Pancreatic Hormones

- Insulin (β-cells); Glucagon (α-cells)
- Diabetes Mellitus

- A disease characterized by high blood sugar level?

- A disease characterized by insulin deficiency?

- A metabolic disorder manifested by abnormalities in CHO, lipid and protein metabolism

- 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; juvenile-onset; IDDM

- 10-20% of diabetics

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

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

- Type I DM pts have little or no pancreatic function
- Often pts present with ketoacidosis
- Characterized by downhill course-severe type of DM (mortality is high)
- Easy to diagnose (pts usually present C/O wt. loss; easy fatigability; polyuria; polydipsia; polyphagia…)

- Type I DM in most cases is associated with HLA types (histocompatibility antigens) and presence of β-islet cell antibodies suggesting an autoimmune-mediated destruction of insulin producing cells and hence to a near total loss of endogenous insulin production
- Insulin lack could be idiopathic

- **Type II; maturity or adult-onset; IIDM**

- 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 strong family Hx (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 (pre-receptor; receptor; post-receptor mechanisms)

- **Symptomatology:**

- Early

- Late

- **Early manifestations:**

Polyuria

Polydipsia

Polyphagia

Ketoacidosis (type I)

- **Late manifestations or complications:**

Atherosclerosis & IHD

Retinopathy

Nephropathy

Neuropathy

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

- **Diagnosis:**

- Clinical manifestations

- Lab. Tests:

  Random blood sugar (RBS)

  Fasting blood sugar

  Glycosylated hemoglobin

  Glucose tolerance test

- **Management:**

- Type I:

Diet

+ Insulin therapy

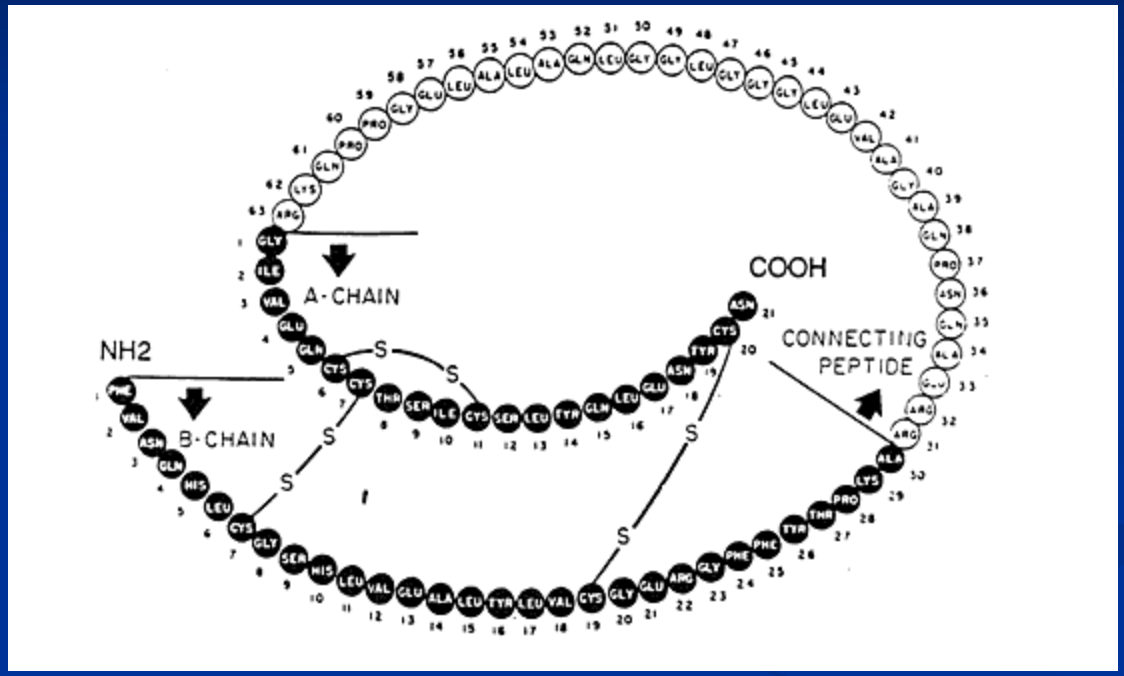
- Type II:

Diet + exercise

± Oral hypoglycemic agents

± Insulin

Insulin



Insulin

Protein; A (21 aa) & B (30 aa) chains; disulfied bonds

- **Biosynthesis of insulin:**

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:**

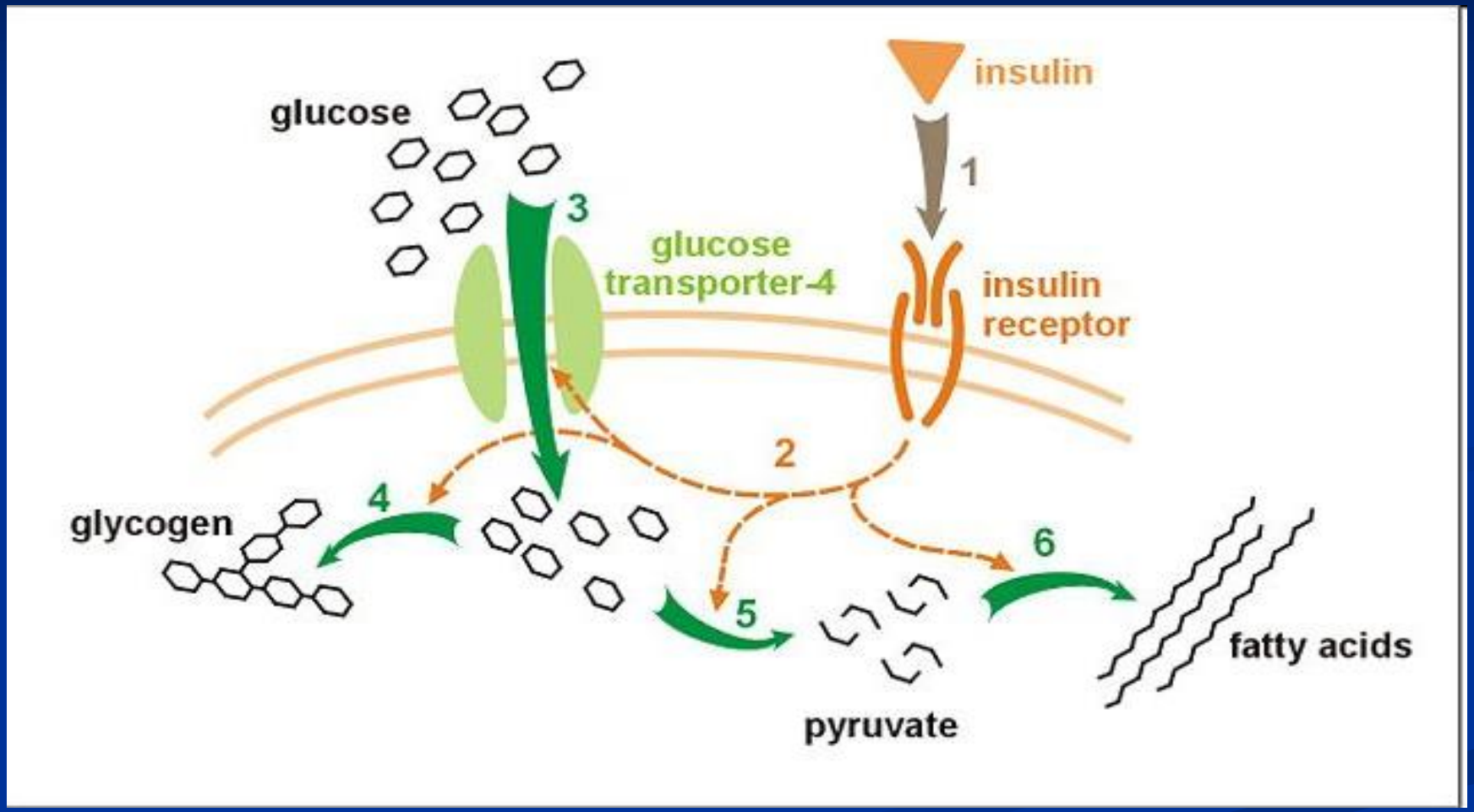
Glucose; a.a's; F.A's; GH; glucagon; ACTH; sulfonylureas; β-adrenergics, cholinergic drugs…

- **Factors/drugs ↓ release:**

α-adrenergics; anticholinergics; phenytoin; alloxan; streptozotocin (streptozocin)

- **Insulin mechanism of action**

Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor leading to phosphorylation of insulin-receptor complex (1) which in turn starts many protein kinases activation cascades (2). These include: translocation of Glu transporter-4 to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).


glucose
insulin
1
3
glucose
transporter-4
insulin
receptor
2
4
glycogen
6
5
fatty acids
pyruvate

- **Insulin effects:**

- ↑ glucose uptake or transport → muscles & adipocytes
- ↑ glucose oxidation by muscles
- ↓ hepatic gluconeogenesis
- ↑ hepatic glycogen synthesis and storage; ↓ glycogenolysis
- ↑ a.a uptake and protein synthesis by muscles and liver
- ↓ 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 $t_{1/2}$ due to problems with its stability

- Synthetic

rHI to all preparations are available

Insulins are classified according to duration of action (DOA)

** Ultra-rapid onset; very short acting:

	O (hr)	P (hr)	DOA (hr)
- 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 (Ultralente)	4-6	16-18	24-36

Insulin Glargine	1-2	-	24-36
(peakless insulins)			
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

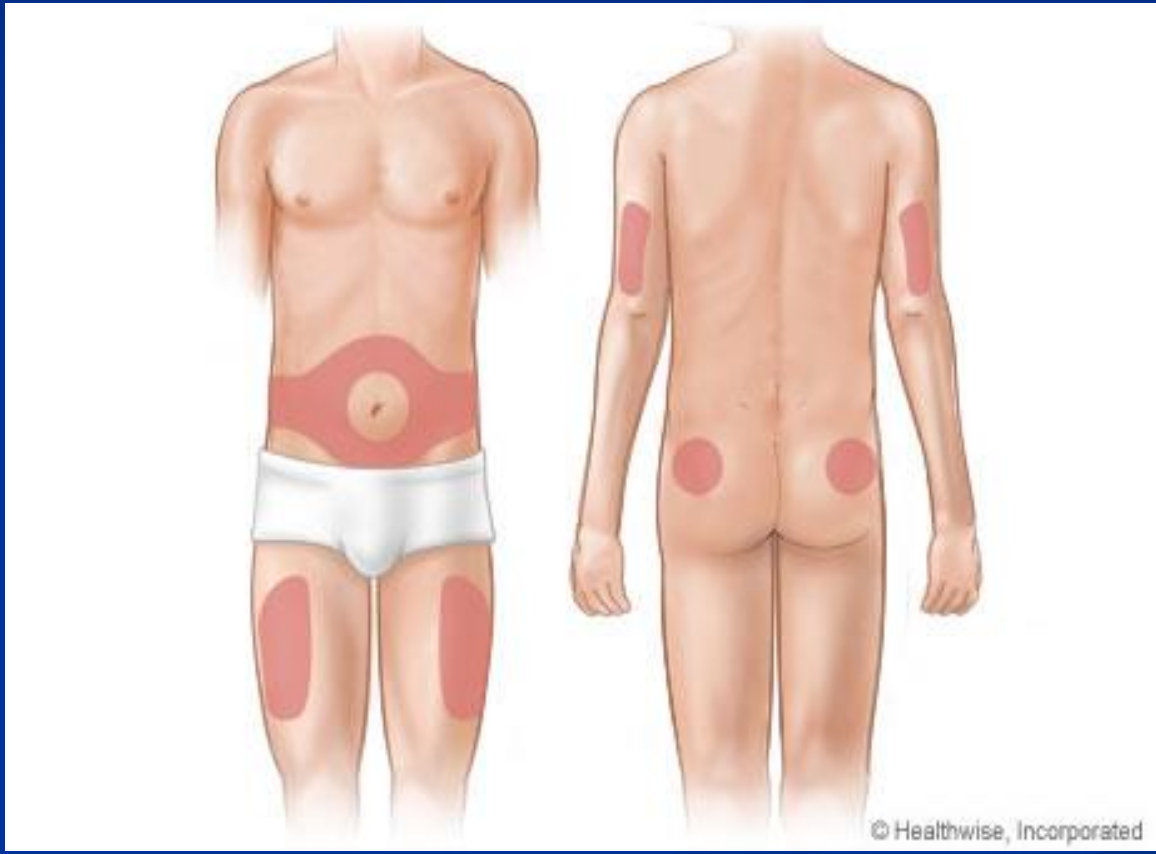
All insulin preparations are mainly given S.C except regular insulin, insulin Glulisine & insulin Aspart (SC & I.V)… Instructions to pt

- Advantages of peakless insulins over intermediate-acting insulins:

- Constant circulating insulin over 24hr with no pronounced peak

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

- Clear solution that does not require resuspension before administration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- **Factors affecting insulin absorption:**

- Site of injection:

abdomen > arm > buttocks > thigh

- Exercise = blood flow at site
- Depth of injection
- Concentration and dose of insulin
- 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

- **Methods of insulin administration:**

- Insulin Syringes
- Pre-filled insulin pens
- Insulin Jet injectors
- External insulin pump

* Under Clinical Trials

- Oral tablets
- Inhaled aerosol
- Intranasal, Transdermal patches
- Buccal spray


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Autopen
Apidra SoloStar
insulin glulisine (rDNA origin) injection
100 units/mL
3 mL Prefilled Pen
Humalog Mix 50/50
KwikPen


SCIENCEphotoLIBRARY

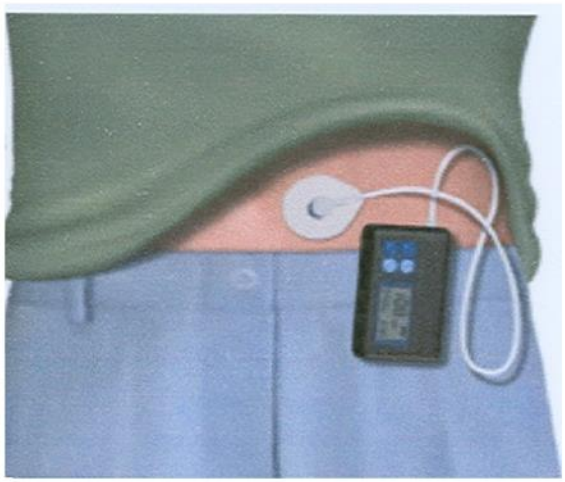
The HumaPen has a memory that records the dose, date and time of the past 16 injections. The device uses insulin cartridges

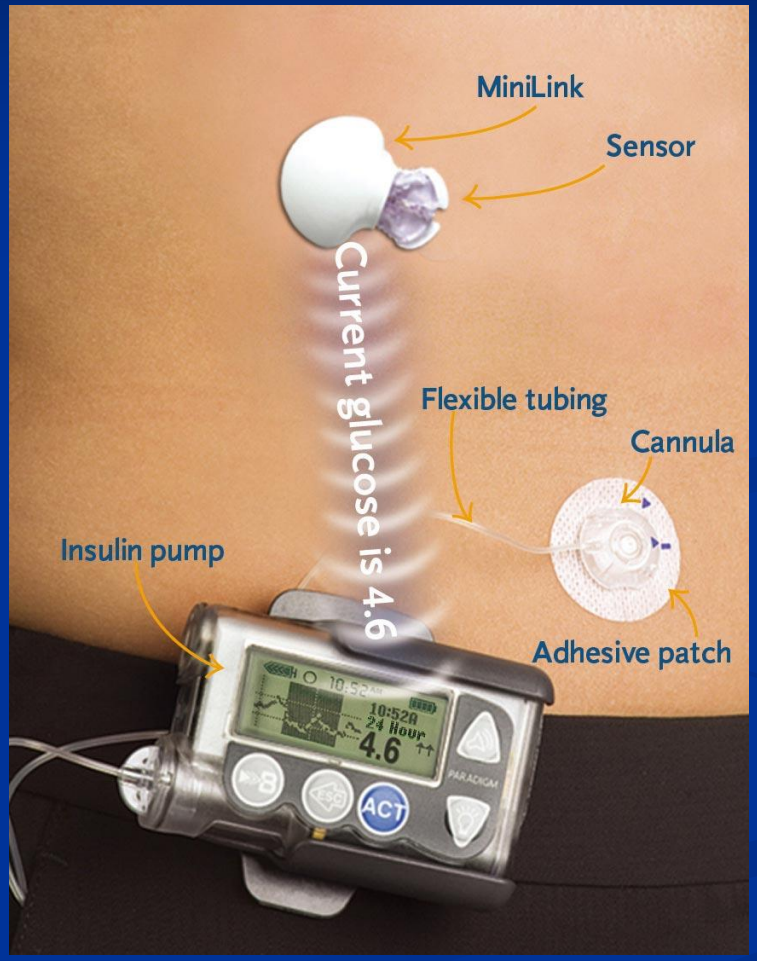
- Cont. insulin delivery systems

- Jet Injectors

These devices look like a large pen, but they do not use needles. They send a fine spray of insulin through the skin using a blast of high-pressured air. Insulin jet injectors tend to be costly


100 U




MiniLink
Sensor
Current glucose is 4.6
Flexible tubing
Cannula
Insulin pump
Adhesive patch
10:52
24 Hour
4.6
ACT

- **Dose of insulin:**

Insulin is given in units and its need varies tremendously

- **Side effects to Insulin therapy:**

- Hypoglycemia; ↑ sympathetic activity (instructions to pts)
- Lipodystrophy
- Allergy
- Induration

** Diabetic → to E.R with coma; management?!!!!