

Unique Considerations in Treating Women with Diabetes

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Objectives:

- Describe differences in diabetes incidence/prevalence in women
- Discuss how complications differ for women with diabetes
- Review management options for women with diabetes

Case #1

- 48 year-old, type 2 diabetes for 8 years, referred
- No complications, history of hypertension
- Currently taking metformin BID and glimepiride
- Last A1c 8.2%, BMI 32
- Works as a teacher, has 2 kids in middle school, very busy and unpredictable schedule
- Worried about medication side effects, weight gain and cost

Our conversation...

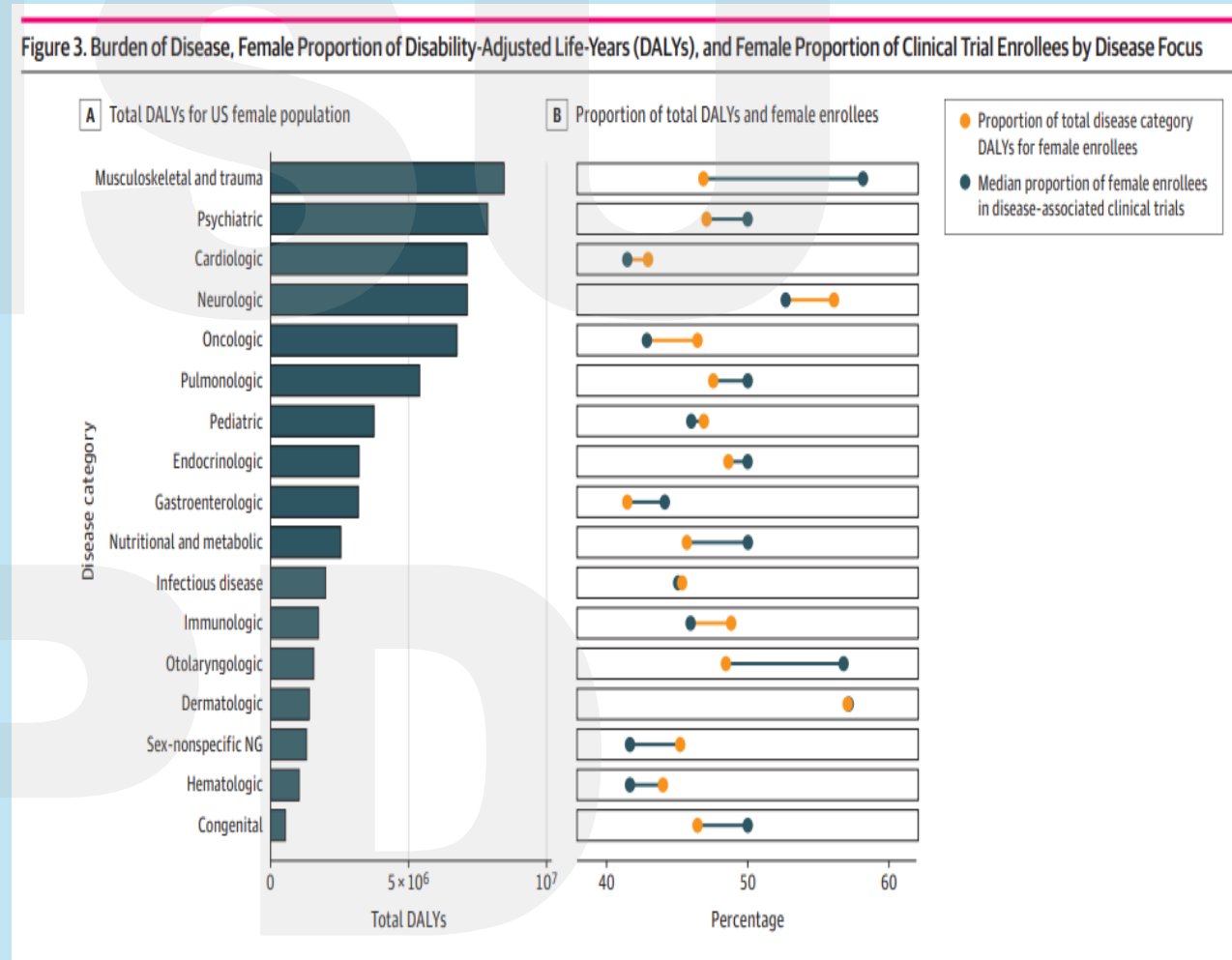
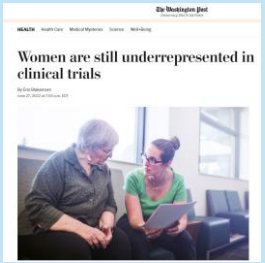
- "Getting the kids up and going in the morning is such a challenge, I don't have time to eat", so grabs something at Starbucks
- "My schedule at school is really unpredictable, and having high or low sugars is awful"
- "I don't have any time to exercise"
- Becomes tearful talking about her weight, frustrations with her inability to lose, blames herself for not working hard enough
- Has seen advertisements on TV for diabetes products and curious if they might work for her?

Questions to consider...

- How is her diabetes/risk different since she is a woman?
- Are there different therapies we should offer to her to manage her diabetes, because of her sex?
- What other tools/supports should we consider to help her succeed?

Significant limitations in the literature

- Women excluded to ensure homogeneity, reduce maternal-fetal liability
- In 1993, NIH policy created to ensure women and minorities included in all clinical research
- 1433 trials, women were under-represented in CV disease, psychiatry and oncology
- Ongoing need for better representation to reflect health burdens for women, and look at outcomes



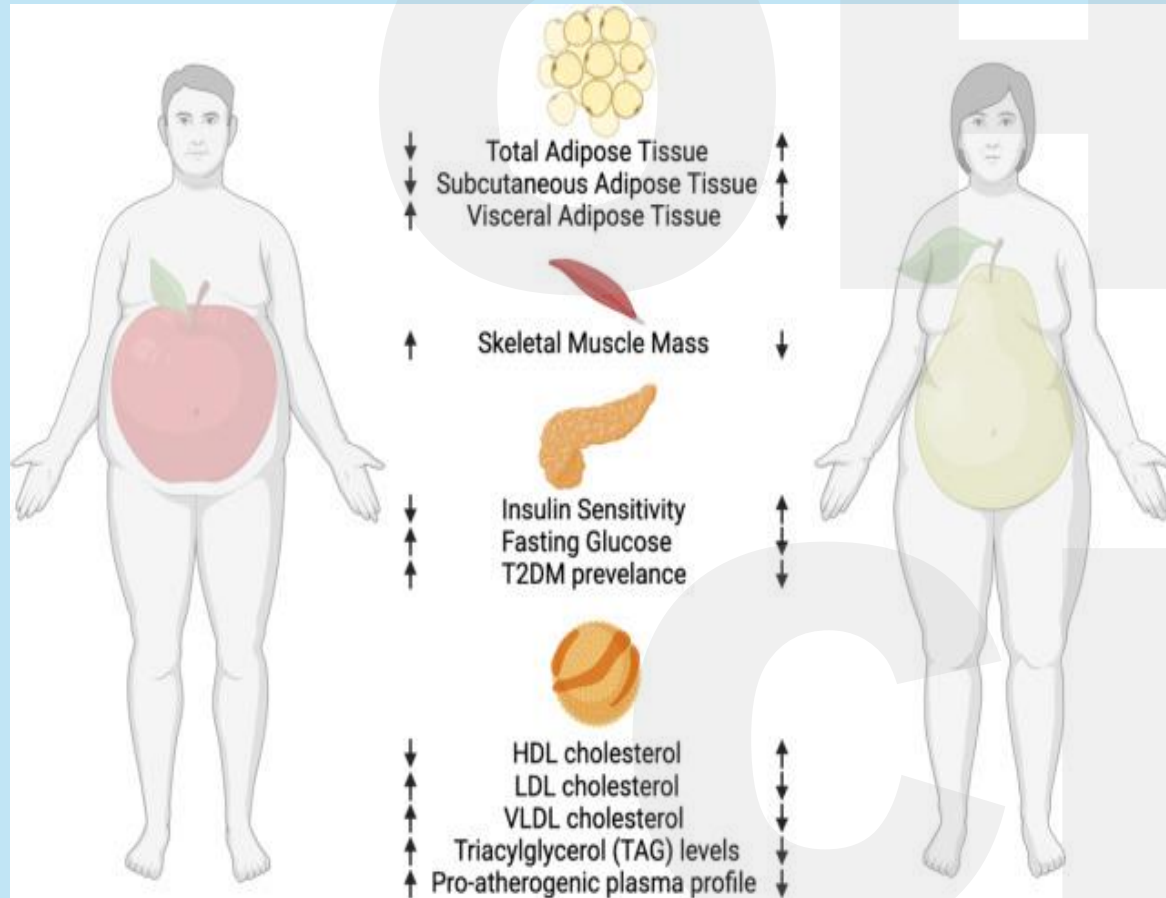
Diabetes in Women

Table 1a. Estimated crude prevalence of diagnosed diabetes, undiagnosed diabetes, and total diabetes among adults aged 18 years or older, United States, 2017–2020

Characteristic	Diagnosed diabetes Percentage (95% CI)	Undiagnosed diabetes Percentage (95% CI)	Total diabetes Percentage (95% CI)
Total	11.3 (10.3–12.5)	3.4 (2.7–4.2)	14.7 (13.2–16.4)
Age in years			
18–44	3.0 (2.4–3.7)	1.9 (1.3–2.7)	4.8 (4.0–5.9)
45–64	14.5 (12.2–17.0)	4.5 (3.3–6.0)	18.9 (16.1–22.1)
≥65	24.4 (22.1–27.0)	4.7 (3.0–7.4)	29.2 (26.4–32.1)
Sex			
Men	12.6 (11.1–14.3)	2.8 (2.0–3.9)	15.4 (13.5–17.5)
Women	10.2 (8.8–11.7)	3.9 (2.7–5.5)	14.1 (11.8–16.7)

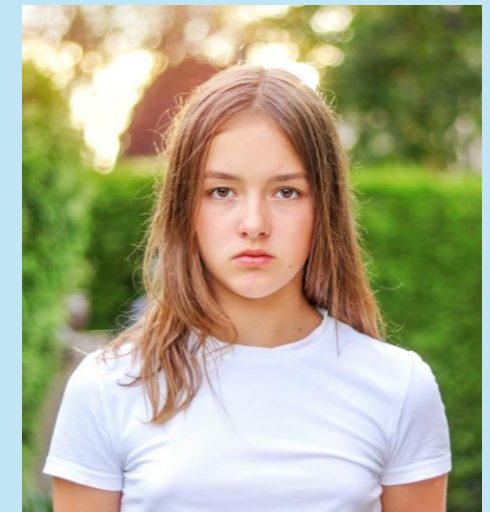
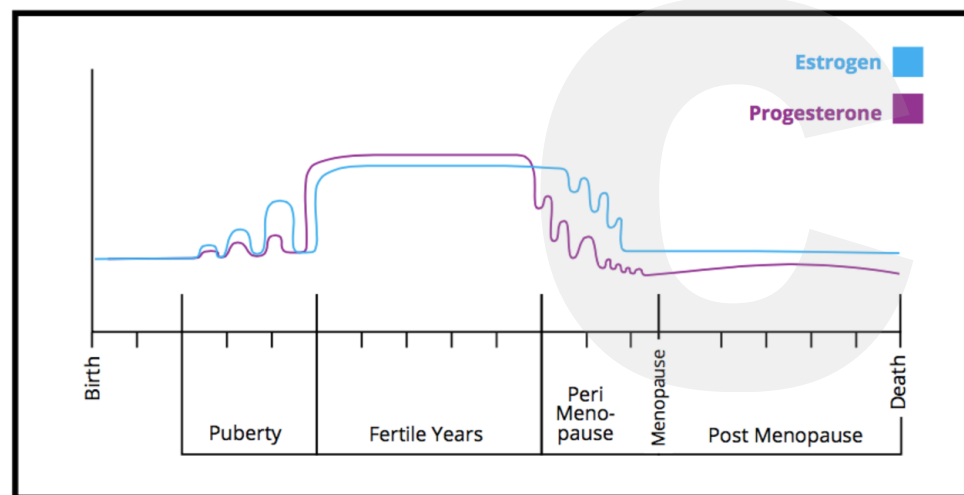
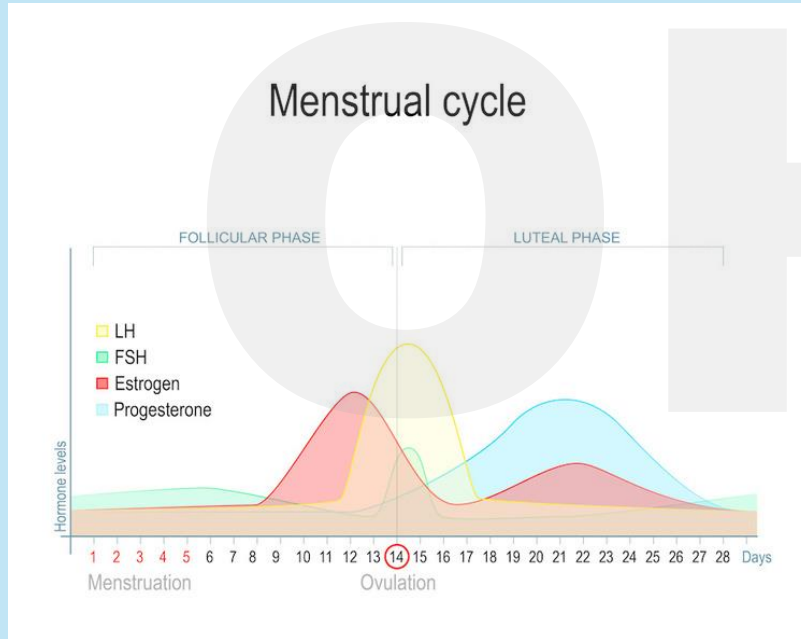
- 2023 US population, 334,914,895 people
 - 50.4% women
- Diabetes: 38.4 million people, 11.6% of the population (14.7% of those > age 18)
- Prediabetes: 97.6 million, 38% of population
- In 2021, 17.7 million more men living with DM
- 2/3 of children/adolescents with type 2 DM are female

Biological Differences



- Estrogen increases insulin sensitivity, glucose-stimulated insulin secretion, mitigates beta-cell apoptosis
 - Progesterone associated with insulin resistance, impaired beta cell function
- In women, testosterone associated with insulin-resistance, oxidative stress and beta-cell dysfunction (PCOS)
 - In men, testosterone deficiency associated with obesity/insulin resistance
- Higher body fat percentage c/w men
 - More peripheral than central, changes with menopause
- BMI increases have more impact in women
 - In those with a BMI 35, RR for DM is 60.9-fold for women, c/w 40-fold in men

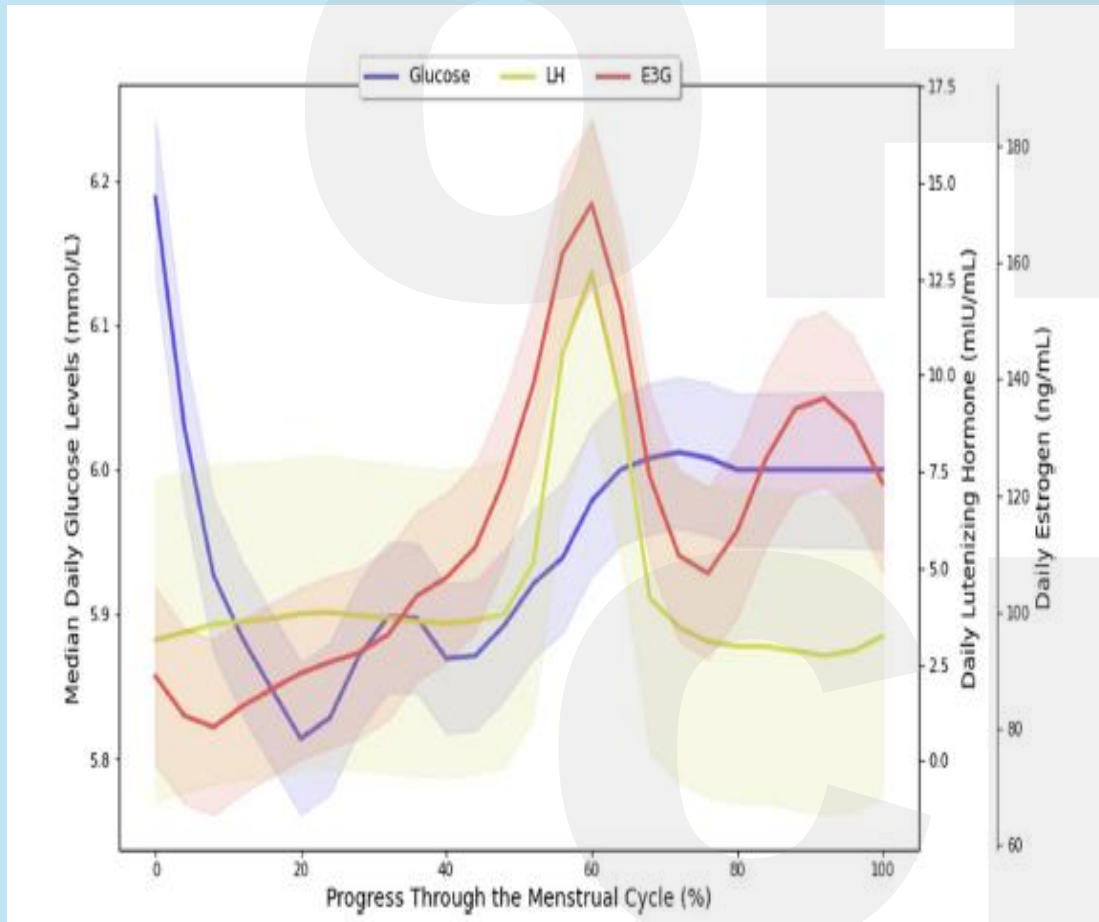
Hormonal Changes through a Woman's Life



Diabetes through A Woman's Life

- **Puberty:**
 - Increase in insulin resistance related to growth hormone, IGF1, diet changes and adherence in those with type 1 DM
 - Earlier age at menarche associated with higher risk/prevalence of obesity, insulin resistance, and risk of type 2 diabetes
- **Menstrual cycles and diabetes:**
 - Higher prevalence of PCO in women with type 2 dm, insulin as mediator
 - Irregular menses associated with increased risk for type 2 dm
- **Pregnancy:**
 - Gestational diabetes (GDM) affects women with greater insulin-resistance/obesity, or reduced beta-cell function
 - 70% higher risk for type 2 dm over 3 years c/w prediabetes or normoglycemia

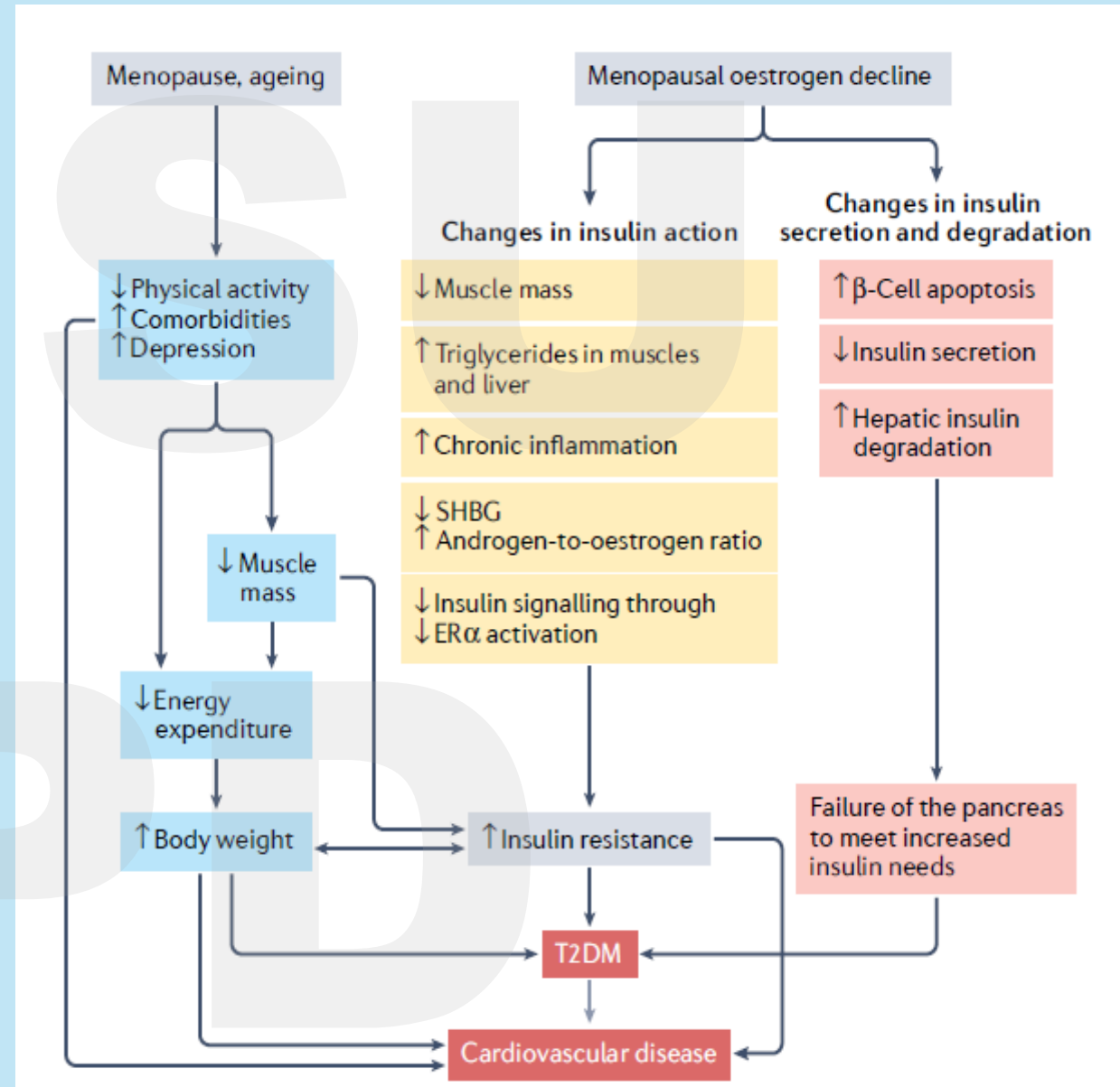
Menstrual Cycles and Diabetes



- Variability in glucose noted in type 1 diabetes
 - Retrospectively described in 2/3 of those with type 1 dm
 - Significant increases in hyperglycemia during the luteal phase noted on CGM
 - Particularly post-prandial
- Hypoglycemia with start of menses
- Review could not draw conclusions
 - Small samples, varied glycemic metrics, definition of cycle phases

Diabetes and Menopause

- Effect of type 2 DM on menopause onset unclear
 - Menopause may ↑ risk of diabetes
- Hormonal therapy ↓ risk of type 2 dm
 - Meta-analysis, ↓ incidence by 30% and ↓ insulin resistance (IR) 13%
 - Improved glucose control, A1c in those with DM
- Studies not designed to prevent DM or treat pre-existing DM



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Complications and Mood in Women

- **Limited evidence for sex differences in microvascular disease:**
 - No differences in retinopathy
 - Women report more frequent/greater neuropathic pain c/w men
 - Suggestion of higher risk of renal failure/insufficiency in women, possibly due to less intensive risk factor management
 - Higher risk of mortality with dialysis
- **Higher rates of depression and anxiety in women**
 - Major depressive disorder (MDD) 2.55x more likely in women with DM c/w those without
 - Gender gap noted to peak between ages 40-49 years for MDD

What is diabetes distress?

- Worries, concerns, fears and threats that are associated with a demanding chronic disease like diabetes
- Prevalence in type 2 DM- 36%
 - More common in women and those with depressive symptoms
- Strategies include meeting the person where they are, provide evidence-based hope, and collaborate on a "healthy, good enough" goal/plan for action





Complications: Cardiovascular

- Women with type 1 or 2 DM have a 40-58% higher risk of incidence CHD c/w with men with DM
- 27% increased risk of stroke c/w men with diabetes in systematic review
- Canadian study showed hospitalization/mortality due to CVD was 2x higher in women c/w men
- Medication adherence and/or prescriptions to treat CVD risk are lower in women
 - Fewer prescriptions for lipid-lowering therapy, or ACEI c/w men with type 2 DM

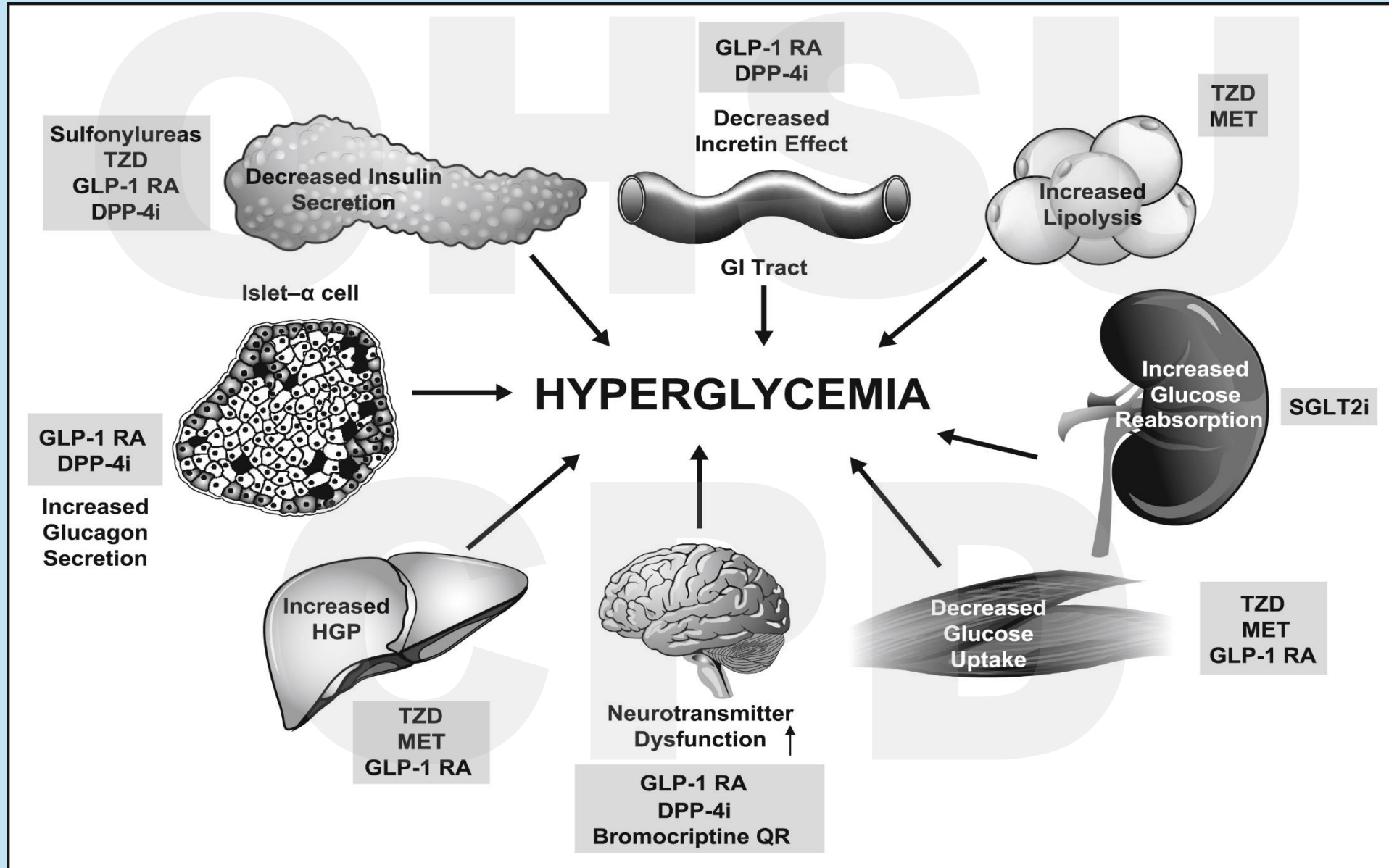
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Drugs for DM Management



TYPE 2 DIABETES

12 Different Classes of Therapy

Reduce Hepatic Glucose Production

- Metformin + XR

Enhance Insulin Secretion/Effect

- Sulfonylureas
 - Glipizide, glyburide, glimepiride
- Meglitinides (short acting)
 - Repaglinide, nateglinide
- Insulin- injectable

Attenuate Glucose Absorption

- α -glucosidase inhibitors
 - Acarbose
 - Miglitol

Other:

- Bromocriptine
- Salsalate
- Colesevelam
- Amylin Analogs

Insulin Sensitizers

- Thiazolidinediones
 - Pioglitazone

SGLT 2 Inhibitors

- Canagliflozin, Dapagliflozin, Empagliflozin, ertugliflozin

Incretin Therapies

- *GLP/GIP Analogs*
 - Tirzepatide
- *GLP Analogs*
 - Exenatide XR weekly
 - Liraglutide, semaglutide, dulaglutide, lixisenatide

- *DPPIV Inhibitors*

- Sitagliptin, Saxagliptin, Linagliptin, Alogliptin

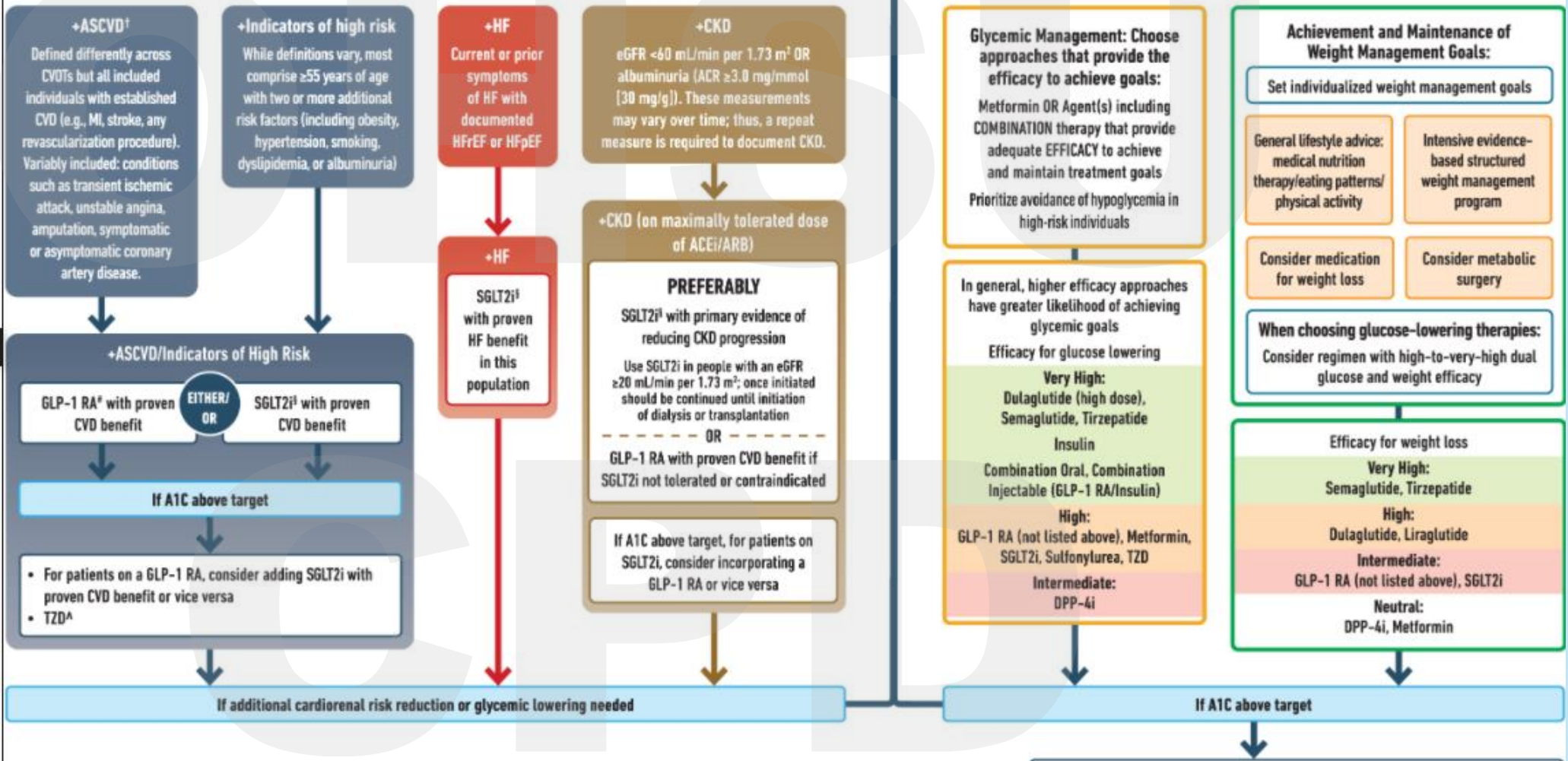
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes (in addition to comprehensive CV risk management)*

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HFrEF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

ADA
Guidelines
2024

Summary of Medications: Sex differences

- **Metformin: no difference in glucose efficacy**
 - More effective in diabetes prevention in women with history of GDM
- **Sulfonylurea: men respond better to SU, but hypoglycemia risk similar between sexes**
 - Long-term use associated with higher risk of CHD in women
- **Pioglitazone: women with more side effects (edema, weight gain)**
 - Also increased risk of fracture
- **DPP4i: no sex differences**
- **Insulin: women achieve A1c targets less often with basal insulin**
 - Higher risk for nocturnal hypoglycemia with NPH or glargine

SGLT2-Inhibitors

Examples: dapagliflozin,
canagliflozin, empagliflozin,
ertugliflozin

- **Considerations:**

- **Basics:**

- **Mechanism: inhibit glucose reabsorption in the proximal tubule**
 - **A1c lowering: .5-1%, \$500-600/month**
 - **Oral, less hypoglycemia risk**
 - **Glucose benefit primarily in those with eGFR > 45 mL/min**

- **Pros:**

- **Modest weight loss (1-4kg), BP ↓, CV and heart failure benefit**
 - **Reduction in proteinuria, GFR benefit**

Challenges with SGLT2i

- **Volume depletion**
 - Assess BP, if at goal, consider ↓ BP meds, especially diuretics
 - Monitor renal function, consider at one month after initiation
- **Genital mycotic infections**
 - Consider risk in those with hx of recurrent infections/incontinence
 - Increased risk of Fournier's gangrene
- **Amputations**
 - All associated, but particularly canagliflozin
 - Avoid in those with hx of PVD, ulceration
- **Normoglycemic/Euglycemic DKA**
 - Educate, especially those on insulin
 - Stop 48-72 hours before procedures, d/c with fever/illness, long fasts
 - **DO NOT RESTART SGLT2i**

Sex differences with SGLT2i

- **Used more frequently in men**
 - Trend for better glycemic response in men
- **Meta-analysis of 11 studies, greater ↓ in major cardiac events in females (RR .76, vs .8 for men)**
 - Also significant ↓ in CV death, all-cause mortality, CHF hospitalization
- **Empagliflozin and dapagliflozin have similar benefit in men and women with HFpEF with/without diabetes**
- **More recent analysis shows no difference in amputation, fracture risk, GU or UTI between men and women**
 - Canagliflozin higher risk for ketosis and fracture in women

GLP-1 Receptor Agonist

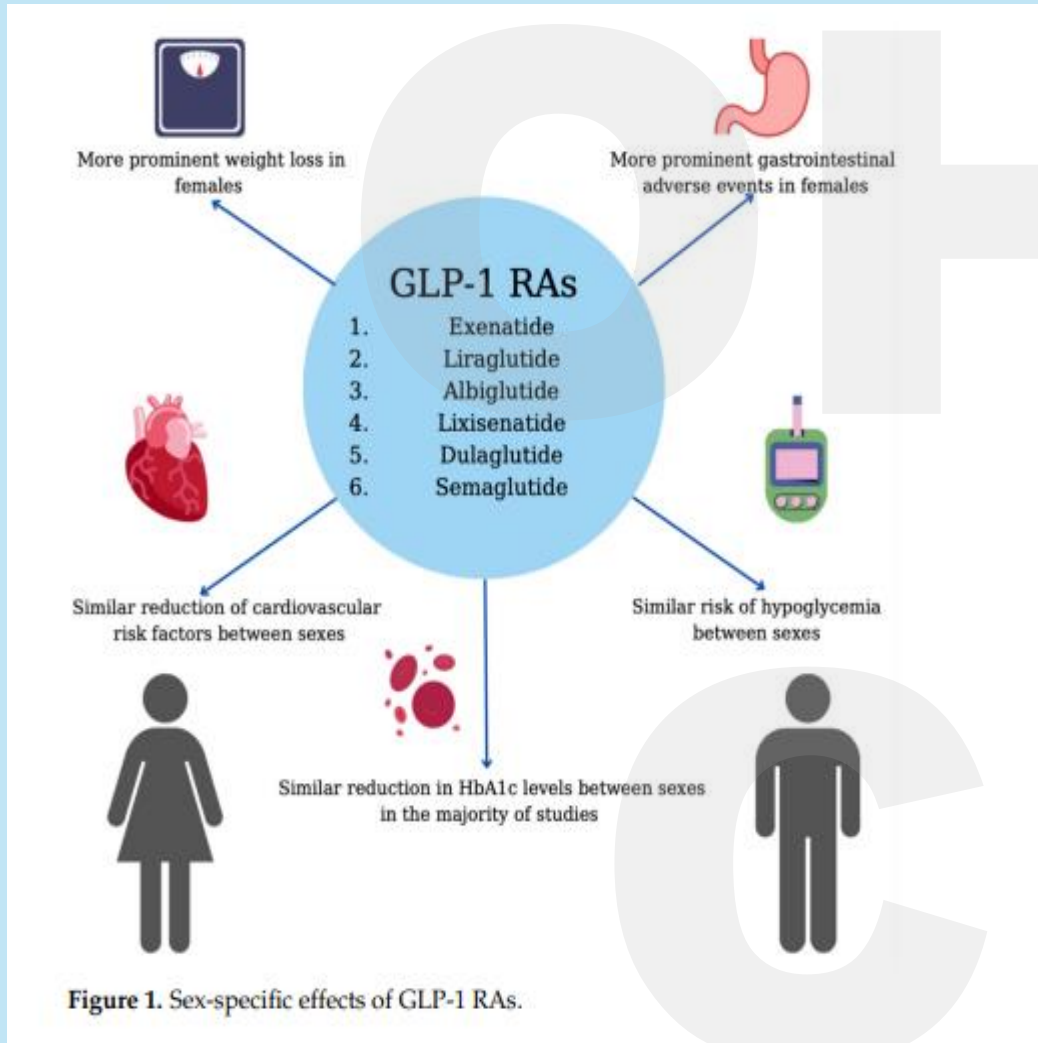
Examples: Exenatide XR,
Dulaglutide, Semaglutide,
Liraglutide

- **General:**
 - Mechanism: mimics native GLP-1, ↓glucagon, slows gastric emptying, increases satiety/decreases appetite
 - A1c lowering: 1-1.5%, \$900-1100/month (goodrx.com)
- **Pros:**
 - Weight loss, renal benefit, CV benefit (MACE outcomes and CHF)
- **Cons:**
 - Cost, GI side effects
 - Rare: risk of pancreatitis, medullary thyroid cancer (in animals), renal issues (exenatide), retinopathy(semaglutide?)

Common questions with GLP-1A

- Hx of Pancreatitis: If thought related to a gallstone, s/p cholecystectomy and no other episodes, most continue
- Hx of Hypertriglyceridemia: If moderate + secondary to hyperglycemia, likely okay to start as improving glycemic control will also bring reduction
- Family history of thyroid cancer: contraindicated in those with personal or family history of medullary thyroid cancer or MEN2 (rare!)
- Retinopathy: noted with semaglutide injectable, not oral, monitor eye health
- GI side effects: usually resolve in 1-2 months, and mild
 - Titrate dosing, eat small meals, listen to satiety signals
 - Avoid if symptoms severe or patient with history of gastroparesis

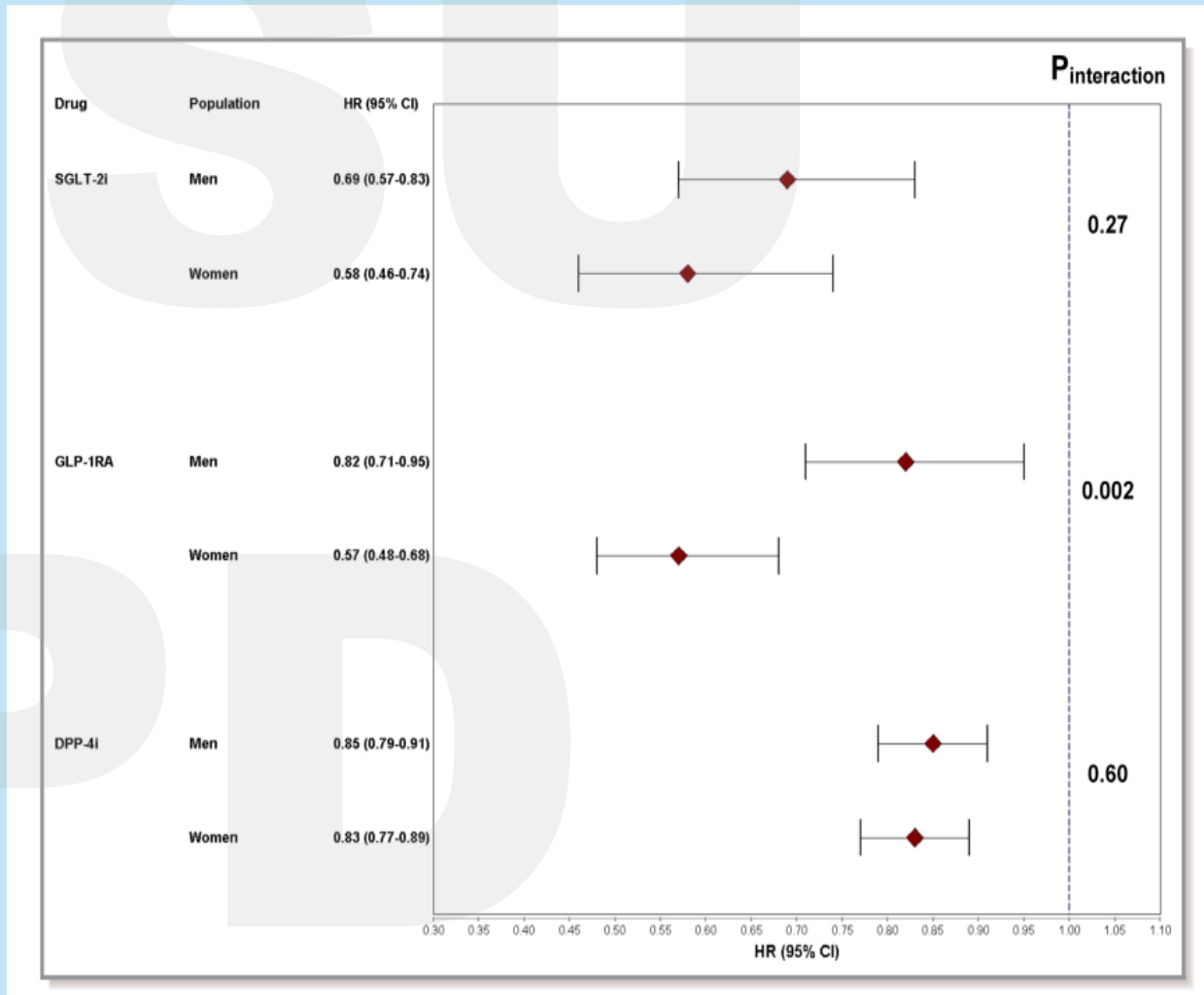
Sex Differences with GLP-1RA



	Differences in Response
Hypoglycemic efficacy	No sex differences noted in the majority of studies (ref. [21,50,51]) Female superiority noted in a few studies (ref. [5,6,52-54]) Male superiority noted in one study (ref. [22])
Weight loss	Female superiority noted in the majority of studies (ref. [6,22,50,56,57])
MACE	No sex differences noted (ref. [68,69])
CVD risk factors	Higher risk in females (ref. [66]) Lower risk in females (ref. [70])
i. WC	Similar reduction between sexes (ref. [5])
ii. BP	Similar reduction between sexes (ref. [5,21])
iii. Lipid profile	Similar alterations (except for no reduction of LDL-C in females ref. [21])
Adverse events	More frequent in females (ref. [57,73,76]) More frequent in females (ref. [76]) No sex differences noted (ref. [57])
i. GI AE	
ii. Headaches	
iii. Hypoglycemia	

CV Outcomes with Newer Meds by Sex

- CV events with SGLT2i, GLP-1RA, and DPP-4i relative to SU, compared women and men
- Included 167,254 people with type 2 DM, on metformin
- 46% women, avg 59 years-old, median 4.5 year follow-up
- Lower risk of side effects c/w SU

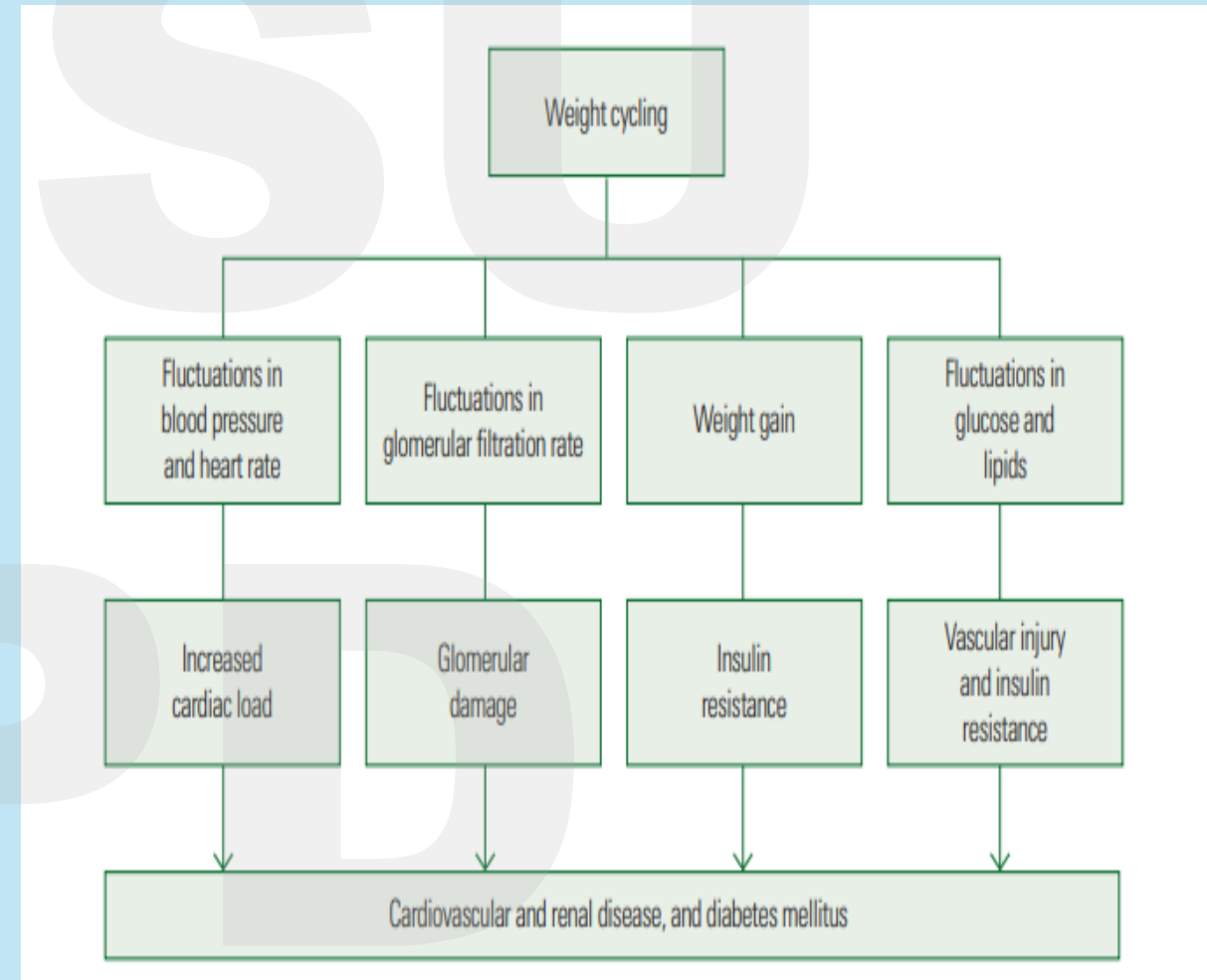


Realities of GLP-1RA Use

- **Cost and coverage**
- **Tolerance**
 - **Avoid high-fat foods, eat smaller portions, listen to satiety signals, stay hydrated**
- **Very hard to find on occasion**
 - **Give patients resources (calling pharmacies, alternative agents)**
 - **Can be heavy workload for patients and clinical staff**
- **Need for chronic/ongoing use**
 - **One study with semaglutide showed 2/3 of their weight was regained after one year off medication**

Weight Cycling and Possible Risks

- Prevalence of 20-55% in women, studies inconsistent/no universal definition
 - NHANES, 70-75% of women > 55yo wanted to weigh less
- Mechanisms for health effects include "repeated overshoot" and increased visceral energy repartitioning
- Also increased risk for eating disorders, type 2 DM, CV events



Case #1

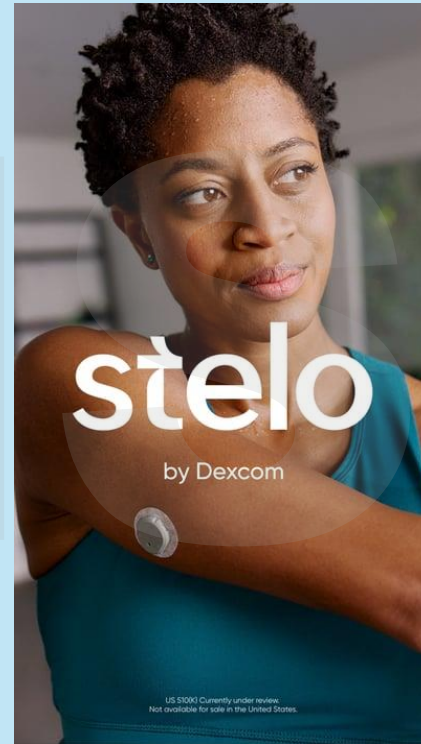
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 - Higher risk for CV disease and mood disorders
- Are there different therapies we should offer to her to manage her diabetes, because of her sex?
 - Consider GLP-1 if affordable
- What other tools/supports should we consider to help her succeed?

Can Technology Help?

- No noted differences between sexes with use of CGM
- Reduction in A1c, hypoglycemia risk
- Better satisfaction c/w SMBG
- Clinics and patients need to have way to access glucose data
 - Not a small thing!
- May increase anxiety if education/support not provided or available



Create Community for Women with Diabetes

- Your local diabetes educator
- Mental Health/Coping
 - Diabetes Burnout, Bill Polonsky
 - Diabetes Sucks, and you can handle it, Mark Heyman
- Podcasts!
 - ADCES's The Huddle
 - Juicebox
 - Diabetes Connections
 - Just my type- the Diabetes Podcast
 - TCOYD
 - Embracing Diabetes



Diabetessisters.org

The logo for diaTribe Learn features the text "diaTribe Learn" in a teal, sans-serif font. Below it, the tagline "MAKING SENSE OF DIABETES" is written in a smaller, grey, sans-serif font. The background is white.

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MAKING SENSE OF DIABETES

Diatrube.org



Beyondtype2.org

<https://beyondtype2.org/diabetes-podcasts/>

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THE END

Questions?

