Primary Care
MED437

Diabetes Mellitus

Objectives:

- Discuss the definition, etiology and classification of diabetes
- Explain the diagnosis and screening criteria for prediabetes and diabetes.
- Discuss comprehensive approach for diabetic patients could be provide in the clinic.
- List the essential Investigations and when should be done.
- Identify the glycemic targets for diabetic patients.
- Enumerate the microvascular and macrovascular complications of diabetes.
- Discuss the management including non-pharmacological and pharmacological for a diabetic patients.

Done by:

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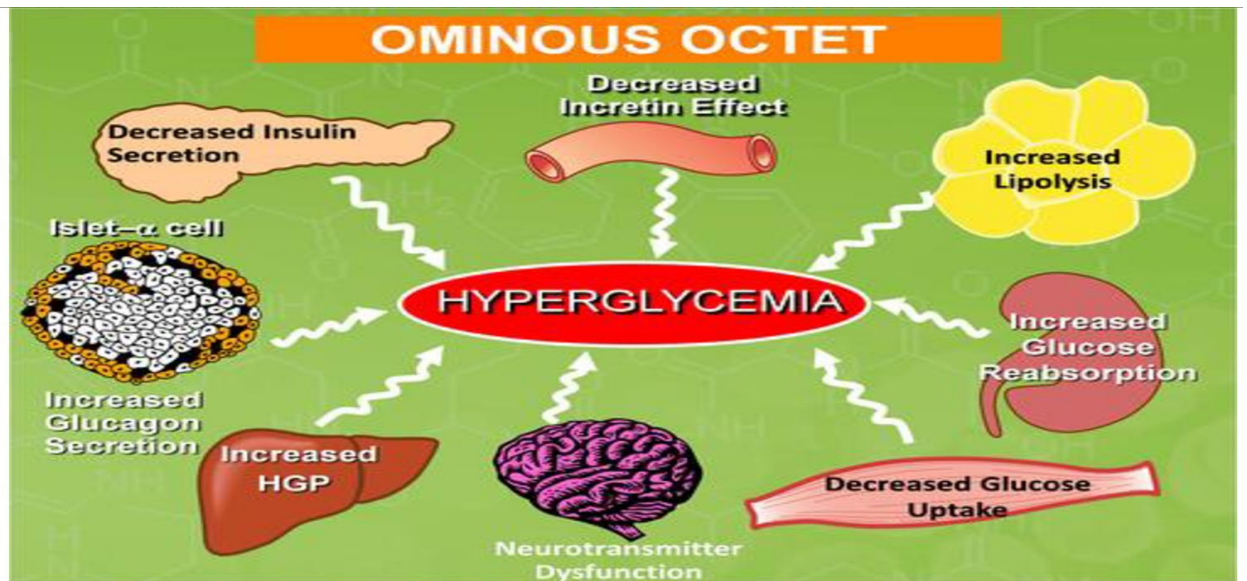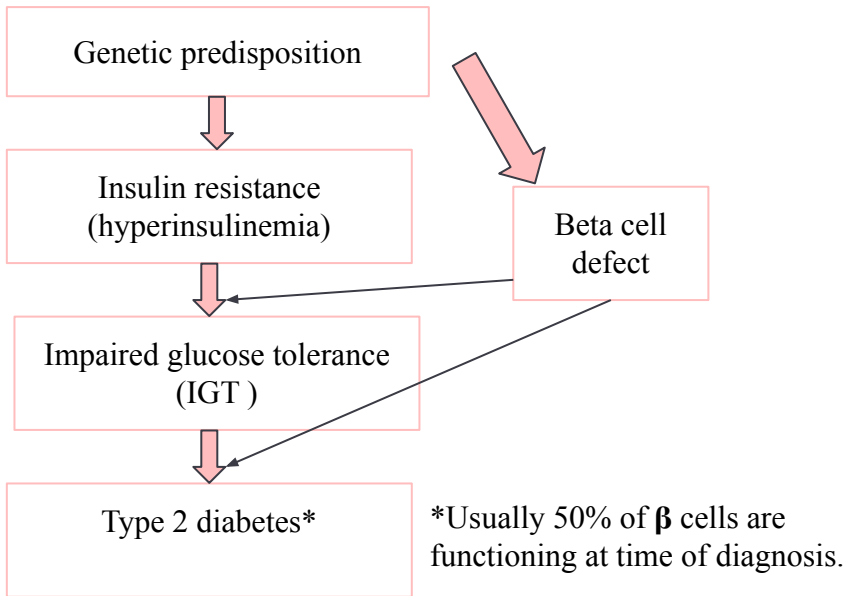Revised by: Salem AlAmmari, Sondos Alhawamdeh

References
- Doctor's slides and notes

Important	*Notes*	*Extra*	*Golden*

Pathophysiology:

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┌─────────────────────────┐
│  Genetic predisposition │
└─────────────────────────┘
            │
            ▼
┌─────────────────────────┐          ┌──────────────┐
│   Insulin resistance    │          │  Beta cell   │
│   (hyperinsulinemia)    │          │   defect     │
└─────────────────────────┘          └──────────────┘
            │
            ▼
┌─────────────────────────┐
│ Impaired glucose tolerance │
│        (IGT )           │
└─────────────────────────┘
            │
            ▼
┌─────────────────────────┐      *Usually 50% of β cells are
│    Type 2 diabetes*     │      functioning at time of diagnosis.
└─────────────────────────┘
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Recently, they found that the pathophysiology of type 2 DM is not limited to insulin resistance and relative reduction of insulin secretion. Other factors such as:

1- increased glucagon secretion

2- incretin system dysfunction

3- increased intestinal absorption of glucose

4- Brain Neurotransmitters that control satiety and hunger.

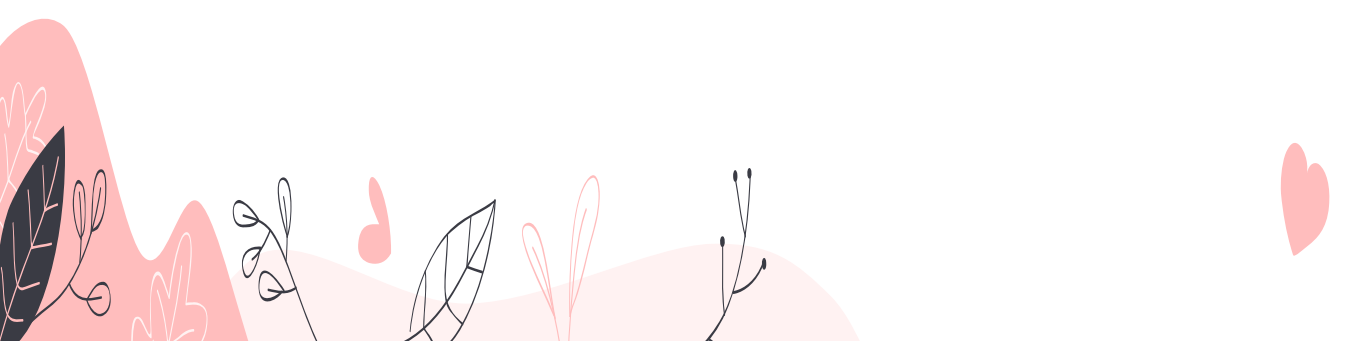So, new drugs are developed to act on these factors.

Prevalence of DM in Saudi Arabia

1. A community-based study of 17232 subjects conducted between 1995 and 2000 in KSA.
2. The examining age group, 30-70 years of selected households during 5-year period
3. The overall prevalence of DM obtained from this study is 23.7% in KSA.
4. The prevalence in males and females were 26.2% and 21.5% respectively ($p<0.00001$).
5. A large number of diabetics 1116 (27.9%) were unaware of having DM.

1 out of 4 are diabetic in SA. That's why screening is essential since most of them are asymptomatic

Classification diagnosis of diabetes

1. Type 1 diabetes (due to autoimmune **β-cell destruction**, usually leading to **absolute insulin deficiency**)

2. Type 2 diabetes (due to a **progressive loss of β-cell** insulin secretion frequently on the background of **insulin resistance**)

3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation) It's recommended to screen pregnant lady at 24-28w of gestation.

4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug-or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

Diagnostic Tests for Diabetes: (IMP)

1. FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least **8 h**.*

<div align="center">or</div>

2. 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.*

<div align="center">or</div>

3. A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*

<div align="center">or</div>

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, with a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

*in the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in 2 separate test sample,

If any of the previous tests is abnormal and the patient is symptomatic = Diagnose patient as diabetic
If the patient is asymptomatic = **Repeat** abnormal tests to diagnose patient as diabetic
Symptoms usually develop if HbA1c is 9 or above, or random plasma glucose above 250 or 300.

Pre-diabetic (IMP)

1. FPG 100 mg/dL (5.6 mmol/L) to 125 g/dL (6.9 mmol/L) (Impaired Fasting Glucose 'IFG')

<div align="center">or</div>

2. 2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (Impaired Glucose Test 'IGT')

<div align="center">or</div>

3. A1C 5.7-6.4% (39-46 mmol/mol)

*for all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range

In pre-diabetes, only 3 tests. **No** random plasma glucose as in DM diagnosis .
You need to **repeat** test even if the patient symptomatic.
EXTRA:There is no preferable test, you can choose any test but we usually do all the tests

Screening for diabetes: (IMP)

1. Testing should be considered in overweight or obese (BMI ≥ 25 kg/m2 or ≥23kg/m2 in Asian Americans) adults who have one or more of the following risk factors:

   a. First-degree relative with diabetes

   b. High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)

   c. History of CVD

   d. Hypertension (≥ 140/90 mmHg or in therapy for hypertension)

   e. HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L)

   f. Women with PCOS

   g. Physical inactivity

   h. Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

2. Patients with prediabetes (A1C ≥ 5.7% [39 mmol/mol], IGT or IFG) should be tested yearly.

3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.

4. For all other patients, testing should begin at the age 45 years.

5. 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.

When to screen for diabetes.
1- Anyone above 45y
2- Below 45y and BMI above 25 with any of the above factors: Family history, Hypertension and etc..
3- Prediabetic = yearly
4- History of gestational diabetes = every 3y
If testing is normal = repeat after 3y
If testing is abnormal = repeat every year

Prevention or delay of type 2 diabetes (IMP)

RECOMMENDATIONS:

1. At least annual monitoring for the development of type 2 diabetes in those with prediabetes is suggested. **E**
2. **Lifestyle interventions:**
    a. Refer patients with prediabetes to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. **A**
    Lifestyle modification:
    1- Physical activity: brisk walking for 150 min per week. Can be tailored as patient desire(3d with 50 min each or 5d with 30 min each) ''brisk walking كأن الواحد بيلحق على الركعة''
    2- Weight loss (7-10% of total body weight)
    b. **Based on patient preference, technology assisted diabetes prevention interventions may be effective in preventing type 2 diabetes and should be considered. B**
3. **Pharmacologic interventions**
    a. **Metformin** therapy for prevention of type 2 diabetes should be considered in those with **prediabetes**, especially for those with BMI ≥35 kg/m2, those aged <60 years, and women with prior GDM. **A**
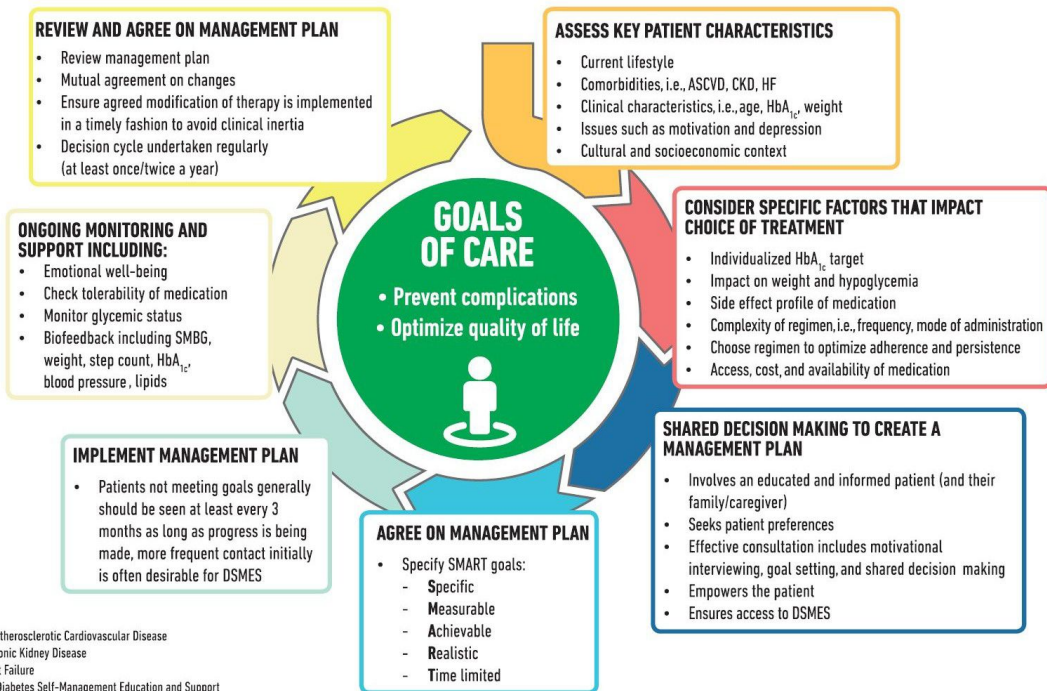   This topic is frequently asked in clinical practice, when to intervene pharmacologically as prevention ?
    Simply, **prediabetic** patients with:
    1- BMI > 35
    2-Age <60y
    3- Women with gestational diabetes

    Drugs that are proven to reduce progression of pre-diabetes to diabetes are:
    1-Metformin
    2- Acarbose
    3- Pioglitazone (TZD)
4. **Prevention of Cardiovascular disease**
    a. Prediabetes is associated with heightened cardiovascular risk; therefore,screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. **B**

Comprehensive Medical Evaluation And Assessment Of Comorbidities:

REVIEW AND AGREE ON MANAGEMENT PLAN
- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

ASSESS KEY PATIENT CHARACTERISTICS
- Current lifestyle
- Comorbidities, i.e., ASCVD, CKD, HF
- Clinical characteristics, i.e., age, HbA$_{1c}$, weight
- Issues such as motivation and depression
- Cultural and socioeconomic context

ONGOING MONITORING AND SUPPORT INCLUDING:
- Emotional well-being
- Check tolerability of medication
- Monitor glycemic status
- Biofeedback including SMBG, weight, step count, HbA$_{1c}$, blood pressure, lipids

CONSIDER SPECIFIC FACTORS THAT IMPACT CHOICE OF TREATMENT
- Individualized HbA$_{1c}$ target
- Impact on weight and hypoglycemia
- Side effect profile of medication
- Complexity of regimen, i.e., frequency, mode of administration
- Choose regimen to optimize adherence and persistence
- Access, cost, and availability of medication

GOALS OF CARE
- Prevent complications
- Optimize quality of life

IMPLEMENT MANAGEMENT PLAN
- Patients not meeting goals generally should be seen at least every 3 months as long as progress is being made, more frequent contact initially is often desirable for DSMES

AGREE ON MANAGEMENT PLAN
- Specify SMART goals:
  - **S**pecific
  - **M**easurable
  - **A**chievable
  - **R**ealistic
  - **T**ime limited

SHARED DECISION MAKING TO CREATE A MANAGEMENT PLAN
- Involves an educated and informed patient (and their family/caregiver)
- Seeks patient preferences
- Effective consultation includes motivational interviewing, goal setting, and shared decision making
- Empowers the patient
- Ensures access to DSMES

ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

RECOMMENDATIONS :

1. A complete medical evaluation should be performed at the initial visit to: Confirm the diagnosis and classify diabetes. **B**

2. Evaluate for diabetes complications and potential comorbid conditions. **B**

3. Review previous treatment and risk factor control in patients with established diabetes. **B**

4. Begin patient engagement in the formulation of a care management plan. **B**

5. Develop a plan for continuing care. **B** don't just evaluate the blood sugar instead you have to evaluate all the risk factors for developing complications and these summarized in **ABCS** (Hb**A**1c, **B**lood pressure, **C**holesterol, **S**moking)

Table 3.1 – Components of the comprehensive diabetes medical evaluation at initial and follow-up visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history** • Characteristics at onset (e.g., age, symptoms) • Review of previous treatment regimens and response • Assess frequency/cause/severity of past hospitalizations	✓ ✓ ✓		
	Family history • Family history of diabetes in a first-degree relative • Family history of autoimmune disorder Vitiligo, Hashimoto thyroiditis and etc.	✓ ✓		
	Personal history of complications and common comorbidities • Macrovascular and microvascular • Common comorbidities • Presence of hemoglobinopathies or anemias • High blood pressure or abnormal lipids • Last dental visit • Last dilated eye exam • Visits to specialists	✓ ✓ ✓ ✓ ✓ ✓ ✓	✓	✓ ✓ ✓
	Interval history • Changes in medical/family history since last visit		✓	✓
SOCIAL HISTORY	**Assess lifestyle and behavior patterns** • Eating patterns and weight history • Sleep behaviors and physical activity • Familiarity with carbohydrate counting in type 1 diabetes • Tobacco, alcohol, and substance use • Identify existing social supports	✓ ✓ ✓ ✓ ✓	✓ ✓	✓ ✓
	Interval history • Changes in social history since last visit		✓	✓
MEDICATIONS AND VACCINATIONS	• Medication-taking behavior • Medication intolerance or side effects • Complementary and alternative medicine use • Vaccination history and needs	✓ ✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓ ✓
TECHNOLOGY USE	• Assess use of health apps, online education, patient portals, etc. • Glucose monitoring (meter/CGM): results and data use • Review insulin pump settings	✓ ✓ ✓	✓ ✓	✓ ✓ ✓
SCREENING	**Psychosocial conditions** • Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted • Consider assessment for cognitive impairment*	✓ ✓		✓ ✓
	Diabetes self-management education and support • History of dietitian/diabetes educator visits • Screen for barriers to diabetes self-management • Refer or offer local resources and support as needed	✓ ✓ ✓	✓ ✓	✓ ✓ ✓
	Hypoglycemia • Timing of episodes, awareness, frequency and causes	✓	✓	✓
	Pregnancy planning HbA1c below 7(recommended) • For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

Table 3.1 – Components of the comprehensive diabetes medical evaluation at initial and follow-up vis

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	• Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	• Blood pressure determination	✓	✓	✓
	• Orthostatic blood pressure measures (when indicated)	✓		
	• Fundoscopic examination (refer to eye specialist)	✓		✓
	• Thyroid palpation *Autoimmune diseases!! Mainly type 1*	✓		✓
	• Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	• Comprehensive foot examination *Inspection, palpation, vibration and monofilament exam*			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)	✓	✓	✓
	• Screen for PAD (pedal pulses; refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10–g monofilament exam	✓		✓
LABORATORY EVALUATION	• A1C, if the results are not available within the past 3 months	✓	✓	✓
	• If not performed/available within the past year			
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides[#]	✓		✓^
	• Liver function tests[#] *LFTs; As a baseline, beside some diabetic drugs affect liver. Also most of diabetic patients will be on statins*	✓		✓
	• Spot urinary albumin–to–creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate[†]	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes[#]	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics[†]	✓		✓
ASSESSMENT AND PLAN	**Goal setting**			
	• Set A1C/blood glucose target and monitoring frequency	✓	✓	✓
	• If hypertension diagnosed, establish blood pressure goal	✓		✓
	• Incorporate new members to the care team as needed	✓	✓	✓
	• Diabetes education and self-management support needs	✓	✓	✓
	Cardiovascular risk assessment and staging of CKD			
	• History of ASCVD	✓	✓	✓
	• Presence of ASCVD risk factors (see Table 9.2)	✓	✓	✓
	• Staging of CKD (see Table 10.1)[†]	✓	✓	✓
	Therapeutic treatment plan			
	• Lifestyle management	✓	✓	✓
	• Pharmacologic therapy	✓	✓	✓
	• Referrals to specialists (including dietitian and diabetes educator) as needed	✓	✓	✓
	• Use of glucose monitoring and insulin delivery devices	✓	✓	✓

Assessment And Treatment Plan: (assessment and treatment planning is an essential component of initial and all follow-up visits)

Assess risk of diabetes complications
1. ASCVD and heart failure history
2. ASCVD risk factors and 10-year ASCVD risk assessment
3. Staging of chronic kidney disease
4. Hypoglycemia risk

Goal setting
1. Set A1C/blood glucose target
2. If HTN present, establish blood pressure target
3. Diabetes self-management goals (e.g., monitoring frequency)
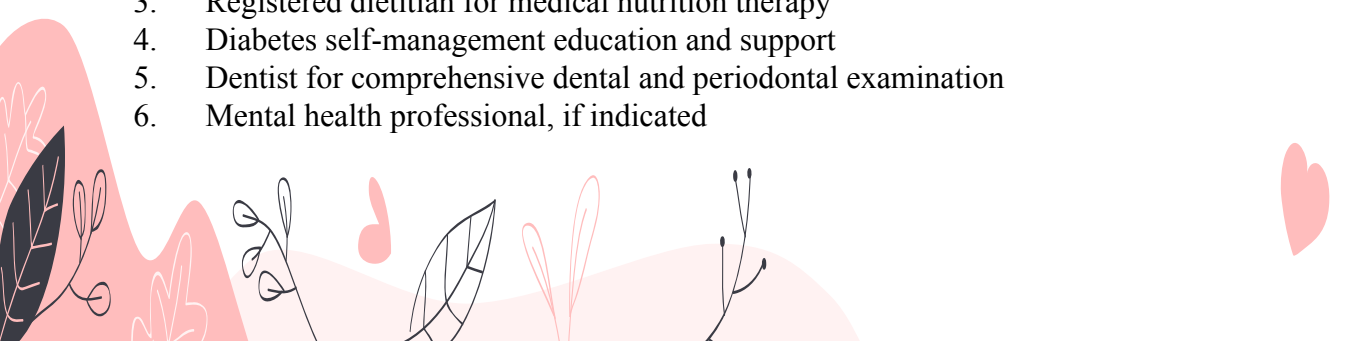
Therapeutic treatment plan
1. Lifestyle management
2. Pharmacologic therapy (glucose lowering)
3. Pharmacologic therapy (cardiovascular disease risk factors and renal)
4. Use of glucose monitoring and insulin delivery devices
5. Referral to diabetes education and medical specialist (as needed)

Assessment Of Hypoglycemia Risk

Factors that increase risk of treatment-associated hypoglycemia:
1. **Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)**
2. Impaired kidney or hepatic function
3. **Longer duration of diabetes**
4. Frailty and older age
5. **Cognitive impairment**
6. Impaired counterregulatory response, hypoglycemia unawareness
7. Physical or intellectual disability that may impair behavior response to hypoglycemia
8. Alcohol use
9. **Polypharmacy** (especially ACE inhibitors, angiotensin receptor blockers, non selective **β**-blockers).

Referral For Initial Care Management: Multidisciplinary approach
1. Eye care professional for annual dilated eye exam
2. Family planning for women of reproductive age
3. Registered dietitian for medical nutrition therapy
4. Diabetes self-management education and support
5. Dentist for comprehensive dental and periodontal examination
6. Mental health professional, if indicated

Glycemic targets

HbA1C Testing recommendation:
1. Perform the A1C test at least two times a year (every 6 mo) in patients who are meeting treatment goals (and who have stable glycemic control). **E**
2. Perform the A1C test quarterly (every 3 mo) in patients whose therapy has changed or who are not meeting glycemic goals. **E**
3. Point-of-care testing for A1C provides the opportunity for more timely treatment changes. **E**

HbA1C goals recommendation: See below *
1. A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). **A**
2. Providers might reasonably suggest more stringent AIC goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular Disease. **C.**
3. Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of **level 3 hypoglycemia** (altered mental and/or physical state requiring assistance), limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. **B**
4. Reassess glycemic targets over time based on the criteria. **E**

*Based on the patient condition:
1-life expectancy
2- DM duration
3- Comorbidities
4- other factors
85y w/ multiple comorbidities, HbA1c of 8 or 9 can be accepted. In contrary, the target of young healthy may be below 6.5

in general, the diabetic targets are:
1-HbA1c <7
2-Preprandial 80-130
3-Postprandial <180

HbA1c not alway a reliable test and can be misleading like for example a patient can have <7% and has high variability in the daily readings, also in case of hemoglobinopathies the hemoglobin lifespan is affected (hemolysis: shorter lifespan: less glucose saturation: low HbA1c reading,, and the opposite in iron deficiency anemia longer lifespan: more glucose saturation: high HbA1c reading)

TABLE 4. Summary of Glycemic Recommendations for Many Nonpregnant Adults With Diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Hypoglycemia: (IMP)

Don't get in details of hypoglycemia

1. **Level 1 hypoglycemia** is defined as a measurable glucose concentration <70 mg/ dL (3.9mmol/L).

2. **Level 2 hypoglycemia** (defined as a blood glucose concentration <54 mg/ dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event.

3. **Level 3 hypoglycemia** is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Recommendations in hypoglycemia

1. Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**
2. Glucose (15- 20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if Self-monitoring of blood glucose (SMBG) shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **E**
    Management of hypoglycemia:
    Remember role of 15
    1- 15g of simple sugar(juice, honey or soft drinks)
    2- Reassess after 15min
    Don't give chocolate because it contains lipids that may reduce glucose absorption.
3. Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/ dL (3.0 mmol/L), so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care Professionals. **E**
4. Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger reevaluation of the treatment regimen. **E**
5. Insulin treated patients with hypoglycemia unawareness or an episode of level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**
    Neuroregulatory mechanisms are adapted to hypoglycemia since patient had several attacks of hypoglycemia. So, the patient will not be aware of hypoglycemia.
    This is a very serious condition. We usually raise glycemic targets of patient. 200 for pre prandial instead of 80-130. This will be for a while to let nerves and other organs to recover. Then we return everything to normal.
6. Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition or declining cognition is found. **B**

Cardiovascular Disease And Risk Management

Hypertension/Blood Pressure Control: Recommendations for Screening and Diagnosis:

1. Blood pressure should be measured at every routine clinical visit. Patients found to have elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**
2. All hypertensive patients with diabetes should monitor their blood pressure at home. **B**

Cardiovascular Disease: Recommendations for Screening

1. In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as ASCVD risk factors are treated. **A**
2. Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**
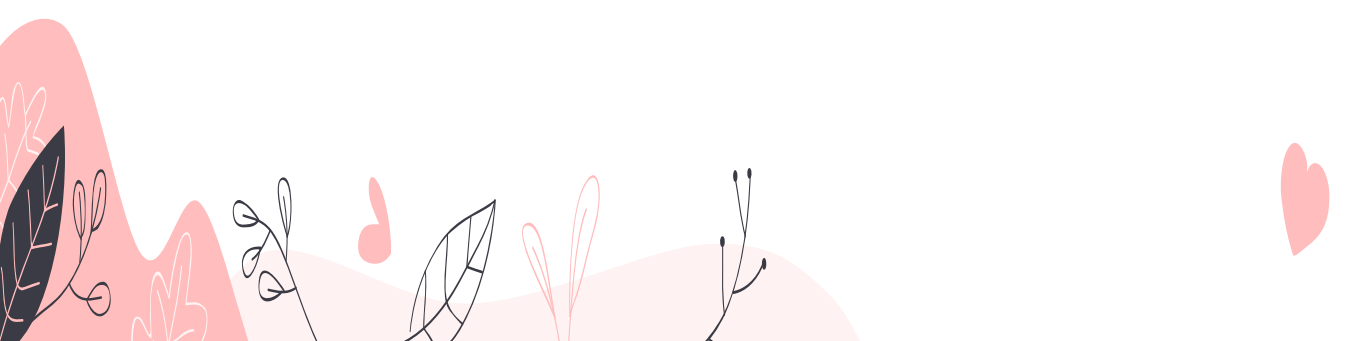
Usually diabetic patient would have:
1-HTN = target <140/90
2- Dyslipidemia

Antiplatelet Agents: Recommendations

1. Consider aspirin therapy (75-162 mg/day) as a primary prevention strategy in those with type 1 **or** type 2 diabetes at increased cardiovascular risk **C**
2. Includes most men or women with diabetes **age ≥50 years** who have at least one additional major risk factor, including:
    a. Family history of premature ASCVD
    b. Hypertension
    c. Smoking
    d. Dyslipidemia
    e. Albuminuria
1. Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effect from bleeding likely offset potential benefits: **C**
    a. Low risks such as in men or women with diabetes aged <50 years with no major additional ASCVD risk factors
2. In patients with diabetes <50 years of age with multiple other risk factors (e.g.,10 year risk 5-10%), clinical judgment is required. **E**
3. Use aspirin therapy (75–162 mg/day) as secondary prevention in those with diabetes and history of ASCVD. **A**
4. For patients w/ ASCVD & aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
5. Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. **B**

Lipid management in diabetic patients
Will be discussed later

Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9. *In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin—based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

Table 10.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–50%)
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

Other combination therapy: recommendations

- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not Recommended. **A**
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not Recommended . **A**

Microvascular complications and foot care

Briefly
DM 1 = screening after 5y of diagnosis
DM 2 = screening at diagnosis (normal > repeat yearly)

Eye > ophthalmologist
Kidney > nephrologist
Neuropathy
Foot care = podiatrist

Chronic Kidney Disease: Recommendations for Screening:

At least once a year, assess urinary albumin (e.g., spot urinary albumin to creatinine ratio) and eGFR in patients with type 1 diabetes with duration of ≥5 years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. **B**

Diabetic Retinopathy: Recommendations

1. Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**
2. Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**
3. Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
4. Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
5. If there is no evidence of retinopathy for one or more annual eye exam and glycaemia is well controlled, then exams every 1- 2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight threatening, then examinations will be required more frequently. **B**

CONT.

Continue Diabetic Retinopathy: Recommendations

1. Telemedicine programs that use validated retinal photography with remote reading by an ophthalmologist or optometrist and timely referral for a comprehensive eye examination when indicated can be an appropriate screening strategy for diabetic retinopathy. **B**
2. Women with preexisting type I or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
3. Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**
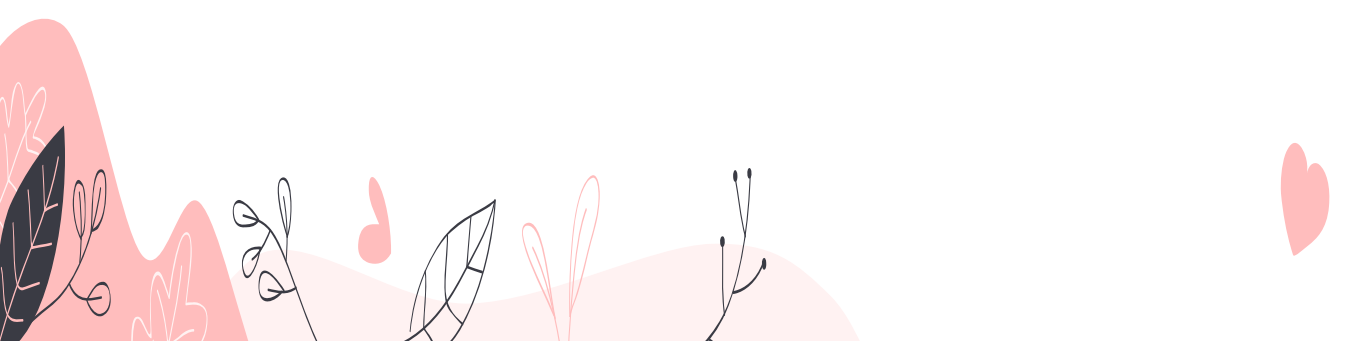
Neuropathy: Recommendations for Screening

1. All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
2. Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small fiber function) and vibration sensation using a 128 Hz tuning fork (for large fiber function). All patients should have annual 10 g monofilament testing to identify feet at risk for ulceration and amputation. **B**
3. Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **E**

Inspection, palpation, vibration and monofilament exam

Foot Care: Recommendations

- Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **B**
- Patients with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **C**
- Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**
- The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10 g monofilament testing with at least one other assessment: pinprick, temperature, vibration), and vascular assessment including pulses in the legs and feet. **B**
- Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle brachial index and for further vascular assessment as appropriate. **C**
- A multidisciplinary approach is recommended for individuals with foot ulcers and high risk feet (e.g., dialysis patients and those with Charcot foot or prior ulcers or amputation). **B**
- Refer patients who smoke or who have histories of prior lower extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **C**
- Provide general preventive foot self care education to all patients with diabetes.**B**
- The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, or history of amputation. **B**

Diabetes management:

Non-Pharmacological
1- Diet
2-Exercise(Physical activity)

Pharmacological
1-Oral Hypoglycemic Drugs
2-Insulin

Diet therapy and exercise:

They are the cornerstone for the management of diabetes Their effect appears within 1-4 weeks If they did not control hyperglycemia within 3-6 month, start anti-diabetic agent .

Non-Pharmacological:

Lifestyle modification: This what I need you to know regarding non-pharmacological management.

1- Physical activity: brisk walking for 150 min per week. Can be tailored as patient desire (3d with 50 min each or 5d with 30 min each) "brisk walking كأن الواحد بيلحق على الركعة"

2- Weight loss (7-10% of total body weight)

Table 5.1—Medical nutrition therapy recommendations

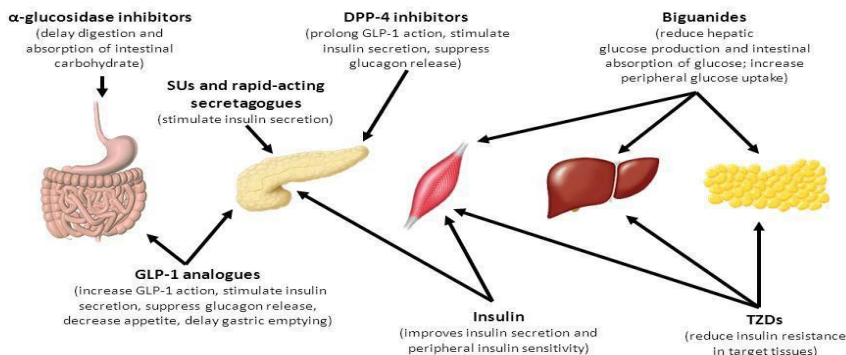| Topic	Recommendations	Evidence rating
Effectiveness of nutrition therapy	**5.6** An individualized medical nutrition therapy program as needed to achieve treatment goals, preferably provided by a registered dietitian, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus.	A
	5.7 A simple and effective approach to glycemia and weight management emphasizing portion control and healthy food choices may be considered for those with type 2 diabetes who are not taking insulin, who have limited health literacy or numeracy, or who are older and prone to hypoglycemia.	B
	5.8 Because diabetes nutrition therapy can result in cost savings **B** and improved outcomes (e.g., A1C reduction) **A**, medical nutrition therapy should be adequately reimbursed by insurance and other payers. **E**	B, A, E
Energy balance	**5.9** Weight loss (>5%) achievable by the combination of reduction of calorie intake and lifestyle modification benefits overweight or obese adults with type 2 diabetes and also those with prediabetes. Intervention programs to facilitate weight loss are recommended.	A
Eating patterns and macronutrient distribution	**5.10** There is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins for people with diabetes; therefore, meal plans should be individualized while keeping total calorie and metabolic goals in mind.	E
	5.11 A variety of eating patterns are acceptable for the management of type 2 diabetes and prediabetes.	B
Carbohydrates	**5.12** Carbohydrate intake should emphasize nutrient-dense carbohydrate sources that are high in fiber, including vegetables, fruits, legumes, whole grains, as well as dairy products.	B
	5.13 For people with type 1 diabetes and those with type 2 diabetes who are prescribed a flexible insulin therapy program, education on how to use carbohydrate counting **A** and in some cases how to consider fat and protein content **B** to determine mealtime insulin dosing is recommended to improve glycemic control.	A, B
	5.14 For individuals whose daily insulin dosing is fixed, a consistent pattern of carbohydrate intake with respect to time and amount may be recommended to improve glycemic control and reduce the risk of hypoglycemia.	B
	5.15 People with diabetes and those at risk are advised to avoid sugar-sweetened beverages (including fruit juices) in order to control glycemia and weight and reduce their risk for cardiovascular disease and fatty liver **B** and should minimize the consumption of foods with added sugar that have the	B, A
Protein	**5.16** In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations. Therefore, carbohydrate sources high in protein should be avoided when trying to treat or prevent hypoglycemia.	B
Dietary fat	**5.17** Data on the ideal total dietary fat content for people with diabetes are inconclusive, so an eating plan emphasizing elements of a Mediterranean-style diet rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk and can be an effective alternative to a diet low in total fat but relatively high in carbohydrates.	B
	5.18 Eating foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended to prevent or treat cardiovascular disease **B**; however, evidence does not support a beneficial role for the routine use of n-3 dietary supplements. **A**	B, A
Micronutrients and herbal supplements	**5.19** There is no clear evidence that dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) can improve outcomes in people with diabetes who do not have underlying deficiencies and they are not generally recommended for glycemic control.	C
Alcohol	**5.20** Adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men).	C
	5.21 Alcohol consumption may place people with diabetes at increased risk for hypoglycemia, especially if taking insulin or insulin secretagogues. Education and awareness regarding the recognition and management of delayed hypoglycemia are warranted.	B
Sodium	**5.22** As for the general population, people with diabetes should limit sodium consumption to <2,300 mg/day.	B
Nonnutritive sweeteners	**5.23** The use of nonnutritive sweeteners may have the potential to reduce overall calorie and carbohydrate intake if substituted for caloric (sugar) sweeteners and without compensation by intake of additional calories from other food sources. For those who consume sugar-sweetened beverages regularly, a low-calorie or nonnutritive-sweetened beverage may serve as a short-term replacement strategy, but overall, people are encouraged to decrease both sweetened and nonnutritive-sweetened beverages and use other alternatives, with an emphasis on water intake.	B

Physical Activity

1. Children and adolescents with type 1 or type 2 diabetes or prediabetes should engage in 60 min/day or more of moderate− or vigorous−intensity aerobic activity, with vigorous muscle−strengthening and bone−strengthening activities at least 3 days/week. **C**
2. Most adults with type 1 **C** and type 2 **B** diabetes should engage in 150 min or more 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. Shorter durations (minimum 75 min/week) of vigorous−intensity or interval training may be sufficient for younger and more physically fit individuals.
3. Adults with type 1 **C** and type 2 **B** diabetes should engage in 2−3 sessions /week of resistance exercise on nonconsecutive days
4. All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior. **B** Prolonged sitting should be interrupted every 30 min for blood glucose benefits, particularly in adults with type 2 diabetes. **C**
5. Flexibility training and balance training are recommended 2−3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and Balance. **C**

PHARMACOLOGICAL:

Different classes that act on different targets

Main Classes of Glucose-Lowering Medications

α-glucosidase inhibitors (delay digestion and absorption of intestinal carbohydrate)

DPP-4 inhibitors (prolong GLP-1 action, stimulate insulin secretion, suppress glucagon release)

Biguanides (reduce hepatic glucose production and intestinal absorption of glucose; increase peripheral glucose uptake)

SUs and rapid-acting secretagogues (stimulate insulin secretion)

GLP-1 analogues (increase GLP-1 action, stimulate insulin secretion, suppress glucagon release, decrease appetite, delay gastric emptying)

Insulin (improves insulin secretion and peripheral insulin sensitivity)

TZDs (reduce insulin resistance in target tissues)

TZD = thiazolidinedione; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide
Krentz AJ, Bailey CJ. Drugs 2005;65:385-411
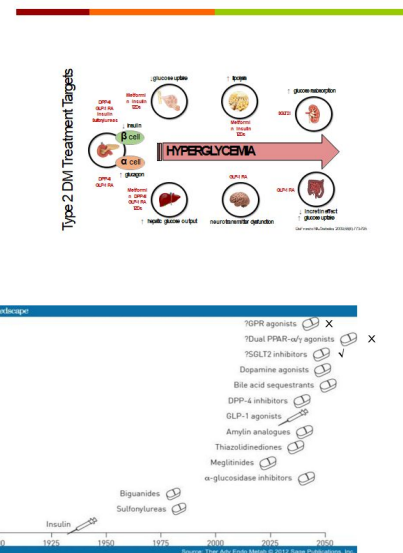
Drug Therapy Of Diabetes

- **Insulin**
- **Oral Hypoglycemic Agents**

1. Insulin sensitizing agents
   Reduce blood sugar by making the body tissue more sensitive to insulin
   a. Biguanides (metformin)
   b. Thiazolidinediones (TZD)/ glitazone
2. Insulin secretagogues
   Stimulate release of insulin from pancreatic beta cells
   a. Sulfonylurea
   b. Meglitinides
3. Incretin based therapy
   a. DPP-4 Inhibitors
   b. GLP-1 receptor agonist
4. α glucosidase inhibitor
5. SGLT-2 Inhibitors
   Inhibit reabsorption of glucose in the distal tubules of the kidney

> "OH PANCREAS! OPEN YOUR GATES OF CALCIUM AND UNLEASH THE INSULIN
> SULFONYLUREAS SUMMON INSULIN
> MEDICOWESOME 2016
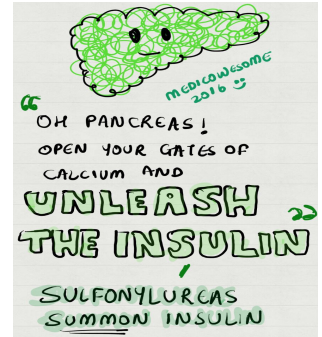
SGLT2 Inhibitors: Like Canagli**flozin**
Loze >> lose , in this drug glucose along with Na will be lost

- Sulfonylurea
- MEglitinide "will MIMIC sulfonylureas

💡 Mnemonics

Thiazolidinediones (TZD)
TZD تــزد من الزيادة ، وهذا الدواء يزيد من المويا الموجودة في الجسم ويزيد من نسبة حصول الكسور
Increase water >> not recommend in heart and renal failure

GLP and DPP

> G - GLP 1 / GIP
> L
> I - Inhibits Incretin degradation
> P - Di peptidyl peptidase-4 (DPP 4 inhibitor)
> Medicowesome 2016
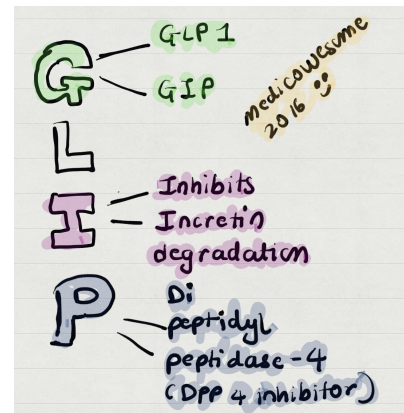
Oral Hypoglycemic Agents

Drug Class	M.O.A	HbA1C lowering %	Advantage	Disadvantage	ADVERSE EFFECT	Doses & routes
Biguanides Metformin *Glucophage **Glucophage XR *30% GI side effects **5-6% GI side effects" Encapsulated Glucophage" Act primarily on the liver	Insulin−sensitizing agents: reduce blood sugar by making the body's tissues more sensitive to insulin. Primary mechanism of action(MOA): Inhibit hepatic gluconeogenesis Secondary MOA: Increase insulin sensitivity	Decrease HgA1C by 1.0 to 2.0%	•The first line for oral treatment of type 2 diabetes •High efficacy with **no hypoglycemia** •Weight neutral But some people may have weight loss •lipid−lowering activity[1] •Decreased all−cause mortality and a decreased rate of (MI) in overweight and obese patients	•GI side effect[2] •Potential for vitamin B−12 def •Lactic acidosis (rare) •Discontinue during acute illness and Before radiographic procedures requiring Contrast •Contraindicated in Renal insufficiency (discontinue if eGFR ≤ 30)	B12 deficiency is a long term side effect because it reduces intestinal absorption of B12. الحين يوزعونه توزيع لمرضى السكر وهذا خطأ Metformin does not cause renal impairment. Drug discontinuation or dose adjustments are required in case of renal impairment to avoid lactic acidosis. Glomerular filtration rate(GFR) based Recommendations: <60 = observe carefully <45 = half 1/2 dose <30 = discontinue medication	Glucophage: 500, 850, 1000 mg (PO) Glucophage XR: 500, 750 mg (PO)
Thiazolidinediones: TZDs -Pioglitazone -Rosiglitazone Acts primarily on the peripheral tissue	Insulin−sensitizing agents: Increase insulin sensitivity by acting on adipose, muscle, and liver to increase glucose utilization and decrease glucose production.	When used as monotherapy, they reduce hemoglobin (A1C) values by 1.5 %.	• High efficacy with no hypoglycemia •show benefit in NASH • no dose adjustment	(Pioglitazone) •Increase risk for bladder Cancer (Rosiglitazone) •Increased risk for cardiovascular event (Progressive ischemia ,MI, HF) •Increased LDL	•All TZDs cause weight Gain •Fluid retention so contraindicated in heart failure (Peripheral edema occurs in 4 to 6 %) •Decrease bone density and increase fracture risk , particularly in women •FDA Black Box: CHF >>pioglitazone & rosiglitazone. •Not recommended in renal impairment due to fluid Retention	Pioglitazone (actos): 15, 30, 45 mg Rosiglitazone (avandia): 2, 4, 8 mg **Issues** with this group: -Weight gain -Fluid retention = contraindicated in HF or CKD -Edema -Osteoporosis (fractures) -Bladder cancer The drugs need time to show its effects (3-4 months)

[1] lipid-lowering activity, : decrease in serum triglyceride and free fatty acid concentrations, a small decrease in serum low-density-lipoprotein (LDL) cholesterol concentrations, and a very modest increase in serum high-density-lipoprotein (HDL) cholesterol concentrations

[2] GI:metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and soft bowel movements or diarrhea

Drugs Class	M.O.A	HbA1C lowering %	Advantage	Disadvantage	ADVERSE EFFECT
Sulfonylureas (2ND GENERATIONS) •Glipizide (Minidab) •Gliclazide •Glibenclamide (Glyburide) **(3RD GENERATION)** •Glimepiride	Insulin Secretagogues: stimulate release of insulin from pancreatic beta cells Stimulate insulin secretion for 24h So, usually is taken once daily.	Lower hbA1c by 1- 2%	Safe in CVD and renal impairment (except glyburide) High efficacy with risk of hypoglycemia (b/c it stimulates the release of insulin)		•Hypoglycemia (most common) •Nausea, Skin reactions (including photo sensitivity) •Weight gain
Meglitinides •Repaglinide •Nateglinide *Meglitinides are pharmacologically distinct from sulfonylureas and may be used in patients who have an allergy to sulfonylurea medications.	Insulin secretagogues: stimulate release of insulin from pancreatic beta cells before each Meal,		•Repaglinide safe in pt. with decrease GFR or renal failure Repaglinide is very safe in renal impairment. We can use it even if the GFR is 15 or 20. No need for dose adjustment		. Hypoglycemia & Weight gain(less than sulfa) •Dosing frequency

Sulfonylurea

Sulfonylureas

Drug	Duration of biologic effect, hour	Usual daily dose, mg	Dosing per day
First-generation sulfonylureas			
Acetohexamide	12 to 18	500 to 750	Once or divided
Chlorpropamide (Diabinese)	24 to 72	250 to 500	Once
Tolbutamide (Orinase)	14 to 16	1000 to 2000	Once or divided

Sulfonylureas
2nd generation Sulfonylureas

Glipizide (minidab)	Glucotrol (OD or divided) Glucotrol XL (OD)	(2.5), 5, 10 mg (XL)	Up to 40 mg Up to 20 mg
Gliclazide	Diamcrone R (BID) /Glaze Diamcrone MR (OD)	40,80 mg 30 , 60 mg	Up to 320 mg Up to120 mg
Glibenclamide (Glyburide)	Doanil Diatab	2.5 , 5 mg	OD or BID Up to 10 mg

3rd generation Sulfonylurea

Glimepiride	(Amaryl)	1, 2, 4 mg	OD tablets Up to 8 mg

meglitinides

Repeglinide	0.5 before meal Max 4 mg before each meal
Nateglinide	120 mg immediately before each meal

Drug Class	M.O.A	HbA1C lowering %	Advantage	Disadvantage	ADVERSE EFFECT
DPP-4 Inhibitors •Sitagliptin •Saxagliptin •Vildagliptin •Linagliptin the best for renal impairment, bc it excreted in feces. •Alogliptin	**Incretin Based Therapy** Main functions: 1- intestines: delay gastric emptying 2- Alpha cells: inhibit glucagon secretion 3- Beta cells: stimulate insulin secretion 4- Brain : increase satiety DDP4 degrades GLP-1	Reduce HbA1c between 0.6 − 1.1% Less than GLP-1	•Intermediate efficacy with no hypoglycemia •No effects on body weight Safe profile Does not cause hypoglycemia" even it stimulates insulin secretion "because it works only when carbs are ingested, and blood glucose is elevated.	•Potential CV risk in saxagliptin and alogliptin •Require dose adjustment except Linagliptin	•Headache, nasopharyngitis ,and upper respiratory tract infection •Joint pain, myalgias , muscle weakness, and muscle spasms. •Urticaria & angioedema •Acute pancreatitis in 1 out of 800 Thyroid carcinoma is only proven in animals. But in practice, if there is a background or family history of thyroid carcinoma, we avoid to prescribe it.
GLP1 receptor Agonists: •Liraglutide •Semaglutide •Dulaglutide •Exenatide DPP4 and GLP-1 share similar features since they act on the same target (incretin system)	**Incretin Based Therapy** Main functions: 1- intestines: delay gastric emptying 2- Alpha cells: inhibit glucagon secretion 3- Beta cells: stimulate insulin secretion 4- Brain : increase satiety	1-1.5% above target More than DPP4 Saxenda is a derivative of Liraglutide which is approved for obesity management.	•High efficacy with no hypoglycemia •Weight reduction The drugs are proven to reduce weight •Decrease ASCVD **Reduce CVD risk(CVD Benefit)** in Liraglutide >Semaglutide > Exenatide ER Non glucose effect : •↓ 3-4 kg OF WEIGHT •↓ 2-3 mmHg of BP •↑ 2-3 beats/min of HR	Injectable	•GI side effect (nausea, vomiting, diarrhea) Initiating/increasing dose >> Potential risk of AKI Liraglutide is safe •FDA Black Box >>cell hyperplasia /medullary thyroid tumors (avoid it only for family or personal history of thyroid cancer) •Pancreatitis(1;800) rare but serious •injection site reaction.

DPP-4 inhibitor

1-Sitagliptin	(Januvia)	25, 50, 100 mg	
2-Saxagliptin	(Onglyza)	2.5, 5 mg	
3-Vildagliptin	Galvas	50 mg	OD −BID *
4-linagliptin	Tradjenta	5 mg once daily	
5-Alogliptin	Nesina, Kazano,	25 mg once daily	

GLP-1 Agonist

EXENATIDE	5 mcg subQ	BID Up to 10 BID
Extended-release:	2 mg subQ	once /week
LIRAGLUTIDE	0.6 mg subQ OD	Up to 1.8 mg OD

Understanding the Natural Role of Incretins

Considerations for incretin selection

Clinical variables	DPP-4 inhibitors	GLP1 RA
Glycemic effects		
Effective A1C reduction	0.5 − 1.0% above target	1.0 − 1.5% above target
Fasting glucose reduction	0 − 30 mg/dl	20 − 70 mg/dl (long-acting > short-acting)
Post-prandial glucose reduction	• <60 mg/dl	60 − 100 mg/dl (short-acting >long-acting)
Non-glycemic effects		
Weight	neutral	1−4 kg decrease
Blood pressure	neutral	0 - 3 mmHg decrease
Other		
GI side effects	none	5-20% nausea
Renal insufficiency	Linagliptin no dose adjustments	none indicated in severe renal insufficiency
Cost	$$	$$$

Drug Class	M.O.A	HbA1C lowering %	Advantage	Disadvantage	ADVERSE EFFECT
Alpha Glucosidase Inhibitors •Acarbose (50 and 100 mg TID) •Miglitol •Voglibose	Slow absorption of glucose and reduce postprandial Blood glucose concentration Inhibit intestinal absorption of glucose Need to be taken 10-15min before meal	lowering (A1C) By only 0.4 to 0.9%	if the HbA1c is not high and the post prandial is the main problem, those drugs are very effective Safe drugs but GI upset is really irritating to patients	Need to be given before each meal.	•Flatulence •Diarrhea Like GLP 1, patient may stop it due to GI upset.
SGLT2 Inhibitors: •Canagliflozin •Dapagliflozin •Empagliflozin	Inhibit the reabsorption of glucose in the distal tubules of the kidney Inhibit renal absorption of glucose = losing glucose in urine beside calories(weight loss)	Up to 1%	•Weight loss •Good CV effect **Reduce CVD risk(CVD Benefit)** and specifically heart failure patient (Empagliflozin And Canagliflozin) •Delay progression of CKD (empagliflozin And canagliflozin) •Intermediate efficacy with no Hypoglycemia •lipid−lowering activity Diuretic effect, so it can be used in case of HF glucose will drag water	• FDA Black Box: risk Of amputation (canagliflozin) •It needs GFR > 45 to initiate the treatment In General, safe drugs	•Genitourinary infections 10% •Risk of bone Fracture (Canagliflozin) •DKA risk (all agents, rare in T2DM) •Increase LDL Cholesterol •Risk of volume depletion and hypotension, so we advise the patient to drink lots of water •Acute kidney injury

FDA Approved SGLT2 Inhibitors

Agent	Canagliflozin INVOKANA®	Dapagliflozin FARXIGA™	Empagliflozin JARDIANCE®
Dosing	Initial: 100mg daily Max: 300mg daily	Initial: 5mg daily Max: 10mg daily	Initial: 10mg daily Max: 25mg daily
Administration	Before the first meal of the day	In the morning with or without food	In the morning with or without food
Renal Dose Adjustments	Yes	Yes	Yes
Cost	~$350 for 30 tablets	~$350 for 30 tablets	TBD

Diabetes Management :Continues

Insulin:
•Powerful agent
•Necessary in 20-30%
•Inexpensive

Can cause:
•Hypoglycemia
•Weight gain
•High level of patient fear

Insulin	Onset	Peak	Duration
Apidra Humalog Novolog	10-15 mins	60-90 mins	4-5 hours
Regular	30-60 mins	2-4 hours	5-8 hours
NPH	1-3 hours	5-8 hours	12- 18 hours
Levemir	90 mins	Relatively peakless	12-24 hours
Lantus	90 mins	Peakless	24 hours
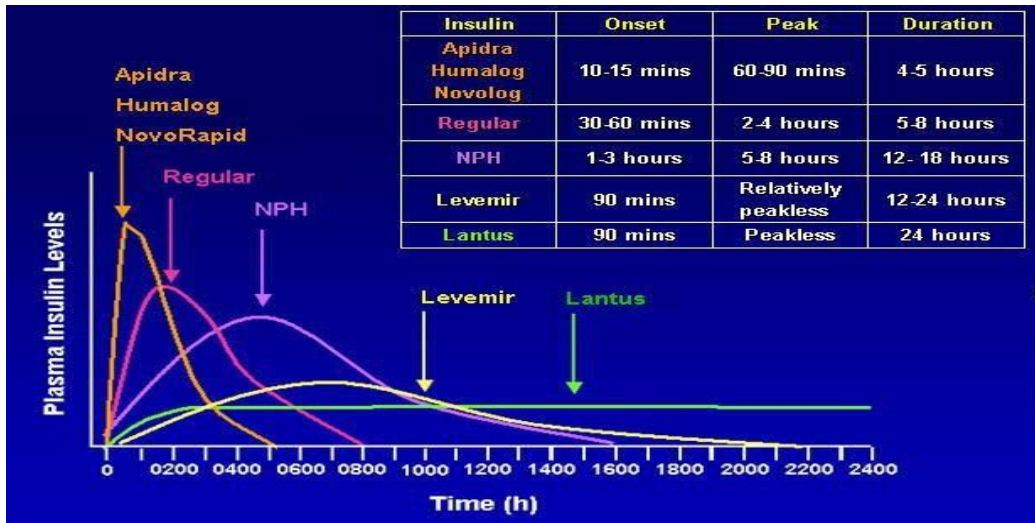
TREATMENT REGIMENS OF TYPE 1 DM

In general, there are two types:
1- Prandial (short acting)
2- Basal (long acting)

1. **Conventional Insulin Therapy:**
    a. Two injections of NPH and Regular Insulin
2. **Mixed Insulin:** (basal/prandial)
    a. Two injections of 70/30 or 60/40 or 50/50
3. **Multiple Insulin Injections**
    a. 1 or 2 injections of NPH plus 3 injections of Regular or Rapid Insulin.
    b. One injection of Glargine or Detemir plus 3 injections of rapid insulin(Lispro/Aspart)

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide† > sema-glutide > exenatide extended release	Neutral	High	SQ	Benefit: liraglutide	• Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.

If You Have DM Pt On Metformin With HbA1c Above Target, What To Do?

1. Established ASCVD or CKD.
2. Without established ASCVD or CKD:
    a. To minimize hypoglycemia
    b. To promote weight loss or minimize weight gain
    c. Cost is a major issue

If HbA1c still above target despite dual/triple therapy, What to do?

1. Consider GLP−1 RA in most prior to insulin.
2. Consider insulin as first injectable if:
    a. HbA1c very high > 11%
    b. Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency.
    c. If type−1 diabetes is a possibility.
    d. If already on GLP−1 RA or if GLP−1 RA not appropriate or Insulin preferred

Sometimes we may prescribe insulin in catabolic stage, even if the patient is newly diagnosed.
Catabolic stage:
1-HbA1c 9 or above
2-weight loss
3- severe polyuria, polydipsia and polyphagia
4-glucose toxicity

If HbA1c still above target despite adequately titrated basal insulin OR once basal insulin > .7 − 1.0 IU/kg OR FPG at target, What to do?

1. Add prandial insulin (one dose with the largest meal).
2. If HbA1c still above target:
    a. Stepwise additional injections of prandial insulin (ex. two, then three additional injections).
3. If HbA1c still above target:Proceed to full basal-bolus regimen.
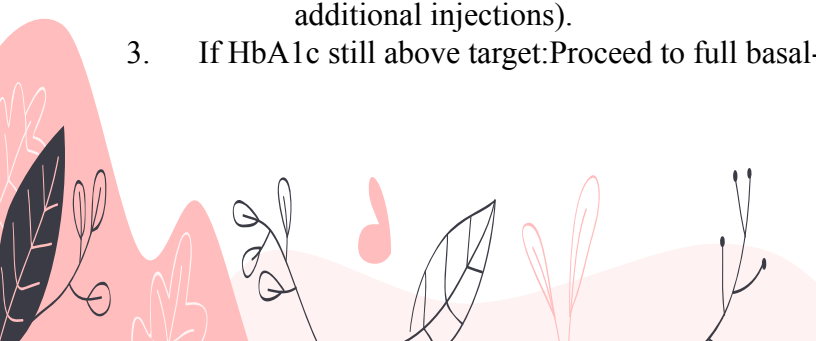
CV safety studies

Agents	Saxagliptin	Alogliptin	Sitagliptin	Lixisenatide	Empagliflozin	Liraglutide	Semaglutide
Trial name	SAVOR-TIMI	EXAMINE	TECOS	ELIXA	EMPA-REG	LEADER	SUSTAIN-6
Primary endpoint	Neutral	Neutral	Neutral	Neutral	Benefit	Benefit	Benefit
CV Death	Neutral	Neutral	Neutral	Neutral	Benefit	Benefit	Neutral
Non-fatal AMI	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Non-fatal Stroke	Neutral	Neutral	Neutral	Neutral	Harm(trend)	Neutral	Benefit
HF	Harm	Harm	Neutral	Neutral	Benefit	Neutral	Neutral
Renal	Neutral	Neutral	Neutral	Neutral	Benefit	Benefit	Benefit

Retinopathy Harm

Large Non-Insulin CV Outcomes Trials in T2D

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-I	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
N	16,500	5400	14,000	6000	8300
Results	2013	2013	June 2015	2018	2017

SAVOR: NEUTRAL; EXAMINE: NEUTRAL; TECOS: NEUTRAL; CAROLINA: NEUTRAL

Study	LEADER	ELIXA	SUSTAIN6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
N	16,500	14,000	6000	5400	8300
Results	2016	2015	2016	2018	2019

LEADER: BENEFICIAL!; ELIXA: NEUTRAL; SUSTAIN6: BENEFICIAL!; EXSCEL: NEUTRAL

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	Sept 2015	2017	2018	2020

EMPA-REG: BENEFICIAL!; CANVAS: BENEFICIAL!

Scirica BM, et al. N Engl J Med. 2013;369:1317-1326.; White WB, et al. N Engl J Med. 2013;369:1327-1335.; Green JB, et al. N Engl J Med. 2015;373:232-242.; Marx N, et al. Diab Vasc Dis Res. 2015;12:164-174.; ClinicalTrials.go (NCT01897532).; Marso SP. et al. Am J Heart. 2013;166:823-830.; Pfeffer MA. et al. N Engl J Med. 2015;373-2247-

Antihyperglycemic Agents and Renal Function

CKD Stage	5	4	3b	3a	1 or 2
eGFR (mL/min/1.73 m²):	<15	15–29	30–44	45-59	≥ 60

Class	Drug	Renal function bands
Alpha-glucosidase Inhibitors	Acarbose	30
Biguanides	Metformin	30 / 500-1000 mg daily / 45
DPP-4 Inhibitors	Alogliptin	6.25 mg daily / 30 / 12.5 mg daily / 60
	Linagliptin	15
	Saxagliptin	15 / 2.5 mg daily / 50
	Sitagliptin	25 mg daily / 30 / 50 mg daily / 50
GLP-1 Receptor Agonists	Dulaglutide	15
	Exenatide	30 / 50
	Exenatide QW	30 / 50
	Liraglutide	15
	Lixisenatide	30
Insulin Secretagogues	Gliclazide	30 / 60
	Glimepiride	30 / 60
	Glyburide	60
	Repaglinide	60
SGLT2 Inhibitors	Canagliflozin*	45 / 100 mg daily / 60
	Dapagliflozin	60
	Empagliflozin	30 / 45
Thiazolidinediones	Pioglitazone	60
	Rosiglitazone	60
	Insulins	30

Legend:
- ■ Use alternative agent
- ■ Dose adjustment required
- ■ Caution
- ⧄ Do not initiate
- ■ Dose adjustment not required

Efficacy of Non-insulin Anti-diabetes Agents*

Drug	A1c Reduction (%)
Metformin	1.5–2.0
Secretagogue (SFU/Glinide)	1.5–2.0
GLP1RA	1.0-1.5
TZD	1.0–1.5
SGLT2i[1]	0.8-1.5
DPP4i[1]	0.5–1.5
α–GI	0.5–1.0
Bromocriptine IR[2]	0.6-0.9
Amylin[2]	0.4-0.7
Colesevelam[2]	0.3-0.5

*Not head to head. Baselines and background therapies differ. Information derived from multiple studies.

[1]http://resources.aace.com. [2]Information taken from manufacturer PL.

Important Summary of the criteria

Use principles in Figure 9.1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)

If HbA$_{1c}$ above target despite dual/triple therapy

Consider initial injectable combination (i.e., GLP-1 RA + basal insulin or prandial/basal insulin) if HbA$_{1c}$ >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target

INITIATION FOR GLP-1 RA
- Initiate starting dose (varies across class)

TITRATION FOR GLP-1 RA
- Gradual titration to maintenance dose (varies across class)

Consider GLP-1 RA in most prior to insulin[1]
Consider: • INITIATION • TITRATION

Consider insulin as first injectable if
- HbA$_{1c}$ very high >97 mmol/mol (11%)
- Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
- If type 1 diabetes is a possibility

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

If above HbA$_{1c}$ target

INITIATION FOR BASAL
- Start 10 IU a day OR 0.1-0.2 IU/kg a day

TITRATION FOR BASAL
- Patient self titration is more effective
- Set FPG target that correlates to HbA$_{1c}$ target
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

Add basal insulin
Consider: • INITIATION • TITRATION

For patient on GLP-1 RA and basal insulin
Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi)
But note max dose of insulin in the FRCs

INITIATION
- If on GLP-1 RA use 10-16 dose steps (iDegLira) or 10-15 units (iGlarLixi)

TITRATION
- Titrate to FPG target and tolerability

INITIATION FOR PRANDIAL
- 4 IU a day or 10% of basal dose
- If HbA$_{1c}$ <64 mmol/mol (8%) consider lowering the total dose by 4 IU a day or 10% of basal dose

If above HbA$_{1c}$ target
Despite adequately titrated basal insulin OR once basal dose >0.7-1.0 IU/kg OR FPG at target

If above HbA$_{1c}$ target
Additional basal insulin or additional prandial insulin

TITRATION FOR PRANDIAL
- Increase dose by 1-2 IU or 10-15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%

Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion
Consider: • INITIATION • TITRATION

INITIATION
- In insulin-naive patients 10-12 IU or 0.3 IU/kg
- If on existing insulin regimen usually unit to unit at the same total insulin dose but may require adjustment to individual needs

If above HbA$_{1c}$ target

Consider twice or three times daily premix insulin regimen

Caution higher risk of hypoglycemia and/or weight gain
Consider:
• INITIATION
• TITRATION

INITIATION OF STEPWISE PRANDIAL
- Stepwise addition of prandial insulin every 3 months if HbA$_{1c}$ > target is associated with lower risk of hypoglycemia and increases patient satisfaction compared with immediate introduction of full basal-bolus regimen

Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Consider: • INITIATION • TITRATION

TITRATION
- Individual dose adjustment depends on type of biphasic insulin
- More complex if on three times daily regimen

TITRATION FOR PRANDIAL

If above HbA$_{1c}$ target

INITIATION FOR PRANDIAL

TITRATION FOR PRANDIAL

Proceed to FULL basal-bolus regimen, i.e., basal insulin and prandial insulin with each meal
Consider:
• INITIATION • TITRATION

⚠ **IF HbA$_{1c}$ DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL-BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES**
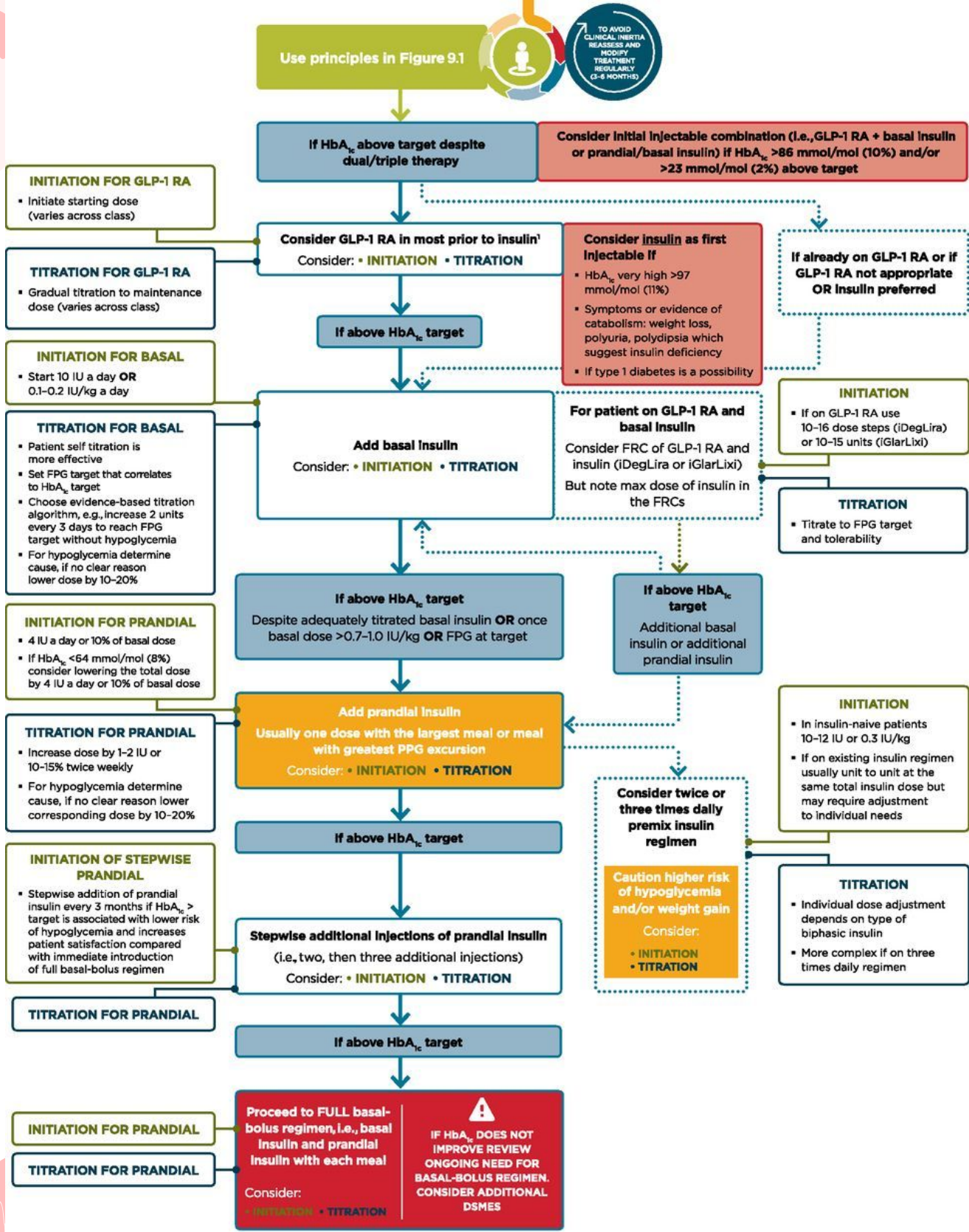
1. When selecting GLP-1 RA, consider: patient preference, HbA$_{1c}$ lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

FIGURE 4. Intensifying to injectable therapies. FRC, fixed-ratio combination; GLP-1 RA, GLP-1 receptor agonist; Hba$_{1c}$, glycated hemoglobin; iDegLira, insulin degludec/liraglutide; iGlarLixi; insulin glargine/lixsenatide; max, maximum; PPG, postprandial glucose. Adapted from Davies MJ, D'Alessio DA, Fradkin J, et al. *Diabetes Care* 2018;41:2669–2701.

Doctor's notes regarding DM Management

A patient w/ glycemic picture(Abnormal HbA1c , etc)
1- **Lifestyle modification + metformin (first line)**
If the patient is still **not controlled** (abnormal HbA1c, etc)
Ask yourself **two questions**:
1-Has the patient have **clinical ASCVD** (MI,stroke, abdominal aneurysm or etc.)?
Then prescribe drugs that are proven to **reduce ASCVD(GLP-1 and SGLT2)**
2-Has the patient have **heart failure(HF) or chronic kidney disease (CKD)**?
Then prescribe drugs that are proven to **reduce HF or CKD** (**SGLT2** b/c it acts as diuretic)
If the two questions **does not fit** your patient, then selection can be **categorized into 3**:
1- Hypoglycemia represent a major issue - so, prescribe drugs **that don't cause hypoglycemia** (**TZD, DPP4, GLP1 or SGLT2**)
2- Weight loss represent a major issue - so, prescribe drugs that **promote weight loss** (**GLP1 or SGLT2**)
3- Cost represent a major issue - so, prescribe **cheap drugs(sulfonylurea SU or TZD)**
If the patient is **still not controlled with dual or triple medications** - then you can **prescribe insulin**

Important clues or features of DM drugs:
1-Drugs that cause **hypoglycemia (SU, Meglitinides or insulin)**
2-Drugs that cause **weight gain (SU, Meglitinides ,insulin or TZD)**
3-Drugs that are **weight neutral (Metformin, Acarbose or DPP4)**
4-Drugs that cause **weight loss (GLP-1 or SGLT2)**
5-Drugs that posses **CVD benefit(GLP-1 or SGLT2)**
6-Drugs that are **safe in renal impairment(Meglitinides or linagliptin"DPP4")**
7-Drugs that are **contraindicated in HF or CKD(TZD)**
8-Drugs that are **beneficial in HF or CKD (SGLT2)**

Questions

1) Majority of patients with type 2 diabetes are overweight or obese. which of the following whould be most appropiate in the diabetes management with potential of causing weight loss ?

A-gliclazide and glargine
B- liraglutide and dapagliflozin
C- metformin and acarbose
D- metformin and sitagliptin

2)A major disadvantage of the use of sulfonylureas in patients with diabetes is :

A- vitamin B12 malabsorption
B- weight loss
C- treatment cost
D- risk of hypoglycemia

3)Target of pre-prandial blood glucose is ?

A- 80 - 140 mg/dl
B- 70-130 mg/dl
C- 80-130 mg / dl
D- 90-140 mg/dl

4)Hypoglycemia is classified into ?

A- 2 levels
B- 3 levels
C- 4 levels
D- 5 levels

Questions

5) A 60 year old woman with BMI of 33 attends your clinic . Her FBS is 8 mmol/l (144mg) . She has already tried to practise lifestyle modification for four months without much success . which is the most likely drug as first choice for this patient ?

A- acarbose
B- glibenclamide
C- metformin
D- pioglitazone

Answers :

1. B
2. D
3. C
4. B
5. C