Diabetes Mellitus

- **Masterclass**

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Objectives

- When to screen for diabetes ?
- How to diagnose diabetes?
- Management approach
- Diabetes Complications
- Cardiovascular risk prevention

Case

- A 48-year-old man, was seen in the primary care clinic for obesity management and routine follow-up of hypertension , for which he had been treated for the past 8 years. His only medication was lisinopril, 20 mg/day. Home blood pressure monitoring averaged 128/82 mmHg. He had a family history for hypertension, type 2 diabetes, and coronary artery disease. He reported 9.07 kgs weight gain over the past year, along with a sedentary lifestyle with no regular exercise routine. Other medical history was negative, including symptoms of fatigue, polyuria, or polydipsia. He denied past or current tobacco use.

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Cont. Case:

He presented with a waist size of 106 cm, BMI of 34 kg/m^2, and blood pressure of 125/80 mmHg.

A subsequent lipoprotein profile demonstrated the common pattern associated with pre-diabetes, including a low HDL cholesterol (30 mg/dl) and a high triglyceride level (185 mg/dl). The LDL was mildly elevated (132 mg/dl), and total cholesterol was 199 mg/dl. His fasting glucose was 111 mg/dl, with a repeated value of 115 mg/dl one week later.

1) How many risk factor does the patient have , that necessitate screening for Pre-DM / DM?
   - what are the other conditions / risk factors in the criteria of screening for PRE-DM /DM?
2) Initial dx vs. finial dx?
3) What interventions should be offered ? / referral to ..?
4) When to repeat testing for pre-Dm in this case?

Metabolic syndrome

Definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%[Δ]; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance[◇] or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	**≥3 of:**	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol[§]	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides[§]	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)[¥]	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

* Most commonly agreed upon criteria for metabolic syndrome. Note that abdominal obesity is **not** a prerequisite for diagnosis; the presence of any 3 of the 5 risk criteria constitutes a diagnosis of metabolic syndrome.

¶ For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

Δ Insulin resistance measured using insulin clamp.

◇ High risk of being insulin resistant is indicated by the presence of at least 1 of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans; family history of type 2 diabetes, hypertension or CVD; history of gestational diabetes or glucose intolerance; non-White race; sedentary lifestyle; BMI 25 kg/m^2 or waist circumference 94 cm (men) or 80 cm (women); and age 40 years.

§ Treatment with 1 or more of fibrates or niacin.

¥ In Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

UpToDate®

https://www.uptodate.com/contents/metabolic-syndrome-insulin-resistance-syndrome-or-syndrome-x?search=metabolic%20syndrome&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2

Screening for diabetes

Testing should be considered in adults who are overweight or obese (BMI >25 kg/m2 or >23 kg/m2 in Asian Americans) and have one or more of the following risk factors:
– First degree relative with diabetes
– High risk race/ethnicity (e.g., African American, Latino, Native American, Asia American, Pacific islander)
– History of CVD
– Hypertension (>140/90 or on therapy for hypertension)
– HDL cholesterol level <35 mg/dl and/or a triglyceride level >350 mg/dl
– Women with polycystic ovary syndrome
– Physical inactivity
– Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

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

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

For all other patients, testing should begin at 35 years old.

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.

People with HIV

CVD: cardiovascular disease, GDM: gestational diabetes, IFG: impaired fasting glucose, IGT: impaired glucose tolerance.

Table 3.3 – Criteria for screening for diabetes or prediabetes in asymptomatic adults

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/screening-for-diabetes-table-3-3-and-table-3-4/

Prediabetes

https://saudifamilymedicine.com/index.php/documentation/section-1-im/chapter-3-diabetes/diagnosis-of-diabetes-table-3-5/

FPG 100 mg/dl (5.6 mmol/L) to 125 mg/dl (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dl (7.8 mmol/L) to 199 mg/dl (11 mmol/L) (IGT)
OR
A1C 5.7-6.4%

FPG: fasting plasma glucose, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, OGTT: oral glucose tolerance test. 2-h PG: 2 h plasma glucose *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

Table 3.6 – Criteria defining prediabetes*

Case

A 46-year-old woman who attends requesting a check-up. She is asymptomatic. You see from her medical file that she has no adverse past medical history or family history, she is on no medication and that two of her four children had birth weights ; **4.1** kgs. Examination shows: BMI **32** kg/m^2, BP **142/87** (over the last several visits there was elevated BP ranging from 138/80 to 148/89). She has no signs of eye disease, neuropathy or foot disease.

1) What conditions will you investigate for ?
2) What lab test will you order?
3) Are there any limitations to these tests that you need to consider?
    1. Limitations to RBG?
        - ❖ Absence of symptoms
    2. Limitations to HBA1C:
        - ❖ Conditions interfere with HBa1c assay and exclude its use ? (falsely low vs. falsely high)???

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Cont. case

The patient comes back to see you in the PHC for reviewing the lab tests. Results show:

HbA1C (**6.9**%), FBG (**158** mg/dl)

Serum Creatinine 0.8 mg/dL (70.72 umol/L), eGFR : 92 ml/min/1.73 m^2

T.Chol (140 mg/dl), HDL (**38** mg/dl),LDL (87 mg/dl),TG (97 mg/dl)

1) What is your diagnosis?
2) Is diagnosis of DM confirmed ?
3) What is your initial management?
    1) Lifestyle changes.
    2) Medications :
        1) Hypoglycemic agents
        2) Antihypertensive medications
        3) Moderate-intensity Statin therapy
    3) Screen for other ?

HbA1c limitations

Factors that decrease HbA1c	Factors that increase HbA1c
Decrease RBC lifespan: Hemolytic anemias e.g., SCD, Thalassemia Recovery from acute hemorrhage Spherocytosis, hypersplenism Erythropoietin therapy	**Increase RBC lifespan:** Splenectomy
Hemodilution Blood transfusion Pregnancy	**Decrease percentage of reticulocytes** Aplastic anemia
Decrease glycation High dose of vitamin C, E Some antibiotics e.g., trimethoprim cotrimoxazole	**Increased glycation** Iron, vitamin B12, and folate deficiency
Assay related artifact Some Hemoglobinopathies and hemoglobin variants	**Assay related artifact** Alcoholism (hemoglobin acetaldehyde) Uremia (carbamylated hemoglobin) Smoking (carboxyhemoglobin) Aspirin induced acetylated hemoglobin Hyperbilirubinemia Hypertriglyceridemia Some hemoglobinopathies and hemoglobin variants
Miscellaneous Chronic liver disease HIV (RBC destruction or using of anti-HIV medications)	**Miscellaneous** Genetics (African, Caribbean)

Table 3.8 – Factors that falsely increase or decrease HbA1c

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/glycemic-targets-and-assessment-of-glycemic-control/

Diagnosis of diabetes

FBS >126 mg/dl (7.0 mmol/L), fasting is defined as no caloric intake for at least 8h.
OR
2-h PG >200 mg/dl (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. *
OR
A1C >6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. *
OR
In a patient with classic symptoms of hypoglycemia or hyperglycemic crises, a random plasma glucose >200 mg/dl (11.1 mmol/L)

DCCT: Diabetes Control and Complications Trial, FPG: fasting plasma glucose, OGTT: oral glucose tolerance test, WHO: World Health Organization, 2-g PG: 2-h plasma glucose, * In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Table 3.5 – Criteria for the diagnosis of diabetes

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/diagnosis-of-diabetes-table-3-5/

Case

A 45-year-old woman presents to your office complaining of general fatigue and abdominal bloating. Today's fasting serum glucose is **150** mg/dL. She visited the clinic 2- weeks backs her FBS was **140** mg. On examination she has body mass index (BMI) of 30 kg/m^2 .

<u>You decide to order laboratory test before proceeding :</u>

- K+4.0 , Na+140 , HCO3 28
- Serum Creatinine 0.82 mg/dL (72.49 umol/L), eGFR : 90 ml/min/1.73 m^2
- HbA1C **6.7%**
- Urine: no ketones

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Cont. Case:

1. What is the diagnosis?
    - Diabetes mellitus type II.
2. What is the Management plan ?
3. Management plan
    A. Non-pharmacological therapy
    B. Pharmacological therapy : Initial medications
    C. Referral
    D. Follow-up

Management of DM II

A) Non-pharmacological therapy

1. **Physical exercise**
   - Type : aerobic, resistance, and stretching exercises
   - Intensity: moderate to vigorous intensity.
   - Duration: **150** minutes or more per week at least three days per week with no more than two consecutive days without activity

2. **Weight reduction**
   - Reduction of weight is essential for both pre-diabetes and diabetes
   - In prediabetes, the weight loss goal is **7–10%** for preventing progression to DM2
   - A structured lifestyle plan that combines dietary modification and exercise is vital for weight reduction

3. **Dietary modifications**
   - include reducing daily calories between **250–500** calories, keeping in mind that the total daily calorie intake should not be less than **1200** calories.

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/lifestyle-modification/

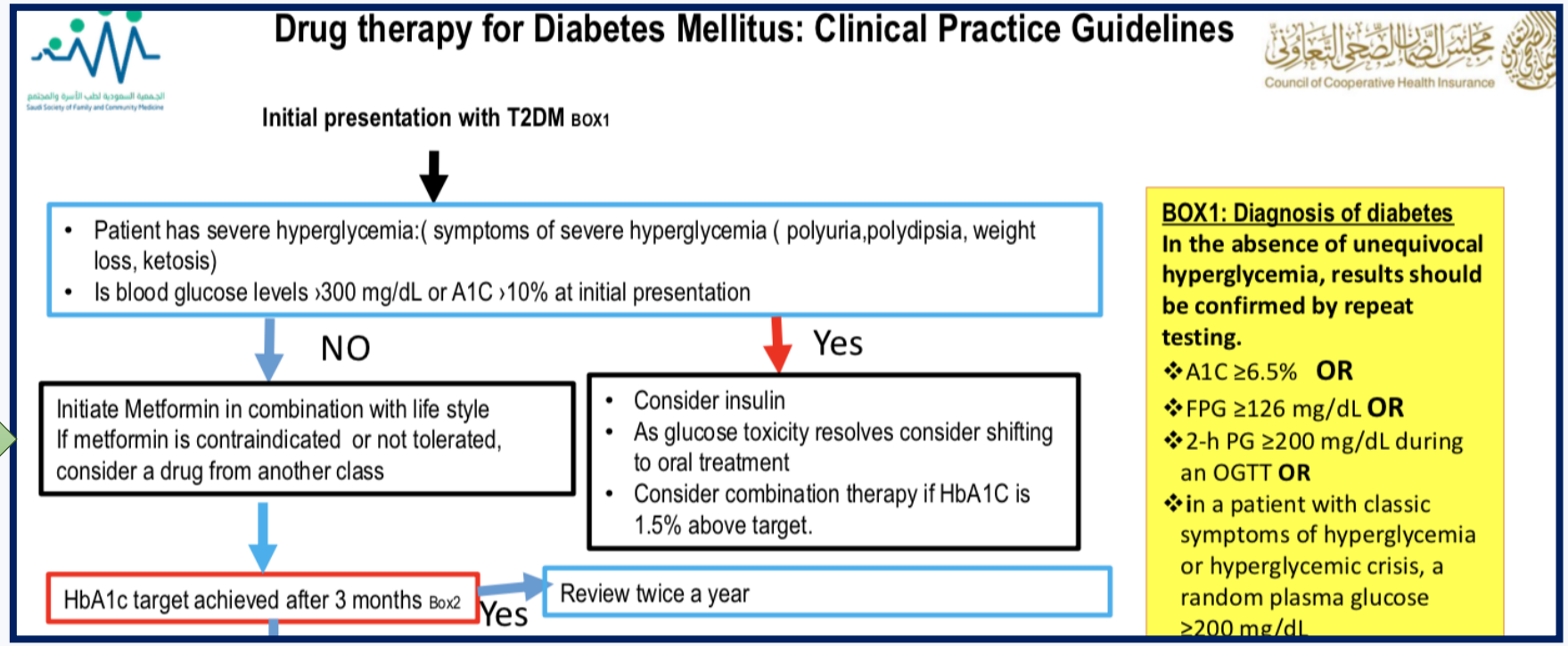
Cont.Management of DM. II

B) Pharmacological therapy
Initial therapy

- Metformin should be started when type 2 diabetes is diagnosed unless there are contraindications.
- The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure)

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/pharmacologic-therapy-for-dm2/

Drug therapy for Diabetes Mellitus: Clinical Practice Guidelines



BOX1: Diagnosis of diabetes

In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

- A1C ≥6.5% **OR**
- FPG ≥126 mg/dL **OR**
- 2-h PG ≥200 mg/dL during an OGTT **OR**
- in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

Box2:HbA1c target

- ≤ 7% : individuals with recent onset DM, intact hypoglycaemia awareness and no concurrent illnesses
- 7--8% :a more relaxed individualized target based on age , co-morbidities, duration of DM, risk of hypoglycaemia , patient motivation ,adherence and life expectancy.
- check every 3 months until target achieved then every 3-6 months

https://chi.gov.sa/AboutCCHI/CCHIprograms/Documents/Diabetes%20Mellitus.pdf

Cont.Management of DM. II

C) Referral

- Ophthalmology
- Podiatry: Comprehensive foot care
- Vaccinations :

Vaccination	Age group	Frequency
Influenza	All patients	Annually
Hepatitis B	All unvaccinated adults	Three doses series
Pneumococcal	19-64 years	One dose
PPSV23	≥65 years	2nd dose, at least 5 years apart
Pneumococcal	19-64 years	None
PCV13	≥65 years	One dose
Td	All adults	Booster every 10 years
Zoster	≥50 years	Two doses
Covid-19	All patients	Two doses

Table 3.13 – Recommended vaccinations for adults with diabetes

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/immunizations-and-diabetes/

Case

A 52 years old male with type 2 diabetes mellitus, obesity, osteoarthritis and a history of cornary artery disease sees you for follow up of his DM with persistent symptoms of polyuria, polydipsia and polyphagia. His hemglobin A1c has increased from **7%** **to** **8.7%** despite therapy with metformin 1g twice daily with minimal GI upset. He is not exercising regularly due to knee pain, and he is not on specific diet.

- What is the HbA1c goal ?
- What is the next step in the management?
- Is there any medication preferences for this patient ?

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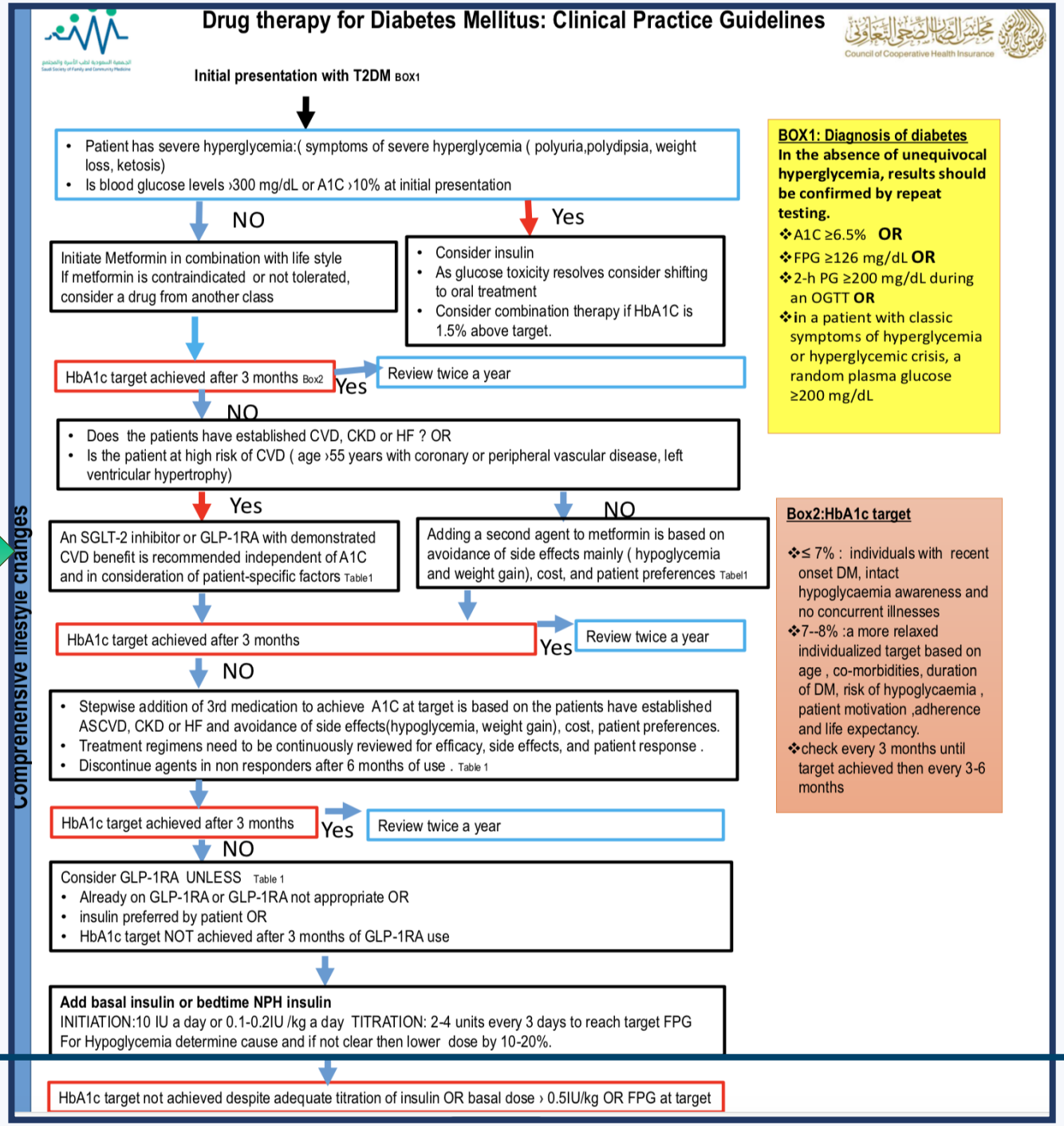
Drug therapy for Diabetes Mellitus: Clinical Practice Guidelines



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	Efficacy	Hypoglycemia	Weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
Metformin	High	No	Loss	Benefit	Neutral	Neutral	-Review dose if CrCl ‹45 -Stop if CrCl drops below 30	-Nausea, anorexia, GI upset, transient diarrhea, taste disturbance, lactic acidosis, potential for B12 deficiency. -Suspend prior to tests requiring intravenous iodine-containing contrast and elective surgery, restart 48 hours after procedure providing renal function returned to baseline.
Dose: start 500 mg with breakfast titrate over several weeks up to 2g daily in divided doses						Ramadan: advise 2/3 of daily dose with Iftar and 1/3 with Suhur		

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/pharmacologic-therapy-for-dm2/

	Efficacy	Hypoglycemia	Weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
SGLT-2 inhibitor **Empagliflozin** **Canagliflozin**	Intermediate	No	Loss	Benefit: Empagliflozin and canagliflozin	Benefit	Benefit	-Required: reduce Empagliflozin to 10 mg if GFR is less than 60 mL	-Volume depletion (gastrointestinal infections, use of diuretics, age of above 75, avoid in liver impairment. -Risk of DKA, increased LDL, risk of Fournier's gangrene & long bone fracture. -FDA black Box-Risk of amputation with canagliflozin.
Dose: Empagloflozin 10-25mg daily once						Ramadan: consider reducing the dose of concomitant antidiabetic treatment and changing the timing of the medication		

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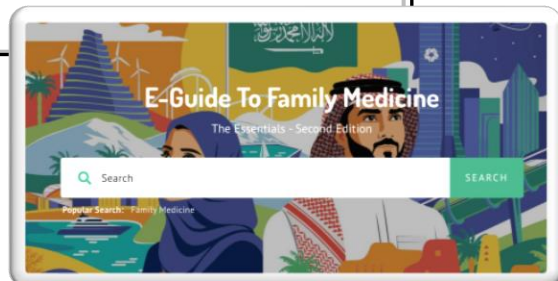

	Efficacy	Hypoglycemia	Weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
GLP-1 RA **Exenatide** **Liraglutide** **semaglutide** **(oral)**	High	No	Loss	Benefit	Neutral	Benefit Liraglutide	-Required: Exenatide Lixisenatide	-Gastrointestinal (discomfort, and dry mouth, burping, constipation, diarrhea, nausea, altered taste, toothache, gall bladder disorder, decreased appetite), headaches, dizziness, skin reactions, increased risk of infections. -Avoid in severe impairment. -FDA black Box-Risk of thyroid C-cell tumor with Liraglutide, dulaglutide, exenatide extended release
Dose: Initially 0.6mg daily for at least 1 week, increase to 1.2 mg daily for at least 1 week, then increase to 1.8 mg if necessary daily.						Ramadan: consider reducing the dose & change timings on concomitant antidiabetic treatment		

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/pharmacologic-therapy-for-dm2/

	Efficacy	Hypoglycemia	Weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
DPP-4 inhibitor **Linagliptin** **sitagliptin**	Intermediate	No	Neutral	Neutral	Risk saxagliptin	Neutral	-Not required for linagliptin -sitagliptin 50 mg if CrCl 30-50 ml/ minute and 25 mg ifCrCl less than 20 ml/minute	-uremia, nasopharyngitis, cough, increased serum lipase, urticaria, GI disturbances, peripheral edema, URI, dry mouth, headache, rash. -Risk of pancreatitis
Dose: Linagliptin 5mg once daily						Ramadan: no dose adjustment, take with Iftar		

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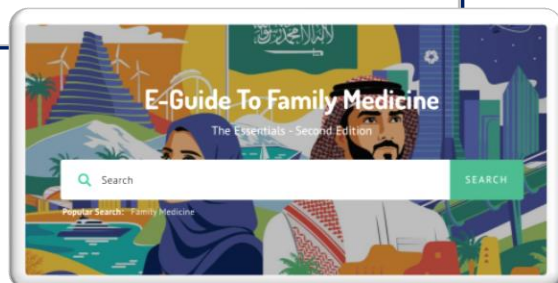
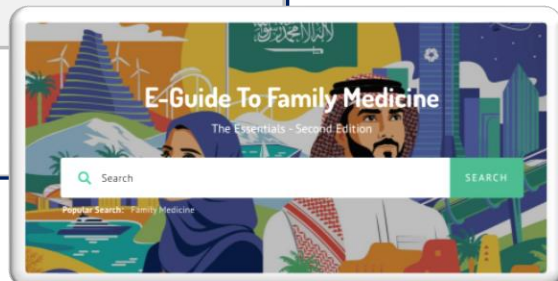


	Efficacy	Hypoglycemia	Weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
TZD Pioglitazone	High	No	Gain	Benefit: pioglitazone	Risk	Neutral	Not required	-Anemia, headache, vertigo, sweating, visual disturbances,impotence, fatigue, insomnia -Caution: increase risk of fractures, bladder cancer, undiagnosed hematuria -Benefit in NASH. -FDA black Box-Risk of heart failure.
Dose: 15-45 mg once daily no relation to food						Ramadan: no dose adjustment required		

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/pharmacologic-therapy-for-dm2/



	Efficacy	Hypoglycemia	Weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
Sulfonylurea	High	Yes	Gain	eutral	Neutral	Neutral	Not Required, use with caution	-usually well tolerated, nausea, vomiting, diarrhea, constipation, disturbance in liver function, rarely hyponatremia with Amaryl and Minitab, hypersensitivity reactions, blood disorders, avoid or reduce dose if severe impairment
Dose: glibenclamide: initially 5 mg with or immediately after breakfast, max 15 mg daily. long acting so use with caution in elderly or if insulin is needed. Glimepride: take shortly before or with the first meal. initial 1 mg adjust according to response. Max dose 6 mg daily						Ramadan: consider single dose at Iftar		

https://saudifamilymedicine.com/index.php/documentation/section-1-fm/chapter-3-diabetes/pharmacologic-therapy-for-dm2/

Table 1 : drug- specific and patients factors to consider when selecting antihyperglycemic treatment

	Efficacy	Hypoglycemia	weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
Metformin	High	No	Loss	Possible Benefit	Neutral	Neutral	review dose if CrCl ‹45 stop if CrCl drops below 30	nausea, anorexia, GI upset ,transient diarrhea, taste disturbance, lactic acidosis, potential for B12 deficiency. suspend prior to tests requiring intravenous iodine- containing contrast and elective surgery , restart 48 hours after procedure providing renal function returned to base line
Dose: start 500mg with breakfast titrate over weeks up to 2g daily in divided doses						**Ramadan**: advice 2/3 of daily dose with Iftar and 1/3 with Suhur		
SGLT-2 inhibitor Empagloflozin Canagliflozin Dapaglifozin Ertuglifozin	Intermediate	No	Loss	Benefit: Empagloflozin canagliflozin	Benefit	Benefit	Required renal dose adjustment for all SGLT-2 inhibitors	volume depletion(gastrointestinal infections , use of diuretics, age of above 75, avoid in liver impairment . Risk of DKA . Increase LDL , risk of Fournier's gangrene & long bone fracture **FDA black Box**-Risk of amputation with canagliflozin.
GLP-1 RA Exenetide Liraglutide **Dulaglutide** **Semaglutide (weekly)** semaglutide (oral)	High	No	Loss	Benefit Liraglutide Dulaglutide Semaglutide	Neutral	Benefit Liraglutide Dulaglutide Semaglutide	Required :Exenetide	gastrointestinal (discomfort, and dry mouth, burping, constipation, diarrhea, nausea, altered taste, toothache and gall bladder disorder, decreased appetite), headaches, dizziness, skin reactions, increased risk of infections, Avoid in severe impairment. **FDA black Box**-Risk of thyroid C-cell tumor with Liraglutide, dulaglutide, exenatide extended release
DPP-4 inhibitor Linagliptin Sitagliptin Vildagliptin Saxagliptin	Intermediate	No	Neutral	Neutral	Risk saxagliptin	Neutral	Required for all except linagliptin	uremia , nasopharyngitis ,cough, increased serum lipase ,urtricaria, GI disturbances, peripheral edema, URI, dry mouth, headache, rash Risk of pancreatitis
TZD Pioglitazone	High	No	Gain	Benefit: pioglitazone	Risk	Neutral	Not required, generally not recommended in renal impairment as potential risk of fluid overload.	anemia, headache, vertigo, sweating ,visual disturbances, impotence, fatigue, insomnia, caution: increase risk of fractures , bladder cancer ,undiagnosed hematuria Benefit in NASH. **FDA black Box**-Risk of heart failure.
Sulfonylurea Gliclazide Glibenclamide Glimepride Glipazide	High	Yes	Gain	Neutral	Neutral	Neutral	Glipizide and Glimepiride initiate conservatively to avoid hypoglycaemia	usually well tolerated ,nausea ,vomiting , diarrhea, constipation, hypersensitivity reactions.

https://chi.gov.sa/AboutCCHI/CCHIprograms/Documents/Diabetes%20Mellitus.pdf

When to refer patient ?

- Type 1 DM
- GDM and uncontrolled on diet
- Complex patient and/or uncontrolled DM-2 in PHC .

Reference

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THANK YOU.

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Health Specialties