

# Hypothyroidism: evaluation & management

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Mohsen Eledrisi, MD, FACP, FACE

Department of Internal Medicine

Hamad Medical Corporation

Doha, Qatar

[www.eledrisi.com](http://www.eledrisi.com)

# CASE 1

- A 42-year-old lady presents with fatigue, joint pains and weight gain for 3 months
- No significant past medical history
- Exam: dry skin, small thyroid, weight 65 kg
- TSH done 2 months ago: 12.2 (normal, 0.4-4.5)
- Today TSH 15, Free  $T_4$  8 (10-19)
- **How would you approach?**

# Screening for thyroid disease

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- **ATA/AACE guidelines:**
  - The presence of any of the following:
    - Autoimmune disease (type 1 DM, pernicious anemia)
    - Abnormal thyroid examination
    - Psychiatric disorder
    - Neck radiation
    - Thyroid surgery
    - On amiodarone or lithium
    - First degree with autoimmune thyroid disease
    - Consider for persons age > 60 years

# **Screening for thyroid disease**

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- United States Preventive Services Task Force: “no evidence”
- Royal college of physicians-UK: “unjustified”

# Laboratory assessment for thyroid disease: which test?

- TSH
- TSH, FT<sub>4</sub>
- TSH, FT<sub>4</sub>, FT<sub>3</sub>
- TSH, TG Ab
- TSH, TPO Ab

# Symptoms of hypothyroidism

- May be mild
- Dry skin, weight gain, cold sensitivity, fatigue, muscle cramps, hair loss, voice changes, constipation
- Menstrual abnormality (heavy bleeding, delayed period)
- Abnormal sleep pattern, anxiety

# **Physical examination in hypothyroidism**



**Non-pitting  
edema**



**Periorbital  
edema**

# Interpretation of thyroid function tests

- High TSH:
  - Indicates primary hypothyroidism
  - Defect in thyroid (mostly autoimmune)
  - Repeat in 4-6 weeks to confirm
  - Can add Free T4 to confirm
- Normal (or low) TSH and low Free T4:
  - Indicates secondary hypothyroidism
  - Rare

# Causes of hypothyroidism

- Chronic autoimmune thyroiditis
  - Most common (>95%)
  - Goiter or small thyroid
- Iatrogenic disease
  - Thyroidectomy
  - Radioiodine treatment
  - External radiation therapy
- During acute/subacute thyroiditis
- Secondary or tertiary (pituitary or hypothalamic disorder)

# CASE 1: assessment & plan

- Assessment:
  - High TSH
  - Confirmed on a repeat test with low Free  $T_4$
  - Diagnosis:
    - Primary hypothyroidism
- Plan:
  - Start levothyroxine

# Levothyroxine dose

- **How much?**
  - ◆ 1.6 micrograms/kg/day
- **How to start?**
  - A) Full dose at start for:
    - Non-elderly (age <65 years)

# **Levothyroxine dose**

## **B) Low dose for:**

- 1) Patients with active coronary artery disease
    - A randomized trial showed no problem with full dose in asymptomatic cardiac patients\*
  - 2) People >65 years without heart disease  
(expert opinion)
- Start with (25 or 50 mcg/d), increase every 4 weeks

American Thyroid Association. Thyroid 2014;24:1670.

\* Roos A, et al. Arch Intern Med 2005;165:1714.

# Factors affecting choice of thyroxine dose

- Level of TSH
  - ◆ Lower levels: consider lower dose
- Weight:
  - Actual body weight has been used
  - Some studies showed that ideal body weight is better than actual body weight
  - Many physicians still use actual body weight
- Advancing age:
  - Requirement decreases

# **Education on thyroxine**

- When to take it?
  - Take at least 30 minutes before breakfast
  - Can take it at bedtime ( $\geq 3$  hours after the last meal)
- Timing of improvement of symptoms?
  - Improvement takes usually 2-4 weeks
  - But full improvement may take a few months
  - Tell this to your patient
- Pregnancy?
  - Do not stop it
  - Follow up soon

# CASE 1: PLAN

- Weight is 65 kg
- Start Levothyroxine 100 mcg/day
- Follow up?
  - After 4-6 weeks
  - What labs?
  - TSH only (no need for free  $T_4$ )

# Follow up after starting thyroxine

- Symptoms alone are not sensitive
- What is the target TSH?
  - Within normal
- Increment of dose change: (12.5-25 mcg/day)
- Some patients have symptoms when TSH is on the higher side of normal
  - Consider target TSH <2.5

# CASE 1: follow up

- Levothyroxine 100 mcg qd
- F/U after 2 months:
  - TSH 6.1 (0.4-4.5)
  - Ask if she is adherent to thyroxine, taking it right, or taking any other medications
- Plan?
  - Increase the dose to 125 mcg/day
- F/U in 4-6 weeks:
  - TSH 2.2
  - Great !!

# Hypothyroidism: follow up plan

- TSH every 3 months till 2 normal levels
- Then once a year
- **Instructions to the patient:**
  - Come back earlier if:
    - Planning pregnancy
    - Pregnancy
    - New symptoms
    - Let us know if you start taking new medications

# CASE 2

- A 35-year-old lady was diagnosed with hypothyroidism 9 months ago
- She was on thyroxine 100 mcg daily
- She reports fatigue
- As TSH was 6.5, dose was ↑ to 125 mcg daily
- After 2 months, she feels better but has palpitations  
TSH 0.1 (0.4-4.5), Free T<sub>4</sub> 20 (10-19)
- **How would you approach?**

# **Make thyroxine dose simple!**

- Most patient will do fine on a **single daily dose**
- Rarely, patients will need different dosing:
- **Our patient:**
  - Under-replaced on 100 mcg qd (TSH 6.5)
  - Over-replaced on 125 mcg qd (TSH 0.1)
    - **What is the plan?**

# Usual available thyroxine doses



100 mcg



50 mcg



25 mcg

© 2005 GS

Other doses (88, 112, 137...) are available in some countries

# CASE 2: thyroxine dose

- Under-replaced on 100 mcg & over-replaced on 125 mcg qd

- ◆ **Options of management:**

- 1) Use a dose of 112 mcg (but not available everywhere)
- 2) Or take 100 mcg and half of the 25 mcg = 112.5 mcg/day
- 3) Or alternate daily dosing (100 mcg & 125 mcg) = 112.5 mcg/day
- 4) Take 8 tablets/week (2 tablets on 1 day) = 114 mcg/day
  - (We prefer this)
- 5) Or 100 mcg on weekdays & 125 mcg on weekends = 107 mcg/day
  - I discuss with the patient and see what suits her

# **Tips on the management of hypothyroidism**

- **TSH 0.8 (normal 0.4-4.5):**
  - Physician decreases the dose (wrong decision!)
  - Should keep the same dose as TSH is in target
- **TSH 0.3 (normal 0.4-4.5):**
  - If patient has no symptoms, no need to reduce the dose
  - Repeat after 6 weeks
  - In many times it goes to normal

# Tips on the management of hypothyroidism

- TSH 5.1 (normal 0.4-4.5):
  - Patient has no symptoms
  - Look at the latest TSH (normal or high)
  - Ask about adherence, recent hospitalization
  - Usually, no need to change the dose
  - Laboratory factor or circadian change in TSH levels
  - Repeat after 6 weeks and assess

# CASE 3

- A 32-year-old lady with hypothyroidism diagnosed 1 year ago
- Thyroxine 100 mcg daily
- She reports fatigue and hair loss
- She is not taking any other medications
- TSH 4.1 (0.4-4.5)
- Her physician ordered Free  $T_4$ : normal
- **How would you approach?**

# CASE 3: approach

- Patient is adherent to thyroxine
- Takes thyroxine correctly
- Still has symptoms despite normal TSH
- TSH is on the high normal side 4.1 (0.4-4.5)
- Some data suggest target TSH of < 2.5
- Increase thyroxine, aim for TSH < 2.5
- Reassess when TSH is at target

# CASE 4

- A 25-year-old lady with hypothyroidism for 3 years
- Thyroxine 100 mcg daily
- She has fatigue and hair loss & cannot lose weight
- Weight 70 kg, BMI 29.2, small thyroid
- TSH 1.5
- Her physician ordered Free  $T_4$ : normal
- Referred for symptoms
- **How would you approach?**

# CASE 4: assessment

- Normal thyroid function
- Symptoms are likely not due to the thyroid
- Consider other causes such as:
  - Anemia
  - Polymyalgia
  - Depression
- Reassure the patient about thyroid condition
- Some physicians use T<sub>3</sub> tablets with thyroxine (not recommended by the American Thyroid Association)

# CASE 5

- A 32-year-old lady with hypothyroidism
- Levothyroxine 125 mcg daily for the last 5 years
- TSH has been normal for the last 4 years
- Last one done a year ago was 3.2 (0.4-4.5)
- Today TSH 7.1
- **How would you approach?**

# CASE 5: questions

- Is the patient taking thyroxine daily?
- Is she taking thyroxine correctly?
- Weight change? (increased weight increases thyroxine requirement)
- On other medications?
- Pregnancy?
- Change in thyroxine brand? (changing companies may have an effect)

**What medications can affect  
thyroid gland or thyroid  
medication?**

# **Medications that interfere with thyroid hormone absorption**

Calcium salts

Ferrous sulphate (oral)

PPI

Orlistat

Sevelamer (phosphate binder)

Bile acid sequestrants

# **Medications that interfere with thyroid hormone production/secretion**

- Amiodarone
- Lithium
- Interferon alfa
- Monoclonal antibody therapy (e.g. Alemtuzumab)
- Cancer therapy (e.g. tyrosine kinase inhibitors)

# **Medications that affect thyroid hormone clearance or binding**

- **Increase requirement for thyroxine:**
  - Estrogen, Carbamazepine, Rifampin
  - Phenobarbital, Phenytoin
- **Decrease requirement for thyroxine:**
  - Androgens

# Managing medications with thyroxine

- Medications that affect absorption:
  - Separate them from thyroxine (at least 4 hours)
- Other medications:
  - Monitor TSH
  - Adjust thyroxine dose if needed

# Changing thyroxine brands

- Any issue with changing thyroxine brand?
- Any issue with changing from brand to generic?
- Switching between levothyroxine products could result in variations in the administered dose
- It should be generally avoided

# Changing between thyroxine products

- Avoid the switch particularly in:
  - Early childhood
  - Pregnancy
  - Frail patients
  - High risk thyroid cancer
- If the switch is done:
  - Reassess patient condition
  - Monitor TSH level

# CASE 6

- A 36-year-old lady diagnosed with hypothyroidism 4 years ago
- She is on thyroxine 300 mcg daily
- Reports fatigue, weight gain and dry skin
- Weight 68 kg, BMI 28. Thyroid is not palpable
- TSH 25 (0.4-4.5)
- Free  $T_4$  7 (10-19)
- **How would you approach?**

# CASE 6: assessment

- Thyroxine dose is much more than her requirement
- Her requirement is (weight  $64 \times 1.6 = 110$  mcg)
- TSH is high
- Is she taking thyroxine regularly?
- Is she taking thyroxine correctly?
- Is she taking other medications?
- Ask about vitamins, supplements, oral contraceptives
- Look at previous labs (TSH, FT<sub>4</sub>)
- Social history, psychological issues?

# CASE 6: approach

- Causes of high TSH despite high doses of thyroxine:
  - Poor adherence to medication
  - Poor absorption of medication
- Assess adherence by  $T_4$  absorption test:
  - Ask the patient to take the weekly dose (7 tablets) at once **under supervision**
  - Check Free  $T_4$  at baseline and 2 hours after taking tablets
  - Free  $T_4$  should increase by >50%

# **Abnormal T<sub>4</sub> absorption test**

- Indicates poor absorption of thyroxine:
- Can be caused by:
  - H. pylori gastritis, autoimmune gastritis, celiac disease
  - Treat these conditions and retest to assess dose
- Increase thyroxine dose
- Better absorption by:
  - Crushing thyroxine tablet
  - Changing thyroxine to soft gel or solution

# CASE 7

- A 34-year-old lady with hypothyroidism for 4 years
- On levothyroxine 100 mcg qd
- No complaints
- Pregnancy test was positive last week
- TSH 3.8 (0.4-4.5)
- Free  $T_4$  14 (10-19)
- **How would you approach?**

# Hypothyroidism in pregnancy

- Levothyroxine dose usually needs an increase:
  - Generally, 25-50% (variable from 10 to 80%)
- Target TSH:
  - ◆ **<2.5: if planning pregnancy**
  - ◆ **≤2.5: in 1<sup>st</sup> trimester**
  - ◆ **≤3: in 2<sup>nd</sup> & 3<sup>rd</sup> trimesters**

# Management of hypothyroidism in pregnancy

- Monitor TSH every 4 weeks during 1<sup>st</sup> trimester
- Then every 6-8 weeks
- Advise before pregnancy:
  - Increase levothyroxine dose if missed period or positive home pregnancy test
    - One way is to take **9 doses/week (double on 2 days)**
- After delivery: return to pre-pregnancy levothyroxine dose and monitor TSH

# CASE 7: assessment & plan

- TSH of 3.8 is high in pregnancy
- TSH target in 1<sup>st</sup> trimester: **≤2.5**
- Would increase thyroxine from 100 to 125 mcg qd
- Follow up TSH after 4 weeks
- Education on other medications which may affect thyroxine (iron, calcium,..)

# CASE 8

- A 56-year-old lady with type 2 diabetes for 5 years
- Metformin, Empagliflozin, Simvastatin
- No complaints
- Normal BP, weight 66, BMI 27.4. normal examination
- TSH 7.2 (0.4-4.5), Free  $T_4$  15 (10-19)
- A1c 6.5%, normal kidney & liver function tests
- **How would you approach?**

# Subclinical hypothyroidism

- High TSH & normal FT4
- Most have TSH <10
- Affects 4-15% of the population
- Likely over-estimated as elderly have higher TSH
- Most have no symptoms
- Difficult to attribute symptoms (when present) to it

Biondi B, et al. JAMA 2019;322:153.

American Thyroid Association/AACE. Thyroid 2012;22:1200

# Management of subclinical hypothyroidism

- First: **REPEAT TEST** after 2-3 months
- About 60% of TSH levels <10 will normalize within five years
- Progression to overt hypothyroidism: 2-4%/year
- Some recommend checking TPO antibodies
- No benefit from treating people age  $\geq 65$

European Thyroid Association. Eur Thyroid J 2013;2(4):215

American Thyroid Association/AACE. Thyroid 2012;22:1200

TRUST trial. N Engl J Med 2017; 376:2534

# When to treat subclinical hypothyroidism?

- 1) Pregnancy
- 2) Planning pregnancy
- 3) Infertility

# Management of subclinical hypothyroidism

**TSH  $\geq 10$**   
on 2 occasions  
(3 months apart)

**High TSH  $<10$**   
on 2 occasions  
(3 months apart)

**Treat**

**Age  $<65$**

**Age  $\geq 65$**

**Symptoms**

**No symptoms**

**No treatment**

Trial of treatment  
for 6 months

Stop treatment if no  
improvement

# Follow up of subclinical hypothyroidism

- If treatment if indicated:
  - Starting dose of levothyroxine 25 or 50 mcg qd
  - Target is normal TSH
  - Target in pregnancy or planning pregnancy: <2.5
- If no treatment is given:
  - TSH every 6 months for 2 years then yearly

# CASE 8

- A 29-year-old lady in her 3<sup>rd</sup> month of pregnancy
- This is her first pregnancy
- Reports occasional fatigue, headache
- Past history: none
- TSH 3.4 (0.4-4.5), Free T<sub>4</sub> 14 (10-19)
- **How would you approach?**

# Thyroid function in pregnancy

- ↑ TSH [ $>$  upper limit (4)]= subclinical hypothyroidism
  - Treat
- TSH 2.5 to 4 (upper limit of normal):
  - ATA recommends to check TPO antibodies
    - ATA: “consider treatment if TPO Abs positive”
    - Some treat if TPO Abs positive with prior abortions
- If TSH < 2.5 and low  $\text{FT}_4$ :
  - No treatment

# CASE 9

- A 36-year-old lady was diagnosed with hypothyroidism 1 year ago
- Thyroxine 50 mcg daily
- No complaints
- Weight 84 kg, BMI 32. Examination: normal
- TSH 1.1 (0.4-4.5)
- Free  $T_4$  15 (10-19)
- **How would you approach?**

# CASE 9: approach

- TSH is low normal
- Thyroxine dose is much less than her requirement
- Her requirement (weight  $84 \times 1.6 = 135$  mcg)
- Why was thyroxine started?
- Did she have symptoms at the beginning?
- What was TSH level when treatment was started?
- Was it “hypothyroidism” or “subclinical hypothyroidism”?
- Did she have thyroiditis? Was she hospitalized?

# CASE 9: info & plan

- No symptoms when thyroxine started 1 year ago
- TSH was 6.2 at that time
- PLAN?
- Thyroxine was not indicated
- Stop thyroxine
- Check TSH after 2 months
  - TSH 5.2
  - Subclinical hypothyroidism
  - No treatment is needed
  - Follow up

# CASE 10

- A 25-year-old lady
- Has weight gain, fatigue, hair loss for 2 years
- Had several TSH levels: 1.5, 2.2, 3.1 (all normal)
- Free  $T_4$  always normal
- She believes it's hypothyroidism (also Google agrees!)
- She is asking for thyroid treatment
- **How would you approach?**

**It is not  
the thyroid!**

# **Symptoms of hypothyroidism with normal thyroid tests**

- Around 20-25% of people with normal thyroid function report at least one of the symptoms of hypothyroidism
- A randomized controlled trial showed no benefit of levothyroxine in these patients\*
- Levothyroxine is not recommended in euthyroid patients to treat symptoms, obesity or depression
- Look for other causes (anemia, fibromyalgia, depression,...)

Canaris GJ, et al. Arch Intern Med 2000;160:526.

\* Pollock M, et al. BMJ 2001;323:891.

American Thyroid Association. Thyroid 2012;22:1200.

# Summary

- TSH (only) to screen for thyroid disease
- Simplify thyroxine dose (most do fine on a single daily dose)
- Review medications that may affect thyroid function
- Thyroxine dose usually requires ↑ during pregnancy
- Target TSH in pregnancy or planning for pregnancy is lower
- Identify and manage subclinical hypothyroidism
- Many euthyroid people have symptoms of hypothyroidism

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