Common Clinical Conditions in Pediatric Endocrinology:

1. Type 1 Diabetes.

2. Congenital adrenal hyperplasia.

3. Congenital hypothyroidism.

Approach to a Newly-Diagnosed Diabetic Patient

Definition of Diabetes mellitus :

- A metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both.

Classification:

- **Type 1 diabetes :**

- **Type 2 diabetes:**

- **Other specific types:**

  - specific genetically defined forms of diabetes.

  - diabetes associated with other diseases or drug use.

Diagnosis:

- FPG ≥ 126 mg/dL

or

- Random PG ≥ 200 mg/dL + symptoms of diabetes

or

- 2hr PG in a 75-g OGTT ≥ 200 mg/dL

Genetics:

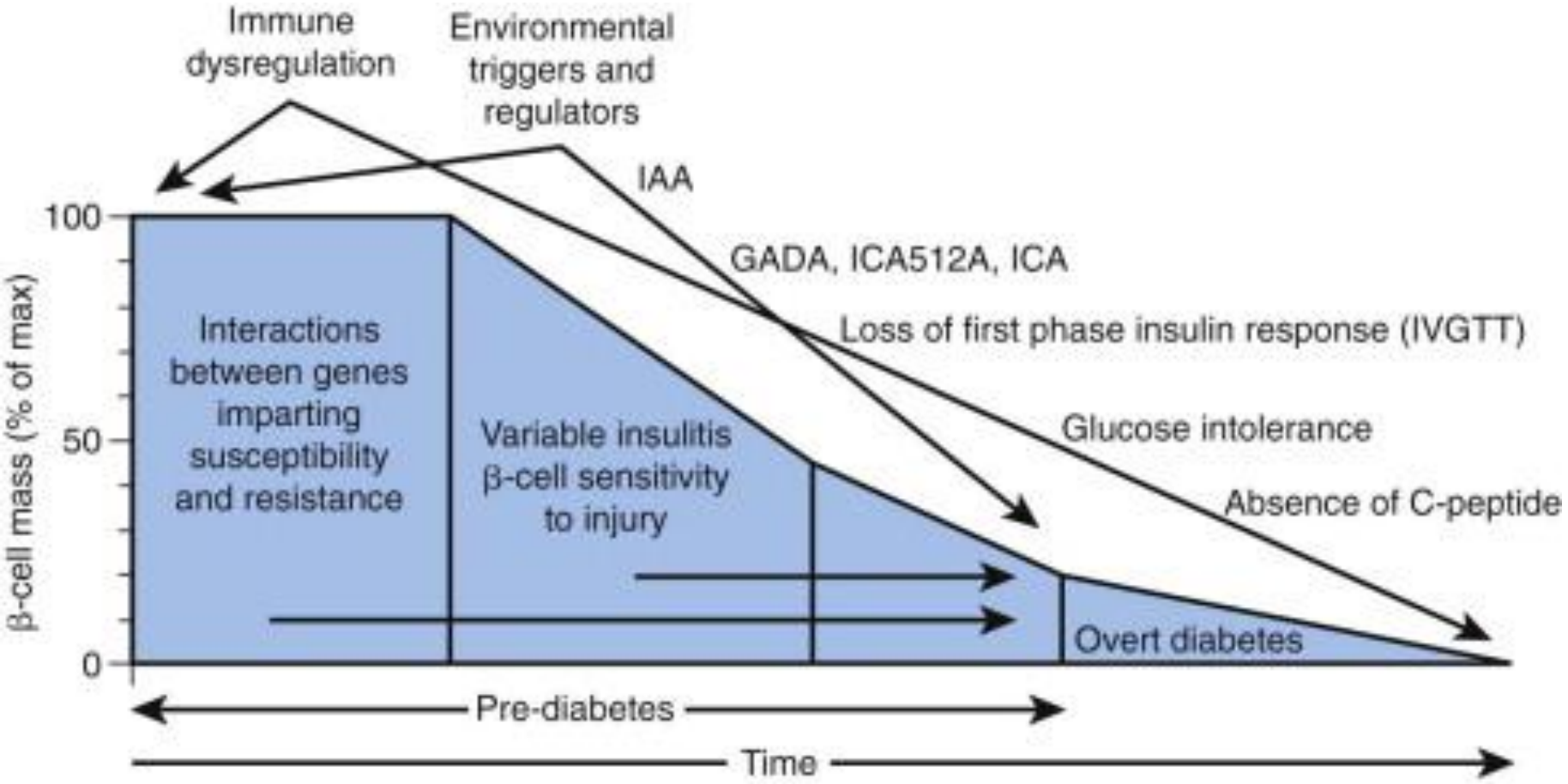
- Familial clustering of T1DM:
  - monozygotic twins 30-65%
  - dizygotic twins 6-10%
  - siblings 6%
  - mother 2%
  - father 7%

- Monogenic Type 1 Diabetes Mellitus: Rare
  ex. IPEX syndrome and APS

Environmental Factors:

- ~ 50% of monozygotic twins are discordant for T1DM.
- Variation in urban and rural areas populated by the same ethnic group.
- Change in incidence with migration.
- Increase in incidence in almost all populations in the last few decades.

Pathogenesis of type 1 diabetes :



Insulin

- Secreted by beta cells of pancreas
- Inhibits glycogenolysis and gluconeogenesis in liver
- Stimulates protein synthesis and lipogenesis
- Inhibits lipolysis and proteinolysis

Absence of Insulin

- ⇓ lipogenesis + ⇑ lipolysis
- ⇓ protein synthesis + ⇑ proteinolysis
- ⇑ glycogenolysis + ⇑ gluconeogenesis

Clinical Manifestations:

- Polyuria, polydipsia, polyphagia
- weight loss
- Fatigability

- DKA as first presentation.

- Progression may be accelerated by intercurrent illness or stress.

Diabetic Ketoacidosis

- The end result of the metabolic abnormalities resulting from a severe deficiency of insulin.

- DKA is 100% preventable.

- Occurs due to:
  - Non compliance to insulin therapy

    or
  - Intercurrent illnesses not managed according to the sick day management guidelines.

Diagnosis of DKA:

- Glucose > 200 mg/dL
- pH < 7.3
- Ketonuria or ketonemia
- Serum Bicarbonate < 18 mmol/L

Maturity onset diabetes of the young (MODY):

- A heterogeneous group of disorders that result in β-cell dysfunction.
- It is rare, accounting for just 1%–2% of all diabetes.

- It is often misdiagnosed as type 1 or type 2 diabetes, as it is often difficult to distinguish MODY from these two forms.

GENETIC DEFECTS OF **β-CELL FUNCTION**
Maturity-Onset Diabetes of Youth

- Onset 9-25 yr,
- AD inheritance
- A primary defect in insulin secretion.
- Diagnostic Criteria:
  - Diabetes in at least 3 generations with AD
  - Diagnosis before age 25 yr in at least 1 affected subject.

Insulin Therapy:

Endogenous Insulin Profile

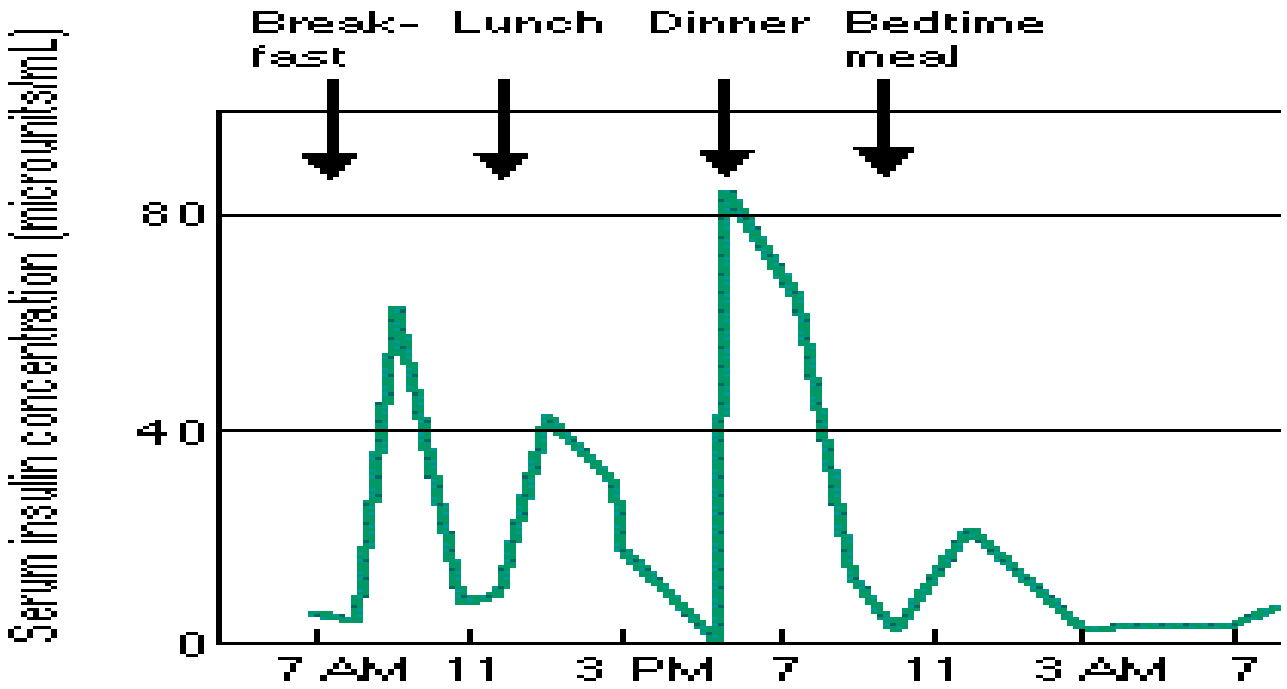
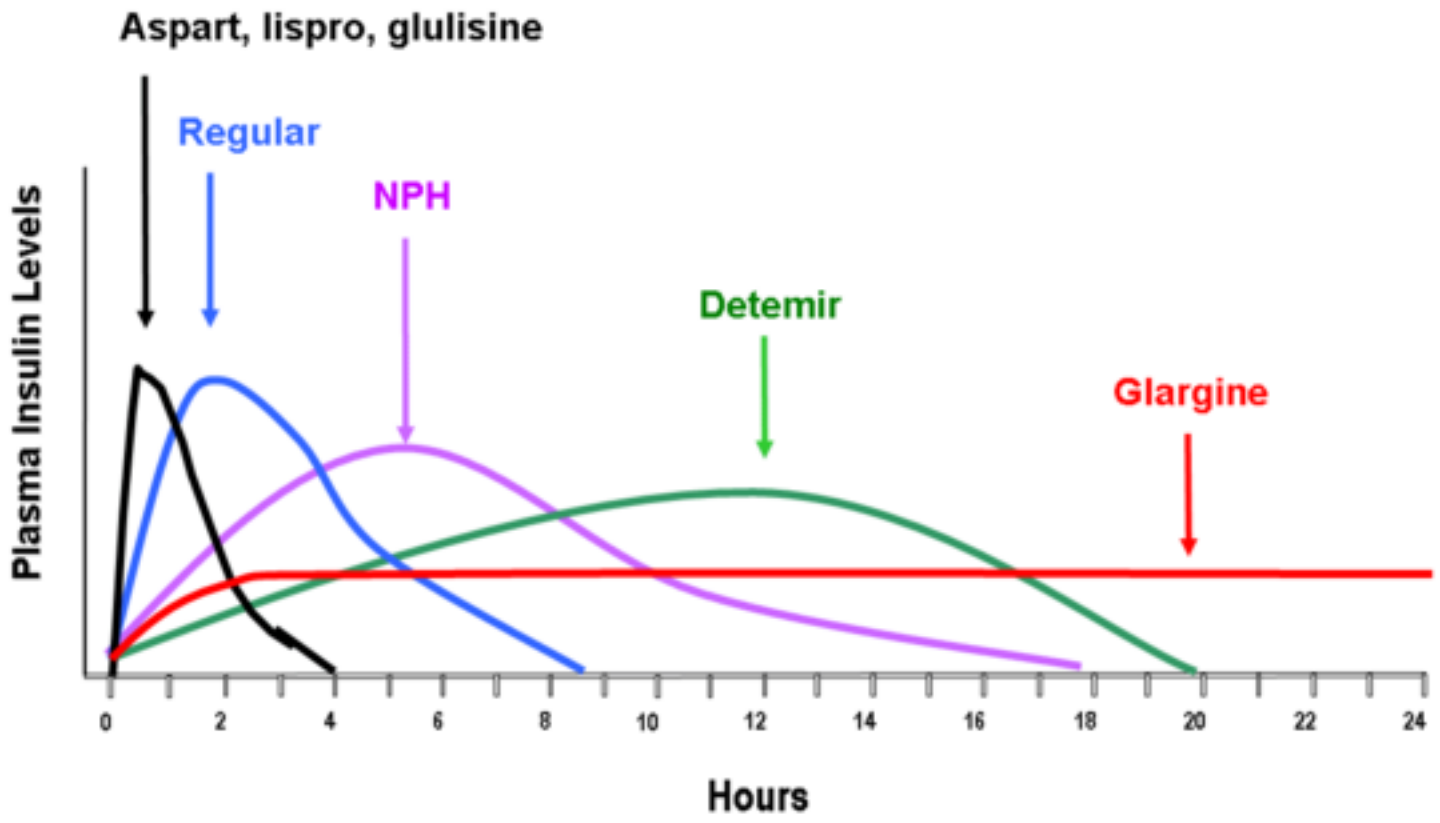


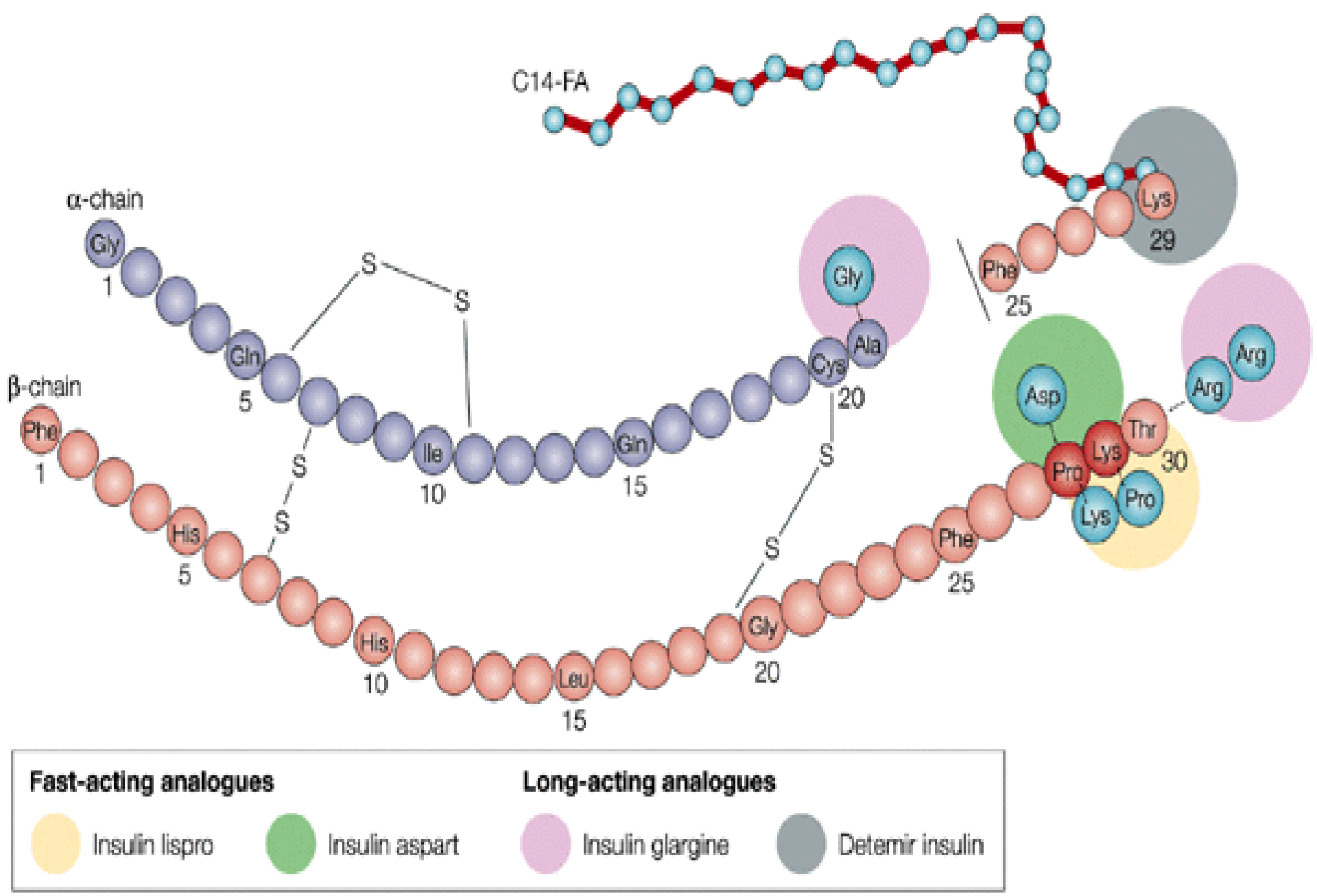
Figure 1. Normal insulin secretion. In the stimulated phase, serum insulin levels increase from within a few minutes before to 30 minutes after a meal. Return to basal level occurs within 2 hours.

Adapted from Galloway and Chance (5).

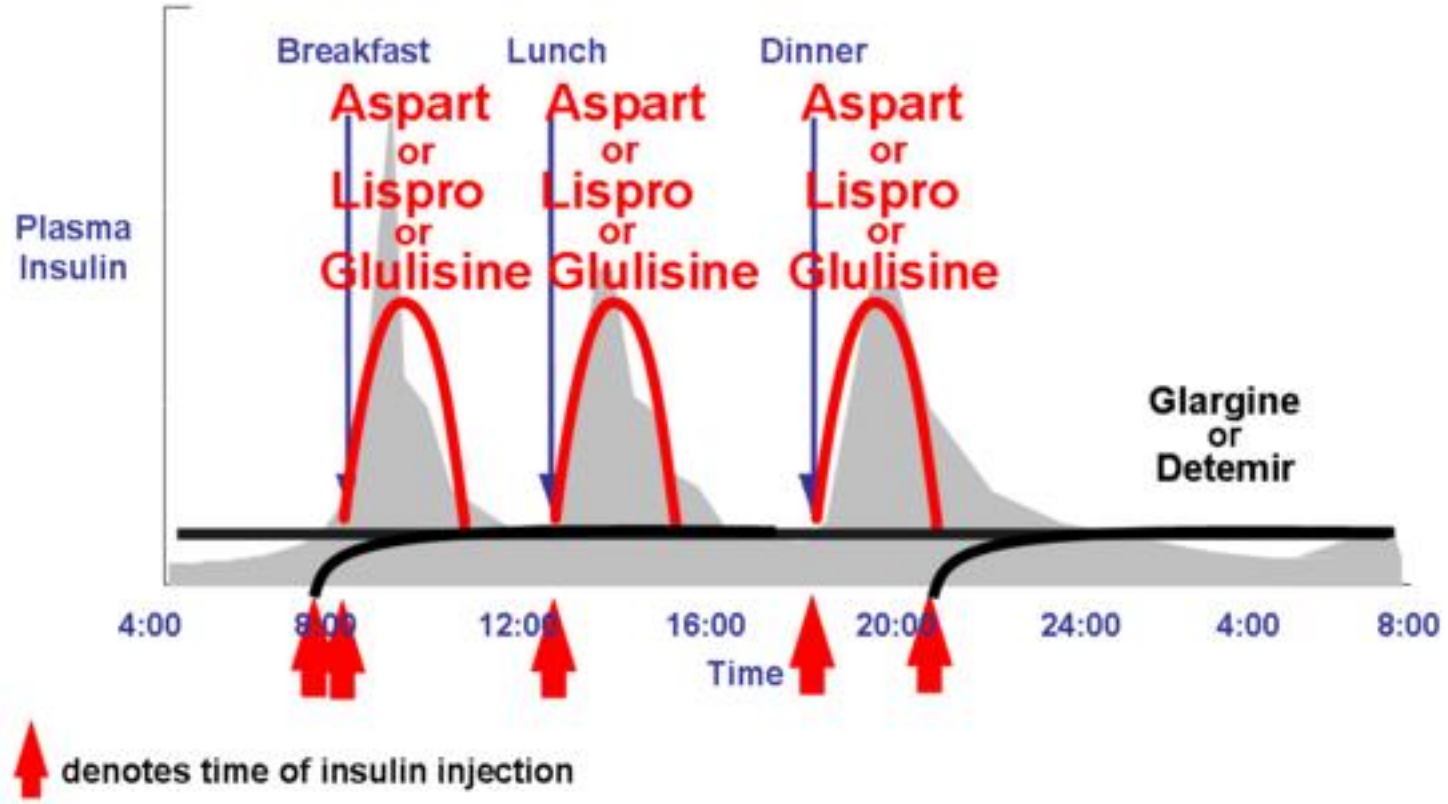
Galloway et al Horm Metab Res 1994

Idealized insulin time-action profiles




C14-FA
α-chain
Gly
1
Gln
5
S
S
Ile
10
Gln
15
Cys
20
Gly
Ala
β-chain
Phe
1
His
5
S
S
His
10
Leu
15
Gly
20
S
S
Phe
25
Phe
25
Lys
29
Asp
Pro
Lys
Pro
Thr
30
Arg
Arg
Fast-acting analogues
Insulin lispro
Insulin aspart
Long-acting analogues
Insulin glargine
Detemir insulin

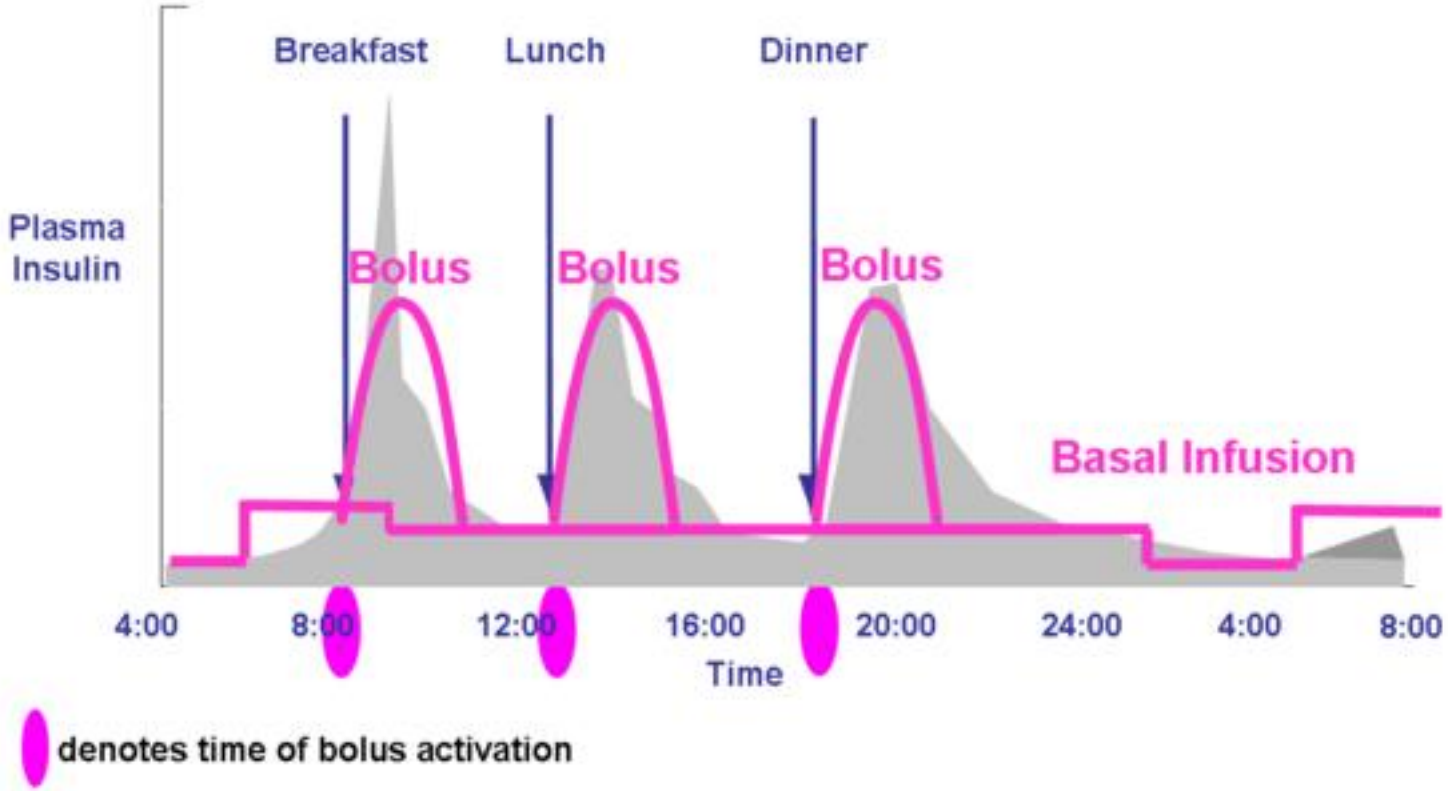
Long **and Rapid- acting insulin**



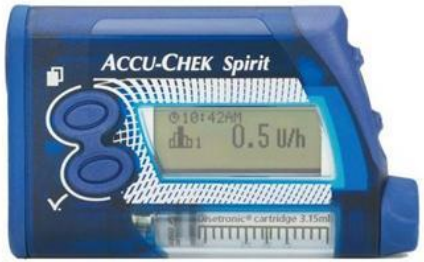
Insulin Syringes:

Insulin Pens :

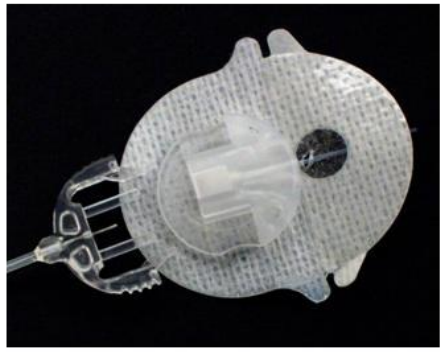
Continuous subcutaneous Insulin Infusion (insulin pump):

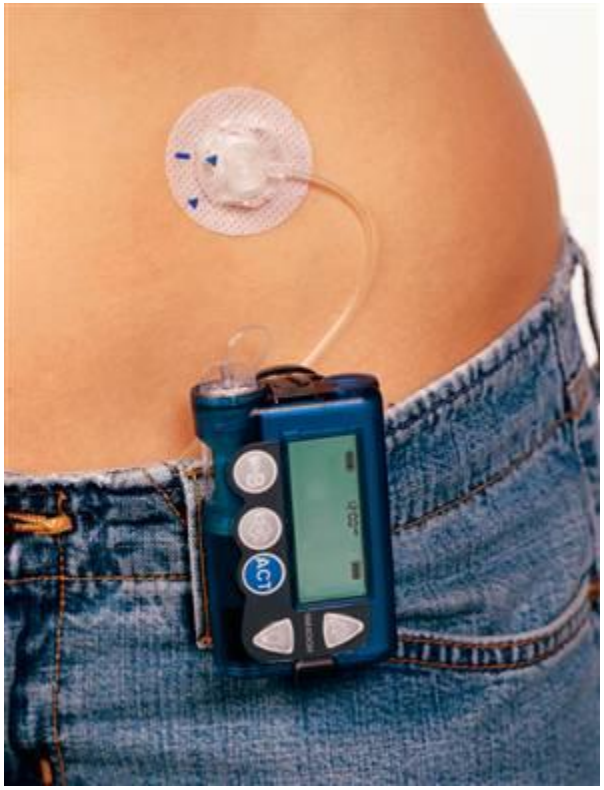


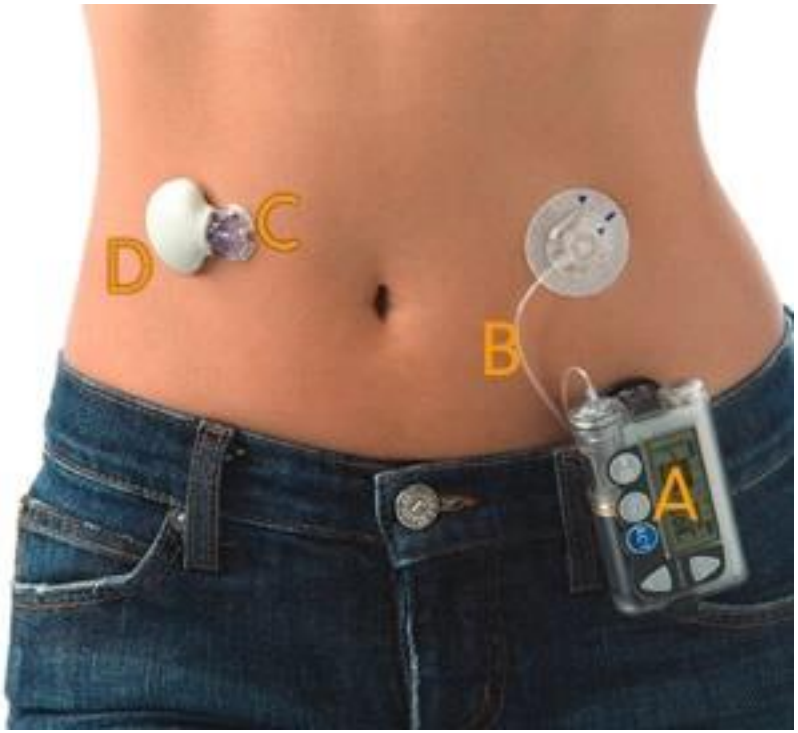
Insulin Pump:



Inserting insulin pump:






D
C
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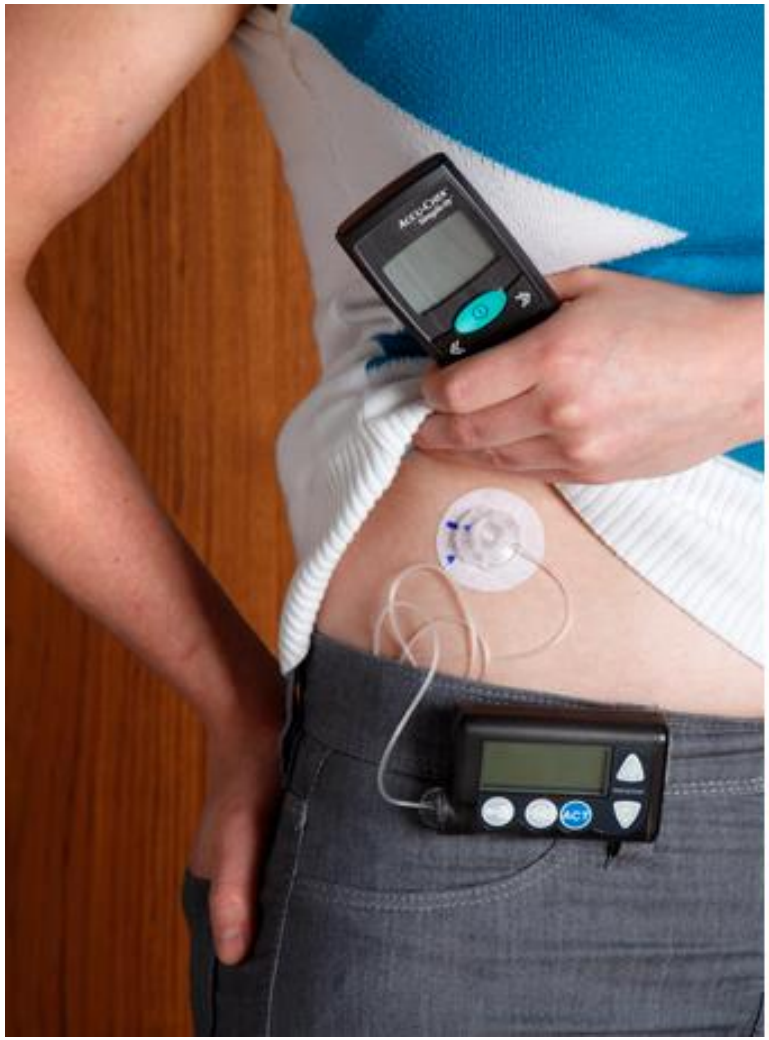
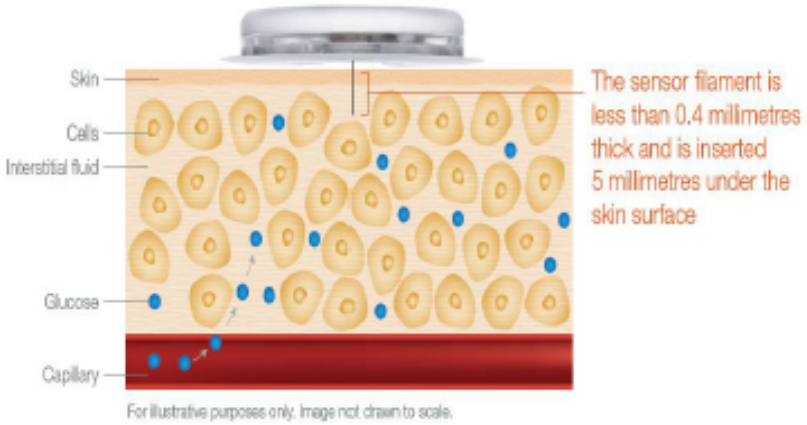


Glucose monitoring system

Monitoring Glucose with Interstitial Fluid

- The FreeStyle Libre system measures glucose in the interstitial fluid, or ISF (the fluid between the body's cells).
- Glucose in ISF has been shown to be a reliable indicator of glucose levels in blood because glucose freely diffuses from capillaries to the interstitial space.[1]
- The FreeStyle Libre sensor contains glucose-sensitive reagents that measure glucose in the ISF continuously.
- Glucose diffusion between capillary and ISF is shown to have a short lag of 5-10 minutes.[2]



1. Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? *Diabetes Technology Ther.* 2000;2(3):461-472. 2. Rebrin K, Sheppard NF Jr, Steil, GM. Use of subcutaneous interstitial fluid glucose to estimate blood glucose: Revisiting delay and sensor offset. J Diabetes Sci Technol. 2010;4(5): 1087-1098.

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HbA1c :

- A reliable index of long-term glycemic control .
- the fraction of hemoglobin to which glucose has been nonenzymatically attached in the blood stream.
- A HbA1c measurement reflects the average blood glucose concentration from the preceding 2-3 mo.

Hypoglycemia

Symptoms of Low Blood Sugar Include:

- Hunger
- Trembling
- Sweating
- Extreme Mood changes
- Extreme tiredness
- Pale
- Dizziness
- Blurred Vision
- Headaches

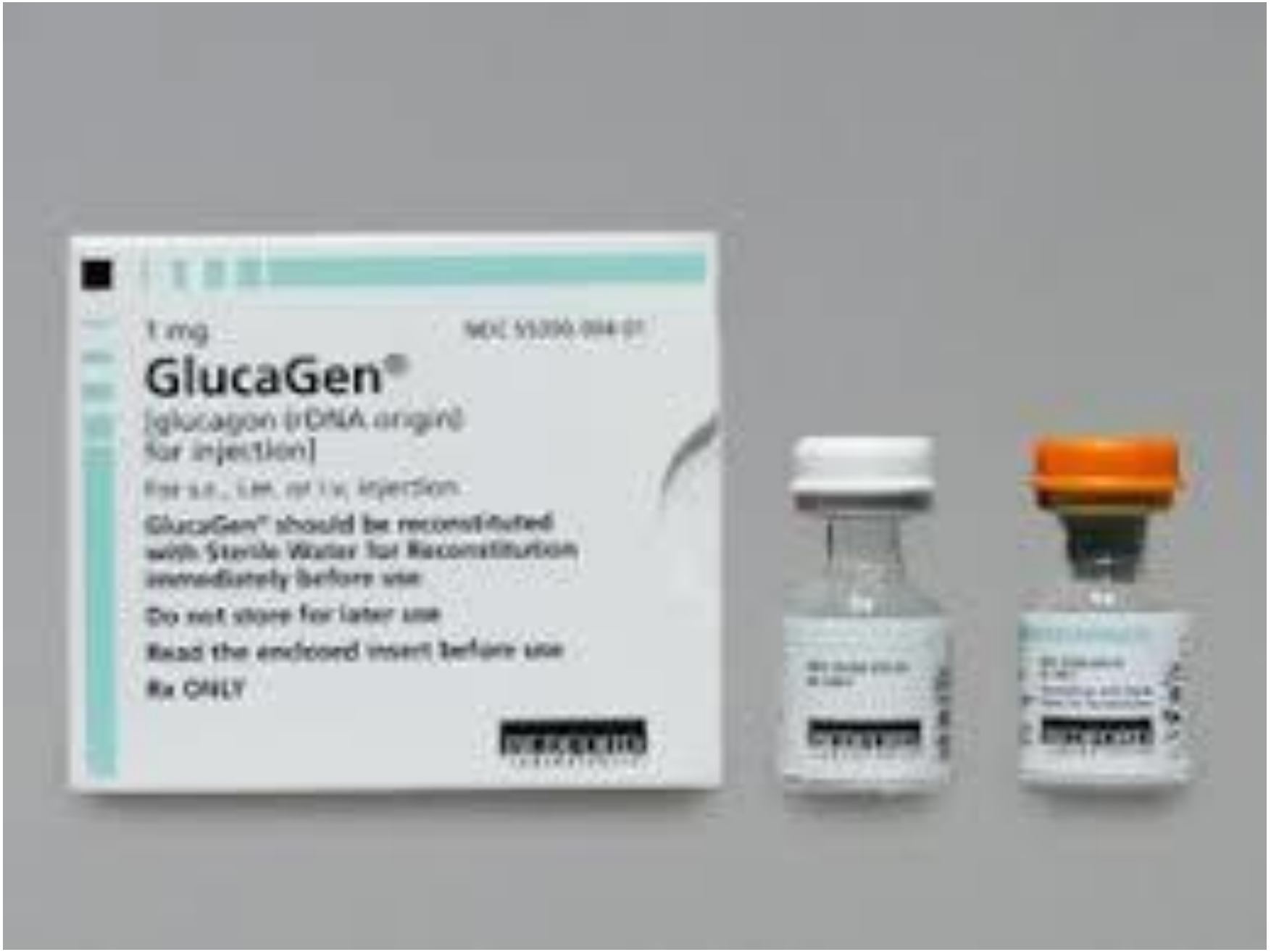
Hypoglycemia

- These symptoms will always preceede NEUROGLYCOPENIA except in long standing type 1 diabetes/hypoglycemia unawareness.

- Action : confirm blood sugar is less than 72 mg/dL and TREAT WITH CARBOHYDRATE

Hypoglycemia

- Make sure the family has GLUCAGON and knows how to use it


1 mg
GlucaGen®
[glucagon (rDNA origin)
for injection]
GlucaGen® should be reconstituted
with Sterile Water for Reconstitution
immediately before use
Do not store for later use
Read the enclosed insert before use
Rx ONLY

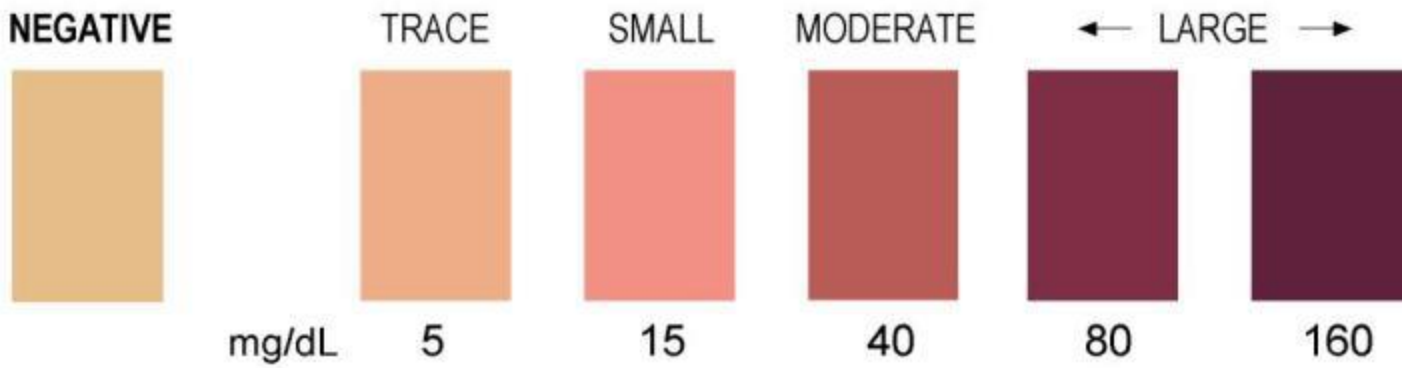
Sick Day Management

- Counter-regulatory hormones blunt insulin action and elevate glucose levels.
- Frequent blood glucose and ketone monitoring with adjustment of insulin doses.
- The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis.
- **DO NOT OMIT INSULIN.**

Intercurrent Illness

- Check ketones EARLY
  - Always test when nausea or vomiting
  - Urine ketodiastix
  - Precision Xtra meter: Earlier detection, no need to collect urine

KETONE-Read at exactly **15 seconds.**



Comorbid Conditions:

- **Autoimmune thyroid disease**

  - 15-30% of individuals with type 1 diabetes .

- **Celiac disease:**

  - 4 to 9% of children with type 1 diabetes.
  - 60 to 70% are asymptomatic.

- **Addison disease:**

  - rare.

ISPAD guidelines for retinopathy and nephropathy screening:

- Annually from age 11 years with after 2 years duration

And

- from 9 years with 5 years duration

Congenital Adrenal Hyperplasia

Salt-Losing Crisis in Infancy:

- - Severe hyponatremic dehydration
  - Hyperkalemia
  - Metabolic acidosis

- A life-threatening condition in infancy that requires immediate treatment to prevent death.

Differential diagnosis for salt-losing crisis:

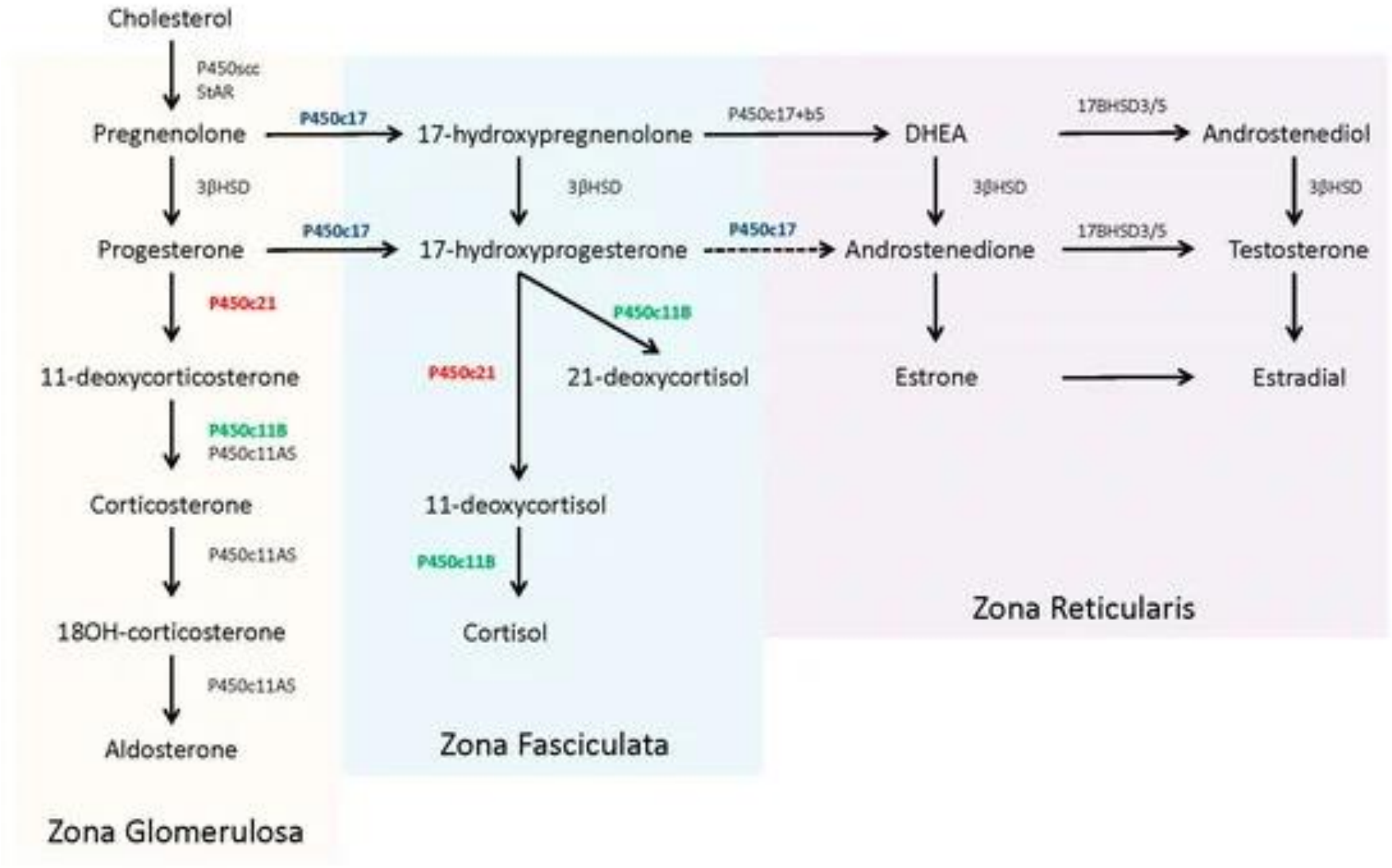
- Congenital adrenal hyp**er**plasia
- Congenital adrenal hyp**o**plasia
- Isolated aldosterone deficiency,
- Pseudohypoaldosteronism

- It is vital to identify this condition and to manage it appropriately, if not → it can result in death.

- All cases benefit from volume replacement.

- Glucocorticoid /mineralocorticoid replacement will not correct electrolyte abnormalities in all cases.

- 21-hydroxylase, deficiency of which is caused by mutations in the CYP21A2 gene:
- Results in defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol
- Accounts for more than 95 percent of cases of congenital adrenal hyperplasia.


Cholesterol
P450scc
StAR
Pregnenolone
P450c17
17-hydroxypregnenolone
P450c17+b5
DHEA
17BHSD3/5
Androstenediol
3βHSD
3βHSD
3βHSD
3βHSD
Progesterone
P450c17
17-hydroxyprogesterone
P450c17
Androstenedione
17BHSD3/5
Testosterone
P450c21
P450c11B
11-deoxycorticosterone
P450c21
21-deoxycortisol
Estrone
Estradial
P450c11B
P450c11AS
Corticosterone
11-deoxycortisol
P450c11AS
P450c11B
18OH-corticosterone
Cortisol
Zona Reticularis
P450c11AS
Aldosterone
Zona Fasciculata
Zona Glomerulosa

- Should treat hypotension, dehydration, correction of electrolyte imbalance and , and cortisol replacement.
- An intravenous bolus of 10 to 20 mL/kg of normal saline should be administered.
- An intravenous bolus of 2 to 4 mg/kg of 10 percent dextrose should be considered if there is significant hypoglycemia.
- Hyperkalemia should be corrected with the administration of glucose and insulin if necessary, although it typically improves rapidly as a result of the potent mineralocorticoid action of high-dose hydrocortisone.

- Mineralocorticoid replacement is not needed during treatment with stress doses of hydrocortisone.
- If the diagnosis of classic 21-hydroxylase deficiency is confirmed, infants should receive glucocorticoid and mineralocorticoid therapy and salt supplementation

Congenital Hypothyroidism

- Diagnosis of congenital hypothyroidism is extremely important.
- Delayed treatment would result in developmental delay within few months.
- Neonatal screening is essential as clinical manifestations are not evident early in life.

Epidemiology

- Prevalence of 1:3500 in white infants.
- Differ significantly among different ethnic groups.
- Female : Male ratio is 2 : 1.

Clinical manifestations of congenital hypothyroidism

- Most infants with C.H. are asymptomatic at birth.
- Birth weight and length are normal, but head size may be slightly increased.
- Prolongation of physiological jaundice may be the earliest sign.
- Decrease activity.
- Feeding difficulties.
- Respiratory difficulties.
- Constipation.
- Subnormal temperature .
- Slow pulse .

- Stunted growth. Short extremities.
- The AF and PF are opened widely.
- Coarse features.
- Protrusion of large tongue.
- Dry, scaly skin.
- Coarse, brittle and scanty hair.
- The muscles are usually hypotonic.

Actions of the thyroid hormones

- Increase the oxidative metabolism: -↑ oxygen consumption -↑BMR -↑glucose metabolism -↑ fat metabolism.
- Promote growth and development.
- Influence nervous system development and function. Essential for normal myelination and development of CNS.
- Augmentation of cardiac function.
- Important for normal reproductive function.

Causes of congenital hypothyroidism

A. Permanent primary hypothyroidism.

↓ T_4 ,↑ TSH .

1. Thyroid dysgenesis: 85% of permanent C.H.

- ectopy - agenesis. –hypoplasia. – hemiagenesis.

2. Thyroid dyshormogenesis :

-Goiter .

3. TSH resistance due to TSH receptor mutation.

B. Permanent central : ↓T4 ,↓ TSH or inappropriately NL TSH.

1. Developmental defect : pituitary or hypothalamic disorders. May have midline defects.

2. Inactivating mutations : - TRH receptor.

- TSH β subunit. – Pit. Transcription factors.

C. TRANSIENT :

1. Severe iodine deficiency.
2. Acute iodine overload from iodine-containing antiseptic. – rare.
3. Maternal antithyroid drug treatment : clears in 3-4 days after birth.
4. Transplacental transfer of TSH-receptor blocking antibodies: - ↓T4, ↑TSH.
5. Hypothyroximia of prematurity:

   -↓T4, ↓T3, NL TSH.

   - adaptation to prematurity rather than true central hypothyroidism.

- Treatment of congenital hypothyroidism:

- Oral Levothyroxine.

THANK YOU