ENDOCRINE
PHARMACOLOGY

#51

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PANCREATIC HORMONES

- **Insulin *(which is secreted from β-cells)*; Glucagon *(which is secreted from α-cells).***

- **Diabetes Mellitus:**

- A disease characterized by high blood sugar level.

- A disease characterized by insulin deficiency. *Not that much correct.*

- A metabolic disorder manifested by abnormalities in carbs, lipid and protein metabolism. *(The best definition).*

- **Diabetes is a major cause of heart disease and stroke.**
- **Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States.**
- **Diabetes is the seventh leading cause of death in the United States.**

- **Types of DM (2 types):**

- **Type I *also known as* juvenile-onset *or* IDDM *(insulin dependent diabetes mellitus.***

- 10-20% of diabetics.

- Most commonly occurs in childhood or adolescence but may occur at any age.

- Mainly affects children at the age 10-14 (not reported in kids less than 6 months).

- Type I DM patients have little or no pancreatic function.

- Often patients present with ketoacidosis.

- Characterized by downhill course-severe type of DM (mortality is high).

- Easy to diagnose (pts usually present complaining of weight loss; easy fatigability; polyuria *excessive urination*; polydipsia *frequent intake of water*; polyphagia *frequent eating*…)

- **Type II; maturity or adult-onset; IIDM *(insulin independent diabetes mellitus, the doctor does not agree with this name because certain patients require insulin therapy to control their high blood glucose level.***

- Represents 80-90% of diabetics

- Usually discovered accidentally after an age of 30-40 yrs.

- Most pts are obese and it is more common in females as compared to males.

- Pts have a strong family history (genetic background).

- Most cases of type II have mild polyuria and fatigue.

- Ketoacidosis is rare in pts with type II DM unless in certain circumstances of unusual stress.

- Insulin blood levels could be low, normal or high.

- Insulin resistance is common, *3 mechanism are responsible to insulin resistance:*

1.pre-receptor mechanism; *presence of specific antibodies directed against insulin*. *مقاومة الانسولين بتصير قبل وصول الانسولين للمستقبِل تبعه*

2.receptor *high levels of insulin could down regulate its own receptors leading to decrease number of receptors or desensitization of receptors.*

(أكثر طريقة لمقاومة الانسولين شيوعًا)

3.post-receptor mechanisms*; excess production of certain hormones that increase the blood glucose level like cortisol, catecholamines and estrogen*.

- **Symptomatology:**

- Early; Polyuria, Polydipsia, Polyphagia, Ketoacidosis (type I).

- Late; Atherosclerosis & IHD, Retinopathy, Nephropathy, Neuropathy.

We always pay attention to diabetic patients to be careful to follow the instructions in order to have normal blood sugar level, otherwise we frighten them even.

***Normalization of blood glucose level corrects immediately early manifestations... late complications???**

There is a big question mark whether good normalization of blood glucose level will totally inhibit such late complications or not.

***Anyway, Good normalization could at least delay the onset of such manifestations*.**

- **Diagnosis:**

- Clinical manifestations

- Lab Tests: Random blood sugar (RBS), Fasting blood sugar, Glycosylated hemoglobin (HbA1c) ***give an idea about the patient's blood glucose level in the past 3 months*****, Glucose tolerance test.**

- **Management:**

- Type I: Diet + Insulin therapy

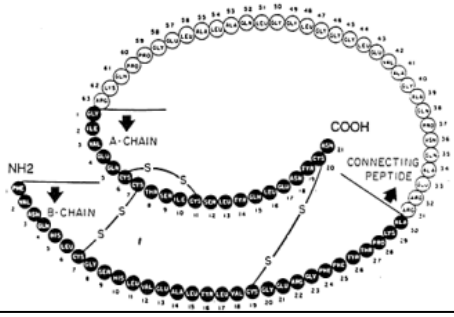
- Type II: Diet + exercise ***(both are required regardless of the case)***

± Oral hypoglycemic agents ***(plus minus means depends on the case)***

± Insulin ***(plus minus means depends on the case)***

Insulin is a Protein that has 2 chains;

A (21 amino acids) & B (30 aa) connected by disulfide bonds.



pro-insulin or insulin precursor.

- **Biosynthesis of insulin:**

Insulin and C-peptide are secreted from beta cells of pancreas at equimolar amount.

C-peptide can be used as a diagnostic tool to test the level of function of the beta pancreas, high C-peptide means high level of pancreatic beta function.

Proinsulin has slight insulin-like activity (1/10 the potency of insulin).

C-peptide is devoid of any insulin-like activity.

- **Secretion of insulin: Ca++ dependent [blood glucose] is the major regulator.**

- **Factors/drugs ↑ release: Glucose, amino acids, growth hormones glucagon, ACTH, sulfonylureas, β-adrenergic, cholinergic drugs…**
- **Factors/drugs ↓ release: α-adrenergic, anticholinergics, phenytoin, alloxan, streptozotocin (streptozocin), *these drugs produce damage to beta cells.***

- **Insulin mechanism of action:**

(1) Insulin binds to its receptor leading to phosphorylation of insulin-receptor complex.

(2) which in turn starts many protein kinases activation cascades.

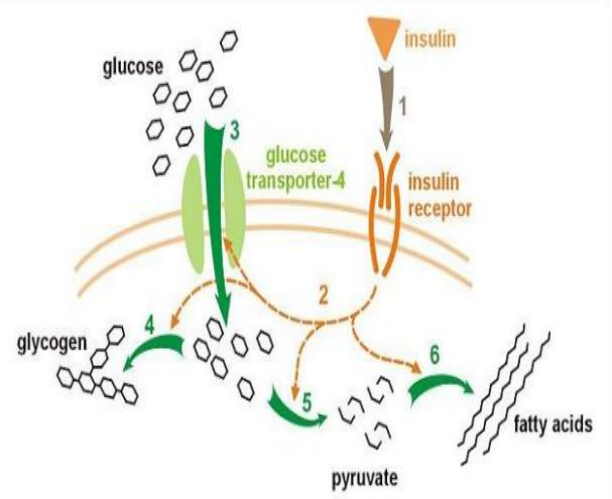
(3) These include translocation of Glu transporter-4 to the plasma membrane and influx of glucose.

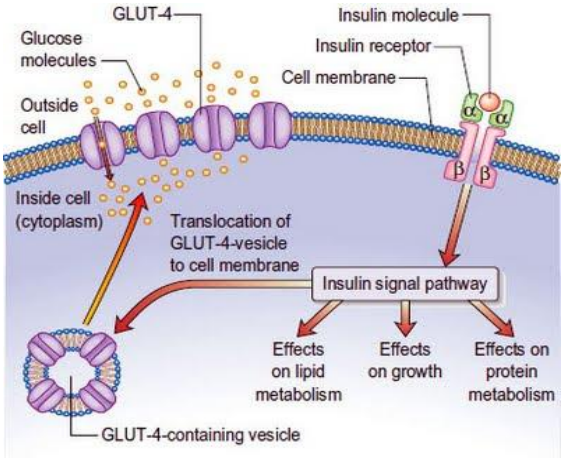
(4) glycogen synthesis.

(5) glycolysis.

(6) fatty acid synthesis.

In addition, not shown in the figure (Incident increase uptake of peripheral cells to K+)





- **Insulin effects:**

↑ glucose uptake or transport → muscles & adipocytes.

↑ glucose oxidation by muscles.

↑ hepatic glycogen synthesis and storage; ↓ glycogenolysis (breakdown of glycogen)

↑ amino acids uptake and protein synthesis by muscles and liver.

↓ hepatic gluconeogenesis.

↓ lipolysis. ↓ ketogenesis.

- **Insulin preparations:**

- Natural >>> Insulins of animal source are no more used and natural human insulin extracted from the pancreas is characterized by having low bioavailability and short t1/2 due to problems with its stability.

- Synthetic >>> rHI (*recombinant human insulin*) to all preparations are available.

- **Insulins are classified according to duration of action (DOA) into:**

	O (hr)	P (hr)	DOA (hr)
** Ultra-rapid onset; very short acting:			
- Insulin Lispro	0.25-0.5	0.5-1	3-4
- Insulin Aspart	10-20 min		
- Insulin Glulisine			
** Rapid onset & short acting:			
- Crystalline zinc (regular; soluble; insulin injection)	0.3-0.7	2-4	5-8
- Insulin zinc prompt (Semilente)	0.5-1	2-8	12-16
** Intermediate onset & action:			
- Insulin zinc suspension (Lente)	1-2	6-12	18-24
- Isophane insulin suspension (NPH; Humulin)	1-2	6-12	20-28
** Slow onset & action:			
- Protamine zinc suspension	4-6	14-20	24-36
- Extended insulin zinc suspension	4-6	16-18	24-36
Insulin Glargine (peakless insulins)	1-2	-	24-36
Insulin Detemir	1-2	-	24-36
** Mixed insulins:			
Int. + short	0.5-1	3-8	20-24
Int. + long	2-4	4-16	22-24

All insulin preparations are mainly given S.C except regular insulin, insulin Glulisine & insulin Aspart (SC & I.V)… Instructions to pt

Let me guess, you are probably asking whether these numbers are for memorizing or not?

For the sake of exam just remember the DOA (duration of action), and specifically the second number of each duration, like 4, 8 ,16 ,24…and so on.

All the types of insulin incidents belong to the ultra, intermediate, slow…etc. is for memorizing absolutely.

***Insulin lispro** is the most widely used incident preparation in what is known as insulin pumps.*
***Crystalline zinc** (regular, soluble, insulin injection) is the most widely proportioned that is used in the management of ketoacidosis or hyperglycemic coma.*
***Insulin suspension** is the most widely used incident in most diabetes.*

- **Advantages of peak less insulins over intermediate-acting insulins:**

- Constant circulating insulin over 24hr with no pronounced peak.

- Safer than NPH & Lente insulins due to reduced risk of hypoglycemia (esp. nocturnal hypoglycemia).

- Clear solution that does not require resuspension before administration.

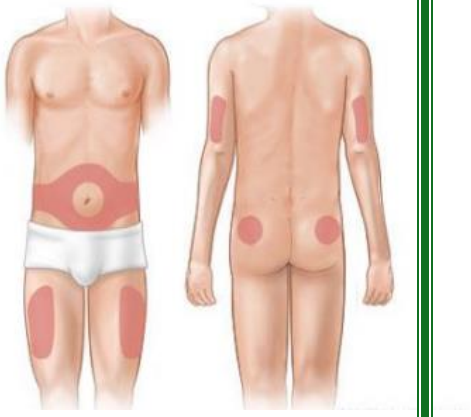
Site of insulin injection **subcutaneously:**

The arms

The buttocks

The thighs

The abdomen



- **Factors affecting insulin absorption:**

1- Site of injection: abdomen > arm > buttocks > thigh ***(subcutaneous abdominal injection is associated with the best bioavailability as compared to other sites)***

2- Exercise = blood flow at site ***(exercise increases the blood flow to the area which in turn increase the viability of the drug)***

3- Depth of injection ***(in term of injection; be careful not to reach the muscle for example, if you reach the muscle and the drug was injected intramuscularly >>> faster onset of action and duration of action will be less)***

4- Concentration and dose of insulin ***(the higher the dose >> the more will enter the blood)***

5- Addition of protamine or isophane to insulin preparations to form a complex delaying absorption and hence alter DOA

- **Insulin is metabolized in tissues (liver, muscles and kidneys) and metabolites are excreted renally.**
- **Dose of insulin: Insulin is given in units and its need varies tremendously.** ***(There is a great variation in insulin dose between diabetic patients depending on their blood glucose level and another determinant. However, it's not difficult to determine the dose)***

- **Side effects to Insulin therapy:**

- Hypoglycemia; ↑ sympathetic activity (instructions to pts)

- Lipodystrophy ***(loss of fat at the site of injection, that's why we advise the patient to change the site of injection).***

- Allergy

- Induration

Hypoglycemia is dangerous while hyperglycemia is not.

At the end of our lecture, imagine yourself a cute doctor in Al-Bashir hospital sitting in the cafeteria, suddenly, a diabetic patient came to emergency room with coma, what's your management?!!!!

Take a blood sample, send it to the lab and immediately put the patient on glucose irrespective whether the patient has hyper/hypo glycemia. After knowing the results, if the patient has hypoglycemia, you continue with glucose. If he has hyperglycemia nothing happened, just remove the drug (glucose), and put another solution which must be insulin with regular, soluble and rapid onset of action like crystalline zinc + potassium.

GOOD LUCK