Therapy of DM

** DM result in chronic complication including microvascular which are prevented by DM treatment and macrovascular which need other interventions

The primary goals of DM management are :

1) To reduce the risk of microvascular and macrovascular disease complications

2) To minimize weight gain and hypoglycemia.

** Diabetic ketoacidosis (DKA)miand hyperosmolar hyperglycemic state (HHS) are severe manifestations of poor diabetes control

TABLE 30-2 Type 1 and Type 2 Diabetes Mellitus

	TYPE 1 Insulin dependant	TYPE 2
Etiology	Autoimmune destruction of pancreatic β-cells Toxins	Insulin resistance, with inadequate β-cell function to compensate, or relative deficiency
Insulin levels	Absent or negligible	Typically higher than normal
Insulin action	Absent or negligible	Decreased
Insulin resistance	Not part of syndrome but may be present (e.g., in obese patients)	Yes
Age of onset	Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis poor control; Muscle Wasting	Hyperglycemia (can lead to hyperosmotic seizures and coma)
Chronic complications	Neuropathy Retinopathy Nephropathy Peripheral vascular disease Coronary artery disease	Same as type 1
Pharmacologic interventions	Insulin	A number of drug classes are available, including insulin if other therapies fail

Type 1 and type 2 diabetes mellitus are both associated with increased blood glucose levels, but the two diseases result from distinct pathophysiologic pathways. In type 1 diabetes mellitus, there is an absolute lack of insulin secondary to autoimmune destruction of pancreatic β-cells. The etiology of type 2 diabetes is less well understood but seems to involve impaired insulin sensitivity and an inadequate level of compensatory insulin production by pancreatic β-cells. Although type 1 and type 2 diabetes have different acute complications (*see text*), they share similar chronic complications. Insulin is the primary pharmacologic intervention for type 1 diabetes, while type 2 diabetes can be treated with a number of different agents.

Resistance
-Nicotinic acud
-Glucocorticoids(metabolic effects+insulin antagonism)
-Growth hormones(reduce insulin snsitivity causing mild hyperinsulinemi and increased blood glucose levels)
-Chronic alcoholism
-Cyclosporine
-Hiv protease inh
-Atypical antipsychotics(weight gain)
-Megestrol acetate
......
Type 1 dm (mneonic: PPI)
-Pyriminil (vacor)(rodenticide)(loss of panceriatic b cells)
-Pentamidine(cytotoxic effect on panceriatic b cells)
-Interferon(viral infection like mumps)(b cell destruction)
...-chronic alcoholism (b cell dysfunction+insulin insinsitivity)
.....
Inhibits insulin secretion
-Diazoxide
-Thiazide(by hypokalemia)
-Cyclosporine(+resistance)
...-hiv protease inh(Insulin diff relative to hyper)glucagonemia
....
Increase glucose production
-Thyroid hormones(increase hepatic glucose production)
-B adrenergic agonist(glycogenolysis and gl[illegible]neogenesis)

Management of DM :

We always start with non pharmacological management then with pharmacological treatments.

Other recommendations:

Blood pressure:

**Systolic/diastolic blood pressure should be treated to <140 mm / <90 mm Hg

** Initial drug therapy should be with an ACEi or ARBs

Antiplatelet Therapy:

** Use aspirin (75-162 mg daily)

Dyslipidemias :

** lifestyle modification , Consider the use of statins according to risks

Hospitalized Patients:

**Critically ill: IV insulin protocol.

**Non-critically ill: scheduled subcutaneous insulin

Delay in the onsit of DM

- Type 1 : by focusing on immunomodulators and low dose insulin, but the results are not yet conclusive

- Type 2 : by the 4 life-style pillars :

A) decrease weight. B) increase aerobic exercise. C) increase fiber in diet. D) decrease fat intake

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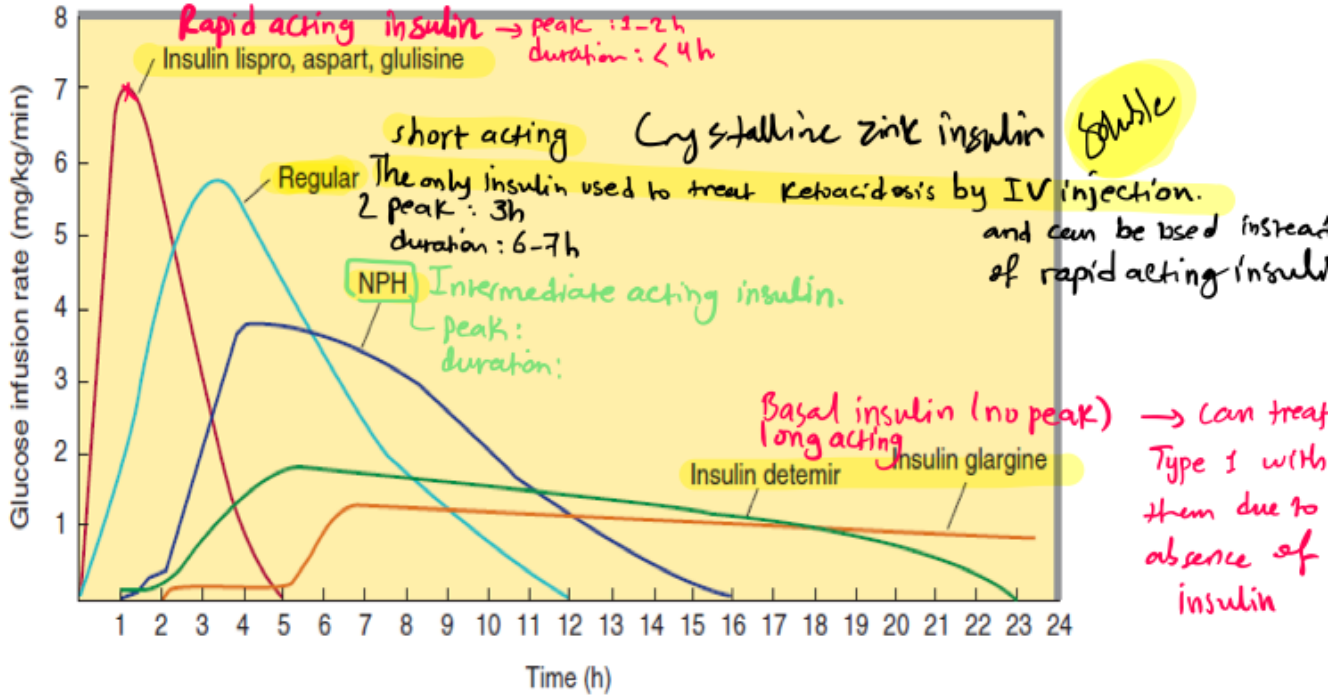
- **Drugs Notes:**

  - **Metformin**: reduces DM2 risk
  - **Rosiglitazone**: reduces DM2 incidence
  - **Acarbose and liraglutide**: reduce DM2 progression
  - Moving the evening NPH dose to bedtime may improve glycemic control and reduce the risk of nocturnal hypoglycemia.
  - Regular insulin is soluble or crystalline zinc insulin.
  - Hypoglycemic unawareness may result from autonomic neuropathy or frequent episodes of hypoglycemia.
  - **Postprandial glycemic control**: **Pramlintide** before meals or **Exenatide**.

- Pharmacological therapy (type 1 DM) :

For IV injections , insulin must be clear such as regular insulin
NPH is turbid so don't mix it with regular insulin

Insulin



مهم نعرف كل نوع ومثال عليه وكم الديوريشن تبعه
لحتى نعرف كم المدة الي رح يشتغلها ومتى نعطي الجرعة الي بعدها

Rapid acting >>> 3-5 hours
Short acting >>> 4-6 hours
Intermediate acting >>> 8-12 hors
Long acting >>> 24 hours

*regular insulin is the only one that is used in the treatment of DKA by IV infusion, could also be used as a substitute of rapid acting insulin

* regular insulin and rapid acting insulin have the same onset of action if given IV (the diagram represents SC injection)

* Continuous subcutaneous insulin famously infusion (CS-II)or insulin pumps using a rapid-acting insulin is the most sophisticated and precise method for insulin delivery, BUT it needs more frequent self monitored blood glucose

Intensive Insulin Regimens

** The morning intermediate-acting insulin dose provides basal insulin during the day and provides "prandial" coverage for the midday meal.

**The evening intermediate-acting insulin dose provides basal insulin throughout the evening and overnight.

**"Basal-bolus" regimens using multiple daily injections may mimic normal insulin physiology, with a combination of intermediate- or long acting insulin to provide the basal insulin, and rapid acting insulin to provide prandial coverage.

Bolus = prandial

	7 am meal	11 am meal	5 pm meal	Bed time
	6	12	6	
2 doses (R or rapid acting) + N	R, L, A, Glu + N rapid or regular + intermediate		R, L, A, Glu + N rapid or regular + intermediate	
3 doses (R or rapid acting) + N	R, L, A, Glu + N	R, L, A, Glu rapid/ regular	R, L, A, Glu + N	
4 doses (R or rapid acting) + N	R, L, A, Glu rapid/ regular only	R, L, A, Glu rapid/ regular	R, L, A, Glu rapid/ regular	N intermediate
4 doses (R or rapid acting) + N	R, L, A, Glu + N	R, L, A, Glu	R, L, A, Glu	N
4 doses (R or rapid acting) + long acting	R, L, A, Glu	R, L, A, Glu	R, L, A, Glu	long acting G or D
CS-II pump	Adjusted basal + Bolus	Adjusted basal + Bolus	Adjusted basal + Bolus	
3 prandial doses	P added to previous regimens	P added to previous regimens	P added to previous regimens	

A, aspart; CS-II, continuous subcutaneous insulin infusion; D, detemir or degludec; G, glargine; GLU, glulisine; L, lispro; N, NPH; P, pramlintide; R, regular.

Pramlintide

- Amylino mimetic
- To control postprandial blood glucose
- Can't be mixed with insulin → additional injection
- Reduce insulin (30-50%) to prevent hypoglycemia
    - suppresses endogenous production of glucose in the liver
    - Slow gastric emptying – vagally mediated.
    - Promote satiety or reduce appetite - centrally.
    - Reduce glucagon secretion.
    - Produces moderate weight loss.
- SEs → Hypoglycemia and GIT disturbances: nausea, vomiting, anorexia.

Therapy of DM (type 2)

- Patients with HbA 1c of 7.5% or less are usually treated with metformin
- Those with HbA 1c> 7.5% but < 8.5% could be initially treated with a single agent, or combination therapy.
- Patients with higher initial HbA 1cwill require two agents OR insulin.
- Obese → metformin
- Not obese → increase insulin secretion “insulin secretagogue” ○ Sulfonylurea

types

1. GLP-1 receptor agonist “Glucagon-like peptide-1 receptor agonists”
2. Sodium glucose cotransporter 2 (SGLT2) inhibitors
3. DPP-4 inhibitors “Inhibitors of dipeptidyl peptidase 4”
4. Sulfonylureas “SU”
    - SE → weight gain and hypoglycemia. No durable glycemic response
5. TZDs “thiazolidinediones “
    - durable glycemic response , no hypoglycemia
    - SE → weight gain, fluid retention and risk of new onset heart failure
6. Insulin

All are high efficacy except → DPP and SGLT

Hypoglycemia

- Insulin high risk
- SU moderate risk
- Other → low risk

WT gain

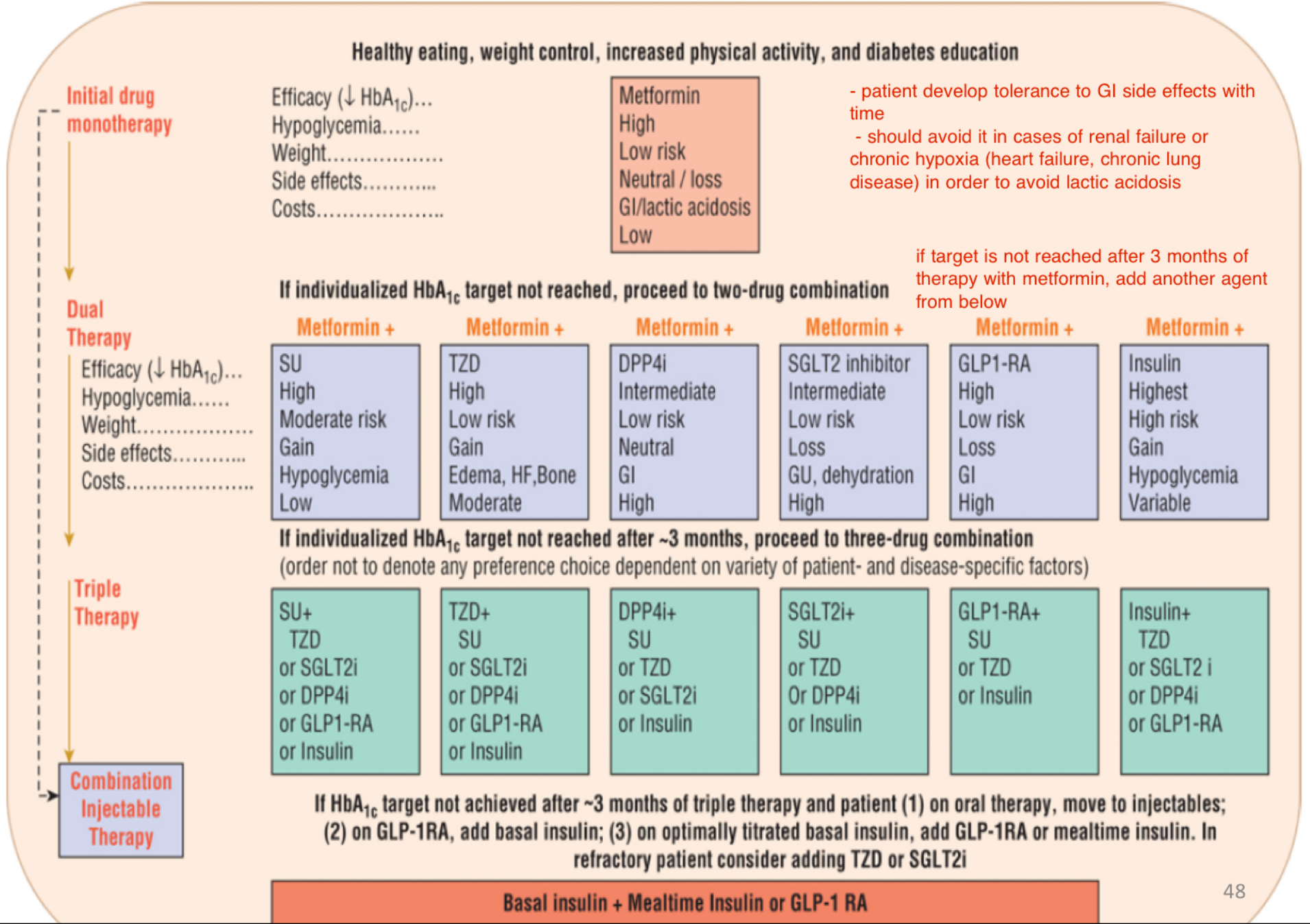
- All → Wt gain except
    - SGLT and GLP, pramlintide → Wt loss
    - DPP, metformin → neutral

⇨ **SGLT2 inhibitors Side Effects:**
UTIs, hypotension, increased LDL, breast and bladder cancer.

⇨ **Sitagliptin Side Effects:**
Nasopharyngitis, URTI, hypoglycemia when combined, acute pancreatitis, allergy.

⇨ **Exenatide Side Effects:**
NVD, acute pancreatitis, AKI

Antihyperglycemic Therapy Recommendations in Type 2 Diabetes. General Recommendations. *(Data from reference 20.)*



- only know the drug class, one example, and the duration of action

Drug & class	Dose (mg)	Duration of action (hours)	Drug	Dose (mg)	Duration of action (hours)
Sulfonylureas					
Glimepiride	1-8	24	Glipizide	2.5-40	12-24
Glyburide	1.25-20	12-24	Glipizide extended release	5-20	24
Micronized glyburide	1-12	24			
Non-sulfonyureas secretagogues					
Rapaglinide	0.5-4	2-3	Nateglinide	60-120	2-4
Biguanides					
Metformin	500-2500	6-12	Metformin extended release	1500-2000	24
Thiazolidinediones					
Rosiglitazone	4-8	Poorly correlated with half-life. Max effect ~ 4 weeks	Poiglitazone	15-45	Poorly correlated with half-life. Max effect ~ 4 weeks
α-glucosidae inhibitors					
Acarbose	25-50	Affects absorption of carbohydrates in a single meal	Miglitol	25-100	Affects absorption of carbohydrates in a single meal
GLP-1 receptor agonists / Incretin mimetics					
Exenatide	5-10 mcg	10	Liraglutide	0.6-1.8	24
DPP-4 inhibitors					
Sitagliptin	100	24	Saxagliptin	2.5-5	24
Linagliptin	5	24			
Amylin mimetics					
Pramlintide	15-60 (type 1 DM) 60 or 120 (type 2 DM)	C_{max} 20 min			
Bile acid sequestrants					
Colesevelam	3750	N/A			

reduce post prandial hyperglycemia (glucose peak) beacause it delays digestion of disaccharides. have GI side effects

Drug selection

Pt has

- CVD → don't use TZD
- GU infection → dont use SGLT
- GI infection or disease → dont use DPP or GLP

arrest β-cell failure combination Tx

- TZD “pioglitazone” and GLP-1 receptor agonist “exenatide” + metformin

Exenatide

- long-acting analogue of GLP-1
- adjunctive therapy for DM 2, treated with metformin or metformin plus sulfonylureas
- SEs→ **N**\V, diarrhea (dose dependent), Acute pancreatitis, ARF
- No hypoglycemia

If pt is insulinopenic

- use insulin injections at bedtime (intermediate- or long-acting basal insulin) while continuing to use oral agents or GLP-1 receptor agonists for control during the day.
    - equal efficacy, less hypoglycemia

Special consideration

- In Children and Adolescents
    a. lifestyle
    b. metformin, sulfonylureas (or TZDs)
    c. Insulin
- In elderly
    a. Metformin (low dose) if Clcr is > 30 mL/min/1.73 m2.
    b. DPP-4 inhibitors, shorter-acting insulin secretagogues, low-dose sulfonylureas, or α-glucosidase inhibitors
    c. Simple insulin regimens with daily basal insulin
- Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State
    a. continuous IV infusion
    b. volume deficits, electrolyte disturbances, and acidosis
- Intercurrent Medical Illness or surgery (pre or post)
    a. If on oral agents → switch to insulin (continuous insulin infusions)
    b. stop metformin (until hemodynamically stable and normal renal function is documented)