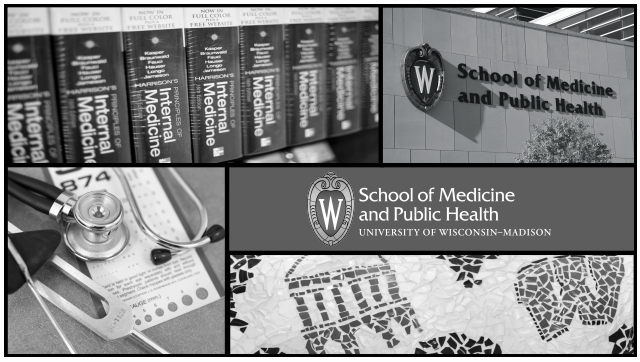

Clinical Pearls: Endocrinology

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Disclosures:

I have no financial arrangements or other conflicts to disclose.

Clinical Pearls: Endocrinology

Outline:

- Discussion of "inappropriately normal"
- Hypothyroidism and medications
- Thyroid nodules
- Male hypogonadism
- Calcium and parathyroid disease

"Inappropriately Normal"

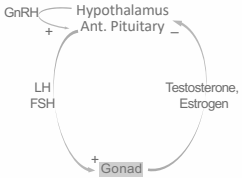
- **Pearl:** Extreme hormone values (deficiency or excess) *should* lead to extreme responses in negative feedback…

"Inappropriately Normal"

- **Pearl:** Extreme hormone values (deficiency or excess) *should* lead to extreme responses in negative feedback…

Example: Gonadal axis

- Low testosterone or estrogen?
- ***Should*** result in high LH and FSH
- So even a "normal" LH and FSH is actually inappropriate → consider problems with pituitary (or hypothalamus)

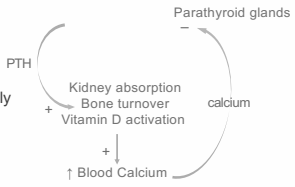


"Inappropriately Normal"

- **Pearl:** Extreme hormone values (deficiency or excess) *should* lead to extreme responses in negative feedback…

Example: Calcium regulation

- High serum calcium?
- ***Should*** result in low PTH
- So even a "normal" PTH is actually inappropriate → suspicion for hyperparathyroidism



Thyroid disorders: Hypothyroidism

Hypothyroidism

Top Medicines by Prescription

DISPENSED PRESCRIPTIONS MN		2017	2018
Total U.S. Market		4,237	4,214
1	atorvastatin	108	114
2	lisinopril	101	98
3	levothyroxine	98	96
4	amlodipine	85	87
5	acetaminophen/hydrocodone	79	68
6	gabapentin	64	67
7	omeprazole	69	63
8	metformin	65	62

(IMS Health, National Prescription Audit, 2018)

Thyroid hormone – it's popular!

Why does it matter?

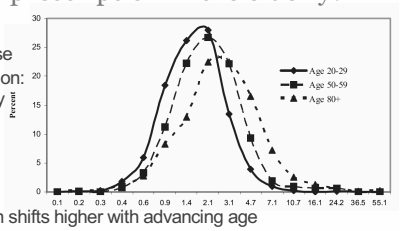
- Narrow therapeutic window
- Requires lifelong monitoring
- Research shows:
  - Over-prescription, over-treatment, and harm (especially in elderly)
  - Single TSH elevation often resolves with time (up to 60%!)
  - No consistent symptom benefit in subclinical hypothyroidism treatment
- Potential for adverse effects
  - Increased risk of A-fib
  - Bone density loss and fracture risk

Levothyroxine!

Over-prescription in the elderly?

NHANES III database of euthyroid population:

- Normal ranges by 95% confidence interval



- TSH distribution shifts higher with advancing age
- Normal TSH upper limit is ~ 7.5 mIU/L in 80+ year olds
- **Pearl:** Subclinical hypothyroidism rates are over-estimated in elderly

Surks & Hollowell. *JCEM*. 2007; 92: 4575-82

Guidelines: Who should be treated?

- Treat with levothyroxine if TSH > 10 mIU/L (usually overt)
- **Consider* treatment with levothyroxine if TSH between 4-10 mIU/L:
  - Classic symptoms of hypothyroidism
  - Presence of + TPO Ab
  - Evidence of atherosclerotic CV disease, heart failure, or associated CV risks (data in ages 40-70 yo)

*Level B recommendation – not based on prospective randomized trials

Also: Different recommendations for pregnancy and fertility planning

AACE/ATA Guidelines:
Garber, et al. *Endo Practice* 2012; 18: 988-1028

Thyroid disorders: Medications

Interfering medications

- Medications that may permanently alter thyroid function:
  - Amiodarone: hypothyroidism, hyperthyroidism, thyroiditis
  - Lithium: hypothyroidism, hyperthyroidism
  - Immune checkpoint inhibitors and TKIs: usually thyroiditis (also hypophysitis and hypopituitarism)
- Generally need to treat (endocrine consultation)

Thyroid disorders: Medications

Interfering medications

- Medications that may transiently alter thyroid function:
  - Corticosteroids: low TSH, normal or low T4 and T3
  - Dopamine: low TSH
- Avoid thyroid testing during acute illness
- Generally can ignore (no treatment) and repeat testing later

Thyroid disorders: Medications

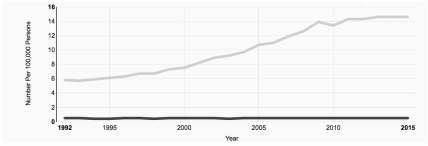
Interfering medications

- Medications that do not alter thyroid function but disrupt thyroid lab results:
  - Biotin (vitamin B7): may interfere with TSH assays (and other hormone assays) – high or low values have been reported
  - Heparin (fractionated or unfractionated): may artificially increase free T4 and free T3 values (displaced from albumin *in vitro*)
- Avoid testing or stop medication (3-7 days) and repeat testing

Pearl: Medications can impact interpretation of TFTs!

Thyroid disorders: Nodules

Thyroid nodules



National Cancer Institute (NIC)
https://seer.cancer.gov/statfacts/html/thyro.html

- The incidence of detected thyroid cancer cases has been rising (greater use of imaging)
- But mortality is stable at 0.5 per 100,000 persons per year

Thyroid disorders: Nodules

Thyroid nodules: General principles

- Thyroid nodules are common, grow slowly, and are low risk
- Over-detection and over-treatment of thyroid nodules can lead to harm
- Mostly cystic (>50%) nodules are rarely cancer[1]
- Small (<1 cm) thyroid nodules are rarely cancer[2]
- Small (<1cm) thyroid cancers rarely grow or metastasize (and can be easily treated if they do)[3] – especially in older adults!

[1] Henrichsen et al. (2010) *J Clin Ultrasound* 38: 361-6
[2] Durante et al. (2015) *JAMA* 313: 926-35
[3] Ito et al. (2012) *Thyroid* 24: 27-34

Thyroid disorders: Nodules

Thyroid nodules:

Approach: Ultrasound, check TSH, then discuss FNA biopsy if:

- ≥ 1 cm – mostly solid (especially if calcifications, irregular margins)
- ≥ 1.5 cm – mostly cystic
- ≥ 2.0 cm – spongiform (or just monitor)
- No FNA for purely cystic
- No FNA for "hot" nodules (very low TSH)

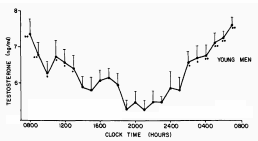
Pearl: No need for FNA of nodules < 1 cm

Male Hypogonadism

Testosterone testing

- Only screen for hypogonadism if signs or symptoms are present (universal screening is not recommended)
- Testing must be approximately 8 AM (levels change with circadian variation)
- Don't test during an acute illness or hospitalization (rhythm is blunted)
- Repeat testing at least 2x (up to 30% may be normal on repeat testing)

Endocrine Society Clinical Practice Guidelines: Bhasin, et al. 2018 JCEM 103: 1-30



Modified from: Bremner, et al. 1983 JCEM 56: 1278-1281

Male Hypogonadism

Testosterone testing

- Screening should usually include total and free (or bioavailable) testosterone testing
- If abnormal, repeat testing should include simultaneous measurement of LH and FSH

Remember: Inappropriately normal?

Endocrine Society Clinical Practice Guidelines: Bhasin, et al. 2018 JCEM 103: 1-30

TABLE 2. Conditions associated with alterations in SHBG concentrations

Conditions associated with decreased SHBG concentrations
Moderate obesity[a]
Nephrotic syndrome[a]
Hypothyroidism
Use of glucocorticoids, progestins, and androgenic steroids[a]
Acromegaly
Diabetes mellitus[a]

Male Hypogonadism

Testosterone testing – confounding factors

- Testosterone levels decline with age… but "normal" range defined in young adults
- Testosterone levels are also lower in men with:
  - *Obstructive sleep apnea
  - *Obesity/adiposity
  - *Chronic opiate use
  - *Hyperprolactinemia

* Potentially reversible – must be considered and treated if possible

Male Hypogonadism

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  - *Chronic opiate use
  - *Hyperprolactinemia

Pearl: Testosterone testing must be done carefully, repeated, and results interpreted with caution!

Calcium and parathyroid disease

Calcium and parathyroid disease

- High serum calcium and "inappropriately" normal or high PTH → usually primary hyperparathyroidism
  - Rule out FHH (24 hour urine calcium)
  - Find a good surgeon (not imaging)
  - Check vitamin D and bone density

Calcium and parathyroid disease

Calcium and parathyroid disease

- What if calcium is normal with high PTH?
- Consider secondary hyperparathyroidism:
  - Vitamin D deficiency, CKD
  - "Normocalcemic" hyperparathyroidism?
  - Test for hidden calcium deficiency?
  - Check 24-hour urine calcium: (low = poor GI absorption or limited dietary intake)
  - Replete vitamin D and give oral calcium challenge, remeasure PTH and calcium

Calcium and parathyroid disease

Calcium and parathyroid disease

- What if calcium is normal with high PTH?
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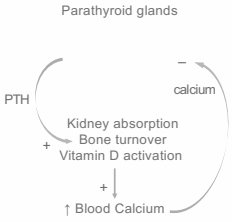

Pearl: Secondary hyperparathyroidism should be suppressible with calcium

Conclusions:

Endocrine Pearls:

- Remember – Extreme values *should* lead to extreme responses in negative feedback… "normal" is not appropriate
- Repeat testing in subclinical hypothyroidism (particularly in the elderly) to avoid over-diagnosis and over-treatment
- Consider medication effects when interpreting thyroid function studies (biotin!)
- Avoid biopsy of nodules < 1 cm (especially in older adults)
- Avoid errors in testosterone testing and consider reversible causes
- Try a "calcium challenge" if PTH is high but calcium is low-normal – normal parathyroid function is suppressible

Questions?

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