Diabetes mellitus

- Epidemiology in brief of Diabetes in Saudi Arabia and over the world (not done)

- Diagnosis of diabetes, Recent guidelines for diagnosis and classification

- Screening for Diabetes

- Highlight on Pre-diabetes and how to prevent development of diabetes

- How to approach a diabetic patient in clinic?

- Role of Diabetic team in management and Goals to be achieved (HbA1C, LDL, HDL and Trig.) and for BP.
- Important aspects of clinical examination, focus on LL examination, Eye, ..
- Essential Investigations (regular visits and annual check up)
- Update in Management especially for Type 2 Diabetes including education, Life style modification, Role of Diet and Exercise

Highlight on oral medications like Biguanides, Sulphonylurea, Glitazones, Incretins, DPP 4 inhibitors, Meglitinides, Liraglutide, Insulin types

- Annual check up (what to do)
- Practical: Examination of the lower limbs in a diabetic patient, How to do?

•Diagnosis of diabetes, Recent guidelines for diagnosis and classification

TABLE. 1. Criteria for the Diagnosis of Diabetes

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

OR

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

OR

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 Diabetes Control and Complications Trial assay.*

OR

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

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

<u>Diabetes can be classification:</u>

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 is not clearly overt diabetes prior to gestation)
4. **Other specifc types**, including monogenic forms of diabetes

•Screening for Diabetes

NOTE

TABLE 2. Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - A1C ≥5.7% (39 mmol/mol), impaired glucose tolerance, or impaired fasting glucose on previous testing
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - Women who were diagnosed with GDM
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. For all patients, testing should begin at age 45 years.
3. 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 (e.g., those with prediabetes should be tested yearly) and risk status.

For patients in whom A1C and measured blood glucose appear discrepant, clinicians should consider the possibilities **of hemoglobinopathy** or **altered red blood cell turnover**

HbA1C values are influenced by red cell survival

- Falsely high values in patients with iron, vitamin B12, or folate deficiency anemia.
- Falsely low values in patients with hemolysis or anemia and those treated for iron, vitamin B12, or folate deficiency, and patients treated with erythropoietin.

•Highlight on **Pre-diabetes** and how to **prevent** development of diabetes

Table 2.3—Categories of increased risk for diabetes (prediabetes)*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
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.

Intensive behavioral **lifestyle** intervention 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

Metformin therapy for prevention of DM2 should be considered in those with prediabetes, especially for those with:

- **BMI≥ 35 kg/m2,**
- **<60 years of age,**
- **women with prior GDM,**
- **rising A1C despite lifestyle intervention.**

Screening for and treatment of modifable risk factors for CVD is suggested for those with prediabetes.

•How to approach a diabetic patient in clinic?

DM visits	Physical Examination	Investigation
•Diabetes care is a team work •**Individualize management** •Set Target goals •**Glycaemic Targets** •**BP goals** •**Lipid goals** •Education	•Height and Weight (BMI) •Blood Pressure (2 readings) •Fundus Examination (Hard and soft exudates, new vessel formation, macular oedema….) •Cardiac examination •Lower Limbs: ❑ **Skin Examination** ❑ **Evaluation of pulses** ❑ **Foot Examination** ❑ **Patellar and Achilles reflexes** ❑ **Neurologic Examination** (proprioception, vibration, and monoflament sensation)	•**FPG** and **2 hr PP** •**HbA1C** (**every 3 m for insulin / every 6m for controlled**) •**Midstream Urine** (for Ketones, protein, pus cells,…) •**Urea and Creatinine** •**Lipid Profile** (total cholesterol,LDLc, HDLc and triglycerides) •Test for **Microalbuminuria** or A/C ratio, 24 hr urine collection for protein and creatinine clearance •**ECG** as baseline. •**Chest X-Ray**

Yearly Check Up

•Urea and Creatinine •Lipid Profile •Albumin to creatinine ratio (A/C ratio), 24hr urine collection for protein (Microalbuminuria 30 -<300 mg while Macroalbuminyria ≥ 300mg)	**Eye:** Fundus Examination / eye referral **Feet :** Visual inspection and Neurovascular status

•Role of Diabetic team in management and Goals to be achieved (HbA1C, LDL, HDL and Trig.) and for BP.

A1C Goals

TABLE 6. 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.*

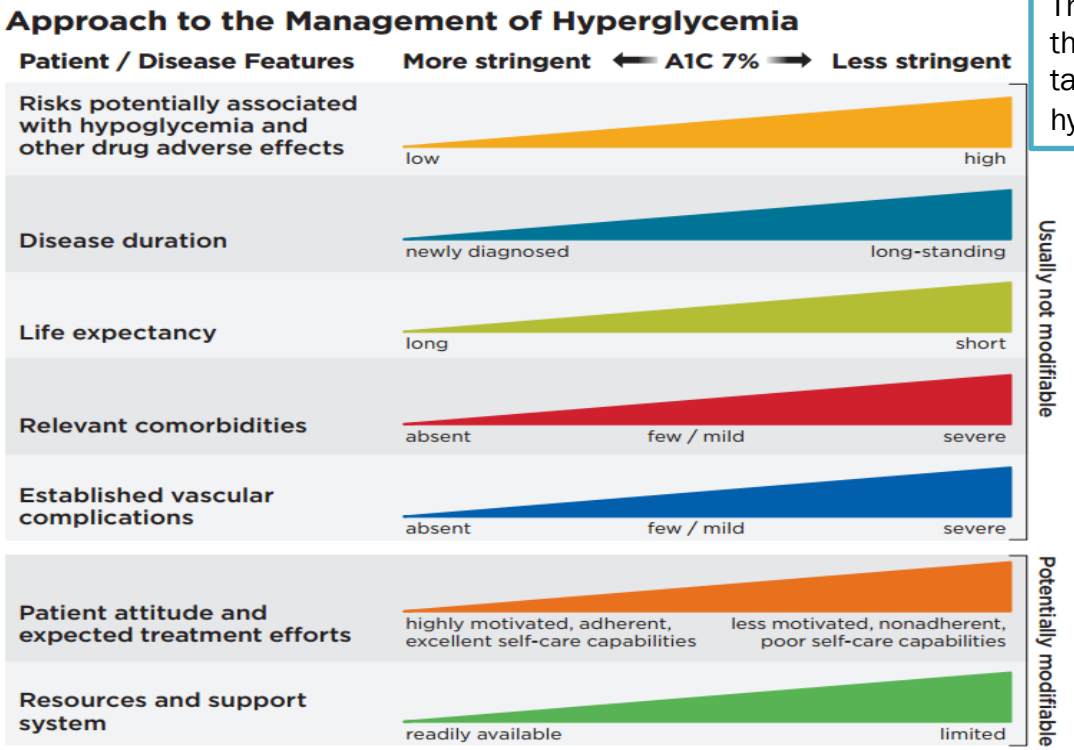


FIGURE 1. Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. Diabetes Care 2015;38:140–149.

The A1C target in **pregnancy** is 6–6.5; <6% may be optimal if this can be achieved without significant hypoglycemia,but the target may be relaxed to <7% if necessary to prevent hypoglycemia

Less stringent A1C goals (such as <8% may be appropriate for patients with ahistory of:

- severe hypoglycemia,
- limited life expectancy,
- Advanced microvascular or macrovascular complications,
- extensive comorbid conditions, or
- long-standing diabetes in whom the goal is diffcult to achieve despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin.

BP control

Most patients with diabetes and hypertension should be treated to a systolic BP goal of **<140 mmHg and a diastolic of 90 mmHg.**

Patients with confirmed office based blood pressure >140/90 lifestyle therapy + pharmacologic therapy	Patients with confirmed office based blood pressure >160/100 lifestyle therapy + two drugs
ACE inhibitor or ABR at the maximum tolerated dose indicated is the recommended first-line treatment for hypertension in patients with diabetes	For patients treated with an ACE inhibitor, ARB, or diuretic: •Serum creatinine / eGFR •Serum potassium levels should be monitored.

TABLE 7. Recommendations for Statin and Combination Treatment in People With Diabetes

Age (years)	Risk Factors	Recommended Statin Intensity*
<40	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy.
**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.

Presence of moderately increased albuminuria (approximately 30-300 mg/g)
should prompt initiation of ACEIor ARBs for its renoprotective effects.

- **LDL-C** < 100 mg/dl
- **HDL-C** > 40 mg/dl (males), > 50 mg/dl (females)
- **TG** < 150 mg/dl

•Update in Management especially for Type 2 Diabetes including education, Life style modification, Role of Diet and Exercise.Highlight on oral medications like Biguanides, Sulphonylurea, Glitazones,
Incretins, DPP 4 inhibitors, Meglitinides, Liraglutide, Insulin types

Life Style Modification

For all patients, advise for

Weight Management :(in overweight/obese patients can improve insulin sensitivity targeting a loss of 7% of body weight)

Exercise (walking 150 mins / week)

Diet (Provided by a Dietitian**)** There is not a one-size-fits-all eating pattern for individuals with diabetes. The Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet, and plant-based diets are all examples of healthful eating patterns.

Can reduce HbA1C by 1-2%

Problems

Poor adherence over time

Education : patients must be educated about daily foot inspections, appropriate footwear and avoiding barefoot activities, and testing water temperature before bathing.

Patients should receive recommended preventive care services (e.g., **immunizations** and cancer screening); **smoking cessation counseling**; and **ophthalmological**, **dental**, and **podiatric referrals**. Clinicians should ensure that individuals with diabetes are appropriately screened for complications and comorbidities

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dl, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

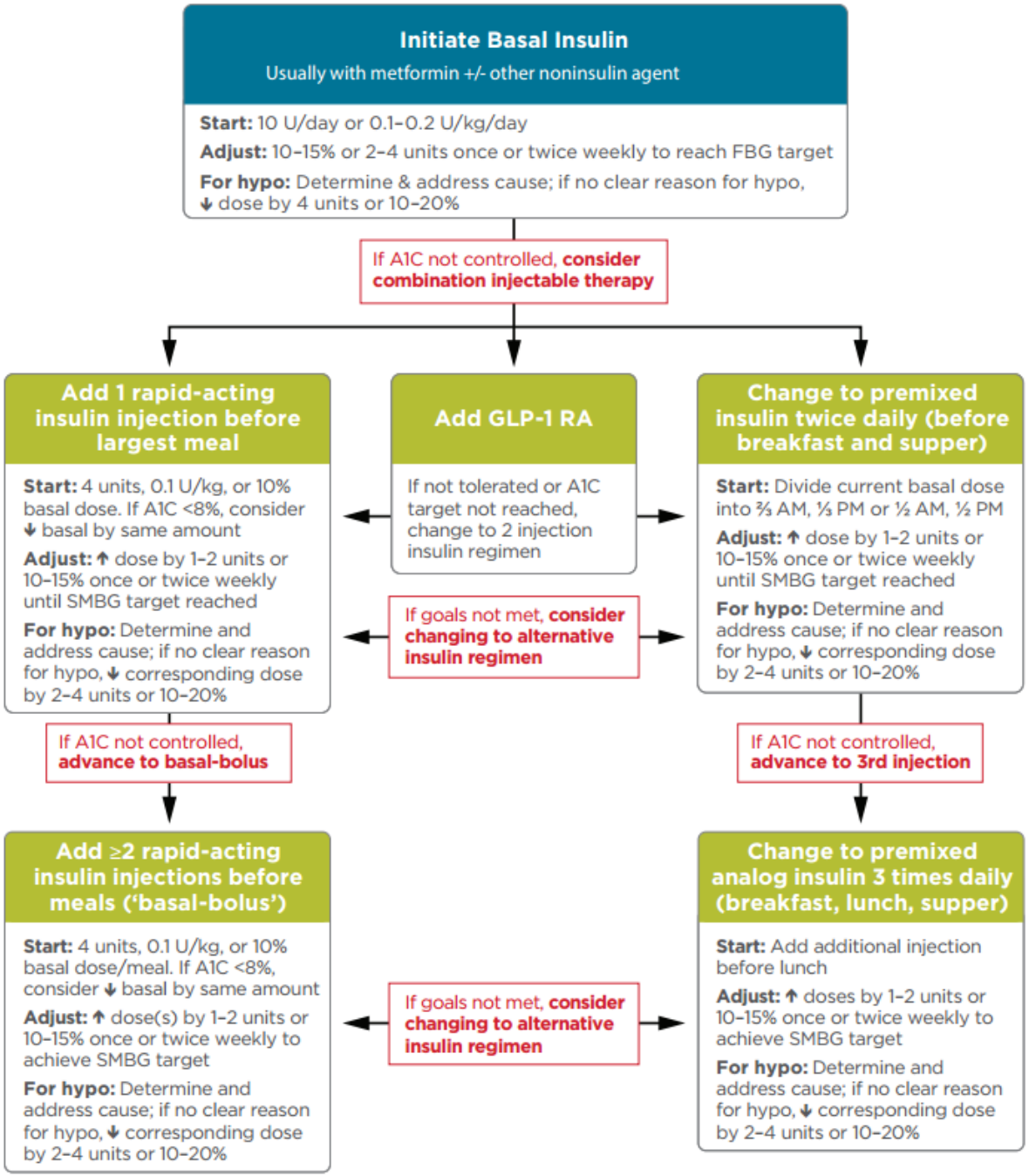
If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e. adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 3)

•Fxs =fractures , G I=gastrointestinal, GU =genitourinary, HF =heart failure, Hypo =hypoglycemia / DPP-4-I =DPP-4 inhibitor, GLP-1 RA =GLP-1 receptor agonist, SGLT2-I =SGLT2 inhibitor,SU =sulfonylurea, TZD=thiazolidinedione

•Usually a basal insulin (NPH, glargine, detemir, degludec)

Combination Injectable Therapy



Notes:

- **Read and Understand the previous algorithms.**
- Metformin, if not contraindicated and if tolerated, is the preferred initial therapy for DM2.
- INDIVIDUALIZED THERAPY, to add on metformin, you can choose any drug according to the patient status or preference and the drug characteristics and side effects. (e.g, a policeman, elderly or patient with previous MI can't afford hypoglycemia, with an overweight person you may think of a drug with weight loss properties)

Insulin sensitizers

Biguanides		Thiazolidinediones	
Metformin		Pio**glitazone** , rosi**glitazone**	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
Oral	**GI disturbance**	**Increase insulin sensitivity**	Fluid retention/CCF Congestive cardiac failure
Low cost	B12 deficiency	-cell preservation?	**Weight gain**
Decrease macrovascular complications ?	Lactic acidosis	Vascular protection?	Bone fractures
Reduce hepatic gluconeogenesis	Contraindications e.gRenal impairment	Decrease hepatic gluconeogenesis	Bladder cancer?
Once daily dosing		Once daily dosing	Costly

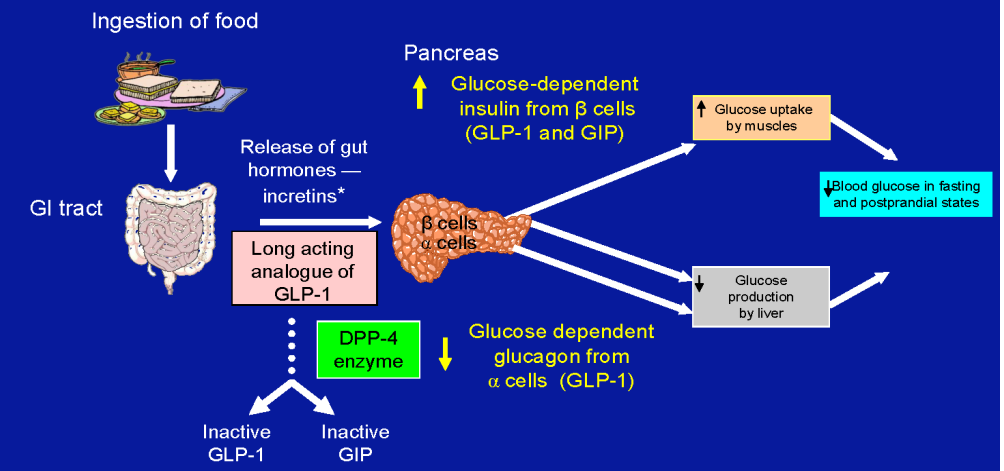
Insulin secretagogues

Sulphonylureas		Meglitinides	
glibenclamide, glipizide, glimepiride, gliclazide.		Repaglinide, nateglinide	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
Oral	Hypoglycaemia	Oral	less risk for hypoglycemia
Decrease microvascular complications	Weight gain	short-acting insulin secretagogues	
Once daily dosing	-cell failure?	Before meals	
Low cost	CV risk ?		

SGLT-2 inhibitor Sodium-glucose co-transporter **2**	
Cana**gliflozin**, Dapa**gliflozin**, Empa**gliflozin**	
Advantages	**Disadvantages**
Oral	**Urinary tract infections**
Lower the renal glucose threshold causing Glycosuria	Genital mycotic
Once daily dosing	**Costly**

INCRETINS

Role of Incretins in Glucose Homeostasis



Adapted from Kieffer TJ, Habener JF. *Endocr Rev.* 1999;20:876–913; Ahrén B. *Curr Diab Rep.* 2003;2:365–372; Drucker DJ. *Diabetes Care.* 2003;26:2929–2940; Holst JJ. *Diabetes Metab Res Rev.* 2002;18:430–441.

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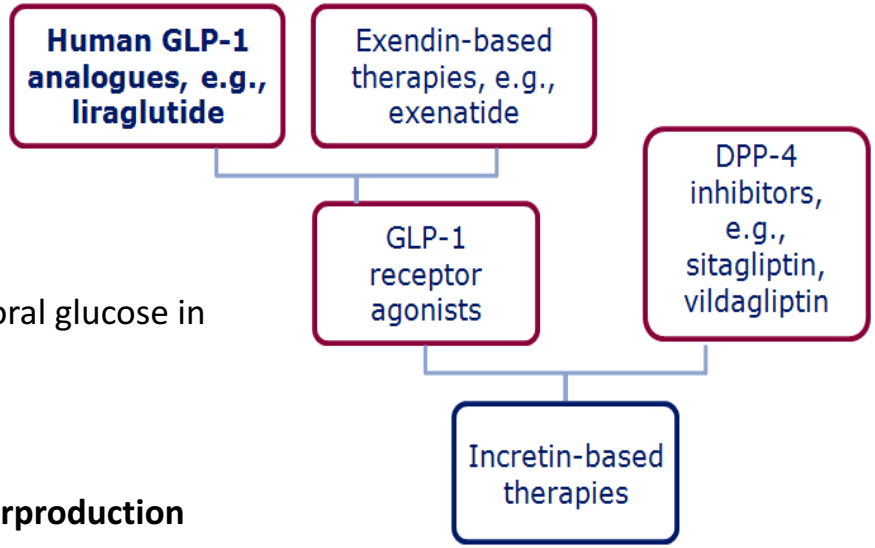
- The incretin system is **impaired** in patients with **T2DM**, which, as a consequence of its insulinotropic actions, contributes to fasting and postprandial hyperglycemia.

- The impairment of **GLP-1** secretion varies directly with the degree of insulin resistance; those who are **more insulin resistant** have a lower rise in **GLP-1** in response to a meal.

The Family of Incretin Based Therapies



Dipeptidyl Peptidase-4 (DPP-4)

GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (**DPP-4**).

Glucagon-like Peptide-1 (GLP-1)

- Secreted throughout the day by intestinal mucosa in response to oral glucose in The gut
- Stimulates all steps of insulin biosynthesis
- Provides continued and augmented release of insulin **without overproduction**
- Acts on islet alpha cells, causing strong inhibition of postprandial glucagon secretion
- **Slows gastric emptying** and acts on brain to promote early satiety

Peptide analogs

GLP-1 analogues		DPP3-inhibitors	
Exenatide, Lira**glutide**, Albi**glutide**, Dula**glutide**.		Sita**gliptin**, Saxa**gliptin**, Lina**gliptin**,	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
Low risk of hypo	**Injection required**	**Low risk of hypo**	Limited long-term clinical experience
Weight loss	Limited long-term clinical experience	Weight neutral	Pancreatitis/ pancreatic ca?
Lower blood pressure	Antibody formation (significance?)	No drug interactions	Heart failure?
CVD protective?	Pancreatitis/ pancreatic, medullary C-cell cancer?	Fixed dose	**Expensive**
	Expensive		

Non glucose effects of GLP-1 receptor agonists

↓ 3-4 Kg

↓ 2-3 mmHg(SBP)

↑ 2-3 beats/min

Ominous Octet

Organ/Cell	Pathophysiology	Medication
1. Muscle	Decreased glucose uptake	Metformin/TZDs/Insulin
2. Liver	Increased gluconeogenesis	Metformin/TZDs/Insulin
3. β Cells	Impaired insulin secretion	Sulphonylureas/DPP-4 Inhibitors/ GLP-1 receptor agonists/Insulin
4. α cells	Increased glucagon secretion	DPP-4 inhibitors/ GLP- receptor agonists
5. Fat	Increased lipolysis and decreased glucose uptake	TZDs
6. Intestine	Decreased/Impaired incretin effect?	DPP-4 Inhibitors/ GLP-1 receptor agonists (α- glucosidase inhibitors)
7. Kidney	Increased glucose reabsorption	SGLT-2 inhibitors
8. Brain	Neurotransmitter dysfunction	GLP-1 receptor agonists/ Bromocriptine

DIABETES
Insulin Types

Insulin

IMIG

		Type	Trade Name	Onset	Peak	Duration
Bolus	Rapid Acting	**aspart** **glulisine** **lipsro**	NovoRapid Apidra Humalog	10-15m	1-1.5h	3-5h
	Short Acting	**Regular**	Humulin-R Novolin grToronto	30-45m	2-3h	6.5h
Basal	Intermediate	**NPH**	Humulin-N Novolin ge NPH	1-3h	5-8h	14-18h
	Long Acting	**detemir** **glargine**	Levemir Lantus	1-2h 1-2h	8-10h no peak	12-24h 22-24h

TREATMENT REGIMENS

Conventional Insulin Therapy

Two injections of NPH and Regular Insulin

Mixed Insulin

Two injections of 70/30 or 60/40 or 50/50 (ratio between long and short acting insulin mixed together in one injection, taken twice daily after large meals to control both basal and post-prandial blood sugar)

Multiple Insulin Injections

1 or 2 injections of NPH plus 3 injections of Regular or Rapid Insulin

One injection of Glargine or Detemir plus 3 injections of rapid insulin (Lispro /Aspart)

INSULIN AS INITIAL THERAPY

- HgA1c >9.5 percent (80.3 mmol/mol)
- FPG >13.9 mmol/L (>250 mg/dL)
- Random glucose consistently >16.7 mmol/L (>300 mg/dL)
- Ketonuria, or Unplanned weight loss with hyperglycemia

INDICATION OF INSULIN IN TYPE 2 DM

If HbA1c is ≥ 9 %

After maximum metformin and suphonylurea

You should consider adding Insulin and taper the Sulphonylurea.

Examination of the lower limbs in a diabetic patient
https://www.youtube.com/watch?v=vwIyulPnXcg
Dumb Way to Remember Insulin (lispro , regular insulin , nph , glargine lantus)
https://www.youtube.com/watch?v=urW-SmYnYHM
Diabetic Drugs - Learn with Visual Mnemonics!
https://www.youtube.com/watch?v=GKSp2Ogv564

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