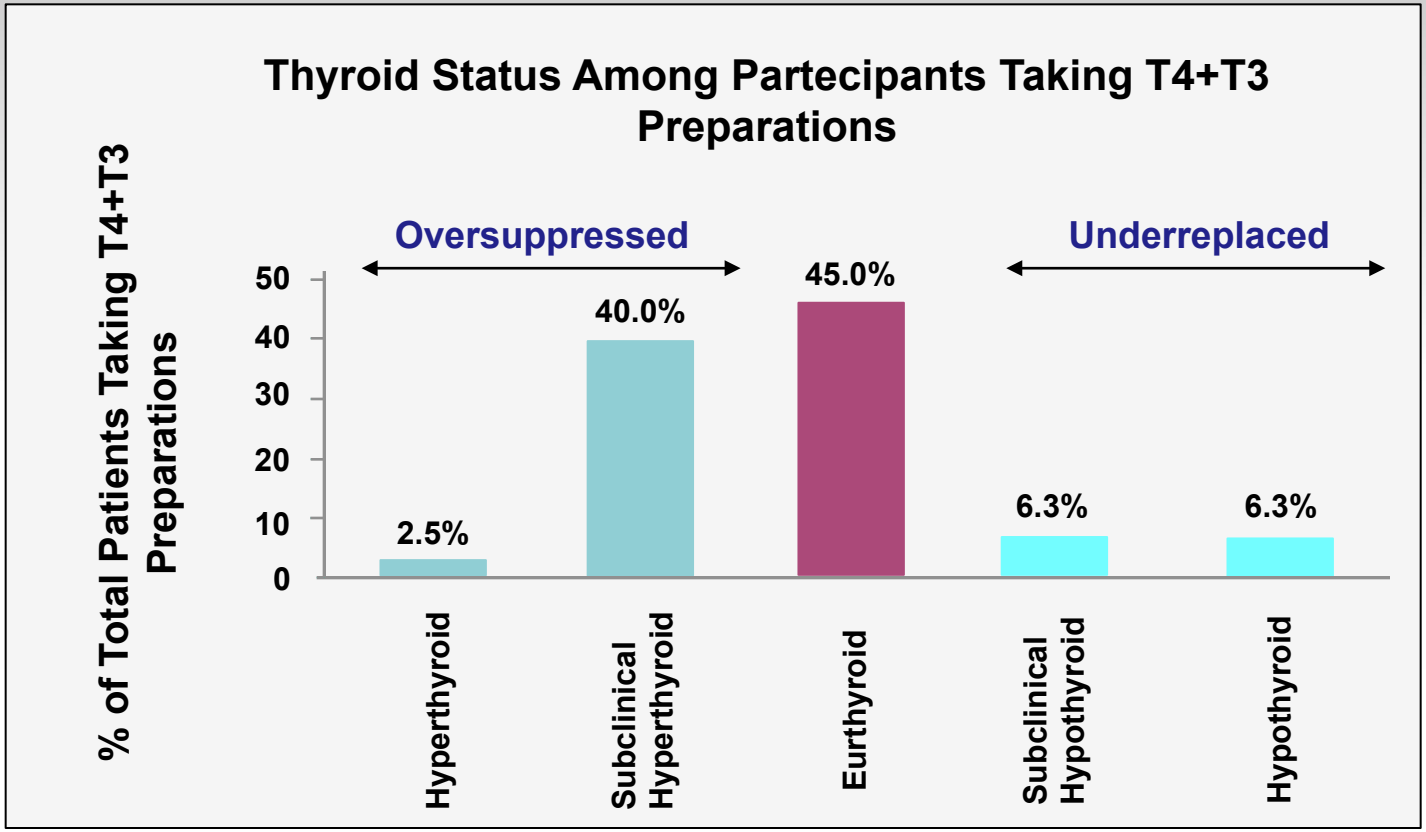
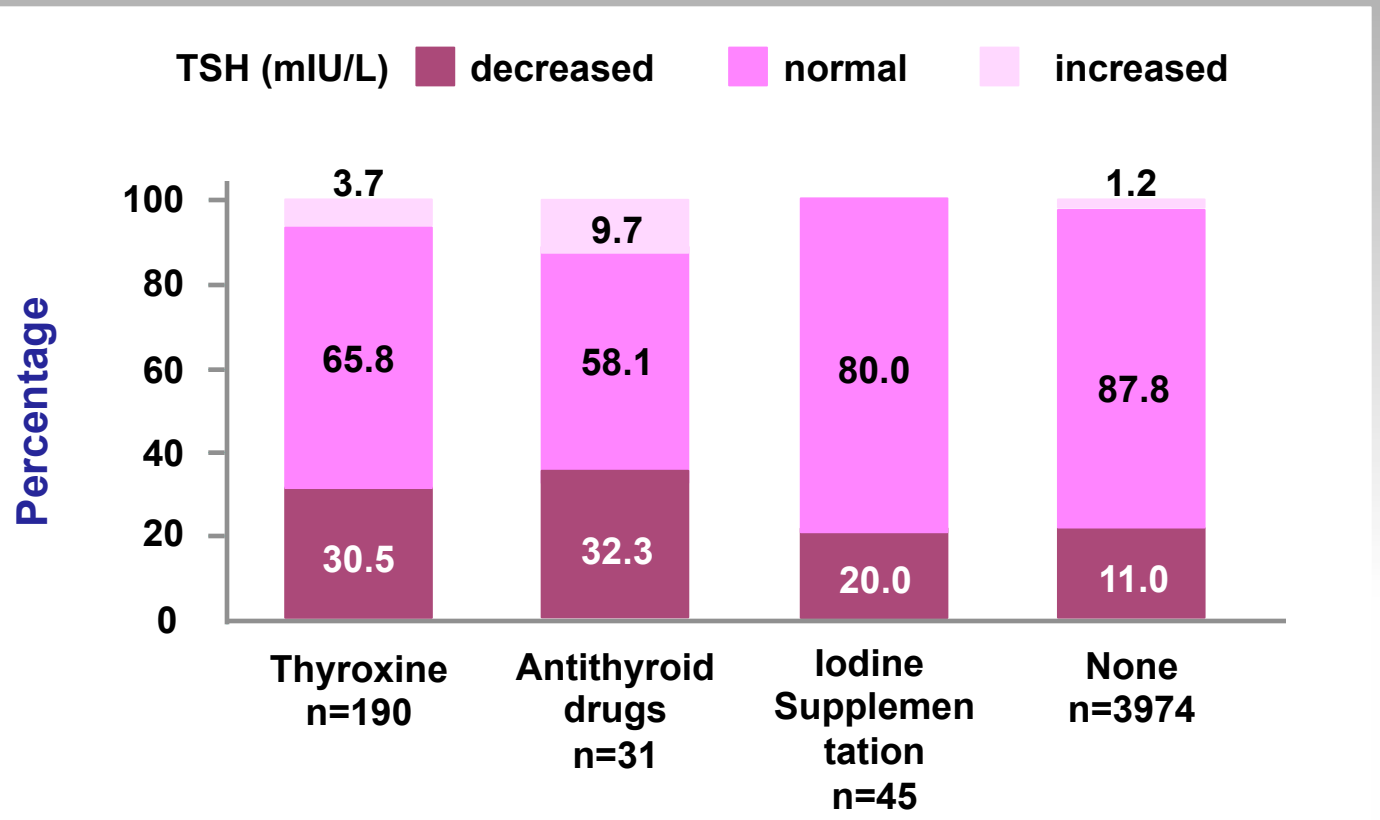


Somwaru LL et al., *J Clin Endocrinol Metab 2009*; 94: 1342-1345

Thyroid Status in Patients Taking Thyroid Medications



Proportion of decreased, normal and increased serum thyroid stimulating hormone (TSH) levels according to the manufacturer's reference range (all ages 0.3-3.0 mIU/L) by type of thyroid medication.

Hannemann A. et al., *BMC Research Notes* 2010; 3:227

Treatment-Refractory Hypothyroidism Case Report

49 year-old man

Clinical history: Graves disease successfully treated with radioiodine ablation 15 years earlier.

TSH: 31.5 mIU/L (0.4-4.5)
FT4: 15.8 pmol/L (10-25)
Dose of LT4: 225 µg/day or 2.7 µg/Kg/daily

Weight: 82 Kg (any change)
Physical exam unremarkable
He reported feeling well
Concomitant medications:
Diltiazem
Any over-the-counter medications or herbal supplements

Ramadhan A. *CMAJ 2012;* 184(2): 205-209

Treatment-Refractory Hypothyroidism Case Report

Laboratory investigations:

Medically *supervised test for the absorption of LT4* was performed. The result of the test showed that only 30% of the medication administered was absorbed.

Biochemistry panel, PTH, 25HydroxyvitaminD, Ferritin, Vitamin B12, Gastrin showed normal results.

A serological test to determine the presence of *Helicobacter pylori* was negative.

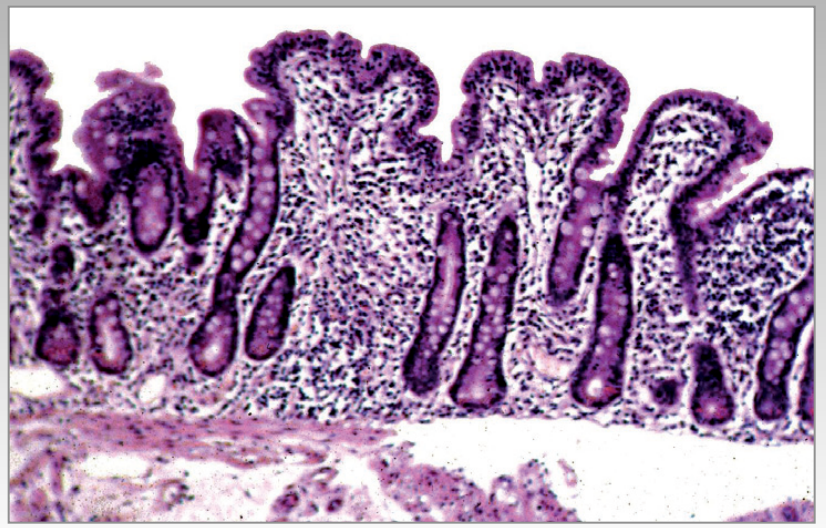
Parietal cell antibody titers were normal.

Ramadhan A. *CMAJ 2012;* 184(2): 205-209

Causes of Treatment-Refractory Hypothyroidism and Suggested Investigations

Transglutaminase Ab IgA: 75.4 U/ml
Negative < 9.0 U/ml
Borderline 9-16 U/ml
Positive >16.0 U/ml

Endoscopic biopsy of the patient's bowel: diagnosis of *celiac disease*



Histologically proven celiac disease affects 3.2%-4.8% of people with autoimmune thyroid disease, compared with 0.4% of the general population.

Screening patients who require higher than expected doses of LT4 to treat their hypothyroidism with tissue transglutaminase antibodies.

The patient's serum TSH levels usually improve after instituting a gluten-free diet for celiac disease or a lactose-restricted diet and lactose-free LT4 formulation for patients with lactose intolerance.

Ramadhan A. *CMAJ 2012;* 184(2): 205-209

Medically Supervised Test for Absorption of Oral Levo-Thyroxine

1. Patient with cardiac or CNS conditions are excluded.
2. Test is conducted in a supervised medical setting.
3. The patient is kept on an overnight fast except for water.
4. The regular LT4 dose is held.
5. Patients are weighed on the morning of the examination and weight is recorded in Kg.

d'Esteve-Bonetti L. et al., *Thyroid 2002*; 12: 633-6
Ogawa D. et al., *Endocr J* 2000; 47: 45-50

Medically Supervised Test for Absorption of Oral Levo-Thyroxine

An oral LT4 load with 1000 µg is administered with a glass of water under medical supervision (50 or 100 µg tablets)

Blood sampling
-30
0
30
60
120
240
360

Most absorption of LT4 takes place within the first and third hours after administration and peak serum FT4 levels are reached within 2 hours after administration.
The 2-hour serum FT4 peak and range reached after the administration of 1000 µg of LT4 have not been validated, but the literature suggests a 2-hour serum peak commonly rising above the upper limit of the reference range with an increment of more than 20 pmol/L in most cases.

***Appendix online*: www.cmaj.ca/lookup/doi:10.1503**

Case Report

- A 44-year-old woman presented to her GP with excessive tiredness
- She had positive TPOAb and TgAb; TSH: 8.37 (0.15-3.5 mU/l); total T4: 86 (60-145 nmol/l)
- She was rendered symptoms free on a dose of 150 µg day, but..

TSH: 14 mU/l (0.15-3-5mU/l)
FT4: 28 (10-27 pmol/l)
FT3: 10 (4.3-7.6 pmol/l)
PRL: 861 (60-390mU/l)

MRI scan: macroadenoma of the right lobe of the pituitary.

Immunocytochemistry: secretion of TSH, PRL, and α-subunit.

Idiculla J.M. et al., *Ann Clin Biochem 2001*; 38: 566-71

Pseudomalabsorption: Case Report

55 year-old woman

Clinical history: total thyroidectomy 15 years previously for multinodular goiter.

Over the years: 100 µg/day ⇒ 300 µg/day ⇒1000 µg/day

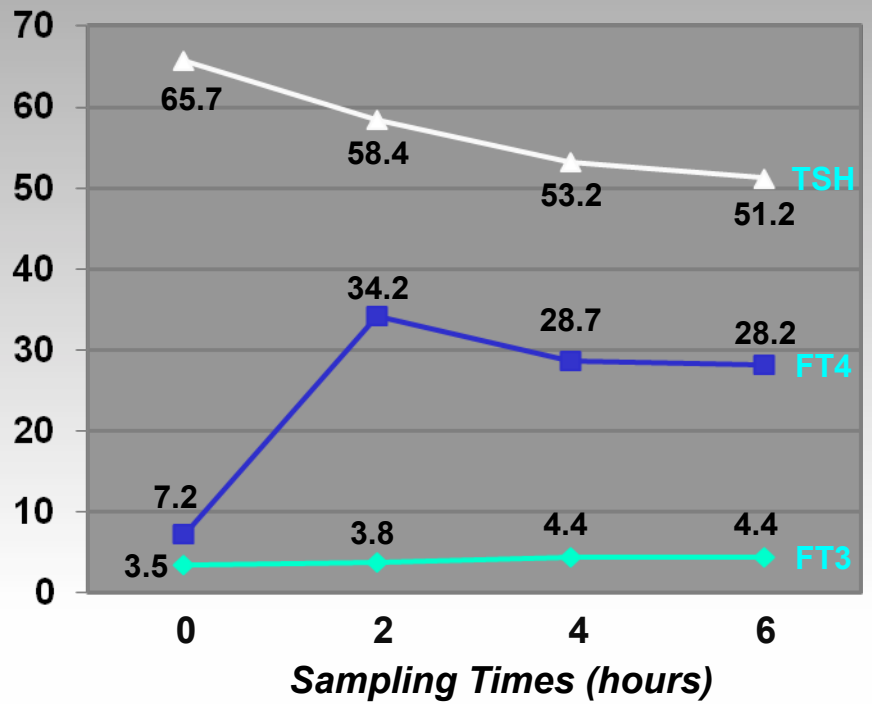
- ✓ TSH: 72.25 mIU/L (0.3-4.2)
- ✓ FT4: 3.5 pmol/L (12.0-22.0)
- ✓ FT3: 3.5 pmol/L (3.1-6.8)
- ✓ Vitamin B_{12}, folate, calcium, ferritin, liver function tests was normal
- ✓ Negative screen for celiac disease

- ✓ Symptoms of hypothyroidism: weight gain and feeling cold
- ✓ No clinical signs of malabsorption
- ✓ Concomitant medications: antihypertensive therapy
- ✓ No medication that might interfere with the intestinal absorption of LT4

Srinivas V. et al., *Endocr. Pract. 2010*; 16(6): 1012-15

Pseudomalabsorption: Case Report

Oral LT4 load with 1000 µg is administered with a glass of water under medical supervision (50 or 100 µg tablets)



Pseudomalabsorption is becoming a common finding in patients with hypothyroidism. This term is applicable when a patient is not taking the prescribed medication regularly. Poor adherence to treatment is a well-recognized problem in patients with chronic disorders. The dose frequency, the treatment duration, the number of medications, the fear of medication-induced side effects, the physician-patient relationship, and the patient's psychiatric background can all contribute to the development of poor adherence treatment.

Srinivas V. et al., *Endocr. Pract. 2010*; 16(6): 1012-15

Thyroxin Overdose due to RF Interferences in TSH-Assays

64 year-old man

- Hypothyroidism was diagnosed after a routine visit to cardiologist who discovered a mildly elevated TSH and initiated LT4 treatment.
- No clinical evidence of hypothyroidism.
- Despite LT4 replacement therapy (*250 µg/day*) there was a *concomitant increase in plasma FT4 and TSH.*

TSH assay interference was suspected.

Georges A. et al., *Clin Chem Lab Med 2011*; 49(5): 873-75

TSH Assay: Antibody Interference

- Immunoassays are susceptible to interferences by anti-hormone antibodies, heterophilic antibodies or rheumatoid factor (RF). Sandwich assays are more susceptible.

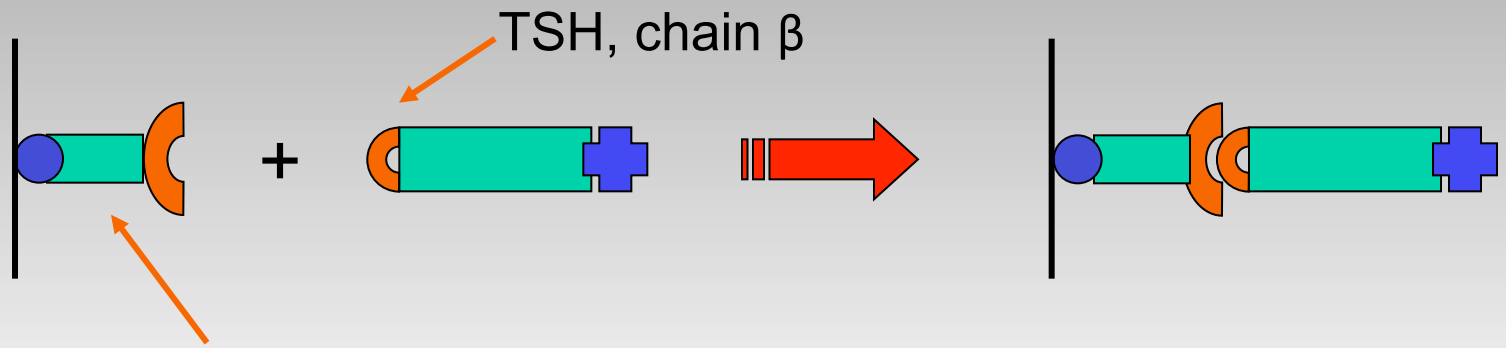
Heterophile antibodies are weak polyspecific antibodies that are capable of cross-linking the capture and detection antibodies leading to a falsely high TSH.

RF is an autoantibody that binds to multiple antigenic determinants on the Fc portion of IgG. RF may be responsible for false determination of TSH concentrations.

Georges A. et al., *Clin Chem Lab Med 2011*; 49(5): 873-75

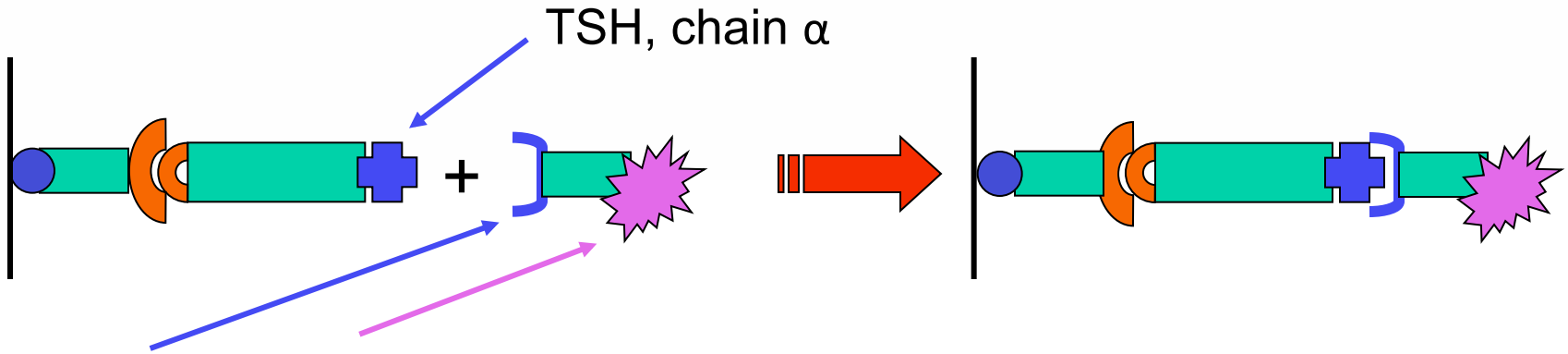
TSH Sandwich Assay

1st Incubation



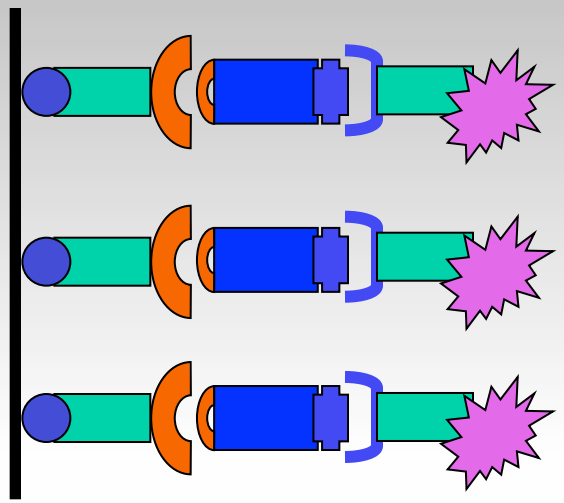
Monoclonal Abs against β-TSH (*capture Ab*), bound to solid phase

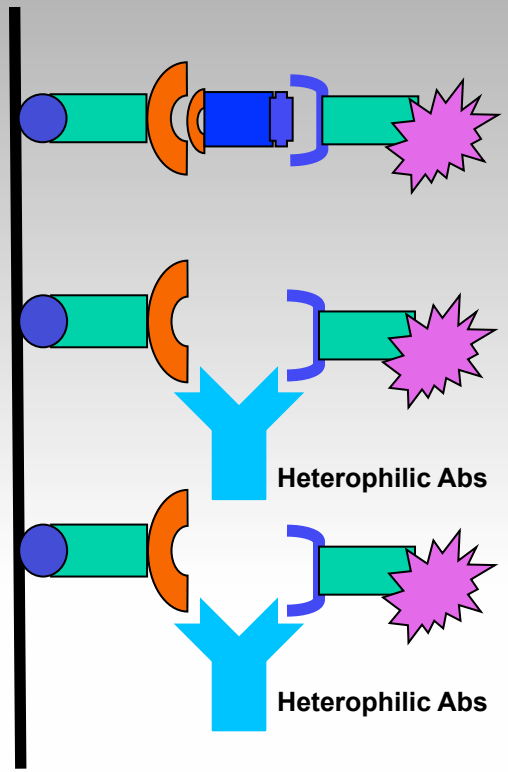
2nd Incubation



Monoclonal labelled Abs against α-TSH (*detector Ab*)

TSH Assay: Antibody Interference

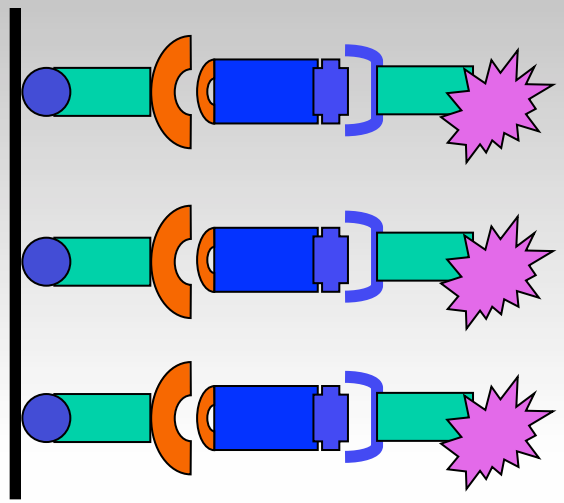


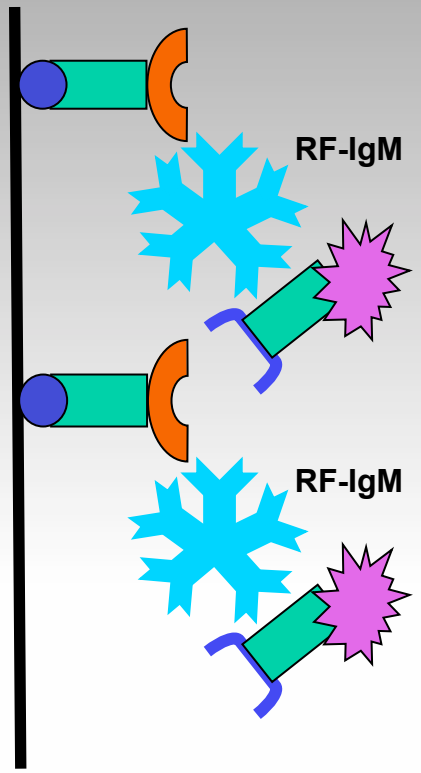


TSH Sandwich Assay:
Non competitive sandwich assay based on capture Abs bound to solid phase and labelled detection Abs.

Abs interference in the TSH assay:
The presence of endogenous heterophilic antibodies was responsible for the falsely increased TSH concentrations.

TSH Assay: Antibody Interference





TSH Sandwich Assay:
Non competitive sandwich assay based on capture Abs bound to solid phase and labelled detection Abs.

Rheumatoid Factor Interference:
RF (IgM and anti-human IgG) may bind to multiple antigenic determinants on the Fc portion of IgG.

Thyroxin Overdose due to RF Interferences in TSH-Assays

64 year-old man

- Hypothyroidism was diagnosed after a routine visit to cardiologist who discovered mildly elevated TSH and initiated LT4 treatment.
- No clinical evidence of hypothyroidism.
- Despite LT4 replacement therapy (*250 µg/day*) there was a concomitant increase in plasma FT4 and TSH.

TSH assay interference was suspected.

Analytical investigation revealed:

- ✓ Non linear concentrations of TSH after serum diluition
- ✓ Decreased TSH concentrations after removal of heterophilic antibodies
- ✓ Appropriately decreased TSH concentrations in alternate TSH assays
- ✓ Identification of increased concentrations of RF

Georges A. et al., *Clin Chem Lab Med 2011*; 49(5): 873-75

THE LANCET, OCTOBER 7, 1972

REVERSIBLE HYPOTHYROIDISM IN ADDISON'S DISEASE

HOSSEIN GHARIB
STEPHEN F. HODGSON
CLIFFORD F. GASTINEAU
DONALD A. SCHOLZ
LUCIAN A. SMITH

Mayo Clinic and Mayo Foundation,
Rochester, Minnesota 55901, U.S.A.

Hypothyroidism and Adrenal Insufficiency Case Report

- A 24 yr diabetic patient
- Malaise, lethargy, recurrent hypoglicemia
- T4: 40nmol/l (60-140); T3:1.2nmol/l (1.6-3.0); TSH: 90mIU/l (<8.0)

- Tx: LT4 50µg

- Within 2 days: hypoglicemia; hypotension
- Na: 128mmol/l; K: 5.8mmol/l
- Hypothyroidism confirmed

- ACTH: 514ng/l (<80);Cortisol: 150nmol/l (150-600)
- Tx: Hydrocortisone 30mg; LT4 Tx withdrawn
- The patient remained euthyroid in the next months

Burrows AW. *Postgrad Med J 1981*; 57: 368-70

Hypothyroidism and Adrenal Insufficiency

- Several interactions between glucocorticoid and pituitary-thyroid axis have been reported
- It is suggested that the physiological concentration of glucocorticoid has a suppressive effect on TSH secretion

- Glucocorticoid deficiency may be one of the causes of the increase in TSH

Hypothyroidism Refractory to Oral Therapy Case Report

47 year-old woman

Clinical history: two years earlier, total thyroidectomy and lymphadenectomy had been performed for left-sided *papillary thyroid cancer* (pT3N0M0), followed by ablative radioiodine treatment (3.7 GBq). Prior to thyroid surgery she had normal thyroid function.

LT4 substitution was begun, however hypothyroidism persisted despite increasing LT4 dosages (75 ⇒ 300 µg/day).

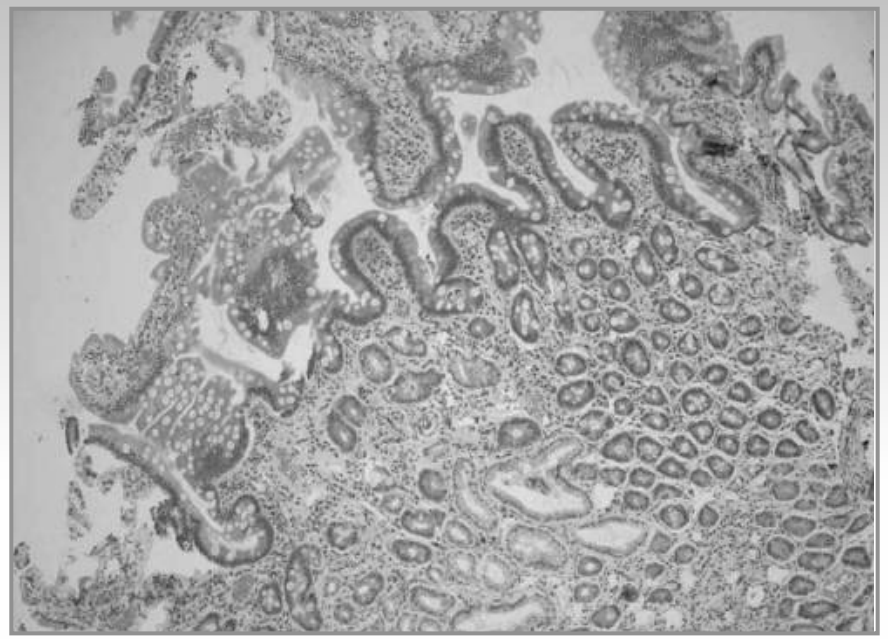
- ✓ TSH: 77.4 mIU/L (0.3-4.2)
- ✓ FT4: 7.1 pmol/L (12.0-22.0)
- ✓ FT3: 2.3 pmol/L (3.1-6.8)
- ✓ Negative screen for celiac disease, atrophic gastritis, HP infection

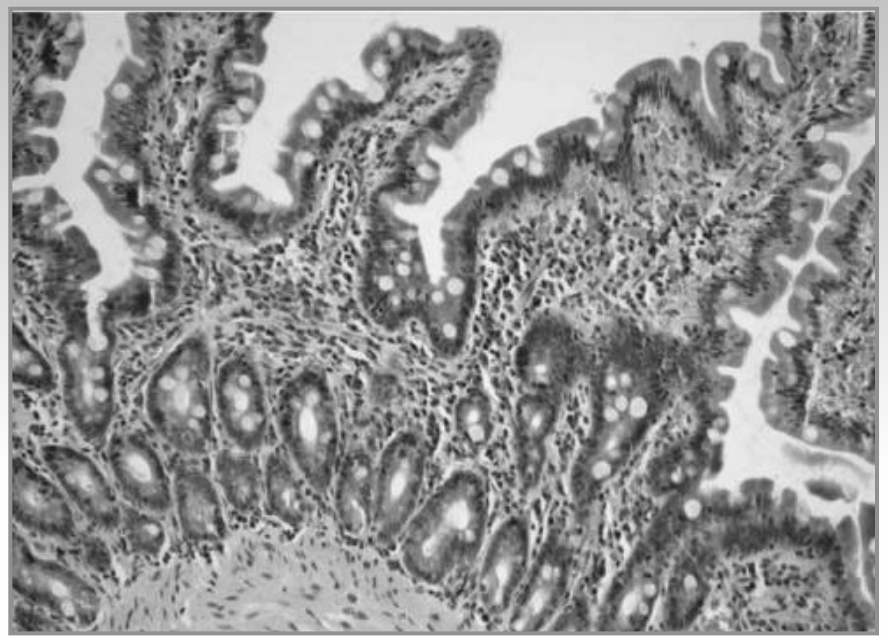
- ✓ Symptoms of hypothyroidism: weight gain, lack of energy, depression
- ✓ She had puffy, dry skin, delayed relaxation of ankle jerks, peripheral edema
- ✓ Concomitant medications: ramipril, metoprolol

Tonjes A. et al., *Thyroid 2006*; 16(10): 1047-51

Hypothyroidism Refractory to Oral Therapy Case Report

Histology of small bowel biopsies

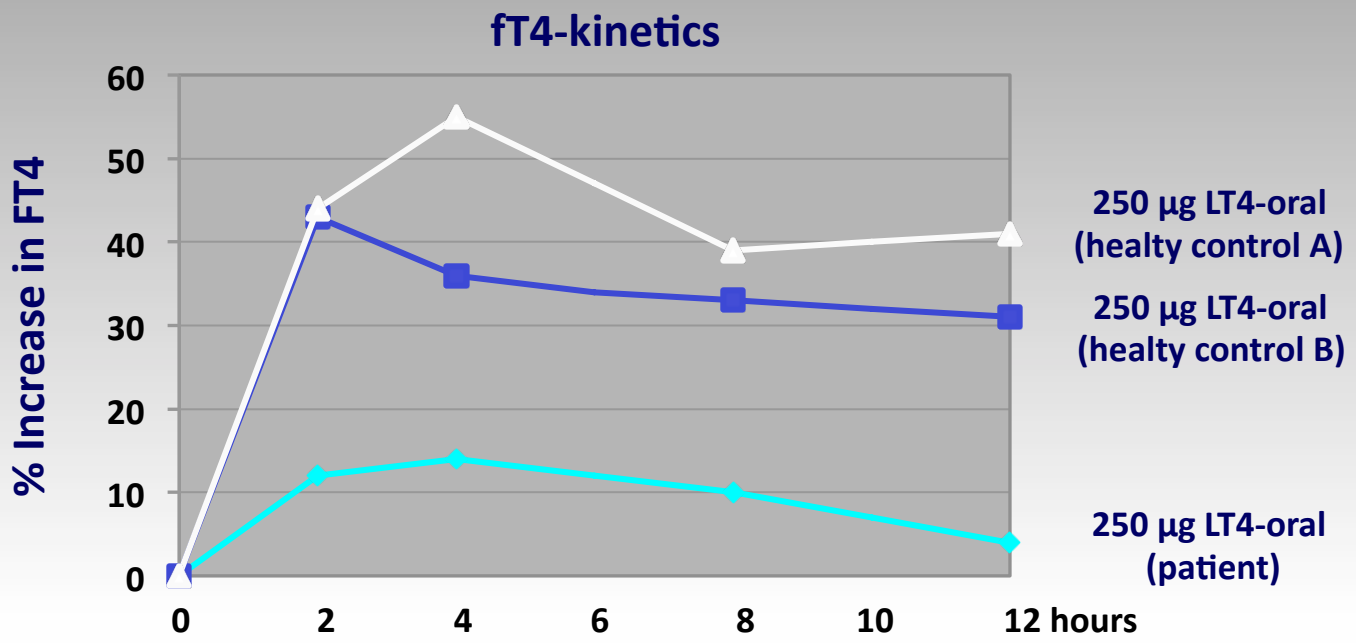




Duodenal biopsy: Low-grade inflammatory changes

Tonjes A. et al., *Thyroid 2006*; 16(10): 1047-51

Hypothyroidism Refractory to Oral Therapy Case Report

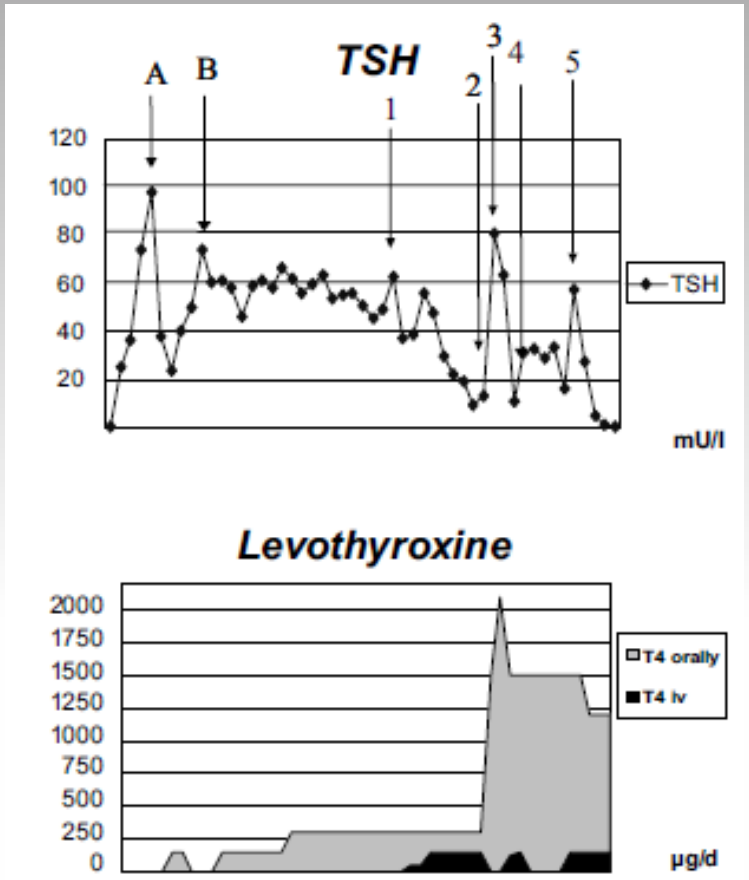


Kinetics of enteral levo-thyroxine absorption

Comparison of oral LT4 administration in the patient and two healty female controls confirmed a marked impairment in intestinal absorption in the patient.

Tonjes A. et al., *Thyroid 2006*; 16(10): 1047-51

Hypothyroidism Refractory to Oral Therapy Case Report



Because hypothyroidism persisted despite supervised administration of oral LT4 preparations, a permanent intravenous supply of LT4 was commenced using a morphine pump device.

Follow-up showed stable normal TSH values over a period of more than 6 months on continuous intravenous administration of 288 µg/day of LT4.

A: first WBS (june 2001); B: second WBS (october 2001); 1: initiation of additive iv LT4 substitution 250 µg twice weekly (october 2003); 2: discontinuation of iv substitution (february 2004); 3: reinitiation of iv LT4 substitution (april 2004); 4: discontinuation of iv substitution (july 2004); 5: reinitiation of additive iv LT4 substitution 250 µg 3 times per week (october 2004)

Tonjes A. et al., *Thyroid 2006*; 16(10): 1047-51

Case Report

- Celiac disease
- TSHoma + TAI
- Pseudomalabsorption
- Interferences in TSH assay
- Adrenal insufficiency
- Hypothyroidism Refractory to Oral Therapy

Treatment-Refractory Hypothyroidism

KEY POINTS

When LT4 requirements exceed 2.5 µg/Kg daily (the mean treatment dosage of thyroxine is 1.6 µg/Kg daily), treatment-refractory hypothyroidism is a possibility.

A supervised test for the absorption of oral LT4 can exclude patient nonadherence to the medication.

The results of investigations for causes of decreased absorption or increased demand for LT4 will guide treatment.

Causes of Treatment-Refractory Hypothyroidism and Suggested Investigations

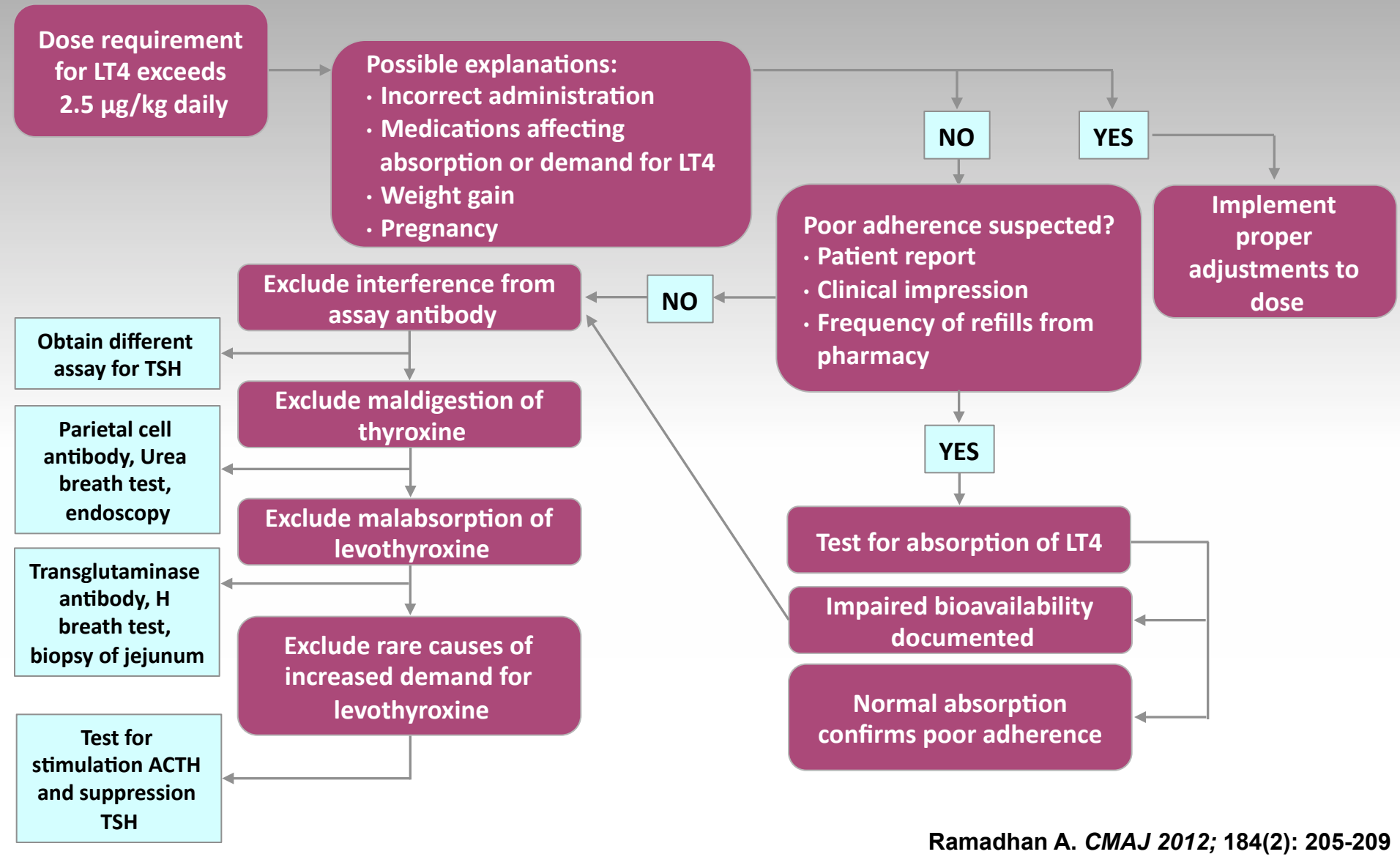
Decreased bioavalability

Poor Adherence to drug therapy	Patient report, clinical impression or frequency of prescription refills at pharmacy Absorption of oral levothyroxine
Maldigestion related to hypochlorhydria Proton-pump inhibitor therapy Autoimmune atrophic gastritis Gastric infection with *Helicobacter pylori*	Medication history Antiparietal cell antibodies Carbon-14 urea breath test, esophagogastroduodenoscopy
Intestinal malabsorption of L-thyroxine Luminal factors (food, coffee and medications) Intramural factors (short bowel syndrome, lactose intolerance, gluten enteropathy, inflammatory bowel disease, infiltrative enteropathy, infection with *Giardia)*	Diet and medication history (including herbal and over-the-counter medications) Transglutaminase antibodies Esophagogastroduodenoscopy with jejunal biopsy Hydrogen breath test for lactose intolerance Culture and microscopy of stool for ova and parasites

Ramadhan A., Tamilia M., *CMAJ 2012;* 184(2): 205-209

Suggested Approach to Treatment-Resistant Hypothyroidism

Roma,
9-11 novembre 2012



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