Telehealth and Thyroid Disorders for the Primary Care Provider

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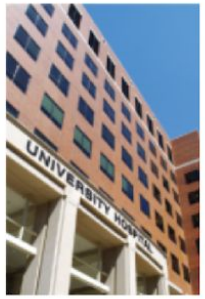
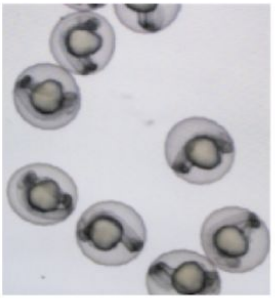







Case Presentation

A 50 YOWF presents for a TER visit of a recently discovered thyroid nodule. She has no previous history of thyroid disease, and on physical examination you visualize a 4.0 cm mobile nodule in the right thyroid lobe that does not move with deglutination.

Which of the following blood test would be the most in establishing the diagnosis?

A. Serum thyroxine
B. Serum triiodothyronine
C. Serum thyrotropin
D. Antithyroid antibodies
E. None of the above

Case Presentation

The patient's serum thyrotropin level (TSH level) completely suppressed. Which of the following would be the most appropriate next step?

A. Fine needle aspiration biopsy of the nodule
B. Thyroid ultrasound
C. Surgical consultation
D. Thyroxine therapy
E. Thyroid scan and uptake

Subclinical Hyperthyroidism

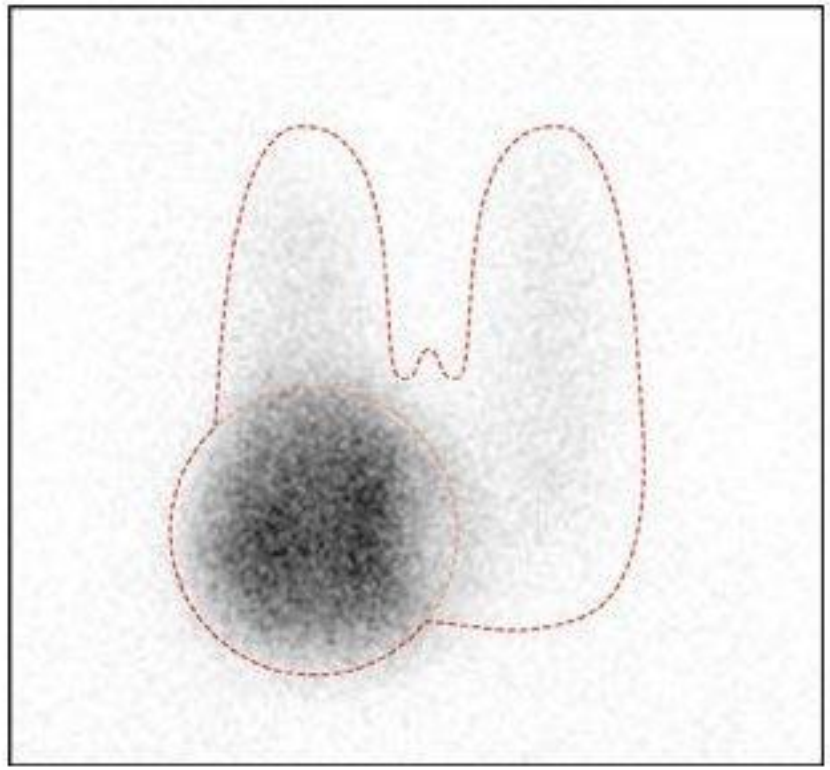
- Diagnosed with a low TSH in the presence of a “normal range” value for serum total T4 and free T4 as well as normal values for total and free T3.

- Causes
  - Exogenous thyroid hormone
  - Multinodular goiter
  - Autonomously Functioning Nodules
  - Graves Disease
  - Thyroiditis

Subclinical Hypothyroidism

- By definition, normal total and free T4 and T3 concentrations with modest elevation of serum TSH concentrations and no symptoms or signs of hypothyroidism
- The usual cause is chronic autoimmune thyroiditis
- Treatment for patients with thyroid enlargement and those with nonspecific symptoms

Scintigram of a Solitary Functioning Nodule in the Right Thyroid Lobe



Hegedus L. N Engl J Med 2004;351:1764-1771

Serum TSH Levels

- Higher in white populations
- Change in hypothalamic – pituitary-thyroid axis with aging
- Higher in overweight patients (leptin stimulates TRH)

Table 5. Patients at High Risk of Developing Hypothyroidism

High-Risk Patients
Individuals with a personal or family history of autoimmune thyroid disorders
Associated autoimmune endocrine conditions (T1DM, adrenal insufficiency, ovarian failure, etc)
Associated nonendocrine autoimmune disorders (coelic disease, vitiligo, pernicious anemia, Sjogren syndrome, multiple sclerosis, primary pulmonary hypertension, etc)
Postpartum women
Underlying thyroid, pituitary, or hypothalamic disorders
Previous treatment that can destroy thyroid, pituitary, or hypothalamic tissue
Previous head and neck external radiation therapy
Down's and Turner syndromes
Subjects with a history of having given up smoking
Patients submitted to bone marrow transplantation
Smokers

Endocr Rev. 2014 Jun;35(3):433-512. doi: 10.1210/er.2013-1083.

Table 7. Symptoms and Signs of Primary Hypothyroidism and CH

Condition	Symptoms and Signs
Primary overt hypothyroidism	
In young and middle-aged patients	Fatigue Weight gain Dry skin and cold intolerance Slow thinking Puffy eyes Coarseness or loss of hair Goiter Constipation Cold intolerance Hoarseness Muscle weakness and cramps Delayed relaxation of deep tendon reflexes Memory impairment Decreased concentration Neurocognitive deficits Irregular or heavy menses Infertility Myalgias Hyperlipidemia Bradycardia Hypothermia CHD Mixedema in severe hypothyroidism
In elderly patients	Memory and mental impairment Dementia Anemia Depression Heart failure CHD

Endocr Rev. 2014 Jun;35(3):433-512. doi: 10.1210/er.2013-1083.

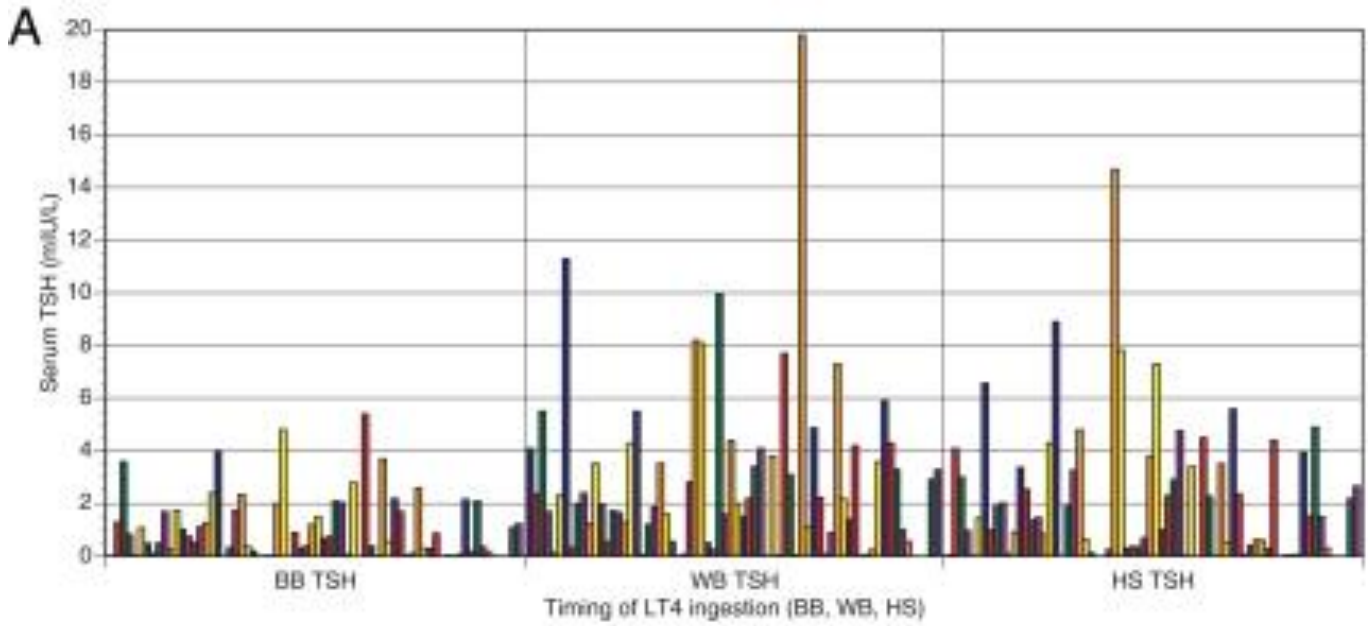
Chronic Lymphocytic Thyroiditis (Hashimotos's Thyroiditis)

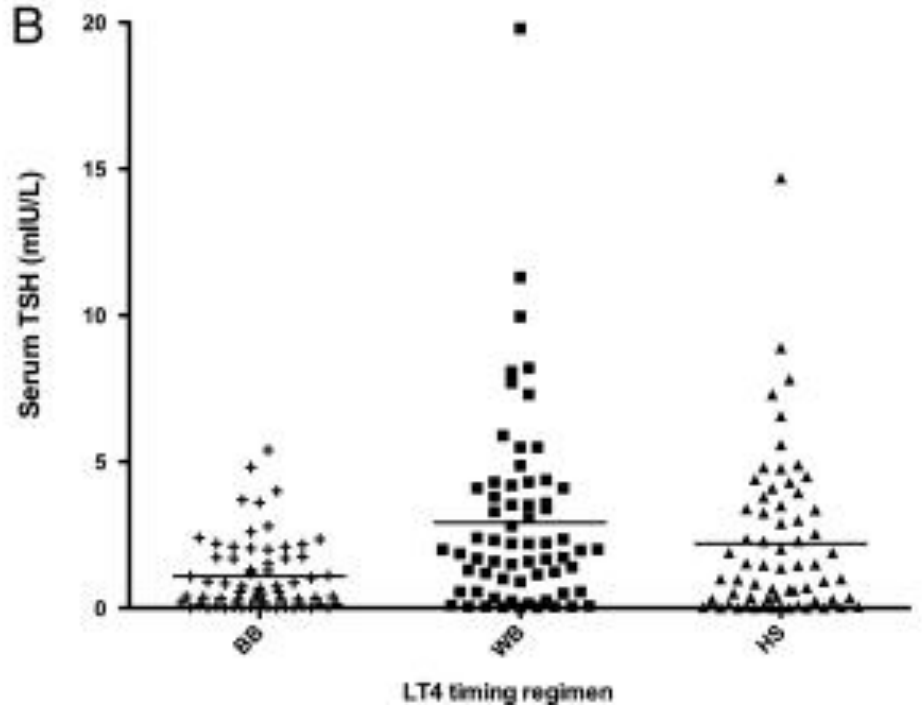
- The most common cause of both thyroiditis and non-iatrogenic hypothyroidism
- Women account for 95% of the cases
- Two to fifteen percent of the female population is affected
- Immune dysregulation caused production of humoral and cellular immune responses to thyroid antigens which cause progressive destruction of the thyroid gland

Presentation

- Patients are usually asymptomatic. Goiters are one and one half to three times the size of normal. The gland is firm and rubbery and has an irregular surface. About 20% of the patients present with hypothyroidism, and 5% present with hyperthyroidism.
- An overlap syndrome between Graves' disease and Hashimoto's disease may exist in some patients
- Antithyroid antibodies are present in high titer in 70-80% of patients
- Antibodies against the thyroid peroxidase enzyme are most common

- BMI <25 1.8mcg/kg
- BMI >25 1.3mcg/kg
- Proton pump inhibitors (increased gastric ph → ↓ pill dissolution (LT4 release)
- TSH 30% lower in afternoon than morning
- Summary: Poor Control Considerations
  1. Compliance
  2. Monitoring and Communication
  3. Interfering of food
  4. Interfering medication
  5. Duration of therapy
  6. Weight, Gender, Age
  7. Substitution of LT4 preparation
  8. Aberrant and results of TSH assay





Timing of levothyroxine administration affects serum thyrotropin concentration. Bach-Huynh TG. J Clin Endocrinol Metab.2009 Oct; 94(10) 3905-3912

Drugs Interfering with L-T4 Administration

- Lithium: inhibition of thyroid hormone synthesis and release, cytotoxic effect, thyroid autoimmunity
- Amiodarone: 200mg tablet has 7mg iodine, inhibits T4 transport to liver - so see 20% to 40% higher levels and also see transient increases in TSH
- Cytokines
- Tyrosine kinase inhibitors
- Estrogens
- Heparin, furosemide transiently increase Free T4
- Antiepileptic Drugs

You perform a PHO visit on a 50-year-old male who has been taking Synthroid 150mcg daily for the last 10 years for treatment of hypothyroidism. At his annual visit, you obtain the following lab studies: a free T4 of 1.2 (normal 0.8 – 1.8) and a TSH of 12 (normal 0.32 - 5.500). He has made no change in his regimen of medication. Over the last 15 years, he has always had a normal TSH level. Your best interpretation of the data is:

A. He has developed a pituitary macroadenoma

B. He has a pituitary resistance to thyroid hormone

C. He stopped taking thyroid hormone for a few weeks ago and just restarted it on his reminder for the visit

D. He had a recent contrasted dye study

E. He has developed elevation in TSH due to aging

A 24-year-old white female who is six months postpartum presents for a TER visit with the following laboratory studies: free T4 elevated at 3.0, TSH suppressed at less than 0.05. She states that she has lost weight to her pre-pregnancy weight. However, she has noticed some palpitations and increased tremulousness. You obtain thyroid levels showing a free T4 elevated at 2.5 and a TSH suppressed at less that 0.05. Which of the following would be the appropriate next step?

A. Begin therapy with methimazole or PTU and a beta blocker

B. Send patient for a surgical evaluation

C. Treat her with a beta blocker and schedule a follow-up appointment for one year

D. Order a thyroid scan and a radioactive uptake

E. None of the above

Affects of Pregnancy on Thyroid Function

- Gland increases in size
- Production of T4 and T3 increases
- Daily iodine requirement is increased
- Serum FT4 decreases
- TBG increases
- Total T4 should be adjusted by a factor of 1.5

Postpartum Thyroid Disease

- An autoimmune disorder with lymphocytic infiltration of the thyroid
- Transient hyperthyroidism with low or no radioactive iodine uptake due to leakage of performed thyroid hormone. ESR may be increased. Thyroid pain is generally absent. Hyperthyroidism resolves spontaneously.
- Transient primary hypothyroidism is characterized by an increased TSH. Goiter and positive antithyroid antibodies are usually present. Depression may be prominent.
- Resolution occurs in most patients

You are asked to evaluate a 28 year old female who underwent a total thyroidectomy in her early 20's for Graves Disease. She is maintained on levothyroxine sodium 100mcg one tablet daily and had normal TSH at initial MFM visit. She is 6 weeks pregnant with her first child and is taking an OTC prenatal vitamin. Which of the following statements is correct:

1. She should increase her thyroid hormone requirement by 30%
2. She should confirm that her prenatal vitamin does not contain iodine
3. She should have TRAb levels checked at the end of 2nd trimester
4. She should wait until fetal thyroid gland is formed at 12 weeks to recheck thyroid levels

A. 1, 3
B. 1, 2, 3
C. 2, 4
D. 4 only
E. All of the above

A 28 year old female with a history of Hashimoto's Thyroiditis sends a portal message to discuss thyroid hormone levels obtained from her OB office. She is 14 months postpartum and continues breastfeeding. She is on no prescription medication and has returned to pre-pregnancy weight of 70kg and denies heart racing.

At her recent book club meeting (masked) she described dry skin and nails and hair clogging her shower drain.

You reviewed labs and FT4 3.1 (0.71-1.81) and TSH 2.4 (0.35-5.50). She has no clinical signs of thyroid orbitopathy and gland is normal size without nodularity.

What would you recommend?

A. Thyroid scan and uptake to assess for postpartum thyroiditis
B. Institution of anti-thyroid medications
C. Review of the minutes from the book club meeting
D. Schedule Thyroid ultrasound for consideration of FNAB
E. Send her an outside order for Thyroid Stimulating Immunoglobulin

Table 1. Classification of Drug Effects on the Thyroid.*

Interference with endogenous thyroid function
Disruption of hypothalamic–pituitary control
Decreased thyroid hormone production or release
Increased thyroid hormone production
Enhanced thyroid autoimmunity
Destructive thyroiditis
Changes in thyroid hormone–binding proteins
Inhibition of thyroid hormone activation (T_4-to-T_3 conversion)
Displacement of thyroid hormone from binding proteins
Increased thyroid hormone metabolism or elimination
Interference with thyroid hormone therapy
Decreased pill dissolution
Decreased thyroid hormone absorption
Decreased free thyroid hormone levels
Increased thyroid hormone metabolism or elimination
Interference with thyroid laboratory testing in euthyroid persons
Falsely elevated thyroid hormone levels
Falsely low thyroid hormone levels
Falsely low serum thyrotropin levels
Falsely elevated thyrotropin-receptor antibody levels

* T_3 denotes triiodothyronine, and T_4 thyroxine. For a detailed list of drugs interacting with the thyroid, see Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

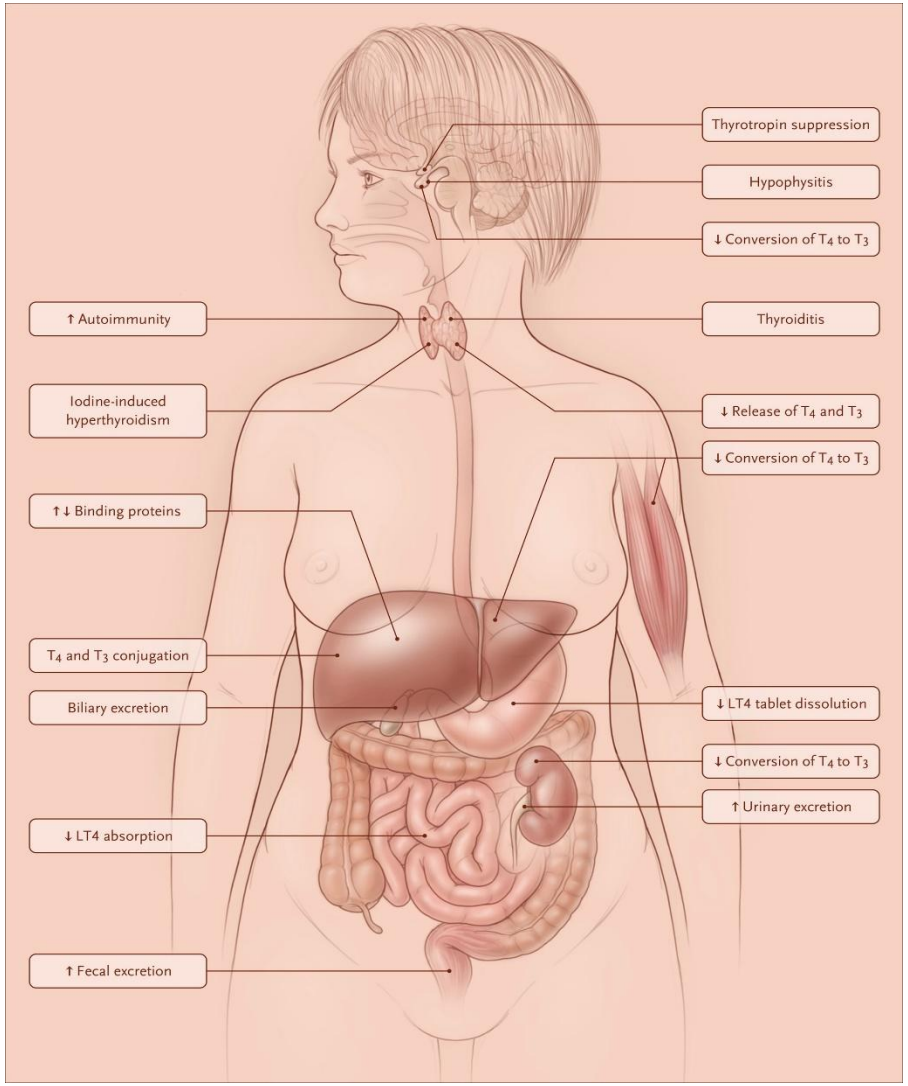


Figure 2. Anatomical Sites of Interactions between Drugs and Thyroid Function.

Multiple sites of interaction between various drugs and the thyroid have been identified, including central control at the pituitary–hypothalamic level, direct effects on thyroid hormone synthesis, initiation of destructive thyroiditis, interference with protein binding or delivery to target tissues, and interference with activation and disposition of thyroid hormone. Unique drug interactions occur in patients taking exogenous thyroid hormone, including inhibition of pill dissolution and levothyroxine malabsorption. LT4 denotes levothyroxine.

Drug Effects on the Thyroid Burch H.B.; N Engl J Med 2019; 381:749-761

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Table 2. Drugs That Cause Spurious Thyroid Test Results in Euthyroid Persons.

Drug	Drug Class	Test Results			Condition Mimicked
		Thyrotropin	Free T_4	T_3	
Amiodarone	Class III antiarrhythmic agent	High end of normal range	High	Low end of normal range	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Biotin	Micronutrient	Low	High	High	Primary hyperthyroidism
Carbamazepine and oxcarbazepine	Antiepileptic agent	Normal	Low	Low end of normal range	Central hypothyroidism
Enoxaparin	Anticoagulant	Normal	High	High	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Heparin	Anticoagulant	Normal	High	High	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Phenytoin	Antiepileptic agent	Normal	Low	Low end of normal range	Central hypothyroidism
Salsalate	Nonsteroidal anti-inflammatory drug	Normal	Low end of normal range	Low end of normal range	Central hypothyroidism

Drug Effects on the Thyroid Burch H.B.; N Engl J Med 2019; 381:749-761

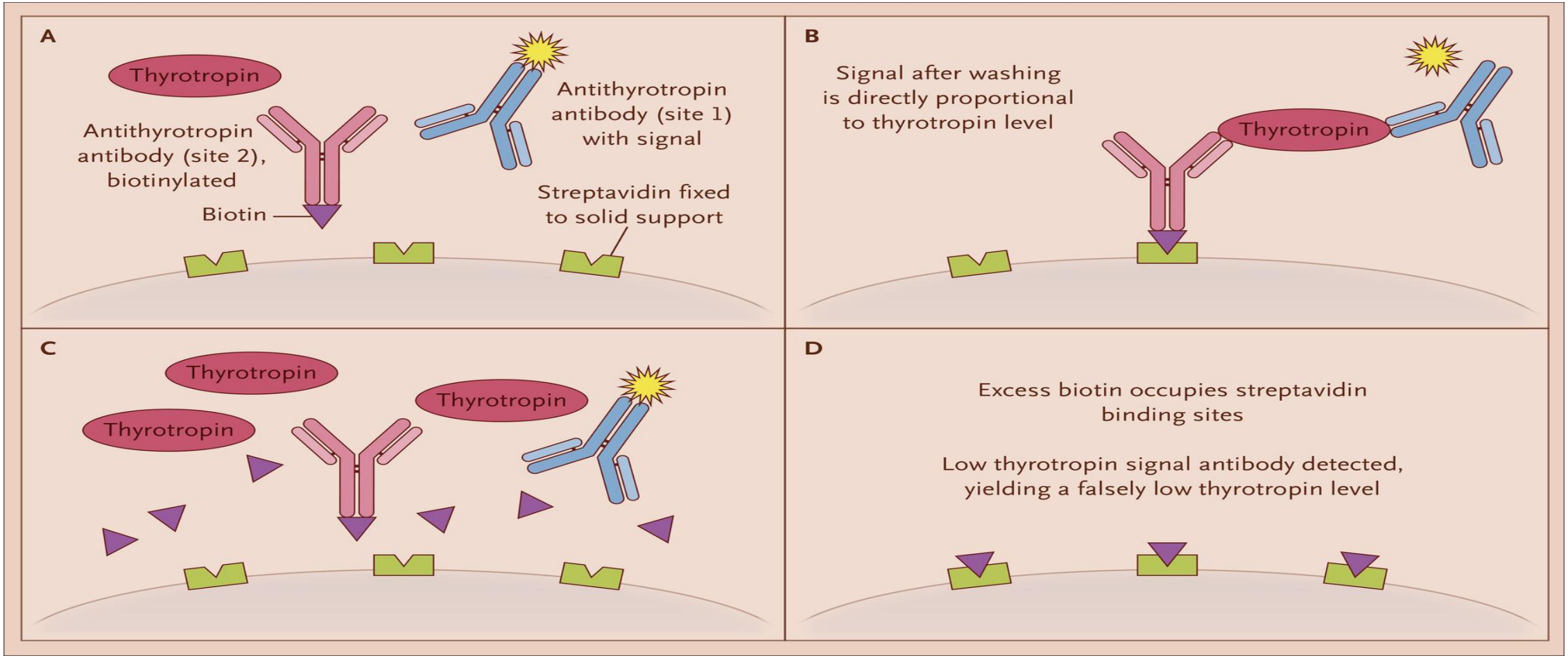


Figure 3. Biotin-Related Interference in Two-Site Thyrotropin Assay Measurements.
Excess biotin results in variable interference in assays using biotinylated reagents. In two-site (sandwich) assays, including those for thyrotropin, the thyrotropin level is falsely low or undetectable. Assay components include a biotinylated antithyrotropin antibody as the capture antibody and a second antithyrotropin antibody to which a signal component has been attached (Panel A). Under normal conditions, the complex consisting of thyrotropin bound to the two antithyrotropin antibodies, one of which is biotinylated, binds to streptavidin, which has been fixed to a solid phase such as an enzyme-linked immunosorbent assay well. After washing, the signal will be directly proportional to the level of thyrotropin in the specimen (Panel B). In the presence of excess biotin (Panel C), the complex of thyrotropin with the antithyrotropin antibodies cannot compete effectively for streptavidin binding on the solid phase. After washing, a low signal results in a falsely low thyrotropin value (Panel D).

Drug Effects on the Thyroid Burch H.B.; N Engl J Med 2019;
381:749-761

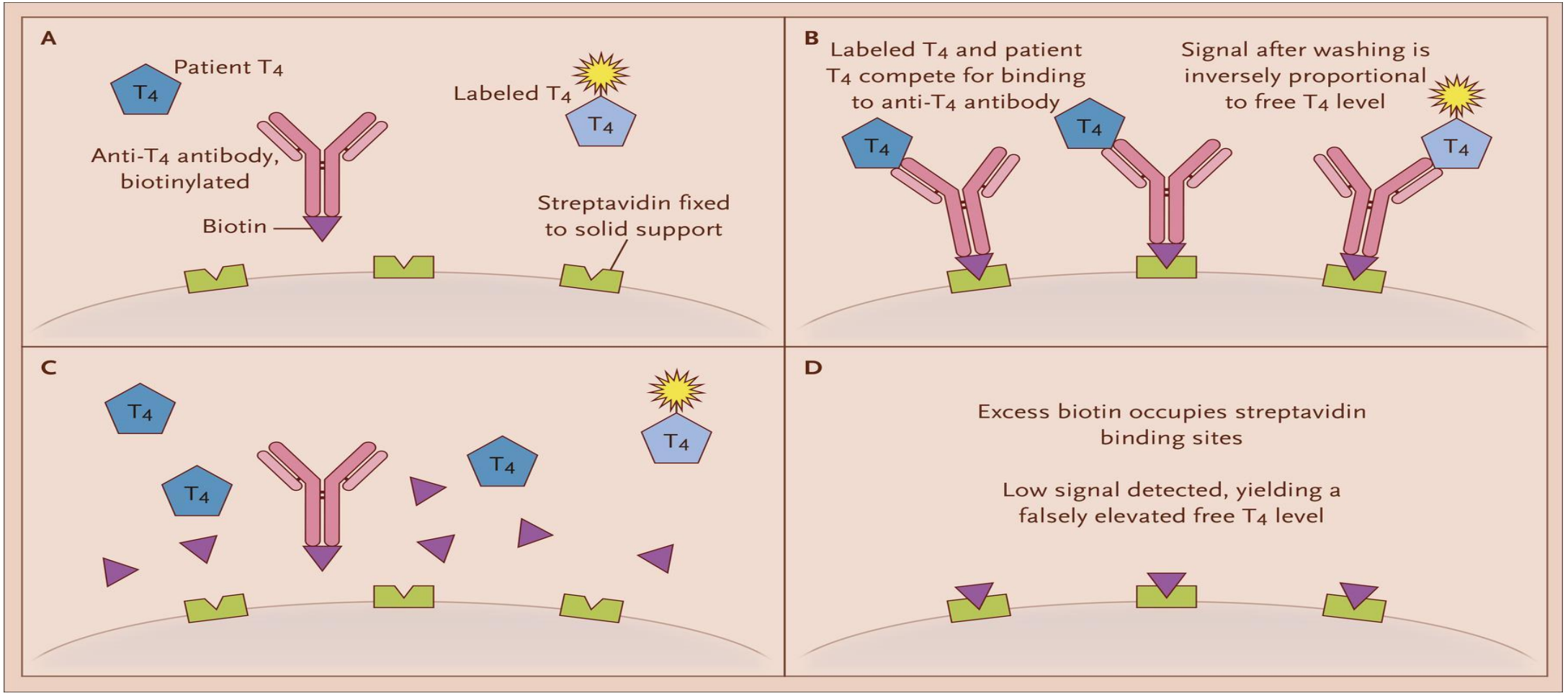


Figure 4. Biotin-Related Interference in Competitive Free T4 Immunoassays.
In some competitive immunoassays, including those for free T4, free T3, and thyrotropin receptor antibodies, the results may be falsely elevated. Free T4 assay components include labeled T4 and a biotinylated anti-T4 antibody, as well as streptavidin bound to a solid phase, such as beads coated with streptavidin (Panel A). Free T4 in serum from the patient competes with labeled T4 for binding to the biotinylated anti-T4 antibody (Panel B). The amount of signal after washing will be inversely proportional to the level of free T4 in the patient's serum. Excess biotin in the serum monopolizes the streptavidin binding sites, preventing binding of either free T4–anti-T4 antibody or labeled T4–anti-T4 antibody complexes (Panel C). Since the patient's free T4 value in the assay is inversely proportional to the amount of label still present after washing, the low or absent signal leads to calculation of a falsely elevated free T4 value (Panel D).

Drug Effects on the Thyroid Burch H.B.; N Engl J Med 2019;
381:749-761

Case Presentation

A 38YOF consults you with neck discomfort that developed 2 weeks ago. She states a few weeks prior to the neck pain, she developed COVID-19 and had minimal symptoms and quarantined. On exam she has a boggy nodular thyroid gland that was difficult to examine due to pain. She denies weight loss or hyperdefecation though has some heart racing. She had labs showing FT4 3.62 and TSH<0.01. Which of the following conditions is most likely?

A. Hyperfunctioning Nodule
B. Hemorrhagic Thyroid Cyst
C. Subacute Thyroiditis
D. Grave's Disease
E. Hashimoto's Thyroiditis

Subacute Thyroiditis

- Subacute thyroiditis is thought to be of viral origin.
- Characterized by a viral prodrome including fever, myalgia, and URI followed by thyroid pain and tenderness that can radiate to the jaw or ear.
- Course is self limited and consists of a hyperthyroid phase lasting up to three months followed by a mild hypothyroid phase lasting up to two months and then recovery which is usually permanent.

COVID-19 and the Thyroid Gland

- Clinical presentations resembling subacute thyroiditis in critically ill patients
- Classic subacute thyroiditis shows that 5-20% of patients develop permanent hypothyroidism
- Steroids, B-blockers and nonsteroidal anti-inflammatory drugs

You are contacted by the MIST Line to assist a local provider in management of a 72 year old female that recently started immune checkpoint inhibitor therapy (ipilimumab and nivolumab) for a malignancy and has developed abnormal TFTs (FT_4 3.4 (0.1-1.81) and TSH 0.04 (0.35-5.50). She has lost a few pounds and has fatigue and heart racing. In addition to starting the patient on B Blockade, which of the following would you recommend:

A. Suggest that the patient discontinue ICI therapy
B. Start antithyroid medication and check CBC
C. Recheck TFTs in 2-3 weeks and consider decreasing Beta Blocker and starting levothyroxine therapy
D. Refer the call to the access center for next available appointment
E. Tell the referring provider to recheck thyroid levels in 3 months

Immunotherapy and the Thyroid

- 44% of US cancer patients eligible for immune checkpoint inhibitor (ICI) treatment (2018)
- Autoimmune Side Effect in up to 60%
  1. Hypothyroidism 10-30%
  2. Hypophysitis 5-11%
  3. Type 1 DM 0.4-2%

Immunotherapy and the Thyroid

- Leverages the immune system to fight cancer cells
- Checkpoint Inhibitors Release the Brakes
  - CTLA-4 Blockade (ipilimumab) 2011 1st one
  - PD-1 Blockade (nivolumab) 2014
  - PD-L1 Blockade

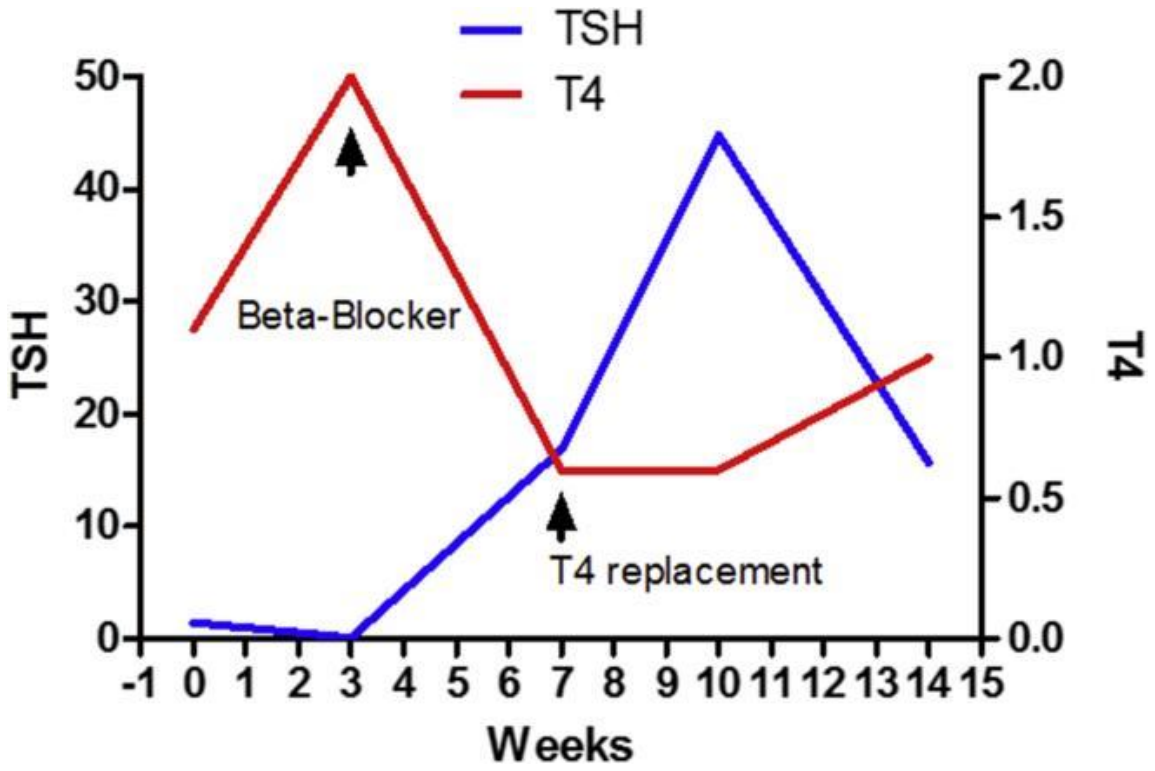
Thyroiditis

- Destructive thyroid gland inflammation, likely cell mediated
  - (CD3, B cells, CD4, CD8)
  - Predominant T cell destruction
- Limited role for TPO and Tg antibodies
  - (20-40%)
  - TPO positive patients have 5x increased risk
  - Reasonable to check TSI if suppressed TSH doesn't return

Immune-related adverse events from checkpoint inhibitors

- Interrupt treatment
- Permanent Organ Dysfunction
- Increased hospitalizations
- Increased deaths


Initially thyroiditis
2-3 weeks (dual)
5-8 weeks (mono)
Hyperthyroid Phase
(4-6 weeks)
Hypothyroid Phase
(rapid, permanent)
10-12 weeks
Treated Euthyroid



Immune-related endocrine disorders in novel immune checkpoint inhibition therapy. Genes Dis. 2016 Dec;3(4):252-256. Le Min

Treatment

- Hyperthyroidism: reassurance, close monitoring, symptomatic B-blocker though done titrate due to rapid fall in T4
- Transition Phase
  - Check every 3 weeks
  - TSH may lag as FT4 falls more rapidly
- Hypothyroid Phase
  - Destructive process
  - 50-90% permanent
  - Absorption issues with replacement
  - Could also have TSH issues from nonthyroidal illness, hypophysitis and steroids
- No use for steroids and no need to stop immunotherapy
- Development of side effects suggests survival benefits of treatment

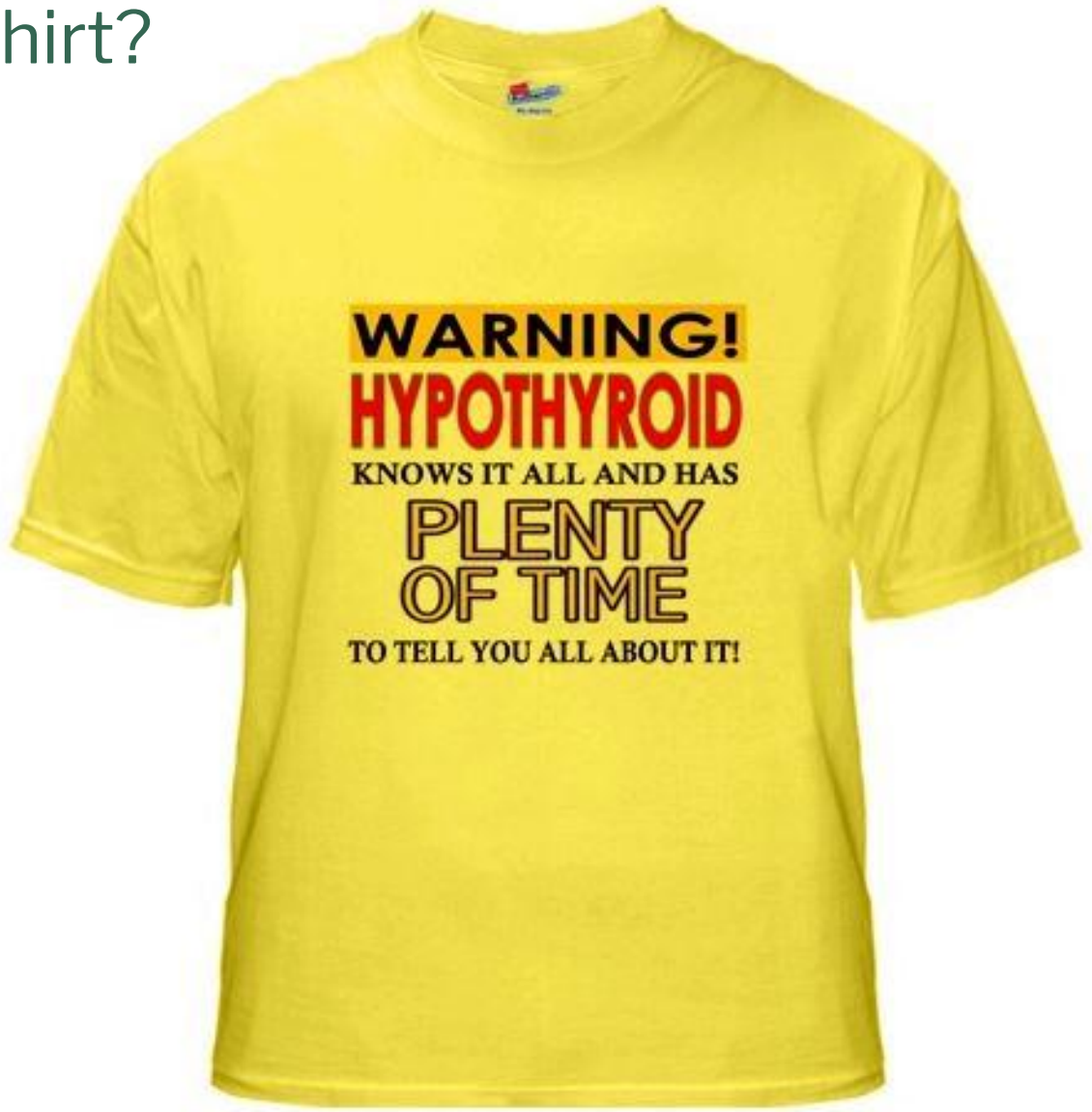
Thyroid Telehealth Tips

- Do you have a primary care provider?
- Have you seen an endocrinologist in the past? Why are you seeing another one?
- Who started you on thyroid medication and when? Do you remember why they started you on medication?
- How do you take your thyroid medication?
- Are you on name brand medication or generic medication?
- In the last 30 days how many thyroid pills have you missed?
- Do you fill medication every 30 or 90 days?
- Are you on calcium, iron, or biotin?

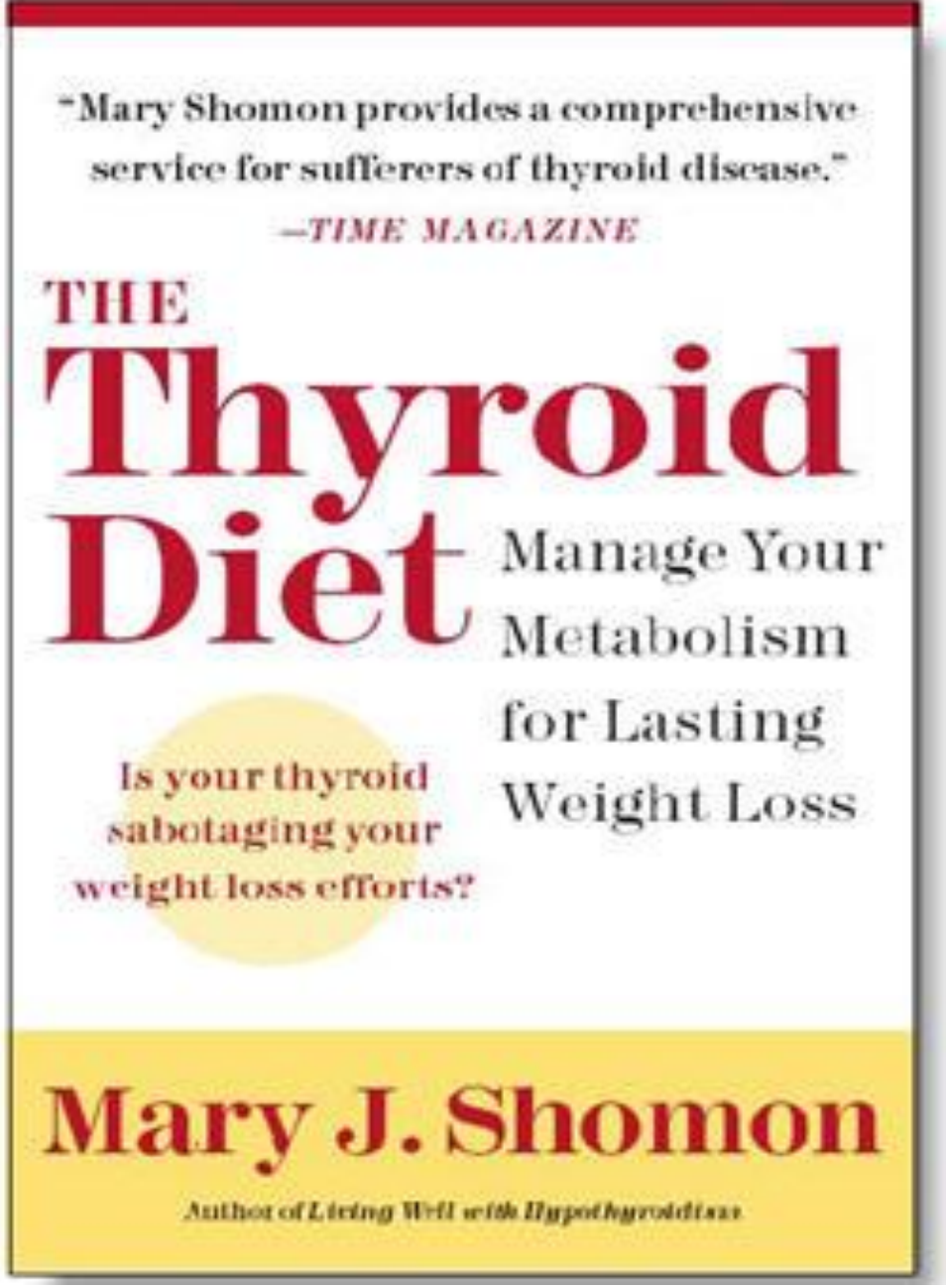
Thyroid Telehealth Tips (cont)

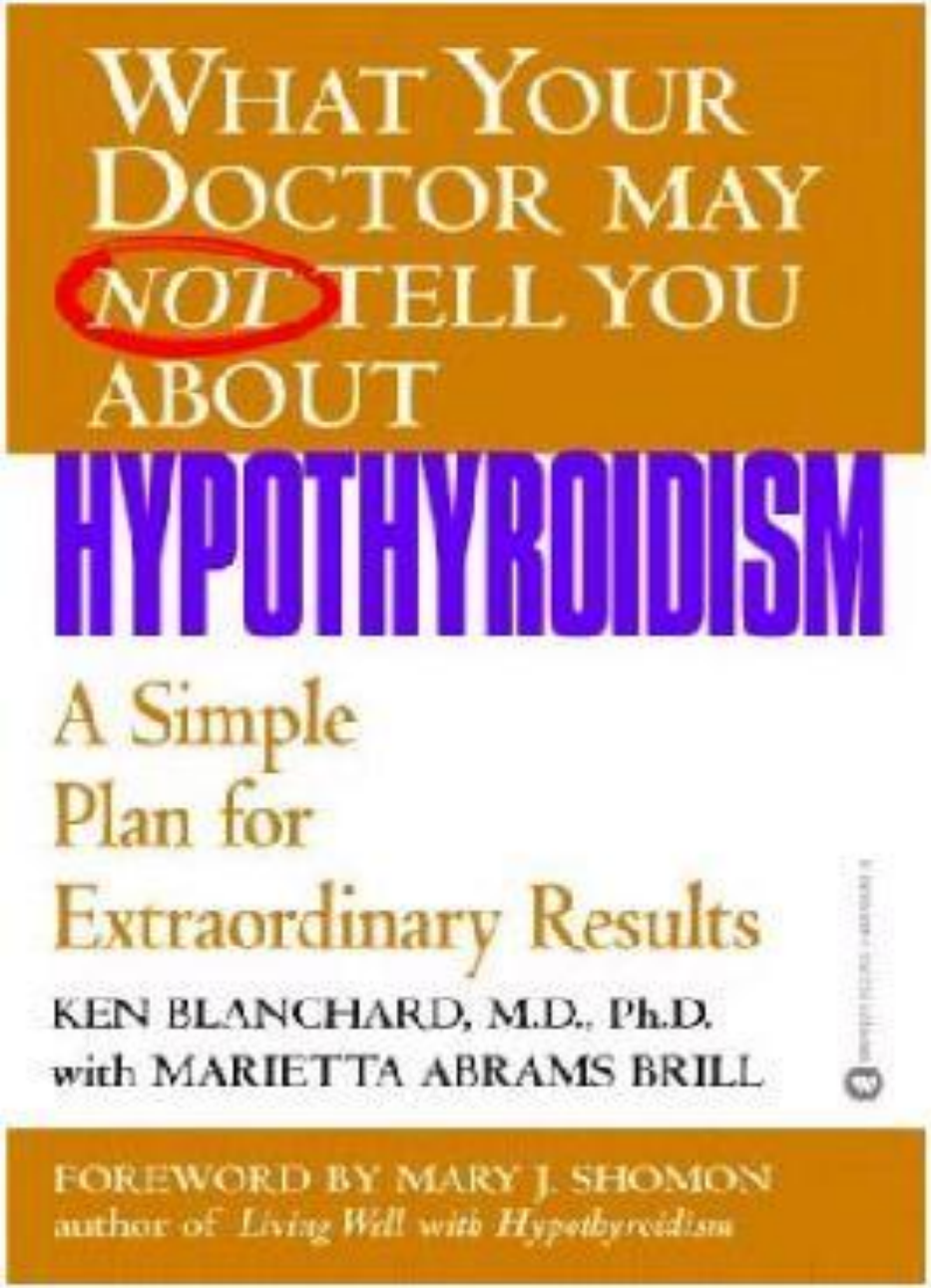
- Do you have hoarseness or trouble swallowing?
- Have you had thyroid imaging in the past?
- Have you received I-131 therapy in the past?
- Has someone suggest to remove thyroid in the past?
- Do you take OTC supplements or compounded products?
- Are you on Armour Thyroid or Nature Thyroid?

Do you have a thyroid shirt?



Do you have a Thyroid Book?


"Mary Shomon provides a comprehensive service for sufferers of thyroid disease."
—TIME MAGAZINE
THE
Thyroid
Diet
Manage Your Metabolism for Lasting Weight Loss
Is your thyroid sabotaging your weight loss efforts?
Mary J. Shomon
Author of Living Well with Hypothyroidism


WHAT YOUR DOCTOR MAY NOT TELL YOU ABOUT
HYPOTHYROIDISM
A Simple Plan for Extraordinary Results
KEN BLANCHARD, M.D., Ph.D.
with MARIETTA ABRAMS BRILL
FOREWORD BY MARY J. SHOMON
author of Living Well with Hypothyroidism

good luck today!

☆ Don't forget to ask for the book club minutes...

and [redacted] make sure the prenatal vitamins DO have iodine ☆