

Chapter 9

Endocrine Pharmacology

Part 1: Diabetes Mellitus and Antidiabetic Drugs

Definition of DM: It is a clinical syndrome characterized by disturbance in carbohydrates, fat, & proteins metabolism due to either *insulin deficiency* or *insulin resistance*.

Manifestations:

- Polyuria, polydipsia, polyphagia, and loss of weight.

- **Complications** of DM e.g. recurrent infections, **B.V Degeneration**, **angiopathy**, **retinopathy**, **nephropathy**, DKA, etc.

or Autonomic NP
نصبي من غدة الكلى
أو يجمعش بالعاجلة لما يمسكها
... RES, GIT, GHS

Laboratory investigations:

- Urine analysis for glucosuria & ketonuria.
- Blood glucose: fasting and 2-hr after oral 75 g glucose.
- Glycated hemoglobin (HbA_{1c}): indicates average blood sugar level for the past 2-3 months

يعني أنت في طريقك
Diabetes يصير معاك

Histology

There are 4 types of cells in the **islets of Langerhans**.

- **α cells** (20%) : secrete **glucagon**.
- **β cells** (75%) : secrete **insulin** and islet associated polypeptide (amylin).

Delta Cells

- **δ cells** (3-5%) : secrete **somatostatin**.

- **F cells** < 2% : secrete **pancreatic polypeptides** (facilitate digestive process).

- **ε cells** < 1% , secrete **Ghrelin** (stimulate feeling of hunger).

النسبة النيرة من ال fundus of stomach

ينظم إفراز
ال Cells
طوق 8.8
Epsilon +

	Normal	IGT*	DM
Fasting BG	< 100 mg/dl	100-126	> 126 mg/dl
2 hr after oral 75 g glucose	< 140 mg/dl	140-200	> 200 mg/dl
HbA_{1c}	< 6%	6-6.5%	> 6.5%
Elevated levels mean uncontrolled DM over the last 2-3 months. على الأقل 2-3 م عندك مرتفع "DM" وانت مش عامل Controlling هذه صعب الـ blood sugar الـ مرضيا مزمنة من هذا الاختبار			

* **IGT = Impaired glucose tolerance (prediabetes):** it can be controlled by **diet regime** alone.

Common types of DM:

- **Type 1 DM:** (old name: insulin dependent DM)
- **Type 2 DM:** (old name: non-insulin dependent DM)
- **Gestational DM:** appears during pregnancy and disappears after labor.

	Type 1 (IDDM)	Type 2 (NIDDM)
Pathophysiology:	Autoimmune condition against the pancreatic beta cells. The damaged pancreas doesn't make insulin.	The pancreas usually produces some insulin. But either the amount is not sufficient , or the body's cells are resistant to it.
Onset (age):	< 30 years	>30 years (adult-onset)
Body built:	Usually <u>undernourished</u> سوء تغذية	Usually obese
Insulin therapy:	Essentially required.	Required in 20% of patients
Oral drugs:	Not required.	Essentially required.

Less common types of DM:

- **Latent autoimmune diabetes of adults (LADA):** is a condition in which type 1 DM develops in adults.
- **Maturity onset diabetes of the young (MODY):** is a condition in which type 2 DM develops in children or young adults who develop persistent, asymptomatic hyperglycemia without progression to diabetic ketoacidosis.

N.B. Adults with LADA or children with MODY are frequently **misdiagnosed** as having type 2 or type 1 DM, based on age rather than etiology. بعض حالات MODY يُشخصن خطأً على أنهن من النوع 1 أو النوع 2 بناءً على العمر بدلاً من السبب.

- **Secondary DM:** 2ry to drugs, infections, endocrine diseases, etc. T2DM ممكن يكون MODY.

Lines of treatment:

- **Diet control.**
- **Diet + insulin (type 1).**
- **Diet + oral antidiabetic drugs (type 2).**
- **Exercise:** to enhance peripheral glucose utilization.

DIET REGIME

It is the **first line** of treatment in all types of DM.

- ★ **Glycemic Index (GI):** كلما كان الأكل به مستوى السكر في الدم أعلى كان له GI أعلى. $GI > 85 \rightarrow$ High GI

—! It describes the capacity of a food to raise blood glucose in normal glucose

tolerant individuals.

- ! Foods with a high GI may be associated with ↑ risk of obesity and the postprandial hyperglycaemia, with such foods may also ↑ the risk of T2DM.

Caloric requirements of patients

Average wt: 70 kg	30-35 c/kg/d
Children or thin:	40-45 c/kg/d
Obese:	20-25 c/kg/d

Distribution of food elements

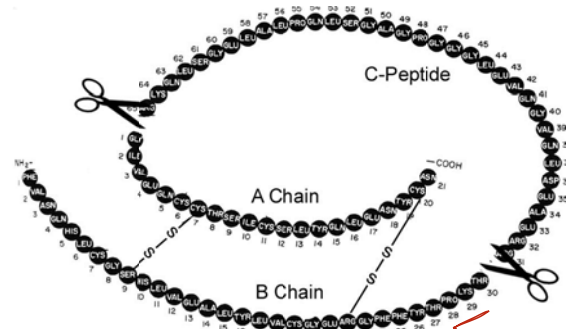
15 % from proteins
55 % from carbohydrates
30 % from fats

INSULIN

Chemistry

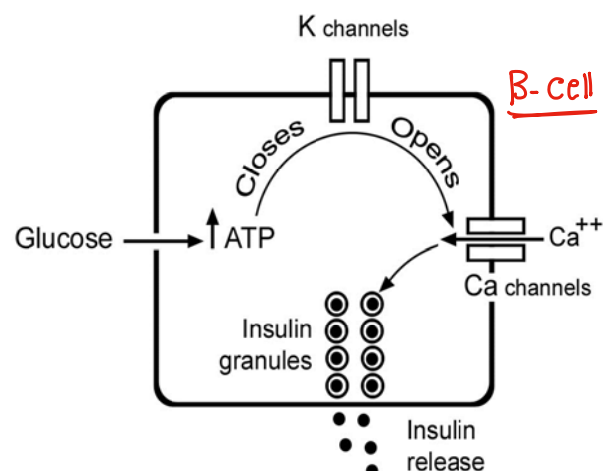
- ! 2 peptide chains: A (21 aa) and B (30 aa) linked by 2 disulfide bonds.
- ! Insulin is secreted as **proinsulin** then cleaved (within the storage granules in the β cells) into insulin and connecting peptide "C-peptide".

N.B. Measurable C-peptide levels indicate the presence of endogenously produced insulin and functioning β -cells.



Secretion

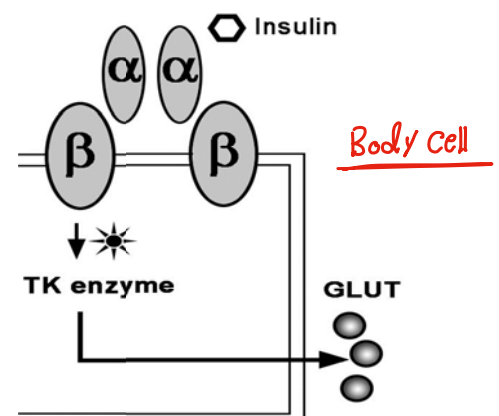
- ! Glucose enters β cells → ↑ ATP → closure of ATP-dependent K^+ channels → opening of voltage-gated Ca^{2+} channels → ↑ Ca^{2+} influx → insulin release.



Insulin receptors

- ! A **tyrosine kinase receptor** consists of 2 extracellular α -subunits and 2 transmembrane β -subunits.
- ! Binding of insulin to the α -subunits causes activation of the β -subunits → activation of **tyrosine kinase enzyme** which triggers a series of intracellular effects that ↑ number of **glucose transporters** (especially **GLUT4**) on the cell membrane → ↑ transport of glucose into the cell.

• *GLUT4 Found Primarily in: Heart, muscles, liver and Adipose tissue, that is why it's the most important one between the 14 GLUT types.*



Normal insulin in BS:5-15 $\mu\text{g/ml}$ (Fasting) , 60-90 $\mu\text{g/ml}$ (Post Prandial, "PP")**Up-regulation of insulin receptors:**

- ! **Insulin deficiency** (e.g. in fasting)
- ! **Drugs: INSULIN SENSITIZERS:**
 - a)! Thiazolidinediones: e.g. pioglitazone & rosiglitazone.
 - b)! Trace elements: e.g. selenium & chromium.

Down-regulation of insulin receptors:

- ! **Insulin excess (Obesity).**
Obesity causes continuous stimulation of β -cells $\rightarrow$ hyperinsulinemia $\rightarrow$ down regulation of insulin receptors.
- ! **Drugs: e.g. corticosteroids**

Pharmacokinetics of insulin▪! **Endogenous insulin:**

–! The pancreas releases insulin in the portal vein in small bouts at short intervals according to blood glucose levels. The liver clears ~ 50% of the secreted amount; the rest is distributed all over the body and cleared by receptor-mediated uptake and intracellular degradation.

⊖! The normal blood level of insulin is **5-15 $\mu\text{U/ml}$** (fasting) and **60-90 $\mu\text{U/ml}$** (postprandial).

▪! **Exogenous insulin:**

–! Insulin is not administered orally because it is rapidly destroyed by GIT enzymes. It is given **s.c.** (common) or **i.v.** (in emergencies).

–! The plasma **half-life** of insulin given **intravenous** is **10-12 min**.

Sources of commercial insulin▪! **Traditional (animal) insulin:**

–! Prepared from animals (beef and pork).

–! PORk insulin differs from human insulin in One aa (*alanine* in pork and *threonine* in human) while bEEf insulin differs from human in thrEE aa.

–! Animal insulin may contain traces of animal proteins and proinsulin, so it is **more antigenic** and can cause insulin resistance.

له بعض الاستجابة مناعية
مثل الحساسية
▪! **Human insulin:**

بسبب مهاجمة الـ Ab
للـ Animal insulin
بسبب الـ law / 3aa الغريب فعاد.

–! It is identical to human insulin and is prepared by recombinant DNA technology (genetic engineering) from yeasts or bacteria.

–! Advantages: **Less antigenic** and rare development of insulin resistance.

▪! **Insulin analogs:**

–! Recombinant insulin analogs are now available in which some amino acids in the "normal" insulin have been switched (e.g. insulin lispro) or replaced (e.g. insulin glargine), making a "different molecule" so as to get different pharmacokinetic properties.

Common examples of insulin preparations

Common C₁
Medication 5 Differences between insulin lispro and glargine?

	Insulin lispro	Insulin glargine
Preparation	Insulin lispro is a rapid-acting insulin analog. It is prepared by recombinant DNA technology, resulting in a sequence of amino acids that is the reverse of the sequence in human insulin.	Insulin glargine is a long-acting insulin analog. It is prepared by recombinant DNA technology, resulting in a sequence of amino acids that is the same as human insulin.
Onset and duration	Onset: 15-30 min Duration: 3-5 h	Onset: 1-2 h Duration: 24 h
Notes	It has rapid onset (15-30 min), and short duration of action (3-5 h). It is suitable for background therapy to control blood glucose levels.	It has a long duration of action (24 h), and is suitable for background therapy to control blood glucose levels.

Category Generic name/Brand Features

3 RAPID ACTING ANALOGS

- Insulin glulisine — Pro-Lys-Glu — *Glutamide*
- Insulin lispro — Pro-Lys-Asp — *Aspartic Acid*
- Insulin aspart — Pro-Lys-Asp-His — *Aspartic Acid*

لقد الأخرى تكون فيها
ال Insulin على صيغة Monomer
بمساحة B منطقة مع A
نوت Hexamers وليست AA
كل ال يوجد.

1 SHORT ACTING INSULIN

- Regular; soluble; neutral (Humulin R; Novolin R)

2 INTERMEDIATE ACTING

- NPH (isophane)* (Humulin N; Novolin N)

4 LONG ACTING INSULIN

- Insulin glargine (Lantus)
- Insulin detemir

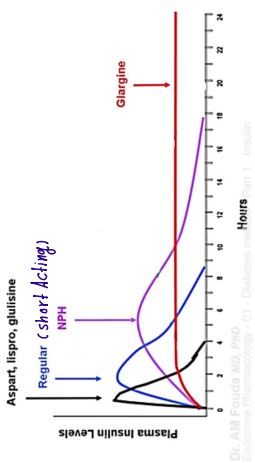
Insulin zinc suspension
لقد تكونت ال Hexamer
والتي تكونت ال Hexamer
والتي تكونت ال Hexamer

PREMIXED INSULIN (Biphasic)

- Humulin 70/30; Mixtard (70% NPH – 30% regular)
- Humalog Mix 75/25 (75% NPH – 25% lispro)

Insulin ال Hexamer
NPH = Neutral Protamine Hagedorn
NPH = Neutral Protamine Hagedorn

- Regular insulin can be mixed with NPH in the same syringe. The mixing order should be the clear regular drawn up first then the cloudy NPH (i.e. “clear-to-cloudy”).
- NPH, insulin zinc and biphasic insulin are cloudy in appearance.



- They are human insulins that have been modified at 1–2 amino acids in the B chain to increase their solubility.
- They are the fastest acting insulins. They must be injected just before meals.

- It is identical to human insulin → لا يوجد به اضافات أو تغييرات.
- It is the only type that can be given i.v. in diabetic emergencies e.g. diabetic ketoacidosis.

- It is made by addition of the protein Protamine to Neutral insulin to prolong its duration.

- They are insulin analogs with minor amino acid changes to make them long acting “peakless”.
- It is human insulin added to ↑ amount of zinc
- They are usually administered once daily.

- They provide rapid onset and relatively prolonged duration
- They are usually injected twice daily.

صممت أقوال العنان بحيث الازيف (NPH) والكم (NPH) ويوجد في 30 و 70 و 100 و 150 و 200 و 300 و 400 و 500 و 600 و 700 و 800 و 900 و 1000 و 1500 و 2000 و 3000 و 4000 و 5000 و 6000 و 7000 و 8000 و 9000 و 10000 و 15000 و 20000 و 30000 و 40000 و 50000 و 60000 و 70000 و 80000 و 90000 و 100000 و 150000 و 200000 و 300000 و 400000 و 500000 و 600000 و 700000 و 800000 و 900000 و 1000000 و 1500000 و 2000000 و 3000000 و 4000000 و 5000000 و 6000000 و 7000000 و 8000000 و 9000000 و 10000000 و 15000000 و 20000000 و 30000000 و 40000000 و 50000000 و 60000000 و 70000000 و 80000000 و 90000000 و 100000000 و 150000000 و 200000000 و 300000000 و 400000000 و 500000000 و 600000000 و 700000000 و 800000000 و 900000000 و 1000000000 و 1500000000 و 2000000000 و 3000000000 و 4000000000 و 5000000000 و 6000000000 و 7000000000 و 8000000000 و 9000000000 و 10000000000 و 15000000000 و 20000000000 و 30000000000 و 40000000000 و 50000000000 و 60000000000 و 70000000000 و 80000000000 و 90000000000 و 100000000000 و 150000000000 و 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Insulin administration

- All insulins are given by **s.c. injection**.
- **Regular insulin** is the only type that can be given **i.v.** in **diabetic emergencies**.
- The standard insulin concentration is 100 units/mL (U-100). It should be injected with a standard U-100 syringe.

measures the biological activity "The amount of Insulin needed to lower B.Glu 45-63mg/dL."

Insulin requirement and long term regimens

احتياج ال insulin اليومي لمريض DM 0.55 unit x 70kg = 38.5 unit.kg

- Generally, the total daily insulin requirement in units is equal to 0.55 times the person's weight in kilograms. A **conservative** total daily dose (TDD) of **0.4 units/kg/d** is given **initially** to a **newly diagnosed patient**; the dose is then **adjusted** according to the blood glucose level.

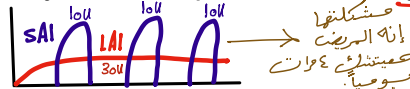
Conservative Dose

بتكون أقل من العتبة الأولى
عشرات أضعف ال Hypoglycemia
لنصف بدني أشوف استجابة المريض.

First way

Basal-bolus regimen:

- ! Give **long acting insulin** at bed time; plus **three daily injection of short acting insulin** before each meal. The **long-acting insulin** provides **basal level** of insulin that controls blood glucose during **night** and **in-between meals**, and the **short acting insulin** controls **postprandial hyperglycemia**.
- ! It is commonly used for patients with **Type-1 DM** and in pregnant women with diabetes.



عشكرتها
لأنه المريض
صحيته في عوارض
بوميا

منقلا ال pancreas
بسطر Basal level
حلول اليوم وبعد
الوصف PP
نريد انزل ال insulin

Sec way

Twice-daily biphasic insulin regimen:

- ! Use biphasic insulin. The average daily requirement is 0.5 units/kg. Use the two-thirds rule:
- ! Give the **2/3** of the TDD in the **morning** and the **1/3** at **evening**.
- ! It is commonly used for patients with Type-2 DM
- use **mixture insulin**.

Insulin Pump



- **Insulin pump** (artificial pancreas): **insulin** is **automatically released** according to **continuous measurement of blood glucose by electronic sensor**.

uses Rapid Acting insulin.
insulin lasts for 28 Days out of Fridge.

سأزله لو أعطيتة
بفضل بعد 30min أو 4h
عملك العصاره فينظف وصحت
أزله من تأثيره ببطء فيخرج
يغذف insulin فانز وتالست
ومعنا يرفع Hypoglycemia
منزله الجوار
من خاصم
أزله ال SAI/LAI
بده وقت

Methods of administration

- ! S.c. injection (using **insulin syringes**).
- ! Portable **pen injector** (Novo® pen).

كلما كانت أعنف
يعني 40 في الدم



Follow up of insulin therapy

By estimation of glucose in **urine** using **urine dipsticks** or from **capillary** blood glucose level using portable **glucometers**.

لشو / لمین
بأستغدره / بماعضیه

- ↑ Glu أعطيه K^+ نزيه للمغذ K^+ أعالج ال
وال insulin عيب Glu ↓، فإلزام أعوضه ال Glu.



- ! Post-receptor defect (intracellular): abnormal signal transduction due to **genetic** defect.
- ! Local insulin resistance: due to degradation of insulin in s.c. tissue by proteolytic enzymes. It is diagnosed by changing the route of administration to i.v. injection. If there is good response, then the resistance is local.

Hepatitis C makes people three to four times more likely to develop type 2 DM and insulin resistance.

- Life-style modification:**
 - Strict diet control.
 - Weight reduction.
 - Physical exercise.
- Correction of any precipitating factor:** e.g. **infection** or **stress**.
- Metformin:** to improve receptor sensitivity and ↓ intestinal glucose absorption (see later).
- Thiazolidindiones (Insulin sensitizers):** e.g. pioglitazone to ↑ insulin sensitivity (see later).
- Change the site of injection regularly In cases of **local** insulin resistance

ORAL ANTIDIABETIC DRUGS

1. Sulfonylureas

- ! Sulfonylureas are the most widely used medications for the treatment of T2DM.
- ! All of the sulfonylureas are well absorbed after oral administration and bind to plasma proteins.

Classification

- **First-generation compounds:** chlorpropamide, tolbutamide, acetohexamide. *Kidney*
- **Second-generation compounds:** glibenclamide, glyclazide and glipizide; they are up to 200 times more potent than first-generation agents, Duration 6-12h, Given for R.I. *↑*
- **Third-generation compounds:** e.g. glimepiride; these compounds may interact with different cellular proteins than other sulfonylureas. *Amorin 2 mg*



Mechanism of action

- ❗ **Pancreatic action:**
 - ❗ Sulfonyleureas ↑ insulin secretion by pancreatic β cells. They block K^+ channels in β cells, leading to depolarization, increased Ca^{2+} entry via voltage-dependent calcium channels, and increased insulin secretion.
 - ! They $\downarrow$ **serum glucagon**, which opposes the action of insulin.

■ Extrapankreatic action:

- ! They $\uparrow$ insulin receptor sensitivity, may be by increasing the number of insulin receptors. However, sulfonylureas do not decrease the insulin requirements of patients with type I diabetes.
- ! They $\downarrow$ hepatic output of glucose (gluconeogenesis).



Therapeutic uses

- Type 2 DM (they are not effective in type 1 DM).
- **Chlorpropamide** may be used in treatment of nephrogenic diabetes insipidus (it $\uparrow$ sensitivity of renal tubules to ADH).
 $\uparrow$ sensitivity of V_2 -ReCs.

Adverse effects

- ! **Hypoglycemia** especially with long acting drugs (chlorpropamide) or in elderly patients with hepatic or renal dysfunction .. (contraindicated in renal failure).
- ! Increased appetite and **weight gain**. يعني من 10 أشخاص أول مرة ياخذوا الدواء 3-8 هفتات منهم لن يؤثر الدواء عليهم.
- ! **Pharmacologic failure** is common, initially affecting 15%–30% of patients (1ry failure) and 90% after 6–7 years of therapy (2ry failure). It is due to progressive decline in β cell function. بعد 6 سنوات من كل 10 مريض الدواء 90% كان تشغل معهم، في 10 منهم هم يبطئ يؤثر فيهم.

Due to Sulfur.

- ! **Hepatotoxicity** (cholestatic hepatitis) .. (contraindicated in liver disease).

- ! **Allergic reactions.** Due to sulfur. Sulfonamid + Sulfonylurea
Both have Sulfur and Cause HyperSensitivity "Allergy".

2. Meglitinides: repaglinide and nateglinide

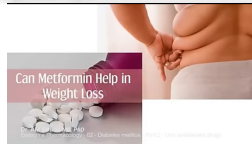
- They **increase insulin secretion** by the same mechanism like sulfonylureas although the binding site on the β -cells is different. $\rightarrow$ No sulfonylurea group.
- They have very **fast onset** and **short duration** so; they are taken **orally** just before meals to control **postprandial hyperglycemia**.
- They **don't contain sulfur**, so they can be used in patients allergic to sulfonylureas.
- **Hypoglycemia** is the major side effect.
- They should be used with caution in patients with **hepatic or renal impairment**. حذر

3. Biguanides: metformin



Mechanism of action

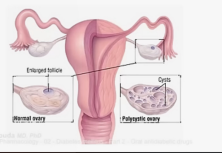
- $\downarrow$ intestinal glucose absorption and $\downarrow$ hepatic gluconeogenesis. It does **not** increase insulin secretion (so it doesn't cause hypoglycemia).
- $\uparrow$ insulin receptors sensitivity. شرط أنه الدواء يعمل Hypoglycemia
- Activate Anaerobic glycolysis. أنا يكون نشغل على B-Cells ويزود ال insulin secretion مثل ال MTN + SUV
 - $\rightarrow$ Aerobic way depends on insulin and O_2 to happen.
 - $\rightarrow$ Anaerobic way doesn't depend on insulin neither O_2 .
 - $\rightarrow$ Glycolysis $\downarrow$ Glu, $\uparrow$ Lactic Acid.



Therapeutic uses

- 70% of POS is associated with 1- IR 2- ↑ Androgen
- ❑ Type 2 DM either alone (in mild cases) or in combination with other drugs. !!!
- ❑ To enhance weight loss in **obese patients** (↓ glucose absorption). لذلك عيان مع T2DM Metformin مباشرة obesity
- ❑ Recent studies showed that metformin is useful in the treatment of **polycystic ovary syndrome (POS)**; it lowers serum androgen levels and restores normal menstrual cycles and ovulation.

metformin: 1- ↑ insulin sensitivity → ↓ IR. 2- ↓ Androgen → ovulation happens now.



Try infertility لم تنجب سابقاً والآن لا تنجب.

Try infertility أنجبت سابقاً والآن لا تنجب.

Adverse effects

- ❑ GIT upset (the most common): anorexia, vomiting, and diarrhea.
- ❑ ↓ absorption of vitamin B₁₂: rarely a clinical problem.
- ❑ Lactic acidosis: due to increased **anaerobic glycolysis** (especially) in patients with severe **renal** or **hepatic** diseases or if taken with alcohol.

4. Thiazolidinediones (insulin sensitizers): Pioglitazone – Rosiglitazone*

Mechanism of action PPAR ← α ↓ TGs + ↓ cholesterol. β ↑ sensitivity, ↑ GluT → insu. γ

- ❑ They act on nuclear genes called peroxisome proliferator-activated receptor-gamma (PPAR-γ) present in muscles, adipose tissue, and liver cells **leading to**:

- ! They ↑ insulin receptor **sensitivity** (by about 60%) and ↓ insulin resistance.
- ! They ↑ number of glucose **transporters** → ↑ glucose uptake.
- ! They have beneficial effect on serum **lipoprotein** levels (↓ TGs).

- ❑ They have slow onset and prolonged duration because their mechanism involves gene regulation.

Therapeutic uses: To improve **insulin resistance** in **type 2 DM**.

Adverse effects

- ! **Hepatotoxicity** – Pioglitazone induces bladder cancer.
- ! Fluid retention leading to peripheral edema & **weight gain**. (They should be avoided in patients with CHF). Congestive Heart Failure.

***N.B** pioglitazone is now the only thiazolidinedione on the market. Bladder Cancer



5. α-Glucosidase inhibitors (starch blockers): Acarbose – Miglitol

- ❑ They act by **competitive inhibition** of intestinal α-glucosidase enzyme → ↓ digestion & absorption of carbohydrates. صعوب يبلع معقولات mono sacari عشان يتم امتصاصه
- ❑ **GIT side effects** are common: flatulence, diarrhea, abdominal pain.
- ❑ They should be avoided in patients with **inflammatory bowel disease**.
- ❑ Not for hepatic disease patients because it is Hepatotoxic.

Fermentation

NEWER ANTIDIABETIC DRUGS

Incretins are group of metabolic peptides released by gastric and intestinal cells after eating to stimulate insulin secretion and lower plasma glucose. They are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4). The most important incretin peptide is **glucagon-like peptide-1 (GLP-1)**.

1. Incretin (GLP-1) mimetics: Exenatide

Exenatide is a synthetic 39-amino acid GLP-1 analog; **liraglutide** is longer acting analog and more resistant to metabolism.

له صمو الزفصل
شربه بديش اتشتمل
كثير.

Mechanism of action

- They $\uparrow$ insulin secretion and $\downarrow$ glucagon secretion. $\rightarrow$ β -Activation
- They slow gastric emptying and $\downarrow$ appetite. $\rightarrow$ α -Inhibition

يشعرونا
بالشبع +

Therapeutic uses

- Type 2 DM either alone or in combination with oral drugs. (It should not be given with insulin).
- They are given parenterally (s.c.) 60 min before breakfast and dinner. (It should not be given after a meal).

ليجى نزول كل الطعام
لا Intestin مرة واحدة
لمينغ ال Hypoglycemia

له شربه في عنبر ال DPP-4
صمغوت تم تنشيطه عنان يسره.

شربه خلايا ال B قصير
من كثر التعفن Exhausted
نفس كدة ال Phx. Failure
في ال Sulfonylureas.

Major adverse effects: nausea, vomiting, and pancreatitis (may be serious).

2. Dipeptidyl peptidase 4 inhibitors (Gliptins): Sitagliptin - Saxagliptin

Mechanism of action

- They inhibit dipeptidyl peptidase 4 (DPP-4), the enzyme responsible for the proteolysis of the incretin GLP-1.
- DPP-4 inhibitors may also improve β -cell function.

Therapeutic uses

- Type 2 DM either alone or in combination with metformin.
- They are given orally; most common **side effects** are headache and nausea.

3. Amylin analogs: Pramlintide

- Pramlintide** is a synthetic amylin analog. Amylin is a polypeptide secreted by β -cells of the pancreas, and it acts in concert with insulin to reduce blood sugar.
- It is injected s.c., typically with insulin.
- Common side effects are hypoglycemia and nausea.

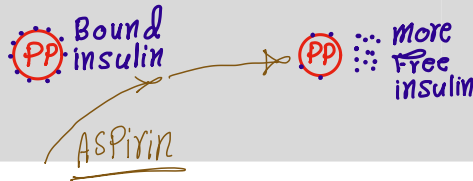
Drug interactions with oral hypoglycemic drugs

صعنا نتكلم
عن ال S. urea

Drugs potentiate the hypoglycemic effect:

- Microsomal enzyme inhibitors.
- β-blockers:** ↓ hepatic glycogenolysis
- Salicylates:** displacement of sulfonylureas from plasma proteins.

B2 ← Found on liver for Glycogenolysis.

minoxidil
VD → Hypo-T
علاج ضغط الدم

Drugs antagonize the hypoglycemic effect:

- Microsomal enzyme inducers.
- β-agonists:** ↑ hepatic glycogenolysis.
- Thiazides and diazoxide:** they open ATP sensitive K⁺ channels → ↓ insulin release and ↓ peripheral glucose utilization.
- Anti-insulin hormones: e.g. steroids and glucagon. Cortison

TREATMENT OF DIABETIC COMPLICATIONS

Hypoglycemic coma

Causes:

- Large dose of insulin or sulfonylurea. + Meglitinides.
- Missed meal while taking insulin or sulfonylureas.
- Vigorous muscular exercise without dietary adjustment.

Manifestations:

- Sympathetic overactivity: tremors, cold sweating, mydriasis, tachycardia, etc.
- Hunger pain, mental confusion, and coma.

Treatment:

- If the patient is conscious or semiconscious → give oral sugar solution.
- If the patient is in deep coma: (1) i.v. glucose 10%; (2) Glucagon 1 mg i.m.

حبة
عسلون 10% . i.v . (slowly)

حقنة 1mg . Glucagon i.m.

Hyperglycemic coma (diabetic ketoacidosis; DKA):

Causes:

- Excess food intake.
- Inadequate insulin administration.
- Infection or stress condition.

Manifestations (DKA):

- Dehydration and dry shrunk tongue.
- Ketosis: smell of acetone in breath and ketones in urine.
- Acidosis (pH < 7.3) → acidotic breathing (rapid and deep).
- Deep coma in late cases.

leads to



important
↓ insulin → ↓ Glu. uptake and metabolism
→ ↑ lipid metabolism → ↑ Ketone bodies (Excessive)
Like Acetone, Acetoacetate, and β-hydroxybutyrate (BHB)
→ Leading to lower pH (Keto Acidosis).

In kidney ↑ Glu = osmolarity
water retention.
Diuresis.

Permanent Brain Damage

Normal is pH = 7.4

Treatment:

Isotonic

- 0.9% NS
- 0.9g of NaCl for each 100ml of water
- In Hypotonic → Cell Burst
- In Hypertonic → Shrinkage

Fluid replacement: fluid deficit = 4-5L.

يعتبر المريض يكون داخل الطوارئ فاخذ حوالي 4-5L من الـ Fluid

Use normal (0.9%) saline. Ringer's lactate is also acceptable choice.

لنرى فيه أول ما عتبت 500ml/h، بعد 6h

Start with 1-2 L/h for the first 2 hours, followed by 500 mL/h for 6 hours.

في Hypo K+ من الـ 100ml/h

Potassium: is routinely added to the i.v. fluid as 20 mEq KCl/1L.

20mEq with each 1L N. Saline.

1. Fluid loss due to Glu Com take K+ in urine, May not.

2. Dilutional HypoK+ due to Normal saline.

3. I will give DKA Patient an insulin which makes K+ shift into cells.

Regular insulin:

Start with a bolus of dose of 0.1 units/kg i.v. followed by an infusion of 0.1 units/kg/hour. → 0.1 U/kg i.v Direct + 0.1 U/kg/hour in Normal saline.

Emergency

Insulin infusion should continue until serum electrolytes, pH, and glucose level are normalized.

Insulin infusion 0.1 U/kg/hour في الـ 100ml/h NS مع 20mEq K+ في الـ 100ml/h NS

HCO₃⁻ / K⁺ / Na⁺

Glucose 5 % is given when blood glucose falls to ~250 mg/dl to prevent cerebral edema.

العلاج كات الـ 100mg/dl سر أضع الـ 500mg/dl في الـ 100ml/h NS مع 20mEq K+ في الـ 100ml/h NS

Bicarbonate (HCO₃): is not routinely given unless there is severe acidosis (pH < 7.1).

Hyperosmolar hyperglycemic state (HHS):

HHS was previously termed hyperosmolar hyperglycemic nonketotic coma (HHNC); however, the terminology was changed because coma is found in fewer than 20% of patients with HHS.

أخطر من الـ DKA

It is a life-threatening medical emergency that is more common in old age.

Pathogenesis: severe hyperglycemia causes ↑ water loss (osmotic diuresis) with little sodium loss → severe dehydration with hyperosmolarity. **Ketoacidosis is absent.**

	DKA	HHS
BG (500/400/300)	> 250 mg/dl	> 600 mg/dl
pH	< 7.3	> 7.3
Ketoneuria	++ Found	-- Absent

Treatment: similar to DKA **except in:**

Fluid replacement: fluid deficit >5L.

Rapid and aggressive i.v. isotonic saline is the principal treatment. The patient may require 8-10 L of saline.

Fluid replacement alone can reduce glucose levels.

Insulin i.v.i similar to DKA. Insulin used without concomitant vigorous fluid replacement increases the risk of shock.

Hypokalemia is usually less marked but **potassium** may be required early in the treatment.

LMWH to prevent thrombotic complications.

لنرى حقنة الـ Clethane (Heparin) (Low Dose) لزيادة الدم أصبح more viscous بسبب فقد الماء يعني أكثر عرضة لـ Thrombosis



Glucose Dipsticks Can measure both Glu and Ketons, we use it to know if the patient is HHS or DKA

| Diabetic neuropathy

Diabetic neuropathy is the most common complication of diabetes mellitus (DM), affecting as many as 50% of patients with type 1 and type 2 DM. It may be cranial, sensory, sensory-motor or autonomic. DN is an irreversible process.

Pathogenesis

- ! **Advanced glycated end-products:** elevated intracellular levels of glucose cause a non-enzymatic covalent bonding with cellular proteins, causing microvascular damage, ischemia, hypoxia, and nerve damage.
- ! **Polyol pathway (sorbitol/aldose reductase pathway):** elevated intracellular glucose is converted into sorbitol via the enzyme *aldose reductase*. Sorbitol is toxic to tissues.

Treatment

- ! Tight, stable glycemic control is the most important factor for slowing progression of DN.
- ! **For neuropathic pain**, and tingling sensation: duloxetine (antidepressant drug) 30 mg/12h orally (first choice) or pregabalin (second choice). Lyrica
- ! **For diabetic gastroparesis:** metoclopramide
- ! **For erectile dysfunction:** sildenafil