- Qs in exam about 1) SC insulin vs. IV.
  2) Hypoglycemia.

* Microvascular are prevented by Tx while macrovascular we need other interventions.

Therapy of Diabetes Mellitus

* Intermediate NPH
* Basal insulin long acting
* Prandial insulin
* Split-mix

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Therapy of Diabetes Mellitus

- **Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by hyperglycemia.**
- **It is associated with abnormalities in carbohydrate, fat, and protein metabolism.**
- **It may result in chronic complications including microvascular, macrovascular, and neuropathic disorders.**

Therapy of Diabetes Mellitus

- DM is the leading cause of blindness and end-stage renal disease.
- It may result in lower extremity amputations, and cardiovascular events.

premature atherosclerosis.

TABLE 30-2 Type 1 and Type 2 Diabetes Mellitus

	TYPE 1	TYPE 2
Etiology	Autoimmune destruction of pancreatic β-cells	Insulin resistance, with inadequate β-cell function to compensate
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 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.

GGCC N

PPI • We have to know so we can reverse DM sometimes.

Drug-induced Diabetes Mellitus

1. Pyriminil (Vacor) (rodenticide) – loss of pancreatic β-cells.
2. Pentamidine – cytotoxic effect on pancreatic β-cells (type 1).
3. Nicotinic acid – insulin resistance.
4. Glucocorticoids – Metabolic effects and insulin antagonism.
5. Thyroid hormones – increase hepatic glucose production.
6. Growth hormone - reduces insulin sensitivity resulting in mild hyperinsulinemia, and increased blood glucose levels
7. Diazoxide: inhibition of insulin secretion.

Drug-induced Diabetes Mellitus

Diazoxide + thiazide

8. β-adrenergic agonists – glycogenolysis, and gluconeogenesis.
9. Thiazides – hypokalemia-induced inhibition of insulin release.
10. Interferone – β-cell destruction (type 1)
11. Chronic alcoholism - insulin insensitivity and pancreatic β-cell dysfunction. Type II
12. Cyclosporine – suppresses insulin production and release. It may produce insulin resistance.

Immunosuppressant.

- A child gets mumps later on diagnosed with type 1 DM, due to the child's secreted interferones during the viral infection.

Drug-induced Diabetes Mellitus

13. **HIV protease inhibitors - insulin resistance with insulin deficiency relative to hyper-glucagonemia.**
14. **Atypical antipsychotics (clozapine and olanzapine) – weight gain and insulin resistance.**
15. **Megestrol acetate – insulin resistance.**
16. **Others …**

BM suppression

can also cause AA) Aplastic anemia so monitor: 1) CBC. 2) Blood glucose

v.imp

progestin (Contraceptive).

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 gluconeogenesis)

Therapy of Diabetes Mellitus

Desired Outcome:

The primary goals of DM management are:

1. **To reduce the risk of microvascular and macrovascular disease complications.**
2. **To ameliorate symptoms.**
3. **To reduce mortality.**
4. **To improve quality of life.**
5. **To minimize weight gain and hypoglycemia.**

Causes insulin resistance and ↓ efficacy of treatment

hypoglycemia couldn't be avoided but should be minimized.

2 due to treatment

Therapy of Diabetes Mellitus

- **Early diagnosis and treatment to near-normoglycemia reduces the risk of developing microvascular disease complications (retinopathy, nephropathy, and neuropathy).**

Therapy of Diabetes Mellitus

- **Aggressive management of cardiovascular risk factors: smoking cessation, treatment of dyslipidemia, intensive blood pressure control, and antiplatelet therapy are needed to reduce the risk of developing macrovascular disease (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease).**

Therapy of Diabetes Mellitus

- Hyperglycemia also contributes to poor wound healing by compromising white blood cell function and altering capillary function.
- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are severe manifestations of poor diabetes control, always requiring hospitalization. + IV insulin.

Non-pharmacologic Management

for old obese patient for example

1. **Screening (for the presence of DM).**
2. **Monitor for:**

- **blood glucose, HbA_{1c}, fasting lipid profile, urinary albumin (urine albumin-to-creatinine ratio [UACR]) and glomerular filtration rate (GFR), diabetic neuropathy, and dilated eye examination.**

1 2 3 4

in Type II, to reduce macravascular Complicat's

microvascular

nephropathy

neuropathy

retinopathy

gloves and socks neuropathy

- Dipstick is not useful to assess the nephropathy compx. of DM → you should measure UACR + GFR through measuring CR clearance (Cl_{CR})

- Mostly in type II DM you need to treat those complications while type I they didn't occur yet at the time of dx.

Non-pharmacologic Management

3. **Glycemic goals:**

- **HbA_{1c} goal for males and non-pregnant females of <7%, or of <6.5%* without significant hypoglycemia.**
- **Critically ill (Hospital) glucose: 140-180 mg/dL, or more strict guidelines down to 110-140 mg/dL (without hypoglycemia).**

near normoglycemic

- **(*The above percentages may differ depending on the method of HbA_{1c} measurement*).**

Non-pharmacologic Management

*v.imp

1. **Medical nutrition therapy:**

- only fat not muscle; so they need specific diet regimens

- **Weight loss is recommended for all insulin-resistant, overweight or obese individuals.**

a) **Either low-carbohydrate, low-fat, calorie-restricted diets, or Mediterranean diets.** Greek diet olive oil dependant (delays macrovascular ...).

b) **Healthier eating behaviors leading to sustained weight loss over time is more important than a specific diet.**

قليل دائم خيرمن كثير منقطع.
eat some (not never eat) but in very small amounts

Non-pharmacologic Management

- **In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations.**
  * gluconeogenesis from amino acids.
- **Therefore, carbohydrate sources high in protein should NOT be used to treat or prevent hypoglycemia.** bc they don't increase glucose sufficiently.
- **Saturated fat should be <7% of total calories.**
  Animal fat

Non-pharmacologic Management

- A Mediterranean-style eating pattern, rich in monounsaturated fatty acids (olive oil), may benefit glycemic control and reduce CVD risk factors.
- Consider financial and cultural food issues. of the patient.
- Discourage bedtime and between-meal snacks, and set realistic goals.

Non-pharmacologic Management

- A diet low in fat is recommended for patients with CVD.
- Avoid a high-protein diet in patients with nephropathy.
- Supplement with all of the essential vitamins and minerals.

Non-pharmacologic Management

5. **Physical Activity:**

- **Aerobic exercise improves insulin sensitivity, modestly improves glycemic control, reduces cardiovascular risk, contributes to weight loss or maintenance, raises HDL-cholesterol and improves well-being.**

- **Physical activity goals include at least 150 min/wk of moderate intensity exercise spread over at least 3 days/week with no more than 2 days between activities.**

Non-pharmacologic Management

- **Resistance/Strength training is recommended at least 2 times a week in patients without proliferative diabetic retinopathy, and ischemic heart disease.**

Non-pharmacologic Management

6. **Patient Education:**

- **It is NOT appropriate to give patients with DM brief instructions and a few pamphlets.**
- **Diabetes education, at initial diagnosis and at ongoing intervals over a life-time, is critical.**
- **Healthy behaviors include healthy eating, being active, monitoring, taking medication, problem solving, reducing risk, and healthy coping.** with problems

Non-pharmacologic Management

- **The patient must be involved in the decision-making process with knowledge of the disease and associated complications.**
- **Emphasize that complications can be prevented or minimized with good glycemic control and managing risk factors for CVD.**
- **Motivational interviewing techniques to encourage patients to identify barriers that hinder achieving health goals, and then work to solve them, are essential.**

Other Recommendations

140/90 like pregnant

A. **Blood pressure:**

- **Systolic/diastolic blood pressure should be treated to <140 mm / <90 mm Hg.**
- **Lower goals <130 mm Hg / <80 mm Hg may be appropriate for younger patients.**
- **Life-style intervention such as weight loss, and diet including reducing sodium and increasing potassium.**

prevent microalbuminuria (loss of albumin in urine that causes nephropathy).

- **Initial drug therapy should be with an ACEi or an angiotensin-receptor blocker (ARB); if intolerant to one, the other should be tried.**

Other Recommendations

B. **Dyslipidemia:**

- **Lifestyle modification focusing on the reduction of saturated fat, and cholesterol intake; increasing omega-3 fatty acids intake, use of viscous fiber, and plant sterols; weight loss, and increased physical activity should be recommended.**
- **Consider the use of statins according to risks.**

Other Recommendations

C. **Antiplatelet Therapy:**

- **Use aspirin (75-162 mg daily) for secondary cardioprotection.** Low dose. Only for patients with IHD

D. **Hospitalized Patients:**

- **Critically ill: IV insulin protocol.**
- **Non-critically ill: scheduled subcutaneous insulin with basal, nutritional, and correction coverage.**

Type I is already treated with insulin, but type II critically ill pts should convert from oral → IV hypoglycemic agents insulin due to stress and cortisol secretion.

E. **Psychosocial:**

- **Assess the patient's psychological and social situation as an ongoing part of the medical management of diabetes.**

Prevention of Diabetes Mellitus

A. Efforts to prevent type 1 diabetes focused on immunomodulators and low dose insulin, but the results are not yet conclusive.

B. Prevention of type 2 diabetes:

1. The "4 life-style pillars" for the prevention of type 2 diabetes are to:

a) decrease weight.

b) increase aerobic exercise.

c) increase fiber in diet.

d) decrease fat intake.

Prevention of Diabetes Mellitus

2. **Drugs:**

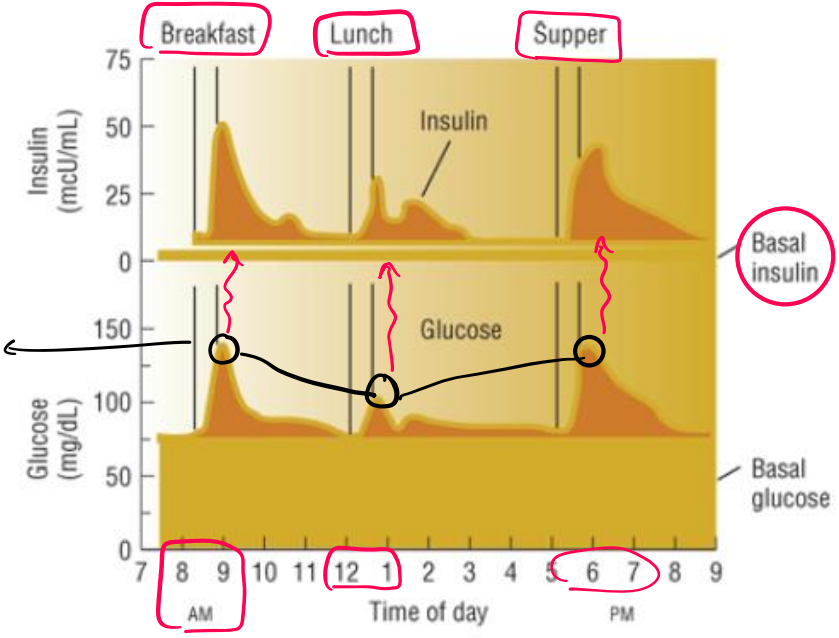
a. *** **Metformin therapy reduces the risk of developing type 2 DM, especially in obese and <60-year-old patients and women with prior gestational diabetes mellitus (GDM).**

b. **Rosiglitazone** (reduces insulin resistance) **reduces the incidence of type 2 diabetes.**

c. **Acarbose** (prevents glucose peak) **and liraglutide decrease progression to type 2 DM.**

Pharmacologic Therapy (Type 1 DM)

- **All patients with type 1 DM require insulin.**



Healthiest eating pattern

In the eastern culture, breakfast and supper are the main meals (large meals)

Relationship between insulin and glucose over the course of a day.

Pharmacologic Therapy (Type 1 DM)

- **Attempt to mimic normal secretion of insulin.**
- **One or two injections of insulin daily will in NO way mimic normal physiology, and therefore, is unacceptable.**
- **The timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve adequate blood glucose control throughout the day.**

Insulin

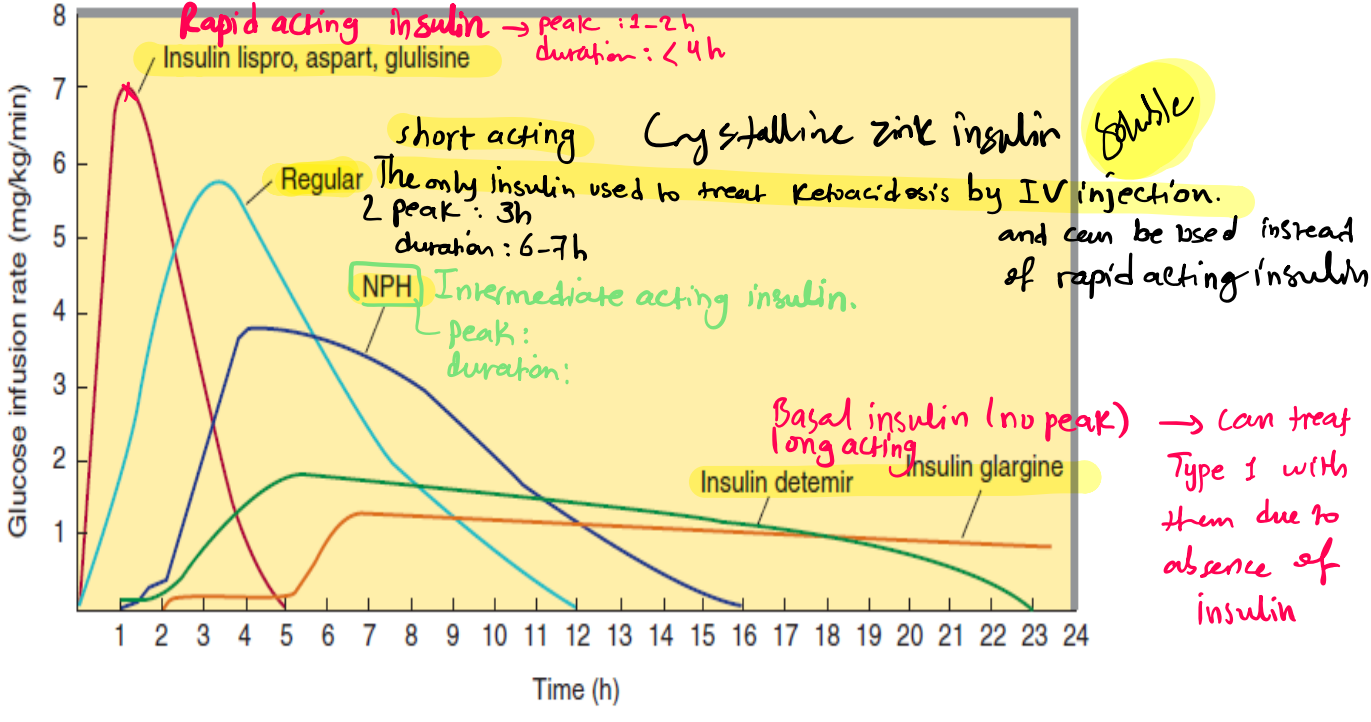


FIGURE 41–5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

Pharmacokinetics of Select Insulins Administered Subcutaneously

- for IV injections, insulin must be clear e.g: Regular
- NPH (turbid)
- Don't mix turbid + clear
- * e.g: NPH with rapid or regular.
- كل واحد لحاله مختلطة؟
- .SC

Type of Insulin	Onset (Hours)	Peak (Hours)	Duration (Hours)	Maximum Duration (Hours)	Appearance
Rapid acting					
Aspart	15-30 min	1-2	3-5	5-6	Clear
Lispro	15-30 min	1-2	3-4	4-6	Clear
Glulisine	15-30 min	1-2	3-4	5-6	Clear
Technosphere[a]	5-10 min	0.75-1	~3	~3	Powder
Short-acting					
Regular	0.5-1.0	2-3	4-6	6-8	Clear
Intermediate acting					
NPH	2-4	4-8	8-12	14-18	Cloudy
Long acting					
Detemir	~2 hours	__[b]	14-24	20-24	Clear
Glargine (U-100)	~2-3 hours	__[b]	22-24	24	Clear
Degludec	~2 hours	__[b]	30-36	36	Clear
Glargine (U-300)	~2 hours	__[b]	24-30	30	Clear

v.imp

crystalline zinc insulin (clear not turbid)

24h

[a]Technosphere insulin is inhaled. powder

[b]Glargine is considered "flat" though there may be a slight peak in effect at 8-12 hours, and with detemir at ~8 hours, but both have exhibited peak effects during comparative testing, and these peak effects may necessitate changing therapy in a minority of type 1 DM patients. Degludec and U-300 insulin glargine appears to have less peak effect compared to U-100 insulin glargine.

Intensive Insulin Regimens

You start with 2 always and according to results your manage and change to other regimens.

Multiple dose infect.

	Regimens / Time of meals	6 am meal	12 am meal	6 pm meal	Bed 12 time
1	2 doses (R or rapid acting) + N	R, L, A, Glu + N (its effect continues)		R, L, A, Glu + N (prevents nocturnal hyperglycemia)	(No meal but insulin)
2	3 doses (R or rapid acting) + N (physiological mimetic)	R, L, A, Glu + N	R, L, A, Glu	R, L, A, Glu + N (But can cause hypoglycemia)	
3	4 doses (R or rapid acting) + N	R, L, A, Glu	R, L, A, Glu	R, L, A, Glu	N (8-10 am)
4	4 doses (R or rapid acting) + N	R, L, A, Glu + N	R, L, A, Glu	R, L, A, Glu	N
5	4 doses (R or rapid acting) + long acting	R, L, A, Glu	R, L, A, Glu (Prandial coverage)	R, L, A, Glu	G or D (Long acting Basal insulin)
6	CS-II pump (Not for all or any patients)	Adjusted basal + Bolus	Adjusted basal + Bolus	Adjusted basal + Bolus	
7	3 prandial doses	P added to previous regimens (2 injections / insulin + P)	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.

(Amylin agonist.)

Pharmacologic Therapy (Type 1 DM)

- The simplest regimens that can approximate physiologic insulin release use "split-mixed" injections consisting of a morning dose of an intermediate-acting insulin (NPH) and a "bolus" rapid-acting insulin or regular insulin prior to the morning and evening meals.
- The morning intermediate-acting insulin dose provides basal insulin during the day and provides "prandial" coverage for the midday meal.

Pharmacologic Therapy (Type 1 DM)

- **The evening intermediate-acting insulin dose provides basal insulin throughout the evening and overnight.** Preventing nocturnal hyperglycemia. 1, 2, 3, 4
- **This may be acceptable when patients have fixed timing of meals and carbohydrate intake.**
- **However, This regimen may NOT achieve good glycemic control overnight without causing nocturnal hypoglycemia.**
- **Moving the evening NPH dose to bedtime may improve glycemic control and reduce the risk of nocturnal hypoglycemia.**

Pharmacologic Therapy (Type 1 DM)

- "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 a rapid-acting insulin to provide prandial coverage.
- Long-acting insulins include insulin detemir, glargine, or degludec.

Pharmacologic Therapy (Type 1 DM)

- Bolus or prandial insulin can be provided by either regular insulin or rapid-acting insulin analogs: lispro, aspart, or glulisine.
- The rapid onset and short duration of action of the rapid-acting insulin analogs more closely replicate normal physiology than does regular insulin.
- (Remember that regular insulin is soluble insulin, or crystalline zink insulin).

Pharmacologic Therapy (Type 1 DM)

- Bolus → quick acting before meals.
- Basal → longer acting – steady levels night and day.

Not always but ↓

- **Approximately 50% of total daily insulin replacement should be in the form of basal insulin and the other 50% in the form of bolus insulin, divided between meals.**
- **For new patients, the initial total daily dose is usually between 0.5 and 0.6 units/kg/day.**

Pharmacologic Therapy (Type 1 DM)

- Continuous subcutaneous insulin infusion (CS-II) or insulin pumps using a rapid-acting insulin is the most sophisticated and precise method for insulin delivery.
- In highly motivated patients, it achieves excellent glycemic control more than MDI.
- Insulin pump therapy may also be paired to continuous glucose monitoring (CGM), which allows calculation of a correct insulin dose, as well as alert the patient to hypoglycemia and hyperglycemia.

Pharmacologic Therapy (Type 1 DM)

- Insulin pumps require greater attention to details and more frequent self-monitored blood glucose (SMBG) than does a basal-bolus multiple daily injections regimen.
- Patients need extensive training on how to use and maintain their pump.

Pharmacologic Therapy (Type 1 DM)

- All patients treated with insulin should be instructed how to recognize and treat hypoglycemia. v.imp
- At each visit, patients with type 1 DM should be evaluated for hypoglycemia including the frequency and severity of hypoglycemic episodes.

Pharmacologic Therapy (Type 1 DM)

- **Hypoglycemic unawareness may result from autonomic neuropathy or from frequent episodes of hypoglycemia.** ~ they can't distinguish anymore.
- **The loss of warning signs of hypoglycemia is a relative contraindication to continued intensive therapy.** Like the table in slide 31.

Pharmacologic Therapy (Type 1 DM)

- Patients who have erratic postprandial glycemic control despite proper insulin dose may benefit from addition of the amylinomimetic pramlintide.
- Amylin suppresses endogenous production of glucose in the liver.
- Pramlintide taken prior to each meal can improve postprandial blood glucose control.
- It is NOT a substitute for bolus insulin.

Pharmacologic Therapy (Type 1 DM)

- **Pramlintide can NOT be mixed with insulin requiring the patient to take an additional injection at each meal.** so there should be two injections at different site (pramlintide + insulin).
- **When pramlintide is initiated, the dose of prandial insulin should be reduced by 30 - 50%, to prevent hypoglycemia.**

Pharmacologic Therapy (Type 1 DM)

- Explanation of why we reduce the insulin dose :

Pramlintide:

1. Slows gastric emptying – mediated by the vagus nerve.
   ↳ thus we don't have peak in blood glucose or reduced peak bc glucose is not going rapidly from stomach to intestines to be absorbed and that's why requirements of insulin should be reduced. (shallow curve)
2. Reduces glucagon secretion. (hyperglycemic hormone)
   ↳ thus less glucose production.
3. Promotes satiety or reduce appetite - centrally.
   ↳ thus less glucose intake.
4. Produces moderate weight loss.

- Main adverse effects include: (1) Hypoglycemia (v. imp) and GIT disturbances (2) (nausea & vomiting), and (3) anorexia).
  (really disturbing to the pt.)

Pharmacologic Therapy (Type 2 DM)

1. Symptomatic patients (or with DM complications) may initially require treatment with insulin or combination therapy.
2. All patients are treated with therapeutic life-style modification.
3. Patients with HbA_{1c} of 7.5% or less are usually treated with metformin (euglycemic agent) (which is unlikely to cause hypoglycemia).

numbers differ bw labs

4. Those with HbA_{1c} > 7.5% but < 8.5% could be initially treated with a single agent (metformin), or combination therapy.

Pharmacologic Therapy (Type 2 DM)

5. **Patients with higher initial HbA_{1c} will require two agents OR insulin.**
6. **All therapeutic decisions should consider the needs and preferences of the patient, if medically possible.**
7. **Obese patients without contraindications are often started on metformin which is titrated up to 2,000 mg/day.**

- bc metformin slightly reduces Wt.

↳ bc it has GIT adverse rxns. and with titration; tolerance to the GIT adverse rxns occurs.

- 850 mg once daily → for one week.
- 850 mg twice daily → second week.
- full dose 850 mg (2500 mg) → third week

Pharmacologic Therapy (Type 2 DM)

* obese → normal or high insulin but there is resistance.

8. **Non-obese patients are more likely to be insulinopenic** (low insulin), **necessitating medications that may increase insulin secretion.**
9. **An insulin secretagogue such as a sulfonylurea, is often added second.**

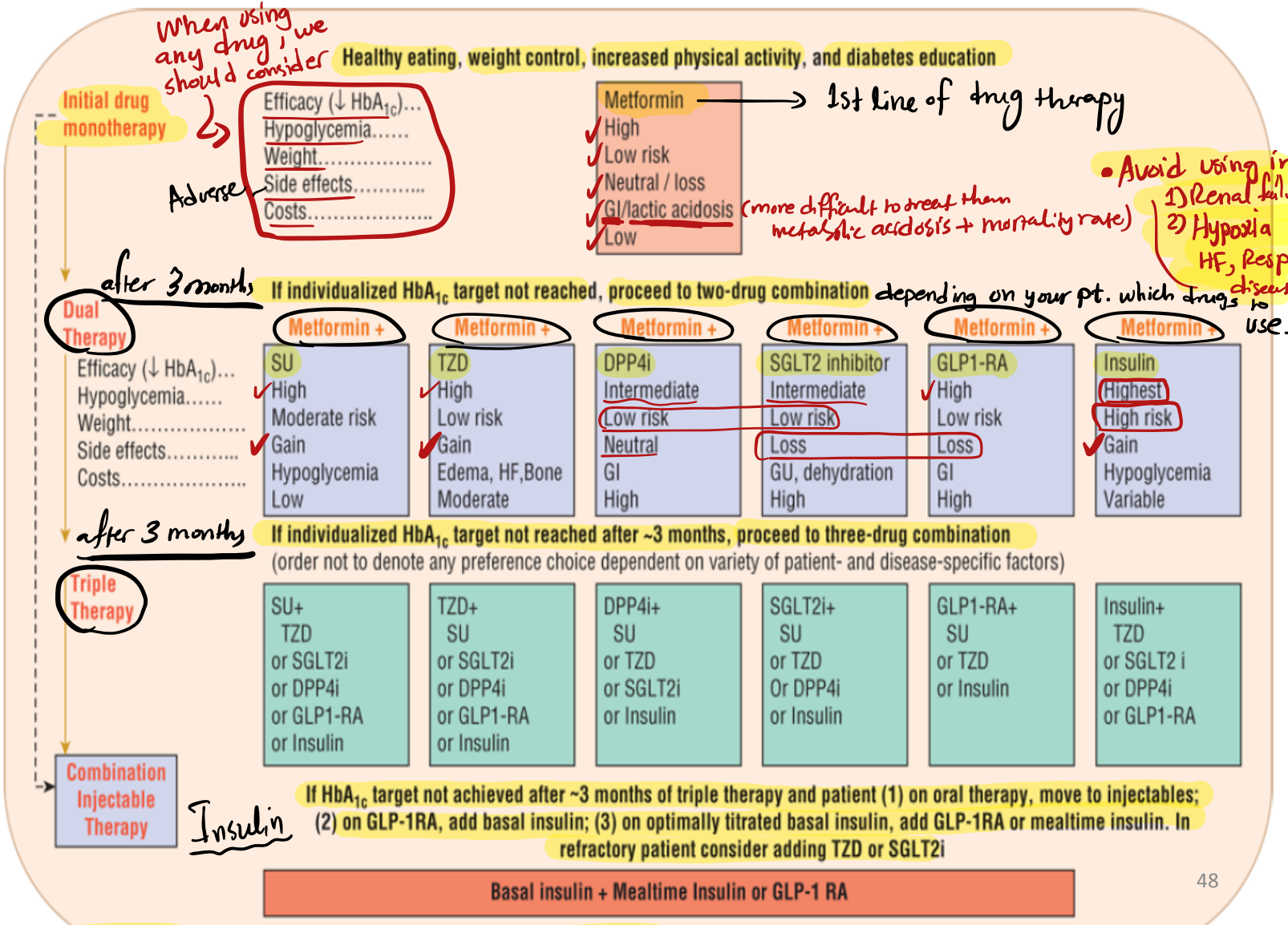
- **Sulfonylureas have several potential drawbacks including weight gain** (thus ↑ ins. resis) (1) **and hypoglycemia** (2). patients should be educated about their wt. gain.
- **They do NOT produce a durable glycemic response.** We can't depend on them for long time, bc pt will not respond to the drug later on so we should change the drug

Pharmacologic Therapy (Type 2 DM)

10. Better choices include Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) and GLP-1 receptor agonist but they have therapeutic and safety limitations.

11. Thiazolidinediones (TZDs) produce a more durable glycemic response and are unlikely to cause hypoglycemia, but weight gain, fluid retention and the risk of new onset heart failure have limited their use.

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



Drug & class	[redacted]	Duration of action (hours)	Drug	[redacted]	Duration of action (hours)
Sulfonylureas					
Glimepiride	1-8	24 once daily	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 like rapid acting insulin	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 to reduce post prandial hyperglycemia	25-50 + adverse effects GIT.	Affects absorption of carbohydrates in a single meal no glucose peak post prandial	Miglitol	25-100	Affects absorption of carbohydrates in a single meal
GLP-1 receptor agonists / Incretin mimetics					
Exenatide	5-10 mcg	10	Liraglutide for prevention of type 2 DM	0.6-1.8	24
DPP-4 inhibitors					
Sitagliptin	100	24 single dose is given	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			

Pharmacologic Therapy (Type 2 DM)

Treatment selection should be based on multiple factors:

1. **A patient who has had diabetes for several years, due to progressive failure of β-cell function, is more likely to require insulin therapy.**
2. **If the patient has multiple co-morbidities (CVD, dementia, depression, osteoporosis, heart failure, recurrent genitourinary (GU) infections, some medications may be poor choices based on their potential adverse effects.**

Pharmacologic Therapy (Type 2 DM)

3. If the patient's postprandial blood glucose readings are the primary reason for poor control, pick a medication that addresses postprandial blood glucose fluctuations.
4. If the patient's fasting blood glucose readings are consistently elevated, a medication that addresses fasting blood glucose would be a better choice.

Short-acting non-sulfonylureas insulin secretagogue

while controlled the rest of the day

Morning blood glucose.

• Note: Assessement of diabetes control by fasting blood glucose isn't enough, HgbA1C is better.

Pharmacologic Therapy (Type 2 DM)

5. **Adverse effect profile, contraindications, hypoglycemia potential, and tolerability by the patient, should be considered when selecting therapy.**
6. **Motivation, resources, and potential difficulties with adherence should also influence treatment selection.**

Pharmacologic Therapy (Type 2 DM)

elderly in health

7. If the patient is an older adult, the risk of hypoglycemia and other adverse effects increases and life expectancy diminishes. These factors should influence medication choices and HbA1c goals. ممكن نترجمه target الـ.
8. Non-glycemic effects (CVD reduction with medications, lipid effects, blood pressure effects, weight, and durability of HbA_{1c} reduction) may all influence the decision.

To delay the onset of DM.

Pharmacologic Therapy (Type 2 DM)

9. **It is unlikely that any one drug class will arrest β-cell failure, necessitating combination therapy.**

- **The combination of a TZD and GLP-1 receptor agonist is a good one:**

a) **TZDs reduce apoptosis of β-cells.**

b) **GLP-1 receptor agonists augment pancreatic function.** (↑ proliferation of beta cells).

- **Metformin, pioglitazone, and exenatide are promising.** TZD Liraglutide

Glucagon-like peptide-1 (GLP-1) from the GIT

• Normally in all individuals

1. It enhances insulin release in response to an ingested meal.
2. It suppresses glucagon secretion. no glucose production
3. It delays gastric emptying.
4. It decreases appetite.
5. It is degraded by dipeptidyl peptidase-4 (DPP-4).

inhibition of DDP-4 → prolonged effect of GLP → reduces hyperglycemia.

Pharmacologic Therapy (Type 2 DM)

1) Liraglutide (duration of action longer than exenatide).

2) **Exenatide:**

- **It is a long-acting analogue of GLP-1, Acts as agonist at GLP-1 receptors.**
- **Used as adjunctive therapy in patients with type 2 diabetes treated with metformin, or metformin plus sulfonylureas who still have suboptimal glycemic control.**
- **Delays gastric emptying.**
- **Suppresses postprandial glucagon release.**

Pharmacologic Therapy (Type 2 DM)

- **It increases insulin secretion in a glucose-dependent manner. The increased insulin secretion is speculated to be due in part to:**

a) **an increase in beta-cell mass, from decreased beta-cell apoptosis.**

b) **increased beta-cell formation.**

c) **or both. (Noticed in culture)** — cell — we don't know how it's in vivo, but this is promising.

- **Suppresses appetite.**
- **Associated with weight loss.**

improves insulin sensitivity.

Pharmacologic Therapy (Type 2 DM)

Adverse effects: very bad ones

1. **Nausea, vomiting, diarrhea:** major adverse effect is nausea (45%), which is dose-dependent and declines with time. but does n't disappear.
2. **Acute pancreatitis.** ∴ loss of beta cells and DM development.
3. **Renal impairment and acute renal injury.**

- **Not associated with hypoglycemia unless used in combination.**

Pharmacologic Therapy (Type 2 DM)

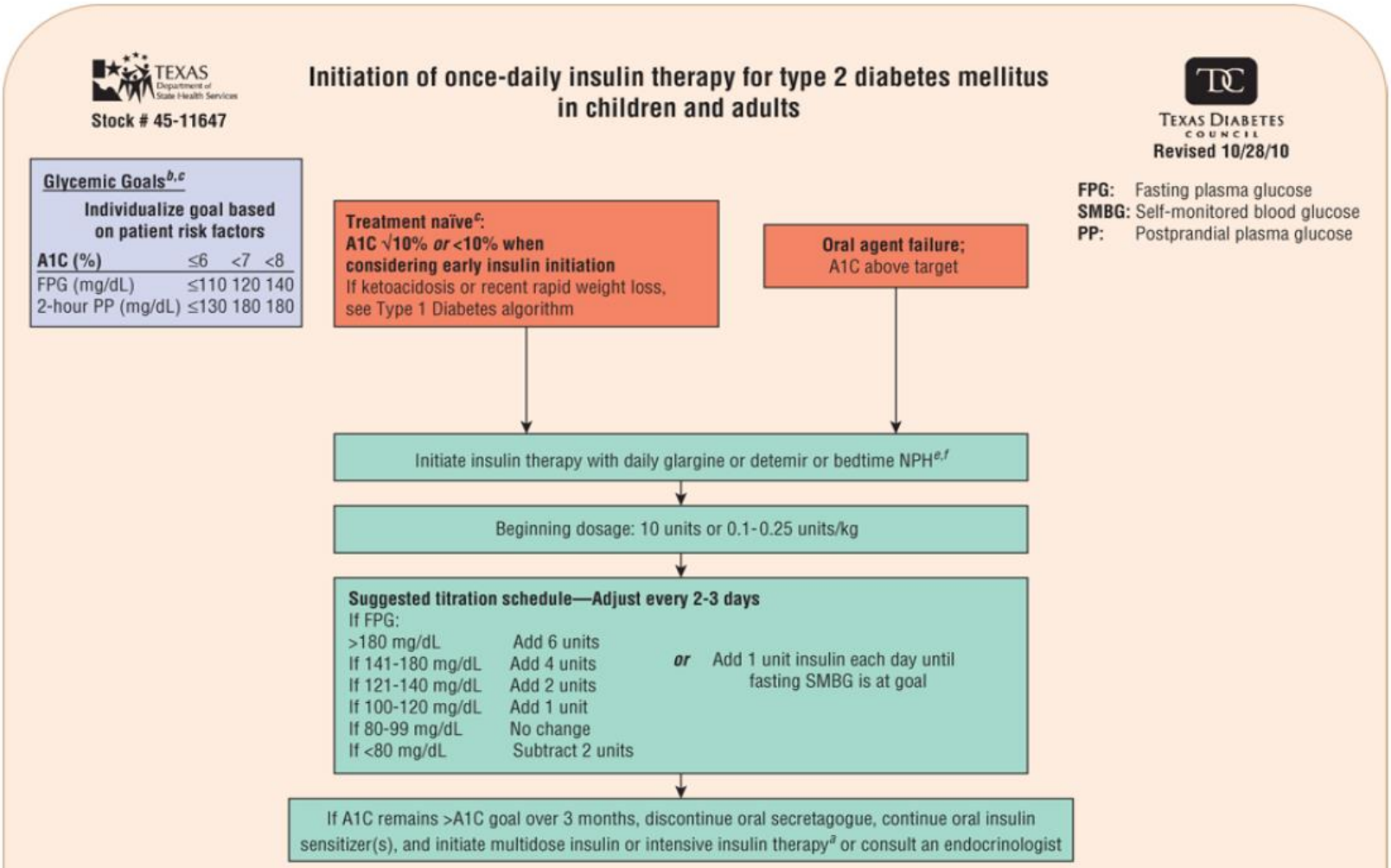
- **With time some patients with type 2 DM become relatively insulinopenic necessitating insulin therapy.** 10%
- **In these patients use insulin injections at bedtime (intermediate- or long-acting basal insulin) while continuing to use oral agents or GLP-1 receptor agonists for control during the day.**

NPH

Pharmacologic Therapy (Type 2 DM)

- **This strategy is associated with less weight gain, equal efficacy, and lower risk of hypoglycemia when compared to starting prandial insulin or split-mix twice daily insulin regimens.** (along with basal insulin)
- ***Any modification of this strategy should depend on fasting and posprandial glucose monitoring, HbA_{1c} monitoring, and times of development of hypoglycemia*** and hyperglycemia.

Simplified Insulin algorithm for type 2 DM in children and adults. See: *www.texasdiabetescouncil.org* for current algorithms. *(Reprinted from the Texas Diabetes Council.)*



The SI equivalents for A1C from the figure are: 4% (0.04; 20 mmol/mol Hb), 6% (0.06; 42 mmol/mol Hb), 7% (0.07; 53 mmol/mol Hb), 8% (0.08; 64 mmol/mol Hb), 10% (0.10; 86 mmol/mol Hb), and 1% change (0.01; 11 mmol/mol Hb).

The SI equivalents for glucose from the figure are: 80 mg/dL (4.4 mmol/L), 99 mg/dL (5.5 mmol/L), 100 mg/dL (5.6 mmol/L), 110 mg/dL (6.1 mmol/L), 120, and 121 mg/dL (6.7 mmol/L), 130 mg/dL (7.2 mmol/L), 140 and 141 mg/dL (7.8 mmol/L), 180 mg/dL (10 mmol/L).

Just the adverse effects

Comparative Pharmacology of Antidiabetic Agents

Agent/Generic Name (Brand Name)/Mechanism	[illegible]	[illegible]	Adverse Effects	[illegible]
Insulin Replaces or augments endogenous insulin	Monotherapy; combined with any oral agent	↓ A1C[b] ↓FPG[b] ↓ PPG[b] ↓ TG	Hypoglycemia, weight gain, lipodystrophy, local skin reactions	Offers flexible dosing to match lifestyle and glucose concentrations. Rapid onset. Safe in pregnancy, renal failure, and liver dysfunction. Drug of choice when patients do not respond to other antidiabetic agents.
Insulin-Augmenting Agents				
Nonsulfonylurea secretagogues (glinides) Repaglinide (Prandin) Nateglinide (Starlix) Stimulates insulin secretion	Monotherapy; combined with metformin or TZD	Monotherapy: ↓ A1C ~1% (repaglinide) ↓ A1C ~0.5% (nateglinide) Combination: additional 1% ↓ A1C	Hypoglycemia, weight gain	Take only with meals. If a meal is skipped, skip a dose. Flexible dosing with lifestyle. Safe in renal and liver failure. Rapid onset. Useful to lower PPG.
Sulfonylureas Various; see Table 53-28. Stimulates insulin secretion. May decrease hepatic glucose output and enhance peripheral glucose utilization.	Monotherapy; combined with metformin; combined with insulin (glimepiride)	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Hypoglycemia, especially long-acting agents; weight gain (5–10 pounds); rash, hepatotoxicity, alcohol intolerance, and hyponatremia rare	Very effective agents. Some can be dosed once daily. Rapid onset of effect (1 week).

Incretin-Based Therapies				
Glucagonlike peptide-1 receptor agonists/incretin mimetic Exenatide (Byetta) Liraglutide (Victoza) Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Monotherapy (exenatide only) Combined with metformin, SFU, or TZD, combined with metformin + SFU; combined with metformin + TZD	Monotherapy: ↓ A1C 0.8%–0.9% Combination: additional 1% ↓ in A1C	GI: nausea, vomiting, diarrhea; hypoglycemia (with SFUs); weight loss; reports of acute pancreatitis	Weight loss. Exenatide: take within 60 minutes before morning and evening meals or before two main meals of the day (≥6 hours apart). Liraglutide: Do not use if personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Do not use in patients with gastroparesis or severe GI disease. Administered by SC injection; pen device in use does not need to be refrigerated. Rare cases of pancreatitis with both drugs.
DPP-4 inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Stimulates insulin secretion and reduces postprandial glucagon levels	Monotherapy; combined with metformin, SFU, or TZD; insulin (sitagliptin only)	Monotherapy: ↓ A1C 0.5%–0.8% Combination: ↓ A1C 0.5%–0.9%	Headache, nasopharyngitis, hypoglycemia (with SFU), rash (rare)	Dosed once daily. Taken with or without food. No weight gain or nausea. Need to adjust sitagliptin and sazagliptin dose in renal dysfunction. Reduce dose of SFU when combined. Rare reports of pancreatitis.

Amylin Receptor Agonists				
Amylin mimetic Pramlintide (Symlin)	Type 1: Adjunct to mealtime insulin	T1: ↓ A1C 0.33% T2: ↓ A1C 0.40%	GI: nausea, decreased appetite	Take only immediately before meals; administered by SC injection. Do not use in patients with gastroparesis.
Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Type 2: Adjunct to mealtime insulin; ± SFU and metformin		Headache; hypoglycemia; weight loss (mild)	
Insulin Sensitizers				

Insulin Sensitizers

Biguanides Metformin (Glucophage) ↓ Hepatic glucose output; ↑ peripheral glucose uptake	Monotherapy; combined with SFU or TZD; or with insulin	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	GI: nausea, cramping, diarrhea; lactic acidosi (rare)	Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain; weight loss possible. Mild reduction in cholesterol. Do not use in patients with renal or severe hepatic dysfunction.
Thiazolidinediones Rosiglitazone (Avandia) Pioglitazone (Actos) Enhances insulin action in periphery; increases glucose utilization by muscle and fat tissue; decreases hepatic glucose output	Monotherapy; combined with SFU, TZD, or insulin; combined with SFU + TZD	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Mild anemia; fluid retention and edema, weight gain, macular edema, fractures (in women)	Can cause or exacerbate HF; do not use in patients with symptomatic HF or class III or IV HF. Rosiglitazone may increase risk of MI. Increased risk of distal fractures in older women. Pioglitazone may increase risk of bladder cancer when used for >1 year. Slight reduction in TG with pioglitazone; slight increase in LDL-C with rosiglitazone. LFTs must be measured at baseline and periodically thereafter. Slow onset (2–4 weeks).

Delayers of Carbohydrate Absorption

α-Glucosidase inhibitors Acarbose (Precose) Miglitol (Glyset) Slow absorption of complex carbohydrates	Monotherapy; combined with SFUs, metformin, or insulin	Monotherapy: ↓ A1C ~0.5% Combination: additional ~0.5% ↓ A1C	GI: flatulence, diarrhea. Elevations in LFTs seen in doses >50 mg TID of acarbose	Useful for PPG control (↓ PPG 25–50 mg/dL). LFTs should be monitored every 3 months during the first year of therapy and periodically thereafter. Because miglitol is not metabolized, monitoring of LFTs is not required. Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain. If used in combination with hypoglycemic agents, advise patients to treat hypoglycemia with glucose tablets because absorption is not inhibited as with sucrose.
[redacted]	Combined with metformin, SFU, or insulin	↓ A1C 0.3%–0.4%	Constipation, dyspepsia [redacted]	Added benefit of ↓ LDL-C (by 12%–16%). Administer certain drugs 4 hours before. Take with a meal and liquid.

[a]Comparative effectiveness data provided for SFUs, glinides, TZDs, and α-glucosidase inhibitors.[307]

[b]Theoretically, unlimited glucose lowering with insulin therapy.

A1C, glycosylated hemoglobin; DPP-4, dipeptidyl peptidase-4; FDA, Food and Drug Administration; FPG, fasting plasma glucose; GI, gastrointestinal; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; MI, myocardial infarction; PPG, postprandial glucose; SC, subcutaneously; SFU, sulfonylureas; TG, triglycerides; TID, three times a day; T1, type 1 diabetes; T2, type 2 diabetes; TZD, thiazolidinediones.

Effect of Some Antidiabetics on Body Weight

Drug	Effect on body weight
Insulin	Weight gain
Sulfonylureas	Weight gain
Meglitinides	Weight gain
Metformin	No change or reduce
Thiazolidinediones	Weight gain + fluid retention
Amylin Analogues -pramlintide	Moderate weight loss
GLP-1 analogues (exenatide)	Weight loss
DPP-4 inhibitors (sitagliptin)	Weight neutral

Insulin secretagogues

Fat deposition

despite that they inhibit degradation of GLP-1

Special Populations (Children and Adolescents with Type 2 DM)

- Type 2 DM is increasing in adolescence probably caused by obesity and physical inactivity.
- Need extraordinary efforts on life-style modification measures.
- If failed, use metformin, sulfonylureas (or TZDs) or any combination of these that may improve glycemic control.

*MODY
Maturity onset diabetes of the young

Metformin
Sulfonylurea
Insulin

Special Populations (Children and Adolescents with Type 2 DM)

- **Insulin therapy is the standard of care when glycemic goals can NOT be achieved or maintained with metformin and sulfonylurea.**

Special Populations (Elderly patients with Type 2 DM)

- Consideration of the risks of hypoglycemia, the extent of co-morbidities, self-care, nutritional status, social support, falls risk, mental status, and life expectancy should all influence glycemic goals and treatment selection.
- Avoidance of both hypo- and hyperglycemia is extremely important.

(forgets meds ∴ hyperglycemia) (can't distinguish if it's due to hypoglycemia or what?)

Try to avoid strict glycemic control ∴ ↑ target is needed

We care about hypoglycemia more.

Special Populations (Elderly patients with Type 2 DM)

- **Elderly patients may have an altered presentation of hypoglycemia because of loss of autonomic nerve function with age.**
- **DPP-4 inhibitors (Sitagliptin), shorter-acting insulin secretagogues (rapaglinide), low-dose sulfonylureas, or α-glucosidase inhibitors may be used.**

might not detect hypoglycemia

we need moderate efficacy drugs, so no hypoglycemia occurs.

DPP-4i → URTIs.
DPP4i + GLP → pancreatitis

Special Populations (Elderly patients with Type 2 DM)

- **DPP-4 inhibitors or α-glucosidase inhibitors have low risk of hypoglycemia.** if alone, but combinations always have high risk
- **Metformin may be used at low doses if Cl_{cr} is > 30 mL/min/1.73 m².** not in renal failure.
- **Simple insulin regimens with daily basal insulin may be appropriate.**
  - no multiple injections with meals.
  - we don't want aggressive blood glucose reduction.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (Sitagliptin)

- Inhibit DPP-4, the enzyme that degrades incretin hormones.
- Prolong the half-life of endogenous GLP-1.
- Decrease postprandial glucose levels.
- Decrease glucagon concentration.
- Increase circulating GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and thus, insulin concentrations in a glucose-dependent manner.

bc they (① + ②) are secreted with meals.

Sitagliptin

- **Most commonly used in combination with a TZD or metformin, or sulfonylureas.**
- **May be used as monotherapy.**
- **Used for type 2 DM orally, peaks within 1–4 hours, and has a half-life of approximately 12 hours.**
- **Dosage should be reduced in patients with impaired renal function**
- **Weight neutral.**

Sitagliptin

Adverse effects:

1. **Nasopharyngitis, upper respiratory infections, headaches**
2. **Hypoglycemia when the drug is combined with insulin secretagogues or insulin. Not associated with hypoglycemia when used alone.**
3. **Acute pancreatitis which may be fatal.**
4. **Allergic reactions.**

in (Type 1) in (Type 2) in (elderly)

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Admit the patient → ?
start insulin SC →

- **These are true emergencies.**
- **Insulin given by continuous IV infusion (regular insulin = soluble insulin = crystaline zinc insulin) to restore the patient's metabolic status is the cornerstone of therapy.**
- **Pay attention to volume deficits, electrolyte disturbances, and acidosis.**
- **Treat the precipitating problem.** e.g.: a child + infection → KA
  stressful events (hospital admission)

↑ الأشخاص عندهم: Insulin ← oral hypoglycemic agents من جولهم ما يدخلوا المستشفى Type II DM المرضى الكبار اللي عندهم
corticosteroids

due to stress.

Hospitalization for Intercurrent Medical Illness

- **Patients on oral agents may need transient therapy with insulin to achieve adequate glycemic control during hospitalization.**
- **It is important to stop metformin in all patients who arrive in acute care settings** as hospitalization **contraindications to metformin are prevalent in hospitalized patients (renal dysfunction, hypoxia..).**
  - bc ①+② can precipitate lactic acidosis.

imp

Perioperative Management

- **Patients who require surgery may experience worsening of glycemia similar to those admitted to hospital for a medical illness.**
- **Acute stress increases counter-regulatory hormones.** Corticosteroids (Insulin antagonists).
- **Therapy should be individualized based on the type of DM, nature of the surgical procedure, previous therapy, and metabolic control prior to the procedure.**

Perioperative Management

- **Patients on oral agents may need to be transiently switched to insulin to control blood glucose, preferably as continuous insulin infusions.**
- **Metformin should be discontinued temporarily after any major surgery until it is clear that the patient is hemodynamically stable and normal renal function is documented.**

Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

- SGLT2 is the main transporter for glucose re-absorption in the proximal tubules (90%).
- Inhibitors include canagliflozin which increases urinary glucose loss.
- Not very effective in chronic renal dysfunction and are even contraindicated.

prevents urinary excretion of glucose

* SGLT-2i

↑ infections

If GFR < 45 ml/min/100 cm^3 (contraindicated)

(SGLT2) Inhibitors

v. imp

Adverse effects:

1. **Increased incidence of genital and urinary tract infections.** (especially in ♀)
2. **Intravascular volume contraction and hypotension ← osmotic diuresis.** (loss of water) * glucose is osmotic diuretic. (That's why diabetic pts have polyurea).
3. **Increase LDL cholesterol.** (Oxidation of LDL is the first step of atherosclerosis.)
4. **Higher rates of breast cancer and bladder cancer.** (urinary)

*** this class is a bad idea (in my opinion!).**

5. Decreased bone mineral density at the lumbar

(SGLT2) Inhibitors

6. Fractures die to osteoporosis and/or falls secondary to hypotension.
7. Risk of leg and foot amputations.
8. Should not be used in patients with type 1 diabetes and in those patients labelled as having type 2 diabetes but who are very insulin deficient and prone to diabetic ketoacidosis.

(SGLT2) Inhibitors

Benefits: (According to "The National Kidney Foundation, USA")

- SGLT2 inhibitors are effective at slowing the progression of kidney disease, reducing heart failure, and lowering the risk of kidney failure ~~and death in people with kidney disease and type 2 diabetes~~.
- SGLT2 inhibitors may protect the kidneys of people with CKD who do not have diabetes.
- May also reduce the risk for heart disease in people with a history of heart disease.
- They may reduce the need for hospitalization for heart failure.

FDA Warnings & Information on SGLT2 Inhibitors

- Serious Infection Of The Genital Area
- Increased Risk Of Leg And Foot Amputations With Canagliflozin
- Strengthens Kidney Warnings
- Increased Risk Of Leg And Foot Amputations, Mostly Affecting The Toes.
- DKA Acid In The Blood And Serious Urinary Tract Infections
- Bone Fracture Risk And New Information On Decreased Bone Mineral Density.

Reference: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sodium-glucose-cotransporter-2-sglt2-inhibitors