

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 \geq 126 mg/dL

or

- Random PG \geq 200 mg/dL + symptoms of diabetes

or

- 2hr PG in a 75-g OGTT \geq 200 mg/dL

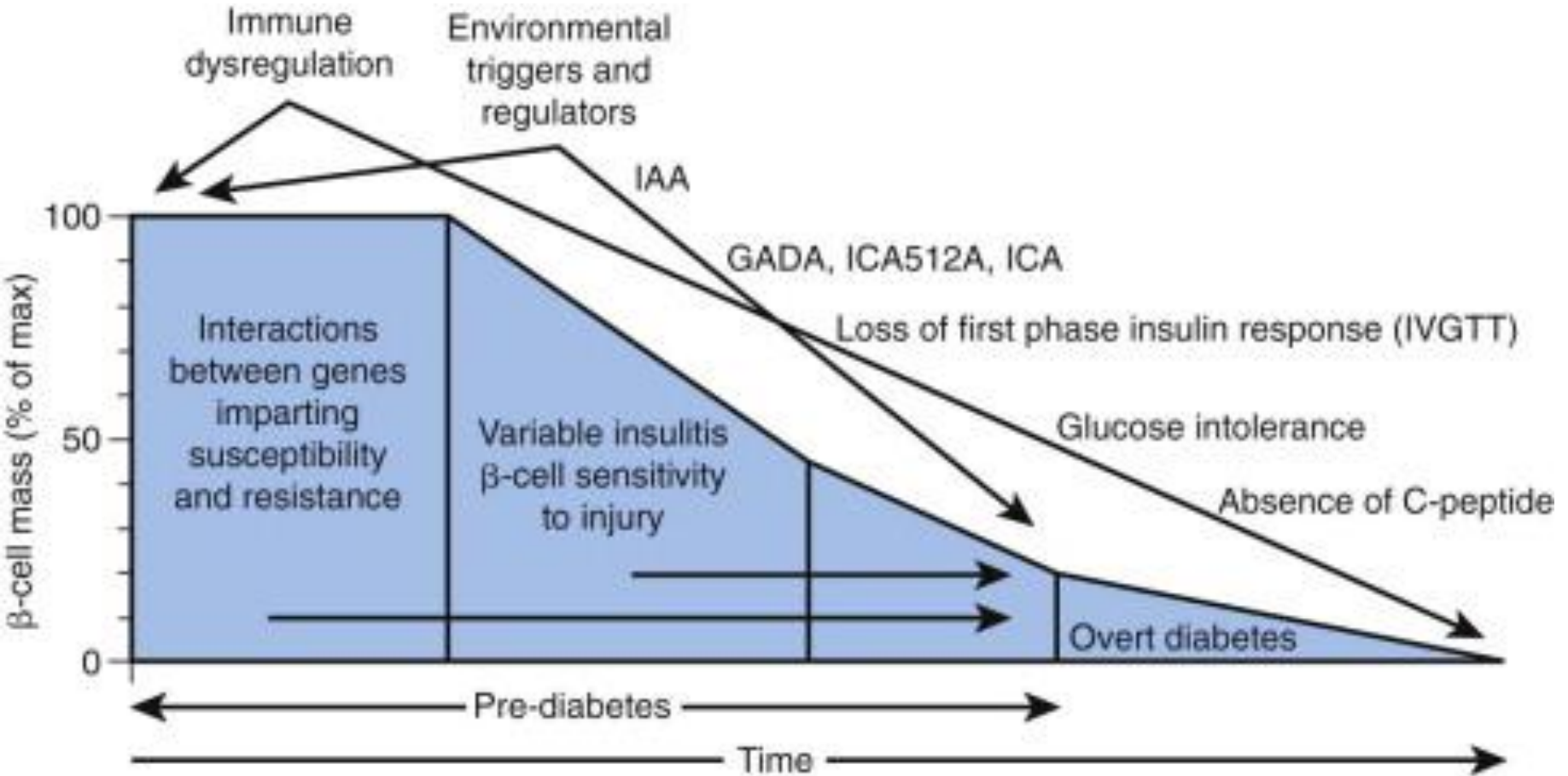
Genetics:

- 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 proteolysis

Absence of Insulin

- \Downarrow lipogenesis + \Uparrow lipolysis
- \Downarrow protein synthesis + \Uparrow proteinolysis
- \Uparrow glycogenolysis + \Uparrow 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

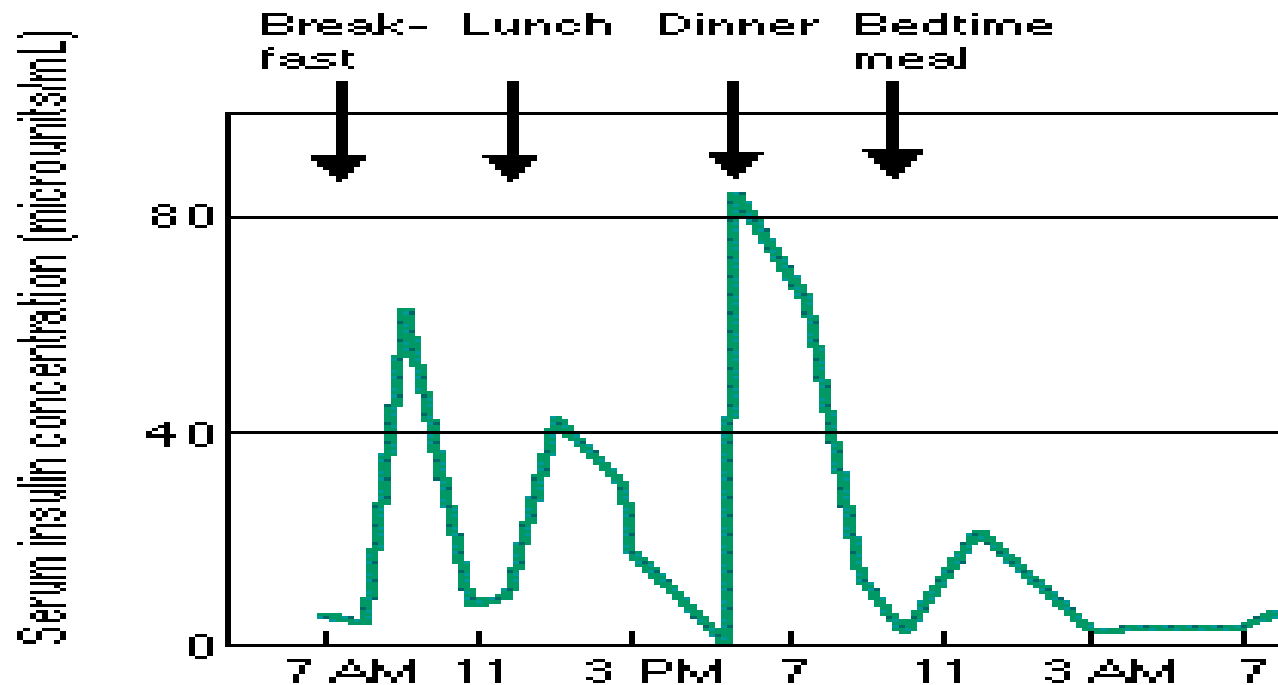
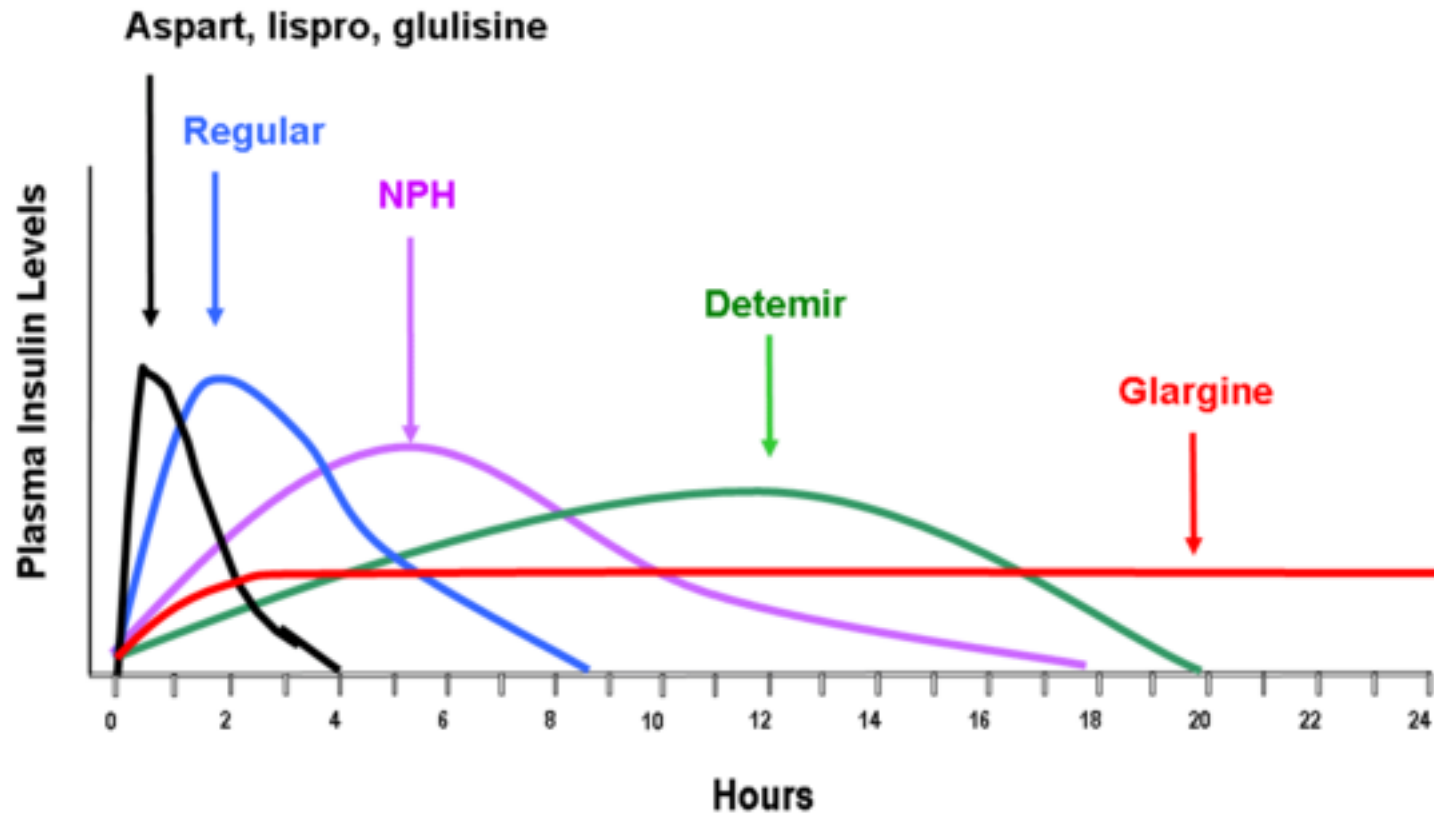
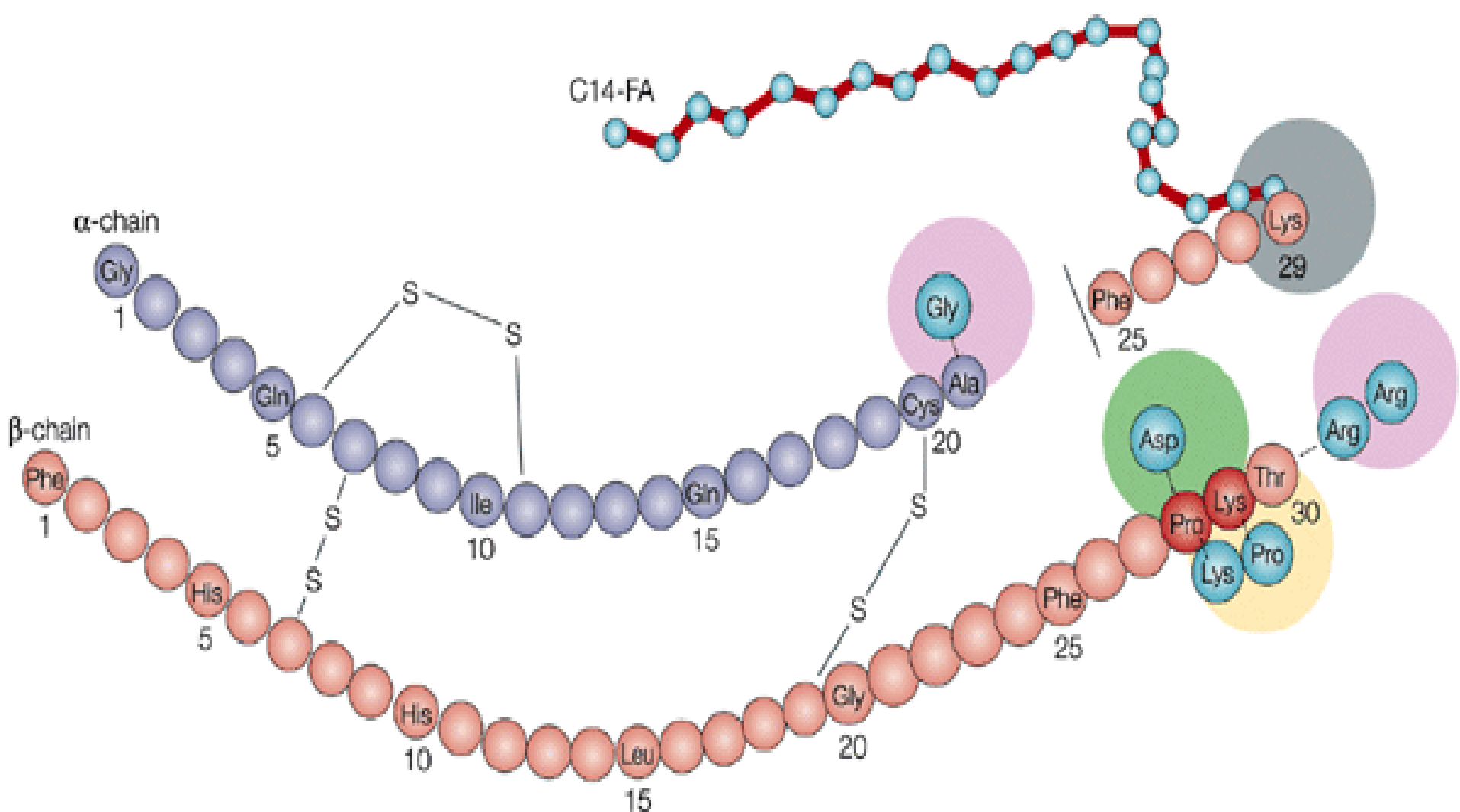


Figure 1. Normal insulin secretion. In the stimulated phase, serum insulin levels increase from within a few minutes before to 30 minutes after a meal. Return to basal level occurs within 2 hours.

Adapted from Galloway and Chance [5].

Idealized insulin time-action profiles





Fast-acting analogues

 Insulin lispro

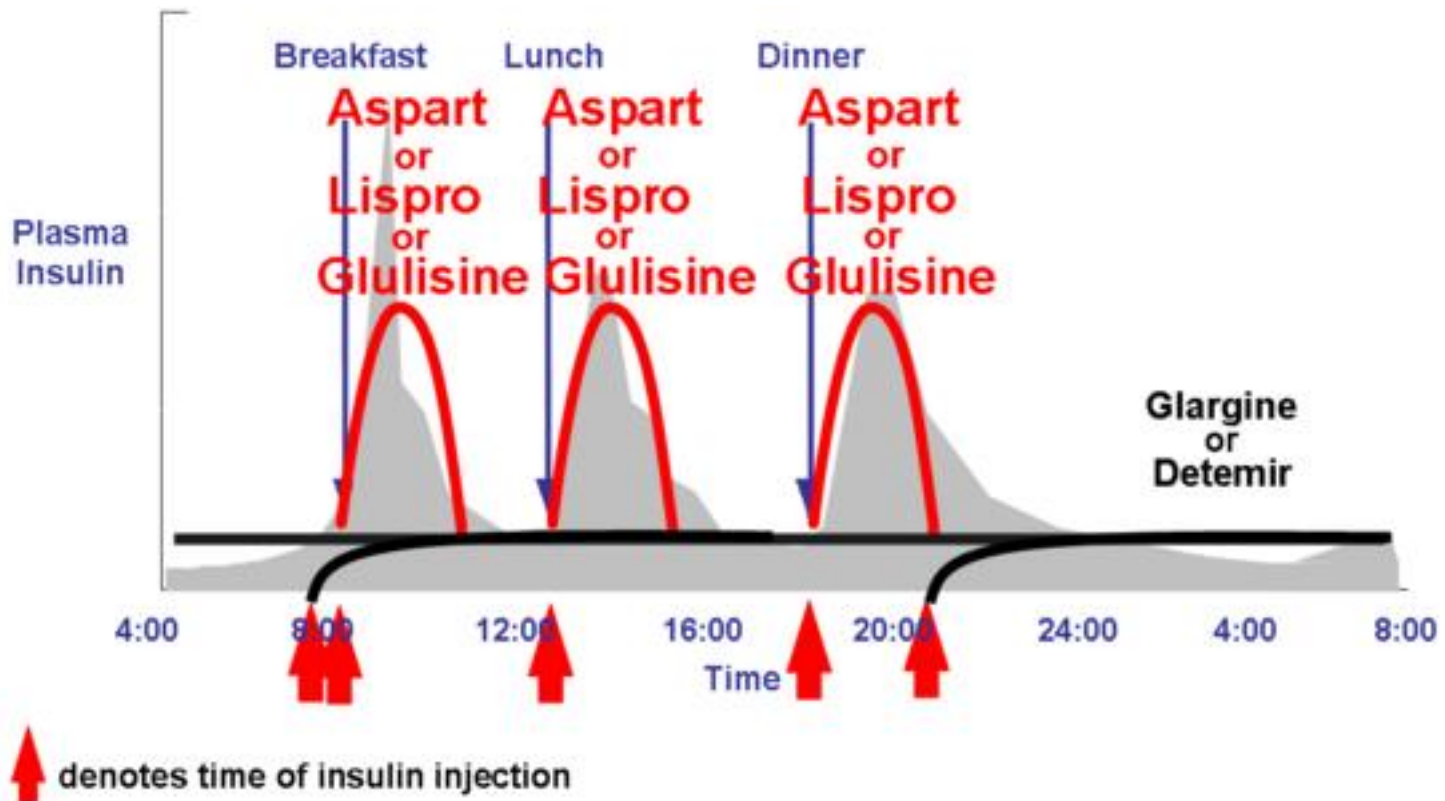
 Insulin aspart

Long-acting analogues

 Insulin glargine

 Detemir insulin

Long and Rapid-acting insulin



Insulin Syringes:

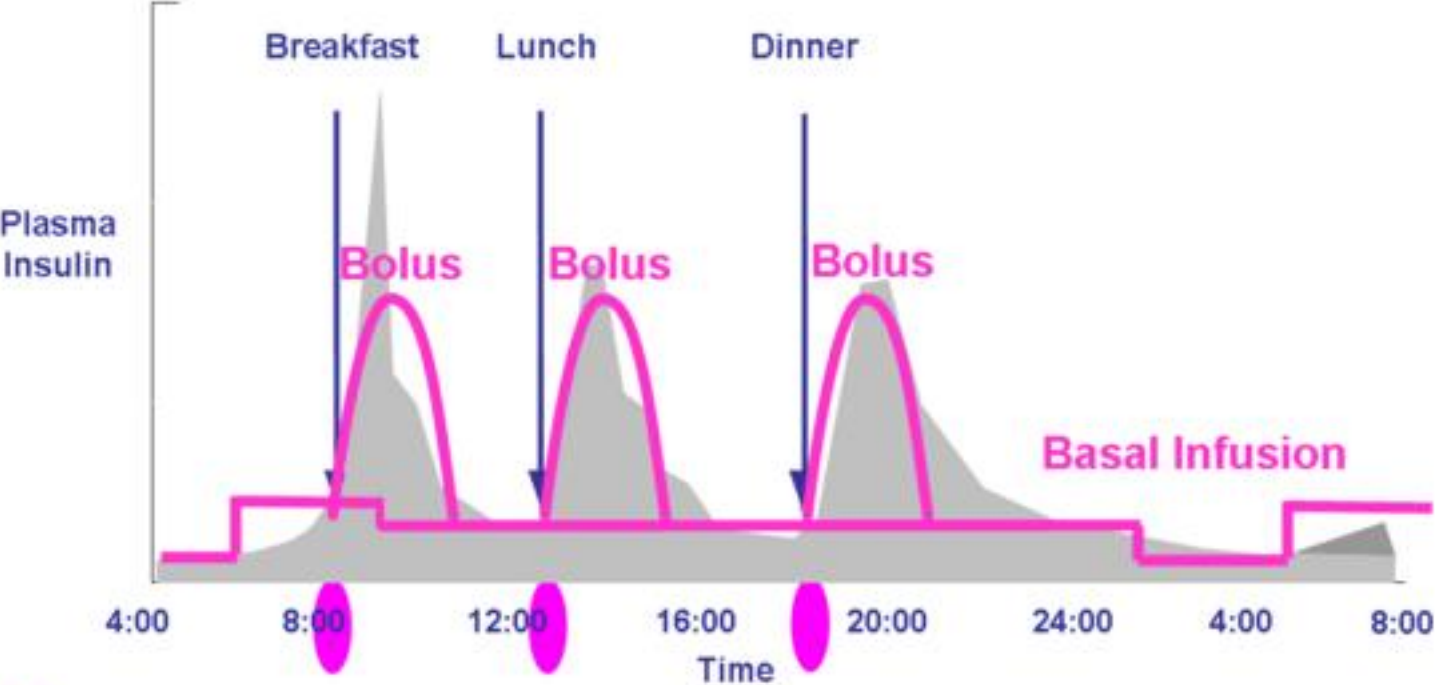



Insulin Pens :



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Continuous subcutaneous Insulin Infusion (insulin pump):

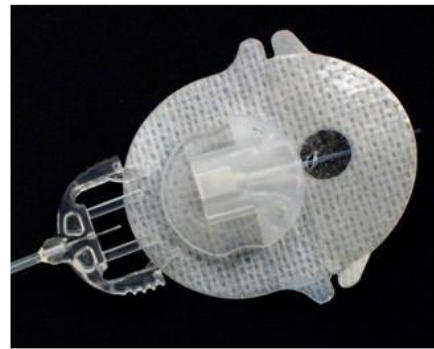


 denotes time of bolus activation

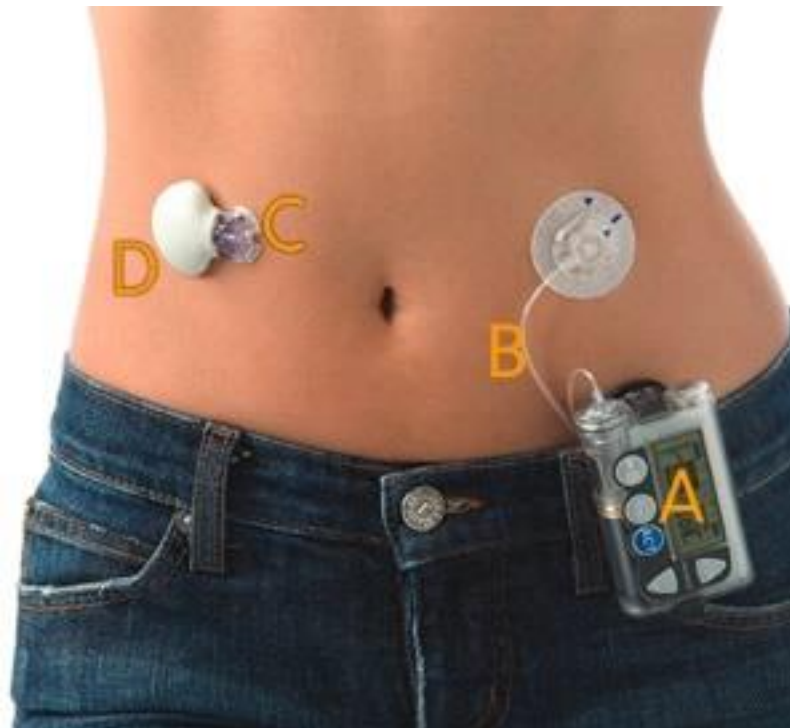
Insulin Pump:



Inserting insulin pump:







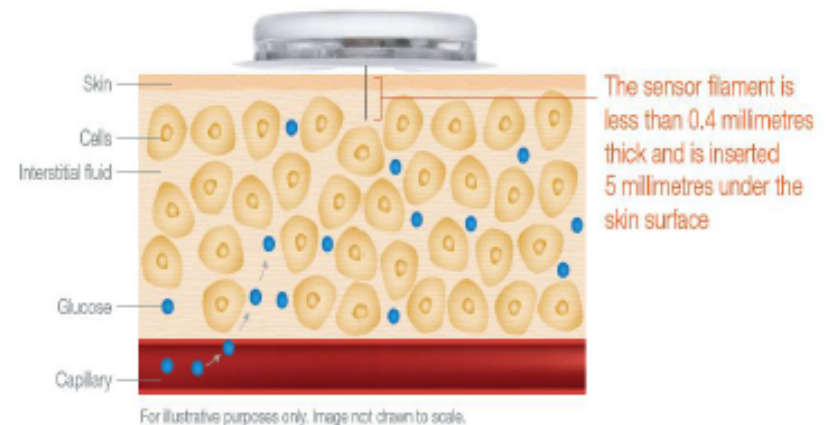


Glucose monitoring system



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.

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:

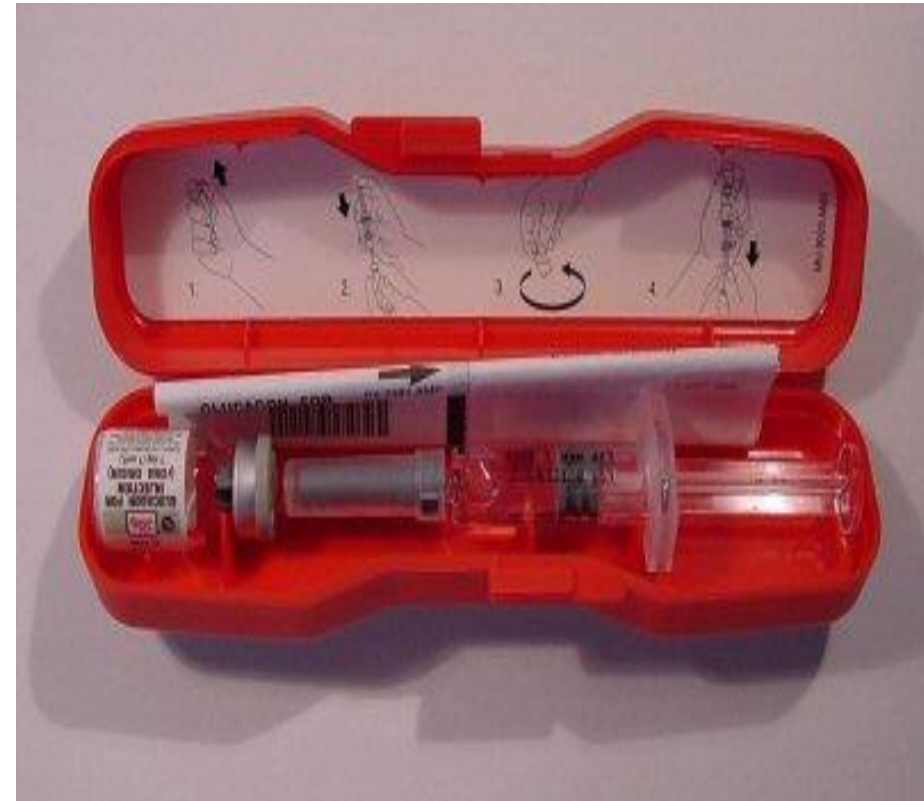
- Hunger
- Trembling
- Sweating
- Extreme Mood changes
- Extreme tiredness
- Pale
- Dizziness
- Blurred Vision
- Headaches

Hypoglycemia

- These symptoms will always precede 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

NEC 51390-044-01

GlucaGen[®]

[glucagon (rDNA origin)
for injection]

For s.c., i.m., or i.v. 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

AMGEN
Astellera



Sick Day Management

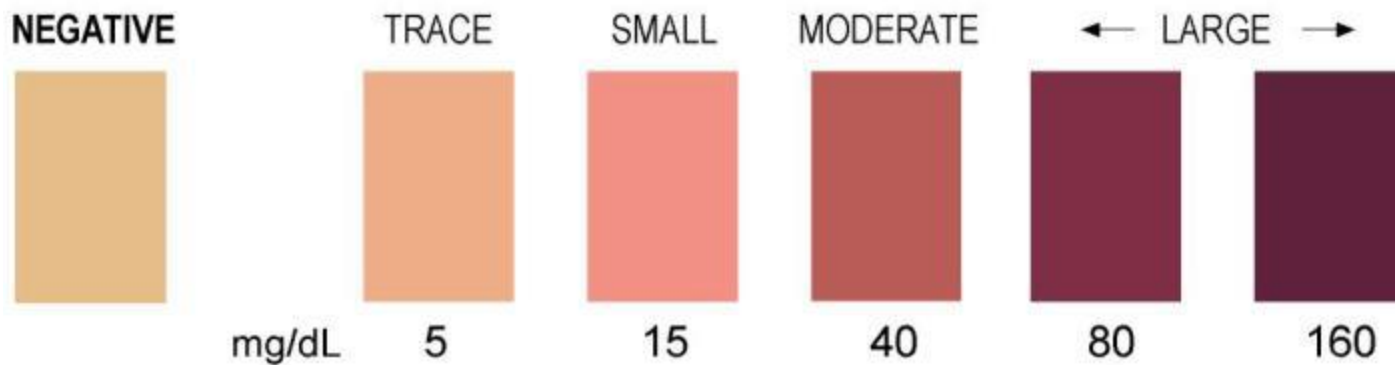
- Counter-regulatory hormones blunt insulin action and elevate glucose levels.
- Frequent blood glucose and ketone monitoring with adjustment of insulin doses.
- The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis.
- **DO NOT OMIT INSULIN.**

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 hypererplasia
- Congenital adrenal hypoplasia
- 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.

- 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.

↓ T₄, ↑ 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 : \downarrow T4 , \downarrow 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: - \downarrow T4, \uparrow TSH.
5. Hypothyroximia of prematurity:
 - \downarrow T4, \downarrow T3, NL TSH.
 - adaptation to prematurity rather than true central hypothyroidism.

- Treatment of congenital hypothyroidism:
 - Oral Levothyroxine.

THANK YOU