MAKING A GOOD START

ADDRESSING PRE-DIABETES MEANINGFULLY

www.youtube.com/watch?v=pT9ZsmuRP8I

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OBJECTIVES

- Identify the laboratory diagnostic findings of prediabetes
- List treatment priorities for prediabetes
- Compare selected anti-diabetes medications with regard to their effects on insulin resistance, inflammation, Beta-cell preservation, cardiovascular risks and weight loss

MEET YOUR PATIENT: SONJA

- 49 y/o Hispanic woman in for annual follow-up, complains of mild perimenopausal symptoms and 20 lbs weight gain in 1 year
- **Hx**: of hypertension, carpal tunnel, 2 normal births—no GDM
- **FHX**: unknown
- **Rx:** lisinopril, no HRT per choice
- **BP**: 132/82; BMI: 32; WC 36 inches
- **LABS**:
  - LDL,(132 mg/dl; HDL (30 mg/dl); TGs (195 mg/dl)
  - FBG (111 mg/dl) repeated (115)
  - Chem profile noncontributory

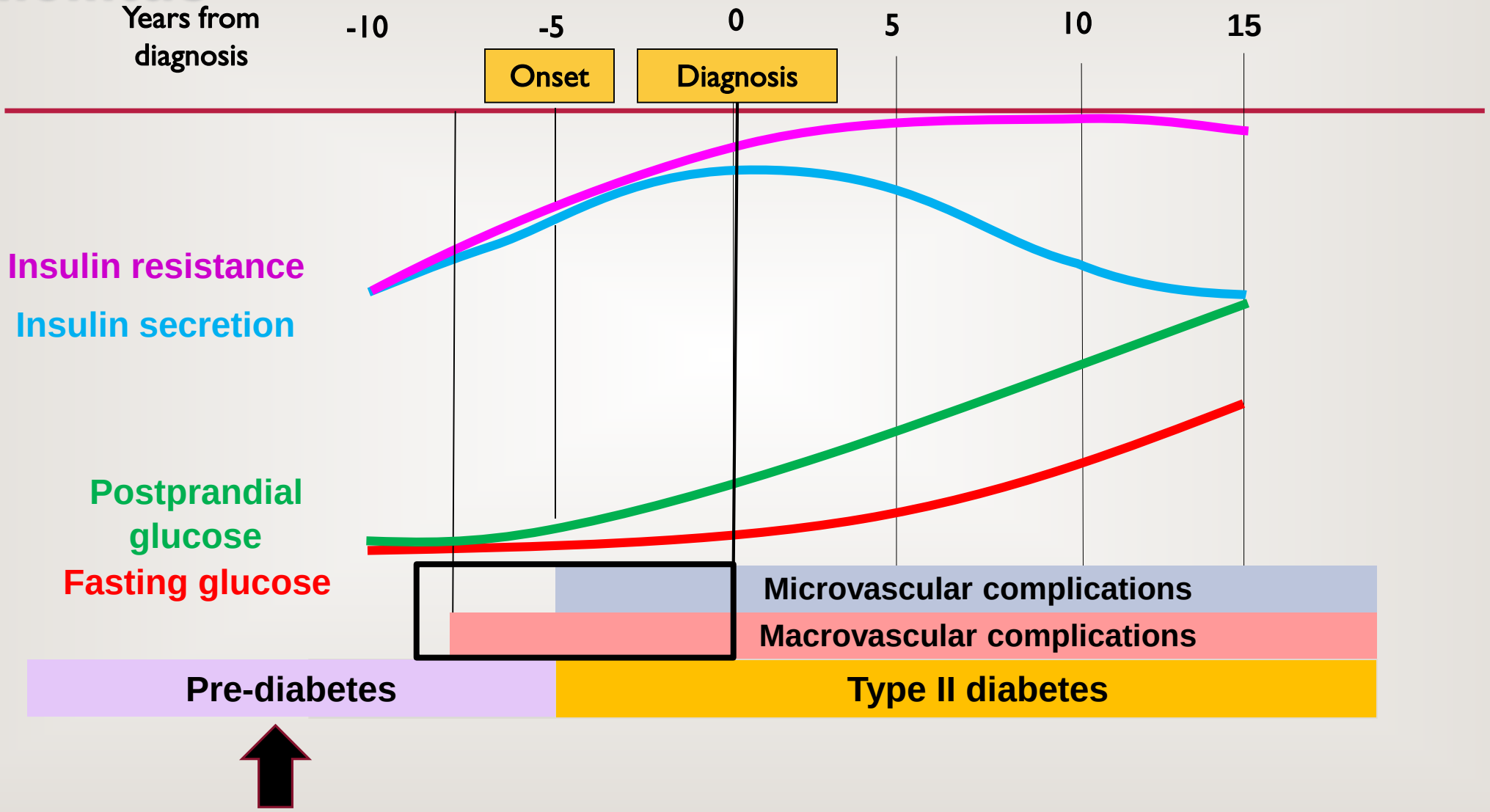
Does this patient have PreDM?

SO…..

1. What more do you want to know about Sonja?
    1. Labs
    2. History
    3. DM-related risks
    4. Physical assessment data
2. When should you screen your patients for pre-diabetes?
3. What are the primary reasons for intensive treatment of prediabetes?
4. How should pre-diabetes be treated in primary care settings?

It is essential to identify and treat prediabetes early in order to prevent/ delay disease progression and the development of related morbidities (esp. CV & Kidney disease)

Reminder: Natural History of Type II Diabetes Mellitus



Adapted from: Diabetes. 2017 Feb;66(2):241-255

WHAT IS THE CURRENT FOCUS FOR DIABETES CARE?

- Improving glycemic control
- Preventing Beta Cell failure
- Cardiometabolic health *(macrovascular)*
  - Reduce insulin resistance
  - Weight (adiposity) reduction
  - Reducing NAFLD
  - Lipid & BP stabilization
  - Monitor for PAD
  - Monitor for hypothyroidism & other CMD risk
- Screening for & treatment of the "opathies" *(microvascular)*
  - Retinopathy
  - Nephropathy
  - Neuropathy (peripheral & autonomic)

Real focus on lifestyle: dietary, activity, behaviors

Avoid hypoglycemia

Will better glycemic control help macro- & microvascular impairment?

Criteria for testing asymptomatic adults for DM or prediabetes

- **Consider testing adults with overweight or obesity**
  - **(BMI ≥25 kg/m2 *or ≥23 kg/m2 in Asian)***
- **Or who have one or more of the following risk factors:**
  - First-degree relative with diabetes (or autoimmune disease)
  - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
  - **History of insulin resistance or clinical conditions associated with IR**
    - **CVD**
    - **Hypertension (≥140/90 mmHg or on HTN meds)**
    - **HDL <35 mg/dL and/or a triglyceride level >250 mg/dL**
    - **Central adiposity or Morbid obesity**
    - **Women with polycystic ovary syndrome**
    - **Acanthosis nigrins**

We will address treating these in future lectures

Diabetes Care 2023;46(Supplement_1):S19–S40

Criteria for testing asymptomatic adults for DM or prediabetes

- Patients with prediabetes (A1C ≥5.7%], IGT, or IFG) should be tested yearly.
- Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
- For all other patients, testing should begin at age 45 years.
- If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
- Or in those with hx of HIV, CVD, GDM, Hashimoto's Thyroiditis, etc

Diabetes Care 2023;46(Supplement_1):S19–S40

Risk-based assessment in children/adolescents for Prediabetes or T2DM

- Consider testing in in youth who have overweight (≥85th percentile) or obesity (≥95th percentile)
- **And who have one or more diabetes risk factors:**
- • Maternal history of diabetes or GDM during the child's gestation
- • Family history of type 2 diabetes in first- or second-degree relative
- • Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- • **Signs of insulin resistance or conditions associated with IR:**
  - **acanthosis nigricans,**
  - **hypertension, dyslipidemia (elevated TGs)**
  - **polycystic ovary syndrome,**
  - **small-for-gestational-age birth weight**

Diabetes Care 2023;46(Supplement_1):S19–S40

CRITERIA DEFINING PREDIABETES*

- FPG :100 mg/dL to 125 mg/dL (IFG)
  - OR
- 2-h PG during 75-g OGTT: 140 mg/dL to 199 mg/dL (IGT)
  - OR
- A1C: 5.7–6.4%

OTHER CONTRIBUTORY LABS

- C-peptide (do not fast prior!) and draw with tandem blood glucose
- Full chemistry panel (interest in Liver and Kidney function)
- TSH
- UCAR
- Beta cell autoantibodies if NO evidence of insulin resistance
- Other useful information: CBC, UA, uric acid, CRP

LAB POINTERS

- When doing an **oral glucose tolerance test for diabetes**, make sure intake of adequate carbohydrate intake (at least 150 g/day) for 3 days prior to testing.
- **C-peptide** is useful to determine beta-cell reserve and possible presence of Insulin Resistance
  - Best done non-fasting (interested in the insulin response to blood glucose—it should rise higher in presence of higher BG)
  - So obtain a tandem blood glucose with the C-peptide

FYI: more often the PP sugars rise before FBG in PreDM

EARLY INTERVENTION FOCUS IN PREDIABETES

- **Diabetes education!**
- **Lifestyle interventions:**
  - Dietary choices
  - Food insecurity assessment
  - Physical activity
  - Behavioral therapy as needed
- **Pharmacotherapy:**
  - Decrease inflammation:
  - Delay progression to full diabetes (beta cell preservation)
  - Reduce Insulin resistance
  - Reduce CVD disease risk (& preserve renal function along the way)
  - Reduce adiposity (weight & fatty liver)

MORE THINGS TO CONSIDER:

- Adequacy of sleep
- History of physical & emotional stress
- Issues with pain
- History of macrosomic birth
- Patient’s perceived cause of diabetes
- Gut health--- dysbiosis
- Others

Kessler's foodie tips in beginning the diabetes treatment journey.

Food Insecurity: Hunger Vital Sign™

- **If they answer that either or both of the following two statements* is 'often true' or 'sometimes true' (vs. 'never true'):**
  - Within the past 12 months, we worried whether our food would run out before we got money to buy more.
  - Within the past 12 months, the food we bought just didn't last and we didn't have money to get more.

- http://www.childrenshealthwatch.org/wp-content/uploads/FINAL-Hunger-Vital-Sign-2-pager1.pdf (accessed 4/1/2023

ADA ADULT PHYSICAL ACTIVITY RECOMMENDATIONS

- For most adults T1DM or T2DM:
  - at least 150 minutes of moderate- to vigorous-intensity aerobic activity per week (spread over at least 3 days/week),
  - with no more than 2 consecutive days without activity.
- Engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.
- Flexibility training in older patients
- Prolonged sitting should be interrupted every 30 mins for BG benefits

- *Clin Diabetes* 2023;41(1):4–31

Initiating pharmacotherapy in prediabetes & diabetes

Safety FIRST

OTHER DIABETES MEDICATION PRESCRIBING POINTS

- **Is there a CV or Kidney benefit?**
- **Does it cause weight gain?**
- Sigh—cost prohibitive?
- *“Guilty until proven innocent”*

PATIENT DON'T TAKE THEIR MEDS?!

(retrospective study of 324,080 pts)

Most pts with T2DM stop taking their meds

58% within a year

44% within 6 months

31% within 3 months

And less that half of those pt will restart

The meds within the following year

Latts I et al. ADA 2018, Abstract 135-OR

Remember to think about the metabolic effects of your drug choices.

So I'm going to help you out….

Metabolic Effects of Anti-DM Drugs

Drug	↓Inflammation	↓Insulin resistance	↓Beta Cell demise	↓CVD risk	↓Weight / NAFLD	No Hypoglycemia risk
Metformin	✓	✓	✓	✓	✓ / ✓	✓
TZD *	✓	✓	✓	✓	X / ✓	✓
Bromocriptine	✓	✓	?	✓	✓ / ✓	✓
GLP-1	✓	✓	✓	✓	✓ / ✓	✓
SGLT2i	✓	✓	✓	✓	✓ / ✓	✓

* Thiazolidinediones (TZD), especially Pioglitazone (Actos) is weight neutral at low dose but increases weight in doses at =/> 30 mg/day.

Table created by speaker

Metformin

An oldie but goodie!

Biguanides: Metformin

IR: 500 mg, 850 mg, 1000 mg; ER: 500 mg, 750 mg 1000 mg

Dosing: 500 to 2550 mg daily, BID IR, once daily with XR
Max dose 1000 mg/day for eGFR 30-45, increase monitoring

Mechanism: Inhibits hepatic gluconeogenesis, decreases intestinal absorption, improves peripheral glucose uptake/utilization

Common side effects: GI upset, diarrhea

Monitoring: renal function (q3-12 months), A1c (q3-6 months), B12 (annually or if sx)

Contraindications:–Do not use if eGFR <30, not recommended to start if eGFR <45, hx of lactic acidosis; severe/progressive hepatic disease; hemodynamic instability; ETOH abuse

Cautions: Hold for IV contrast or acute dehydration/stress*

MORE INFO ON METFORMIN (WOW)

- Can take if 10 yrs & older & use in prediabetes
- Uncertain HOW it works but know it positively affects the biomarkers of cardiometabolic disease
- Decreases hepatic gluconeogenesis & lipogenesis (reduces liver fat)
- Decreases insulin resistance
- Increases antioxidant sensitivity (has anti-inflammatory effects)
- May decrease LV hypertrophy?
- Can lead to 2-4% weight loss
- Helps longevity and Slows aging: Decreases cancer (in T2DM), cognitive decline-dementia, stroke & more!
- Believed to work on the gut Microbiome (also decreases gut glucose absorption)

Obesity, diabetes mellitus, and cardiometabolic risk: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2023https://doi.org/10.1016/j.obpill.2023.100056

METFORMIN

Pros

- Inexpensive (generic)
- Long track record
- PO
- Unlikely to cause hypoglycemia
- Weight neutral

Cons

- GI issues
- Renal/hepatic limitations
- Swallowing issues (large pills)

Strategies for success

Doses >2000mg/day = marginal benefit, increased side effects

XR often better tolerated

Take with food

Ramp the dose

METFORMIN USE IN CKD

EGFR (ML/MIN/1.73 M2)	WHAT YOU SHOULD CONSIDER
• ≥ 60	• No renal contraindication (regardless of creatinine); Monitor GFR annually
• ≥ 45 and ≤ 60	• Continue use; monitor GFR every 3-6 months • Initiating metformin not recommended
• <45 and > 30	• Use lower dose (50% maximum dose) • Monitor GFR every 3 months
• <30	• Metformin contraindicated--stop

Exercise caution in patients low muscle mass or on concurrent nephrotoxic drugs (e.g. NSAIDS)

Cochrane Database Syst Rev. 2017 Feb 3;2:CD011880. doi:10.1002/14651858.CD011880.pub2

Thiazolidinediones (TZD) (pioglitazone- Actos)

THIAZOLIDINEDIONES (TZD)

- **Available agents:** Pioglitazone (Actos); Rosiglitazone (Avandia),

  Dosing: Pioglitazone (Actos) initiate at 15-30 mg daily (max 45 mg) (6-12 weeks to kick in); Rosiglitazone 4 mg/d to start, increase to 8 mg if needed)

  Mechanism of action: reduce insulin resistance & glucose production (work on adipose, muscle & liver)

  Cautions: avoid with symptomatic heart failure, increased risk for bone loss/fracture, risk of bladder cancer (pioglitazone)

  contraindicated in NYHA class III or IV congestive heart failure

  Side Effects: Weight gain, edema (dose related)

  Monitoring: Ha1c q3-6 months; LFTs prior and following IF liver dx; symptoms of HF,weight gain and/or bladder CA

Actos 15 mg 3 times weekly—Benefits with less side effects !!

MORE POINTS ON PIOGLITAZONE

- Inexpensive (generic pioglitazone)
- Reduces blood glucose without hypoglycemia
- Significant decrease in Insulin Resistance
- Potent anti-inflammatory effects (esp on liver fat & endothelium)
- Reduces severe hypertriglyceridemia
- Reduces fat mass within NAFLD
- Improved systolic & diastolic heart function
- 30% reduction in Atrial fibrillation risk
- Reduces infarct size following STEMI

Bromocriptine-QR (Cycloset)

What about Cabergoline?

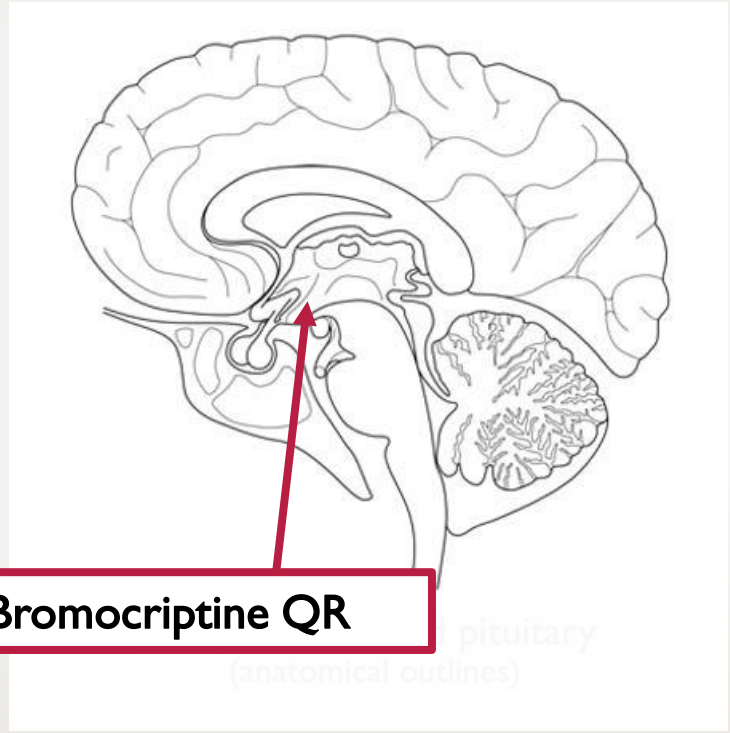
BROMOCRIPTINE-QR

- **Dopamine-2 receptor agonists**
- Originally introduced for prolactinomas, pituitary tumors, and Parkinson's disease
- Found to have significant effects on lowering blood glucose level
- Has anti-inflammatory effects
- So, how does this work?

Circadian effects of Dopaminergic (D2) Tone

↓ Dopaminergic activity late **PM**

↑ Hepatic glucose output
↑ Free Fatty Acids (FFA)
↑ Triglycerides
↑ Inflammation/coagulation
↑ **Insulin resistance**



Bromocriptine QR

Improved glucose tolerance

↑ Dopaminergic activity in **AM**

↓ Hepatic glucose output
↓ Free Fatty Acids (FFA)
↓ Triglycerides
↓ Inflammation/coagulation
↓ **Insulin resistance**

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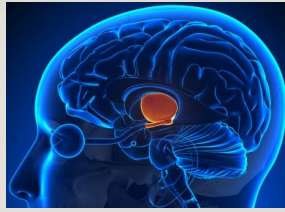

CIRCADIAN EFFECTS ON INSULIN RESISTANCE, BLOOD GLUCOSE & ADIPOSITY

Dopamine 2 effects are normally <u>reduced at night</u>

- ***Relates to "hibernation" of animals and our night-time sleep***
- We become <u>INSULIN RESISTANT (IR)</u> at night
- We increase gluconeogenesis & lipolysis (more BG & free fatty acid)
- **Has circadian release <u>(increases 2 hrs after wakening);</u> *Then-***
  - <u>Decreased</u> liver gluconeogenesis & lipolysis
  - <u>Increased</u> insulin sensitivity (reduces IR)

Luo S, et al.. Circadian peak dopaminergic activity response at the biological clock pacemaker (suprachiasmatic nucleus) area mediates the metabolic responsiveness to a high-fat diet. J Neuroendocrinol. 2018 Jan;30(1):e12563.

CIRCADIAN EFFECTS ON INSULIN RESISTANCE, BLOOD GLUCOSE & ADIPOSITY

- ***Reduced* Dopamine 2 circadian *recovery*—leads to persistent IR**
  - Seen in T2DM & prediabetes
  - Causes Insulin resistance with:
    - Increased liver gluconeogenesis & lipogenesis/TGs
  - Decreased prandial insulin release **(high post prandial BG)**
  - ***Weight gain***
  - **Increased metabolic syndrome!!!**

Seen when eating high fat or refined sugar food in late evening
(or eat 25% of your calories AFTER dinner)

Luo S et al. Circadian peak dopaminergic activity response at the biological clock pacemaker (suprachiasmatic nucleus) area mediates the metabolic responsiveness to a high-fat diet. J Neuroendocrinol. 2018 Jan;30(1):e12563.

SUMMARY INFO ABOUT BROMOCRIPTINE (CYCLOSET)

- Can only use if still have beta-cell function *(making insulin)*
- *Best used in prediabetes or in* T2DM
- ***Promotes insulin sensitivity (in circadian pattern—works in hypothalamus)***
- Helps post **prandial sugars**
- *Take with food* ***within 2 hours of awakening***
- Gradual weekly dose titration: 0.8, add another pill to max dose 1.6-4.8 mcg
- Potential reduction of CV risks
  - Lowers risk for MI, CVA, PVD by 42%;
  - Seduces TGs 29%
  - Systolic BP down 2.3 mg/Hg.
- Reasonable cost

What about Acarbose in PreDM?

A recommendation by AACE

ACARBOSE (PRECOSE)

- Is a Alpha-Glucosidase Inhibitor; blocks GI carbohydrate uptake
- Reduces post prandial blood sugar—*does cause weight loss*
- Initially 25 mg PO q8hr, at meals (with first bite)
- Can increase to 50 or 100 mg PO q8hr at 4- to 8-wk intervals based on 1 hour postprandial glucose levels, and on tolerance (max dose is 200 mg 3 times a day)
- *NEVER take with alcohol or with pramlintide*
- Caution with many other drugs: esp. anti-diabetes drug (SU & insulin increase hypoglycemia risk) and antivirals (59 drug interactions)
- Moderate GI side effects—flatulence (carb-anti-abuse); not well tolerated

Altay M. Acarbose is again on the stage. World J Diabetes. 2022 Jan 15;13(1):1-4.

BACK TO SONJA

- 49 y/o Hispanic woman in for annual follow-up, complains of mild perimenopausal symptoms and 20 lbs weight gain in 1 year
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  - Chem profile noncontributory

SO WHAT NOW….?

- What are your concerns for her?
- What history do you want to know?
- What other labs or data do you require?
- What would be your first intervention for Sonja?
- What underlies your priority choice of interventions?
- *Prepare for some “zinger” data that may change your choices.*

SINCE YOU ARE SO SMART--- WHAT ABOUT THESE PATIENTS?

- 72 y/o Adam with eye-rolling morbidities
- 22 y/o Jamie with PCOs and more
- 10 y/o Joey with an interesting family history

MONOGENIC DIABETES SYNDROMES

RECOMMENDATIONS FOR ASSESSMENT

- All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes.
- Children & those diagnosed in early adulthood who have diabetes not characteristic of type 1 or type 2 diabetes, seen in successive generations (autosomal dominant inheritance)
- They are negative diabetes-autoantibodies, nonobese, no metabolic features, again with strong family history of diabetes.
- Stable, mild fasting BG (100–150 mg/dL), stable A1C (5.6% -7.6%)
- *Consultation with a geneticist in diabetes genetics.*
- *Typically only need sulfonylureas if treatment required*

Time to stop and rest your brains

Freepik.com

Questions?

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RESOURCES:

- https://www.cdc.gov/diabetes/index.html
- AACE Diabetes Guidelines 2023
  - https://www.endocrinepractice.org/article/S1530-891X(23)00034-4/fulltext
- ***Standards of Care in Diabetes—2023* Abridged for Primary Care Providers**
  - *Clin Diabetes* 2023;41(1):4–31