Endocrinology Update 2018

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Discussion Topics

- Management of incidentally discovered lesions
  - Adrenal
  - Pituitary
  - Thyroid
- Diabetes therapies – focus on type 2
- Androgen replacement therapy: magic bullet or not?
- Subclinical hypothyroidism: when to treat?
Adrenal “Incidentalomas”

- Adrenal masses found incidentally on abdominal imaging done for unrelated reasons
  - CT, MRI, rarely ultrasound
- Incidence approximately 1-4% in general population
- Up to 9% of patients have been found to have incidental adrenal masses at autopsy
- Most are benign
- However, some need further investigation
Adrenal Incidentalomas

- Most are non-functioning and of no clinical consequence, however:
  - Goal is to evaluate for functioning tumors
  - If so, then removal is in order
- Nonsecretory $< 4$ cm – observe
- If enlarging or $\geq 4$ cm – consider removal even if nonsecretory
Differential Diagnosis: Incidental Adrenal Masses

- Nonfunctioning cortical adenoma
- Functioning adenoma
- Cyst
- Hemorrhage
- Myelolipoma
- Pheochromocytoma
- Adrenal carcinoma
- Metastatic cancer
- Infectious
  - Abscess
  - Tuberculosis
  - Fungal (histoplasmosis, coccidiomycosis)
- Amyloidosis
- Fibroma
Frequency of Findings

- Adenoma: 54%
- Carcinoma: 12%
- Pheo: 11%
- Myelolipoma: 8%
- Cysts: 5%
- Metastases: 4%
- Neuronal tumor: 4%
- Other: 2%

CT Imaging

- Typical pre-contrast Hounsfield unit (HU) values:
  - Adipose tissue: -20 to -150 HU
- Adenoma phenotype:
  - Hypodense
  - Homogenous
  - Precontrast density < 10 Hounsfield units
  - > 50% contrast washout at 10 min
CT Imaging

- **Pheochromocytoma**
  - Increased attenuation (> 20 HU)
  - Delayed contrast washout (< 10%)
  - High signal intensity on T2 MRI
  - Cystic – hemorrhagic

- **Adrenocortical carcinoma**
  - Irregular shape
  - Inhomogeneous density
  - Often > 4 cm
  - High unenhanced density (> 40 HU)
  - High to intermediate T2 on MRI
Incidentally discovered pheochromocytoma
Adrenocortical carcinoma
Fine needle aspiration of adrenal masses

- Not recommended for most incidental tumors
- Concern for “seeding” if this is a primary malignancy
- Imaging phenotype will screen out benign tumors with nearly 100% sensitivity/specificity
- **Biochemical evaluation imperative for all lesions**
- FNA indicated for:
  - Suspected metastatic lesion
  - Infectious lesion
Screening for subclinical Cushing syndrome

- Overnight (1 mg) dexamethasone suppression test is recommended
- Suppression < 1.8 μg/dL (50 nmol/L) is normal
- False positives may occur
- Abnormal values require further evaluation
  - 24 hour urine free cortisol
  - Plasma ACTH
  - Consider referral to endocrinology
Failure to diagnose Cushing’s syndrome

- Overnight DST is not complex to perform
- Abnormalities should be evaluated by an endocrinologist
- Failure to diagnose Cushing’s syndrome: #1 endocrinology malpractice claim for primary care
Screening for pheochromocytoma

- Plasma free metanephrines
- 24 hour urinary metanephrines and catecholamines
- Some patients with pheochromocytoma are normotensive or only mildly hypertensive between episodes
Screening for primary aldosteronism in patients with HTN

- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA)
- PAC/PRA ratio > 20 suspicious for primary aldosteronism
- Further evaluation needed before performing adrenalectomy
  - Adrenal vein sampling to confirm unilateral hypersecretion
  - Remember: 25% of cases are due to bilateral hyperplasia
Pituitary Incidentalomas

- Combined autopsy data: average frequency of pituitary adenoma = 10.6%
- Microincidentalomas (< 1 cm) seen on CT in 4-20% and 10-38% of those who underwent imaging for another reason
- Macroincidentaloma (≥ 1 cm) much less common (0.2%).
All patients with a pituitary incidentaloma, including those without symptoms, should undergo clinical and laboratory evaluations for hormone hypersecretion or hypopituitarism.
Incidental Thyroid Nodules

- American College of Radiology
  - Do not recommend ultrasound for incidental thyroid nodules found on CT, MRI or non-thyroid-focused neck ultrasound in low-risk patients unless the nodule meets age-based size criteria or has suspicious features:
    - < 35 years of age with normal life expectancy and nodule $\geq 1$ cm.
    - $\geq 35$ years of age with normal life expectancy and nodule $\geq 1.5$ cm.
Incidental thyroid nodules

- Suspicious features on CT, MRI or US include signs of local invasion, and the presence of abnormal lymph nodes (enlarged nodes, nodes with cystic change, calcification, or increased enhancement).
- Size criteria for enlarged lymph nodes:
  - ≥1.5 cm in short axis for jugulodigastric nodes
  - ≥1 cm for other nodes
Incidental thyroid nodules

- Clinical risk factors: Patients with history of head, neck or chest radiation, family history of thyroid cancer, or diseases that increase the risk of thyroid cancer should be further evaluated regardless of nodule size.
Type 2 Diabetes Update
Anti-hyperglycemic Therapy: Oral agents & non-insulin injectables

- Biguanides
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- SGLT-2 inhibitors
- Dopamine-2 agonists
- Bile acid sequestrants
- GLP-1 receptor agonists (incretin mimetics)
- Amylinomimetics (pramlintide)

<table>
<thead>
<tr>
<th>Non-insulin therapies: mean reduction in hemoglobin A$_{1c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>Insulin secretagogues (sulfonylureas, meglitinides)</td>
</tr>
<tr>
<td>Incretin mimetics (GLP-1 agonists—exenatide, liraglutide)</td>
</tr>
<tr>
<td>DPP-IV inhibitors (sitagliptin, linagliptin, saxagliptin, alogliptin)</td>
</tr>
<tr>
<td>α-glucosidase inhibitors (AGIs) - (acarbose, miglitol)</td>
</tr>
<tr>
<td>Amylin agonist (pramlintide)</td>
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<tr>
<td>Thiazolidinediones (pioglitazone, rosiglitazone)</td>
</tr>
<tr>
<td>Bile acid sequestrants (colesevelam, colestipol)</td>
</tr>
<tr>
<td>SGLUT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)</td>
</tr>
<tr>
<td>Dopamine agonist (bromocriptine)</td>
</tr>
</tbody>
</table>
Approach to Starting and Adjusting Injectable Therapy in DM2

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

- Start: 10 U/day or 0.1-0.2 U/kg/day
- Adjust: 10-15% or 2-4 units once or twice weekly to reach FBG target
- For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10-20%

If A1C not controlled, consider combination injectable therapy

Add 1 rapid-acting insulin injection before largest meal

- Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
- Adjust: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to basal-bolus

Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')

- Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
- Adjust: ↑ dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

Add GLP-1 RA

- If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, consider changing to alternative insulin regimen

Add premixed insulin twice daily (before breakfast and supper)

- Start: Divide current basal dose into ⅓ AM, ⅔ PM or ⅓ AM, ⅔ PM
- Adjust: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to 3rd injection

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

- Start: Add additional injection before lunch
- Adjust: ↑ doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%
<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak activity</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate - human NPH (N, neutral protein Hagedorn) (U-100)</td>
<td>2-4 hr</td>
<td>4-9 hr</td>
<td>10-16 hr</td>
</tr>
<tr>
<td>Glargine (long acting analog) (U-100, U-300)</td>
<td>2-4 hr</td>
<td>Minimal</td>
<td>20-24 hr</td>
</tr>
<tr>
<td>Detemir (long acting analog) (U-100)</td>
<td>2-4 hr</td>
<td>8-10 hr</td>
<td>16-20 hr</td>
</tr>
<tr>
<td>Degludec (long acting analog) (U-100, U-200)</td>
<td>2-4 hr</td>
<td>Minimal</td>
<td>36-42 hr</td>
</tr>
<tr>
<td>Human regular* (U-100)</td>
<td>30-60 min</td>
<td>2-3 hr</td>
<td>5-8 hr</td>
</tr>
<tr>
<td>Human regular* (U-500)</td>
<td>30-60 min</td>
<td>4-8 hr</td>
<td>12-14 hr</td>
</tr>
<tr>
<td>Rapid acting analogs (lispro, aspart, glulisine) (U-100)*</td>
<td>5-15 min</td>
<td>30-90 min</td>
<td>4-6 hr</td>
</tr>
</tbody>
</table>

*lispro also available in U-200 pen
Glycemic Control Algorithm

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk

INDIVIDUALIZE GOALS

A1C > 6.5% For patients with concurrent serious illness and at risk for hypoglycemia

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*
- GLP-1 RA
- SGLT-2i
- TZD
- Basal Insulin
- DPP-4i
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

SYMPTOMS

NO
- DUAL Therapy

OR
- TRIPLE Therapy

YES
- INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

PROGRESSION OF DISEASE

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

LEGEND
- Few adverse events and/or possible benefits
- Use with caution

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LOW T: An Epidemic?

TREATMENT: The Magic Bullet?
Loss of Building Blocks: an Epidemic?
Or Fad?
ARE YOU:
• FATIGUED
• IRRITABLE or DEPRESSED
• LACKING ENDURANCE
• UNABLE TO BUILD MUSCLE
• TROUBLE SLEEPING
• LOW LIBIDO

LOW TESTOSTERONE LEVELS
MAY BE THE CAUSE

FIND OUT FOR FREE
START LIVING A
HIGH PERFORMANCE
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TESTOSTERONE
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WE ARE GOING TO BRING THE REAL YOU BACK.

Texoma Wellness
LOW-T CENTER
SIGNS & SYMPTOMS

- Decreased beard & body hair growth
- Loss of energy
- Erectile dysfunction/decreased libido
- Osteoporosis
- Diminished muscle mass
- Altered fat distribution
- Fine wrinkling of skin
- Diminished male pattern baldness
- Decreased aggression
Hormonal Evaluation

- Total testosterone (AM; fasting)
- Free testosterone/SHBG in certain individuals (obesity)
- If abnormal:
  - Prolactin
  - FSH/LH
- If FSH/LH inappropriately low:
  - MRI of pituitary
  - TSH, free T₄, serum cortisol, ACTH
- When in doubt, send to endocrinology!
Total vs. Free Testosterone

- Testosterone circulates mostly bound to SHBG (sex hormone binding protein)
- ~3% circulates as free testosterone
- Only the free portion is biologically active
- Often patients will have slightly low total with normal free T levels
- You can’t just stick the guy with “low T” on testosterone without further evaluation
**Total vs. Free Testosterone**

- Always check T level in the morning (levels are lowest in the afternoon)
- Should be fasting (levels are affected by food)
- If low, confirm with free T, SHBG (sex hormone binding globulin)
  - Most cases of slightly “low T” are due to (a) levels being checked in the afternoon or (b) low SHBG (almost always due to obesity).
EVALUATION OF HYPOGONADISM

FREE TESTOSTERONE

NORMAL:
NO FURTHER WORKUP

LOW OR LOW NORMAL:
LH, FSH

ELEVATED:
TREAT AS HYPERGONADOTROPIC HYPOGONADISM

MRI OF SELLA
Prolactin
Other pituitary hormones
NORMAL:
TREAT AS 'IDIOPATHIC' HYPOGONADOTROPIC HYPOGONADISM
ABNORMAL:
EVALUATE AND TREAT
MONITORING

- Clinical symptoms
  - reliability varies with patient
- Testosterone levels
  - peak vs. trough levels with esters?
  - simpler with transdermal preparations
- Monitor hematocrit yearly
- Monitor for signs of OSA (or worsening of OSA if already on CPAP)
MONITORING

- Baseline digital rectal examination and PSA before starting TRT
- PSA should be checked 6–12 weeks after initiation of androgen therapy
- Check PSA and digital rectal examination annually as long as patient remains on TRT
- PSA velocity > 0.75 ng/mL/y, regardless of baseline PSA, or a nodule on digital rectal examination while on TRT requires referral to urology.
Current literature examining the relationship between TRT and CVD outcomes is conflicting.

Two meta-analyses showed no statistically significant differences in cardiovascular events between patients receiving TRT and patients receiving placebo.
Take-Away Points

- Male hypogonadism exists, but is not nearly as prevalent as the popular media suggests.
- In select patients it may offer benefits but is rarely a “magic bullet”.
- Evaluate properly before considering treatment.
- Treatment is not without risks/side effects.
- Rare patients have serious underlying conditions which require expert management.
- Treat cautiously in older individuals with comorbid conditions.
Subclinical Hypothyroidism
Subclinical Hypothyroidism

- Mildly elevated TSH
- Low normal to normal T₄ levels
- Absence of clinical symptoms
- When to treat?
- Treatment traditionally felt to be benign if monitored properly
- But is it really? Many considerations must be made
Symptoms of thyroid disease are nonspecific

- Euthyroid
- Mild Thyroid Failure
- Hypothyroid

Percent Positive Symptoms

McDermott and Ridgway, JCEM, 2001
Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine.

- Hypothyroid patients treated with resultant normalized TSH are still likely to feel poorly  

(Saravan Clinical Endo 2002; Boeving Thyroid 2011)

Treatment: TSH between 5 and 10

- Treatment should be considered particularly if they have symptoms suggestive of hypothyroidism, positive anti-TPO antibodies or evidence of atherosclerotic cardiovascular disease, heart failure or have associated risk factors for these diseases.
- Evidence not fully generalizable to stated recommendation and there are no prospective, interventional studies.

Hazards of Overtreatment – Cardiac, Bone, Psychiatric

- High risk of subclinical hyperthyroidism in patients on thyroid medication
  - Colorado Prevalence Study, 2000
  - 20.7% (316) of patients on thyroid medication had subclinical hyperthyroidism
  - 0.9% (13) had overt hyperthyroidism
- More adverse effects with poor monitoring
  - Only 56% received standard monitoring
  - Atrial fibrillation, unstable angina with poor monitoring

Increased risk of developing atrial fibrillation in patients with subclinical hyperthyroidism

McDermott and Ridgway
Role of T₃ in Treatment of Hypothyroidism

- Trials have been relatively short
- Studies to date mixed
- T₃ has a short half-life and ideally is given at least twice a day
- Combination therapy still not yet completely understood in the setting of patient preferences
- Addition of T₃ cannot routinely be recommended at this time
Patients with hypothyroidism should be treated with L-thyroxine monotherapy.

Evidence does not support using L-T4 and L-T3 combinations to treat hypothyroidism.

Some unresolved issues raised by studies reporting some patients prefer and some patient subgroups may benefit from L-T4 and L-T3 combination.
**Initiating therapy in overt hypothyroidism**

- When initiating therapy in young healthy adults with overt hypothyroidism, beginning treatment with full replacement doses should be considered.
- When initiating therapy in patients older than 50-60 years old with overt hypothyroidism without evidence of coronary heart disease, L-T₄ dose of 50 µg daily should be considered.
In patients with subclinical hypothyroidism, the initial L-T4 dose is generally lower than what is required in the treatment of overt hypothyroidism.

- Daily dose of 25 to 75 μg should be considered, depending on degree of TSH elevation.
- Further adjustments should be guided by clinical response and follow up laboratory determinations including TSH values.
Thank you!

Questions?