Annual Internal Medicine Review

ENDOCRINOLOGY

PART 3

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Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

2015

Obesity (BMI $\geq 30$ kg/m$^2$)

- Missing Data
- $14.0\%–17.9\%$
- $18.0\%–21.9\%$
- $22.0\%–25.9\%$
- $\geq 26.0\%$

Diabetes

- Missing data
- $<4.5\%$
- $4.5\%–5.9\%$
- $6.0\%–7.4\%$
- $7.5\%–8.9\%$
- $\geq 9.0\%$

Question 1

Who Has Diabetes Mellitus?

A. 30 year old obese African American male with a fasting blood sugar of 105 mg/dL and HbA1c 6.0%

B. 57 year old Caucasian male with renal disease on Epoetin Alpha injections for anemia with a fasting blood sugar of 130 mg/dL, 134 mg/dL on repeat and HbA1c of 4.7%

C. 67 year old thin Southeast Asian female with fasting blood sugar of 120 mg/dL, 124 mg/dL on repeat. She checks her sugar with her husband’s glucometer 2 hours after meals when she feels dizzy and gets readings in the 80s

D. 18 year old obese Hispanic female with acanthosis, polyuria and polydipsia and a random plasma glucose of 188 mg/dL
### Table 2.2—Criteria for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.</td>
<td>*</td>
</tr>
<tr>
<td>2-h PG ≥200 mg/dL (11.1 mmol/L) during OGGT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.</td>
<td>*</td>
</tr>
<tr>
<td>A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.</td>
<td>*</td>
</tr>
<tr>
<td>In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).</td>
<td></td>
</tr>
</tbody>
</table>

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S13-S27
Diagnostic Criteria for the Diagnosis of Diabetes in Nonpregnant Adults

<table>
<thead>
<tr>
<th>Table 2.4—Categories of increased risk for diabetes (prediabetes)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>A1C 5.7–6.4% (39–47 mmol/mol)</td>
</tr>
</tbody>
</table>

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.
Hemoglobin A1c
(Glycosylated Hemoglobin)

May not be accurate in any condition which affects red blood cell turnover or hemoglobinopathies
A 68-year-old woman with diabetes for 20 years has begun to have labile glucose measurements. Originally well controlled on oral drugs, she now requires basal-bolus insulin therapy. She also has a history of Hashimoto’s hypothyroidism. On physical examination, she is thin. An anti–glutamic acid decarboxylase antibody titer is positive.
Question 2

Which is the most likely diagnosis?

A. Type 1 Diabetes Mellitus
B. Type 2 Diabetes Mellitus
C. Latent Autoimmune Diabetes of Adulthood
D. Maturity Onset Diabetes of the Young
Type 1 Diabetes Mellitus

- Immune attack on the Beta Cells
  - Will have antibodies on blood tests
    - Anti-Insulin antibodies
    - Glutamic acid decarboxylase antibodies (GAD)- *most specific*
    - Islet cell-associated antigen antibodies
- Absolute insulin deficiency
- High risk for diabetic ketoacidosis (DKA)
- 20% will have other autoimmune disease
- Age of onset usually childhood and adolescence
Type 2 Diabetes Mellitus

- Metabolic disorder that is characterized by insulin resistance, relative insulin deficiency & hyperglycemia

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Role</strong></td>
<td></td>
</tr>
<tr>
<td>Pancreatic beta cells</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>Muscle</td>
<td>Inefficient glucose uptake</td>
</tr>
<tr>
<td>Liver</td>
<td>Increased endogenous glucose secretion</td>
</tr>
<tr>
<td><strong>Contributing Role</strong></td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Increased FFA production</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>Decreased incretin effect</td>
</tr>
<tr>
<td>Pancreatic alpha cells</td>
<td>Increased glucagon secretion</td>
</tr>
<tr>
<td>Kidney</td>
<td>Increased glucose reabsorption</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Neurotransmitter dysfunction</td>
</tr>
</tbody>
</table>
Other Diabetes Syndromes

• Latent Autoimmune Diabetes of Adulthood (LADA)
  • Older, usually lean patients
  • Autoimmune markers present
  • Gradual destruction of beta-cells results in absolute insulin deficiency
  • Additional autoimmune endocrine disorders are common (ex. Hypothyroidism)

• Maturity Onset Diabetes of the Young (MODY)
  • Hereditary autosomal dominant form of diabetes caused by mutations in a single gene; may respond well to sulfonylureas

• Defects in insulin action: lipodystrophy

• Diseases of the exocrine pancreas
  • Cystic Fibrosis
  • Hemochromatosis
  • Pancreatitis
Other Diabetes Syndromes

• Gestational
  • Diabetes that develops during pregnancy (usually not until 2\textsuperscript{nd} trimester)
  • Increased risk of fetal macrosomia, neonatal hypoglycemia, jaundice
  • Typically resolves after birth but frequently recurs with subsequent pregnancies

• Endocrinopathies: Acromegaly, Cushing's, Pheochromocytoma

• Stress Hyperglycemia

• Drug induced:
  • Steroids
  • HCTZ, Beta-blockers, Niacin, Statins, Immune Checkpoint Inhibitors
High Risk for the Development of DM2 = Who to Screen

- Age ≥45 years
- Family history of T2D or cardiovascular disease
- Overweight or obese
- Sedentary lifestyle
- Non-Caucasian ancestry
- Previously identified IGT, IFG, and/or metabolic syndrome
- PCOS, acanthosis nigricans, or NAFLD
- Hypertension (BP >140/90 mmHg)
- Dyslipidemia (HDL-C <35 mg/dL and/or triglycerides >250 mg/dL)

- History of gestational diabetes
- Delivery of baby weighing >4 kg (>9 lb)
- Antipsychotic therapy for schizophrenia or severe bipolar disease
- Antiretroviral therapy for HIV
- Chronic glucocorticoid exposure
- Sleep disorders
  - Obstructive sleep apnea
  - Chronic sleep deprivation
  - Night shift work
Acanthosis Nigricans

• Acanthosis nigricans is characterized by velvety hyperpigmented patches most prominent in intertriginous areas

• Cutaneous marker of insulin resistance

• Present in ~90% of patients with Type 2 DM
**ATP III: The Metabolic Syndrome**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
</tr>
<tr>
<td>(Waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>TG</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

*Diagnosis is established when at least 3 of the criteria are present*
Metabolic Syndrome

• Also called the “insulin resistance syndrome” or “Syndrome X”
• 35% of the US adult population
  • Higher risk in Mexican and African Americans
• 2-3.5 fold increase in risk of Type 2 DM
• 2 fold increase risk of Cardiovascular Disease

• Associated with:
  • PCOS
  • Sleep Apnea
  • Hyperuricemia and Gout
  • Chronic Kidney Disease
  • NAFLD / NASH

• Treat each individual component to prevent development of Type 2 DM and CVD
Diabetic Ketoacidosis

A collection of severe and potentially life-threatening metabolic disturbances:

- Hyperglycemia $\rightarrow$ Osmotic diuresis
  - Urinary loss of fluids & electrolytes
  - ECFv contraction
  - Depletion of total body $K^+$ stores
    (even though may be hyperkalemic 2° to cell shift)
- Ketone production $\rightarrow$ Metabolic acidosis
  - Compensatory Respiratory alkalosis
- Uncontrolled lipolysis $\rightarrow$ severe $\uparrow$ TG
DKA: Treatment

1. Intensive Monitoring (Consider ICU)
2. IV Fluid Resuscitation (3-9L deficit)
3. IV insulin
4. Potassium
   - $K^+$ deficit 3-5 mEq/Kg
5. Calcium, Phosphate, and Magnesium replacement
6. Identify & Rx underlying cause
   - Noncompliance, infection, MI, etc.
Pitfalls of DKA Treatment

1. Potassium supplementation should start once K is < 4.5-5 mg/dL if normal renal function

2. Goal glucose decline is no more than 75-100 mg/dL/hr; once glucose <200-250 add dextrose to fluids

3. Don’t forget calcium, phosphate, and magnesium replacement

4. Remember to overlap insulin gtt with SubQ insulin
HONK or HHS
Hyperosmolar Non-Ketotic State | Hyperosmolar Hyperglycemic State

• T2DM, elderly (mean age 60-73)
• Pathogenesis poorly understood
• Mild ECFv↓ instigating factor
• Insulin/Glucagon ratio sufficient to limit DKA
• Diminished thirst or access to water
• Vicious cycle develops...
Monitoring for Diabetes Complications

• Every visit
  • BP measurement
  • Foot inspection

• Every 3-6 months
  • Hemoglobin $A_1c$ measurement

• Annually
  • Spot urine for albumin to creatinine ratio
  • Dilated ophthalmologic examination
  • Comprehensive foot examination (monofilament)
  • Lipid profile
Diabetic Neuropathy

• Any part of the peripheral or autonomic nervous system may be affected
• Peripheral Symptoms: pain, numbness, hyperesthesia, paresthesia
  • Stocking/Glove distribution
  • High risk for diabetic foot
• Autonomic symptoms: tachycardia, orthostatic hypotension, gastroparesis, diarrhea, erectile dysfunction
Diabetic Neuropathy Treatment

New Recommendation for 2017:

• Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes

Diabetic Foot

• Sensory loss and loss of proprioception leads to abnormal gait and repeated trauma to the tarsal bones and soft tissue

• Risk Factors
  • Polyneuropathy
  • Peripheral Arterial Insufficiency
  • Obesity
  • Poor diabetes control

• Foot ulcers → osteomyelitis → gangrene → amputation

• Screening for early loss of vibratory sensation, reflexes, and light touch (monofilament)

• Patient education about foot care
Diabetic Retinopathy

- Related to long history or poor control
  - Microaneurysms
  - Hemorrhages and exudates
  - Proliferative changes
  - Retinal retraction due to vitreous clot
  - Retinal artery thrombosis

Management advances and a conscientious patient can preclude such disasters.
Diabetic Retinopathy

• 35% of diabetics will develop ESRD
• Diabetes is the most common cause of renal failure needing dialysis in the US
• The first sign is albumin in the urine
  • albumin-to-creatinine ratio >30mg/g creatinine
• Screening: yearly urine albumin and eGFR
• Treat with ACE/ARB and BP control
• Optimize glucose control
Necrobiosis Lipoidica Diabeticorum

- Chronic granulomatous rash on the lower legs
  - Slightly raised shiny red-brown patches
  - The centers are often yellowish and may develop open sores that are slow to heal
- More common in women
- Strong association with diabetes
  - ~25% of patients lesions develop before the onset of diabetes
DCCT: Relationship of HbA$_{1c}$ to Risk of Microvascular Complications

Question 3

How to prevent a cardiac event?

A 65 year old male comes to you because he is about to become a grandparent and is worried about dying of a heart attack like his father and brother did before they ever got to meet their grandchildren.

He is obese with a BMI of 32.3 and does not exercise regularly.

He has had Type 2 DM for 12 years and is on Insulin Glargine 30 units QHS, Glimepiride 4mg daily, Metformin 1000mg BID and Sitagliptin 100mg daily. He has mild neuropathy, no retinopathy and a urine microalbumin/creatinine ratio of 30. HbA1c is 8% and fasting blood sugars are 120-160.

He takes Enalapril 20mg daily with a blood pressure of 154/84 mmHg.

He takes simvastatin 40 mg daily and the most recent lipid panel showed total cholesterol 210 mg, triglycerides 205, LDL 90, HDL 40.

He also takes a baby aspirin daily.
If you could make one change at this visit which would be the most effective to prevent a cardiac event?

A. Stop his oral diabetic medications and switch him to basal/bolus insulin using insulin glargine and insulin aspart titrated to a HbA1c goal of <7%

B. Increase his simvastatin to 80 mg daily

C. Increase his enalapril to 40 mg daily

D. Add fenofibrate
CV Disease and Risk Management

- CVD is the major cause of morbidity & mortality for those with diabetes

- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for CVD

- Diabetes diagnosis confers independent risk

- Strong evidence for managing individual cardiovascular risk factors in primary and secondary prevention

- **BP goal <140/90 (some say 130/80)**
- **moderate- high intensity statin**
Risks of Hypoglycemia

• Intensive insulin or oral hypoglycemic agents pushing A1c to <6.5% can lead to hypoglycemia

• Repeated hypoglycemic episodes attenuate the counter-regulatory response to hypoglycemia

• Hypoglycemia with or without diabetic dysautonomia prolongs the QT interval

• Increased cardiac death rates have precluded the benefits of tight control in treating Type 2 diabetes
Therapeutic Targets for DM

Adapted from Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S55-S64
Guidance Statement 2: Clinicians should aim to achieve an \( \text{HbA}_1c \) level between 7% and 8% in most patients with type 2 diabetes.

Guidance Statement 3: Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve \( \text{HbA}_1c \) levels less than 6.5%.
The Progressive Nature of Type 2 Diabetes

![Diagram showing the progression of type 2 diabetes from normal to late complications.]

- Normal glucose tolerance
- Impaired glucose tolerance
- Type 2 diabetes
- Late type 2 diabetes complications

- Insulin sensitive
- Normal insulin secretion
- Normoglycemia
- Hyperglycemia
- Insulin resistance
- β-cell exhaustion

Preventing Diabetes: Results from the Diabetes Prevention Program

Risk Reduction
31% by metformin
58% by lifestyle

Cumulative Incidence (%)

Placebo
Metformin
Lifestyle

Placebo (n=1082)
Metformin (n=1,073, P<0.001 vs. placebo)
Lifestyle (n=1,079, P<0.001 vs. metformin, P<.001 vs. placebo)

Years from Randomization

Pharmacologic Therapy for T2DM

• Biguanides: Metformin
  
  *The first oral agent used should be metformin*
  
  • Mechanism: decrease hepatic glucose output and enhance hepatic & muscle insulin sensitivity without a direct effect on beta-cell function
  
  • Side Effects: GI upset, metallic taste, B12 deficiency
  
  • Because of concerns about lactic acidosis, Metformin is contraindicated in patients with:
    
    • impaired renal function
    
    • administration of radiocontrast material
    
    • known hepatic disease, hypoxemic conditions, severe infections, or alcohol abuse

• Alpha Glucosidase Inhibitors: Acarbose, Miglitol
  
  • Mechanism: Slow the hydrolysis of complex carbohydrates and carbohydrate absorption
  
  • Side Effects: Flatulence, bloating, diarrhea
Pharmacologic Therapy for T2DM

• Sulfonylureas/Meglitinides: glimepiride, glyburide, glipizide, repaglinide, nateglinide
  • Mechanism: promote insulin secretion from beta cells
  • Side Effects: Weight gain and hypoglycemia
  • Caution in renal disease

• Thiazolidinediones: rosiglitazone, pioglitazone
  • Mechanism: improves peripheral insulin sensitivity (PPARγ)
  • May take 10-12 weeks for full effect
  • Side Effects: weight gain, fluid retention, osteoporosis
  • Black box warning: may cause or exacerbate CHF
Pharmacologic Therapy for T2DM

- **DPP4 Inhibitors: sitagliptin, saxagliptin, linagliptin, alogliptin**
  - Mechanism: Block DDP4 the enzyme responsible for cleavage inactivation of GLP-1 and GIP
    - Stimulates insulin in response to elevated glucose levels
    - Inhibits release of glucagon following a meal
  - Side Effect: rare
  - Safe in renal disease (may require decreased doses)
  - Weight neutral
  - Pancreatitis risk, Heart failure risk

- **Bile Acid Sequestrants: colesevelam**
  - Mechanism unclear
  - Lowers LDL
  - Side Effects: gastric upset, increased triglycerides

- **Dopamine D2 Receptor Agonists: quick release bromocriptine**
  - Mechanism: Modulates hypothalamic regulation of metabolism
Pharmacologic Therapy for T2DM

- GLP-1 agonists: exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, semaglutide
  - **Mechanism:**
    - Stimulates insulin in response to elevated glucose levels
    - Inhibits release of glucagon following a meal
    - Slows gastric emptying
    - Increases satiety
  - **Side Effect:** GI upset
  - **Benefits:** Weight loss, ASCVD reduction
  - **?Pancreatitis risk**
  - **Contraindicated in patients with personal/family history of medullary thyroid cancer or MEN2**
Pharmacologic Therapy for T2DM

- Sodium Glucose Transporter 2 Inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
  - Mechanism: Blocks reabsorption of glucose from the proximal tubule
  - Benefits: ASCVD and Heart Failure reduction, decreased CKD progression, weight loss
  - Side Effects: UTIs and genital candida infections and Fournier’s gangrene, volume depletion, DKA, fractures, amputation, increased LDL
  - Should be discontinued with illness or prior to surgery to avoid risk of DKA
  - Decreased A1c lowering efficacy as GFR decreases
Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al.
Intensifying to injectable therapies

If injectable therapy is needed to reduce A1C:
- Consider GLP-1 RA in most patients prior to insulin
  - INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
  - TITRATION: Titration to maintenance doses (varies within class)
- If above A1C target

Add basal insulin:
- Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 6.3 for insulin cost information.
- Add basal analog or bedtime NPH insulin
  - INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a day
  - TITRATION:
    - Set FPG target (see Section 6: Glycemic Targets)
    - Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
    - For hypoglycemia determine cause, if no clear reason lower dose by 10-20%
- Assess adequacy of basal insulin dose
  - Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.6 IU/kg, elevated bedtime-monring and/or post-prandial, high variability, hypoglycemia [aware or unaware], high variability)
- If above A1C target

Consider GLP-1 RA if not already in regimen
- For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors
  - Add prandial insulin
    - Usually one dose with the largest meal or meal with greatest PPQ excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
  - TITRATION:
    - 4 IU a day or 10% of basal insulin dose
    - If A1C <9% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose
  - If above A1C target

Stopwise additional injections of prandial insulin (i.e., two, then three additional injections)

Consider self-mixed split insulin regimen
- Can adjust NPH and short/rapid-acting insulins separately
  - INITIATION:
    - Total NPH dose = 80% of current NPH dose
    - 2/3 given before breakfast
    - 1/3 given before dinner
    - Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
  - TITRATION:
    - Titrate each component of the regimen based on individualized needs
  - If above A1C target

Consider twice daily premix insulin regimen
- INITIATION:
  - Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
- TITRATION:
  - Titrate based on individualized needs

If on bedtime NPH, consider converting to twice-daily NPH regimen
- Conversion based on individual needs and current glycemic control. The following is one possible approach:
  - INITIATION:
    - Total dose = 80% of current bedtime NPH dose
    - 5/3 given in the morning
    - 1/3 given at bedtime
  - TITRATION:
    - Titrate based on individualized needs
Treatment of DM - Insulin

• Essential treatment for Type 1 Diabetes
• ~58% of patients with Type 2 Diabetes will eventually require exogenous insulin
• Risk of Hypoglycemia
• Weight Gain
Question 4

• 32 yo woman who has had T1DM for 16 years reports 3 weeks of fatigue, excessive sweating and occasional headache on awakening.
• She is using 32 units of premixed insulin BID (75/25 neutral protamine lispro/lispro mix)
• She exercises each evening after work and occasionally experiences hypoglycemic symptoms around lunchtime if she doesn’t eat enough.
• She monitors sugar BID. BG log shows fasting glucose readings 125-146 mg/dL and pre-dinner readings average 176. Recent HbA1c 7.0%
• She is engaged and will be planning pregnancy in the next year and hopes to get her A1c lower pre-conception
• Examination reveals normal weight and blood pressure, and no evidence of diabetic complications

Adapted from MKSAP 16
Which of the following is the most likely cause of her symptoms?

• A Nocturnal Hypoglycemia
• B Dawn Phenomenon
• C Sleep Apnea
• D Pheochromocytoma
Which of the following options is the most appropriate management to improve her glucose control?

A. Increase the dose of the morning premixed insulin and decrease the dose in the evening
B. Increase the dose of both the morning and the evening premixed insulin
C. Switch to self-mixed NPH and lispro before breakfast and supper
D. Change insulin to glargine at bedtime with three premeal injections of lispro a day
E. Reduce caloric consumption
Normal Secretory Pattern of Insulin

- **Breakfast**
- **Lunch**
- **Dinner**

- “Prandial” Insulin
- “Basal” Insulin
Physiologic Multiple Insulin Injections
“Basal/Bolus”

- **Breakfast**: Rapid (lispro, aspart, glulisine, inhaled)
- **Lunch**: Rapid (lispro, aspart, glulisine, inhaled)
- **Dinner**: Rapid (lispro, aspart, glulisine, inhaled)

Other medications:
- Degludec, detemir, or glargine

**Plasma insulin**

- **4:00 AM**
- **8:00 AM**
- **12:00 PM**
- **16:00 PM**
- **20:00 PM**
- **24:00 PM**
- **4:00 AM**
- **8:00 AM**
A type 2 diabetic patient is admitted to trauma service ICU after a MVA. On his home meds he is taking Insulin glargine (Lantus) 50 units BID and Humalog 40 units with meals. He weighs 80kg. He is intubated and sedated and requiring pressors. He will require surgery in the AM. You are writing his admission orders. Blood glucose on SMA7 is 362.
What is the most appropriate treatment regimen at this time?

A. Insulin glargine (Lantus) 50 units BID (home dose)
B. Start Humalog sliding scale insulin Q6h for BG 0-150= 0 units 150-200=1u, 151-200=2u, 201-250=3u, 251-300=4u, 301-350=5u, 351-400=6u, 400-450=8u, >450=10u and call MD
C. Regular insulin IV drip
D. Insulin glargine (Lantus) 20 units daily (weight-based dose)
Diabetes Care in the Hospital

• Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold $\geq 180$ mg/dL

• A basal bolus correction insulin regimen, with the addition of nutritional insulin in patients who have good nutritional intake, is the preferred treatment for noncritically ill patients

• Sole use of sliding scale insulin in the inpatient hospital setting is strongly discouraged

• Target glucose range of 140-180 mg/dL is recommended for the majority of critically ill patients and noncritically ill patients
Insulin Infusions in the Critically Ill

ICU setting
• BG targets on insulin 140-180mg/dL
• More stringent goals of 110-140 mg/dL, may be appropriate for selected patients, if this can be achieved without significant hypoglycemia
• IV insulin is the preferred method for achieving and maintaining glucose control in the critically ill

• Initial results in surgical patients after trauma or open heart surgery have shown benefit with intensive control of sugar with IV insulin protocols
• MICU/CCU results have been counterproductive
Gestational Diabetes

• Definition: Diabetes diagnosed during pregnancy
• May be undiagnosed Type 2 diabetes OR hyperglycemia due to pregnancy induced insulin resistance that goes away once baby is delivered

• Complications:
  • Fetus Malformations (Hyperglycemia 1st Trimester)
  • Pre-eclampsia
  • Macrosomia and delivery complications
  • Fetal Death
  • Increased risk of Type 2 Diabetes in mother and infant
Gestational Diabetes

- Screening
  - High risk women in the first trimester
  - Most women at 24-28 weeks

- Treatment
  - Diet
  - Insulin *preferred*
    - Newer trials show safety with oral agents
      - Metformin
      - Sulfonylureas
  - Post-pregnancy screening for persistent DM
    - 2hr OGTT 6 weeks post-partum
Diabetic Patient Pre-conception Counseling

• Preconception A1c target
  • Lower is better (< 6 or 6.5%)

• Risk of development and/or progression of diabetic retinopathy

• Medications to be avoided
  • Statins: Category X
  • ACE/ARB: Category D
  • ASA: Category D
Pregnancy and Diabetes

Women with type 1 or type 2 diabetes should be prescribed low-dose aspirin 60–150mg/day (usual dose 81 mg/day) from the end of the first trimester until the baby is born in order to lower the risk of preeclampsia.

American Diabetes Association Standards of Medical Care in Diabetes. Management of Diabetes in Pregnancy Diabetes Care Volume 42, Supplement 1, January 2019
Highly Recommended Immunizations for Adult Patients with Diabetes (Condensed)

**Hepatitis B**
Age: <60 years of age; ≥60 years of age discuss with doctor | Frequency: 2- or 3-dose Series | Ref 1: CDC

**HPV**
Age: ≤26 years of age; 27–45 yrs may be vaccinated after discussion with doctor | Frequency: 3 doses over 6 months | Ref 2: MMWR 2019;68:698–702.

**Influenza**
Age: All patients; | Frequency: Annually | Ref 3: Demicheli, 2018;2:CD004876

**Pneumonia (PPSV23)**
Age: 19–64 years of age | Frequency: 1 dose | Ref 4: MMWR 2010;59:1102–1106

**Pneumonia (PCV13)**
Age: 19-64 years, no recommendation; ≥65 years w/o immune-compromising condition discuss with doctor | Frequency: 1 dose | Ref 6: MMWR 2019;68:1069–1075

**Tetanus, diphtheria, pertussis (TDAP)**
Age: All adults; pregnant women - an extra dose | Frequency: Booster every 10 years | Ref 7: MMWR 2020;69: 77–83

**Zoster**
Age: ≥50 years of age | Frequency: Two-dose Shingrix, even if previously vaccinated | Ref 8: MMWR 2018;67:103–108

Adapted from: American Diabetes Association, Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2021, Diabetes Care 2021;44(Suppl. 1):S40–S52 | https://doi.org/10.2337/dc21-S004
Highly Recommended Immunizations for Adult Patients with Diabetes (Condensed)

1. CDC. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60: 1709–1711
Which patient is at higher risk for Type 2 DM and Heart Attack?
A 54-year-old man with prediabetes and hyperlipidemia is concerned about his risk of developing type 2 diabetes mellitus and cardiovascular disease. He understands that he needs to lose weight. He has incorporated exercise into his routine by adding brisk walking for 25 minutes 3 to 4 times per week and has begun weight training under the guidance of a trainer but has not seen a significant change in his weight.
Question 7

Which of the following diets is most likely to lead to long-term weight loss for this patient?

A. Low-fat diet
B. Low-carbohydrate diet
C. Vegetarian diet
D. Mediterranean diet
E. Dietary Approaches to Stop Hypertension (DASH diet)
Which of the following diets is most likely to reduce the risk of major cardiovascular events?

A. Low-fat diet
B. Low-carbohydrate diet
C. Vegetarian diet
D. Mediterranean diet
Obesity

• Etiology
  • Genetic and epigenetic influences- 70%
  • Acquired: 30%
  • Increased caloric intake
  • Biological influences of hormones (leptin, adiponectin etc.)
  • Gut microbes
  • Imbalance of signals related to energy regulation
  • Hypothalamic lesion (RARE)

• Weight loss of as little as 5-15% of initial weight improves many obesity-related co-morbidities
## Overweight / Obesity Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body Mass Index (BMI) Category (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25.0-26.9 (or 23.0-26.9*)</td>
</tr>
<tr>
<td>Diet, physical activity &amp; behavioral therapy</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
</tr>
<tr>
<td>Metabolic surgery</td>
<td></td>
</tr>
</tbody>
</table>

* Asian-American individuals

† Treatment may be indicated for selected, motivated patients.

*Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S65-S72*
Obesity Treatment: Lifestyle

• Diets: Only total calories matter- NOT macronutrient composition
• Popular diets (Weight Watchers, Ornish, Atkins, South Beach) all result in 7-10% weight loss (JAMA 2006)
• Mediterranean diet may be best for CAD prevention
• Key is adherence!
## CURRENT PHARMACOLOGICAL THERAPY FOR OBESITY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Contraindications</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Appetite- suppressant drug. Causes NE release. minor DA release.</td>
<td>Cardiovascular disease, hyperthyroidism, glaucoma, agitated states, pregnancy</td>
<td>Insomnia, dry mouth, constipation, agitation, HTN</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Modulates dietary absorption of fats by reducing fat hydrolysis &amp; absorption by inhibiting gastric &amp; pancreatic lipases</td>
<td>Chronic malabsorption syndrome, cholestasis, pregnancy</td>
<td>Oily spotting, flatus with discharge, diarrhoea, faecal urgency</td>
</tr>
<tr>
<td>Phentermine/Topiramate</td>
<td>Topiramate: neurostabilizer, enhance thermogenesis. Phentermine: appetite suppressant</td>
<td>Glaucoma, hyperthyroidism, pregnancy</td>
<td>Parasthesia, dizziness, dysguesia, insomnia, constipation, dry mouth</td>
</tr>
<tr>
<td>Naltrexone/Bupropion SR</td>
<td>Bupropion: stimulates POMC. Naltrexone: blocks orexigenic effects of β endorphin activity</td>
<td>Uncontrolled HTN, seizures, chronic opioid use, pregnancy</td>
<td>Nausea, constipation, headache, insomnia, dry mouth, diarrhoea</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 receptor agonist. Directly stimulates POMC and other anorexigenic neurons. Activates reward system: ventral trigeminal area, nucleus accumbens</td>
<td>Personal/family history of medullary thyroid Ca, MEN type 2, pregnancy</td>
<td>Nausea, hypoglycemia, diarrhoea, constipation, decreased appetite, dyspepsia, abdominal pain</td>
</tr>
</tbody>
</table>
Bariatric (Metabolic) Surgeries

Restrictive
  • Adjustable gastric banding
  • Sleeve gastrectomy

Malabsorptive
  • Roux-en-Y gastric bypass
  • Biliopancreatic diversion +/- duodenal switch
Mechanisms of Weight Loss

Intestinal Malabsorption:
- Reducing the intestinal surface of nutrient absorption (J-I bypass)
- Distal diversion of pancreatic and biliary secretions (maldigestion)

Gastric Restriction:
- Limits the capacity of the stomach- early satiety and smaller meals
- Dumping syndrome: Anticipation fear
Acute Complications

- Mortality (0-1.1%)
- Anastomotic Leaks
- Pulmonary Embolism
- Bleeding
- Obstruction
- Infections
- Stomach Prolapse (banding)
Long-Term Complications

- Vomiting and Dumping Syndrome
- Protein Malnutrition
- Hair Loss
- Gallstones
- Ulcers (marginal, difficult endoscopy)
- B12 deficiency
- Iron Deficiency
- Vitamin D deficiency
- Thiamine Deficiency
Long-Term Complications

- Rapid Weight Loss Neuropathy
- Intestinal obstruction/strictures
- Incisional Hernia
- Fertility - Unwanted Pregnancy
- Redundant Skin (cosmetic surgery)
- Weight Regain
- Hyperinsulinemia / Nisedeoblastosis
## Improvements of DM2 with different Bariatric Surgeries

<table>
<thead>
<tr>
<th></th>
<th>Roux-en-Y</th>
<th>Bilio-pancreatic diversion</th>
<th>Gastric Banding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission of DM2</td>
<td>84%</td>
<td>&gt;95%</td>
<td>48%</td>
</tr>
<tr>
<td>Recurrence after 10 yrs</td>
<td>Rare</td>
<td>Rare</td>
<td>More Frequent</td>
</tr>
<tr>
<td>Evolution</td>
<td>Days to weeks</td>
<td>Days to weeks</td>
<td>&gt; 6 months</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Marked</td>
<td>Most marked</td>
<td>Less</td>
</tr>
<tr>
<td>Incretins</td>
<td>Increased</td>
<td>Increased</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>
Question 9

• A 19-year-old woman is referred for evaluation of hypoglycemia. For 10 months, she has had episodes of somnolence, extreme fatigue, and difficulty being aroused from sleep.
• Symptoms usually appear overnight or 3 to 4 hours after a meal- they are always relieved by drinking orange juice
• Findings from her physical examination are unremarkable except for being overweight (BMI = 27.1 kg/m2)
• Her family history is significant for her twin brother having Type 1 DM on insulin since age 11. Past medical history is significant for depression.
During a spontaneous episode of hypoglycemia in your office occurring 2 and a half hours after a meal, the following laboratory values are obtained:

- Serum glucose 38 mg/dL
- Plasma insulin 25.2 μIU/mL (nl 2-17)
- C-peptide 0.3 ng/mL (nl 0.78-1.89)
- Pro-insulin 1 pmol/L (nl 6.4-8.9)
- Sulfonylurea level is undetectable
Question 9

What is the most likely cause of the patient’s hypoglycemia?

A. Insulinoma
B. Factitious use of insulin
C. Reactive hypoglycemia
D. Adrenal Insufficiency
E. Growth hormone deficiency
Hypoglycemia

• Definition as a disease: Whipple’s Triad
  • Documented hypoglycemia
  • Neuroglycopenic symptoms during time of hypoglycemia
  • Resolution of symptoms with administration of glucose

• Hypoglycemia
  • Lower limit of normal glucose 70 mg/dL
  • Release of counter-regulatory hormones (65-70 mg/dL)
  • Symptoms of hypoglycemia (50-55 mg/dL)

• Neuroglycopenic Symptoms
  • Caused by sympathetic nervous activation
  • Tremor, Palpitations, Anxiety, Sweating, Hunger, Paresthesias, Cognitive impairment, Seizure, Coma
Hypoglycemia Etiologies

- Drugs
- Alcohol
- Critical Illness
- Tumors that make IGF-1 or IGF-2
- Hormone Deficiency (cortisol, glucagon, epinephrine)
- Exogenous Hyperinsulinism
  - Very common in diabetics on insulin
  - Surreptitious or Malicious use of insulin
- Endogenous Hyperinsulinism
  - Insulinoma
  - Functional beta-cell disorders
  - Autoimmune
  - Sulfonylurea

Check insulin, pro-insulin, sulfonylurea and c-peptide levels during an episode of hypoglycemia
# Hypoglycemia Etiologies

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Insulin</th>
<th>C-peptide</th>
<th>Proinsulin</th>
<th>Sulphonylurea in plasma or urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous insulin</td>
<td>↑↑</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>-</td>
</tr>
<tr>
<td>Sulphonylurea use</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>+</td>
</tr>
</tbody>
</table>

↑ = increased; ↓ = decreased
Insulinoma

- Rare, incidence 1:250,000
- Associated with MEN1 Syndrome
- Fasting Hypoglycemia (diagnose with 72hr fast)
- Weight gain in 20% of patients

**Treatment**
  - Surgical Resection
  - Medications that inhibit secretion of insulin
    - Diazoxide
    - Octreotide
A 38 year old healthy female is admitted to the hospital with acute onset abdominal pain
Her only medication is birth control pills
No family history of CVD or hyperlipidemia
Selected Laboratory Data:
  • Total Cholesterol: 458
  • LDL: 120
  • HDL: 38
  • Triglycerides: 3000
  • Glucose: 89
  • Amylase: 5 x ULN
  • Thyroid, Liver and Renal Function normal
Question 10
The most likely diagnosis is?

A. Dysbetalipoproteinemia Type III- Hyperlipoproteinemia
B. LCAT deficiency
C. Familial Hypercholesterolemia
D. Drug induced hypertriglyceridemia
E. CETP deficiency
Atherogenic and Anti-atherogenic Plasma Lipoproteins

Chylomicronemia Syndrome
Type I Hyperlipoproteinemia

• Clinical Features: lipemic plasma, lipemia retinalis, eruptive xanthomas, recurrent pancreatitis
• Plasma lipids and lipoproteins: Elevated plasma triglycerides, chylomicrons, and VLDL
• Molecular defects: Deficiency in lipoprotein lipase or ApoC-II
A 44 year old man is admitted to the hospital with chest pain for rule out MI
He reports a history of high triglycerides for which he takes fenofibrate
Family history is significant for his father d. at age 54 from a MI and his brother had CABG at age 50
Selected Laboratory Data:
  • Total Cholesterol: 174
  • LDL: 100
  • HDL: 4
  • Triglycerides: 280
  • Fasting Glucose: 88
  • Thyroid, Liver and Renal Function normal
Question 11

Physical Exam
The most likely diagnosis is?

A.  Tangier Disease
B.  Lipoprotein Lipase Deficiency
C.  Beta Sitosterolemia
D.  Abetalipoproteinemia
E.  CETP deficiency
Tangier Disease – Defect in the ABCA1 Transporter

• Clinical Features: Orange tonsils, premature CVD, cloudy cornea, peripheral neuropathy, hepatosplenomegaly, pancytopenia

• Plasma lipids and lipoproteins: Low plasma HDL, elevated triglycerides with low LDL. Heterozygotes will have 50% normal levels of HDL. Very low plasma ApoA-I and ApoA-II

• Molecular defect: Defect in the ABCA1 Transporter
LCAT Deficiency

• Clinical Features: severe cloudy cornea (fish eye disease), chronic renal disease. NO CVD

• Plasma lipids and lipoproteins: Very low plasma HDL, elevated triglycerides with low LDL. Very low plasma ApoA-I and ApoA-II

• Molecular defect: Defect in LCAT enzyme
LCAT Deficiency – Fish Eye Disease
Avoid routine multiple daily self-glucose monitoring in adults with stable type 2 diabetes on agents that do not cause hypoglycemia.

Once target control is achieved and the results of self-monitoring become quite predictable, there is little gained in most individuals from repeatedly confirming. There are many exceptions, such as for acute illness, when new medications are added, when weight fluctuates significantly, when A1C targets drift off course and in individuals who need monitoring to maintain targets. Self-monitoring is beneficial as long as one is learning and adjusting therapy based on the result of the monitoring.

Don’t routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function.

Many practitioners become confused when ordering a vitamin D test. Because 1,25-dihydroxyvitamin D is the active form of vitamin D, many practitioners think that measuring 1,25-dihydroxyvitamin D is an accurate means to estimate vitamin D stores and test for vitamin D deficiency, which is incorrect. Current Endocrine Society guidelines recommend screening for vitamin D deficiency in individuals at risk for deficiency.

Serum levels of 1,25-dihydroxyvitamin D have little or no relationship to vitamin D stores but rather are regulated primarily by parathyroid hormone levels, which in turn are regulated by calcium and/or vitamin D. In vitamin D deficiency, 1,25-dihydroxyvitamin D levels go up, not down.

Unregulated production of 1,25-dihydroxyvitamin D (i.e., sarcoidosis, granulomatous diseases) is an uncommon cause of hypercalcemia; this should be suspected if blood calcium levels are high and parathyroid hormone levels are low and confirmed by measurement of 1,25-dihydroxyvitamin D. The enzyme that activates vitamin D is produced in the kidney, so blood levels of 1,25-dihydroxyvitamin D are sometimes of interest in patients on dialysis or with end-stage kidney disease. There are few other circumstances, if any, where 1,25-dihydroxyvitamin D testing would be helpful.

Serum 25-hydroxyvitamin D levels may be overused, but when trying to assess vitamin D stores or diagnose vitamin D deficiency (or toxicity), 25-hydroxyvitamin D is the correct test.
Don’t routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.

Thyroid ultrasound is used to identify and characterize thyroid nodules, and is not part of the routine evaluation of abnormal thyroid function tests (over- or underactive thyroid function) unless the patient also has a large goiter or a lumpy thyroid. Incidentally discovered thyroid nodules are common. Overzealous use of ultrasound will frequently identify nodules, which are unrelated to the abnormal thyroid function, and may divert the clinical evaluation to assess the nodules, rather than the thyroid dysfunction. Imaging may be needed in thyrotoxic patients; when needed, a thyroid scan, not an ultrasound, is used to assess the etiology of the thyrotoxicosis and the possibility of focal autonomy in a thyroid nodule.

Don’t order a total or free T3 level when assessing levothyroxine (T4) dose in hypothyroid patients.

T4 is converted into T3 at the cellular level in virtually all organs. Intracellular T3 levels regulate pituitary secretion and blood levels of TSH, as well as the effects of thyroid hormone in multiple organs; a normal TSH indicates an adequate T4 dose. Conversion of T4 to T3 at the cellular level may not be reflected in the T3 level in the blood. Compared to patients with intact thyroid glands, patients taking T4 may have higher blood T4 and lower blood T3 levels. Thus the blood level of total or free T3 may be misleading (low normal or slightly low); in most patients a normal TSH indicates a correct dose of T4.

Don’t prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.

Many of the symptoms attributed to male hypogonadism are commonly seen in normal male aging or in the presence of comorbid conditions. Testosterone therapy has the potential for serious side effects and represents a significant expense. It is therefore important to confirm the clinical suspicion of hypogonadism with biochemical testing. Current guidelines recommend the use of a total testosterone level obtained in the morning. A low level should be confirmed on a different day, again measuring the total testosterone. In some situations, a free or bioavailable testosterone may be of additional value.