

Thyroid Function Disorders Hyperthyroidism and Hypothyroidism

National Nurse Practitioner Symposium
Keystone, Colorado
July 11, 2020
1:30-3:00 PM

Michael T. McDermott MD
Director, Endocrinology and Diabetes Practice
University of Colorado Hospital

Disclosures

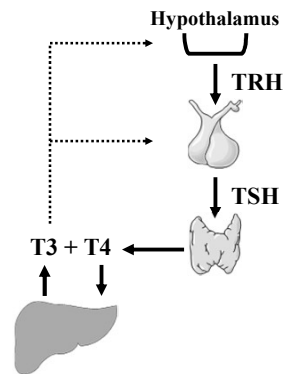
- Michael T. McDermott MD is on an Advisory Board for Novo Nordisk.
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed.

Thyroid Function Disorders

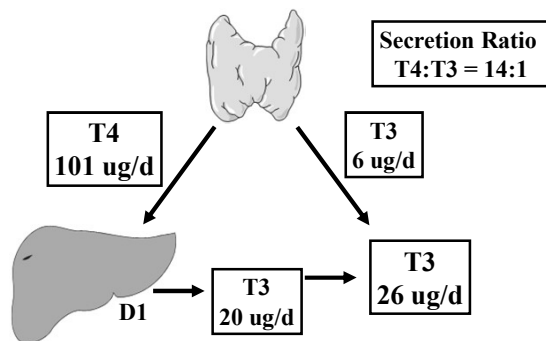
Learning Objectives

- Explain the diagnostic tests for hyperthyroidism and hypothyroidism.
- Discuss the clinical significance of overt and subclinical disorders of thyroid function.
- Review the management recommendations for thyroid function disorders and strategies for patients who have persistent symptoms while on biochemically adequate thyroid treatment.

Thyroid Function Regulation



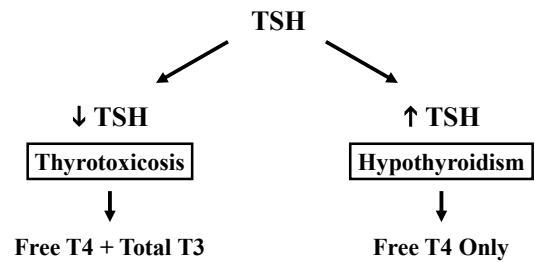
Thyroid Hormone Production



Pilo A, Am J Physiol 1990; 258:E715-26

Thyroid Function Testing

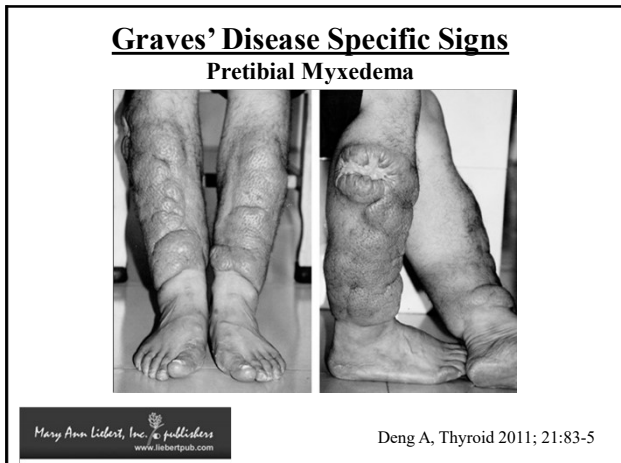
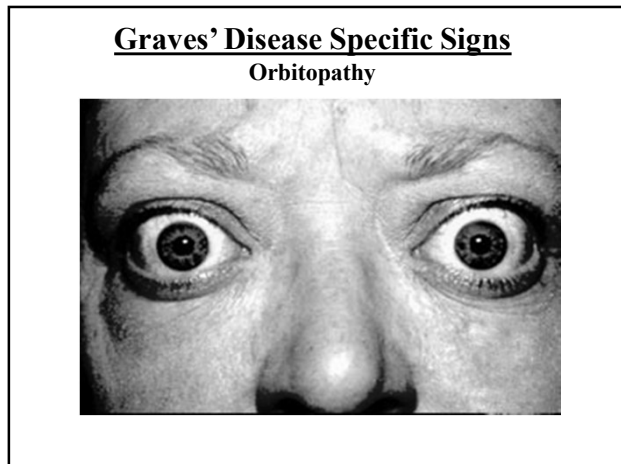
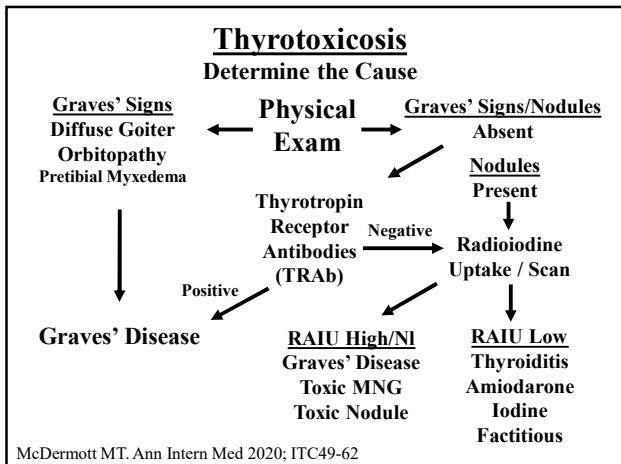
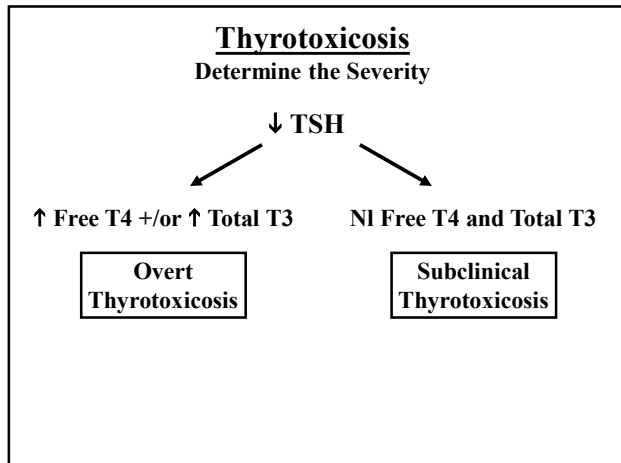
Screening / Case Finding



Case

A 28 year old woman with 4 month history of fatigue, palpitations and heat intolerance.
PE: BP 148/70 P 108 Ht 5'6" Wt 115 lb.
Thyroid: diffusely enlarged (3 x normal)
Lab: TSH < 0.03 mU/L (nl: 0.45-4.5)
 Free T4 7.8 ng/dl (nl: 0.8-1.8)
 Total T3 698 ng/dl (nl: 90-190)

Which single test is most likely to yield the correct diagnosis?
 A. Radioactive iodine uptake and thyroid scan
 B. Thyroid ultrasound
 C. Thyrotropin antibody (TRAb) measurement
 D. Thyroperoxidase (TPO) antibody measurement



Thyrotoxicosis
Differential Diagnosis - RAIU

<p>RAIU High/NI</p> <ul style="list-style-type: none"> ▪ Graves' Disease ▪ Toxic MNG ▪ Toxic Nodule ▪ TSH Tumor ▪ HCG Tumor 	<p>RAIU Low</p> <ul style="list-style-type: none"> ▪ Postpartum Thyroiditis ▪ Silent Thyroiditis ▪ Subacute Thyroiditis ▪ Amiodarone Induced ▪ Iodine Induced ▪ Factitious T4/T3 Use
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Tests Sometimes Needed for Differential Diagnosis
TRAb, TSI, TPO, Thyroglobulin, ESR, Ultrasound

Thyrotoxicosis
 Radioiodine Uptake High or Normal

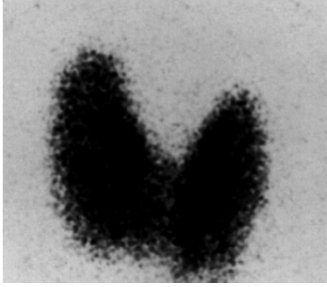
RAIU High/NI

- Graves' Disease
- Toxic MNG
- Toxic Nodule
- TSH Tumor
- HCG Tumor

Hyperthyroidism
 This term applies only to thyrotoxicosis with high or normal RAIU


Thyroid Scan → Diffuse Uptake
 Patchy Uptake
 Solitary Uptake

Graves' Disease
 Diffuse Uptake



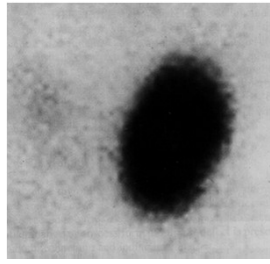
TSH Receptor Antibodies
 Autonomous Thyroid Function in All Thyroid Cells

Toxic Multinodular Goiter
 Patchy Uptake



Activating Mutations
 Autonomous Function in Multiple Nodules

Toxic Thyroid Nodule
 Solitary Uptake



Activating Mutations
 Autonomous Function in Single Nodule

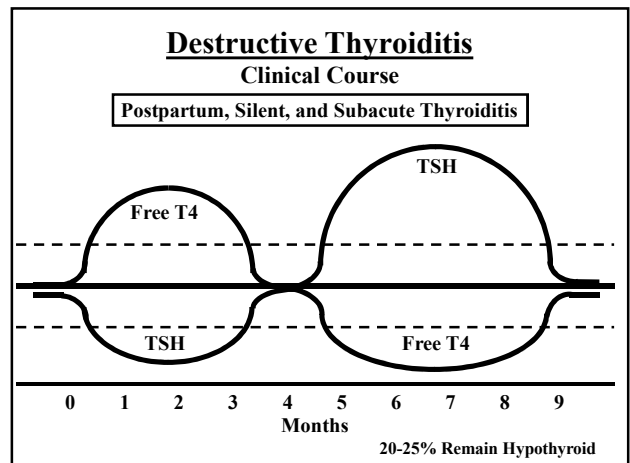
Thyrotoxicosis
 Radioiodine Uptake Low

Destructive Thyroiditis

T4 and T3
 Spill into Circulation

- Postpartum Thyroiditis
- Silent Thyroiditis
- Subacute Thyroiditis
- Amiodarone Induced
- Iodine Induced
- Factitious T4/T3 Use

No Thyroid Scan Needed



Case

A 28 year old woman with 4 month history of fatigue, palpitations and heat intolerance.

PE: BP 148/70 P 108 Ht 5'6" Wt 115 lb.

Thyroid: diffusely enlarged (3 x normal)

Lab: TSH < 0.03 mU/L (nl: 0.45-4.5)

Free T4 7.8 ng/dl (nl: 0.8-1.8)

Total T3 698 ng/dl (nl: 90-190)

RAIU: 74% (6 hr.) **Scan:** Homogeneous

What treatment do you recommend?

Graves' Disease

Medical Treatment

Anti-Thyroid Drugs for 12-18 Months

- **Methimazole:** Initial dose based on Free T4 level:
 - Free T4 1.0-1.5 x upper limit - Methimazole 5-10 mg QD
 - Free T4 1.5-2.0 x upper limit - Methimazole 10-20 mg QD
 - Free T4 \geq 2.0-3.0 x upper limit - Methimazole 30-40 mg QD
 - Reduce dose in 1-2 months
- **Beta Blocker:** until euthyroid, then stop

Goal: Symptom Relief \rightarrow Remission: ~ 50%

Side Effects

- Methimazole (\uparrow Alk Phos), PTU (Liver Failure)
- Agranulocytosis ~1/200 (CBC: Febrile/Sore Throat)

Ross DS. Thyroid 2016; 26:1343-1420
McDermott MT. Ann Intern Med 2020; ITC49-62

Graves' Disease

I-131 Ablation or Surgery

Radioiodine (I-131)

- Hypothyroidism: ~ 80-100% (3-12 Months)

Thyroidectomy

- Hypothyroidism: ~ 80-100% (1-2 Weeks)

Ross DS. Thyroid 2016; 26:1343-1420
McDermott MT. Ann Intern Med 2020; ITC49-62

Graves' Disease

Monitoring Labs During and After Treatment

Anti-Thyroid Drugs

- **One month:** Free T4 + Total T3 (TSH lags behind)
 - If FT4 + TT3 low / normal: \downarrow ATD dose 25-50%
- **2-3 months later, then every 3-6 months:** TSH + FT4 (+/- T3)
 - Adjust to maintain TSH in reference range

Radioiodine or Thyroidectomy

- **One month:** Free T4 + Total T3 (TSH lags behind)
 - If FT4 + TT3 low: Start LT4 Therapy
- **2-3 months later, then every 6-12 months:** TSH
 - Adjust to maintain TSH in reference range

McDermott MT. Ann Intern Med 2020; ITC49-62

Toxic MNG / Nodule

Treatment

Anti-Thyroid Drugs

- For 4-6 weeks prior to I-131 or Surgery
- Chronic low dose therapy when patient does not want or has contraindication to I-131 or Surgery

Radioiodine (I-131)

- Hypothyroidism: ~ 50% (3-12 Months)

Thyroidectomy

- Hypothyroidism: ~ 50% (1-2 Weeks)

Monitor As Recommended for Graves' Disease

Ross DS. Thyroid 2016; 26:1343-1420
McDermott MT. Ann Intern Med 2020; ITC49-62

Destructive Thyroiditis

Treatment

Postpartum, Silent, and Subacute Thyroiditis

Thyrotoxic Phase (1-3 months)

- **Beta Blockers:** for symptoms only
- **NSAIDS / Steroids:** for pain
- **Anti-Thyroid Drugs:** NOT EFFECTIVE

Hypothyroid Phase (3-6 months)

- **Levothyroxine:** for symptoms only

Resolution

- **75-80% Return to Normal**

Ross DS. Thyroid 2016; 26:1343-1420
McDermott MT. Ann Intern Med 2020; ITC49-62

Case

A 62 y.o. woman has been experiencing occasional palpitations, fatigue and forgetfulness for a year.

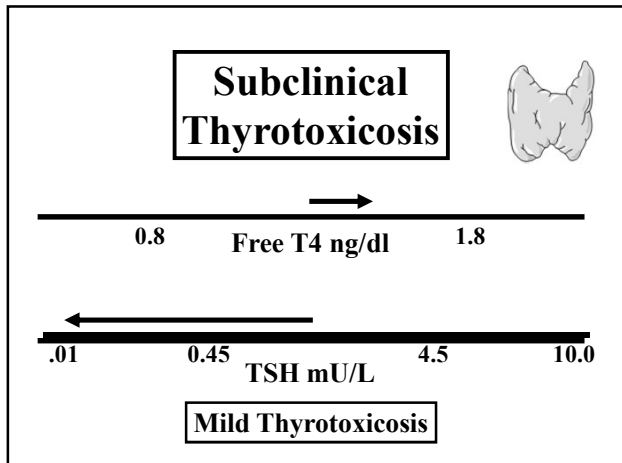
PMH: HTN, DJD Meds: Lisinopril

PE: Ht 5'8" 180 lb. BP 145/80 P 84

Thyroid: nodular goiter

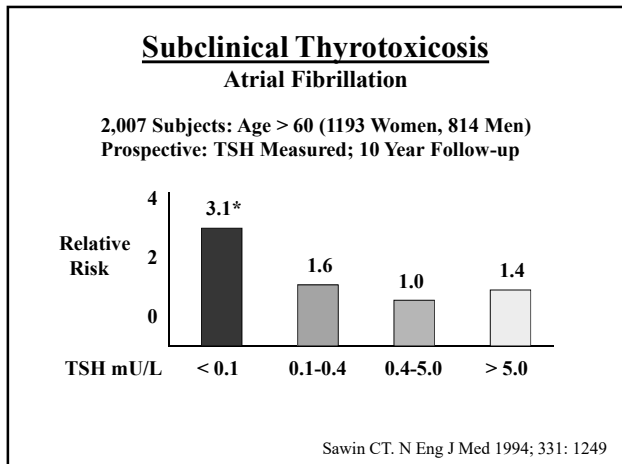
Lab: TSH < .01 mU/L
Free T4 1.4 ng/dl (nl: 0.8-1.8)
Total T3 165 ng/dl (nl: 90-190)

RAIU: 26% (6 hr.) Scan: Patchy Uptake



Subclinical Thyrotoxicosis
Risks

- Atrial Fibrillation
- Osteoporosis
- Mortality



Subclinical Thyrotoxicosis
Osteoporosis Fractures

15 Studies (15 Women, 5 Men)
9 Cross-sectional
3 Longitudinal
3 Retrospective Cohort

- Suppressed TSH (any cause): ↑ Fracture Risk
- LT4 Therapy (if TSH normal): No Effect

Murphy E. Clin Endocrinol 2004; 61:285

Subclinical Thyrotoxicosis
Mortality

Pooled-Analysis: 52,674 Subjects from 10 Cohorts
2,188 Subjects with Endogenous SC Thyrotoxicosis

<u>Condition</u>	<u>HR (95% CI)</u>
Total Mortality	1.24 (1.06-1.46)
CHD Mortality	1.29 (1.02-1.62)
Atrial Fibrillation	1.68 (1.16-2.43)

Collet TH. Arch Intern Med 2012; 172:799-809

Subclinical Thyrotoxicosis Consensus Recommendations

Strongly Consider Treatment: Hyperthyroid Symptoms, Age ≥ 65, Cardiac Risk Factors, Osteoporosis	Consider Treatment: Hyperthyroid Symptoms, Age ≥ 65, Cardiac Risk Factors, Osteoporosis
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.01 0.45

TSH mU/L

Ross DS. Thyroid 2016; 26:1343-1420
 McDermott MT. Ann Intern Med 2020; ITC49-62

Subclinical Hyperthyroidism Treatment

Graves' Disease, Toxic MNG, Toxic Nodule

- **Methimazole 5-10 mg/day: Starting Dose**
- **Recheck TSH: 4-8 Weeks**
- **Titrate Dose: TSH, FT4 in Reference Range**

Ross DS. Thyroid 2016; 26:1343-1420
 McDermott MT. Ann Intern Med 2020; ITC49-62

Biotin Interference with Assays

Depending on the Assay
 High Dose Biotin (> RDA: 30 mcg/day)
 May **Falsely** ↑, ↓ or Not Change:

TSH

Free T4

T4

Free T3

T3

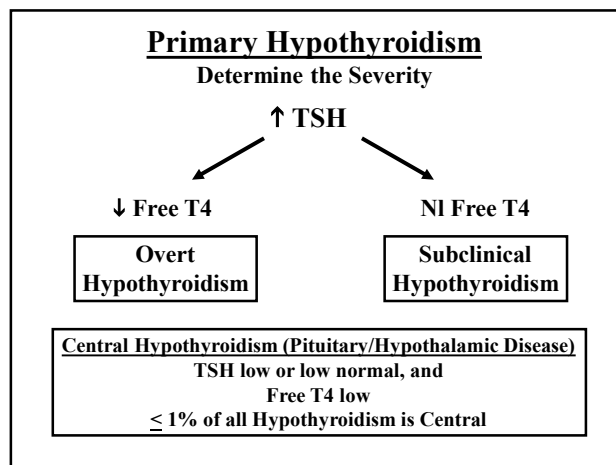
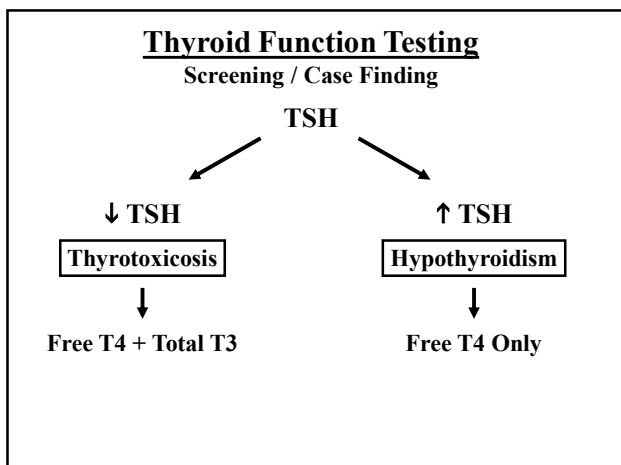
TRAb

May Also Falsely ↑, ↓ or Not Change:

- Parathyroid Hormone
- Cortisol
- Others

Thyrotoxicosis: Summary

- TSH is the best test to screen for thyrotoxicosis
- Physical exam and/or Thyrotropin Receptor Antibody (TRAb) testing can identify Graves' disease as the cause
- RAIU/Scan can also identify the cause of thyrotoxicosis
- High/NI RAIU hyperthyroidism is treated by anti-thyroid medications, radioiodine or surgery
- Low RAIU thyrotoxicosis is self-limited and does not respond to usual thyroid therapies. Treat with beta blockers.
- Subclinical thyrotoxicosis significantly increases the risk of atrial fibrillation, osteoporosis, and mortality.



Primary Hypothyroidism

Determine the Cause

Chronic Lymphocytic (Hashimoto) Thyroiditis

- Thyroperoxidase (TPO) Antibodies positive
- Most common cause

Thyroidectomy - History

I-131 Ablation - History

Medications - History

- Lithium
- Amiodarone
- Alpha Interferon
- Multi-Kinase Inhibitors
- Immune Checkpoint Inhibitors

What Your
Tongue
Says About
Your Thyroid

[Click Here](#)

Hypothyroidism

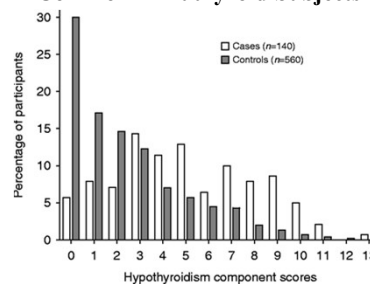
Clinical Features

Symptom	Frequency (1997)
Dry Skin	76%
Cold Intolerance	64%
Coarse Skin	60%
Puffy Eyelids	60%
Weight Gain	54%
Symptom	Frequency (2014)
Fatigue	81%
Dry Skin	63%
Shortness of Breath	51%

Zulewski H. J Clin Endocrinol Metab 1997; 82:771-776
Carlé A. Eur J Endocrinol 2014;171:593-602

Thyroid Related Symptoms

Common in Euthyroid Subjects



Number of hypothyroidism-associated symptoms reported by hypothyroid patients at disease onset and by their region-, age- and sex-matched controls

published by
bioscientifica

Carlé A. Eur J Endocrinol 2014;171:593-602

Case

A 33 year old woman complains of fatigue and weight gain of 15 lb over the past 6 months.

PMH: Type 1 Diabetes Mellitus **Meds:** Insulin Pump Therapy

PE: BP 134/80 P 64 Ht 5'6" Wt 154 lb. (70 kg)

Thyroid: firm, granular thyroid **Eyes:** periorbital edema

Reflexes: delayed reflex relaxation

Lab: TSH 112 mU/L (nl: 0.45-4.5) Free T4 0.3 ng/ml (nl: 0.8-1.8)

TPO antibodies 72.5 units (nl < 0.3)

Which of the following to you recommend as starting therapy?

- Levothyroxine 112 mcg daily (1.6 mcg/kg)
- Levothyroxine 50 mcg daily
- Levothyroxine 100 mcg daily plus Liothyronine 5 mcg BID
- Desiccated thyroid extract 60 mg daily

Overt Hypothyroidism

Treatment

Age < 60 Years and No CAD

- **Levothyroxine: 1.6 mcg/kg QD**
- **TSH Recheck: 6 Weeks**
- **Dose Titration: TSH in Reference Range**

Jonklass J. Thyroid 2014; 24: 1670-1751
McDermott M. Ann Intern Med 2020; XX: ITC (in press)

Hypothyroidism Guidelines

ATA 2014

**Levothyroxine (LT4)
Recommended Treatment of Choice**

- Efficacy in resolving hypothyroid symptoms
- Long-term experience of its benefits
- Favorable side effect profile
- Good intestinal absorption
- Ease of administration
- Long serum half-life
- Low cost

Jonklass J, Thyroid 2014; 24: 1670-1751

Levothyroxine (LT4) Dosing Instructions

Take LT4 dose 1 hour before or 4 hours after a meal

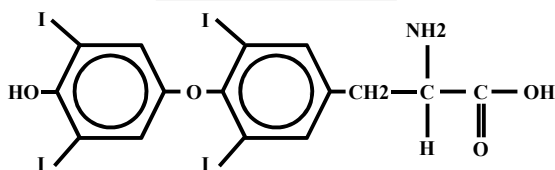
Separate at least 4 hours from iron, calcium and soy

If you miss one or more doses:

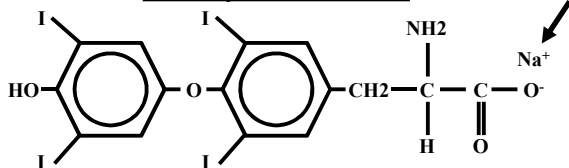
- One dose: take 2 pills the next day
- Two doses: take 2 pills a day the next 2 days

McDermott M. Ann Intern Med 2020; XX: ITC (in press)

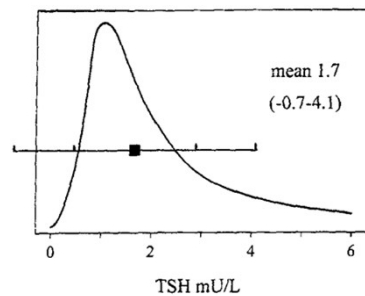
Thyroxine Structure



Levothyroxine Sodium



TSH Distribution in Normal Population



Optimal TSH Goal: 0.5-2.0 mU/L ?

Not Validated by Evidence

TSH Variation Within and Above Normal Range

Effect on Symptoms in Hypothyroid Subjects

138 Patients: Hypothyroidism on LT4 Replacement

RCT: TSH Target Low NI, High NI or Slightly High x 6 months

Outcomes: Health (SF-36), Quality of Life, Mood, Cognition

Samuels MH. J Clin Endocrinol Metab 2018; 103:1997-2008

TSH Variation Within and Above Normal Range

Effect on Symptoms in Hypothyroid Subjects

138 Patients (RCT 6 Mos): Hypothyroidism on LT4 Replacement

Group (TSH)	Low NI	High NI	Slightly High	P
TSH Level (mU/L)	1.85	3.93	9.49	< .001
LT4 Dose (ug/kg)	1.50	1.32	0.78	< .001

Outcomes - No Difference Among the 3 Groups

General Health (SF-36) Thyroid Related Quality of Life
Mood Cognition

Samuels MH. J Clin Endocrinol Metab 2018; 103:1997-2008

Hypothyroidism Treatment Guidelines
ATA/AACE 2012 and ATA 2014

Optimal TSH Goal

Evidence does not support targeting specific TSH values within the normal reference range

This includes the following types of patients:
Obese, Depressed, Athyreotic

Jonklass J. Thyroid 2014; 24: 1670-1751
McDermott M. Ann Intern Med 2020; XX: ITC (in press)

Case

A 72 year old woman complains of fatigue, mild depression and poor memory that have been progressive over 3 years span.
PMH: DJD, GERD **Meds:** ASA, H2 Blocker
PE: BP 150/86 P 80 Ht 5'9" Wt 172 lb. (78 kg) Exam: normal
Lab: TSH 43.6 mU/L (nl: 0.45-4.5) Free T4 0.5 ng/dl (nl: 0.8-1.8)
 Chol 255 TG 165 HDL 45 LDL 177

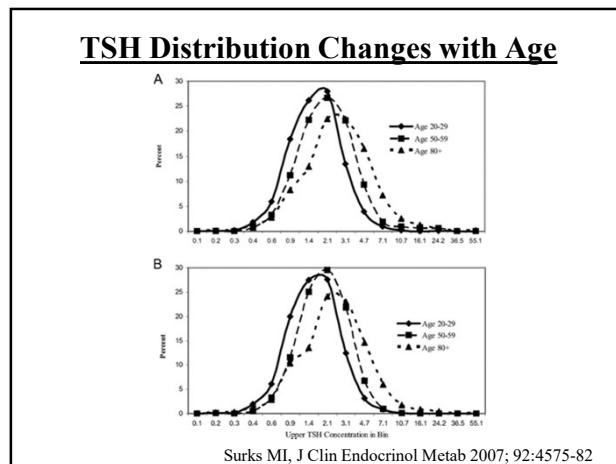
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 B. Levothyroxine 50 mcg daily
 C. Levothyroxine 100 mcg daily plus Liothyronine 5 mcg BID
 D. Desiccated thyroid extract 60 mg daily

Overt Hypothyroidism Treatment

Age > 60 Years or CAD

- Levothyroxine: 25-50 mcg QD
- TSH Recheck: 6 Weeks
- Dose Titration: TSH in Reference Range
- Age ≥ 70: 4.0 < TSH < 6.0 mU/L

Jonklass J. Thyroid 2014; 24: 1670-1751
McDermott M. Ann Intern Med 2020; XX: ITC (in press)



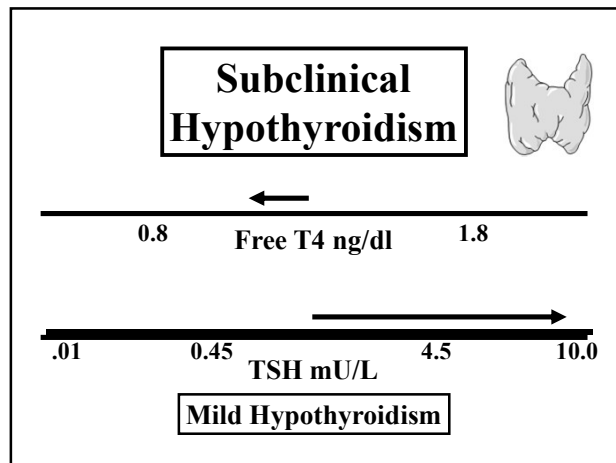
Hypothyroidism Treatment Guidelines
ATA/AACE 2012 and ATA 2014

TSH Goals in the Elderly

Reasonable to raise the target TSH to 4–6 mU/L in persons greater than age 70–80 years

Based on the current evidence

Jonklass J. Thyroid 2014; 24: 1670-1751
McDermott M. Ann Intern Med 2020; XX: ITC (in press)



Subclinical Hypothyroidism

Treatment in Elderly Patients: TRUST Study

Subclinical Hypothyroidism: 737 Subjects \geq Age 65
TSH: 4.99-19.99 mU/L Free T4: in Reference Range
RCT: LT4 Rx (N=368) vs Placebo (N=369) x 1 Year

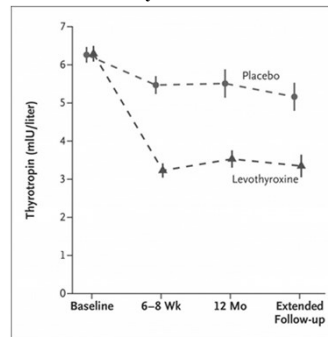
Primary Outcomes

Hypothyroid Symptoms Score
Tiredness Score (Thyroid Related QOL Questionnaire)

Stott DJ. N Engl J Med 2017; 376:2534-44

Subclinical Hypothyroidism

Treatment in Elderly Patients: TRUST Study



Stott DJ. N Engl J Med 2017; 376:2534-44

Subclinical Hypothyroidism

Treatment in Elderly Patients: TRUST Study

Primary Outcome (1 Year)	LT4	Placebo	P
Hypothyroid Symptoms Score	16.6±16.9	16.7±17.5	0.99
Tiredness Score	28.7±20.2	28.6±19.5	0.40

Secondary Outcomes	P
Blood Pressure	NS
Body Mass Index	NS
Waist Circumference	NS
Grip Strength	NS
Hyperthyroid Symptoms	NS

Stott DJ. N Engl J Med 2017; 376:2534-44

Subclinical Hypothyroidism

Treatment Recommendations

Clinical Judgment
Rx Based on Symptoms

Treatment
Recommended

4.5 10.0
TSH mU/L

Age \geq 65: Controversy if Treatment Beneficial

Pregnant Women: Treat All to Trimester Specific Goals

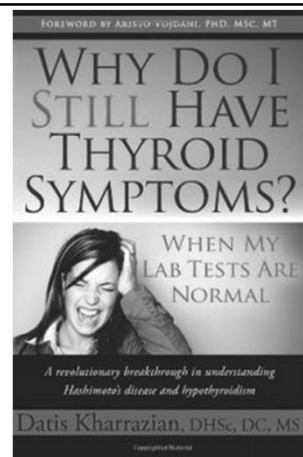
Jonklass J, Thyroid 2014; 24: 1670-1751
McDermott M. Ann Intern Med 2020; XX: ITC (in press)

Subclinical Hypothyroidism

Treatment

- Levothyroxine: 25-50 mcg QD
- TSH Recheck: 6 Weeks
- Dose Titration: TSH in Reference Range
 - Age \geq 70: 4.0 < TSH < 6.0 mU/L

Jonklass J, Thyroid 2014; 24: 1670-1751
McDermott M. Ann Intern Med 2020; XX: ITC (in press)





Persistent Symptoms on LT4 Therapy
ATA Survey: 12,000 Respondents (95% Women)
Satisfaction with Rx – Visual Analog (VA) Scale (1-10): 5 (mean)

Reason for Dissatisfaction	
Fatigue / Low Energy	75%
Body Weight Issues	70%
Memory Problems	55%
Mood Problems	45%
Other	35%

Peterson SJ. Thyroid 2018;28:707-721

Persistent Symptoms on LT4 Therapy

Satisfaction with Doctor - VA Scale (1-10): 5-6 (mean)

Doctor Knowledgeable - VA Scale (1-10): 5-6 (mean)

How Often Have You Changed Doctors	
1-4 Times	45%
5-10 Times	10%

Peterson SJ. Thyroid 2018;28:707-721

Hypothyroidism
Altered Circulating T3 / T4 Ratio on LT4 Therapy

NHANES Survey

	LT4 Patients (469)	Controls (469)	P-Value
TSH (mU/L)	2.13	2.15	0.83
Free T3 (pg/ml)	2.85	3.01	< 0.001
Free T4 (ng/ml)	0.94	0.80	< 0.001
FT3/FT4 Ratio	3.18	3.85	< 0.001

Peterson S, McAninch E, Bianco A. J Clin Endocrinol Metab 2016; 101:4964-73

Hypothyroidism
Altered Circulating T3 / T4 Ratio on LT4 Therapy

	LT4 Patients (469)	Controls (469)	P-Value
BMI	29.8	28.2	< 0.001
Kcal Consumption	1761	1759	0.98
Physical Activity	41%	32%	< 0.01
Anti-Depressant Use	22%	15%	< 0.01

Peterson S, McAninch E, Bianco A. J Clin Endocrinol Metab 2016; 101:4964-73

T4 / T3 Combination Therapy

Subjects: 697 Gender: 84%W Age: 18-75 Dx: Hypothyroid
Design: RCT Double Blind x 52 Weeks
Dosing: (Usual LT4 – 50 ug) + LT4 50 ug
(Usual LT4 – 50 ug) + LT3 10 ug

552 Subjects Genotyped
D2: Thr92Ala Homozygotes = 16%
Thr92Ala: D2 instability loop related to ubiquitination

General Health Questionnaire: Thr92Ala Homozygotes Baseline: Worse GHQ (p = 0.03)
General Health Questionnaire: Thr92Ala Homozygotes LT4/LT3 c/w LT4 Rx: Improved GHQ (p = 0.03)

Panicker V, J Clin Endocrinol Metab 2009; 94:1623-9

Hypothyroidism Treatment Guidelines

ATA/AACE 2012 and ATA 2014

Combination LT4/LT3

No consistently strong evidence of superiority of LT4/LT3 combination therapy over LT4 alone.

Recommend against routine use of combination LT4/LT3 therapy.

Jonklass J, Thyroid 2014; 24: 1670-1751

Hypothyroidism Treatment Guidelines

ATA/AACE 2012 and ATA 2014

Desiccated Thyroid Extract

Potential Safety Concerns of DTE:

1. Supraphysiologic serum T3 levels.
2. Paucity of long-term safety outcome data.

Recommend against routine use of combination DTE therapy.

Jonklass J, Thyroid 2014; 24: 1670-1751

Hypothyroidism Treatment

Persistent Symptoms on LT4 Therapy

Combination LT4/LT3

Desiccated Thyroid Extract (DTE)

- Some patients prefer combined LT4/LT3 or DTE
- Reasonable to use in patients with persistent symptoms if done safely (maintain TSH in reference range)
- Optimal T4:T3 Ratio: 14:1 – 10:1

Jonklass J, Thyroid 2014; 24: 1670-1751
McDermott M. Ann Intern Med 2020; XX: ITC (in press)

Hypothyroidism Treatment

Persistent Symptoms on LT4 Therapy

- Lifestyle Measures: (Sleep, Exercise, Diet, ↓ Stress)
- Medical Illness / Depression: Recognition and Rx
- Regular Follow-up and Support
- Consider Combination T4/T3 or DTE in some Pts:
 - Levothyroxine (T4) + Liothyronine (T3) (10:1 ratio)
 - Desiccated Thyroid Extract (Porcine Thyroid)
 - Maintain TSH within Reference Range

Hypothyroidism: Summary

- TSH is the best test to detect hypothyroidism
- Hashimoto's Thyroiditis is the most common cause
- Treat hypothyroidism with LT4 to normalize TSH
- TSH goal for elderly can be 4.0-6.0 mU/L
- Mild hypothyroidism increases CVD risk/mortality in patients < 65 years old but not those ≥ 65 years old
- Treatment of patients with persistent symptoms requires an individualized approach

Thank You

