

- New
  - ACE in 02/10 stated a position that HbA1c  $\geq 6.5\%$  can be used for Dx of DM but remember that 20% of diabetics will be missed, it is still unclear if 5.5-6.4% is considered pre-diabetes, HbA1c is falsely low in IDA/hemoglobinopathies/liver-dz/renal-dz, etc
  - **ACCORD/VA Trials** showed that tighter control of glucose did not reduce macrovascular complications but actually led to an increased risk of death the tighter the control
  - **ADVANCE Trial** showed that tighter glucose control did not reduce macrovascular complications but did improve renal microvascular however at the risk of increased hypoglycemic events
  - some say that all cause mortality is the same if HbA1c of 6.5 and 10.5
- General
  - Mechanism: GLUT-2 receptor on beta-cells senses glucose  $\rightarrow$  inhibits K inflow  $\rightarrow$  increases Ca inflow  $\rightarrow$  stimulates pro-insulin release  $\rightarrow$  converted into insulin and C-peptide  $\rightarrow$  (1) stimulates glucose uptake during meals (2) suppresses hepatic endogenous glucose production via glycogenolysis/gluconeogenesis during fasting (3) suppresses lipolysis in adipocytes (4) suppresses proteolysis in muscle
  - Old Landmark Trials
    - **UKPDS (UK Protective Diabetes Study)**: landmark trial on T2DM
    - **DCCT (Diabetes Complication and Control Trial)**: landmark trial on T1DM
- For Each Patient
  - Type
  - Hyperglycemic S/S
  - Tx: Meds (Orals/Insulin, Diet (1500,1800,2000,2400 kcal diabetic diet), Exercise, Education (DM/Nutrition))
  - HbA1c Q3mo w/ goal 6-7% (nl 4-6%)
    - you don't want pts "nl" b/c they most likely have undocumented hypoglycemic moments which is more dangerous than the effects of hyperglycemia (7% HbA1c = average 3mo sugar of  $\sim 150\text{mg/dL}$  with 1% change =  $\sim 30\text{mg/dL}$ )
    - you can have false normal HbA1c if you have equally both hypo/hyperglycemia and false low HbA1c if you have anemia decreasing RBC lifespan
  - Home CBGs
    - Morning Fasting Hyperglycemia could represent of one of two problems, to confirm check 3am CBG
      - Dawn Phenomenon: the normal increase in nocturnal secretion of GH/Cortisol results in hyperglycemia in the middle of the night that carries over into the morning, then check 3am CBG, Tx: increase evening intermediate insulin
      - Somogyi Effect: too much evening insulin resulting in hypoglycemia in the middle of the night with subsequent rebound hyperglycemia in morning, then check 3am CBG, Tx: decrease evening intermediate insulin (NB recent studies indicate that this effect is NOT true and that all morning fasting hyperglycemia is 2/2 Dawn Phenomenon)
  - Other
    - Brittle DM: essentially unstable/labile T1DM w/ wide variability in glucose levels along with depression and Somogyi Effect, likely causes is gastroparesis, poor communication, behavioral (adolescents, etc)
    - Honeymoon Effect: improvement of hyperglycemia after Dx and institution of Tx and sometimes pts can be removed from medication for a short while, 2/2 temporary increased insulin secretion as the precipitating event for presentation resolves
    - Latent Autoimmune Diabetes of Adults (LADA) T1DM presenting late in life w/ a very slow onset, can actually be started on oral drugs first
    - Ketosis Prone T2DM, seen in young obese AA/Hispanic pts w/ very strong FMHx of T2DM
  - Acute Complications
    - Hypoglycemia: always have something sweet available
    - DKA: monitor home urine ketones w/ Ketostix/Acetest during (1) ill states, (2) glu  $>300$ , (3) S/S of DKA or (4) pregnant every morning, remember you can have nl CBGs but still be in DKA, all T1 pts should have them
    - HONC/HHC
  - Chronic Complications
    - Macro (ASA 81mg  $>40\text{yo}$  or other Cardiac RFs)
      - Brain: assess Sx, no screening test
      - Heart: assess Sx, baseline EKG w/ low threshold for stress testing
      - PV: assess Sx, PEx (pulses, cap refill, etc), if + then check ABIs
    - Micro (start at time of Dx for T2 and 5yr after Dx for T1, Qyr exam/lab)
      - Eye: dilated eye exam Qyr
      - Kidney: microalbumin Qyr
      - PN: vibration (1<sup>st</sup> metatarsal head  $\rightarrow$  medial malleolus  $\rightarrow$  hand) then if abnormal check proprioception b/c that is the next to go, never to pin prick w/ 10g monofilament test b/c not-sensitive, also test reflexes, foot exam Qyr
    - Foot: exam Qyr, deformities, callouses, dryness, toenail fungal infection, arterial blood flow w/ pulses/cap-refill, venous insufficiency w/ edema/venous stasis changes, have pt inspect every evening, wash, hydrate,

place emollient creams, use socks and comfortable shoes, never walk barefoot, also inspect after new shoes to assess pressure points

- Comorbidities
  - DL: FLP Qyr w/ most stringent goals for LDL (<70) Meds: Statin
  - HTN: BP Qyr w/ most stringent goals for BP ( $\leq 130/\leq 80$ ) Meds: RAAS inhibition, BB, CCB, Diuretics
  - Dental Exam Q6mo
  - Pneumococcal/Influenza Vaccination
- Goals
  - HbA1c = 7%, pre-prandial CBG = 110, 2hr post-prandial CBG <160
- In-Pt
  - assess possibility for increased/decreased sugar, hyperglycemia associated w/ higher in-pt M&M, ICU (140-180mg/dL w/ insulin gtt) vs Non-ICU (Pre-Meal: 100-140mg/dL vs Random: 100-180mg/dL), pts w/ "stress-induced hyperglycemia" often have diabetes in the end so f/u
  - SSI: avoid SSI b/c not physiologic, based on CBGs Q6hrs, Algorithms: A (very insulin sensitive), B (normal insulin sensitivity aka most pts), C & D (very insulin resistant), never leave a pt on SSI alone, even a low dose long acting insulin will help
  - Hold metformin
- Types
  - Type 1 Diabetes Mellitus (T1DM)
    - genetically susceptible Pt (+HLA-DR3/DR4/DQA/DQB, you would think more genetically linked than Type 2 but actually the opposite, only 50% concordance rate b/t identical twins, <20yo (peak 14yo), normal to thin pt) → **precipitating environmental trigger** most likely viral infection that induces damage to pancreas → **exposes previously hidden beta-cell antigens** that are similar to viral antigens → immune response against virus **cross-reacts** with beta-cells resulting in their destruction → auto-Ab: **Anti-Glutamic Acid Decarboxylase-GAD-65 Ab, Anti-Islet-Cell Autoantigen 512 Ab, Anti-Insulin, Anti-Tyrosine Phosphatases IA-2 & IA-2beta** (T1DM-A (+Abs) vs T1DM-B (-Abs)) w/ lymphocytic infiltrate in pancreas → decrease in beta-cell mass and ability to secrete insulin
    - NB oral agents have no role in T1DM, pts typically need insulin at 0.5-1U/kg/d, even when T1 pts are not eating they still need basal insulin
    - NB check for other autoimmune disorders in PGA
  - Type 2 Diabetes Mellitus (T2DM)
    - Genetically susceptible Pt (no HLA link but strong genetic component w/ 100% concordance rate b/t identical twins, >40yo although child incidence is increasing, obese) → **high fat diet w/ central obesity stimulates beta-cells to constantly secrete insulin** → constant elevation of insulin makes **insulin receptors resistant** → beta-cells compensate for the resistance by becoming **hyperplastic** and secreting more insulin → eventually beta-cells cannot keep up and thus **decompensate**, in addition, **fat cells are not able to store excess fat** which then accumulates (1) in other tissues exerting a **lipotoxic effect inhibiting insulin effect** and (2) in pancreas **destroying islet cells becoming insulin deficient**
    - NB T2DM is a high calorie and fat storage problem that only becomes a "sugar" problem in the end
    - NB associated w/ DL/HTN w/ subsequent endothelial dysfxn and vascular inflammation resulting in cardiovascular disease
    - Studies looking at Prevention of Pre-Diabetes to Diabetes: Finnish DPS and US DPP (lifestyle changes decreased progression by ~50%), US DPP / TRIPOD (Metformin), STOP-NIDDM (Acarbose), DREAM (Rosiglitazone), ACT NOW (Posiglitazone), HOPE/LIFE/CHARM study (ACE-I) however NO med is FDA approved nevertheless the current algorithm is: **if IFG or IGT then lifestyle and address RFs, if IFG and IGT and RFs then Metformin, a recent study is showing that valsartan!!! can prevent progression (NAVIGATE study)**
  - Gestational DM
    - Types
      - Pre-Gestational DM (1<sup>st</sup> trimester): Class **B/C/D** = DM that began >20yo/10-20yo/<10yo and lasts <10y/10-20y/>20y and is occurring during pregnancy (NB Class F = Nephropathy, Class R = Retinopathy, Class H = Ischemic Heart Disease, Class T = Prior Renal Transplantation)
      - Gestational DM (GDM) (2<sup>nd</sup>/3<sup>rd</sup> trimester): Class **A1** = Gestational DM controlled with diet alone vs Class **A2** = Gestational DM controlled with diet and meds (7% of pregnancies)
        - Epidemiology: **advanced maternal age, non-white, obesity, previous baby >4000g, previous stillborn**
        - Warning S/S: **edema, polyhydramnios, large for GA**
        - Screen/Dx: at first pre-natal visit if +RFs or at 24-28wks (2<sup>nd</sup> trimester) if -RFs w/ **50g-OGTT** (50g of oral glucose and measure CBG at 1hr) and if CBG >140 then perform **100g-OGTT** (100mg of oral glucose after an 8-14hr overnight fast preceded by a 3day special carbohydrate diet and measure CBG at 1hr intervals) and if  $\geq 2/4$  (>95 fasting, >180 after 1hr, >155 after 2hrs, >140 after 3hrs) then + for GDM
        - Mechanism: **↑hPL** by placenta during 3<sup>rd</sup> trimester ensures nutrient supply for fetus by acting as an **insulin antagonist** in the mother therefore similar to T2DM in that the pt/mother becomes insulin resistant but not b/c of high calorie diet and lipotoxicity
    - Things to Do
      - monitor fetus with NonStress Test (NST) and US for macrosomia at >34wks Q1wk

- do not allow pregnancies to extend >40wks b/c of the increased risk of hypoglycemia as placental function decreases toward end of pregnancy resulting in less hPL production
- Problems
  - High Sugar during 1<sup>st</sup> Trimester: **Congenital Malformations and Delayed Organ Maturation**
  - High Sugar during 2<sup>nd</sup>/3<sup>rd</sup> Trimester: **Fetal (Macrosomia, preeclampsia, preterm, death), Neonatal (hypoglycemia, hypocalcemia, polycythemia, hyperbili, resp-distress), Mother (HTN, increased need for Cesarean section, 50% develop T2DM after 15yrs and/or recurrent GDM hence repeat OGTT 6wks post-partum and then subsequent yearly surveillance)**
- Tx
  - Insulin (requirements increase as the pregnancy proceeds but after delivery requirements drop)**
  - Metformin (not FDA approved but used in Australia as primary Tx)**
  - NO OTHER ORAL AGENTS**
- Genetic Defects
  - Insulin Secretion
    - MODY = Maturity Onset Diabetes of the Young (AD mutation of insulin secreting genes such that beta-cells cannot secrete insulin, occurs 10-20yo, usually mild DM)
      - MODY-1: HNF-4-alpha mutation
      - MODY-2: Glukokinase mutation
      - MODY-3: HNF-1-alpha mutation (most common)
      - MODY-4: IPF-1 mutation
      - MODY-5: HNF-1-beta mutation
      - MODY-6: NeuroD1 mutation
    - Other: Mitochondrial DNA Defects, etc
  - Insulin Action
    - Rabson-Mendenhall Syndrome
    - Type A Insulin Resistance
    - Leprechaunism
- Exocrine Pancreatic Disease: Pancreatitis, Pancreatic Cancer, Pancreatectomy, Neoplasia, CF, Hemochromatosis, etc
- Endocrinopathies: Acromegaly (GH is like glucagon), Cushing (Cortisol is like glucagon), Glucagonoma
- Drugs: Furosemide, Glucocorticoids, OCPs, Thiazides, Nicotinic Acid, Pentamidine, Diazoxide, BB, Alpha-Interferon
- Infection: CMV, Congenital Rubella
- Genetic Syndromes: Prader-Willi, Down's, Klinefelter's, Turner's, etc
- S/S
  - Hyperglycemia
    - Polyruia (hyperglycemia → glycosuria when hyperglycemia >180 → osmotic diuresis → volume depleted)
    - Polydipsia (above + hyperglycemia → pulls water out of cells)
    - Polyphagia/Fatigue (cells are not getting energy so they tell brain I'm starving eat more but regardless pt is still losing weight)
    - Blurred Vision (hyperglycemia → lens swelling)
- Dx
  - CBGs approximate venous glucose w/in 10%, best is side of finger tips but you can also check forearm or palm
  - Screen: >30/45yo Qyr if +/-RFs
  - Check glucose before meals, 90-120 minutes after meals, and at bedtime with fasting goal 70-130 and postprandial goal <180
    - Usually 10% lower than true plasma glucose
    - When: QD Insulin: 1-2x/d, BID Insulin: 2-4x/d, TID Insulin: 3-6x/d
    - Types: OneTouch, Accu-Check, Free-Style, Prodigy, TRUE, Glucocar, EasyGluco, ReliOne

|              | Fasting (after no caloric intake for ≥8hrs) CBG on >2 Occasions | Casual (any time of day w/o regard to time since last meal) CBG w/ +S/S (but pt cannot be in an acute illness) | Oral Glucose Tolerance Test (OGTT) (give pt 75g of glucose dissolved in water and measure glucose after 2hrs, mainly used for research purposes, this is slightly different than the test for GDM, can be used if pre-DM by other tests b/c much more sensitive) |
|--------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Normal       | <100                                                            | <100                                                                                                           | <140                                                                                                                                                                                                                                                             |
| Pre-Diabetes | 100-125<br>"Impaired Fasting Glucose - IFG"                     | 100-199                                                                                                        | 140-199<br>"Impaired Glucose Tolerance - IGT"                                                                                                                                                                                                                    |
| Diabetes     | ≥126                                                            | ≥200                                                                                                           | ≥200                                                                                                                                                                                                                                                             |

- Tx (Goal HbA1c 7%) (NB if pt has kidney dz just start w/ insulin)
  - 1<sup>st</sup> Diet and Exercise

- 2<sup>nd</sup> Start Insulin Sensitizer: 1° Biguanide 2° Thiazolidinedione (second line b/c not as effective, more expensive, new developing SEs) NB use b/c pts are making insulin so make it work as effectively as possible
- 3<sup>rd</sup> Add Insulin Secretagogue: 1° Sulfonylurea 2° Meglitinide (second line b/c not as effective, more expensive, compliance problems) NB use b/c pts are so resistant at this stage that hypoglycemia is not much of a problem and also they just need more insulin
- 4<sup>th</sup> Combine three or more agents, consider newer drugs, add low dose once a day long acting insulin
- 5<sup>th</sup> Insulin
- 6<sup>th</sup> Studies
  - Whole Pancreatic Transplant (wrought w/ problems when done alone, some are successful if done w/ kidney transplant)
  - Islet Cell Transplant (infused thru portal vein into liver, failure is common, multiple infusions are needed)
  - Closed Loop System (insulin pump that communicates w/ continuous glucose monitoring system)
- Insulin
  - Rx: Insulin, Glucometer x1, Glucometer Strips & Lancets x90/mo if you check CBG three times a day (check lateral finger tips and alternate finger to finger, never check anywhere else b/c inaccurate), Syringes x60/mo if you inject twice a day
  - SEs: lipodystrophy (fat build up where you inject)
  - Inject: ab wall → arm → buttock → thigh (absorption rates decrease as you move to the left), massage over injection to facilitate absorption
  - Even when NPO T1DM pts require basal insulin
  - Basal: suppresses hepatic gluconeogenesis/glycogenolysis vs Prandial: metabolize ingested calories
  - CBGs: check pre-prandial (just pick one B/L/D and change each day) and fasting CBG to determine basal insulin
  - In general ½-1U/kg/d
  - All insulin comes in 10cc vials w/ a U-100 strength where 1cc = 100U therefore 1vial = 1000U while each pen has 300U
  - Basal (intermediate BID vs long acting QD) + Prandial (rapid acting) + Correction (rapid acting)
  - Check 1-hr post-prandial (just pick one B/L/D and change each day) to determine pancreas response to food
  - Non-Motivated Pt: long acting insulin alone or give 70/30 (pre-breakfast and pre-dinner, w/ int peak from morning covering lunch) then have pt check fasting CBG in AM and a post-prandial (2hrs) CBG after biggest meal, give 2/3 of total dose in the morning and 1/3 in the evening, some recommend giving the intermediate not pre-dinner but at bedtime so as to avoid overnight hypoglycemia and provides better fasting sugars in morning
  - Motivated Pt: start a SS regimen (lantus SC Qhs w/ dose being 2/3U of insulin you needed the past day + short acting insulin) then have pt check pre-prandial CBG and based on this value pt gives a certain amount of short acting insulin
  - Very Motivated: adjust for estimated carb intake aka "carb-counting" (for every 10-15g of carbs take 1 more unit of rapid acting insulin) and adjust for pre-prandial hyperglycemia (for every 40-50mg/dL of glu above pre-meal target of 120 take 1 more unit of rapid acting insulin), NB look at total carbs (not sugar), if a serving has >5g of fiber then subtract this amount from the total carbs, remember to see who much is one serving size
  - Very Very Motivated Pt: insulin pump, uses only fasting acting insulin, stick and change insulin Q3d, basal rate + boluses
  - NB Exubera (inhaled insulin) is not used much anymore b/c of its variable absorption effects and questionable long term effects on pulmonary function

| Types     | -H = Lilly (US)<br>-N = Novartis (Europe)                         | Onset    | Peak    | Duration | Other                                                                                                                                                                                                                                                                                                                                                                     |
|-----------|-------------------------------------------------------------------|----------|---------|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rapid     | Lispro (Humalog-H)<br>Aspart (Novolog-N)<br>Glulisine (Apidra-?)  | 10-15min | 1-2hrs  | 3-5hrs   | <ul style="list-style-type: none"> <li>AA change to make it rapid acting</li> </ul>                                                                                                                                                                                                                                                                                       |
| Regular   | Regular (Regular)                                                 | 30-60min | 2-4hrs  | 4-8hrs   |                                                                                                                                                                                                                                                                                                                                                                           |
| Interm    | NPH (Humulin-H)<br>NPH (Novolin-N)                                | 1-3hrs   | 4-10hrs | 10-18hrs | <ul style="list-style-type: none"> <li>NPH = Neutral Protamine Hagedorn (NP is the suspension that makes it longer acting while is H is the doctor who created it)</li> </ul>                                                                                                                                                                                             |
| Long      | Glargine (Lantus-H)<br>Determir (Levemir-N)                       | 2.5hrs   | -       | 24hrs    | <ul style="list-style-type: none"> <li>Cannot be mixed w/ other forms of insulin b/c it will crystallize</li> <li>Lantus &gt;24hrs vs Levemir &lt;24hrs</li> <li>As you increase dose change to BID</li> <li>AA change to make crystallize at pH 7.4 such that when it leaves the acidic vial and enters skin it turns into a crystal slowly releasing insulin</li> </ul> |
| Pre-Mixed | 70/30 (70%NPH+30%R)<br>75/25 (70%NPH+25%R)<br>50/50 (50%NPH+50%R) | NA       | NA      | NA       | <ul style="list-style-type: none"> <li>Cannot adjust dose for pre-meal hyperglycemia</li> </ul>                                                                                                                                                                                                                                                                           |

- Orals
  - Insulin Sensitizer
    - Biguanides 1-2%↓HbA1c (FASTING HYPERGLYCEMIA)
      - Metformin (BID: Glucophage, Riomet, QD: Glucophage-XR, Glumetza, Fortamet)

- Mech: improves the sensitivity of liver to insulin thus decreasing gluconeogenesis/glycogenolysis (therefore best for fasting hyperglycemia)
- Good: rapid onset, weight loss/neutral, improves lipid profile, has recently been shown to be safe in pregnant women
- Bad: lactic acidosis (esp w/ the old biguanide: phenformin) in pts with prior h/o lactic acidosis, kidney dz, liver dz, lung dz, or any hemodynamic compromise (IV Contrast, infection, dehydration, surgery, etc NB CHF is NO longer a absolute contraindication unless potential for advanced CHF or high r/o exacerbation), GI SEs (esp ab pain and diarrhea which can be Tx by slow dose titration or use of XR form, eventually it resolves), lower VitB12 (not clinically important)
- Only Absolute Contraindications: Cr  $\geq 1.5M/\geq 1.4F$
- Start low dose and increase Qmo to goal of 1g PO BID
- Thiazolidinediones (-glitazones) 0.5-1%↓HbA1c (POST-PRANDIAL HYPERGLYCEMIA)
  - Rosi-glitazone (Avandia), Pio-glitazone (Actos) use b/c less SEs and a more potent
  - Mech: improves the sensitivity of muscle/fat to insulin (therefore best for post-prandial hyperglycemia)
  - Good: lowers TGL, expensive
  - Bad: variable response, slow onset (takes wks to months), weight gain / edema, anemia, liver damage b/c first generation TZDs caused liver failure so just avoid, unknown mechanism but there is a possible decrease in mesenchymal precursor differentiation into cardiac muscle causing/worsening CHF (don't use on pts w/ III-IV NYHA) and bone causing/worsening osteoporosis w/ weird peripheral fractures equally with both drugs, NB the recent studies showing that Avandia has increased r/o MI are inaccurate
- Insulin Secretagogue
  - Sulfonylureas 1-2%↓HbA1c (long acting compared to meglitinides) (FASTING HYPERGLYCEMIA)
    - Glyburide (DiaBeta, Micronase, Glynase) very short acting/potent therefore not used, Glipizide (Glucotrol, Glucotrol-XL), Glimepiride (Amaryl)
    - Mech: normally when [glucose] increases beta pancreatic cell senses the glucose → increases ATP → inhibits K<sup>+</sup> channel → depolarization → influx of Ca<sup>+</sup> → release of insulin, sulfonylureas directly inhibit K<sup>+</sup> channel → constant release of insulin regardless of [glucose] allowing insulin to overcome resistant tissue
    - Good: cheap, extensive experience
    - Bad: hypoglycemia esp in liver/renal failure b/c that is where they are metabolized/cleared and meals are missed, weight gain, sulfa allergy, effect eventually fails b/c eventually pancreas dies out quicker, questionable increased CV risk b/c cardiac K channels are also affected? and hyperinsulin state
  - Meglitinides (-glinides) 0.5-1%↓HbA1c (rarely used these days) (short acting compared to sulfonylureas, take w/ each meal) (POST-PRANDIAL HYPERGLYCEMIA)
    - Repa-glinide (Prandin), Nate-glinide (Starlix)
    - Mech: same as sulfonylureas but different site, more rapid onset/shorter duration hence must be taken with each meal
    - Good: less hypoglycemia
    - Bad: hypoglycemia, must take before meals hence non-compliant, not as potent as sulfonylureas, weight gain, eventually fails b/c eventually pancreas dies out quicker
- Other
  - Glucosidase Inhibitor (POST-PRANDIAL HYPERGLYCEMIA)
    - Arabinose (Precose), Miglitol (Glyset) 0.5-1%↓HbA1c
    - Mech: inhibits the breakdown of complex sugars into simple absorbable sugars (remember only monosaccharides can be absorbed), take w/ each meal, used for Tx postprandial hyperglycemia
    - Good: safe, weight loss, targets post-prandial glucose
    - Bad: effect depends on diet (the lower carb diet lower the effect), effect is not as great as compared to other drugs, GI SEs (cramping, bloating, flatulence, etc), take w/ meals therefore frequent dosing, expensive
- New
  - Increase Amylin (POST-PRANDIAL HYPERGLYCEMIA)
    - Pramlintide (Symlin)
    - Mech: amylin is a pancreas derived hormone that decreases glucagon, decreases appetite, delay gastric emptying
    - Good: few SEs except for N/V, weight loss
    - Bad: only used in pts already on insulin hence mainly in Type I, SC shot before each meal
    - NB decrease insulin by 50% when starting
  - Increase Incretin (POST-PRANDIAL HYPERGLYCEMIA)
    - Mech: incretin aka glucagon-like-peptide-1 (GLP-1) is a gut derived hormone that decreases glucagon, increases insulin, slows gastric emptying, decreases appetite, stimulates beta-cell growth, etc in response to meal
    - Exanatide (Byetta), Liraglutide (Victoza) Mech: incretin analogue 0.5-1%↓HbA1c

- Good: few SEs except N and rare pancreatitis, weight loss
    - Bad: SC shot 30-60min before each meal
    - NB obtained from the Gila Monster saliva b/c it eats once a year and yet maintains normal glucose all year round
  - Sitagliptin (Januvia) Saxagliptin (Onglyza) Mech: inhibit dipeptidyl peptidase-4 (DPP-4) which slows the inactivation of natural incretins 0.5-1%↓HbA1c
    - Good: few SEs except for HA/URI and rare urticaria/angioedema, PO Qd
    - Bad: takes 1-2mo to take effect
- Acute Complications
  - Hypoglycemia
    - Etiology
      - Reactive/Post-Prandial (Dx: give a meal, check CBG before and Q60min x5hrs or when symptomatic)
        - Acquired: occurs after gastrectomy w/ loss of normal stomach reservoir, food is dumped into SI resulting in brisk release of incretins, hypoglycemia occurs 30-60min after meals, Tx w/ multiple small feedings and avoiding large carb meals
        - Genetic: hereditary fructose intolerance, fructose intolerance, galactosuria, etc
      - Non-Reactive/Fasting (Dx: check urine/plasma sulfonylurea and anti-insulin Ab, 72hr fast under medical observation which is discontinued when glu <45 followed by labs of glucose/insulin/pro-insulin/C-peptide/cortisol Q3-6hrs, if the pt becomes symptomatic then check labs and give glucose and stop test, normally after you fast insulin levels drop as there is hypoglycemia)
        - High Insulin
          - Surreptitious Insulin (high insulin, low pro-insulin, low c-peptide, +anti-insulin Ab)
          - Increased Insulin Production (insulinoma, nesidioblastoma, islet cell hyperplasia)
          - Insulin Stimulating Auto-Antibodies (seen in other autoimmune endocrine states)
          - RF (decreased insulin clearance)
        - High Secretagogue
          - Surreptitious Insulin Secretagogues (high insulin, high pro-insulin, high c-peptide, positive urine/plasma levels)
        - Decreased Glucose Supply
          - Decreased Glucose Intake: Starvation, just missed meals, alcoholism
          - Decreased Glucose Stores: any fast growing tumor that consumes glucose, liver failure, systemic illness, Addison's, GH deficiency, hypoTH, pediatric diseases (glycogen storage diseases, hereditary fructose intolerance, etc)
      - S/S: (1) Glu<60 = rise in counter-regulatory hormones esp epi resulting hypersympathetic state = sweating, palpitations, HTN, anxiety, tremor (2) Glu<40 = unlike other tissues the brain can only use glucose not FFA resulting in neuroglycopenic state = irritable, behavioral changes, weakness, drowsiness, H, confusion, convulsions, coma, death
        - NB for some diabetic pts they live at a glucose of 200s therefore even when they drop into the "normal" range they can develop S/S
        - NB some pts have "hypoglycemic unawareness" esp when they take BB
        - NB CBGs are inaccurate when <60mg/dL hence do a blood draw
        - NB "Whipple's Triad": (1) glucose <50 (2) hypoglycemic symptoms and (3) improvement of symptoms with glucose administration
    - Tx
      - PO: sugar containing foods (4oz OK or 3 graham cracker squares = 15g of carbs = increase CBG bu 25-50)
      - IV: 1amp D50 IV bolus followed by D5W IV gtt
      - IM: 1mg glucagon IM
      - NB determine cause
      - NB give thiamine if pt is alcoholic in order to prevent Wernicke's encephalopathy
  - Hyperglycemia
    - **HyperOsmolar Non-ketotic Coma (HONC) aka Hyperglycemic Hyperosmolar Syndrome (HHS)**
      - Pt: elderly T2DM
      - Mech: Volume deficits much higher in HONC (8-10L down) than DKA (4-6L down) (fluids more important than insulin)
      - Dx: Glu >600, SOsm >320, -serum or urine ketones, nl AG, nl HCO<sub>3</sub>, nl pH
      - S/S: AMS
      - Causes: same
      - Tx: first give NS (NB even NS is hypotonic) then Regular Insulin (never the opposite b/c movement of glucose into cells may reduce intravascular volume so much that pt goes into shock) w/ 0.1U/kg IV bolus then 5-10U/hr IV gtt (non-DKA protocol exists)

- Complications: coma
- NB many times pts can have both HONC/DKA
- **Diabetic Keto-Acidosis (DKA)**
  - Pt: young T1DM
  - Mech: Why ketoacidosis in Type 1 but not in Type 2? b/c in type 2 enough insulin is made to prevent lipolysis, FFA oxidation, and thus ketone production therefore as insulin drops ketones/glucose increase, in T1DM K>G vs T2DM G>K such that T1DM manifest w/ DKA b/f HONC while T2DM do the opposite (insulin more important than fluids) The lack of insulin leads to no liver glucose uptake followed by unrestrained hepatic glucose production and lipolysis leading to increase in FFA which are converted into ketoacids
  - Dx: Glu >250, SOsm 280-320, +serum or urine ketones, AG >12, HCO<sub>3</sub> > 18, pH <7.3, Serum Beta-Hydroxybutyrate and Urine Aceto-Acetate (read as a dilution like 1:16 which is pretty strong), Amylase/Lipase (DKA causes pancreatitis and pancreatitis causes DKA – refer), Corrected Na (add 2.4 Na for every 100 Glu), Phos (hypoPO<sub>4</sub> 2/2 ?), K (below), CXR, Cx, Large MCV (when RBCs filled w/ glucose are mixed w/ isotonic fluid water enters RBCs and are read as a large MCV) K: hyperglycemia causes an osmotic diuresis which pulls K into urine (hypoK) + pts vomit in DKA therefore there is a GI loss of K (hypoK) + increase in SOsm shifts K out of cells (hyperK) = therefore K can appear normal/high but actually be totally body low therefore initially stabilize membranes and don't give K but after a few hours the K will drop and that is when you will give K as below (NB shift K out of cells b/c of acidosis is a myth b/c only non-organic acids shift K not organic acids)
  - S/S: dry, Kussmauls, anorexia w/ weight loss, N/V/ab pain/absent BS, fruity odor, AMS,AGMA, s/s of hyperglycemia/dehydration/ketosis
  - Causes: Insulin deficiency (new onset or insulin noncompliance, pancreatitis, etc), Infection, Inflammation, Ischemia, Intoxications (esp alcohol and illicit drugs), Iatrogenic (glucocorticoids, etc), Intrauterine pregnancy, etc (in general pt does not take into account the increase need for insulin during stressed states)
  - Tx: ICU if sick vs 2J/15R/7R if not-sick, treat underlying cause, initially give bolus w/ NS 1L IV bolus x1 b/c likely dry and Regular Insulin 10U IV bolus x1, Start the following fluids below and then measure Glu Q1hr and adjust rates as shown below, follow BMP specifically Na, K, AG Q4°, after gap closes which usually takes 12hrs add SC NPH overlapping IV Reg Insulin for 2hrs (amount of NPH is based on how much IV insulin they got since admit... calculate how much they would need for a 24hr period then take 2/3 of that and then split into two with NPH), transfer to floor when gap is still closed once insulin gtt d/c and tolerating PO, give Phos when Phos <1, give Bicarb when pH <7.0 and HCO<sub>3</sub> <5 but in general avoid if possible (change NS w/20mEqKCl to 1/2NS w/1ampNaHCO<sub>3</sub> and 20mEqKCl)
  - Complications: cerebral edema, ACS/CVA, ARDS, DVT-PE, arrhythmias

| Raskin Protocol |                            |             |                       |
|-----------------|----------------------------|-------------|-----------------------|
| DFS (mg/dL)     | 1URegInsulin /ccNS (cc/hr) | D5W (cc/hr) | NSw/20mEq KCl (cc/hr) |
| <70             | 0.5                        | 250         | 0                     |
| 70-100          | 1.0                        | 225         | 0                     |
| 101-150         | 2.0                        | 200         | 0                     |
| 151-200         | 3.0                        | 175         | 0                     |
| 201-250         | 4.0                        | 150         | 0                     |
| 251-300         | 6.0                        | 100         | 100                   |
| 301-350         | 8.0                        | 50          | 150                   |
| 351-400         | 10.0                       | 0           | 175                   |
| 401-450         | 12.0                       | 0           | 200                   |
| 451-500         | 15.0                       | 0           | 225                   |
| >501            | 20.0                       | 0           | 250                   |

- Chronic Complications
  - Mechanism
    - **Advanced Glycosylated End Products (AGEs)** Hyperglycemia somehow results in conversion of glucose into glucose-derived dicarbonyl precursors which in turn bind proteins forming these AGEs. Extra-Cellular Matrix AGEs (w/ collagen, laminin, etc) cross-link with each other resulting in abnormal matrix that is resistant to proteolysis and that traps plasma and interstitial proteins (i.e. cholesterol = atherogenesis, albumin = thickened glomerular BM) Extra-Cellular Plasma AGEs can bind receptors resulting in generation of ROSS, cytokines, GFs, pro-inflammatories
    - **Activation of Protein Kinase C:** Hyperglycemia somehow stimulates PK-C in various cells which in turn results in increased vascular endothelial GF, vasoconstrictors, profibrogenic molecules, procoagulants, pro-inflammatory cytokines, etc, NB inhibitors are being developed
    - **Polyol Synthesis:** In tissues that do not need insulin for glucose uptake it is found that the high glucose that invariably builds up *inside* the cells of these tissues because of the hyperglycemia is uniquely metabolized by Aldose Reductase [Glucose → Sorbitol (a polyol)], in this conversion NADPH is used therefore less NADPH is

available for glutathione production and thus cell is susceptible to oxidative stress furthermore b/c sorbitol cannot cross membrane it exerts osmotic gradient

○ Diseases

▪ Hyperinsulinemia

- **Decreased Immune Function**
- **OSA**
- **DVT**
- **OP**
- **Dementia/Depression**
- **Colon/Endometrial Cancer**
- **Cataracts/Glaucoma**
- **Acanthosis Nigricans, Necrobiosis Lipoidica Diabeticorum, Lipodystrophy, Calciphylaxis**
- ***Candida albicans* thrush/vaginitis, *Psuedomonas* otitis externa, *Mucormycoses* of the face, *Rhizopus* of the skin/lungs, Anaerobes (thrive b/c of poor blood supply), Emphysematous Cholangitis**

- **MAcrovascular Disease** (2/2 atherosclerosis but unlike other causes it occurs at an earlier age and to a greater degree, 3x increased risk, more closely related to lipids/BP w/ less effect from glucose effect suggesting that hyperinsulinemia could be the culprit resulting in endothelial-dysfxn/hypercoagulability/vasculitis, DM is a cardiac equivalent meaning it is the same as having a prior vascular event, seen mainly In T2DM)

- **CNS – Cerebral/Carotid (CVA)**
- **Heart – Coronary** (earlier age, more severe, silent/atypical ACS)
- **Peripheral Vasculature – Aorta/Leg Arteries** (gangrene)

- **MIcrovascular Disease** (really no other disease can cause these specific problems, more closely related to degree of hyperglycemia w/ less effect from lipids/BP, seen mainly in T1DM)

- **Kidney – Nephrotic Syndrome** (refer, 30-40% of T1/2DM, beginning screening >5yrs after T1 Dx and at time of Dx for T2)
- **Eye – Retinopathy** (leading cause of blindness in adults, uniquely much more common in T1 than T2, seen in 90% of T1 pts after 15yrs of Dx, Tx: laser photocoagulation) NB retinopathy ALWAYS precedes nephropathy!!!

- Background/Non-Proliferative Retinopathy (no vision changes): **Microaneurysms** (small, round red dots) that then leak (1) lipoprotein forming **Hard Exudates** (irregular in shape and size, but sharply defined yellow markings) and (2) fluid forming **Macular Edema** (?)
- Preproliferative Retinopathy (some vision changes): hard exudates and macular edema compress vessels leading to retinal ischemia/infarcts forming **Soft Exudates aka Cotton-Wool Spots** (whitish/gray areas)
- Proliferative Retinopathy (dramatic vision changes): **Neovascularization** (abnormal vessels) w/ surrounding **Fibrous Tissue** which can contract and cause **Retinal Detachment / Vitreous Hemorrhage**

- **PNS – Chronic Distal Symmetric Peripheral Ascending “Stocking/Glove” Polyneuropathy** (most frequent complication, 2/2 nerve infarction, worse at night, leading cause of impairment of diabetes, Tx: refer)

- Sensory: numbness/hypersensitivity and paraesthesia/dysesthesia
- Motor: absent knee and ankle reflex, Radial N. w/ wrist drop, Common Peroneal N. w/ foot drop, CN3/4/6 w/ diplopia, L2/3/4 N w/ amyotrophy (weakness/pain/atrophy of pelvic girdle and anterior thigh muscle, spontaneously abates after 6-12mo)
- Autonomic: impotence, orthostatic hypotension, alternating C>D, gastroparesis with chronic N and V which causes unpredictable glucose absorption, neurogenic bladder with alternating retention/incontinence, loss of cardiac response to physiologic stimuli like standing, valsava, etc

- **“The Diabetic Foot”** (2/2 combination of macro/microvascular disease, pt cannot feel trauma and when trauma occurs (esp at areas of increased pressure like metatarsal heads and calluses) there is impaired healing which subsequently leads ulceration and subsequent skin then soft-tissue then bone infection, Tx: abx, debridement/surgery, revascularization)