Weill Cornell-Qatar Qatar University

Management of diabetes

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Session objectives

- Discuss the initial approach to patients with newlydiagnosed type 2 diabetes
- Recognize the different non-insulin glucose-lowering agents including their characteristics, indications, advantages and disadvantages
- Explain the indications for insulin therapy and types of insulin
- Describe the aspects of standards of diabetes care

CASE 1

- A 41-year-old man with no past medical history
- Routine check up
- Normal physical exam
- Fasting plasma glucose of 10 mmol (180 mg)
- Kidney and liver function tests: normal
- Repeat (after 3 days) fasting glucose 9.5 mmol (171 mg)
- How would you approach?

Case approach

- Does he have diabetes?
- Fasting glucose 10 mmol (180 mg)
- Repeat glucose 9.5 mmol (171 mg)
- The diagnosis of diabetes can be made as fasting plasma glucose is ≥7 mmol (126 mg) confirmed on a repeat test
- What is next?

Approach to DM: history

- Duration of diabetes
- Medications and any side effects
- Adherence to medications
- Follow up (frequency, regular?)
- Presence of complications (acute or chronic)
- Screening for complications (eye, foot, lab. tests)
- Home glucose monitoring
- Comorbidities (HTN, ASCVD, HF, CKD...)

Approach to DM: history

- Social history: smoking, alcohol, work
- Social determinants of health (family support, housing stability, financial security, transportation access)
- Lifestyle changes (diet, exercise, sleep behaviors)
- Visits to the educator and dietitian
- Visits to the dentist
- Family history (DM, HTN, CVD)
- Vaccination

Approach to DM: physical exam

- Blood pressure
- Weight, height, BMI
- Thyroid
- Skin
- Foot

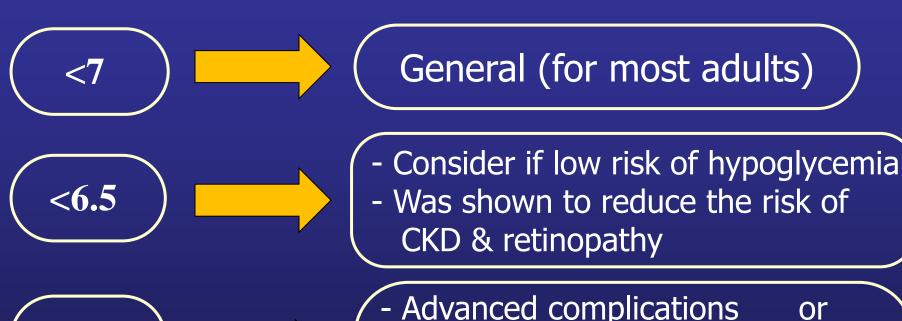
Approach to DM: lab. tests

- A1c
- Complete blood count (CBC)
- Lipids
- Serum creatinine, eGFR
- ALT, AST
- Urine albumin creatinine ratio (UACR)
- TSH for patients with type 1 DM

Setting glucose targets depends on:

- Age
- Duration of DM
- Comorbid conditions
- Vascular complications
- Life expectancy
- Risks associated with hypoglycemia
- Patient needs & preferences

Individualized A1c targets in DM





- Advanced complications
- Extensive comorbid conditions or
- Functionally dependent or
- Severe hypoglycemia or
- Limited life expectancy

Home glucose monitoring: general targets

Before meals: 80-130 mg (4.4-7.2 mmol)

2 hours after meals: <180 mg (10 mmol)



Back to our patient

• Fasting glucose 10 mmol (180 mg)

Repeated 9.5 mmol (171 mg)

• A1c 8.1%

What is next?

Aspects of lifestyle in diabetes

- 1) Education
- 2) Medical nutrition therapy (MNT)
- 3) Physical activity
- 4) Smoking cessation counselling (when needed)
- 5) Psychological care
- 6) Sleep health

Self management education and support

- Provided by a diabetes (or health) educator
- Empower the patient with:
 - Knowledge
 - Skills
 - Decision-making
- Individual or group education
- Regular follow up

Medical nutrition therapy in diabetes

- There is no "diabetic diet"
- There is no ideal calorie percentage (carbs, fat, protein)
- Assess willingness & ability to make behavioral changes
- Meal planning should be individualized
- Individualized session by a registered dietitian
- Consider personal and cultural preferences

Medical nutrition therapy in diabetes

- Aim for weight loss of at least 5% of body weight
- Weight loss of 10-15% in selected patients
- No specific diet has shown superiority
 - Low calorie diet with meal replacements
 - Mediterranean diet
 - Low carbohydrate diet
- Very low carbohydrate & high carbohydrate ketogenic diets are not recommended

Physical activity in diabetes

- Improves glucose, BP, and lipids parameters
- Target of ≥150 minutes/week
- Moderate to vigorous intensity aerobic activity
- Distributed over 3-5 days/week
- No more than 2 consecutive days without activity
- Prolonged sitting should be interrupted every 30 min.
- Resistance exercise: 2-3 sessions/week

Psychological care in DM

- Assessment for:
 - Depression
 - Anxiety
 - Diabetes distress
- Using age-appropriate validated tools (questionnaires)
 at the initial visit & at periodic intervals as needed
- Referral to mental health if positive screening

Sleep health in diabetes

- Higher risk of disturbed sleep, insomnia, obstructive sleep apnea, restless leg syndrome
- Abnormal sleep duration (<6 hours or >8 hours)
 negatively affects glucose, depression, quality of life
- Good quality of sleep improves glucose, BP, lipids, quality of life and ↓ depression
- Early chronotype vs late: has better glucose control

When to start medications in DM 2?

- American diabetes association recommends starting medications at the time of diagnosis
- Canadian diabetes association provides an option to start with lifestyle changes only for 3 months
- If A1c is $\geq 1.5\%$ above target (consider 2 medications)

When to start medications in DM 2?

- In the presence of any of the following (regardless of A1c level):
 - ◆ Atherosclerotic cardiovascular disease (ASCVD)
 - High risk for ASCVD
 - ◆ Chronic kidney disease (CKD)
 - ♦ Heart failure

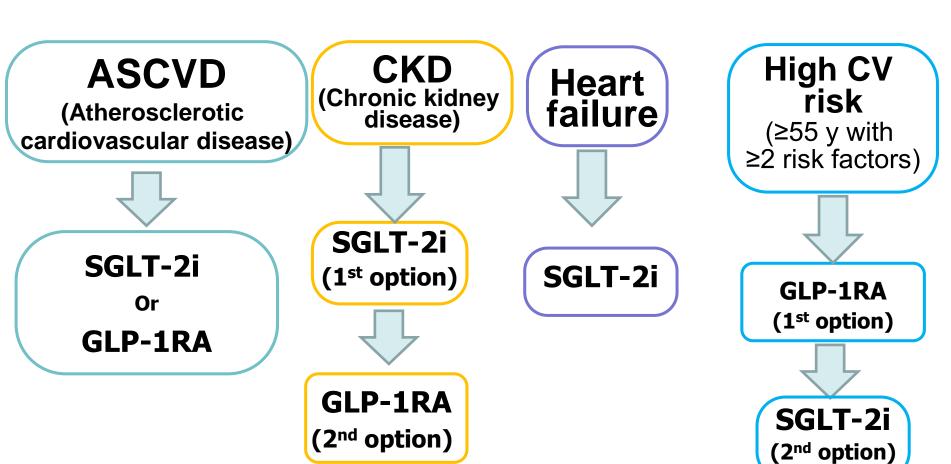
Which medication to choose?

Metformin



Other agents (depending on the situation)

Choice of DM agent and comorbid conditions



Benefits of Metformin

- High efficacy:
 - $-\downarrow$ A1c by 1 to 1.5%
- Rare hypoglycemia
- Weight loss or weight neutral
- Low cost
- Potential ↓ cardiovascular events & CV mortality

Metformin: Side effects

- GI side effects (gastric upset, nausea, diarrhea)
- Vitamin B₁₂ deficiency:
 - Periodic monitoring is recommended after 4 years of use (especially if there is anemia or peripheral neuropathy)
- Avoid in unstable or hospitalized patient with heart failure. Can be used in stable HF
- Hold if contrast procedure when eGFR 30-60.
 Resume after 48 hours if serum creatinine is stable

CASE 2

- A 42-year-old woman with type 2 DM for 2 years
- On Metformin 1000 mg bid
- Following lifestyle changes
- BMI 29
- HbA₁c 8.2%, Fasting glucose 10 mmol (180 mg)
- Kidney and liver function tests are normal
- How to approach?

Case approach

- Complete history, exam and labs
- Adherent to lifestyle changes?
- Follows with educator/dietitian?
- Adherent to medication?
- What are glucose targets?

Patient assessment

- Uncontrolled DM (A₁c 8.2)
- A1c target:
 - **♦** <7
- Patient is already following lifestyle changes
- Metformin alone is not enough
- We need to add another agent
- Which medication?

What's best after Metformin?

- Decision is based on:
 - Comorbidities (such as ASCVD, HF, CKD)
 - Glucose lowering effect
 - Effect on weight
 - Side effects
 - Risk of hypoglycemia
 - Cost
 - Patient preference

2nd line agents

- Sulfonylureas
- SGLT-2 inhibitors
- DPP-4 inhibitors
- GLP-1 receptor agonists
- GLP-1/GIP agonists
- Glitazones (TZD)
- Basal insulin

(Meglitinides & Alpha-glucosidase inhibitors are less commonly used)

<u>Sulfonylureas</u>

- Stimulate insulin secretion
- Examples: Glimepiride, Gliclazide, Glyburide, Glipizide
- Advantages:
 - Effective:
 - Lower A1c by 1 to 1.5%
 - Low cost
- Disadvantages:
 - Hypoglycemia
 - Weight gain
 - Glucose control may not be durable

SGLT-2 (sodium glucose cotransporter) inhibitors

- ↓ Glucose reabsorption at the kidney causing glucosuria
- Canagliflozin, Dapagliflozin, Empagliflozin
- Modest effect: lower A1c by 0.5-0.7%
- ↓ Weight
- Rare hypoglycemia
- Benefit in ASCVD, heart failure and CKD

SGLT-2i: disadvantages

- UTI, genital infections
- Dehydration, hypotension (in high-risk patients such as CKD, elderly, use with diuretics, low BP)
- Diabetic ketoacidosis (rare)
- ↑ risk of bone fractures (Canagliflozin)
- High cost

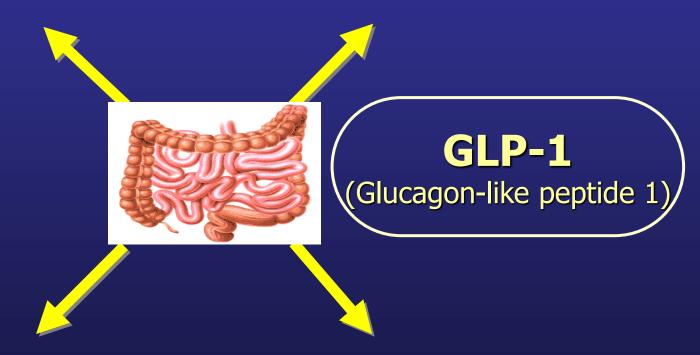
2nd line agents

- Sulfonylureas
- SGLT-2 inhibitors
- DPP-4 inhibitors
- GLP-1 receptor agonists
- GLP-1RA/GIP agonists
- Glitazones (TZD)
- Basal insulin

The incretin system

↑ Insulin secretion

↓ Glucagon secretion



↓ Gastric emptying

↓ Appetite

DPP-4 inhibitors



- DPP-4= "Dipeptidyl peptidase" inhibits GLP-1
- Inhibition of DPP-4 will make more GLP-1 available

DPP-4i: pros & cons

- Moderate effect (↓ A1c by 0.5 to 0.7%)
- Advantages:
 - Well tolerated
 - Weight neutral
 - Rare hypoglycemia
- Disadvantages/side effects:
 - GI upset, upper respiratory tract infections, joint/limb pains, acute pancreatitis
 - High cost

DPP-4 inhibitors (Gliptins)

- Taken with or without food
- Sitagliptin (Januvia[®])
- Vildagliptin (Galvus®)
- Linagliptin (Trajenta[®])
- Saxagliptin (Onglyza®)

GLP-1 receptor agonists

- ↑ GLP-1: leading to ↑ insulin, ↓ glucagon, ↓ appetite
- Effective (↓ A1c by 0.5-1.8%)
- Weight loss
- Rare hypoglycemia
- Benefit in ASCVD
- Benefit in high CV risk
- Kidney benefit (↓ albuminuria)

GLP-1 receptor agonists

- Subcutaneous injection
 - Exenatide, Liraglutide, Dulaglutide, Semaglutide
- Oral formulation (Semaglutide)
- GI side effects (nausea, vomiting, diarrhea)
- Acute pancreatitis?
- Should not be used in cases of medullary thyroid cancer (based on animal studies)
- Gall bladder disease (stones, cholecystitis)
- Very high cost

GIP/GLP-1 receptor agonists

- GIP (glucose-dependent insulinotropic polypeptide) & GLP-1 receptors agonist
- Tirzepatide
- Subcutaneous injection
- Very high glucose lowering efficacy
- Very high weight loss efficacy
- GI side effects (nausea, vomiting, diarrhea)
- Very high cost

TZD (Gitazones)

- † glucose uptake in muscle and fat tissue
- Pioglitazone (Actos[®])
- Taken at any time of the day
- Advantages:
 - Effective (but variable: ↓ A1c 0.5 to 1.5%)
 - Rare hypoglycemia
 - Low cost
 - Potential benefit in ASCVD
 - Benefit in NASH (nonalcoholic steatohepatitis)

Disadvantages of TZD

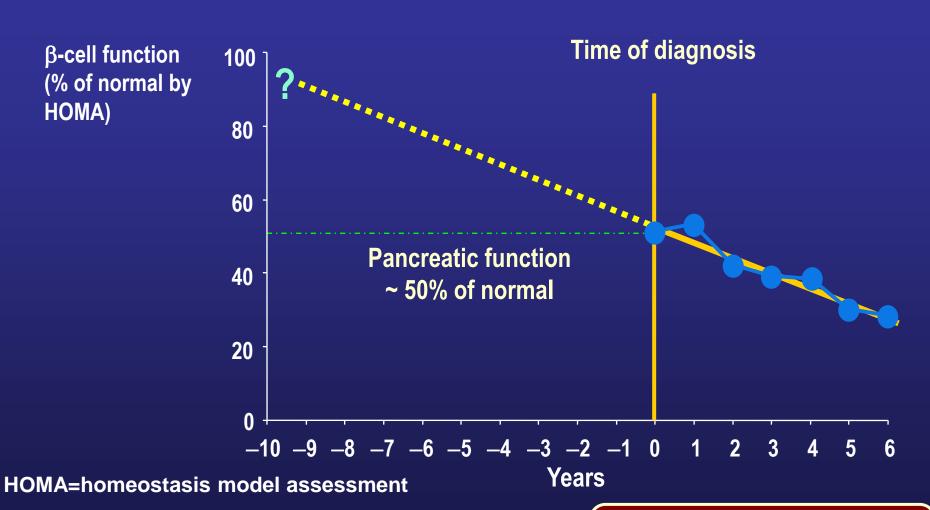
- Lower limb edema
- Weight gain
- Increased risk of heart failure
- Bone fractures
- Urinary bladder cancer (FDA & EMA warnings)

Diagnosis of type 2 DM Lifestyle changes **Assess comorbid conditions** ASCVD, HF, or CKD No ASCVD, HF, or CKD Start Metformin if A1c is not **Irrespective of A1c level or target** at target after 3 months Heart **CKD ASCVD** failure Add next step medication if A1c is atherosclerotic cardiovascular not at target after 3 months SGLT-2i disease) SGLT-2i SGLT-2i **High CV** Glucose Weight Hypoglycemia Cost (Empagliflozin¹ or risk lowering **lowering** concern Canagliflozin²) concern (≥55 y with Or ≥2 risk factors) Ÿ **GLP-1RA** (Liraglutide1 or **GIP/GLP-1** agonist SGLT-2i **GIP/GLP-1** agonist SU Dulaglutide²) **GLP-1RA GLP-1RA** (Semaglutide) **GLP-1RA** (Dula, Sema) **TZD GLP-1RA GIP/GLP-1** agonist **TZD** (Dulaglutide)

CASE 3

- A 52-year-old man with type 2 DM diagnosed
 8 years ago.
- He is on Metformin 1000 mg twice daily,
 Gliclazide MR 60 mg daily, Sitagliptin 100 mg daily,
 and Dapagliflozin 10 mg daily
- He is following the advised diet and exercise.
- HbA1c 8.8. Liver & kidney function tests are normal.
- His physician decided to start insulin.
- Do you agree? How would you approach?

Diabetes: a progressive disease



Holman RR. *Diab Res Clin Pract*. 1998;40(suppl):S21 UKPDS. *Diabetes*. 1995;44:1249

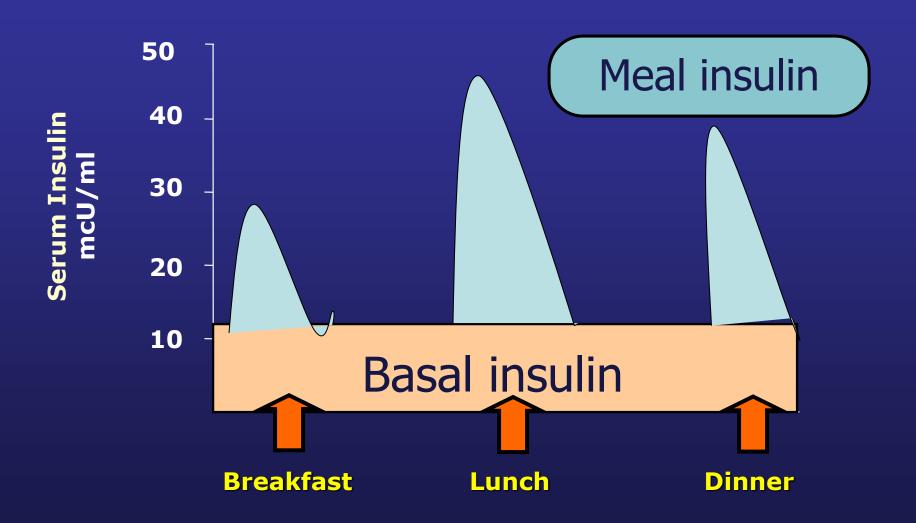
At diagnosis, ~ 50 % of insulin production is lost

Indications for insulin

- Failure of non-insulin glucose-lowering therapy
- Type 1 DM
- Pregnancy
- Significant symptomatic hyperglycemia (≥300 mg or A1c ≥10)
- During hospitalization

Types of insulin

Insulin secretion



Types of insulin

Basal insulin

Meal insulin

Basal insulin

Intermediate -acting:

NPH (Humulin N®, Insulatard®)

Long-acting:

Glargine U-100 (Lantus®)

Glargine U-300 (Toujeo®)

Detemir (Levemir®)

Degludec (Tresiba®)

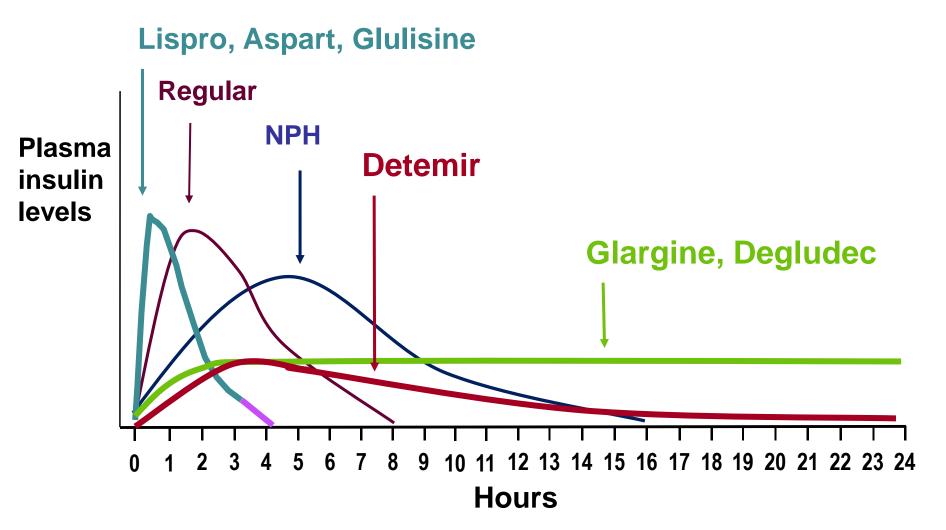
Meal Insulin

Short-acting:

Regular insulin (Actrapid®, Humulin R®, Novolin R®)

- Rapid-acting:
 - Aspart (Novorapid®, Novolog®)
 - Glulisine (Apidra®)
 - Lispro (Humalog®)

Action Profiles of Insulins



Hirsch I. New Eng J Med 2005;352:174 Danne T et al. Diabetes Care 2003;26:3087

Premixed insulins

• 70/30 (Mixtard 30[®], Humulin 70/30[®])

70% NPH, 30% Regular

• Aspart 70/30 (Novomix 30[®], Novolog[®] mix 70/30)

70% Aspart protamine + 30% Aspart

Premixed insulins

Lispro 75/25 (Humalog 25[®], Humalog Mix 75/25[®])

75% Lispro protamine + 25% Lispro

Lispro 50/50 (Humalog 50[®], Humalog Mix 50/50[®])

50% Lispro protamine + 50% Lispro

Which insulin to use?

Depends on:

Glucose control

Patient characteristics

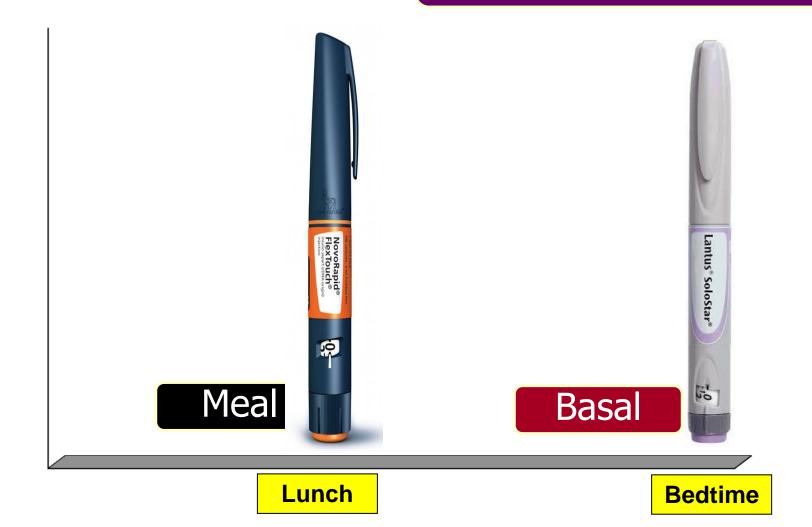
Lifestyle

Patient preference



Bedtime

Basal + 1 Meal



Basal + 2 Meal



Basal + 3 Meal











3 Premixed

Breakfast

Lunch

Dinner

CASE 4

- A 55-year-old man with DM 2 and hypertension
- Tries with lifestyle changes, but no regular exercise
- Metformin, Insulin, Lisinopril, Amlodipine
- B.P. 152/84, BMI 32
- HbA1c 8.1
- LDL 2.4 mmol (92 mg), HDL 1 mmol (38 mg),
 TG 1.7 mmol (150 mg)
- Kidney & liver function tests are normal
- How to apply a comprehensive plan of care?

Standards of diabetes care

- History, physical examination & basic labs
- Lifestyle changes
- Glucose control
- Screening for complications (periodic exams/tests)
- Cardiovascular disease
 - Lifestyle changes
 - Blood pressure
 - Statins for high risk
- Liver health
- Vaccination

Standards of diabetes care

- History, physical examination & basic labs
- Lifestyle changes
- Glucose control
- Screening for complications (periodic exams/tests)
- Cardiovascular disease
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 - Statins for high risk
- Liver health
- Vaccination

Approach to DM: history

- Duration of diabetes
- Medications and any side effects
- Adherence to medications
- Follow up
- Presence of complications (acute or chronic)
- Screening for complications (eye, foot, tests)
- Home glucose monitoring
- Comorbidities (HTN, dyslipidemia,...)

Approach to DM: history

- Social: smoking, work, alcohol
- Social determinants of health (family support & financial status)
- Lifestyle changes (diet, exercise)
- Visits to educator and dietitian
- Psychological status & support
- Family history (DM, HTN, CVD)
- Vaccination

Approach to DM: physical exam

- Blood pressure
- Weight, height, BMI
- Thyroid
- Skin
- Foot

Approach to DM: baseline lab. tests

- A1c
- CBC
- Lipids
- Serum creatinine, eGFR
- ALT, AST
- Urine albumin:creatinine ratio (UACR)
- TSH for type 1 DM

Standards of diabetes care

- History, physical examination, basic labs
- Lifestyle changes
- Glucose control
- Screening for complications (periodic exams/tests)
- Cardiovascular disease
 - Lifestyle changes
 - Blood pressure
 - Statins for high risk
- Liver health
- Vaccination

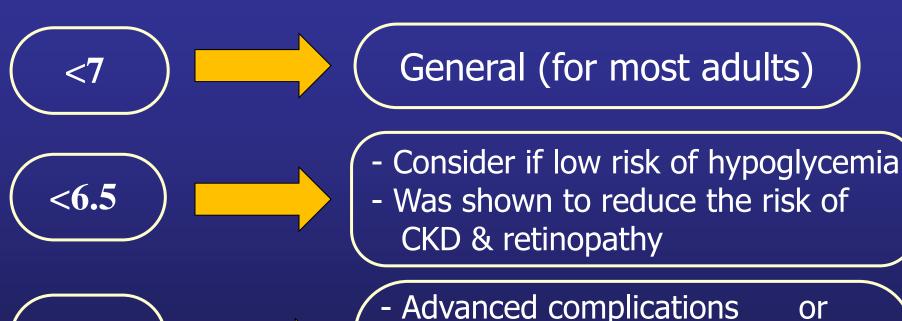
Aspects of lifestyle in diabetes

- 1) Education
- 2) Medical nutrition therapy (MNT)
- 3) Physical activity
- 4) Smoking cessation counselling (when needed)
- 5) Psychological care
- 6) Sleep health

Standards of diabetes care

- History, physical examination, basic labs
- Lifestyle changes
- Glucose control
- Screening for complications (periodic exams/tests)
- Cardiovascular disease
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- Vaccination

Individualized A1c targets in DM

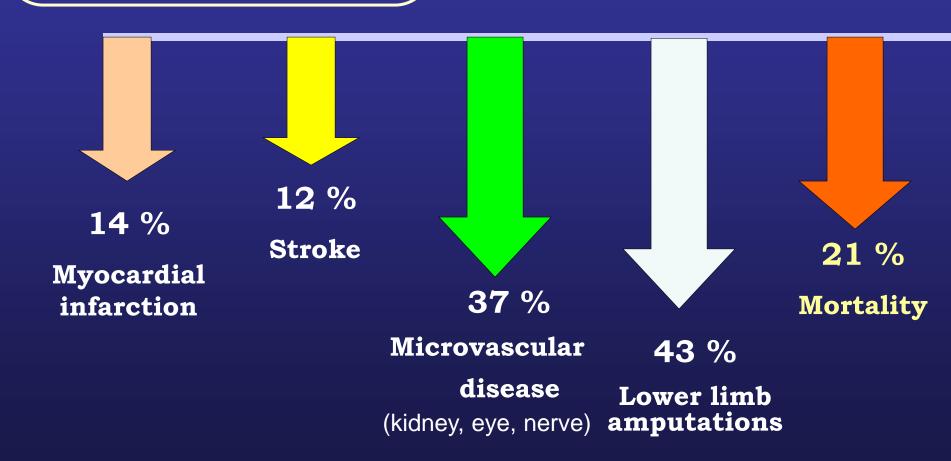




- Advanced complications
- Extensive comorbid conditions or
- Functionally dependent or
- Severe hypoglycemia or
- Limited life expectancy

Benefits of glucose control

Effect of \downarrow A1c by 1 %



Standards of diabetes care

- History, physical examination, basic labs
- Lifestyle changes
- Glucose control
- Screening for complications (periodic exams/tests)
- Cardiovascular disease
 - Lifestyle changes
 - Blood pressure
 - Statins for high risk
- Liver health
- Vaccination

Periodic exams & referrals

- Refer to educator
- Refer to dietitian
- Dilated eye exam
- Comprehensive foot exam
- Dental examination
- Family planning for women of reproductive age

Screening for diabetic retinopathy

Dilated eye examination

- Type 2 DM:
 - At the time of diagnosis then yearly
- Type 1 DM:
 - Start 5 years after diagnosis then yearly

Screening for diabetic neuropathy (distal symmetric)

- History & comprehensive foot examination:
- Type 2 DM:
 - At the time of diagnosis then at least yearly
- Type 1 DM:
 - Start 5 years after diagnosis then every year
 - Inspect feet at each visit for high-risk patients (sensory loss or prior ulceration or amputation)

Foot examination

- Visual inspection
- Vibration sensation (for large fiber function)
- 10-gram monofilament test (for large fiber function)
- Temperature or pinprick sensation (for small fiber function)
- Ankle reflex
- Pedal pulses (dorsalis pedis, posterior tibial)

Periodic lab. tests

1) A1c

- Every 6 months if controlled
- Every 3 months if not controlled
- 2) Serum creatinine, eGFR:
 - Yearly
 - More frequent if CKD or changing HTN medications
- 3) Urine albumin creatinine ratio:
 - Yearly
 - More frequent if abnormal

Periodic lab. tests

- 4) Lipids
 - Yearly
 - More frequent if not at target or changing doses/therapy
- 5) ALT, AST
 - Yearly
- 6) Serum vitamin B₁₂:
 - Monitoring if on metformin for >4 years
 - Every year in such cases
- 7) Complete blood count (CBC):
 - Yearly

DM & the kidneys

- Diabetes: the commonest cause of CKD & dialysis
- Serum creatinine, eGFR at least yearly
- Check random urine albumin:creatinine ratio (UACR)
 - If normal, check every year

Screening for diabetic kidney disease

Urine albumin: creatinine ratio

- Type 2 DM:
 - At the time of diagnosis then yearly
- Type 1 DM:
 - Start 5 years after diagnosis then yearly

Urine albumin:creatinine ratio (UACR)

- A spot random urine sample
- Normal: <3 mg/mmol (30 mg/g)
- If high: Repeat
- Causes of high UACR:
 - Exercise within 24 hours, infection, fever, menses, heart failure, menses, marked hyperglycemia, uncontrolled BP
- **Albuminuria**: 2 out of 3 abnormal UACR samples collected within 3-6 months

Management of albuminuria

- Glucose control
- Blood pressure control
- ACEI or ARB
- Combination of ACEI & ARB is not recommended
- Follow UACR & electrolytes
- ACEI/ARB are not recommended for primary prevention of diabetic kidney disease (normal B.P. & normal UACR)

Standards of diabetes care

- History, physical examination, basic labs
- Lifestyle changes
- Glucose control
- Screening for complications (periodic exams/tests)
- Cardiovascular disease
 - Lifestyle changes
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 - Statins for high risk
- Liver health
- Vaccination

DM & cardiovascular disease

- ↑ Risk of coronary artery disease by 200-400%
- ↑ Risk of ischemic stroke
- ↑ Rate of heart failure hospitalization
- ↑ Short- & long-term mortality after acute coronary syndrome
- ↑ Post-MI complications (recurrent ischemia, failure, shock)
- It is the major cause of death in DM

Primary prevention of CVD in DM

- Lifestyle (diet, exercise, healthy weight)
- Smoking cessation
- Blood pressure control
- Statins for high-risk patients
- Glucose control
- Need for aspirin?

Assess patient's risk of CVD

Using ACC/AHA 10-year ASCVD risk calculator

Diabetes & blood pressure

- Patients with DM have higher risk of hypertension
- Hypertension ↑ risk of cardiovascular complications
 (MI, stroke, PAD)
- Hypertension ↑ risk of microvascular complications (nephropathy, retinopathy, possibly neuropathy)
- Treatment of HTN reduces ASCVD events, heart failure
 & microvascular complications

Lifestyle changes in HTN

Diet

- DASH diet
 - Rich in fruits, vegetables, whole grains, nuts
 - Low fat dairy products, poultry, fish, vegetable oil
 - Reduce saturated and trans fat
 - Limit red meat, sweets and sweet beverages
- Reduced salt (<2300 mg/day)
- Weight loss, physical activity, smoking cessation

CVD protection in DM

HTN control:

- Target BP: < 130/80
- Some guidelines recommend ACEI or ARB as 1st choice

Statins:

- Secondary prevention for ASCVD
- Primary prevention for all patients age ≥40 years

Aspirin:

- Is generally not recommended
- Consider if high CVD risk with low bleeding risk

Statins in DM

With ASCVD

(Atherosclerotic Cardiovascular disease)

All ages



High intensity statin

Statins in diabetes Primary prevention

Age ≥40 years



High intensity statin if:



- Age 40-75 with no CV risk
- Age >75 years

Age 40-75 & ≥1 CV risk factor(s)
 (HTN, smoking, CKD, albuminuria, family history of premature CVD)

Statins in diabetes Primary prevention for age 20-39 years

Consider moderate intensity statin if multiple CV risk factors

Moderate-intensity statins

- Atorvastatin 10 or 20 mg
- Pravastatin 40 or 80 mg
- Rosuvastatin 5 or 10 mg
- Simvastatin 20 or 40 mg

High-intensity statins

- Atorvastatin 40 or 80 mg

- Rosuvastatin 20 or 40 mg

Standards of diabetes care

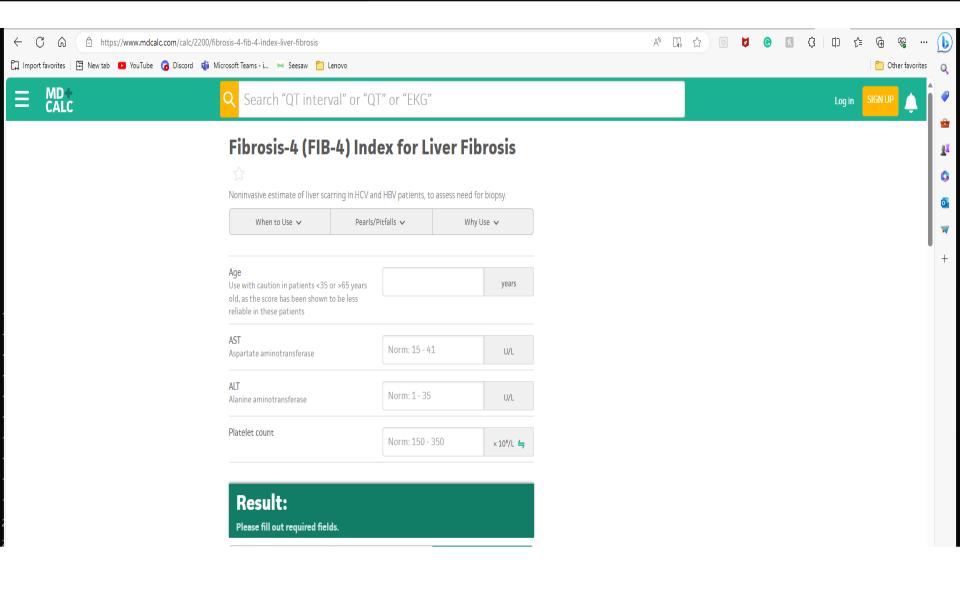
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NAFLD & diabetes

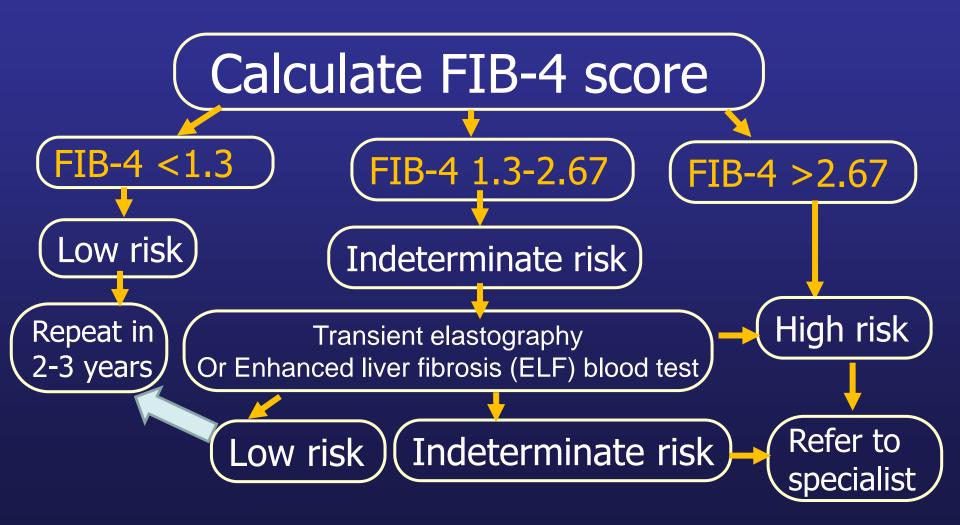
- NAFLD = Non-alcoholic fatty liver disease
- NASH = Non-alcoholic steatohepatitis
- DM 2 is a major risk factor & causes worse outcomes
- Number 1 cause of liver disease in western countries
- The most rapidly growing contributor to liver mortality and morbidity
- Asymptomatic, underdiagnosed & underrecognized

Screening for NAFLD should be done for patients with type 2 DM

• Using FIB-4 index (Age, ALT, AST, platelet count)



Screening for NAFLD in DM 2



Standards of diabetes care

- History, physical examination & basic labs
- Lifestyle changes
- Glucose control
- Screening for complications (periodic exams/tests)
- Cardiovascular disease
 - Lifestyle changes
 - Blood pressure
 - Statins for high risk
- Liver health
- Vaccination

Vaccination in DM

- Influenza
- Pneumococcal
- COVID-19
- Hepatitis B
- Others as people without DM

Do patients with DM need vitamins?

- No evidence for benefit for vitamins or supplements in patients with no deficiency
- Routine supplements with vitamins/antioxidants is not recommended
- Omega-3 supplements are not recommended for the prevention or treatment of CVD

Treatment of DM: Summary

- Lifestyle changes for all patients with DM 2
- ADA recommends medication at the time of diagnosis of DM 2; some start by lifestyle changes alone
- The choice (Metformin or others) depends on:
 - Comorbid conditions, effect on weight, cost, risk of hypoglycemia & patient's preference
- Use insulin if uncontrolled glucose on 3 or 4 agents

Diabetes Care (1)

<u>Lifestyle</u>: Education, diet, exercise, psychological care,

sleep health

Glucose: Target A₁c <7 (individualize)

Vascular: Statins for age ≥40

• **Blood pressure**: Target: <130/80

ACEI or ARB for hypertension

• **Kidneys**: Serum creatinine, urine albumin

creatinine ratio

Diabetes Care (2)

• **Eyes**: Dilated eye exam

• Foot: Comprehensive exam

• Liver health: Screen for NAFLD with FIB-4 index

Vaccination: Influenza, Pneumococcal,

COVID-19, Hepatitis B