Managing Diabetes: An Art and a Science

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2018 Diabetes Summit
Disclosures

- No relevant conflict of interest to report
Upon completion of this program the participant will be able to:

- Apply guidelines for management of diabetic patients’ medications
- Discuss approaches for insulin titration in diabetic patients
- Utilize correction factors for insulin medication management
- Discuss carbohydrate counting in regards to diabetic medication management
Guiding Principles of Selecting Therapy

- Tailor to individual patient preferences (including cost), prognoses and comorbidities
  - type of diabetes
  - age
  - eating patterns
  - weight
  - physical activity habits
  - oral vs injectable
  - etc
Abbreviations

- Dipeptyl peptidase-4 inhibitors (DPP-4i)
- CrCl: Creatinine Clearance
- eGFR: estimated glomerular filtration rate
- GI: Gastrointestinal
- Glucagon Like Peptide-1 agonists (GLP-1a)
- MOA: Mechanism of Action
- MI: Myocardial Infarction
- ROA: Route of Administration
- SCr: Serum Creatinine
- SU: Sulfonylurea
- TZD: Thiazolidinediones
Egregious Eleven
AACE/ACE guidelines

- [https://www.aace.com/publications/algorithm](https://www.aace.com/publications/algorithm)
Metformin

- The Gold Standard
  - preferred initial pharmacological agent for type 2 diabetes
    - if not contraindicated and if tolerated

- Given Orally

- MOA
  - Decreases hepatic glucose production
  - Improves insulin by increasing peripheral glucose uptake and utilization

- Decreases both post-prandial and FPG level
- Insulin secretion does not change = no hypoglycemia
Metformin

- **DOSING**
  - Clinical efficacy generally not seen with doses <1500mg/day (monotherapy)
  - Titrate dose up (GI side effects)
    - Start at a low dose, titrate slowly, take with food
    - Generally start at 500mg/day or 500mg BID then increase by 500mg per week if tolerated until 2000mg/day
    - Max dose 2500mg/day
      - Not much benefit after >2000mg/day
      - Most benefit = 1500-2000mg per day
Metformin

- **BLACK BOX WARNING**
  - **Lactic Acidosis**
    - Rare, but serious that can occur due to metformin accumulation during treatment
    - The risk of lactic acidosis increases with the degree of renal dysfunction and the patients age
    - Risk can be greatly decreased with regular monitoring of renal function and by the use of minimum effective dose
Metformin

- **Contraindications**
  - Renal disease/dysfunction
    - Excretion through the kidneys
  - CHF requiring pharmacologic treatment
    - In patients with stable CHF, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with CHF
  - Known hypersensitivity to metformin HCl
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma
# Metformin

<table>
<thead>
<tr>
<th>eGFR Level (mL/min per 1.73 m²)</th>
<th>Action</th>
</tr>
</thead>
</table>
| ≥ 60                           | No renal contraindication to Metformin  
Monitor renal function annually |
| 45 – 59                        | Continue use  
Increase monitoring of renal function every 3-6 months |
| 30 – 44                        | Prescribe Metformin with caution  
Use lower dose 50% or half of maximum dose  
Closely monitor renal function every 3 months  
Do not start new patients on Metformin |
| < 30                           | Stop Metformin |

Case

- AW is a 57 year old female newly diagnosed with diabetes. A1c = 8.2%. SCr 0.7 mg/dL and eGFR >60ml/min.
- What is the best therapy option based on the information given?
  - A Sitagliptin
  - B Metformin
  - C Canagliflozin
  - D Rosiglitazone
Sulfonylureas (SU)

- **Oral medications**
  - Glyburide (Diabeta®, Micronase®)
  - Micronized Glyburide (Glynase®; Prestab®)
  - Glipizide (Glucotrol®, Glucotrol XL®)
  - Glimepiride (Amaryl®)

- MOA for all SU: Stimulate insulin secretion from the beta cells of the pancreas
Sulfonylureas (SU)

- Contraindications
  - Renal insufficiency
  - Hepatic insufficiency
  - Type 1 Diabetes
  - Sulfonamide Allergy
  - Major Surgery
  - Severe infections/stress/trauma
  - Lactation

- High Risk Patients
  - Elderly (>60 years) whose diet is marginal, Binge drinkers, impaired hepatic or renal function
Case

- DP is an 88 year old female on metformin. Her provider wants to start a sulfonylurea.
- Which FU would be the best choice for DP?
  - A  Glyburide
  - B  Glipizide IR
  - C  Glipizide ER
  - D  Glimepiride
Thiazolidinediones (TZD)

- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)

**MOA:**
- Improves insulin sensitivity in muscle and fat tissue
- Decreases hepatic glucose output (gluconeogenesis)

**ROA:** Oral
Thiazolidinediones (TZD)

- In patients with symptomatic heart failure, thiazolidinedione treatment should not be used
  - Fluid retention leads to or can exacerbate heart failure
  - Treatment with both agents is not recommended in patients with NYHA (New York Heart Association) Class III or IV cardiac status (CHF)
Thiazolidinediones (TZD)

- Precaution
  - Hepatotoxicity
    - Avoid treatment with these agents if transaminases are >2.5x the ULN (Upper limit of normal) at baseline or the patient exhibits signs and symptoms of active liver disease
    - Monitor liver function prior to initiation of therapy, then every 2 months for the first year, and periodically thereafter
Thiazolidinediones (TZD)

- Pearls
  - Slow onset of action – may take up to 2 to 3 months to see full effect
Incretins

- In the body
  - Glucagon Like Peptide-1 (GLP-1)
    - Produced by GI tract when food stimulates insulin
  - Dipeptyl peptidase-4 (DPP-IV)
    - Metabolizes GLP-1

- Drugs related to natural GLP-1 and DPP-IV
  - Glucagon Like Peptide-1 agonists (GLP-1a)
  - Dipeptyl peptidase-4 inhibitors (DPP-4i)
Glucagon Like Peptide-1 agonists

- **ROA:** Subcutaneous injection

- **MOA:**
  - Promotes satiety, reduces appetite
  - Decreases postprandial glucagon secretion
  - Decreased glucagon reduces hepatic glucose output
  - Slows gastric emptying in the stomach
  - Enhances glucose-dependent insulin secretion
  - Resistant to DPP-IV degradation
Glucagon Like Peptide-1 agonists

- Caution
  - Pancreatitis
  - Renal function: in general no dose adjustments
  - Use with rapid insulin
  - Consider decreasing dose of sulfonylurea or basal insulin when used in combination with GLP-1 agonists

- BLACK BOX WARNING
  - Thyroid Cancer
Glucagon Like Peptide-1 agonists

- Products
  - Exenatide
    - Byetta (twice daily, renal dosing)
      - Administer within 60 minutes before morning and evening meals (do not give after meal)
    - Bydureon (once weekly)
  - Liraglutide
    - Victoza (once daily) - Cardiovascular benefit
      - Dose titration important
  - Semaglutide
    - Ozempic (once weekly)
      - Dose titration important
  - Dulaglutide
    - Trulicty (once weekly)
  - Albiglutide - May/June 2018 will no longer be available
    - Tanzeum (once weekly)
  - Lixisenatide
    - Adlyxin (daily)
      - Administer once daily within one hour before the first meal of the day
Case

- A provider decides to put a patient on a GLP-1 agonist. The patient wants a once a week medication.
- Which one of the following GLP-1 agonists is only once a week?
  - A  Exenatide/Byetta
  - B  Exenatide/Bydureon
  - C  Liraglutide/Victoza
  - D  More than one of the above
Dipeptyl peptidase-4 inhibitors

- **MOA:** Inhibit breakdown/metabolism of GLP-1
- **ROA:** Oral administration
- **Administer with or without food**
- **Weight neutral**
- **CAUTION:** Renal dosing
Dipeptyl peptidase-4 inhibitors

- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)
- Linagliptin (Tradjenta®)
- Alogliptin (Nesina®)
Case

- Remember AW from our first case? We decided to put her on metformin.
- Five years later AW is still on the metformin.
- She now needs additional therapy.
- She is scared of injections and terrified of hypoglycemia.
- Please pick the best therapy option based on the information given
  - A Alogliptin
  - B Glyburide
  - C Exenatide
  - D Insulin
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors

- MOA: Lowers renal threshold of glucose
  - insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2

- ROA: Oral
- Caution: Renal Dosing

- Products
  - Canagliflozin (Invokana®)
  - Dapagliflozin (Farxiga®)
  - Empagliflozin (Jardiance®) - - Cardiovascular benefit
  - Ertugliflozin (Steglatro®)
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors

- Adverse Drug Effects
  - Urinary Tract Infections
  - Yeast infections
  - Hypovolemia/Decreased blood pressure
  - Hyperkalemia
  - Increased LDL cholesterol
  - Hypoglycemia with Empagliflozin
  - FDA Safety Announcement: may lead to ketoacidosis (05-15-2015)
Case

- UG is a 69 year old male who is on metformin 2000mg XR once daily by mouth and dulaglutide. His BP is 110/72. SCr ~1. His provider thinks UG needs another agent added to therapy.

- Given the following options, which would be the best choice for UG?
  - A Sitagliptin
  - B Exenatide
  - C Dapagliflozin
  - D Glipizide
Case

- LL is a patient with a high copay for brand name medications. He is already on metformin 850mg three times daily.
- Which of the following classes would be the cheapest option for LL?
  - A SGLT-2 inhibitor
  - B DPP4 inhibitor
  - C Sulfonylurea
  - D GLP-1 agonist
Insulin

- MOA: exogenous source of insulin

- ROA: Insulin is destroyed by stomach acid so it cannot be taken orally.
  - Subcutaneous Injection, Inhalation, intravenous (special situations)
    - Sites for injection: Abdomen, arms, thighs, buttocks
      - rotate within one area systematically
      - do not mix with GLP-1 agonists or inject in same spot

- Goal of insulin therapy: achieve tight control while avoiding hypoglycemia

- Side effects: weight gain, hypoglycemia

- Fear of needles
Insulin

Long Acting (Basal) Insulin

- Insulin glargine (Lantus 100 units/mL) (Toujeo 300 units/mL) (Basaglar 100 units/ml)
  - pH ~4
  - may cause more pain at injection site
  - Per package insert “higher doses of Toujeo were required to achieve similar levels of glucose control compared to Lantus in clinical trials”
  - Pregnancy Category C
- Insulin detemir (Levemir 100 units/mL)
  - pH ~7.4
  - Pregnancy Category B
- Insulin degludec (Tresiba 100 units/mL or 200 units/mL)
  - pH ~7.4
  - Pregnancy Category C
  - Less nocturnal hypoglycemia in studies
Long Acting (Basal) Insulin

- Do not mix or dilute with any other insulin or solution
- Insulin degludec
  - Once daily dosing
- Insulins glargine and detemir
  - Once (Or twice) daily dosing
Intermediate acting insulin

- Humulin N
- Novolin N

- Humulin N: May be mixed with regular or insulin lispro before injection. Regular or insulin lispro should be drawn into the syringe first, with injection occurring immediately after mixing.
- Novolin N may be mixed with regular insulin in the same syringe.
Short Acting Insulin

- Humulin R
- Novolin R

- Give 30-60 minutes before a meal
- May be mixed with longer-acting insulin (excluding regular insulin[concentrated]); regular insulin must be drawn into the syringe first.

- Generally 100 units/ml
Short Acting Insulin

- Humulin R available as a prefilled pen device or vial containing U-500 strength insulin (500 units/mL) for patients who require more than 200 units per day
  - The safety and efficacy of Humulin R U-500 used in combination with other insulins has not been determined.
  - Dosing errors have occurred when Humulin R U-500 was administered with syringes other than a U-500 insulin syringe. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The dose of Humulin R U-500 should always be expressed in units of insulin.
Rapid Acting Insulin

- When compared with regular insulin, rapid acting insulin has a more rapid onset and shorter duration of activity
- Used to control post-prandial sugars
- Should be administered within 15 minutes before or immediately after a meal
- 100 units/mL

- Insulin aspart (Novolog)
  - Pregnancy Category B
  - Also available as Ultra Rapid Acting (Fiasp)
- Insulin lispro (Humalog)
  - Pregnancy Category B
  - Also available 200 units/ml
- Insulin glulisine (Apidra)
  - Pregnancy Category C
Combination Products

- Insulin Mixes
  - Insulin 70/30 (70% NPH 30% Regular)
  - Mixtard 70/30, Novalin 70/30, Humulin 70/30
  - Humulin 50/50 (50% NPH 50% Regular)
  - Humalog 75/25 (75% insulin lispro protamine and 25% insulin lispro)
  - NovologMix 70/30 (70% insulin aspart protamine and 30% insulin aspart)
  - Twice daily dosing generally

- GLP-1/basal insulin
  - Soliqua 100/33: combination of insulin glargine and lixisenatide injection
  - Xultrophy 100/3.6: combination of insulin degludec and liraglutide
GLP-1/basal insulin combination

- **Soliqua 100/33**: combination of insulin glargine and lixisenatide injection
  - In patients inadequately controlled on less than 30 units of basal insulin or on lixisenatide, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily.
  - In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily
  - *Inject once a day within the hour prior to the first meal of the day*
  - *Max dose 60 units per day*

- **Xultrophy 100/3.6**: combination of insulin degludec and liraglutide
  - Recommended starting dosage is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily
  - *Administer once daily at same time each day with or without food*
  - *Max dose 50 units per day*
## Summary Table

<table>
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<tr>
<th>Antihyperglycemic Therapy</th>
<th>Metformin</th>
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<th>TZDs</th>
<th>DPP4-i</th>
<th>SGLT2-i</th>
<th>GLP-1</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
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<td>HIGH</td>
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<td>Neutral</td>
<td>Loss</td>
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<td>Gain</td>
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<td>Adverse effects</td>
<td>GI</td>
<td>Hypoglycemia</td>
<td>Edema</td>
<td>Rare</td>
<td>Genital urinary infections, dehydration</td>
<td>GI</td>
<td>Hypoglycemia</td>
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<td>Costs</td>
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<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Efficacy (A1c lowering)</td>
<td>High (1-1.5%)</td>
<td>High (1-1.5%)</td>
<td>High (1-1.5%)</td>
<td>Intermediate (0.5-1%)</td>
<td>Intermediate (0.5-1%)</td>
<td>High (0.8-1.8%)</td>
<td>Highest (1.5-3.5%)</td>
</tr>
</tbody>
</table>
Case

- OP is a 49 year old male newly diagnosed with diabetes. A1c 12.4%, SCr 0.8. He only wants to be on one medication.
- Which ONE medication would be best for OP
  - A  Sitagliptin
  - B  Metformin
  - C  Dapagliflozin
  - D  Insulin
Insulin

- There are different regimens used for dosing insulin in those who use basal/bolus insulin:
  - Fixed dose (with or without correction scale)
  - Sliding Scale
  - Matching insulin to carbohydrate
- Follow up for titration can include
  - Self titration by patient
  - Diabetic educators
  - Pharmacists
  - RNs
  - Others
- Methods
  - Self-titration
  - Phone
  - Office visit
  - Electronic messaging
Dosing insulin: Fixed dose insulin

- Set amount of insulin is given at each meal (can be the same for each meal or vary)
- Very rigid regimen
  - Based on the assumption that all meals eaten will contain the same amount of carbohydrates
- Good for those who eat the same type and quantity of food on a day-to-day basis or need an easy to use method
Starting Insulin

- Start with bedtime intermediate acting insulin OR bedtime or morning long acting insulin
  - Start with 10 units (non weight based dosing)
  - ~0.2 units/kg (weight based dosing)
Meal time insulin

- If patient’s basal insulin has been optimized but further control is still needed
- Start one injection of meal time insulin to either breakfast or main meal of the day
  - Can use TDD (see below) or start at 2-6 units and titrate up based on blood sugars
- Or if you want to start both basal and bolus at once:
- If patient needs to be on basal and prandial then use 0.3-0.5 units/kilogram for an estimate. (Note: some sources will also say 0.2-0.4 units/kg) (50% long acting 50% prandial) (The 50% of prandial would be split between the number of doses per day. For example if the patient’s insulin requirement was 60 units, 30 units would be for prandial divided into 3 meals would be 10 units with breakfast, 10 units with lunch, 10 units with supper
  - Keep in mind, patient may not need prandial insulin with every meal depending on blood sugars
Adjusting insulin

- Look for patterns
  - Running high or low
  - Reasons for high or low values out of the ordinary
  - Adherence
  - Look at average and range
- Can titrate every ~3 days until glycemic goal is reached
- Example:
  - FBG average >180 mg/dL: Add 4 units basal
  - FBG average 140-180 mg/dL: Add 2 units basal
  - FBG average 110-139 mg/dL: Add 1 unit basal
  - If Blood glucose <70 mg/dL: reduce total dose by 10-20%
  - If Blood glucose <40 mg/dL: reduce total dose by 20-40%
  - If post prandial not <140-<180: increase prandial insulin by ~ 10%
- Self titration – many examples
  - 1 unit per day until fastings <130 mg/dL
Dosing insulin: matching insulin to carbohydrates

- Insulin is based on two factors: amount of carbohydrates eaten and the difference between actual blood glucose and target blood glucose
  - Insulin to carbohydrate ratio: indicates how many carbohydrates 1 unit of insulin will cover
  - Correction factor: indicates the glucose lowering power of 1 unit of insulin
- EX: if an individual had an insulin to carb ratio of 15 and a correction factor of 50, it would mean that they would take 1 unit of insulin for every 15 grams of carbohydrates eaten and 1 unit of insulin would lower their blood glucose by 50
- More flexible than other methods as it allows for differences in carbohydrate intake and pre-meal glucose levels
- More involved than other methods and only for those willing to put in the extra time
Dosing insulin: sliding scale

- Varies the dose of insulin based on the blood glucose level
  - The higher the blood glucose, the higher the insulin dose
- Must monitor blood sugars before meals to get an accurate reading
- Works well for those who want more control over blood glucose and willing to do the extra monitoring
Sliding Scale Pros/Cons

**Pros**
- Fewer calculations for patients than CHO counting
- Fairly convenient for patients

**Cons**
- Does not prevent hyperglycemia
- More frequent glucose checks & nursing time for those in SNF/LTC
- Cannot be personalized
  - Does not take into effect the diet, weight or insulin history
Sliding Scale Examples

- **Very low schedule** *(Insulin-sensitive)*
  - BG 150-199: 0.5 unit *Bolus Insulin* (regular or rapid-acting)
  - BG 200-249: 1 unit *Bolus Insulin*
  - BG 250-299: 1.5 units *Bolus Insulin*
  - BG 300-349: 2 units *Bolus Insulin*
  - BG Over 350: 2.5 units *Bolus Insulin*

- **Low schedule**
  - BG 150-199: 1 unit *Bolus Insulin* (regular or rapid-acting)
  - BG 200-249: 2 units *Bolus Insulin*
  - BG 250-299: 3 units *Bolus Insulin*
  - BG 300-349: 4 units *Bolus Insulin*
  - BG Over 350: 5 units *Bolus Insulin*

- **Medium schedule**
  - BG 150-199: 1 unit *Bolus Insulin* (regular or rapid-acting)
  - BG 200-249: 3 units *Bolus Insulin*
  - BG 250-299: 5 units *Bolus Insulin*
  - BG 300-349: 7 units *Bolus Insulin*
  - BG Over 350: 8 units *Bolus Insulin*

- **High schedule** *(Insulin-resistant)*
  - BG 150-199: 2 unit *Bolus Insulin* (regular or rapid-acting)
  - BG 200-249: 4 units *Bolus Insulin*
  - BG 250-299: 7 units *Bolus Insulin*
  - BG 300-349: 10 units *Bolus Insulin*
  - BG Over 350: 12 units *Bolus Insulin*
Sliding Scale

- Not continually recommended
  - ADA, CMS and AMDA all say not to use
  - ADA: avoid the sole use of SSI, it was recently added to the Beers Criteria for potentially inappropriate medication use in older adults.
  - Leads to wide glucose excursions and is a burden for patients
Correction Factor Insulin

- **Correction factor**: the mg/dL drop in blood glucose caused by 1 unit of insulin
- Used to make insulin adjustments to keep blood glucose levels within target
- Useful when:
  - More insulin is needed at a mealtime to correct for a high glucose level
  - Correct a high blood glucose level outside of a meal time
- In either case, patient will need to know how many mg/dL one unit of insulin lowers their blood glucose level
Calculating Correction Factor

1. Calculate total amount of insulin per day (basal + bolus)
   Ex.) Basal= 15 units, Bolus= 5 units of Novolog three times/day= 15 units
   Total Daily Insulin= 15 + 15= 30 units

2. Divide 1800 by Total Daily Insulin if using RAPID-acting insulin = Correction factor
   Divide 1500 by Total Daily Insulin if using REGULAR insulin = Correction factor

   1800/30 = 60

   Correction Factor= 60

   This means that 1 unit of insulin will lower blood glucose by approximately 60 mg/dL
Using Correction Factor to Calculate Correction DOSE

- Correction bolus formula:
  - \((\text{Current BG} - \text{Target BG}) / (\text{Correction Factor})\)

Ex: Current BG = 220 mg/dL
   Target BG = 100 mg/dL
   Correction factor = 60

- \((220 - 100) / (60) = 120 / 60 = 2\)

- Correction dose = 2 units of insulin
- A correction dose of insulin would be added to the normal dose that would be taken with a meal
  - This ensures that the patient will reach his or her glycemic target after a meal
Take Home Points

- Personalize diabetes medications and goals based on patient factors
- There are many approaches to adjusting insulin. One person may be more conservative, one more aggressive
  - Protocols to follow in many cases
  - We develop our own “style”
- The best medication is the one that the patient will take correctly
- Always encourage lifestyle changes
- If a patient is not at goal, look to increase dose or add on another medication
References

- Diabetes Care 2018
- ACE/AACE 2017 guidelines
- Facts and Comparisons
- Micromedex
- Other references as on slides
THANK YOU!!

- Any questions??

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