DRUG TRETEMENT OF DM part 1

Semester IV

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Learning Outcomes

By the end of the 3 lecture, the students will be able to:

1. List different insulin preparations

2. Describe the mechanism of action of insulin

3. Select appropriate dosage forms in clinical situations

4. Recognize side effects of insulin

5. Describe the mechanism of action and side effects of sulphonylureas, metformin, acarbose, glitazones

6. Recognize side effects of sulphonylureas, metformin, acarbose, glitazones

7. Describe newer antidiabetic drugs.

Diabetes mellitus

- **Definition of DM:** It is a clinical syndrome

- **Manifestations:** Polyuria, polydipsia, polyphagia.

- **Complications:** neuropathy, retinopathy, nephropathy, DKA……….

- **Laboratory investigations:**

1. Urine analysis:

2. Blood glucose: fasting and 2-hrs postprandial.

3. Glycated hemoglobin (HbA1C): Indicates average blood sugar level for the past 2-3 months

	Normal	**Prediabetes**	**DM**
Fasting BG	< 100 mg/dl	100-125 IFG	≥ 126 mg/dl
2 hr after oral 75 g glucose	< 140 mg/dl	140-200 IGT	≥ 200 mg/dl
HbA1C	< 6%	6-6.5%	➤ 6.5% (uncontrolled DM over the last 2-3 m).

Common types of DM:
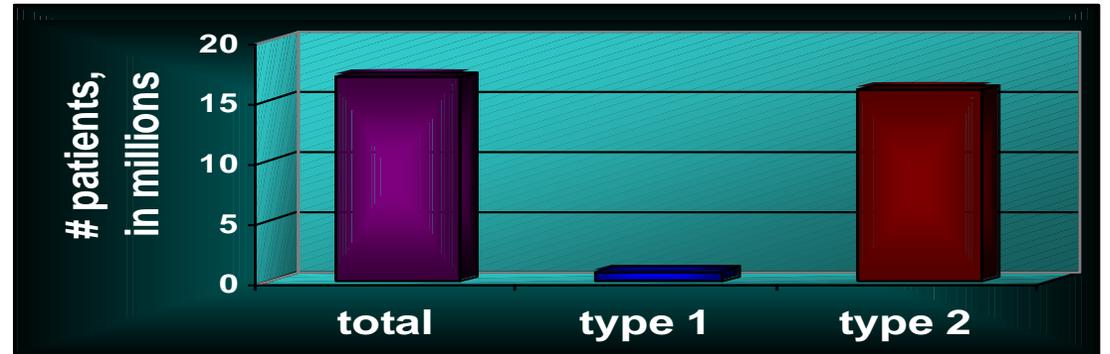
- **Type 1 diabetes:**

can develop at any age, but occurs most frequently in children and adolescents.

- **Type 2 diabetes:**

is more common in adults and accounts for around 90% of all diabetes cases.

- **Gestational diabetes (GDM):**

is a type of diabetes that consists of high blood glucose during pregnancy and is associated with complications to both mother and child.
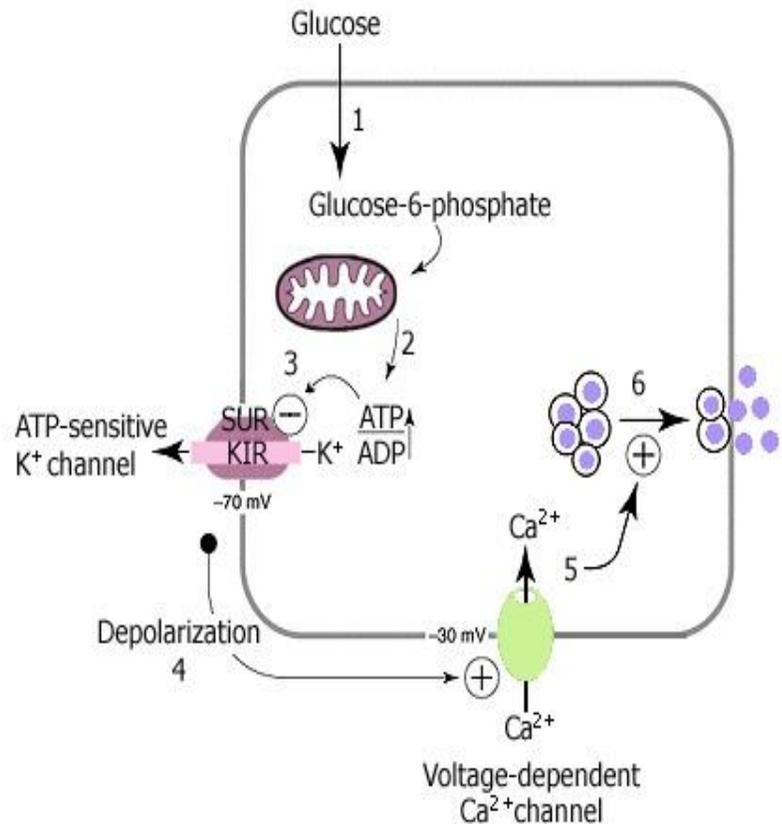
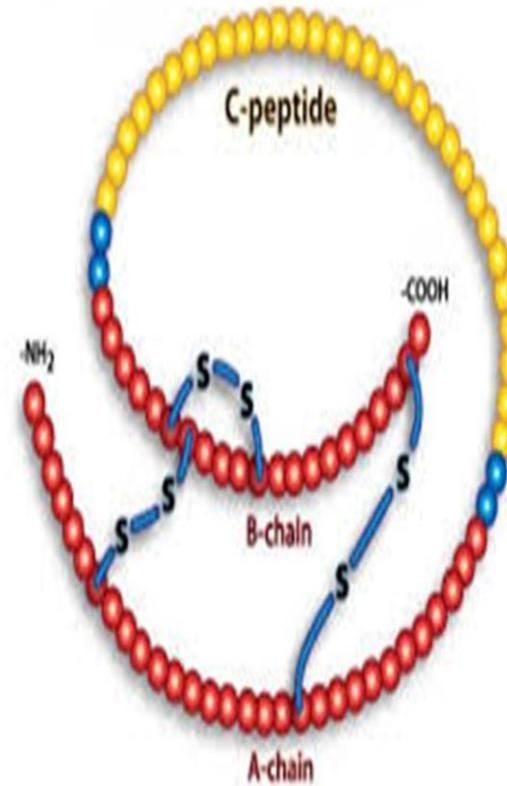# Lines of treatment:

1. Diet control.

2. Diet + insulin (type 1).

3. Diet + oral antidiabetic drugs ± insulin (type 2).

Insulin

Secretion
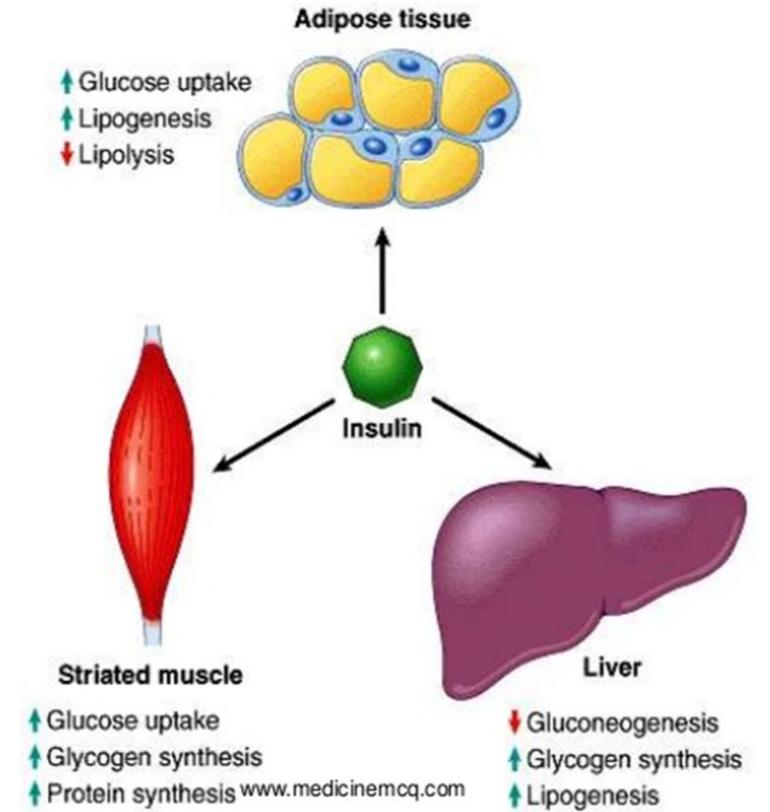

Glucose

1

Glucose-6-phosphate

2

3

ATP-sensitive K+ channel ← SUR / KIR − −K+ | ATP↑ / ADP↓

−70 mV

Depolarization

4

−30 mV

Ca²⁺

Voltage-dependent Ca²⁺ channel

5

6

Chemistry

C-peptide

-NH₂

-COOH

S-S

B-chain

A-chain

Actions

Adipose tissue
- ↑ Glucose uptake
- ↑ Lipogenesis
- ↓ Lipolysis

Insulin

Striated muscle
- ↑ Glucose uptake
- ↑ Glycogen synthesis
- ↑ Protein synthesis

Liver
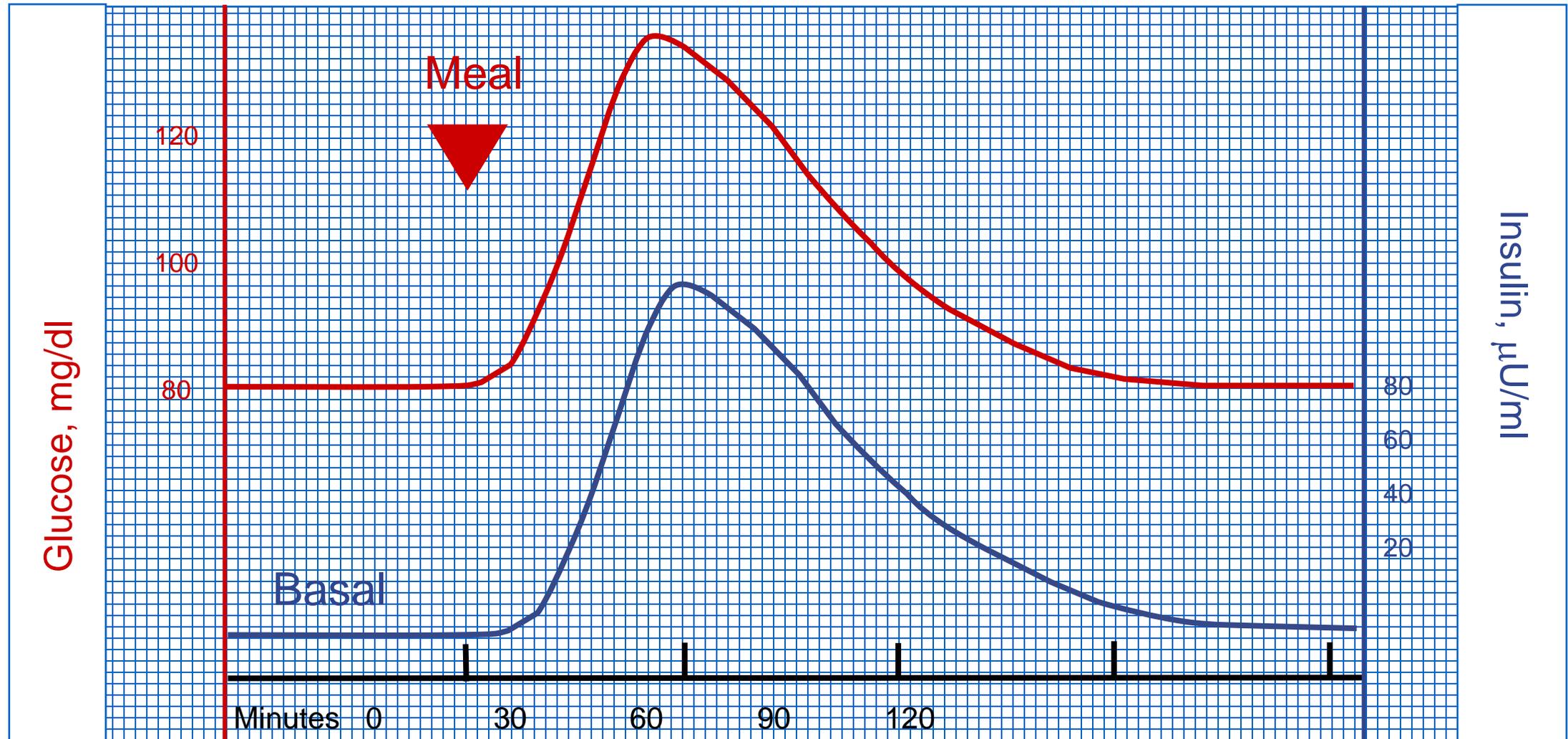- ↓ Gluconeogenesis
- ↑ Glycogen synthesis
- ↑ Lipogenesis

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Insulin release: normal levels

Sources of insulin:

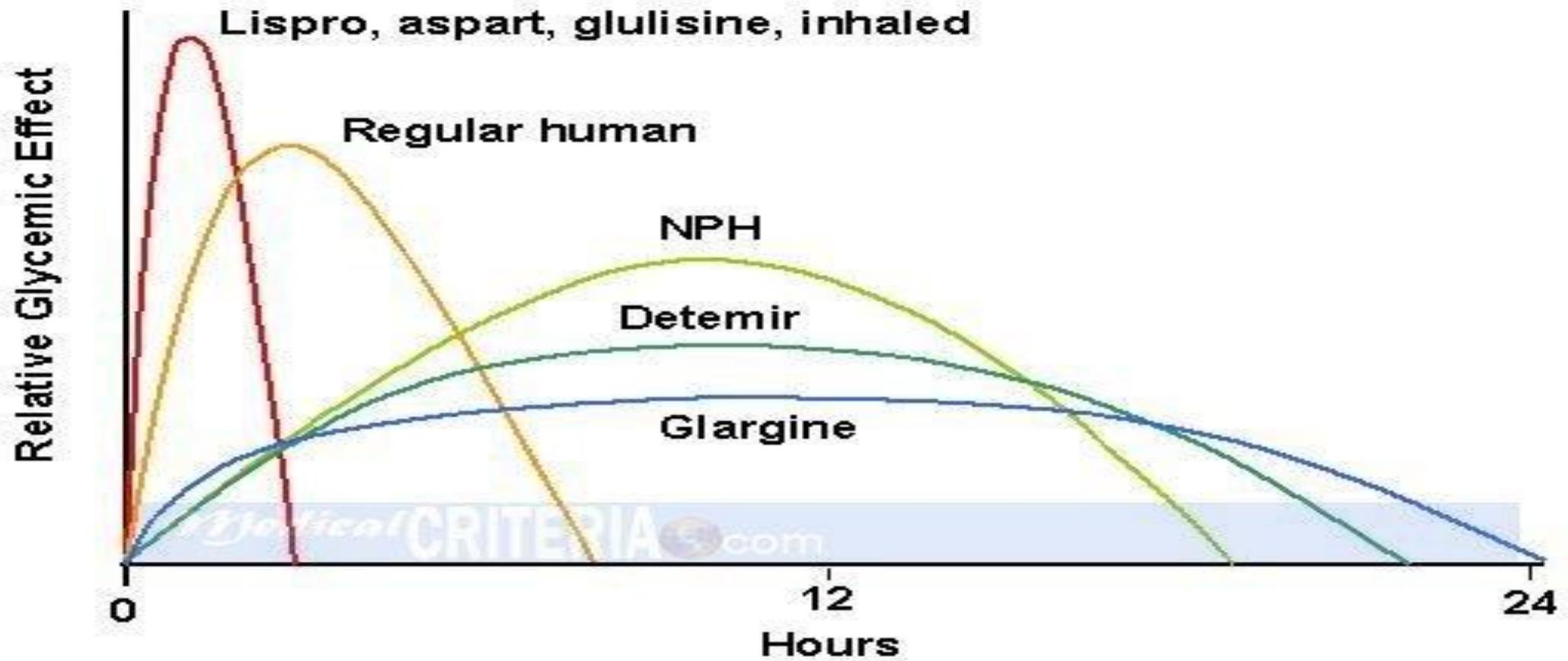❑**Traditional (animal) insulin:**

❑**Human insulin:**

- Identical to human insulin

- Prepared by recombinant DNA technology.

- **Less antigenic &** rare development of insulin resistance.

❑**Insulin analogs:**

- Few a.a. of the human insulin are switched or replaced

- The different molecule have different pharmacokinetic properties.

Insulin preparations:

Category	Generic names	Features	Onset	Peak	Duration
(1) Rapid acting insulin analogs	(1) insulin lispro (2) insulin aspart	Given just before meal	0-15 min	1-2 h.	3-5 h.

Category	Generic names	Features	Onset	Peak	Duration
(2) Short acting insulin	Regular, soluble, neutral	Identical to human insulin (Only one to be given I.V.)	30 min	2-4 h.	6-8 h.

| Category	Generic name	Features	Onset	Peak	Duration
(3) Intermediate acting Insulin:	Isophane insulin (N.P.H.)	Made by adding protamine to insulin to increase the duration of action	1-2 h.	4-6 h.	12-16 h.

Category	Generic name	Features	Onset	Peak	Duration
(4) Long acting insulin:	insulin glargine & detemir	"peakless" Given once daily	1-2 h.		18-24 h.

Category	Generic name	Features	Onset	Duration
(5) Premixed Insulin (Biphasic)	Humalin 70/30 (NPH/Reg.) (mixtard)	Rapid onset Long duration	<30 min	12-16 h.

Mechanism of action of insulin:
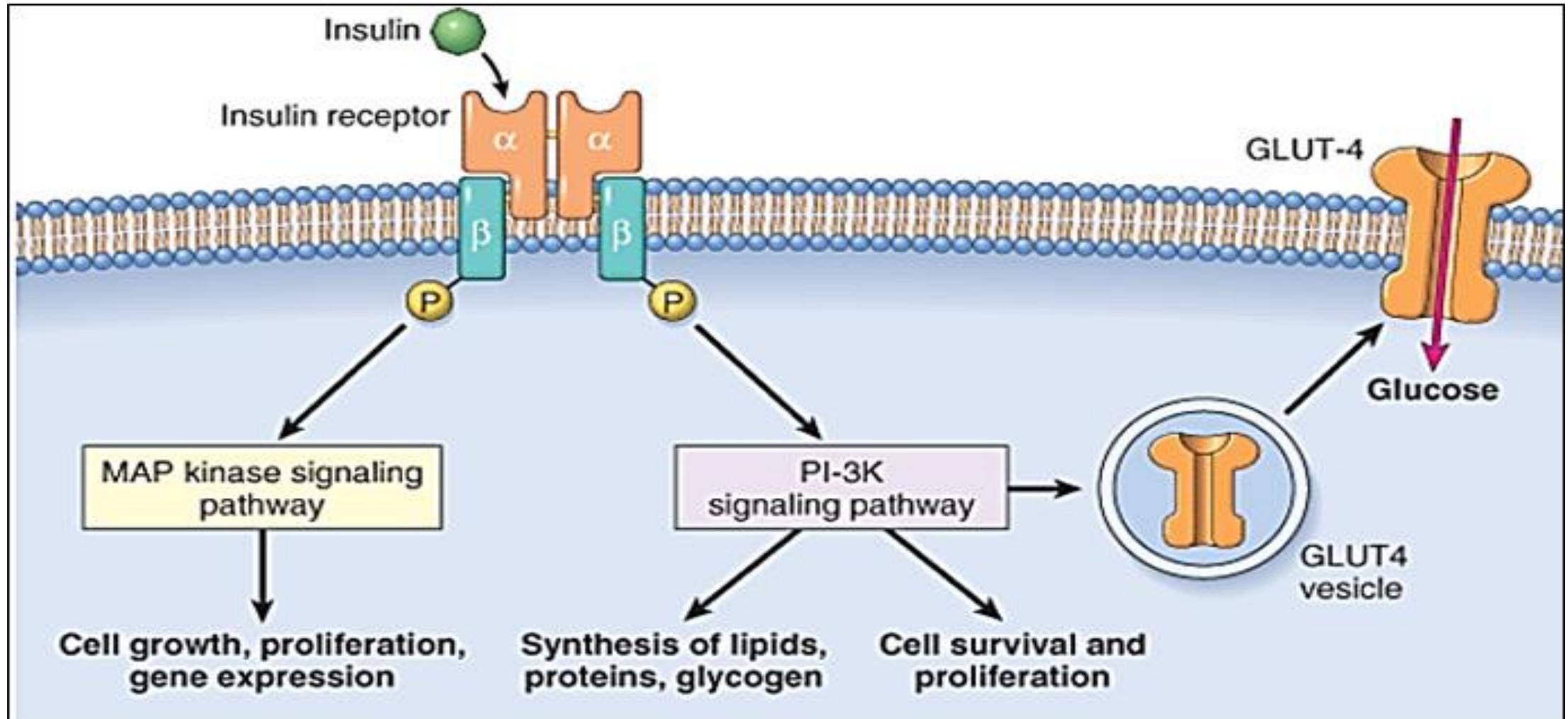
Indications of insulin:

❑ **Type 1 DM.**

❑ **Type 2 DM in some conditions:**

➤ *After failure of oral drugs.*

➤ *"stress conditions" e.g. infections, surgery, or pregnancy.*

❑ **Diabetic ketoacidosis (DKA):**

➤ regular insulin is the only type used **i.v.**

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.

- It should be injected with a standard U-100 syringe.
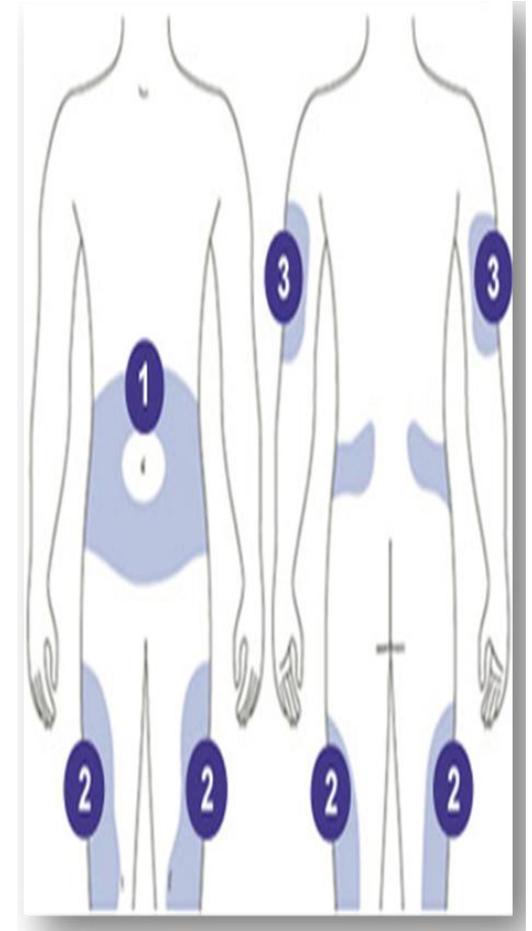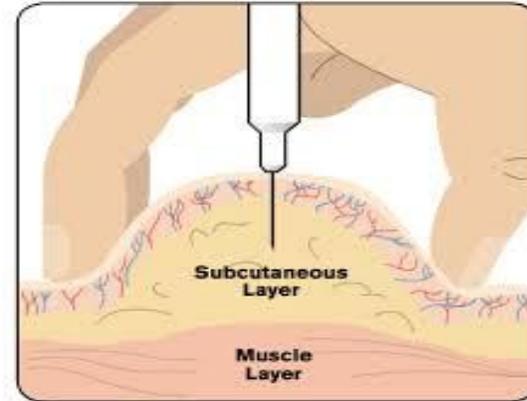
Insulin requirement

- A total daily dose 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.
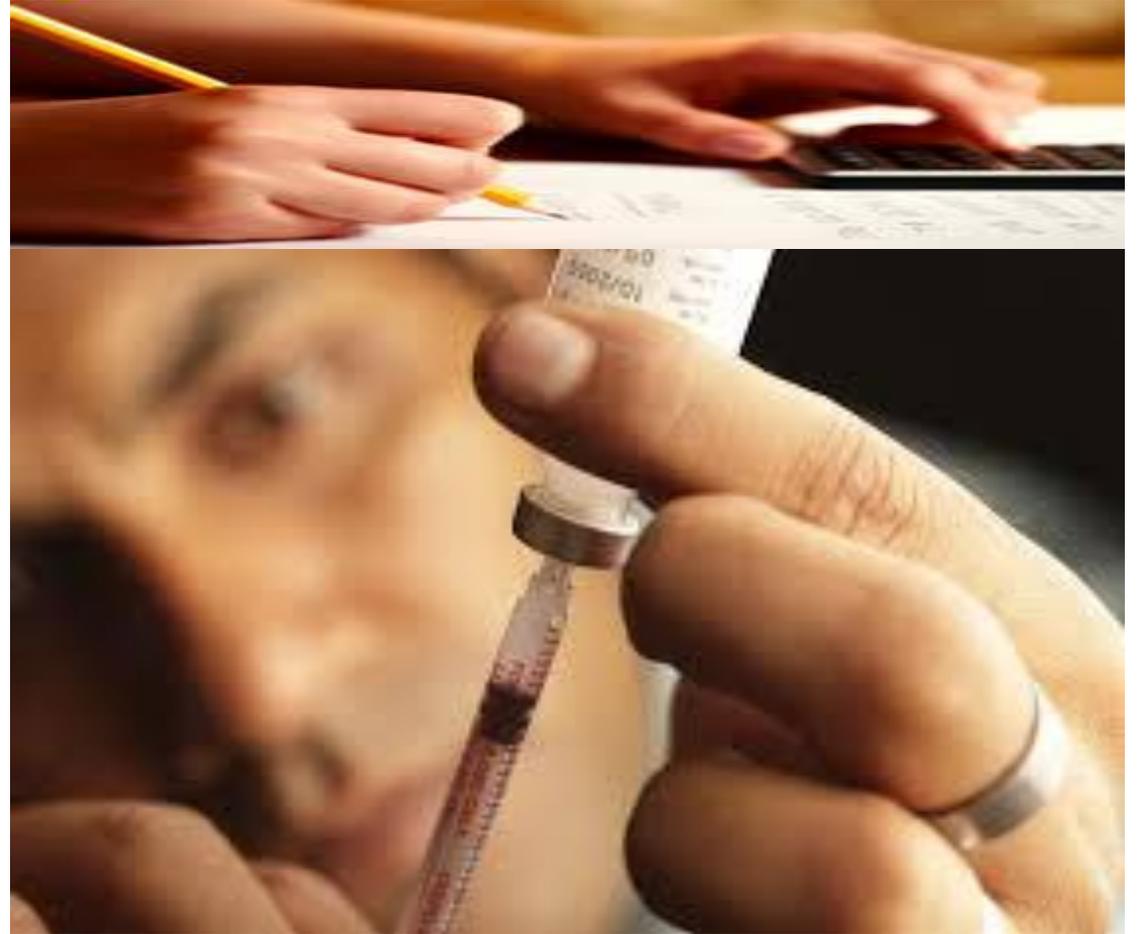
- **<u>Basal-Bolus regimen:</u>**

- 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 (50% of total).

- The **short acting** insulin controls postprandial hyperglycemia (10-20% for each).
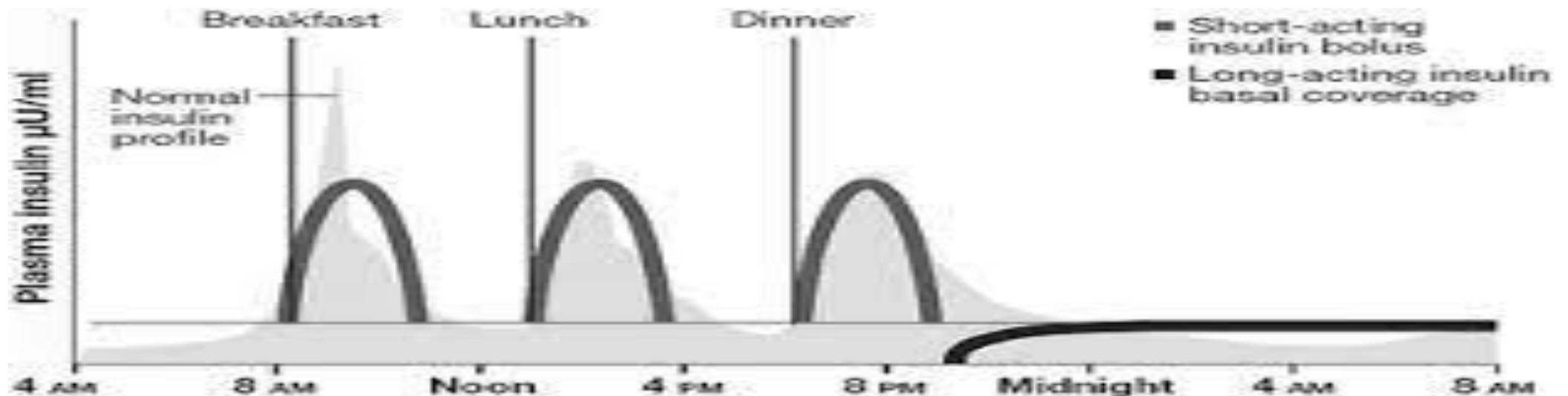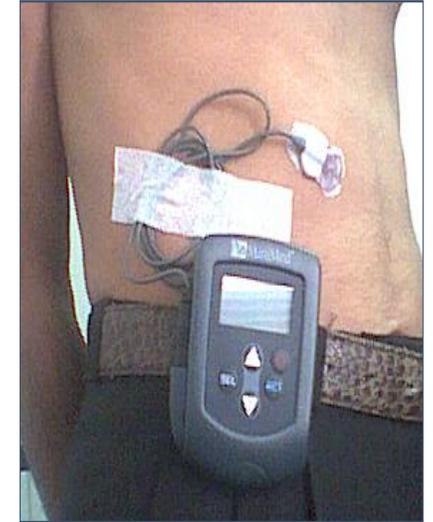
Twice-daily biphasic insulin regimen

- Use biphasic insulin.
   Give the 2/3 of the TDD in the morning
    and the 1/3 at evening.
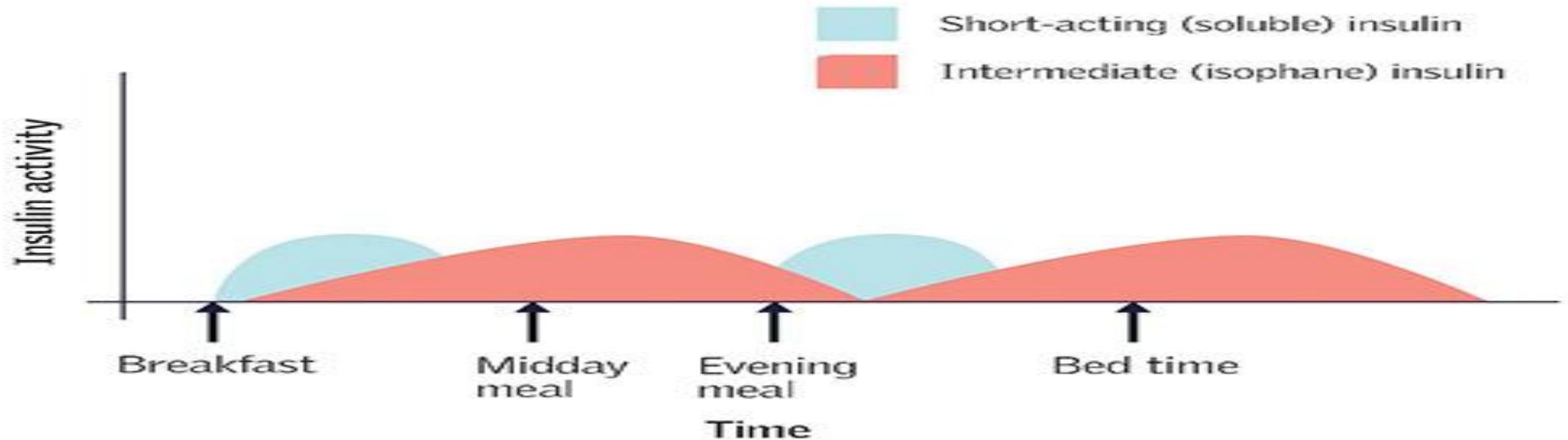
❑**Methods of administration:**

➢S.c. injection (using insulin syringes).

➢Portable pen injector.

➢Pump.

❑**Follow up of insulin therapy:**

➢From **capillary** blood glucose level

➢using portable glucometers

➢Self-Monitoring of Blood Glucose (**SMBG**)

Side effects of insulin:

❑ **Hypoglycemia:** the most common and dangerous side effect.
* **Causes:** Large dose of insulin or Missed meal while taking insulin.
* **Treatment:**

❖If the patient is conscious or semiconscious
   → give him sugar solution.

❖If the patient is in deep coma:
   (1) i.v. glucose
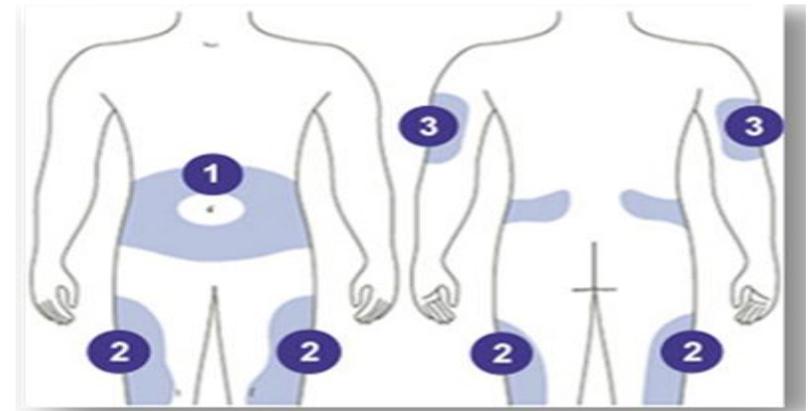   (2) Glucagon i.m.

❑ **Hypersensitivity reactions:**
   urticaria, angioedema or anaphylactic shock.

❑ **Lipodystrophy:**
   (atrophy or **hypertrophy)**of
   S.C. tissue after repeated injections.
   prevented by changing the injection site.

Insulin resistance (IR)

❑**Definition:** failure of the body cells to respond to either endogenous or exogenous insulin. As a result, larger doses of insulin are required to give the desired response.

❑**Causes:**

- The metabolic syndrome - Obesity.

- Pregnancy - Severe infection or stress.

- Drugs: e.g. corticosteroids.

❑**Treatment:**

➢**Life-style modification:** - Weight reduction – Physical exercise.

➢**Correction of any precipitating factor:** e.g. **infection** or **stress**.
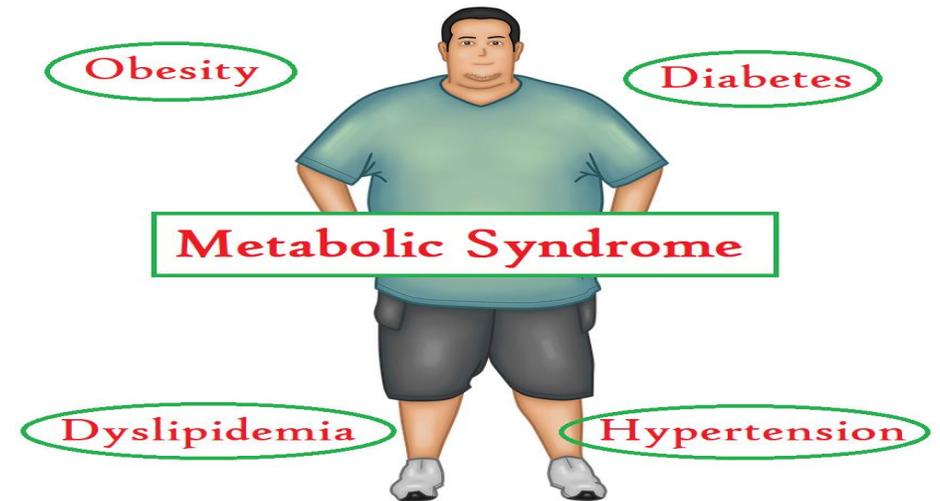
Case Discussion/reflection

➤ This young man has type 1 diabetes mellitus and thus requires replacement insulin therapy in the form of basal bolus regimen using short-acting human insulin or insulin analogs as bolus insulin for prandial coverage and long-acting insulin analogs or neutral protamine Hagedorn (NPH) for basal coverage.

➤ Based on the economic status of this patient, he can be advised regular insulin with each meal and bedtime NPH.

➤ He can be started on 0.5 U/kg/day of total insulin dose which can be split into 40% dose as NPH bedtime and 60% regular insulin for prandial coverage (20% before breakfast, lunch, and dinner).

➤ He must be educated on dietary plan, physical activity, SMBG, and hypoglycemic symptoms.

➤ The insulin has to be titrated based on SMBG reading every 2–3 days.

Q1

Insulin causes reduction in blood sugar level by the following mechanisms, EXCEPT:

a) Increased glucose uptake in the peripheral tissue

b) Reduction of breakdown of glycogen

c) Diminished gluconeogenesis

d) Decreased glucose absorption from the gut

Q2

Insulin can not be administered by:

a) Oral route

b) Intravenous route

c) Subcutaneous route

d) Intramuscular route.

Q3

Correct statements about crystalline (regular) insulin include all of the following, EXCEPT:

a) It can serve as replacement therapy for juvenile-onset diabetes

b) It can be administered intravenously

c) It is a short-acting insulin

d) It can be administered orally

Q4

Diabetic coma is treated by the administration of:

a) Lente insulin

b) Glucose

c) Crystalline insulin

d) Oral anti-diabetic drugs.

Q5

The following is peakless insulin preparation:

A. Regular insulin.

B. NPH insulin.

C. Zinc insulin.

D. Insulin galrgine.

E. Lispro insulin

Q6

Which of the following is an important effect of insulin?

A. Increased conversion of amino acids into glucose

B. Increased gluconeogenesis

C. Increased glucose transport into cells

D. Inhibition of lipoprotein lipase

E. Stimulation of glycogenolysis

Q7

Which of the following agents should be administered to achieve rapid control of the severe ketoacidosis in a diabetic boy?

A. Regular insulin

B. Glyburide

C. Insulin glargine

D. NPH insulin

E. Tolbutamide

Q8

Which of the following is the most likely complication of insulin therapy?

A. Hypoglycemia

B. Increased bleeding tendency

C. Pancreatitis

D. Severe hypertension

Q9

The following regimens is Most appropriate for tight control of diabetes mellitus:

A. Morning injections of mixed insulin lispro and insulin aspart.

B. Evening injections of mixed regular insulin glargine.

C. Morning and evening injections of regular insulin, supplemented by small amounts of NPH insulin at mealtimes.

D. Evening injections of insulin glargine, supplemented by small amounts of insulin lispro at meal times.

Q10

- **The following is a long acting insulin preparation:**
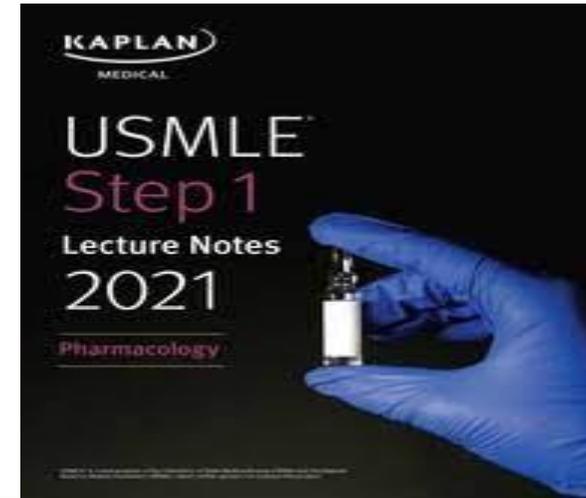
    A. Regular insulin.
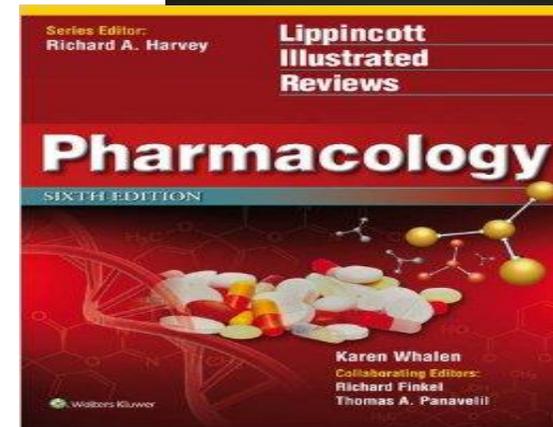
    B. NPH insulin.

    C. Insulin detemir

    D. Lispro insulin

References or further readings

1) Kaplan USMLE STEP1, lecture notes Pharmacology latest edition.

2) Lippincott's illustrated review: Pharmacology, latest edition

Thank you