Diabetes

Let’s Work through it!

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Disclosures

I have no relevant relationships with ineligible companies to disclose within the past 24 months.

Educational Objectives

- Demonstrate treatment selection for a type 1 diabetic
- Demonstrate treatment selection for a type 2 diabetic
- Demonstrate how to select diabetic medications
- Demonstrate how to interpret glucose readings, including the use of continuous glucose monitors


Quick Medication review

Common Oral Meds

Class/Main Action	Name(s)	Daily Dose Range	Considerations
Biguanides • Decreases hepatic output of glucose • 1st Line med	Metformin	500 – 1000 mg qd (usually BID w/ meal)	Side effects: nausea, bloating, **diarrhea** Obtain GFR before starting • If GFR <30; **do not use** • If GFR <45, don't start Metformin • If pt on Metformin and GFR falls to 30-45, eval risk vs benefit; consider decreasing dose Benefits: lowers cholesterol, no hypo or weight gain, cheap Lowers A1C 1.0% - 2.0%
Sulfonylureas • Stimulates sustained insulin release	Glyburide Glipizide Glimepiride	1.25 – 20 mg 2.5 – 40mg 1.0 – 8 mg	Side effects: **hypoglycemia and weight gain**. Eliminated via kidney Can take once or twice daily before meals (EASY) **Low cost** generic Caution: Glyburide (most likely to cause hypoglycemia. Lowers A1C 1.0 – 2.0%

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Class/Main Action	Name(s)	Daily Dose Range	Considerations
SGLT2 Inhibitors • Decreases glucose reabsorption in kidneys	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	100 – 300 mg 1x qd 5 – 10 mg 1 qd 10 - 25 mg 1 x qd 5 – 15 mg 1x qd	Side effects: hypotension, **UTIs, genital infections**, increased urination, weight loss, ketoacidosis **Don't start if A1C is >10: flushes too much gluc** **Heart Failure, CV & Kidney Protection:** 1st LINE Considerations: Limited BG effect if GFR <45, still benefits kidney & heart at lower GFR. For renal protection, use SGLT-2 therapy if GFR >25 & UACR >300. Benefits: Reduce BGs, CV death & HF, slow CKD Lowers A1C 0.6% - 1.5%
DPP-4 Inhibitors • Prolongs action of gut hormones • Increases insulin secretion • Delays gastric emptying	Sitagliptin Linagliptin	25 – 100 mg daily 5mg daily	Side effects: headache and flu-like symptoms Can cause severe, disabling joint pain Benefit: No weight gain or hypoglycemia Lowers A1C 0.6 – 0.8%

Common Oral Meds

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Glucosidase Inhibitors • Delays carb absorption	Acarbose	25 – 100 mg w/meals	Slowly increase dose Side effects: GI effects and Hypoglycemia Caution: Liver and kidney problems Lowers A1C 0.5 – 1.0%
Meglitinides • Stimulates rapid insulin burst	Repaglinide	0.5 – 4mg w/meals	Take before meals Side effects: Hypoglycemia and weight gain Lowers A1C 1.0 – 2.0%

Injectable Meds

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GLP-1 Receptor Agonist • Increases insulin release with food • Slows gastric emptying • Promotes satiety • Suppresses glucagon	Exenatide XR Liraglutide Dulaglutide Semaglutide Semaglutide - oral tablet	2 mg 1 x/week 0.6, 1.2 and 1.8mg qd 0.75, 1.5, 3.0 and 4.5mg 1x/week 0.5, 1.0 and 2.0mg 1x/wk 3, 7, 14 mg daily	Side effects: Nausea, vomiting, weight loss, injection site reactions Risk: **pancreatitis** (severe abdominal pain, vomiting) Black Box Warning: Thyroid c-cell tumor (avoid w/ family hx medullary thyroid cancer) Benefits: Reduces risk of CV death, heart attack, and stroke Lowers A1C 0.5% - 1.6% **Weight loss** of 1.6 to 6.0kg
Dual Incretin Agonist • Same as GLP-1 Rec Agonists	Tirzepatide	2.5, 5.0, 7.5, 10, 12.5 and 15mg 1x/week	Side effects: Nausea, diarrhea, injection site reactions. Risk: pancreatitis Black Box Warning: Thyroid c-cell tumor Caution: Avoid with Fm Hx Medullary thyroid ca Lowers A1C **1.8 – 2.4%** **Weight loss** of ~ 5.4- 10 kg

Insulin

Action		Name(s)	Onset	Peak	Duration	Considerations
Bolus	Very Rapid Acting	Aspart Lispro-aabc	2.5 min 1 min	~ 60 min ~ 60 min	3-5 hrs 4-5 hrs	Bolus insulin lowers after-meal glucose. Post meal BG reflects efficacy. Basal insulin controls BG between meals and nighttime. Fasting BG reflects efficacy. Side effects: Weight gain, hypoglycemia. Dosing: 0.5 – 1.0 units/kg/day total Discard after 28 days. Keep refrigerated.
	Rapid Acting	Aspart Lispro	5-15 min	30-90 min	< 5 hrs	
	Short Acting	Regular insulin	30-60 min	2-4 hrs	5-8 hrs	
Basal	Intermediate	NPH	2-4 hrs	4-10 hrs	10-16 hrs	
	Long Acting	Detemir Glargine Degludec	3-8 hrs 2-4 hrs ~1 hr	No peak	6-24 hrs 20-24 hrs < 42 hrs	
Basal + Bolus	Intermediate + Short	70/30=70% NPH/30% Reg 50/50=50% NPH/50% Reg	30-60 min	Dual peak	10-16 hrs	
	Intermediate + Rapid	Insulin Mix – 70/30 Insuin Mix–75/25, 50/50	5-15 min	Dual peak	24 hrs	

Case #1: Meet Janet

- A 52-year-old female patient with T2DM has received optimal metformin monotherapy for the last 2 years (current dose of 1000 mg BID and tolerates the treatment well
- No episodes of hypoglycemia
- BMI is 28 kg/m^2, which she has worked hard to reduce from 30 kg/m^2 over the last 2 years with diet and exercise

- Recent UTI, which has resolved with antibiotics prescribed from immediate care
- New vaginal itching in which she thinks may be associated with her recent antibiotic use
- No fever, N/V/D or constipation
- Other PMHx:
  - Hypertension - well- controlled on a thiazide plus an angiotensin-converting enzyme inhibitor
  - Hyperlipidemia – controlled on atorvastatin 10 mg daily.
  - Hypothyroidism – controlled on Levothyroxine 75mcg daily.
  - Hx of yeast infections – 2 episodes in the last year.
  - Osteoarthritis – mostly in knees, but mildly in hands
- Patient notes concern about recent A1C level, despite being on medication and states she does not want to be on anything that is going to make it harder to lose weight

Labs

	Result	Normal value
Glucose	189	65-109 mg/dl
Creatinine	0.89	0.5 – 1.4mg/dl
BUN	12	7 - 30 mg/dl
GFR	>90	>90
AST	21	0-40 IU/l
ALT	19	5-40 IU/l
Alk Phosphatase	68	35-125 IU/l
A1C	8.4	4-6%
Urine Microalbumin	28	<30 mg
Lipid panel Total cholesterol HDL LDL TG	 150 40 70 156	 <200 mg/dl >40 mg/dl <100 mg/dl <150 mg/dl

Physical Exam

- General: overweight, NAD
- HEENT: no abnormalities
- Cardio: No edema, No murmur, not tachycardic
- Pulm: Clear to auscultation
- Abdomen: non-tender, normal BS
- Neuro: AAOx3, no focal findings
- Psych: Normal speech, normal thought processing

Current A1C = 8.4%
Goal: A1C <7%

What diabetes medication would be most appropriate for this patient?

- Currently on Metformin 1000mg BID
  - Should she stay on this?
  - Correct dose?
- What other meds should we look at?

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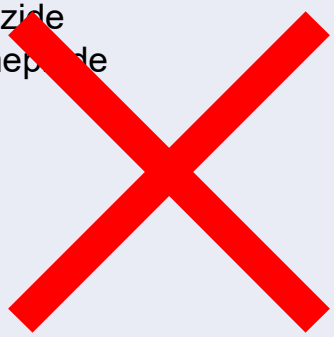
Sulfonylureas • Stimulates sustained insulin release	Glyburide Glipizide Glimepiride 	1.25 – 20 mg 2.5 – 40mg 1.0 – 8 mg	Side effects: **hypoglycemia and weight gain**. Eliminated via kidney Can take once or twice daily before meals (EASY) Low cost generic Caution: Glyburide (most likely to cause hypoglycemia. Lowers A1C 1.0 – 2.0%

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PLAN

- Continue Metformin at max dose (1000mg BID)
- Start GLP-1 Agonist
  - i.e. Dulaglutide, Semaglutide, Tirzepatide
  - Make sure no hx of pancreatitis or family hx medullary thyroid cancer.
  - Titrate up slowly to reduce side effects

- Likely this regimen will reduce A1C enough
- Insulin would be another option to consider if not meeting goal or A1C was much higher and need tighter control

Case #2: Meet Gina

- 59 y.o. female
- Weight 176 lbs (80 kg)
- Kidney Function WNL (GFR >90)
- 8 year history of Type 2 DM
- Current medications:
  - Sitagliptin 100mg daily
  - Metformin 1000mg BID
  - Glargine 50 Units nightly
- A1C 8.4%

Glucose Profile – uses Glucometer

Day	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bedtime
1	86	182	151	220
2	92	145	182	253
3	78	132	176	198
4	81	156	147	190
5	89	147		

What observations can be made looking at these glucose levels?

What is the most appropriate next step?

A. Move existing dose of insulin glargine to the morning

B. Increase insulin glargine to 60 units

C. Add an SGLT-2 inhibitor

D. Add glipizide

What is the most appropriate next step?

A. Move existing dose of insulin glargine to the morning

Long acting, so timing won't make much difference

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Drop fasting glucose even lower -> **HYPOGLYCEMIA**

C. Add an SGLT-2 inhibitor

D. Add glipizide

Increase insulin secretion in the background that have effect on driving down fasting sugars, but no effect on improving post-prandial hyperglycemia

Glucose Profile

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- Problem is post-prandial hyperglycemia
  - particularly after larger meals
- Add an agent that will help with post prandial control
  - SGLT-2 inhibitor
  - Consider switching the DPP-4 inhibitor to a GLP-1 receptor agonist
    - A more potent incretin therapy

Reid T et al. Int J. Clin Pract. 2016 Jan; 70(1): 56-65.; Monnier L et al. Diabetes Care. 2003 Mar; 26(3)881-5.

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- Lower the dose of insulin glargine when starting new medication
- Fasting BG is already at goal, and BG is dropping too much while sleeping
  - What happens if she doesn't eat much dinner and her BG is 130 mg/dL at bedtime?

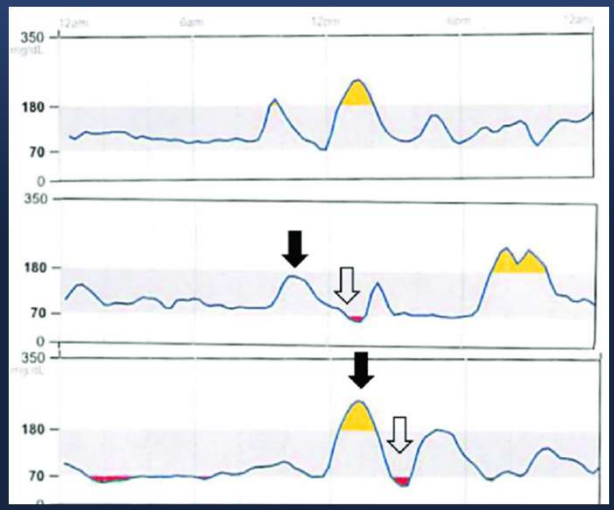
Reid T et al. Int J. Clin Pract. 2016 Jan; 70(1): 56-65.; Monnier L et al. Diabetes Care. 2003 Mar; 26(3)881-5.

Initiate CGM

- Identify unrecognized hypoglycemia
- See all data throughout the day
  - Helps to adjust med dosages

Other benefits:

- Not so many needle sticks
- Patient can see data trends
- Adjust eating patterns or food choices



Glucose Profile

Day	Pre-Breakfast
1	86
2	92
3	78
4	81
5	89

- If you just look at her fasting levels:
  - May think she is doing well
  - Glucose at goal (70 – 90mg/dL)

HOWEVER

Doesn't match A1C of 8.4%

BG must be high at some point

- Add Dapagliflozin 5mg daily and reduce Glargine to 35 units
- Refer to diabetes educator for nutrition recommendations
- Add CGM to learn glucose trends associated with diet

Follow up in 3 months → **A1C 6.9%**

Follow up for Gina 8 years later…

- Now 67 years old
- Last follow up about a year ago
- Health changes: Had MI 3 years ago and underwent CABG
- No other new health issues, but wants to re-establish closer follow up care
- Current Meds: Glargine, Dapagliflozin, Sitagliptin and Metformin (Same as previous)
- A1C is now 9.2%

Recent History

- Stopped using CGM and forgot her meter for the appointment, but states she checks her blood sugar several times a day (not as much as before - conserving supplies).
- Patient recall: Glucose is higher in the morning and lower in the evening
  - Morning glucose ~ 160 – 200
- Dinner glucose level is highest ~220, but dinner is the smallest meal of the day
- No episodes of hypoglycemia

What is the next step?

A. Increase insulin glargine

B. Add glimepiride 1mg

C. Start GLP-1 receptor agonist

D. Have her bring in her meter to collect more BG data

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Glucometer readings

Day	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bedtime
1	124		176	120
2	198	157	169	155
3	137		176	117
4	186	160	147	190
5	130	152		

- She reported morning glucose ~ 160-200
  - Actual 124 – 198
- Upon further investigation, she reports that she had a low blood sugar overnight 8 months ago – caused shaking and nausea -> VERY SCARY
- To avoid lows she doesn't take the full dose of glargine on the nights that bedtime glucose is 120 or lower.

How do we solve this?

Variable BG values may be related to variable dosing of insulin glargine

More therapy is **not** required at this time. Her A1C is high because she is not taking her therapy as prescribed

The correct approach: Reduction in basal insulin to ensure adherence and reassess

Asking the right questions…

- Pays to have all the information
  - Where CGM is helpful!!!
- Pays to ask the right questions

  Having hypoglycemia?

  VS.

  Hypoglycemic episodes in the past?

  Taking medications as prescribed?

Case # 3: Meet Brandon

- 17 yo male with new complaint of fatigue, polyuria, polydipsia and recent weight loss
  - No recent illness
- Family History: HTN, CAD
- BMI 17.2 (Wt 120lbs, Ht 5'10")
- Fasting Labs (done 1 week ago):
  - Glucose 190
  - LDL 70; HDL 85
  - A1C 10.5%
  - All other labs normal

You suspect diabetes **Type 1**

What test do you order next to confirm?
Select all that apply

A. anti-IgE and anti-interleukin-5 (IL-5) antibodies
B. c-peptide
C. anti-cyclic citrullinated peptide-2 (anti-CCP2)
D. anti-GAD antibodies

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- **C-Peptide**
  - Hormone that the pancreas produces in conjunction with insulin.
  - Type 1 DM – **LOW**
- **Anti GAD antibodies**
  - Antibodies that develop as an autoimmune response
  - Type 1 DM – **HIGH (>5)**

- C-peptide = <0.1 (LOW)
- Anti-GAD antibody = 17 (HIGH)

Confirming Type 1 DM

- You decide to get more data and prescribe a glucometer and supplies
- Ask to check glucose routinely (fasting and before bed).

What is the best next step for this patient?

A. See a dietician and follow up in 6 months
B. Start metformin 500mg daily
C. Start pioglitazone 15mg daily
D. Start insulin, including long acting daily and short acting with meals.

What is the best next step for this patient?

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Treatment of Type 1 DM is lifelong

Unable to produce insulin – SO THEY NEED **INSULIN**

Long acting

Provides a continuous base of insulin in the body all the time

Short acting

Provides coverage for each meal

Insulin

Action		Name(s)	Onset	Peak	Duration	Considerations
Bolus	Very Rapid Acting	Aspart Lispro-aabc	2.5 min 1 min	~ 60 min ~ 60 min	3-5 hrs 4-5 hrs	Bolus insulin lowers after-meal glucose. Post meal BG reflects efficacy. Basal insulin controls BG between meals and nighttime. Fasting BG reflects efficacy. Side effects: Weight gain, hypoglycemia. Dosing: 0.5 – 1.0 units/kg/day total Discard after 28 days. Keep refrigerated.
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	Intermediate + Rapid	Insulin Mix – 70/30 Insuin Mix–75/25, 50/50	5-15 min	Dual peak	24 hrs	

Initiating Insulin Dosing

Most adults with newly diagnosed type 1 diabetes can be started on a TDD of 0.2 to 0.5 units of insulin per kg per day

- Long Acting (Basal)
- initiation of basal insulin at 10 units/day or 0.1–0.2 units/kg/day
- adjusted by 10–15% once or twice weekly to reach a target fasting plasma glucose (FPG)

- Short Acting (Bolus)
- 0.1–0.2 units/kg/day (divided between meals)
- Given 15 minutes before the meal

Insulin Initiation and Titration in Patients With Type 2 Diabetes; *Diabetes Spectr* 2019;32(2):104–111

Case # 4: Meet Anna

- 64 yo Type 2 DM for past 9 years
- Sx: worsening blurry vision, polyuria
- Current Meds:

  Metformin 1000mg BID

  Empagliflozin 20mg qd

  Glargine 20 units qhs

  Lispro 5 units - meals 1:50>150 SSI

- Previously tried DM meds:
  - Dulaglutide and Tirzepatide – Unable to tolerated due to GI side effects.
- Exam:
  - General: Obese (Weight 194 lbs; Ht 5’7” = BMI 30.4)
  - Other systems: all normal
- Labs: Glucose 168; A1C 8.1; GFR 82
- Wearing CGM – using appropriately
  - Connected data to clinic

CGM data TIR = 53% (Goal >70)

Glucose

Average Glucose

197 mg/dL

Time in Range

- 23% Very High
- 23% High
- **53% In Range**
- <1% Low
- 0% Very Low

Target Range:
70-180 mg/dL

Sensor Usage

Days with CGM data
100%
14/14

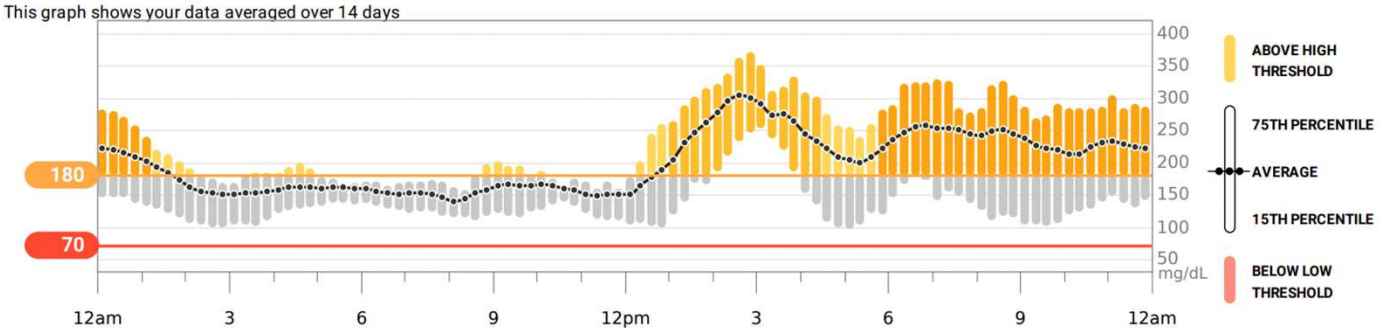
Standard Deviation
78 mg/dL

GMI
8.0%

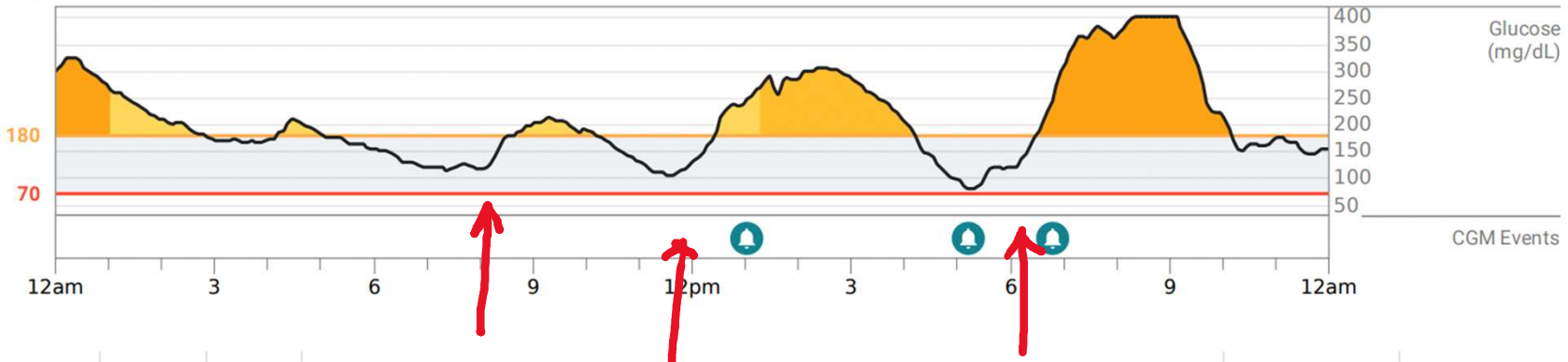
Avg. calibrations per day
0.0

Top Patterns

This graph shows your data averaged over 14 days

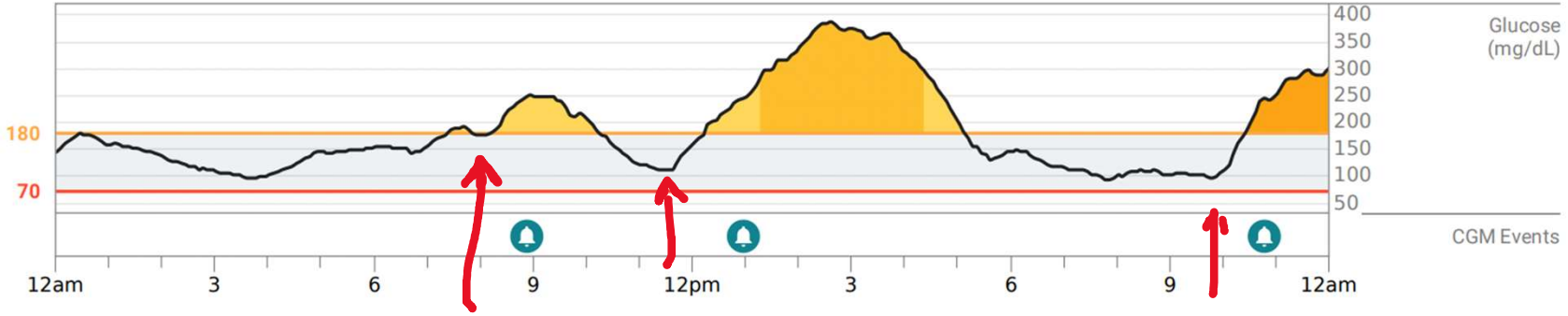


Wed, Dec 13, 2023



Time	Device	Event	Details	Insulin Units	Glucose
6:47 PM	CGM	Alert	High	–	245 mg/dL
5:12 PM	CGM	Alert	Low	–	79 mg/dL
1:02 PM	CGM	Alert	High	–	247 mg/dL

Tue, Dec 12, 2023



What should be changed with treatment?

A. Increase long acting insulin dose by 20% and change it to taking it in the morning
B. Add GLP-1 agonist
C. Increase short acting insulin dose and make sure patient is taking it 15 minutes before the meal
D. Add a sulfonylurea with meals

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Increase short acting insulin dose and make sure patient is taking it 15 minutes before the meal.

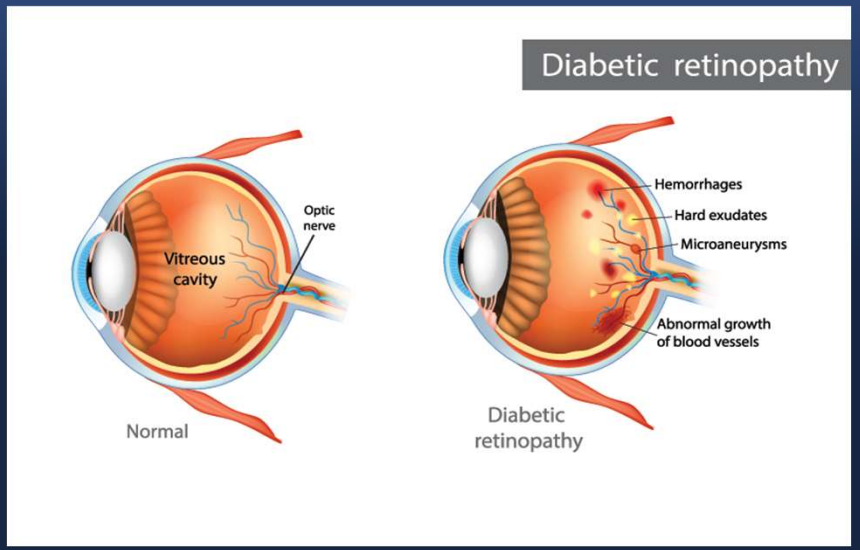
- With this change:
  - Less surge in mealtime glucose
  - Less low glucose levels post meal if takes insulin on time.

- Incorrect Answers:
  - ✗ Increase long acting insulin dose by 20% and change it to taking it in the morning.
    - Patient may benefit from slight increase, but mostly staying steady overall when not eating -> So not best choice.
  - ✗ Add GLP-1 agonist.
    - Did not tolerate other GLP-1 agonists in the past.
  - ✗ Add a sulfonylurea with meals.
    - Should not add Sulfonylurea to patient with insulin. Risk of hypoglycemia and weight gain.

What other recommendations are good to make for this patient?

- Refer to a Dietician/Certified Diabetic Educator
  - Meal choices can be altered to lower post meal glucose levels

- Refer to Ophthalmology
  - Patient has high glucose with blurry vision
  - Want to rule out retinopathy -> Blindness



Case #5: Meet George

- 74 yo male presents for hospital follow up
- Hospitalized 4 weeks ago for respiratory infection associated with RSV
- Breathing better, only mild cough remaining
- States concern that the RSV may have raised his glucose levels
- Checks glucose intermittently
- Glucose ranging 200 - 400

Diabetes History:

- Type 2 DM - Diagnosed 18 years ago
- A1C:
  - Currently 10.6%
  - 6 months ago 8.7%
- Current DM medication plan:
  - Metformin 1000mg BID
  - Glimepiride 4mg daily
  - Semaglutide 1mg weekly (added 6 months ago)

Explanations for his glucose elevation?

Steroid use

- Started on prednisone at the hospital
- Discharged on prednisone taper
- Steroids usually raise glucose 4 - 8 hours later

Steroid	Half-life
Cortisone	4-6 hrs
Prednisone	6-12 hrs
Methylprednisolone	6-12 hrs
Dexamethasone	1-2 days

While on steroids…

- Concentrate on making good food choices
- Check glucose levels routinely
- May need insulin

What option is best for George?

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Cortisone	4-6 hrs
Prednisone	6-12 hrs
Methylprednisolone	6-12 hrs
Dexamethasone	1-2 days

Glycemic Control in Hospitalized Patients with Diabetes Receiving Corticosteroids Using a Neutral Protamine Hagdorn Insulin Protocol: A Randomized Clinical Trial . Khowaja A, Alkhaddo JB, Rana Z, Fish L. Diabetes Ther. 2018 Aug;9(4):1647-1655.
How to Manage Steroid Diabetes in the Patient with Cancer. David S. Oyer, MD, FACE, Ajul Shah, BS, and Susan Bettenhausen, APRN, CDE, 2006

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Insulin Options:

NPH has a half-life of 12 hrs

May need basal bolus if on Dexamethasone

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NPH dosing

- Match insulin to prednisone
  - Usually NPH ½ units compared to dose of prednisone
  - i.e. Prednisone 40mg with NPH 20units
  - Taper NPH with pred taper

Questions

Please feel free to contact me with questions

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