Case Studies in Diabetes

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Disclosures

- none

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Objectives

- Review 2023 ADA and AACE guidelines for pharmacologic management of T2DM
- Prioritize management of complications and comorbidities in patients with diabetes
- Identify “atypical diabetes” and management strategies

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Case 1

68-year-old female with primary hypertension, CAD s/p PCI 9 months ago, and recently diagnosed diabetes mellitus with A1c of 8%. She is a current smoker. Medications include lisinopril, aspirin, and clopidogrel. Family history includes T2DM in her father and paternal uncle. BMI is 35 kg/m^2.

What medication would you start initially?
A) Metformin
B) GLP-1RA
C) Sulfonylurea
D) DPP-4i

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DPP-4i
GLP-1 RA
Basal insulin
GIP/GLP-1 RA
Sulfonylurea
Metformin
Pioglitazone
Prandial insulin
SGLT2i

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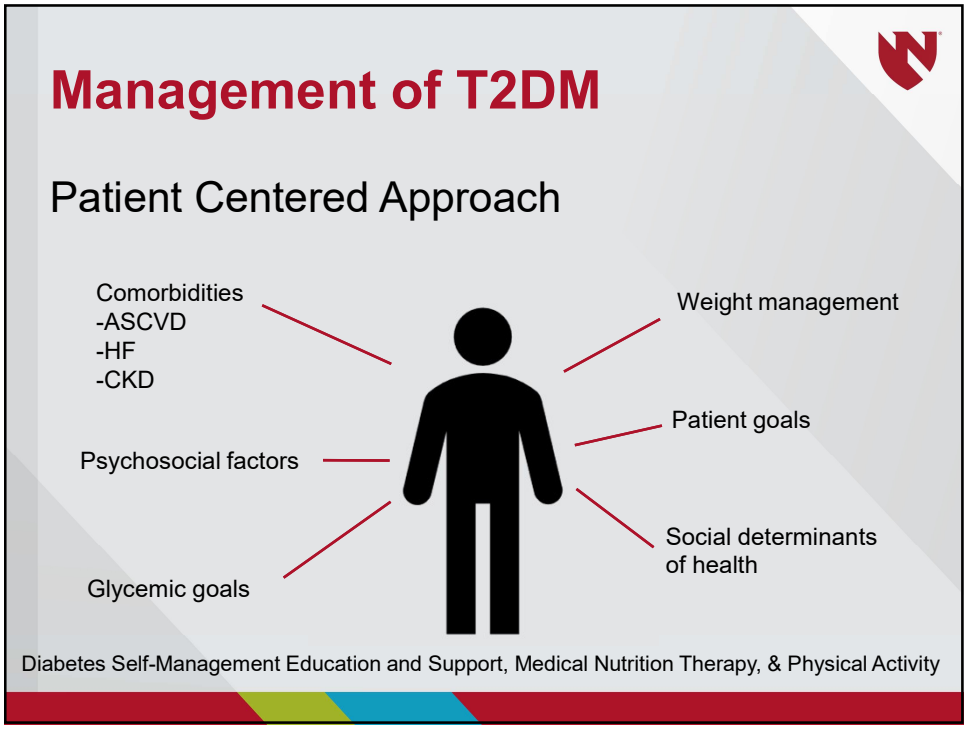
Management of T2DM
Patient Centered Approach
Comorbidities
-ASCVD
-HF
-CKD
Psychosocial factors
Glycemic goals
Weight management
Patient goals
Social determinants
of health
Diabetes Self-Management Education and Support, Medical Nutrition Therapy, & Physical Activity

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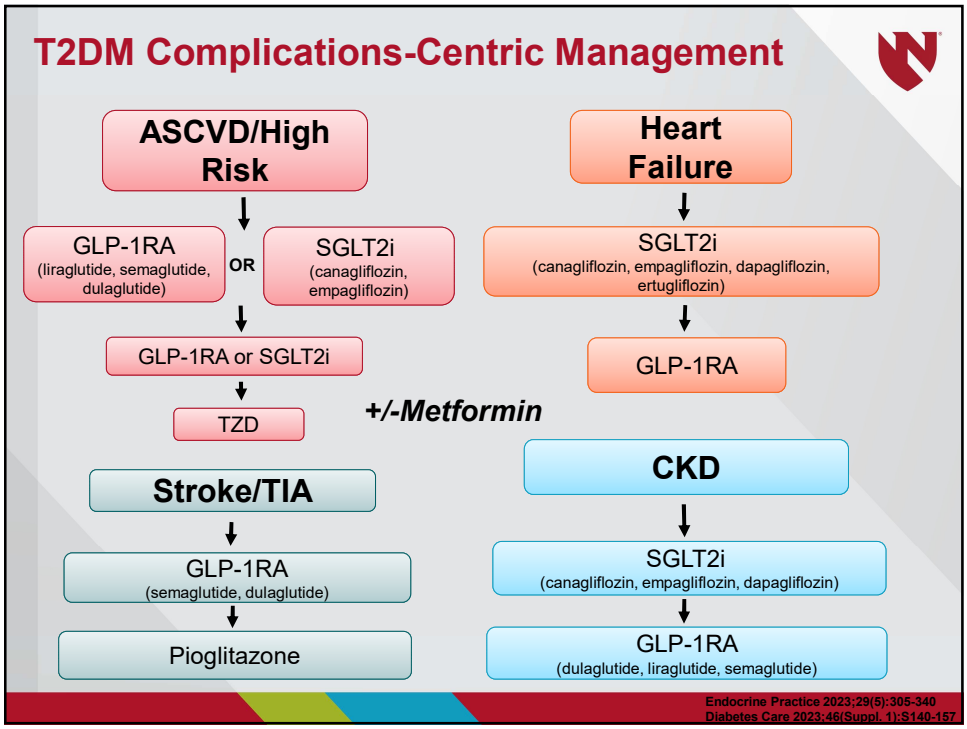
T2DM Complications-Centric Management
ASCVD/High Risk
GLP-1RA (liraglutide, semaglutide, dulaglutide)
OR
SGLT2i (canagliflozin, empagliflozin)
GLP-1RA or SGLT2i
TZD
+/-Metformin
Heart Failure
SGLT2i (canagliflozin, empagliflozin, dapagliflozin, ertugliflozin)
GLP-1RA
Stroke/TIA
GLP-1RA (semaglutide, dulaglutide)
Pioglitazone
CKD
SGLT2i (canagliflozin, empagliflozin, dapagliflozin)
GLP-1RA (dulaglutide, liraglutide, semaglutide)
Endocrine Practice 2023;29(5):305-340
Diabetes Care 2023;46(Suppl. 1):S140-157

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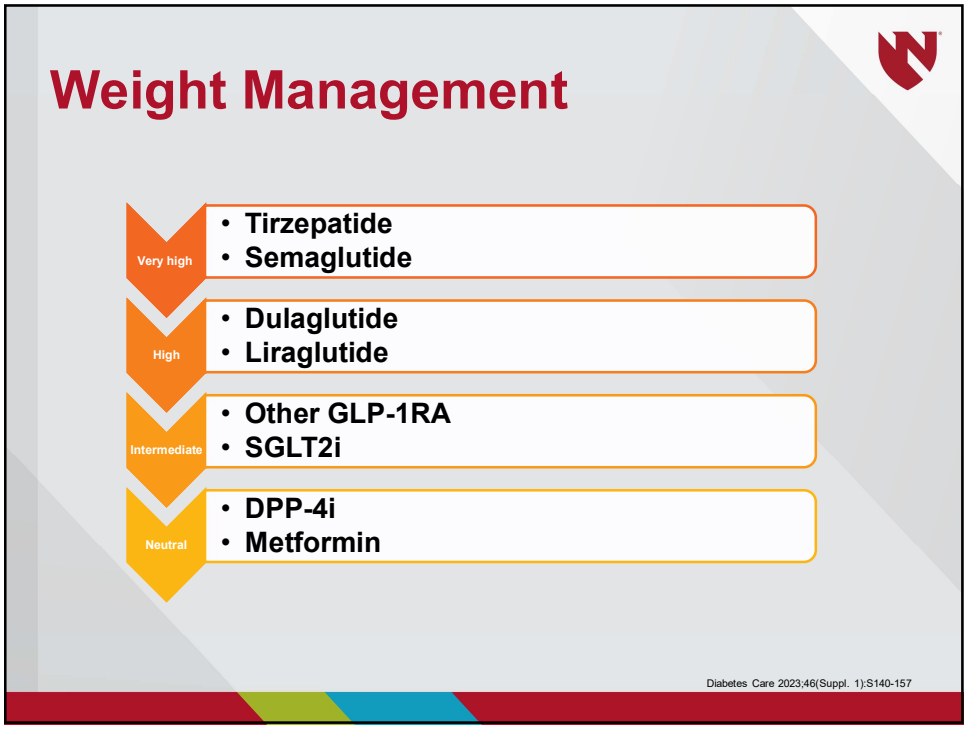
Weight Management
Very high
• Tirzepatide
• Semaglutide
High
• Dulaglutide
• Liraglutide
Intermediate
• Other GLP-1RA
• SGLT2i
Neutral
• DPP-4i
• Metformin
Diabetes Care 2023;46(Suppl. 1):S140-157

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A1c Lowering Hierarchy

Very H

Hig

Interme

Drug	A1c
GIP/GLP-1RA	-2.3
GLP-1RA (high dose)	-1.77 to –2.1
Metformin	-1
SGLT2i	-1.01
Sulfonylurea	-1.17
TZD	-0.98
DPP4i	-0.72

Diabetes Care 2023;46(Suppl. 1):S140-157
NEJM 2021; 385:503-515
Clin Pharmacol Ther 2019; 105:1213-1223
Diabetes Care 2021;44(3):765-773
Lancet Diabetes Endocrinol 2021;9(9)563-574

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Glucose-Centric Management

Lifestyle Intervention

Metformin

Overweight/Obesity

- **1st: GLP-1RA or GIP/GLP-1RA or SGLT2i**
- 2nd: DPP-4i or TZD* (CVD/NAFLD)
- *Avoid SU and Glinides*

High Risk of Hypoglycemia

- **1st: GLP-1RA or GIP/GLP-1RA or SGLT2i**
- 2nd: DPP-4i or TZD
- *Avoid SU and Glinides*

Cost

- **1st: TZD or SU**
- 2nd: Insulin or DPP-4i

Severe hyperglycemia

- **1st: Basal insulin +/- GLP-1RA or GIP/GLP-1RA or Prandial insulin**
- 2nd: Basal insulin + other oral agents

Endocrine Practice 2023;29(5):305-340
Diabetes Care 2023;46(Suppl. 1):S140-157

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Glucose-Centric Management

Uncontrolled
despite lifestyle intervention, maximizing non-insulin medications, behavioral modification, diabetes education

↓

GLP-1RA or GIP/GLP-1RA

↓

Basal insulin
10 units per day or 0.1 - 0.2 units/kg per day with titration
Discontinue SU, Consider CGM

↓

Prandial Insulin
Start with largest meal of the day (10% of basal or 4 to 5 units)
CGM if not already using

Endocrine Practice 2023;29(5):305-340
Diabetes Care 2023;46(Suppl. 1):S140-157

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Case 1

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What medication would you start initially?
A) Metformin
B) GLP-1RA
C) Sulfonylurea
D) DPP-4i

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Case 2

65-year-old male with type 2 diabetes mellitus for the past 4 years, previously controlled with metformin monotherapy. Most recently his HbA1c increased from 7% to 8.2%. His PMH includes hypertension. BMI is 42 kg/m^2. Medications also include atorvastatin and lisinopril. He does not have albuminuria.

What agent would you add?
A) Glipizide
B) GLP-1RA
C) Pioglitazone
D) Basal insulin

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Glycemia Reduction in Type 2 Diabetes – Glycemic Outcomes **GRADE**

5047 participants with T2DM < 10 years duration on metformin with A1c 6.8-8.5% randomized to receive glargine, glimepiride, liraglutide or sitagliptin.
Mean follow up of 5 years

Primary outcome: A1c > 7%

- 77% sitagliptin
- 72% glimepiride
- 68% liraglutide
- 67% glargine

Time (days) to A1c > 7%

- 697 sitagliptin
- 809 glimepiride
- 882 liraglutide
- 861 glargine

NEJM 2022; 387(12):1063-1074

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Case 2

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What agent would you add?
A) Glipizide
B) GLP-1RA
C) Pioglitazone
D) Basal insulin

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Case 2 continued

65-year-old male with type 2 diabetes mellitus, on metformin and ***glipizide*** with A1c </=7% for 2 years, now with A1c of 8.5%. No albuminuria or CKD.

What agent would you add?
A) GLP-1RA
B) SGLT2i
C) Pioglitazone
D) DPP-4i
E) Insulin

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A1c lowering of 3rd agent

Meta-analysis of third agent added to metformin and SU, 15 RCT, 6244 participants

A1c lowering:
GLP-1RA: -0.97
Basal insulin: -0.75
SGLT2i: -0.73
DPP-4i: -0.65

Diabetes Obes Metab. 2018:985-997

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Case 2 continued

65-year-old male with type 2 diabetes mellitus, on metformin and glipizide with A1c </=7% for 2 years, now with A1c of 8.5%. No albuminuria or CKD.

What agent would you add?
A) GLP-1RA
B) SGLT2i
C) Pioglitazone
D) DPP4i
E) Insulin

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Case 3

65-year-old male with newly diagnosed T2DM, A1c of 8% with no comorbidities, he takes no medications. BMI is 35 kg/m^2

What medication(s) would you initiate?
A) Metformin
B) Sulfonylurea
C) DPP-4i
D) Combination therapy (metformin+DPP-4i)

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Combination therapy

VERIFY (**V**ildagliptin **E**fficacy **I**n combination with metfo**R**m**I**n for earl**Y** treatment of T2D)

Metformin vs Metformin + Vildagliptin

Treatment duration of 5 years

Primary endpoint: treatment failure (A1c ≥ 7%)

- 62.1% monotherapy
- 43.6% combination

Time to failure: 36.1 months monotherapy vs 61.9 months combination

Lancet 2019;394:1519-29

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Combination therapy

EDICT (**E**fficacy and **D**urability of **I**nitial **C**ombination **T**herapy for T2DM)

Conventional vs combination

Treatment goal: A1c < 6.5%

- **Conventional:** metformin --> glipizide --> insulin glargine (max 60 units/day)
- **Combination:** metformin + pioglitazone + exenatide

Primary outcome: A1c < 6.5% at 3 years

➢ 41% conventional vs 67% combination

Diabetes Care 2021;44:433-439

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Combination therapy

Increase durability

Target multiple pathways

Avoid therapeutic inertia

Reduce medication burden

Complimentary clinical benefits

AACE: A1c >7.5% start 2 agents, A1c >9% or 1.5% above goal start 2-3 agents

ADA: consider combination therapy if A1c >1.5 - 2% above target

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Case 3

65-year-old male with newly diagnosed T2DM, A1c of 8% with no comorbidities, he takes no medications. BMI is 35 kg/m^2

What medication(s) would you initiate?
A) Metformin
B) Sulfonylurea
C) DPP-4i
D) Combination therapy (metformin+DPP-4i)

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Case 4

80-year-old female with T2DM for 30 years, CKD stage 4, HTN, HLD and osteopenia. A1c is 10.6% on insulin degludec 105 units BID, insulin lispro 70/45/70, semaglutide 0.5 mg weekly (max tolerated dose), Libre 2 CGM. Reports missing lunch dose of lispro on average 3 days per week. Weight is 85kg, BMI 37 kg/m^2

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80-year-old female with T2DM for 30 years, CKD stage 4, HTN, HLD and osteopenia. A1c 10.6% on insulin degludec 105 units BID, insulin lispro 70/45/70, semaglutide 0.5 mg weekly (max tolerated dose), Libre 2 CGM. Reports missing lunch dose of lispro on average 3 days per week.

What would you do next?

A) Add pioglitazone
B) Increase prandial insulin
C) Increase basal insulin
D) Change to U-500
E) Add sulfonylurea

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U-500

- Both basal and prandial actions
  - Onset: 30-45 minutes
  - Peak: 2-4 hours, up to 8 hours with higher doses
  - Duration: 12-24 hours
- For patients using > 200 units/day
- Reduce injection burden, increase adherence
- Pen for safety

Humulin R insulin (U-500) package insert. Indianapolis, IN: Eli Lilly and Company; 2009.

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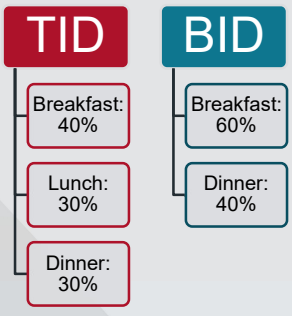
U-500 dosing

24 week open-label randomized clinical trial, patients with T2DM, A1c 7.5-12%, TDD 201-600 units/day randomized to U-500 TID or BID

A1c > 8%, TDD of U-500 = 100% U-100 dose
A1c ≤ 8%, TDD of U-500 = 80% U-100 dose



- A1c lowering similar between both regimens (~1.1-1.2%)
- More nocturnal hypoglycemia in BID group (<50 mg/dL - 49% vs 36%)
- No difference in incidence of severe hypoglycemia

Endocr Practice 2016; 21(7):782:905

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Case 4 follow up

Regimen

- U-500, 180 units before breakfast, 120 units before dinner
- Dapagliflozin 5 mg daily
- Semaglutide 0.5 mg weekly

3 month follow up:
A1c 8.6%

- >250 mg/dL - 34%
- 181-250 mg/dL – 33%
- 70-180 mg/dL - 31%
- 54-69 mg/dL - 2%
- <54 mg/dL - 0%

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Case 5

28-year-old male with 3-year history of diabetes diagnosed by A1c 7.3% after a hospitalization for a MVA revealed an elevated fasting glucose level. He has been treated with metformin 1g BID with persistently elevated A1c, most recently 7.8%. He has never had DKA. He reports a history of diabetes in his mother, maternal aunt and maternal grandfather. BMI 23 kg/m^2. He has no DM complications, including normal lipid levels. Physical exam shows no acanthosis nigricans nor central adiposity.

Is this type 2 diabetes?

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Case 5

28-year-old male with 3-year history of T2DM diagnosed by A1c 7.3% after a hospitalization for a MVA revealed an elevated fasting glucose level. He has been treated with metformin 1g BID with persistently elevated A1c, most recently 7.8%. He has never had DKA. He reports a history of diabetes in his mother, maternal aunt and maternal grandfather. BMI 23 kg/m^2. He has no DM complications, including normal lipid levels. Physical exam shows no acanthosis nigricans no central adiposity.

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Maturity Onset Diabetes of the Young (MODY)

- Monogenic diabetes
- 1/10,000 in adults, <5% of people with diabetes
- Young onset (< 35 years)
- Majority with autosomal dominant inheritance
- Non-insulin dependent

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Who should be tested?

ADA	Experts
Atypical diabetes	Atypical diabetes
Multiple family members with DM not characteristic of T1 or T2	Age <35
	Negative T1 Abs
	+ Neonatal hypoglycemia
	Family members with diabetes not typical of T1 or T2

Diabetes Care 2023;46(Suppl. 1):S19-S40.
JCEM 2021;106(1):237-250

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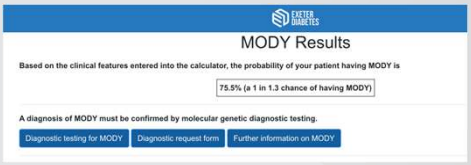
Exeter Diabetes MODY Probability Calculator

- Age at diagnosis
- Sex
- On therapy
- Time to insulin treatment
- BMI
- HbA1c
- Current Age
- Parent affected with diabetes
- Ethnicity
- Other – renal cysts, deafness, partial lipodystrophy, severe insulin resistance in the absence of obesity, severe obesity with other syndromic features



https://www.diabetesgenes.org/exeter-diabetes-app/
Diabetologia. 2012 May;55(5):1265-72

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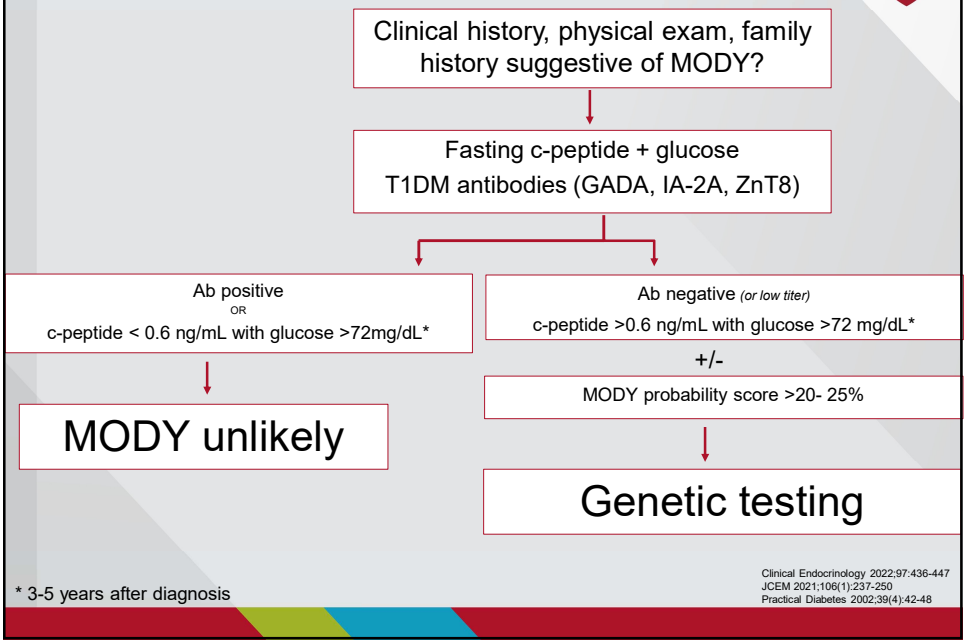
Who to test?



* 3-5 years after diagnosis

Clinical Endocrinology 2022;97:436-447
JCEM 2021;106(1):237-250
Practical Diabetes 2002;39(4):42-48

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Case 5

- Genetic testing revealed HNF1A-MODY (formerly MODY3)
  - Most commonly reported genetic variant (30-65% of all MODY cases)
  - Defective insulin secretion
- Management:
  - First line sulfonylurea
  - Second line: GLP-1RA, DPP4-i, insulin
  - Avoid SGLT2i

JCEM 2021;106(1):237-250

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Case 6

45-year-old female with new diagnosis of diabetes mellitus on screening labs. She has celiac disease. Family history includes T2DM in her father. She takes no medication. BMI 25 kg/m^2. A1c at diagnosis 7.5%.

What would you order for further evaluation?
A) Urine albumin: creatinine
B) Fasting lipid panel
C) C-peptide and glucose
D) GADA
E) A & B
F) A, B, C, D

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Case 6

- Urine albumin: creatinine < 30 mg/g
- Lipid panel – normal
- Fasting c-peptide 2 ng/mL with serum glucose 130
- GADA positive with high titer

What medication would you initiate?
A) Metformin
B) Sulfonylurea
C) SGLT2i
D) Basal insulin

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Latent Autoimmune Diabetes in Adults (LADA)

- Accounts for 2-12% of all patients with adult-onset diabetes

Characteristics
Age > 30 years
Family or personal history of autoimmunity
Reduced frequency of metabolic syndrome
C-peptide level declines more slowly than T1DM
GADA > ICA, IA-2A, ZnT8a
Non-insulin requiring at onset of DM

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Diagnosis of LADA

Diagnostic Criteria
Adult onset (> 30 years)
Presence of diabetes-associated autoantibodies
Absence of insulin requirement for at least 6 months after diagnosis

Diabetes 2020;69:2037-2047

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Who to screen?

- Expert panel suggests all patients with new onset T2DM get GADA - *?cost effective*
- Screen if one of following is present:
  - ✓ Family history of T1DM or autoimmune disease
  - ✓ Normal/slightly overweight BMI (<27 kg/m^2)
  - ✓ Young age at onset (<60 years)
  - ✓ Poor metabolic control

Diabetes 2020;69:2037-2047

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LADA Management

- Higher GADA titer or multiple positive antibodies = greater risk of insulin requirement
- Check c-peptide + glucose to guide treatment

c-peptide

< 0.6 ng/mL	≥0.6 - ≤ 2.1 ng/mL	>2.1 ng/mL
• Insulin	• Follow current guildeines based on co-morbidities • Avoid Sulfonylureas • Caution with SGLT2i • Low threshold for insulin	• Follow current guidelines, follow with repeat c-peptide measurements if deterioration of glucose control

Diabetes 2020;69:2037-2047

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Case 6

45-year-old female with LADA, no CVD, CKD, or HF, normal BMI. C-peptide 2 ng/mL.

What medication would you initiate?
A) Metformin
B) Sulfonylurea
C) SGLT2i
D) Basal insulin

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Case 7

48-year-old man with diabetes mellitus presents for follow up. DM was diagnosed at age 45 on annual labs, he was started on metformin but his A1c continued to rise so glipizide was added. He complains of abdominal pain and unintentional weight loss of 8lb in the last 2 months. BMI 24 kg/m^2. There is no family history of diabetes nor autoimmune diseases. His A1c is now 10%.

What medication would you add?
A) GLP-1RA
B) SGLT2i
C) Pioglitazone
D) Need more information/None of the above

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Case 7 – more history

He was hospitalized at age 43 with alcohol induced pancreatitis and again at age 45. He is now sober. He has intermittent abdominal pain and has foul smelling stools over the last year.

GADA negative

C-peptide 0.5 ng/mL (RR 0.7-4.4 ng/mL), glucose 140 mg/dL

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CT scan

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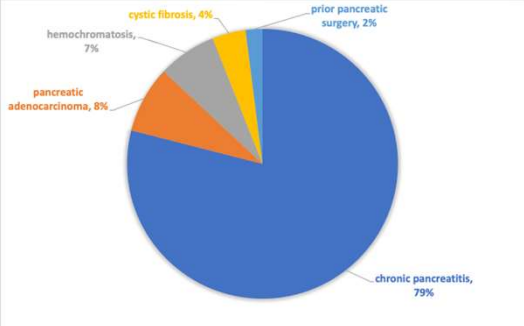
Type 3c or Pancreatic Diabetes

Postpancreatitis diabetes mellitus:

1. Pancreatic exocrine insufficiency
2. Pathologic pancreatic imaging
3. Absence of T1 diabetes associated autoimmunity



Diabetes Metab Res Rev 2012;28;338-342

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Pancreatic Diabetes Treatment

First line:

- Metformin
- Insulin

SGLT2i - risk of DKA if insulin deficient
TZD - risk of bone loss
GLP-1RA/DPP4i - pancreatitis risk
SU - beta cell exhaustion/insulin deficient

Lancet Gastroenterol Hepatol 2016;1(3):226-237

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Case 7

48-year-old man with diabetes mellitus presents for follow up. T2DM was diagnosed at age 45 on annual labs, he was started on metformin but his A1c continued to rise so glipizide was added. He complains of abdominal pain and unintentional weight loss of 8lb in the last 2 months. BMI 24 kg/m^2. There is no family history of diabetes nor autoimmune diseases. His A1c is now 10%. C-peptide is low, GADA negative.

What medication would you add?

1. GLP-1RA
2. SGLT2i
3. Pioglitazone
4. Insulin

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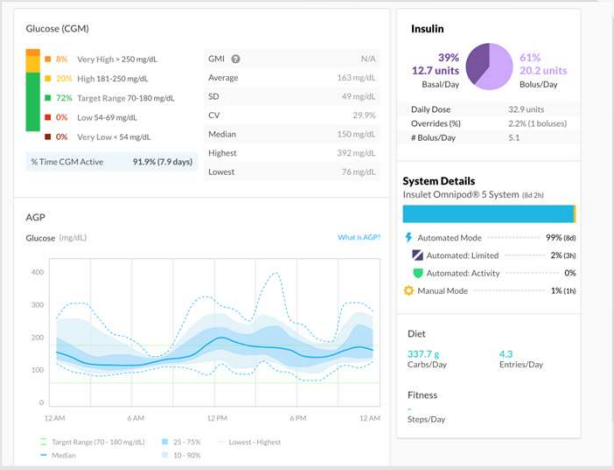
Case 7

Transitioned from MDI to AID with omnipod 5 and dexcom G6



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Case 8

68-year-old female with T2DM for 8 years. She is currently on degludec 125 units daily, semaglutide 2 mg weekly, glipizide 10 mg BID and atorvastatin 40 mg daily. Weight is 93.5 kg, BMI 35 kg/m^2. A1c is 10.5%. She does not have HTN or albuminuria. Confirmed she is taking insulin appropriately, demonstrated good technique.

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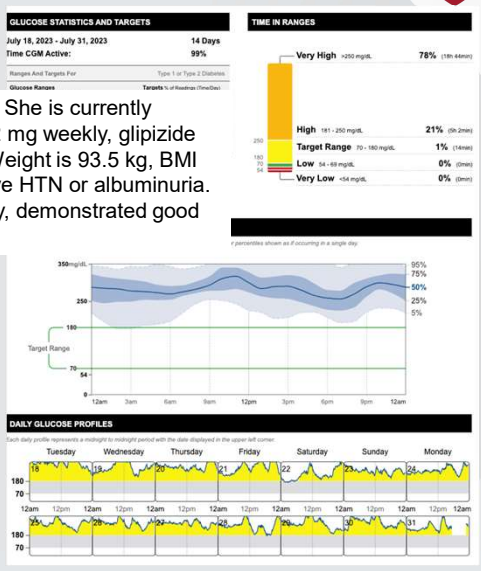
68-year-old female with T2DM for 8 years. She is currently on degludec 125 units daily, semaglutide 2 mg weekly, glipizide 10 mg BID and atorvastatin 40 mg daily. Weight is 93.5 kg, BMI 35 kg/m2. A1c is 10.5%. She does not have HTN or albuminuria. Confirms she is taking insulin appropriately, demonstrated good technique.



What would you change about her regimen?

A) Add SGLT2i

B) Add prandial insulin

C) Increase degludec

D) No change

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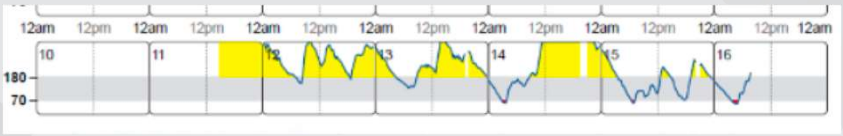
Prandial Insulin

- Add if basal dose is > 0.5 units/kg and glycemic goals are not achieved or BeAM score > 50 mg/dL
- **BeAM score:** Bedtime glucose – prebreakfast glucose



For this patient 0.5 unit/kg = 47 units

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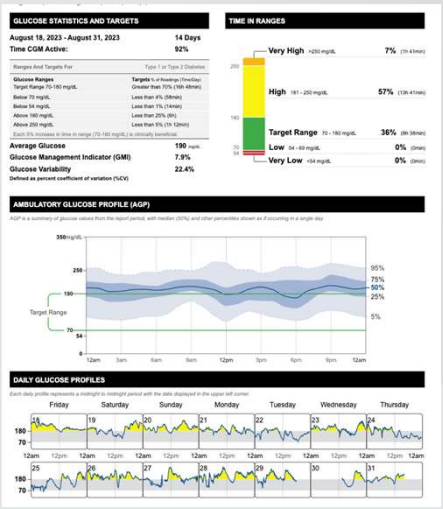
Case 8

Regimen:

- Stopped SU
- Reduce degludec 62 units daily
- Started lispro 20 units TID AC

3 weeks after change



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Case 9

65-year-old male with a 10-year history of T2DM complicated by CKD3b and mild non proliferative diabetic retinopathy, HTN. Medications include tirzepatide 15 mg weekly, glargine 20 units nightly, and losartan 100 mg daily. He had recurrent genitourinary infections on SGLT2i. A1c is 6.6%, urine albumin: creatinine 400 mg/g (1 year ago 250 mg/g), Cr 1.5mg/dL with eGFR 40 mL/min/1.73m2

What would you do next?
A) Continue regimen
B) Add prandial insulin
C) Add finerenone

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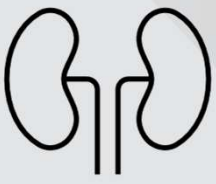
Finerenone

- Nonsteroidal, selective mineralocorticoid receptor antagonist
- Overactivation of mineralocorticoid receptor in cardiorenal diseases leads to inflammation and fibrosis causing progressive kidney and cardiovascular dysfunction



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FIDELIO-DKD

5674 adults with T2DM with CKD randomized to finerenone vs placebo

Primary outcome: composite of kidney failure, sustained decrease of ≥ 40% in eGFR from baseline, death from renal causes

504 pts (17.8%) in finerenone group vs 600 (21.1%) in placebo group
Number needed to treat: 29

Secondary outcome: composite of CV death, nonfatal MI, nonfatal stroke, or HF hospitalization

367 (13%) in finerenone group vs 420 (14.8%) in placebo group
Number needed to treat: 42

NEJM 2021; 385:2252-2263.

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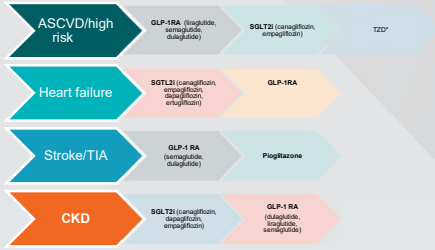
Summary

- Lifestyle and behavioral modifications are always first line for diabetes care
- Diabetes complications should drive medication management
- Prioritize weight management
- Atypical diabetes requires further evaluation to guide treatment



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