Hyperthyroidism [Thyrotoxicosis]

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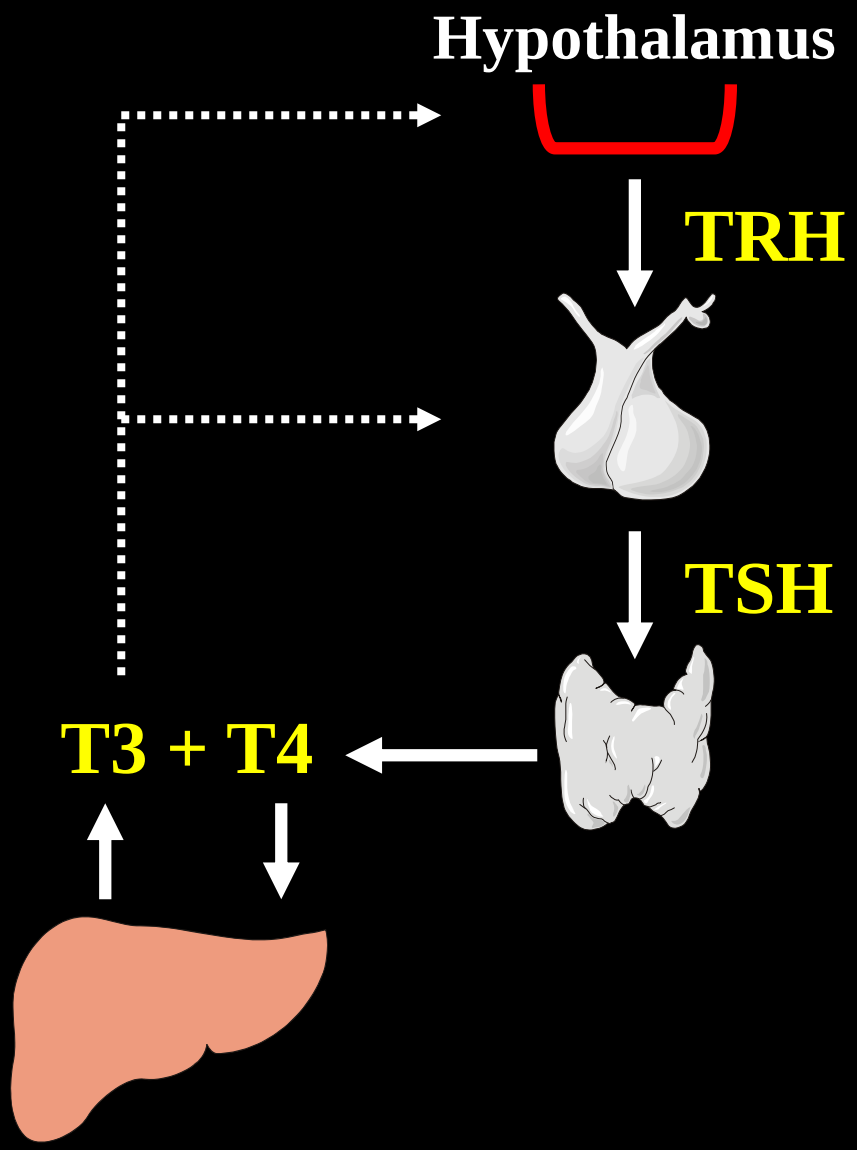
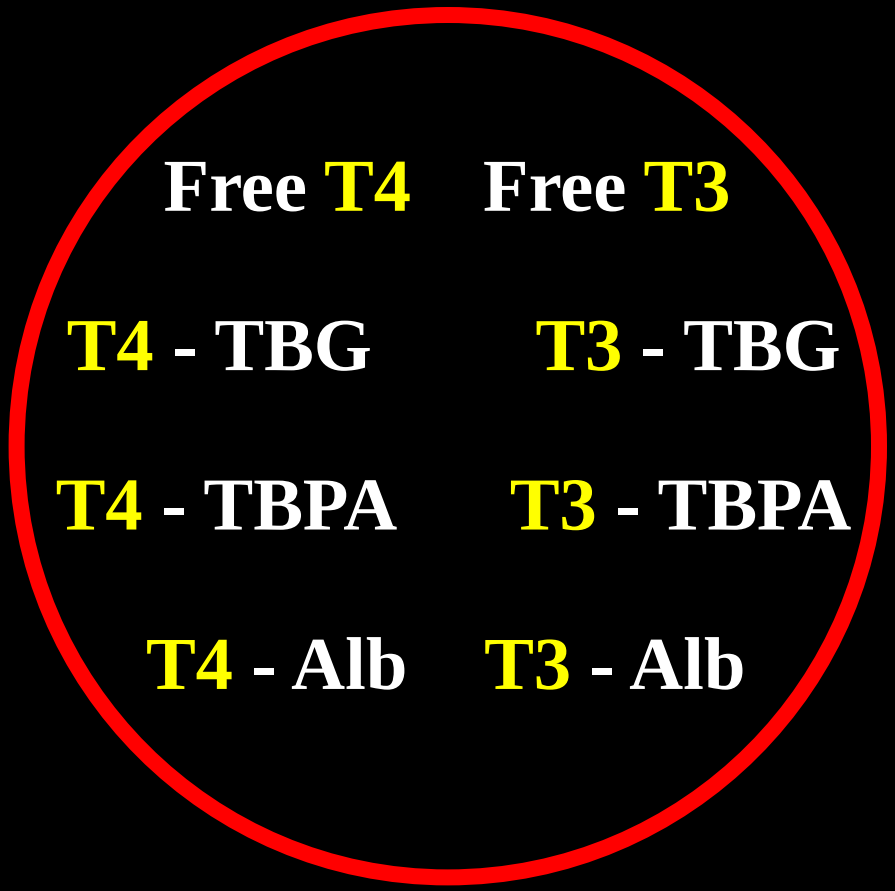
Disclosures:

- Consultantship: Shire, Sanofi Aventis

Thyroid Hormone Regulation



T4 and T3 in the Circulation

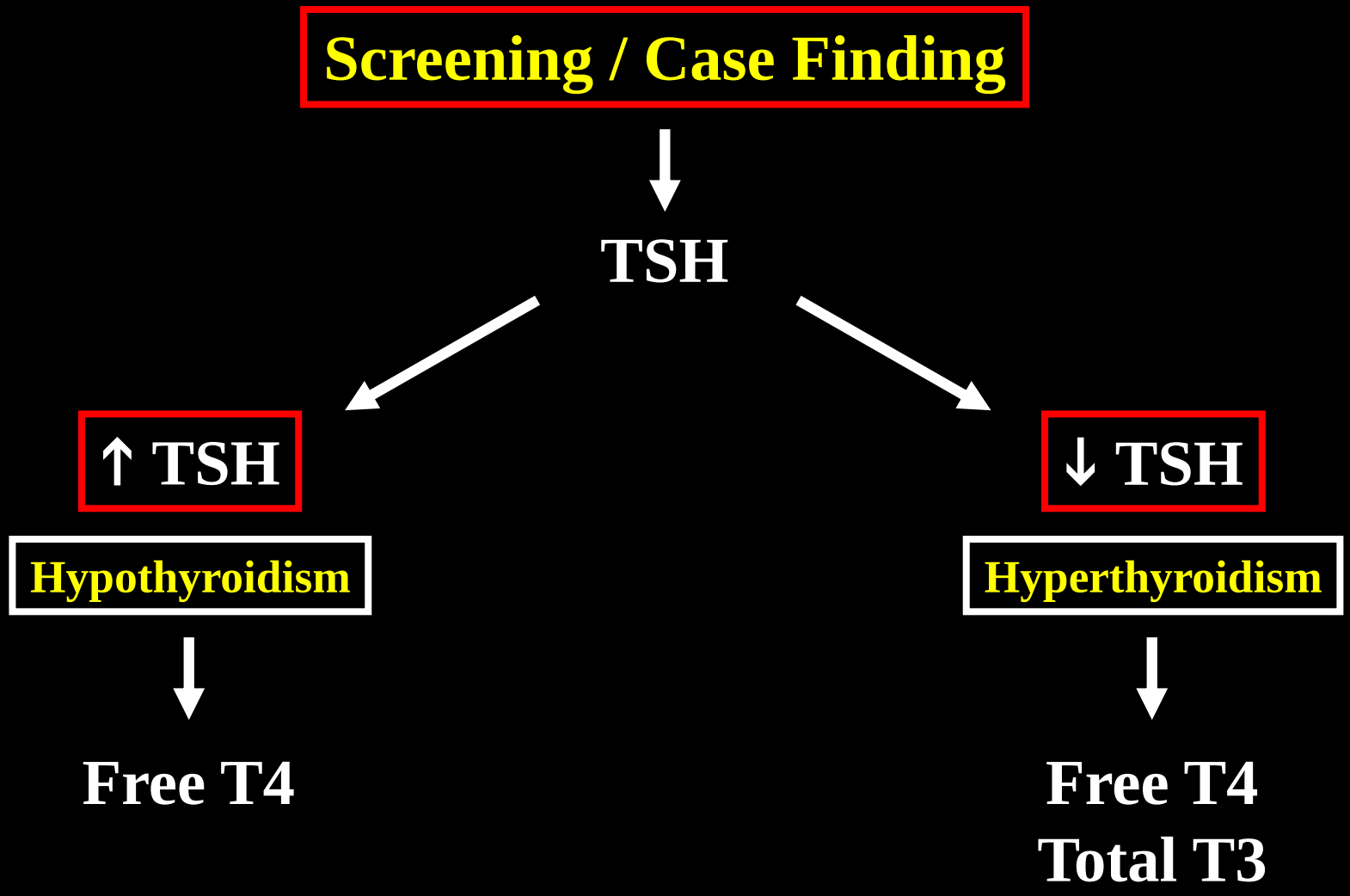


	Bound	Free
T4	99.98%	0.02%
T3	99.70%	0.30%

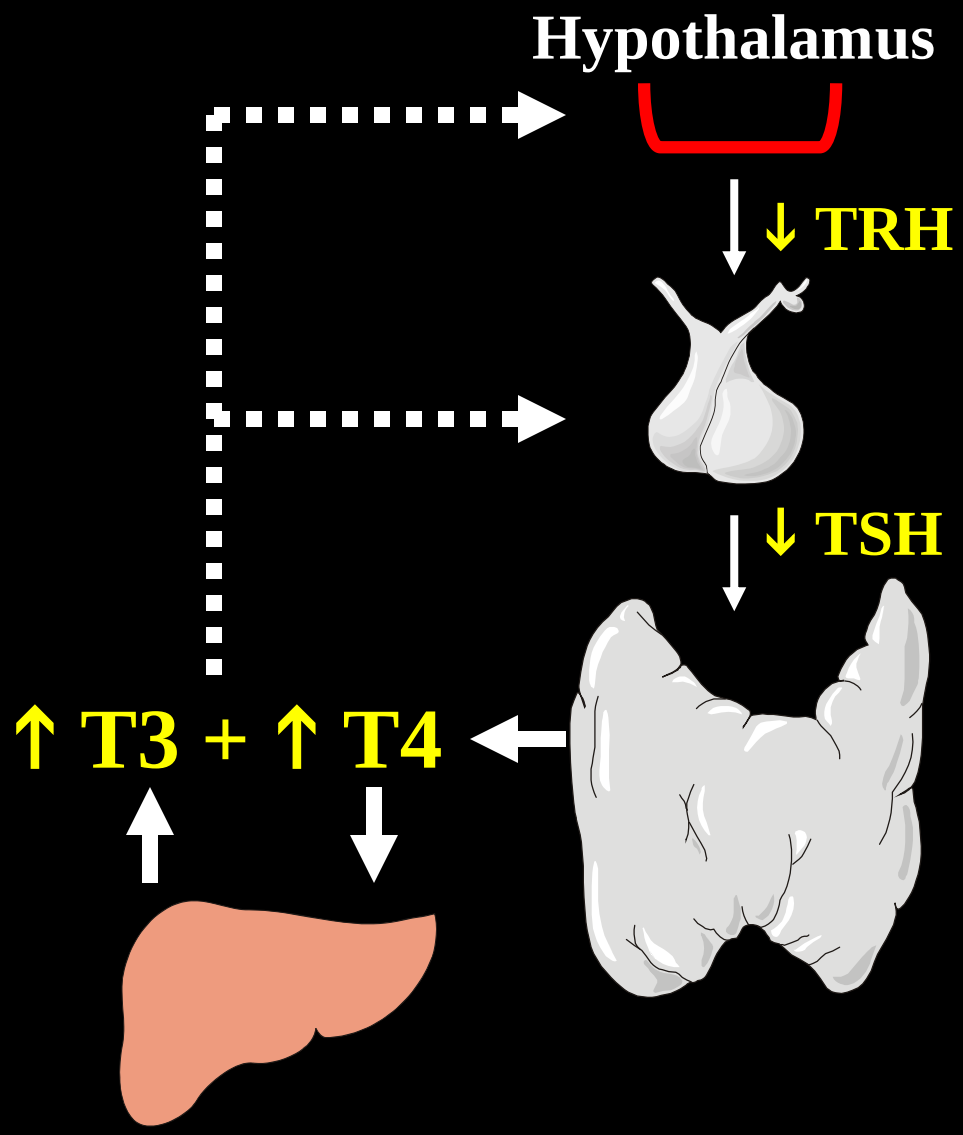
Assay Accuracy	
Adequate	Not Accurate
Free T4	Free T3
Total T4	
Total T3	

Alb: Albumin
TBG: Thyroxine Binding Globulin
TBPA: Thyroxine Binding Prealbumin (Transthyretin)

Thyroid Function Testing



Hyperthyroidism



Overt Hyperthyroidism

↓ TSH
↑ Free T4
↑ Total T3

Subclinical Hyperthyroidism

↓ TSH
Free T4 Normal
Total T3 Normal

Case History

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)

What additional tests are needed to make an accurate diagnosis?

Hyperthyroidism Guidelines

ATA 2016

No Further Tests Needed:

if presentation Characteristic of GD

Radioiodine Uptake (RAIU):

when presentation Not Diagnostic of GD

Thyroid Scan:

if Thyroid Nodules or No Goiter present

RAIU must always be done before I-131 Treatment

Ross DS. Thyroid 2016; 26:1343-1421

Graves' Disease

Characteristic Features

- **Diffuse Vascular Goiter**
- **Graves' Ophthalmopathy**
- **Pretibial Myxedema**
- **Thyroid Acropachy**

Fatourechi V, Endocrine Practice 2014; 20:1333-44
Smith TJ, N Engl J Med 2016; 375:1552-65

Graves' Ophthalmopathy

Pretibial Myxedema

Deng A, Thyroid 2011; 21:83-5

Thyroid Acropachy

Thyrotoxicosis

Differential Diagnosis - RAIU

High RAIU

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

Low RAIU

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

Tests Sometimes Needed for Differential Diagnosis

TRAb, TSI, TPO, Thyroglobulin, ESR, Ultrasound

Thyrotoxicosis

Differential Diagnosis

When is Anti-Thyroid Antibody Testing Needed?

- Graves' Disease is suspected but not certain and RAIU is contraindicated or not desired.

When is a Neck Ultrasound Needed?

- Thyroid nodules are palpable.
- No goiter is present.
- Substernal goiter is present.
- Amiodarone induced thyrotoxicosis is suspected.

Ross DS. Thyroid 2016; 26:1343-1421

Thyrotoxicosis

Differential Diagnosis - RAIU

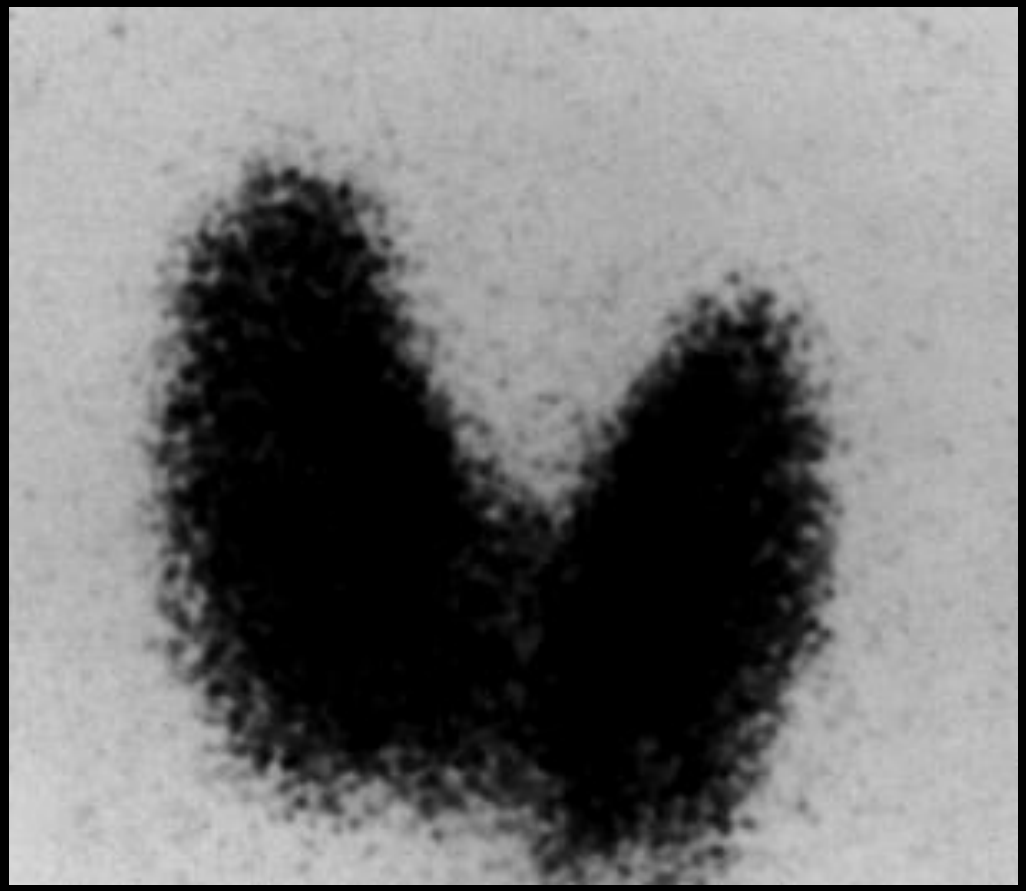
High RAIU

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

Thyroid Scan

Graves' Disease

Diffuse Uptake

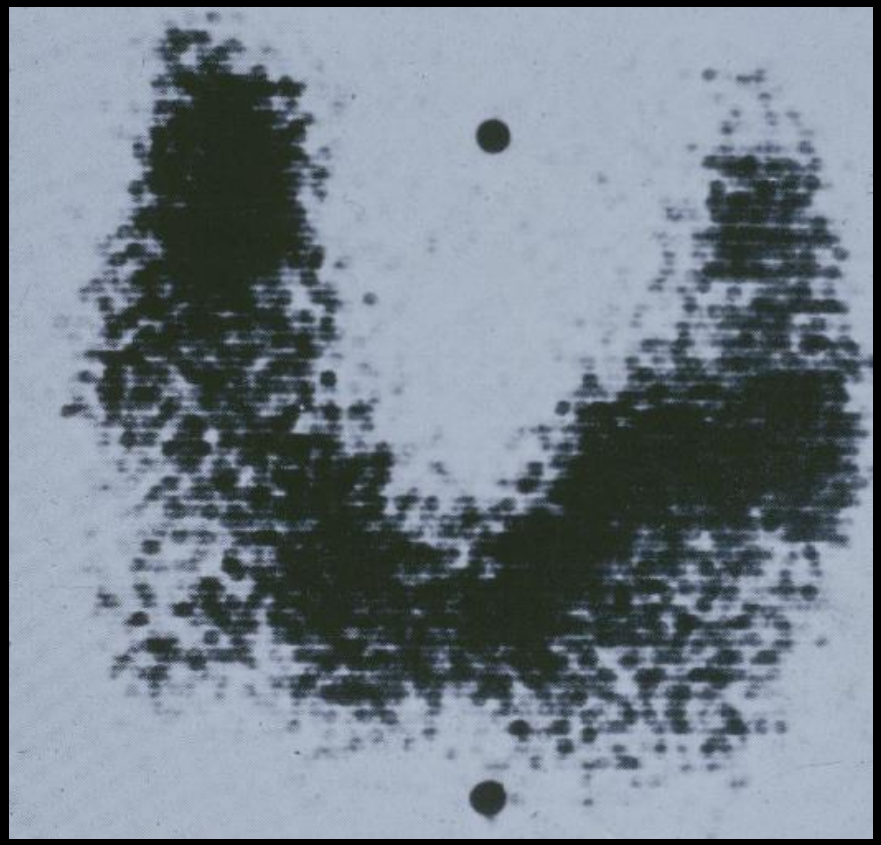


TSH Receptor Antibodies

Autonomous Thyroid Function in All Thyroid Cells

Toxic Multinodular Goiter

Patchy Uptake

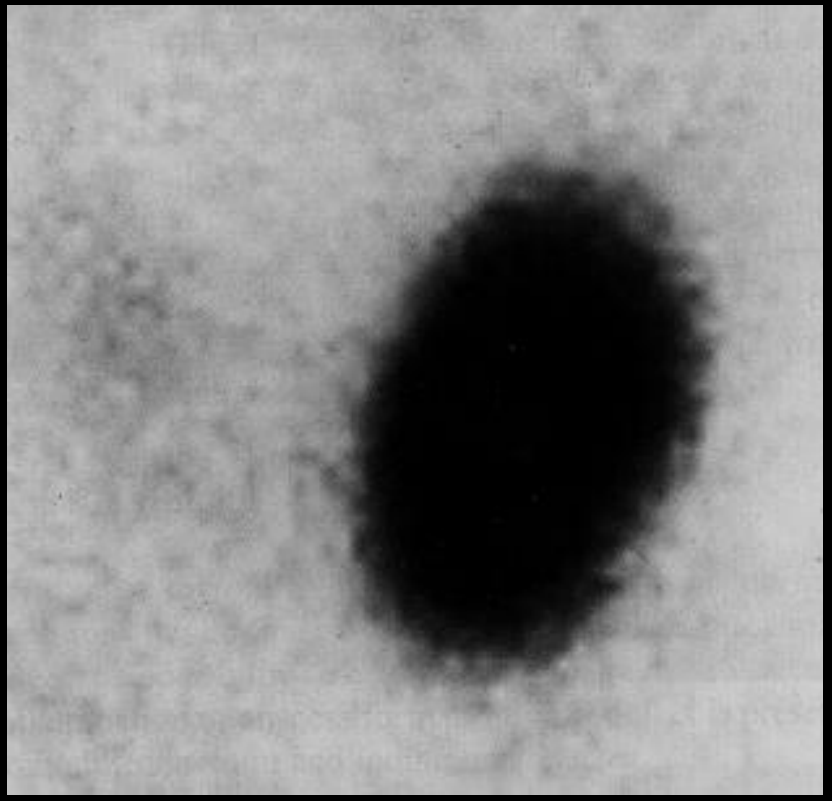


Activating Mutation of TSH Receptor or Alpha Subunit

Autonomous Function in Multiple Nodules

Toxic Thyroid Nodule

Solitary Uptake



Activating Mutation of TSH Receptor or Alpha Subunit

Autonomous Function in Solitary Nodule

Thyrotoxicosis

Differential Diagnosis - RAIU

Low RAIU

Destructive Thyroiditis

- Postpartum Thyroiditis
- Silent Thyroiditis
- Subacute Thyroiditis

T4 and T3 Spilled into Circulation

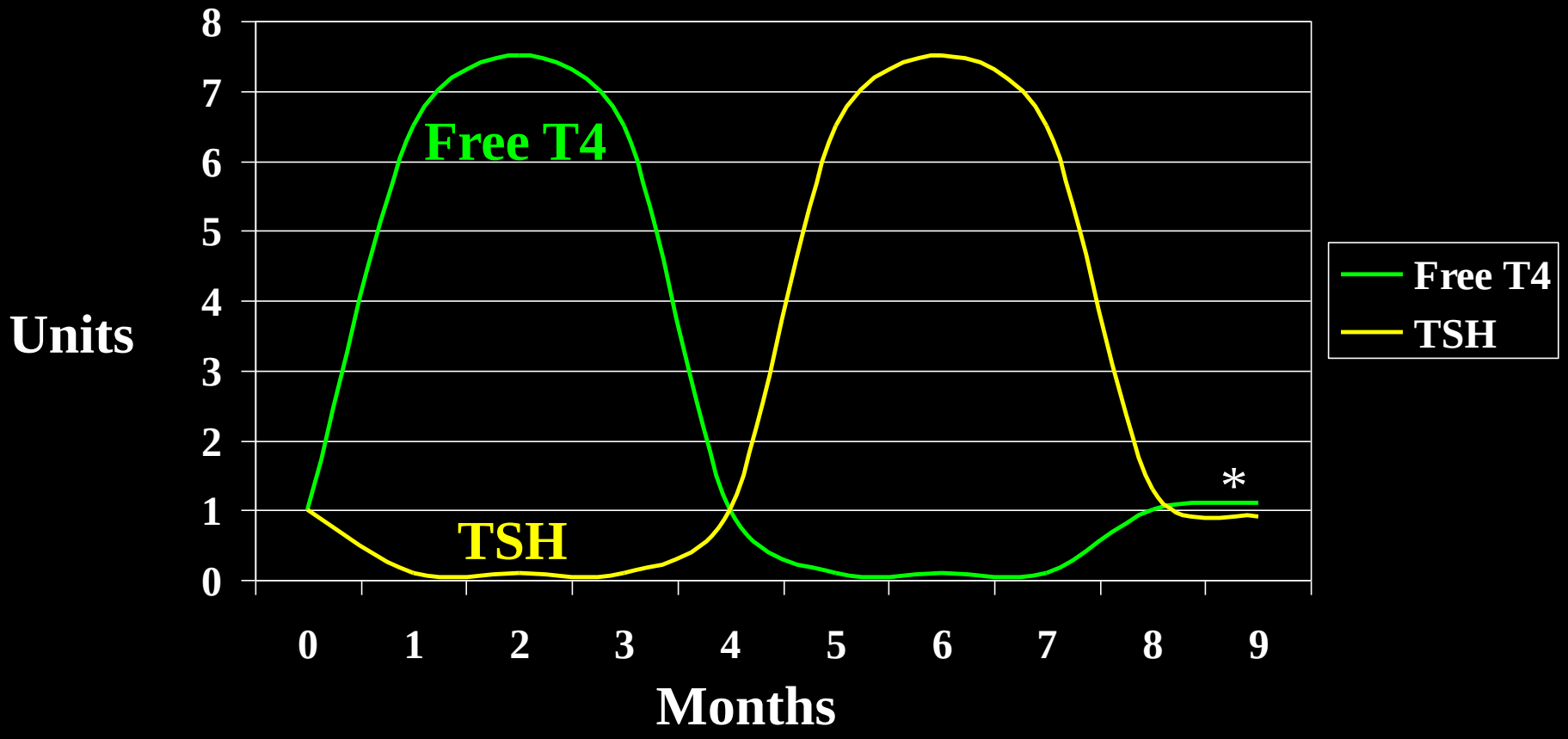
- Amiodarone Induced
- Iodine Induced
- Factitious T4/T3 Use

No Thyroid Scan Needed

Destructive Thyroiditis

Clinical Course

Postpartum, Silent, and Subacute Thyroiditis



***20-25% Remain Hypothyroid**

Case History

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

Treatment Options

"I'm going to pull your endocrine system out of your body."

Gary Busey

Graves' Disease

Treatment

Anti-Thyroid Drugs for 12-18 Months

- **Methimazole:** 30 mg QD; ↓ in 1-2 months (Avoid PTU)
- **Beta Blocker:** until euthyroid
- **Goal:** Symptom Relief → **Remission: ~ 20-40%**
- Methimazole (↑ Alk Phos), PTU (Liver Failure)
- Agranulocytosis ~1/200 (CBC: Febrile/Sore Throat)

Radioiodine (I-131)

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

Thyroidectomy

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

Ross DS. Thyroid 2016; 26:1343-1420
Smith TJ. N Engl J Med 2016; 375:1552-65
McDermott M. Ann Intern Med 2012; 157: ITC 1-14

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: ↓ ATD dose 25-50%
- **2-3 Mos Later, Then Every 3-6 Mos:** TSH + FT4 (+/- TT3)
  - 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 Mos Later, Then Every 6-12 Mos:** TSH
  - Adjust to maintain TSH in reference range

McDermott M. Ann Intern Med 2012; 157: ITC 1-14

Hyperthyroidism Guidelines

ATA/AACE 2011

Methimazole Preferred in Most Patients

PTU Preferred in These Situations:

Thyroid Storm

1st Trimester of Pregnancy

Minor MMI reactions; I-131 + Surgery Refused

Ross DS. Thyroid 2016; 26:1343-1420
Smith TJ. N Engl J Med 2016; 375:1552-65
McDermott M. Ann Intern Med 2012; 157: ITC 1-14

Hyperthyroidism Guidelines

ATA/AACE 2011

Graves' Disease Recurs after Course of ATD

Consider:

I-131 Therapy

Thyroidectomy

Prolonged Low Dose Methimazole (2.5-10 mg/d)

Ross DS. Thyroid 2016; 26:1343-1420
Smith TJ. N Engl J Med 2016; 375:1552-65
McDermott M. Ann Intern Med 2012; 157: ITC 1-14

Hyperthyroidism Guidelines

ATA/AACE 2011

High Risk for Hyperthyroidism Complications after I-131: Extreme Symptoms or FT4 2–3 x Normal

Consider:

Beta-Adrenergic Blockade - prior to I-131 Rx

Methimazole Treatment - prior to I-131 Rx

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Smith TJ. N Engl J Med 2016; 375:1552-65
McDermott M. Ann Intern Med 2012; 157: ITC 1-14

Thyrotoxicosis

Treatment

Which Hyperthyroid Patients Can Be Managed by the Primary Care Provider?

- Diagnosis and cause is certain.
- Thyroid storm not present or imminent.
- Extrathyroidal manifestations absent or mild.

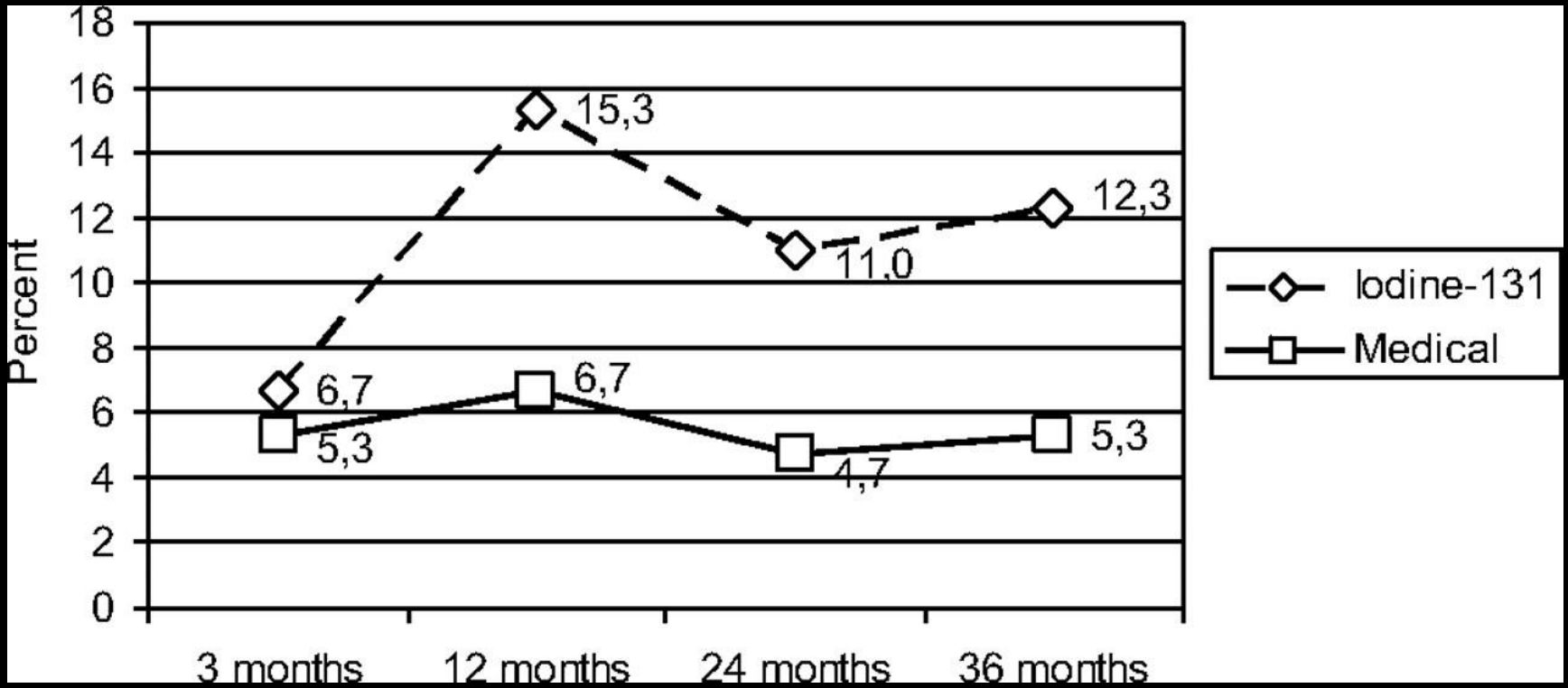
Which Hyperthyroid Patients Should be Referred to an Endocrinologist?

- Diagnosis and/or cause is uncertain.
- Thyroid storm present or imminent.
- Extrathyroidal manifestations moderate or severe.

Graves' Ophthalmopathy

Effects of I-131 Therapy

Worsening Proptosis



THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

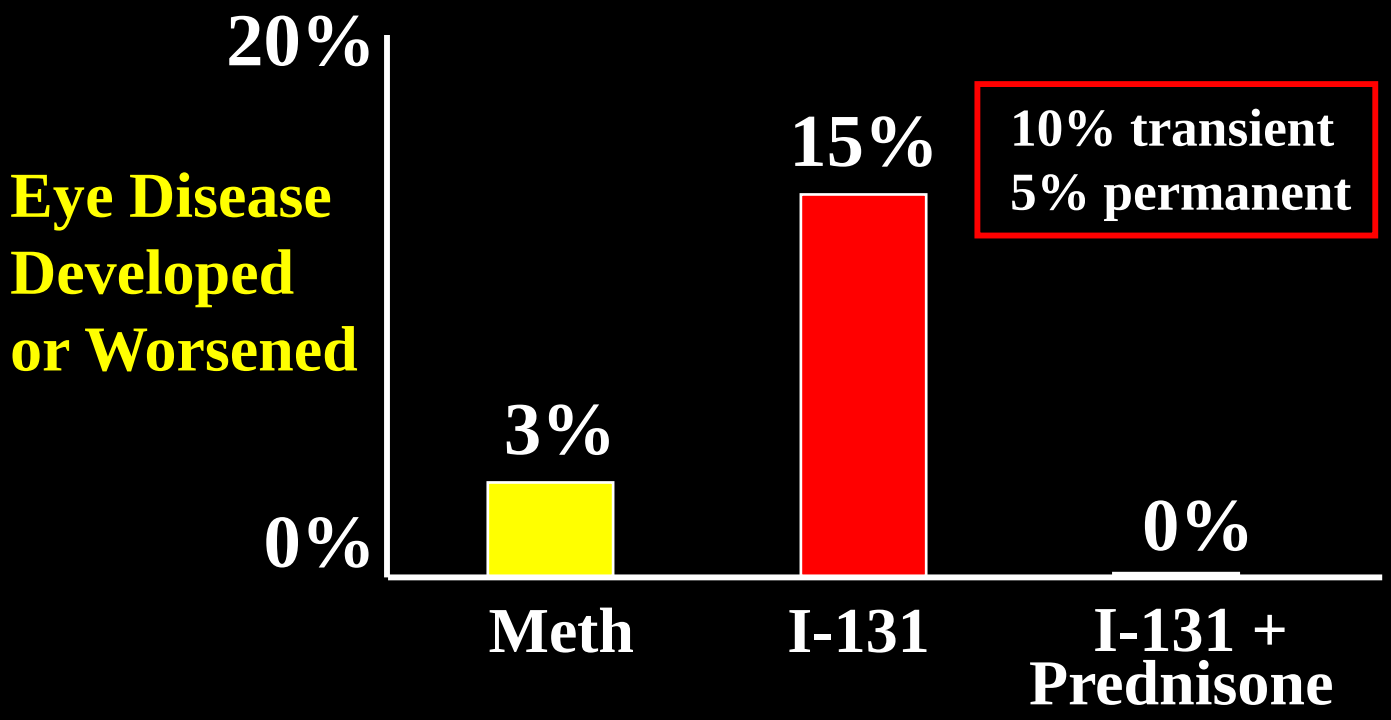
Traisk F. J Clin Endocrinol Metab 2009;94:3700-7

Graves' Ophthalmopathy

Effects of Glucocorticoid Therapy

443 Patients with Graves' Disease

RCT: Methimazole or I-131 vs
I-131 + Prednisone (0.4-0.5 mg/kg)



Bartalena L. N Engl J Med 1998; 338:73

Hyperthyroidism Guidelines

ATA 2016

I-131 Treatment with Graves' Ophthalmopathy (GO)

GO	Risk Factors	I-131 Therapy
Absent		Steroids Not Needed
Inactive		Steroids Not Needed
Active, Mild	None	Steroids Acceptable (+/-)
Active, Mild	Present	Steroids Recommended
Moderate/Severe		I-131 Not Recommended

Highest Risk Factors

Untreated Hyperthyroidism
Very High TRAb (> 8.8 IU/L)
Post-RAI High TSH
Smoking

Ross DS. Thyroid 2016; 26:1343-1421

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 M. Ann Intern Med 2012; 157: ITC 1-14

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 M. Ann Intern Med 2012; 157: ITC 1-14

Case History

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 Hyperthyroidism

0.8 — Free T4 ng/dl — 1.8

.01 — 0.45 — 4.5 — 10.0

TSH mU/L

Mild Hyperthyroidism

Subclinical Hyperthyroidism

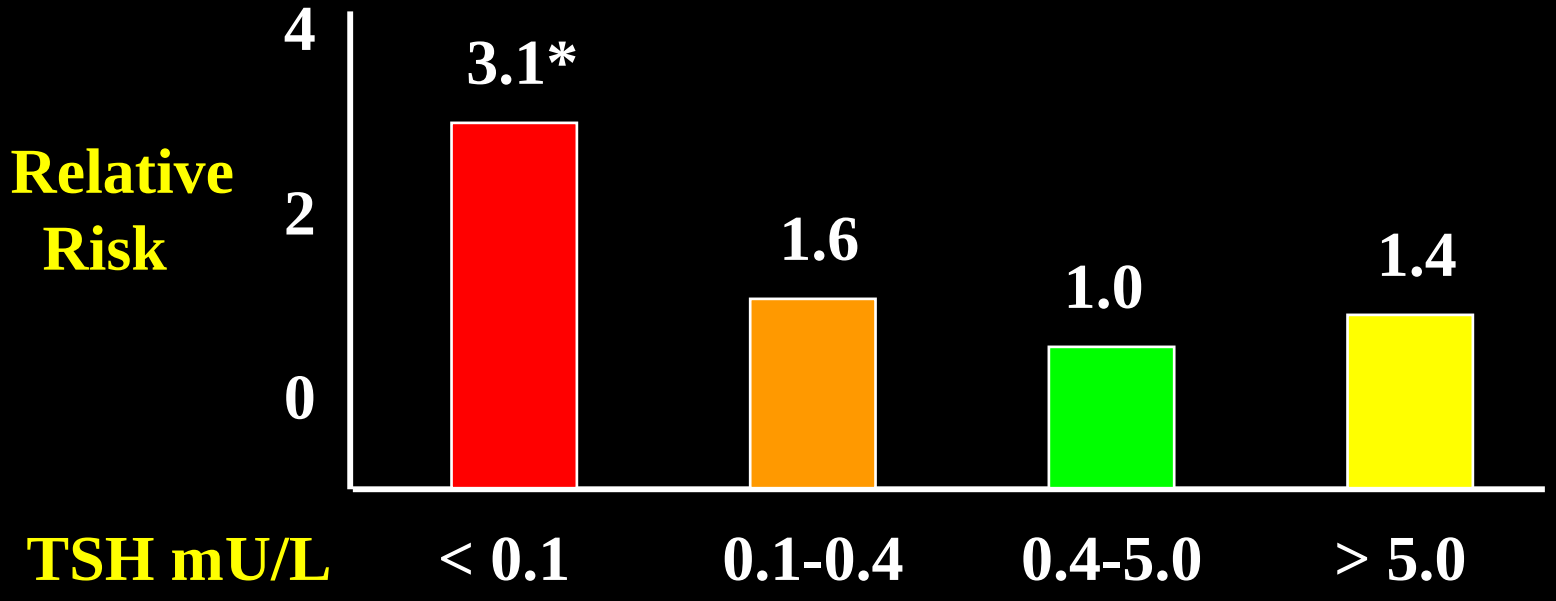
Concerns

- Atrial Fibrillation
- Osteoporosis
- Mortality

Subclinical Hyperthyroidism

Atrial Fibrillation Risk

2,007 Subjects: Age > 60 (1193 Women, 814 Men)
Prospective: TSH Measured; 10 Year Follow-up



Sawin CT. N Eng J Med 1994; 331: 1249

Subclinical Hyperthyroidism

Osteoporosis Risk

15 Studies (15 Women, 5 Men)

- 9 Cross-sectional
- 3 Longitudinal
- 3 Retrospective Cohort

- Suppressed TSH (any cause): ↑ Fracture Risk
- LT4 Therapy (well managed): No Effect

Murphy E. Clin Endocrinol 2004; 61:285

Subclinical Hyperthyroidism

Mortality Risk

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

Condition	HR (95% CI)
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 Hyperthyroidism

Treatment: Consensus Recommendations

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

Consider Treatment:
Hyperthyroid Symptoms, Age ≥ 65, Cardiac Risk Factors, Osteoporosis

.01 0.45

TSH mU/L

Ross DS. Thyroid 2016; 26:1343-1420
McDermott M. Ann Intern Med 2012; 157: ITC 1-14

Subclinical Hyperthyroidism

Treatment

- **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 M. Ann Intern Med 2012; 157: ITC 1-14

Amiodarone Induced Thyrotoxicosis

	AIT Type 1 Iodine Induced	AIT Type 2 Thyroiditis
Physical Exam	Goiter/Nodules	Normal/Firm
Thyroid US	Goiter/Nodules	Nl/Enlarged
Color Doppler	Increased	Nl/Decreased
RAIU	Low	Very Low
Treatment	Antithyroid Drug Perchlorate Lithium	Prednisone Lithium

Graves' Disease

Treatment during Pregnancy

- Propylthiouracil [1st Trimester]
  - Methimazole: Aplasia Cutis and Choanal Atresia when used in 1st Trimester
- Methimazole [2nd and 3rd Trimesters]
- Beta blockers may be used
- Radioiodine contraindicated
- Surgery in 2nd trimester, if needed
- Disease rebounds postpartum

Biotin Interference with Assays

Depending on the Assay Type

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**

Hyperthyroidism: Summary

- TSH is the best test to screen for thyroid disease
- RAIU/Scan can identify the cause of hyperthyroidism
- High RAIU hyperthyroidism is treated by anti-thyroid medications, radioiodine or surgery
- Low RAIU hyperthyroidism is self-limited and does not respond to usual thyroid therapies
- Subclinical hyperthyroidism can increases the risk of atrial fibrillation and osteoporosis

Thank You