Endocrinology, Diabetes and Metabolism
Internal Medicine Update and Board Review

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VA Caribbean Healthcare System

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Disclosure:
No Conflicts of Interest to Disclose

This presentation is intended for educational purposes only and does not replace independent professional judgment.

I am expressing my own views based on my reading, analysis and interpretation of the scientific information.

I am a member of SPED and a Federal Government employee but I am not speaking in representation of or presenting the views of the Veterans Administration, Puerto Rican Society of Endocrinology and Diabetes, State or Federal Government Agency or Department, other Professional Societies, Public or Private Corporation, or Pharmaceutical Company.
At the end of this lecture, participants will be able to:

- Recognize the diagnosis criteria, classifications and changes in the management of the patient with **type 2 diabetes mellitus**.
- Identify the differential diagnosis of **hypoglycemia** in the patient without diabetes.
- Select the recommended evaluation and treatment for the patient with a **thyroid nodule**, **hypothyroidism**, **hyperthyroidism**, and **multinodular goiter**.
- Appreciate the use of **bone mineral density**, how to promote bone health, and recognize the indications for therapy to prevent fractures.
- Recall the indications for parathyroid surgery in the patient with **asymptomatic primary hyperparathyroidism**.
- Identify and evaluate the patient with **resistant hypertension**.
- Acknowledge the endocrinopathies related to the use of **immune check-point inhibitors**.
Diabetes Mellitus
Diabetes Mellitus

- Glycemic control has demonstrated reduction in:
  - Microvascular complications
  - Neuropathic complications

- The evidence of glycemic benefit in macrovascular complications is controversial.
  - There is benefit if there is a comprehensive simultaneous management of ALL risk factors:
    - Hyperglycemia
    - Hypertension
    - Dyslipidemia
    - Smoking
    - Physical inactivity
    - ASA if 50 y/o and additional risk factor
Criteria for Testing for Diabetes or Prediabetes

- BMI $\geq 25\text{mg/kg}^2$ (Asian American $\geq 23\text{mg/kg}^2$) and at least:
  - 1$^{st}$ degree relative with diabetes
  - High-risk ethnicity (AA; Latino, Native American, Asian American, Pacific Islander)
  - History of ASCVD
  - Hypertension (BP $\geq 140/90$ or using antihypertensive Rx)
  - HDL-Chol $< 35\text{mg/dL}$ or triglycerides $>250\text{mg/dL}$
  - Polycystic ovary syndrome
  - Physical inactivity
  - Severe Obesity or acanthosis nigricans

- Pre-Diabetes
- Gestational diabetes mellitus
- 45 years or older

Re-screen in 3 years, except in Pre-Diabetes that should be yearly.
Criteria for the Diagnosis of Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pre-Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting</strong>*</td>
<td>&lt;100mg/dL</td>
<td>100-125mg/dL</td>
<td>≥126 mg/dL</td>
</tr>
<tr>
<td>2-Hr during OGTT*</td>
<td>&lt;140mg/dL</td>
<td>140-199mg/dL</td>
<td>≥200 mg/dL</td>
</tr>
<tr>
<td><strong>A1c</strong>*</td>
<td>&lt;5.7%</td>
<td>5.7-6.4%</td>
<td>≥6.5%</td>
</tr>
<tr>
<td>Random Glucose &amp; Symptoms</td>
<td></td>
<td></td>
<td>≥200 mg/dL</td>
</tr>
</tbody>
</table>

**Fasting** is defined as no caloric intake for at least 8 h

**OGTT**: 75-g anhydrous glucose dissolved in water

**A1c** performed by a NGSP certified method

**Symptoms**: classic symptoms of hyperglycemia or hyperglycemic crisis

* In the absence of unequivocal hyperglycemia, Dx requires two abnormal test results from the same sample or in two separate test samples

Amer Diabetes Assoc *Diabetes Care* 2019; 42(Suppl 1): S13-S28
A1c Less Reliable in:

- Pregnancy & Post-partum
- Hemodialysis and advanced renal insufficiency
- Erythropoietin therapy
- Recent blood loss or transfusion
- HIV treated patient
- Iron deficiency
- Sickle cell disease, Hgb S, C, D, E & F
- Liver disease
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency

A1C and Estimated Average Glucose

<table>
<thead>
<tr>
<th>A1C</th>
<th>eAVG (mg/dL)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>126</td>
<td>100-152</td>
</tr>
<tr>
<td>7.0</td>
<td>154</td>
<td>123-185</td>
</tr>
<tr>
<td>8.0</td>
<td>183</td>
<td>147-217</td>
</tr>
<tr>
<td>9.0</td>
<td>212</td>
<td>170-249</td>
</tr>
<tr>
<td>10.0</td>
<td>240</td>
<td>193-282</td>
</tr>
<tr>
<td>11.0</td>
<td>269</td>
<td>217-314</td>
</tr>
<tr>
<td>12.0</td>
<td>298</td>
<td>240-347</td>
</tr>
</tbody>
</table>

Amer Diabetes Assoc *Diabetes Care* 2019; 42(Suppl 1): S13-S28
Amer Diabetes Assoc *Diabetes Care* 2019; 42(Suppl 1): S61-S70
Diabetes Mellitus Classification

Do NOT use IDDM & NIDDM terms.

- **Type 1** (5-10%)
  - Absolute insulin deficiency
  - Associated with: thyroid, adrenal failure; collagen vascular; vitiligo; alopecia; pernicious anemia; celiac; UC and Chron’s disease.

- **Type 2** (90-95%)
  - Hyperglycemia with insulin resistance or relative insulin deficiency

- **Other**
  - **Drug Related**
    - Glucocorticoids; thiazides, beta blockers, tacrolimus, niacin, HIV protease inhibitors, atypical antipsychotics
  - **Monogenic Diabetes**
    - MODY & Neonatal Diabetes: Genetic defect in beta-cell function
  - **Genetic Syndromes**
    - Down; Klinefelter, Turner, Prades-Willi, myotonic dystrophy, Wolfram (DIDMOAD);
# Patient Centered Approach

<table>
<thead>
<tr>
<th></th>
<th>A1c</th>
<th>Pre-Prandial</th>
<th>Post-Prandial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy</strong></td>
<td>&lt;7.0%</td>
<td>80-130mg/dL</td>
<td>&lt;180mg/dL</td>
</tr>
<tr>
<td>Early after diagnosis</td>
<td>&lt;6.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preconception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy &gt;10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complex Health Issues</strong></td>
<td>&lt;8.0%</td>
<td>90-150mg/dL</td>
<td></td>
</tr>
<tr>
<td>Frequent hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia unawareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy &lt; 10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Very Complex/Poor Health</strong></td>
<td>&lt;8.5%</td>
<td>100-180mg/dL</td>
<td></td>
</tr>
<tr>
<td>Limited life expectancy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multiple ADL dependent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term care placement</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>End-stage diseases</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Amer Diabetes Assoc *Diabetes Care* 2019; 42(Suppl 1): S61-S70
Pharmacologic Approach for Glycemic Control

- Type 1
  - Insulin is required in persons with type 1 diabetes mellitus (T1DM)
    - Pramlintide can be used IN ADDITION to insulin in T1DM
  - **Basal** insulin to maintain glycemic control while fasting and between meals
    - ~40-50% of the total daily insulin
    - The goal is to control gluconeogenesis
  - **Prandial** or **Nutritional** insulin to avoid hyperglycemia after eating
    - ~50-60% of the total daily insulin in the three or more meals a day
    - The goal is to cover the increase in glucose expected from meal intake.
  - **Corrective** insulin to bring down glucose to goal when glucose above goal
    - The goal is to reduce the elevated glucose to the desired pre-prandial goal if hyperglycemic
    - The goal is to increase the elevated glucose to the desired pre-prandial goal, if below target
The most common cause of POST-prandial hyperglycemia is PRE-prandial hyperglycemia.
The most common cause of POST-prandial hyperglycemia is PRE-prandial hyperglycemia.
## Human Insulins and Analogs

The time course of action of insulin may vary in different individuals or within the same individual.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Trade Name</th>
<th>Timing of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog (100/200)</td>
<td>Onset: 5-15 mins</td>
</tr>
<tr>
<td>Aspart</td>
<td>Novolog (100/200)</td>
<td>Peak: ~0.5-1.5 h</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra (100/200)</td>
<td>Duration: ~3-5 h</td>
</tr>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Humulin R</td>
<td>Onset: 30-60 mins</td>
</tr>
<tr>
<td></td>
<td>Novolin R</td>
<td>Peak: ~1-3 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration: 5 - 8 h</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>Humulin N</td>
<td>Onset: 1-4 h</td>
</tr>
<tr>
<td></td>
<td>Novolin N</td>
<td>Peak: 4-10 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration: 12-18 h</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>Levemir</td>
<td>Onset: ~2-4 h</td>
</tr>
<tr>
<td>Glargine</td>
<td>Lantus, Toujeo</td>
<td>Peak: No peak</td>
</tr>
<tr>
<td>Degludec</td>
<td>Tresiba (100/200)</td>
<td>Duration: 12-24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mixtures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70/30, 50/50, 75/25</td>
<td></td>
<td>Onset: ~30 mins</td>
</tr>
<tr>
<td>Degludec/Aspart</td>
<td>Ryzodeg</td>
<td>Peak: ~7-12 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration: ~16-18 h</td>
</tr>
</tbody>
</table>

Note: The time course of action of insulin may vary in different individuals or within the same individual.
Pharmacologic Approach for Glycemic Control
Type 2 Diabetes Mellitus (T2DM)

- Metformin is the first-line oral agent or background therapy in all T2DM, if not contraindicated
  - eGFR 45-60 ml/min: 2,000mg/day is the maximal dose, but need close monitoring
  - eGFR 30-45 ml/min: 1,000mg/day is the maximal dose; monitor renal function
  - eGFR <30 ml/min: Stop Metformin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Expected A1c Reduction Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.0-1.5%</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.0-1.5%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>1.0-1.5%</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>0.7-1.0%</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>0.5-0.6%</td>
</tr>
<tr>
<td>GLP-1 Analogs</td>
<td>1.0-1.5%</td>
</tr>
</tbody>
</table>

- If A1c if $\geq$ 1.5%, dual combination therapy should be considered
- If A1c if $\geq$ 10%, glucose $>300$mg/dL, or having symptoms of hyperglycemia, insulin should be used.
  - Once glucotoxicity resolves, insulin may be weaned off.

Lipska KJ. Diabetes Care 2011;34:1431-1437
Amer Diabetes Assoc Diabetes Care 2019; 42(Suppl 1): S90-S102
FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA1c above target proceed as below

**EVALUATE ASCVD OR CKD**

- **NO**

- **WITHOUT ESTABLISHED ASCVD OR CKD**

- **ASCVD PREDOMINATES**
  - **ETOH/ OR**
  - GLP-1 RA with proven CVD benefit
  - SGLT2i with proven CVD benefit, if eGFR adequate

- **HF OR CKD PREDOMINATES**
  - **PREFERABLY**
  - SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
  - OR
  - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

- **COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA**
  - If HbA1c above target
  - GLP-1 RA
  - SGLT2i
  - TZD

- **COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**
  - If HbA1c above target
  - GLP-1 RA with good efficacy for weight loss

- **COST IS A MAJOR ISSUE**
  - If HbA1c above target
  - SU
  - TZD

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA, strongest evidence for lixisanlute > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual with regard to indicated level of eGFR for initiation and continued use.
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs.
4. Dipeptidase I inhibitors have demonstrated CVD safety.
5. Low dose may be better tolerated though less well studied for CVD effects.
6. Choose later generation SU with lower risk of hypoglycemia
7. Select SU for patients with higher risk of hypoglycemia
8. SGLT2i > lixisanlute > exenatide > glimepiride > insulin glargine
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or weight-related comorbidities)
10. Consider country-region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper.

Amer Diabetes Assoc *Diabetes Care* 2019; 42(Suppl 1): S90-S102
T2DM Patients with ASCVD or CKD

- If ASCVD predominates SGLT-2 inhibitors or GLP-1 are good 1st choice **AFTER METFORMIN**.

- If heart failure or chronic kidney disease predominates consider first SGLT-2 inhibitors **AFTER METFORMIN**.

Amer Diabetes Assoc *Diabetes Care* 2019; 42(Suppl 1): S90-S102
Pharmacologic Approach for Glycemic Control in T2DM Without Established ASCVD or CKD

Remember that you do NOT combine GLP-1 Agonists with DPP4-Inhibitors

Amer Diabetes Assoc *Diabetes Care* 2019; 42(Suppl 1): S90-S102
Avoid Clinical Inertia

If glycemic control is not achieved, look for the reasons, and move on.
Complications

■ DKA and SGLT-2 Inhibitors
  - SGLT-2 inhibitors should not be used in patient with Type 1 DM
  - Avoid SGLT-2 inhibitors in Type 2 DM that are in a catabolic state

■ Hypoglycemia Unawareness
  - Relax glycemic targets
  - Avoid hypoglycemia inducing agents, if possible
  - If unawareness persist after avoidance of hypoglycemia for several weeks, CGM may be considered for early detection and intervention.
  - Hypoglycemia has been associated with myocardial ischemia, QT prolongation, and increased viscosity\(^1\).

\(^1\)Davis, SN. *Diabetes Care* 2019;42:157–163
Complications

- **Retinopathy**
  - Retinopathy may develop or accelerate during pregnancy or with rapid glycemic improvements. Therefore, pre-conception counseling and retina examination should be done upon implementing an intensive treatment.

- **Nephropathy**
  - False positive for Microalbuminuria
    - Acute illness
    - Acute hyperglycemia
    - Heart failure
    - Hypertension
    - Exercise
    - Menstruation
  - ACEi or ARB blockers are **NOT recommended as prevention**
    - Indicated if HTN, albuminuria, or decreased eGFR
Hypoglycemia in Patients without Diabetes Mellitus
Hypoglycemia in Patients without Diabetes Mellitus

- Whipple triad
  - Symptoms
  - Glucose 55mg/dL or lower
  - Resolution of symptoms with glucose ingestion
- Capillary blood glucose are NOT reliable to confirm hypoglycemia

- **C-Peptide Elevated**
  - Secretagogue use
  - Insulinoma
  - Roux-en-Y gastric bypass surgery
  - Autoimmune

- **C-Peptide Suppressed**
  - Exogenous insulin administration
  - Sepsis
  - Liver failure
  - Adrenal insufficiency
  - Malnutrition

| Glucose | B Hydroxybutyrate | Insulin | Sulfonylurea Screening | C-Peptide | Insulin antibodies | Proinsulin |
Thyroid
Thyroid Nodule

- **Radiological diagnosis**
  - “…discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma.”
  - Non-Palpable nodules: **incidentaloma**

- **Goal of Evaluation is to identify clinically relevant nodules:**
  - Harboring cancer ~10%
  - Causing compression symptoms ~5%
  - Thyroid dysfunction ~5%
  - **95% of thyroid nodules are asymptomatic**

Haugen BR, et al. *Thyroid* 2016;26:1-132
Durante C *JAMA* 2018;319:914.
Initial Evaluation

You suspect on H & PE or palpate a lump in the thyroid. How do you proceed?
Clinical Presentation

History
- Most patients are asymptomatic
- Globus sensation
  - Usually >3 cm; close to the trachea
- Dysphagia or swallowing complaints
  - Left Post. compressing esophagus
- Dysphonia or hoarseness
- Dyspnea
- Pain
  - Bleeding inside the nodule

Physical Examination
- Palpation of the thyroid and cervical lymph nodes.
Risk Factors for Malignancy

- Associated hoarseness or dysphagia
- History of rapid growing mass
- Fixation to surrounding tissue
- Associated cervical lymphadenopathy
- Personal history of head and neck or total body xRT
- Exposure to ionizing radiation
- Family history of thyroid cancer or syndrome associated to thyroid cancer

Require Prompt Evaluation

Haugen BR, et al. *Thyroid* 2016;26:1-132
Durante C *JAMA* 2018;319:914.
Thyroid Nodules Initial Evaluation is Serum TSH

- **Normal or High TSH**
  - Thyroid sonography with survey of cervical lymph nodes

- **Low TSH**
  - Radionuclide thyroid scan
  - Thyroid ultrasound
    - Hot nodule(s)
      - Concordant with ultrasound do not require FNA
    - Warm or Cold areas should be evaluated as having normal or high TSH

Haugen BR, et al. *Thyroid* 2016;26:1-132
Test NOT Indicated

- Anti-Thyroid Peroxidase Antibodies
- Anti-Thyroglobulin Antibodies
- Thyroglogulin
- Calcitonin

- **Thyroid Scan** unless the TSH is low

- Routine **TSH suppression therapy** for benign thyroid nodules in iodine sufficient populations.
  - Potential harm outweighs benefit for most patients
If the TSH is within reference range or high, and the ultrasound shows a nodule, then comes the determination if aspiration biopsy should be done or not.
Thyroid Imaging Reporting and Data System
TI-RADS: American College of Radiology

ACR TI-RADS

COMPOSITION
(Choose 1)
Cystic or almost completely cystic 0 points
Spongiform 0 points
Mixed cystic and solid 1 point
Solid or almost completely solid 2 points

ECHOCGENICITY
(Choose 1)
Anechoic 0 points
Hyperechoic or isoechoic 1 point
Hypoechoic 2 points
Very hypoechoic 3 points

SHAPE
(Choose 1)
Wider-than-tail 0 points
Taller-than-wide 3 points

MARGIN
(Choose 1)
Smooth 0 points
Ill-defined 0 points
Lobulated or irregular 2 points
Extra-thyroidal extension 3 points

ECHOCGENIC FOCI
(Choose All That Apply)
None or large comet-tail artifacts 0 points
Macrocalcifications 1 point
Peripheral (rim) calcifications 2 points
Punctate echogenic foci 3 points

Add Points From All Categories to Determine TI-RADS Level

0 Points
TR1 Benign
No FNA

2 Points
TR2 Not Suspicious
No FNA

3 Points
TR3 Mildly Suspicious
FNA if ≥ 2.5 cm
Follow if ≥ 1.5 cm

4 to 6 Points
TR4 Moderately Suspicious
FNA if ≥ 1.5 cm
Follow if ≥ 1 cm

7 Points or More
TR5 Highly Suspicious
FNA if ≥ 1 cm
Follow if ≥ 0.5 cm†

After the aspiration...
FNA Cytology

Haugen BR, et al. *Thyroid* 2016;26:1-132
FNA Cytology

Haugen BR, et al. *Thyroid* 2016;26:1-132
Follow-Up of Nodules with FNA

- Based on sonographic stratification:
  - **High Suspicion:** Repeat US and FNA within 12 months
  - **Low to Intermediate Suspicion:** Repeat US at 12-24 months
    - If new suspicious sonographic feature or growth, then repeat FNA
      - **Growth:**
        - 20% increase in at least 2 dimensions with a minimal increase of 2mm
        - More than 50% increase in volume
  - **Very Low Suspicion:** If US repeated, it should be > 24 months
- **Two benign FNA**
  - No US surveillance indicated

Haugen BR, et al. *Thyroid* 2016;26:1-132
Durante C *JAMA* 2018;319:914.
FNA Cytology

Haugen BR, et al. *Thyroid* 2016;26:1-132
FNA Cytology: Indeterminate Cytology
AUS/FLUS; FN/FSN; Suspicious

Haugen BR, et al. *Thyroid* 2016;26:1-132
Multinodular Goiter

- Most common cause of goiter in older adults in US.
- Each nodule carries an independent risk of malignancy.
- When multiple nodules ≥ 1cm are present, FNA should be performed preferentially based upon nodule sonographic pattern and size.
- If none of the nodules has a high or moderate suspicion sonographic pattern, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodule (≥2 cm) or continue surveillance without FNA.
- Radionuclide scanning may also be considered in patients with multiple thyroid nodules with the goal of identifying and aspirating appropriate hypofunctioning nodules.
Focal uptake in a nodule of 1cm or larger should have FNA done

Diffuse uptake in a patient with chronic lymphocytic thyroiditis does not require further imaging or FNA.

Not routinely recommended for evaluation of indeterminate cytology.

- Sensitivity: 89%; Specificity: 55%; PPV: 41%; NPV: 93%
Thyroid Hormone Therapy

- Routine TSH suppression for benign thyroid nodules in iodine sufficient populations is **NOT** recommended.

- “There are no data to guide recommendations on the use of thyroid hormone therapy in patients with growing nodules that are benign on cytology.”

**TSH suppression**

- ↑ risk of cardiac arrhythmias, osteoporosis, and adverse symptomatology.
- Risks outweigh the benefits

Haugen BR, et al. *Thyroid* 2016;26:1-132
L-T4 Replacement in Differentiated Thyroid Cancer
TSH Goals for Long Term Thyroid Hormone

- TSH 0.5-2.0 mU/L: **No Suppression**
  - Excellent response

- TSH 0.1-0.5 mU/L: **Mild Suppression**
  - Intermediate or Biochemical incomplete response

- TSH < 0.1 mU/L: **Complete Suppression**
  - Structural incomplete

Re-evaluate goal in patients with atrial fibrillation, osteoporosis or osteopenia, age over 60 years, or tachycardic.
Hyperthyroidism

- Hyperthyroidism
  - RAIU indicated if:
    - Symptoms of less than 3 months duration
    - Neck pain
    - Nodule or nodules suspected on palpation
  - RAIU will be low, usually < 10% if:
    - Painless, Post-Partum, or Subacute thyroiditis
    - Amiodarone, lithium, or recent iodinated contrast material administered
    - Exogenous T4/T3 administration
    - Struma ovarii

- If medical therapy is given, methimazole is the anti-thyroid drug of choice
  - Exception: 1st trimester of pregnancy
  - Fatal hepatonecrosis has been associated with PTU
Subclinical Hyperthyroidism

- Suppression of TSH with normal T4 and T3
- Initial approach is observation unless risk of complications is high
  - Repeat thyroid function tests in 6-8 weeks
- Treatment is recommended if TSH persist below 0.1 mU/L and:
  - Symptoms that may related to hyperthyroidism
  - Cardiac risk factors
  - Heart disease
  - Osteoporosis
  - Postmenopausal women not taking estrogen or bisphosphonates
Hypothyroidism

- Iodine deficiency is the most common globally.
- In US autoimmune thyroid disease is the most common cause.
  - Routine Anti-TPO measurement is not necessary
- Levothyroxine is the treatment of choice
  - T3 is NOT recommended

Sub-clinical Hypothyroidism

- Initial approach is observation.
  - Repeat thyroid function tests in 6-8 weeks
- Consider L-T4 replacement if:
  - Repeated TSH is > 10 mU/L
  - TSH between 5-10 mU/L with positive anti-TPO positive

- As we get older the TSH increases.

<table>
<thead>
<tr>
<th>Age/Situation</th>
<th>TSH Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Reference Range</td>
<td>0.4 - 3.6 mIU/L</td>
</tr>
<tr>
<td>70-80 years old</td>
<td>0.4 - 6.0 mIU/L</td>
</tr>
<tr>
<td>Over 80 years old</td>
<td>0.4 – 7.5 mIU/L</td>
</tr>
</tbody>
</table>

Surks MI *JCEM* 2007;92:4575.  
Jacqueline J *Thyroid* 2014;24:1670
Low Bone Density and Osteoporosis
**Low Bone Mass**

- Bone mass depends on the peak bone mass achieved in early 20s and the rate of bone loss over lifetime.
  - Net bone loss occurs when osteoclastic remodeling is faster than osteoblastic bone formation.

- **In persons 50 years or older**, check the T-score:
  - -2.5 or less: Osteoporosis
  - -1.0 to -2.5: Osteopenia
  - Higher than -1.0: Normal BMD

- Fragility fractures, those occurring with minimal trauma, equivalent or less than a fall from a standing height, after age 50 indicate low bone strength and define clinical osteoporosis regardless of BMD.
<table>
<thead>
<tr>
<th>Lifestyle/Modifiable</th>
<th>Non-Modifiable</th>
<th>Medications/Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Race/Ethnicity</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Age</td>
<td>Antiretroviral (Tenofovir)</td>
</tr>
<tr>
<td>BMI&lt;17</td>
<td>Gender</td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td>Low Calcium intake</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; degree relative with ↓ BMD</td>
<td>Calcineurin inhibitors</td>
</tr>
<tr>
<td>Smoking</td>
<td>Genetic</td>
<td>Depo-medroxyprogesterone</td>
</tr>
<tr>
<td>Vitamin D Deficiency</td>
<td>Cystic fibrosis</td>
<td>Glucocorticoids (&gt;5mg/d x ≥3 months)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Hypophosphatasia</td>
<td>Heparin</td>
</tr>
<tr>
<td>Recurrent falls</td>
<td>Ehlers-Danlos</td>
<td>GnRH</td>
</tr>
<tr>
<td></td>
<td>Osteogenesis imperfecta</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Androgen deprivation therapy</td>
</tr>
</tbody>
</table>
Frequent Conditions Associated with Low Bone Mass/Osteoporosis

Basic Evaluation

- Anorexia nervosa
- T2DM
- Hyperparathyroidism
- Hypogonadism
- Thyrotoxicosis
- Bariatric surgery
- Inflammatory bowel disease
- Malabsorption
- Multiple myeloma
- Ankylosing spondylitis
- Rheumatoid arthritis
- AIDS/HIV
- COPD
- ESRD
- Idiopathic hypercalciuria

Basic Evaluation

- CBC
- Ca ++, InP, Mg++
- Kidney function tests
- Liver function test
- TSH
- 25-hydroxy-Vitamin D
- 24-h urinary calcium
DEXA for Osteoporosis Screening

- Women age 65 and older
- Men age 70 and older
- Women and men 50 to 69, based on risk factors
  - Premature menopause; aromatase inhibitors
  - Androgen deprivation therapy
- Glucocorticoid therapy for more than 3 months
- Radiographic findings suggestive of osteoporosis or vertebra deformity
- Primary hyperparathyroidism

DEXA is rarely indicated under 50 years old patients
Therapy

PTH/PTHrp is used up to 2 years. Bisphosphonates are used ~3-10 years

- Look for possible 2^nd causes and treat if possible
- Promote bone health
  - Smoking cessation
  - Adequate calcium intake (~1,200mg/day) & 25-OH-Vit D levels
  - Avoid falls
  - Weight bearing exercises
  - Avoid glucocorticoids, if possible. If not, minimize the dose.

Pharmacologic Therapy
- Hip or spine osteoporotic fracture
- 50 years or older with T-Score -2.5
- If T-score between -1.0 to 2.5, calculate fracture risk using the FRAX Score. Treat if:
  - 10-yr risk of Hip Fx is ≥ 3.0%
  - 10-yr risk of Osteop Fx is ≥ 20%
- Bisphosphonates or Denosumab
- Teriparatide or Abaloparatide
  - High risk for fracture
  - Need antiresorptive Rx after anabolic Rx
https://www.sheffield.ac.uk/FRAX/

FRAX® Fracture Risk Assessment Tool

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Hispanic)  Name/ID:  About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth:
   Age: 65  Date of Birth: Y:  M:  D:  

2. Sex
   Male  Female

3. Weight (kg)  81.7

4. Height (cm)  170.2

5. Previous Fracture
   No  Yes

6. Parent Fractured Hip
   No  Yes

7. Current Smoking
   No  Yes

8. Glucocorticoids
   No  Yes

9. Rheumatoid arthritis
   No  Yes

10. Secondary osteoporosis
    No  Yes

11. Alcohol 3 or more units/day
    No  Yes

12. Femoral neck BMD (g/cm²)
    Hologic  0.705  T-score: -1.3

Clarification

The University of Sheffield launched the FRAX tool in 2008. At that time the University held the World Health Organisation (WHO) Collaborating Centre for Metabolic Bone Disease (1991-2010), and the FRAX tool is based on data generated from that centre. However, FRAX was neither developed or endorsed by WHO. Any references to the WHO tool or to the V Collaborating Centre after it finished its work in 2010 are incorrect.
Osteonecrosis of the Jaw

Atypical Femur Fracture
Guidelines for Parathyroid Surgery in Asymptomatic Primary Hyperparathyroidism

- Serum calcium is consistently >1.0 mg/dL
- BMD at any site is <−2.5 by T-score
  - Significant drop in BMD with T-score between -2.0 and -2.5
- eGFR <60 mL/min
- Age < 50 years old

You do NOT do parathyroid localizing studies unless the patient has agreed to have parathyroid surgery.

Silverberg SJ. *J Clin Endocrinol Metab*. 2014;99:3580
Medication Associated Endocrinopathies

- **Amiodarone**
  - Hypo or Hyperthyroidism

- **Immune checkpoint inhibitors**
  - Hypophysitis
    - Secondary adrenal insufficiency
  - Thyroid
    - Hypothyroidism; Hyperthyroidism; Thyroiditis
    - Abnormal thyroid function tests
  - Type 1 Diabetes Mellitus
  - Primary adrenal insufficiency
  - Ipilimumab (Yervoy™)
  - Nivolumab (Opdivo™)
  - Pembrolizumab (Keytruda™)
  - Atezolizumab (Tecentriq™)
  - Avelumab (Bavencio™)
  - Durvalumab (Imfinzi™)
Resistant Hypertension

- BP $\geq$130/80 in 3 medications
- BP <130/80 in 4 or more medications

Exclude pseudoresistance
- Accurate BP measurement
- Adherence to prescribed regimen
- Exclude ‘white coat’ effect
- Evaluate for excessive alcohol or Na intake
- Discontinue sympathomimetics, stimulants, licorice, ephedra, OCP

Screen for 2\textsuperscript{nd} causes
- Primary aldosteronism
  - Aldosterone/Renin Ratio
- CKD
- Renal artery stenosis
- Pheochromocytoma
  - Plasma fractionated metanephrines
- Obstructive sleep apnea

Try to avoid of mineralocorticoids antagonists until you have ruled out for 1\textsuperscript{st} Aldosteronism.

Whelton PK. *Journal of the American College of Cardiology*. DOI:10.1016/j.jacc.2017.11.006
A1c target is generally <7% but should individualize based on the patient and disease factors.

Lifestyle and metformin is the background therapy.

If additional glucose lowering therapy is needed:

<table>
<thead>
<tr>
<th>If</th>
<th>Recommend:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD</td>
<td>GLP-1 agonist of SGLT-2 inhibitor</td>
</tr>
<tr>
<td>HF or CKD</td>
<td>SGLT-2 inhibitor</td>
</tr>
<tr>
<td>Hypo would be a serious problem</td>
<td>Avoid insulin and sulfonylurea (SU)</td>
</tr>
<tr>
<td>Weight is a significant concern</td>
<td>Avoid SU, Insulin or TZD</td>
</tr>
<tr>
<td>Cost is a major issue</td>
<td>Generics that can be cut in half</td>
</tr>
<tr>
<td>NASH</td>
<td>Thiazolidinediones</td>
</tr>
</tbody>
</table>
Summary/Conclusions

- **Thyroid nodules** threshold for biopsy:
  - Hypoechoic >1 cm
  - Iso or Hyperechoic >1.5 cm

- **Hypothyroidism**, do not use T3.

- **Hyperthyroidism** medical therapy methimazole, except 1st trimester of pregnancy

- In the presence of **fasting hypoglycemia** with C-peptide above suppression consider secretagogue use.

- Do not use BMD and osteoporosis therapy in pre-menopausal women or men under 50 years.

- Always rule out for 1st aldosteronism before Rx mineralocorticoid antagonist in patients with resistant hypertension.