Disclosures: I have no financial arrangements or other conflicts to disclose.

Clinical Pearls: Endocrinology
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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.

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)

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

(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

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

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 + TPOAbs
  - 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


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

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: 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
- Small (<1 cm) thyroid nodules are rarely cancer
- Small (<1cm) thyroid cancers rarely grow or metastasize (and can be easily treated if they do!) – especially in older adults!

1 Herrinham et al. (2013) / Clin Ultrasound 38: 361-6
3 Ho et al. (2012) Thyroid 22: 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)

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

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

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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  - *Obesity/adiposity*
  - *Chronic opiate use*
  - *Hyperprolactinemia*

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

**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

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**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

*Pearl*: Secondary hyperparathyroidism should be suppressible with calcium

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**Calcium and parathyroid disease**

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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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