Common Endocrine Disorders in Children:

1. Approach for diagnosis and management of Type 1 Diabetes
2. Congenital adrenal hyperplasia
3. Congenital hypothyroidism

Approach to a Newly-Diagnosed Diabetic Patient

* Patient CKD + On dialysis → risk for pulmonary edema or metabolic acidosis → Presentation: Tachypnea and SOB

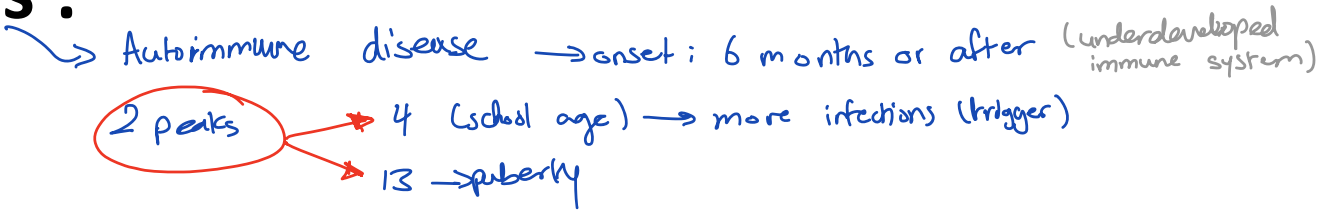
→ Treatment: Give Ca^{2+} then Bicarb

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 → convert to mmol/L by ÷18

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

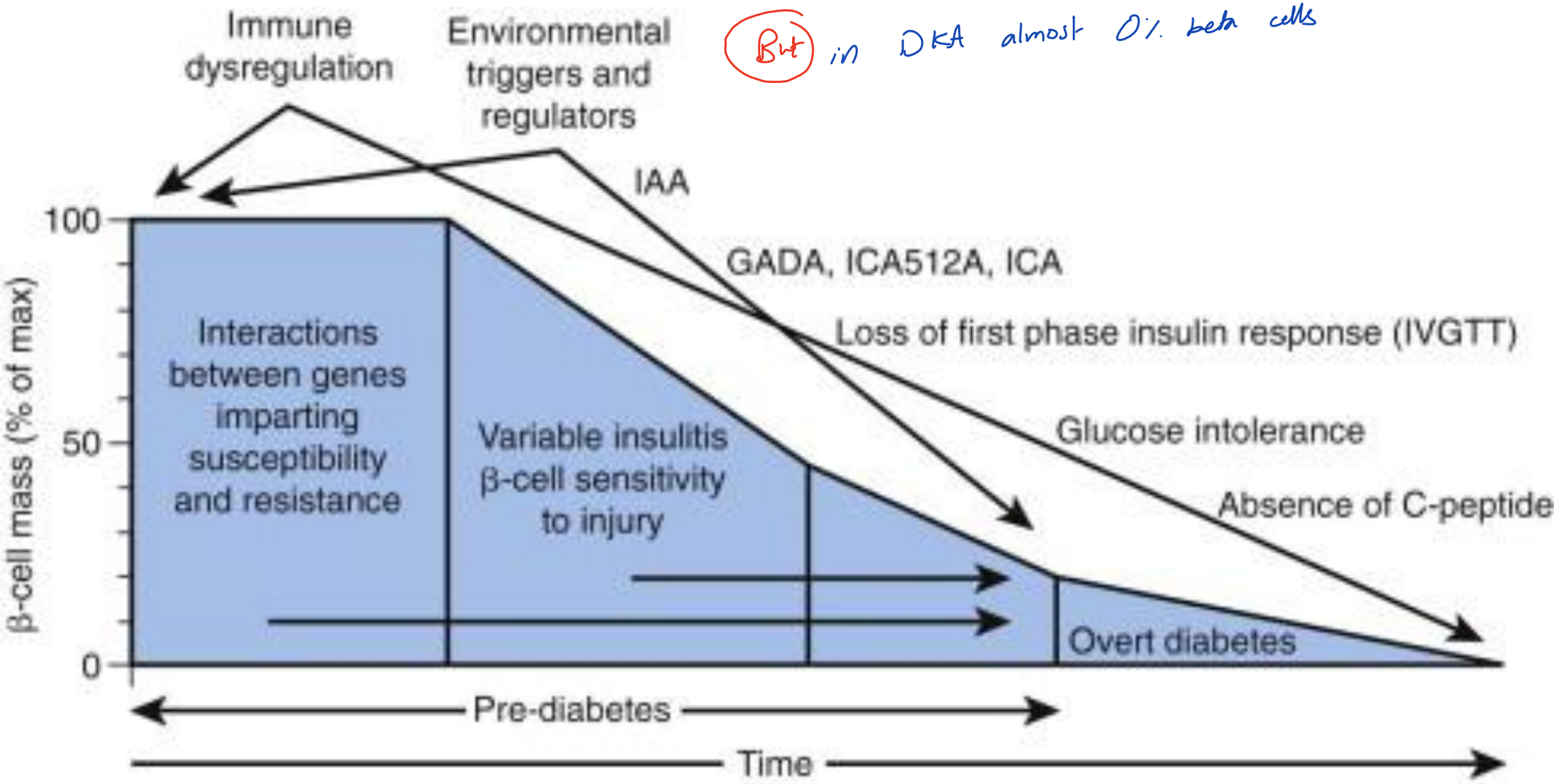
Environmental Factors:

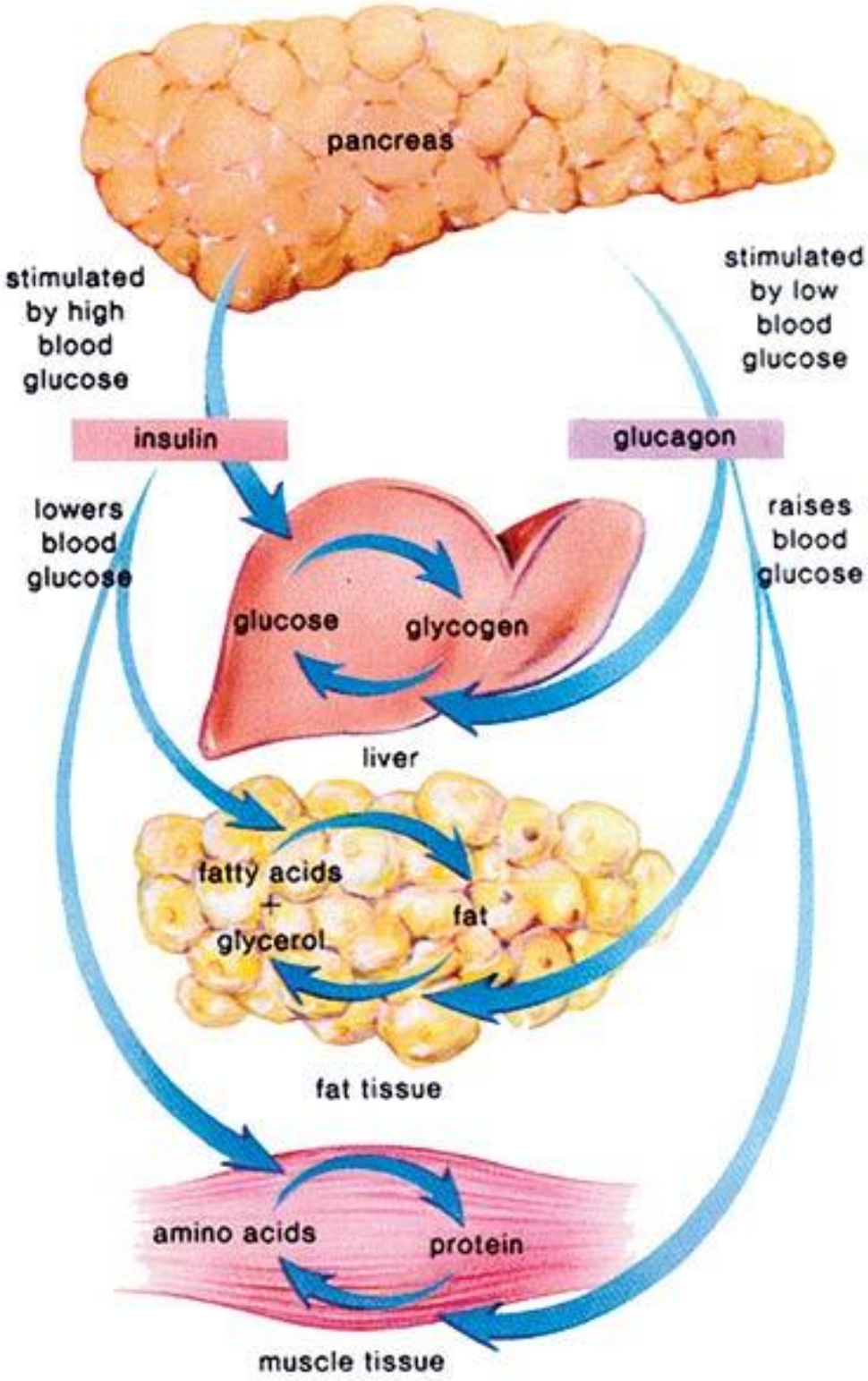
- ~ 50% of monozygotic twins are discordant for T1DM.
- Variation in urban and rural areas populated by the same ethnic group.
- Change in incidence with migration.
- Increase in incidence in almost all populations in the last few decades.

Pathogenesis of type 1 diabetes :

* When Beta cells < 10% → onset of DM symptoms

But in DKA almost 0% beta cells




pancreas
stimulated by high blood glucose
stimulated by low blood glucose
insulin
glucagon
lowers blood glucose
raises blood glucose
glucose
glycogen
liver
fatty acids + glycerol
fat
fat tissue
amino acids
protein
muscle tissue

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

Counter-regulatory Hormones:						
	↓ insulin secretion	↓insulin action	↑Glycog-enolysis	↑Glucon-eogenesis	↑Lipolysis, ketogenesis	↓ glucose utilization
Epinephrine	+	+	+	+	+	+
Cortisol		+	+	+	+	+
GH		+	+	+	+	+
Glucagon			+	+	+	

Clinical Manifestations:

- Polyuria, polydipsia, polyphagia
- weight loss
- Fatigability

- DKA as first presentation.

- Progression may be accelerated by intercurrent illness or stress. (triggers)

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.

or wrong site for injection (lipohypotrophy)
or inappropriate storage.

DKA – History:

1. Polyuria , polydipsia, weight loss
2. Abdominal pain → peritoneum irritation due to acidosis
3. Vomiting
4. Confusion
5. Tiredness
6. Difficulty breathing

DKA – Clinical signs:

- Kussmaul breathing
- Lethargy
- Dehydration
- Signs of infection

Diagnosis of DKA:

- Glucose > 200 mg/dL
- pH < 7.3
- Ketonuria or ketonemia
- Serum Bicarbonate < 18 mmol/L → Do VBG not ABG (safer) to avoid thrombosis (They are at higher risk)

Management: If hyperglycemia only → Subcutaneous insulin

If ketones without acidosis → subcutaneous insulin but in higher doses

*Rate of insulin = 0.1 unit/kg/hour

*When to give glucose saline ?

If blood glucose < 52

or ↓ more than 90–100 mg/dl in one hour

Management of DKA with vascular decompensation:

- ABCs.
- Normal saline 10 mL/kg to expand vascular space.
- Decrease to 5-7 mL/kg/hr with KCl.
- Not to infuse $NaHCO_3$ except in certain circumstances.
- Continuous IV insulin infusion 0.1 units/kg/hr.
- Observation and monitoring.
- If acidosis is improving and BG < 270 mg/dL or falls > 90 mg/dL/hr → change IV to D5/Normal Saline with potassium and decrease insulin infusion rate.

Complications of DKA

- Arrhythmias/cardiac arrest – 2° to electrolyte abnormalities or possibly long QTc
- Venous thrombosis 2° hypercoagulable state (that's why we avoid ABG)
- Pulmonary edema/ARDS
- Acute renal failure (ATN)
- Bowel ischemia – necrosis, stricture formation

Pathophysiology of DKA-related cerebral edema

- Previous hypothesis assumed that fluid shifts caused by osmotic changes were central to DKA-related cerebral edema

- This assumption has not been well supported by clinical data

- Cerebral edema during DKA may be predominantly vasogenic and may result from activation of cell membrane ion transporters in the brain

Risks factors for CE

- Younger age (<5 years)
- New-onset diabetes
- High initial serum urea
- Low initial partial pressure of arterial CO2
- Rapid administration of hypotonic fluids
- IV bolus of insulin
- Early IV insulin infusion (within first hour of administration of fluids)
- Use of bicarbonate

Strategies to prevent Diabetic Ketoacidosis

- To raise public awareness about symptoms and signs of diabetes.

- Beyond diagnosis:
  - Comprehensive diabetes education programs
  - Mental health intervention
  - Home monitoring of ketones or beta-hydroxybutyrate

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 3 consequent generations one of them less than 25 (age of onset)
- 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.

Wolfram Syndrome:

- Diabetes mellitus, diabetes insipidus, optic atrophy, and deafness (DIDMOAD): most prominent findings.
- Other common manifestations:

  - Neurogenic bladder with hydroureteronephrosis,

  - Neurodegenerative illness (most commonly manifesting as ataxia), psychiatric problems, --

  - Hypogonadism.

Insulin Therapy:

Endogenous Insulin Profile

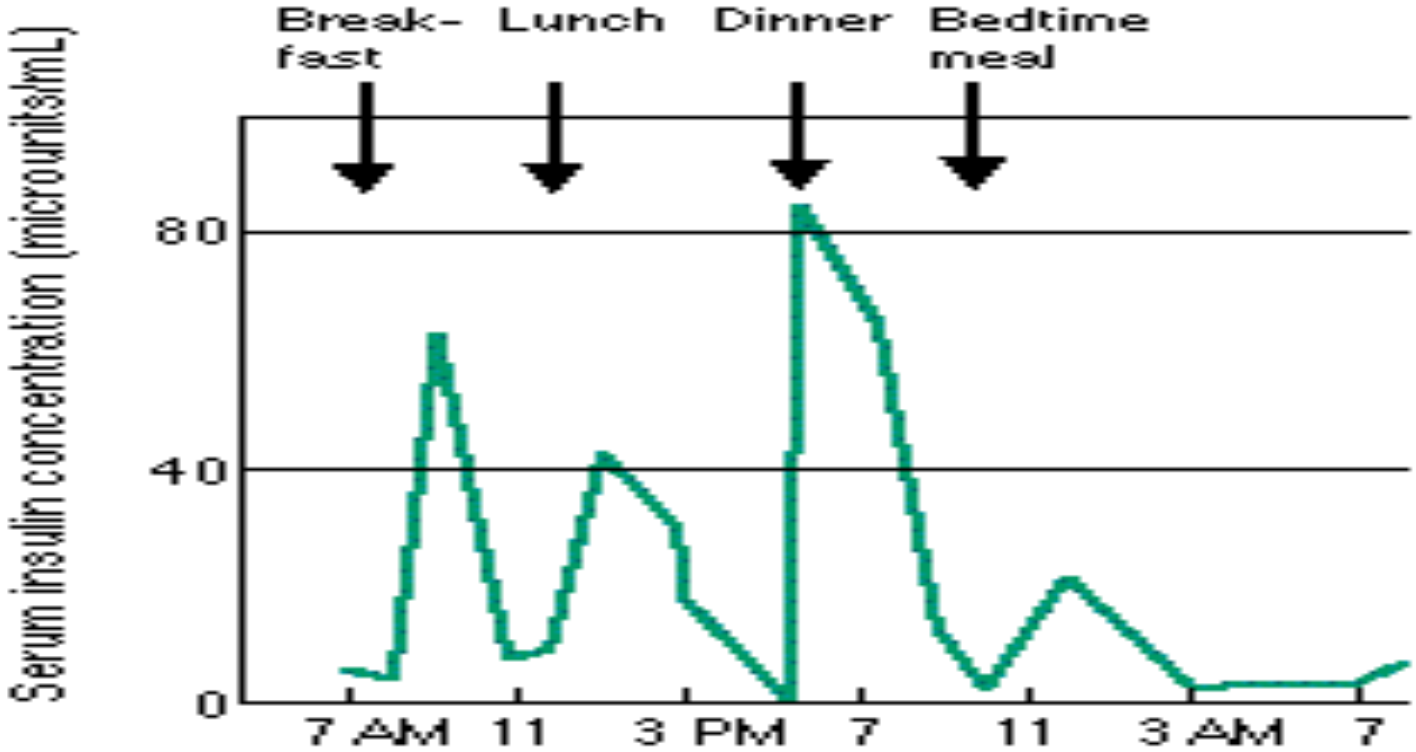
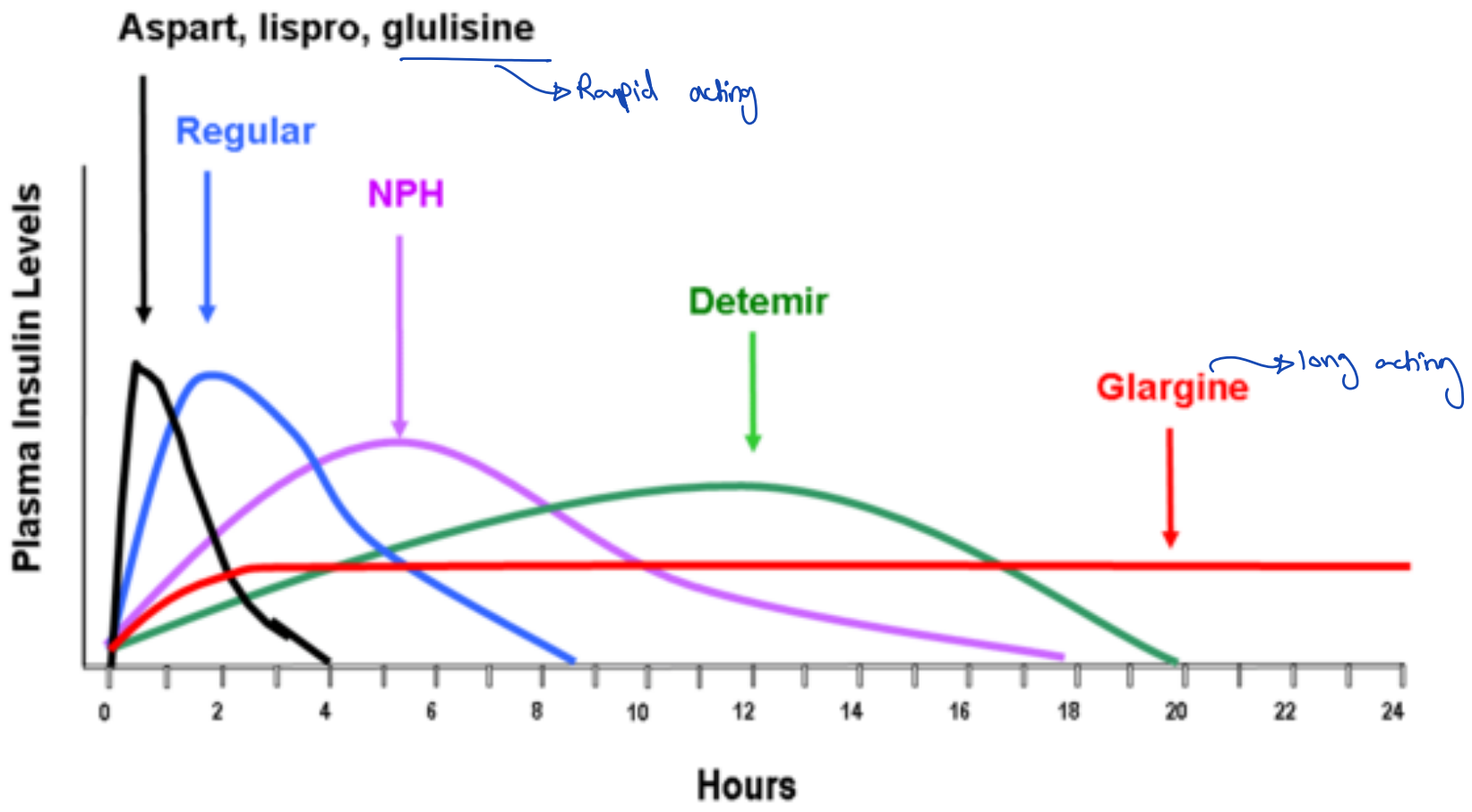


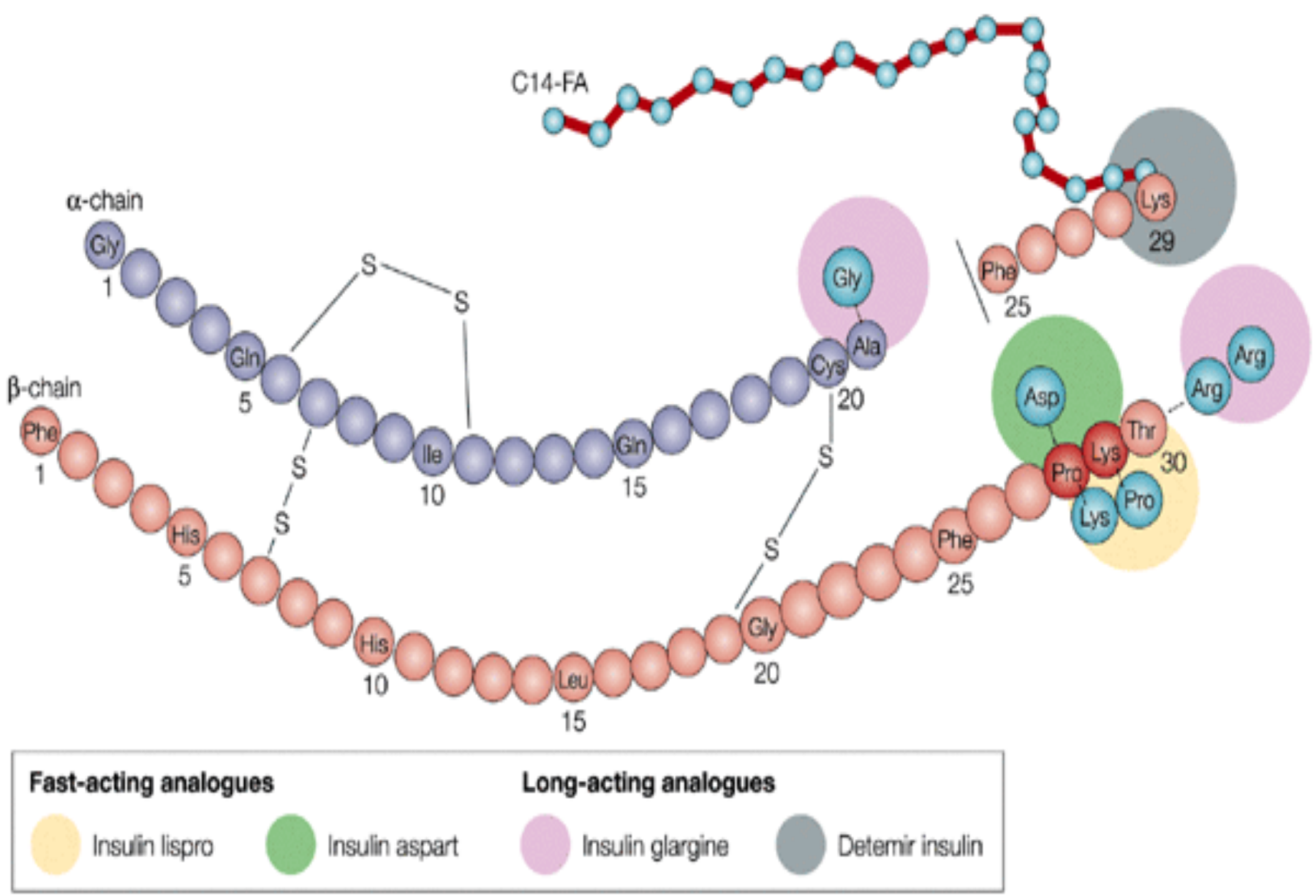
Figure 1. Normal insulin secretion. In the stimulated phase, serum insulin levels increase from within a few minutes before to 30 minutes after a meal. Return to basal level occurs within 2 hours.

Adapted from Galloway and Chance (5).

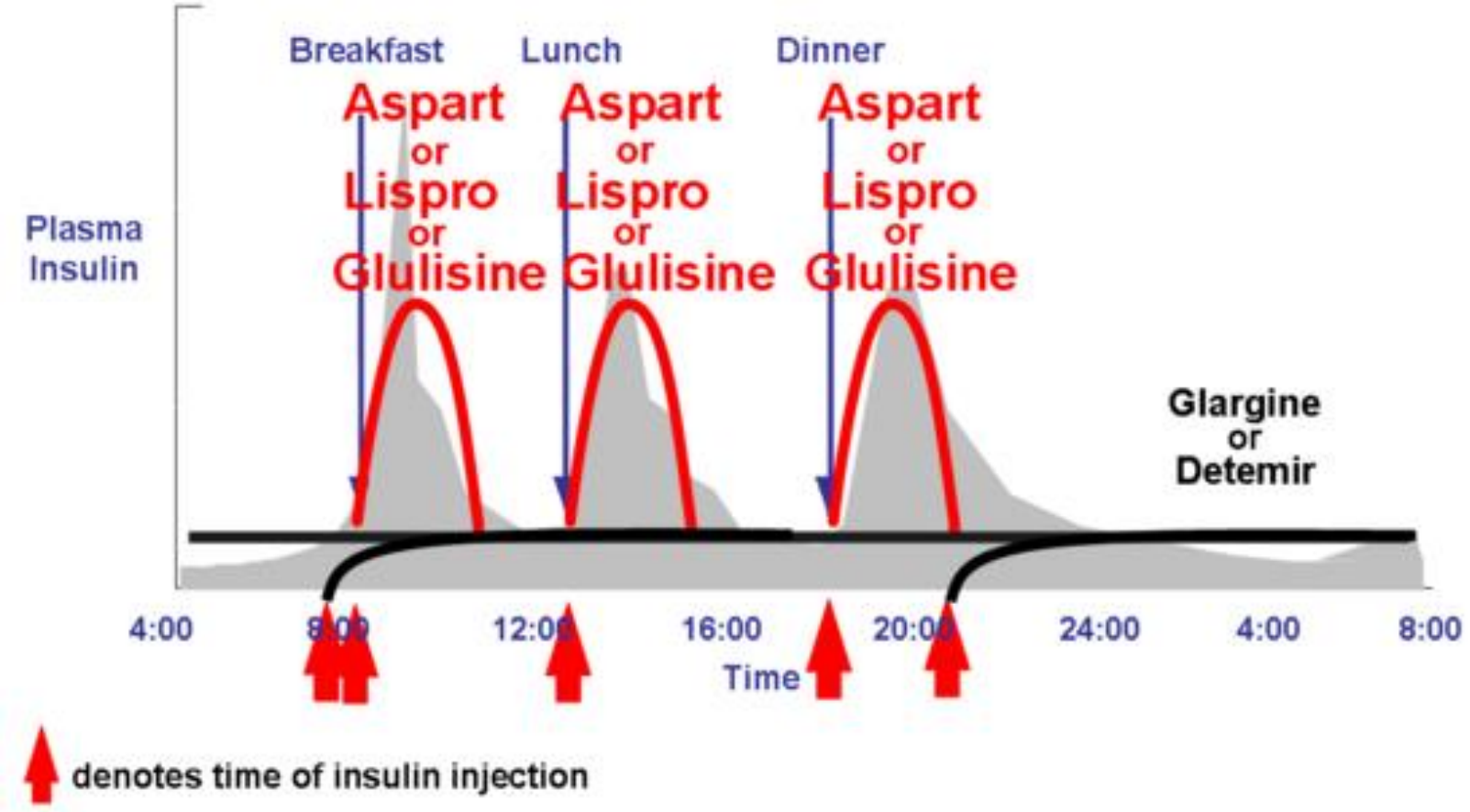
Galloway et al Horm Metab Res 1994

Idealized insulin time-action profiles



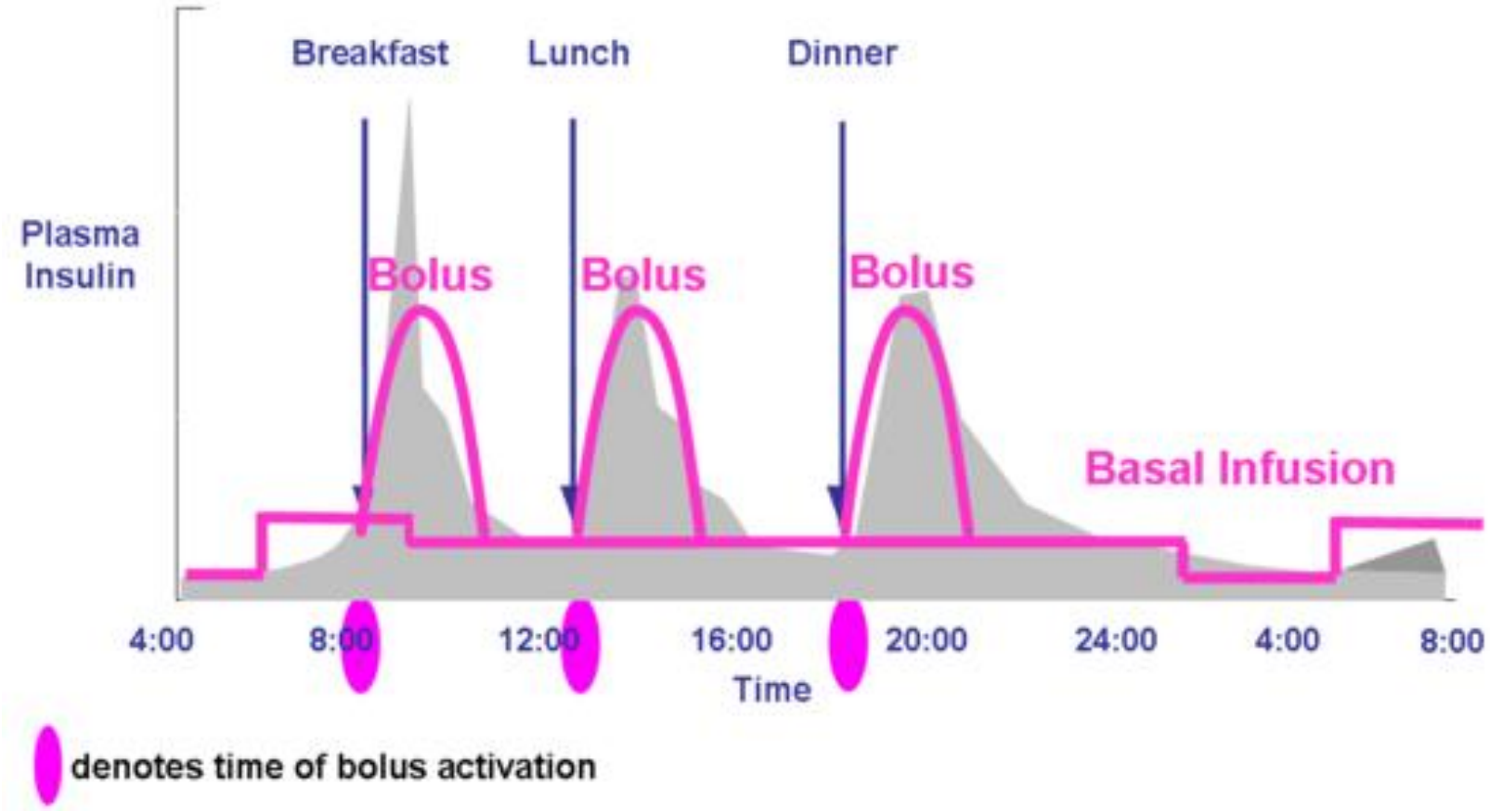

C14-FA
α-chain
Gly
1
Gln
5
Ile
10
Gln
15
Cys
20
Ala
Gly
Phe
25
Lys
29
β-chain
Phe
1
His
5
His
10
Leu
15
Gly
20
Phe
25
Pro
Lys
Pro
Asp
Lys
Thr
30
Arg
Arg
S
Fast-acting analogues
Insulin lispro
Insulin aspart
Long-acting analogues
Insulin glargine
Determir insulin

Long **and Rapid- acting insulin**

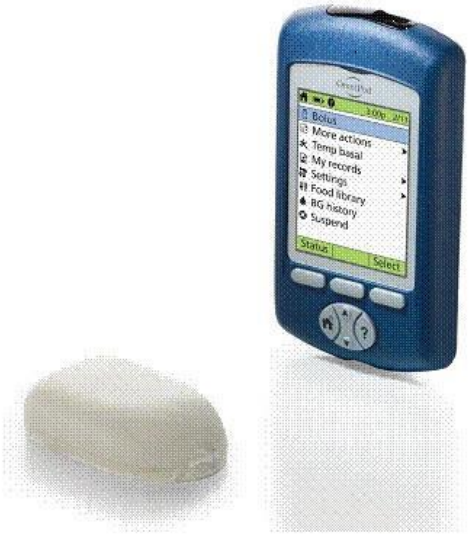


Insulin Pens :

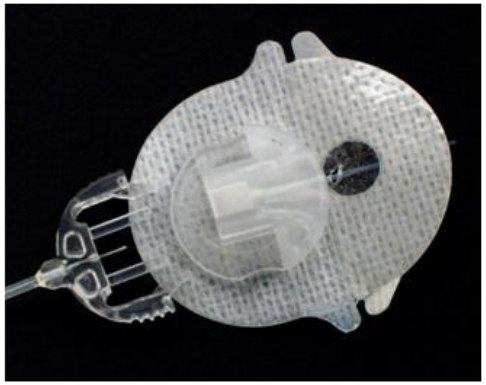
Continuous subcutaneous Insulin Infusion (insulin pump):

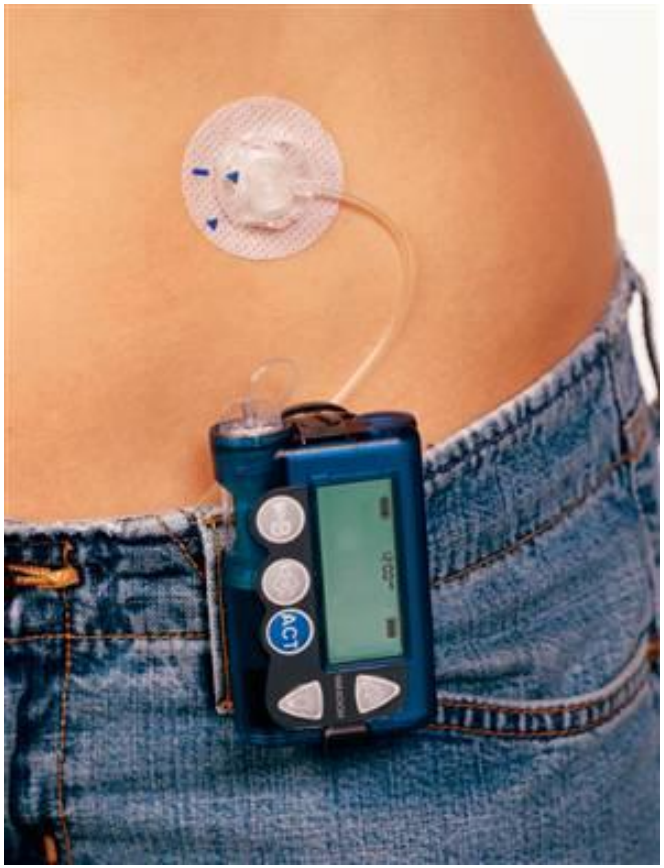


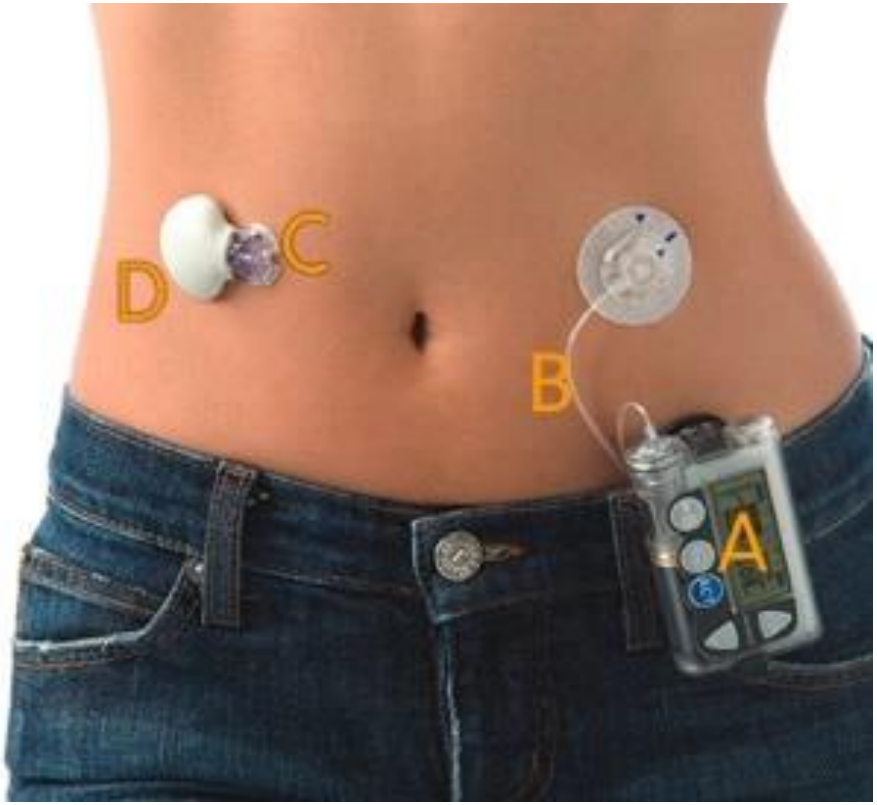
Insulin Pump:



Inserting insulin pump:




ACT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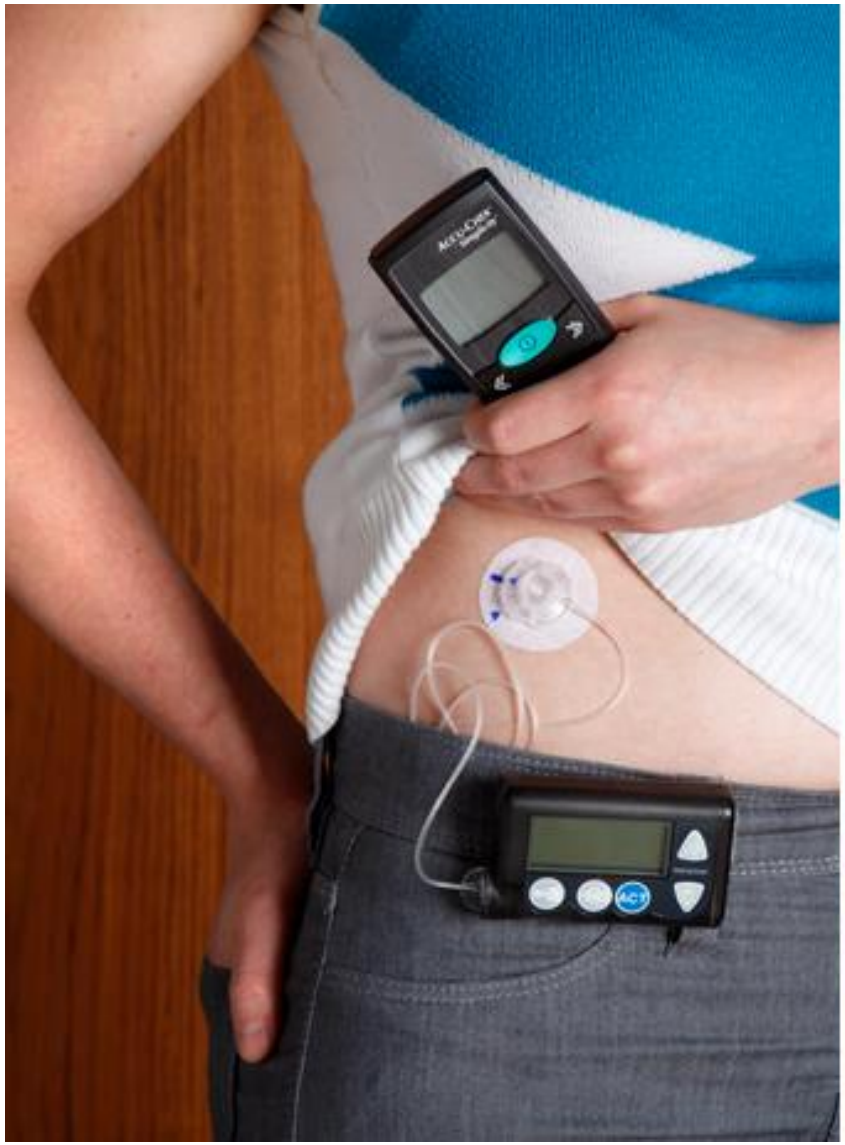
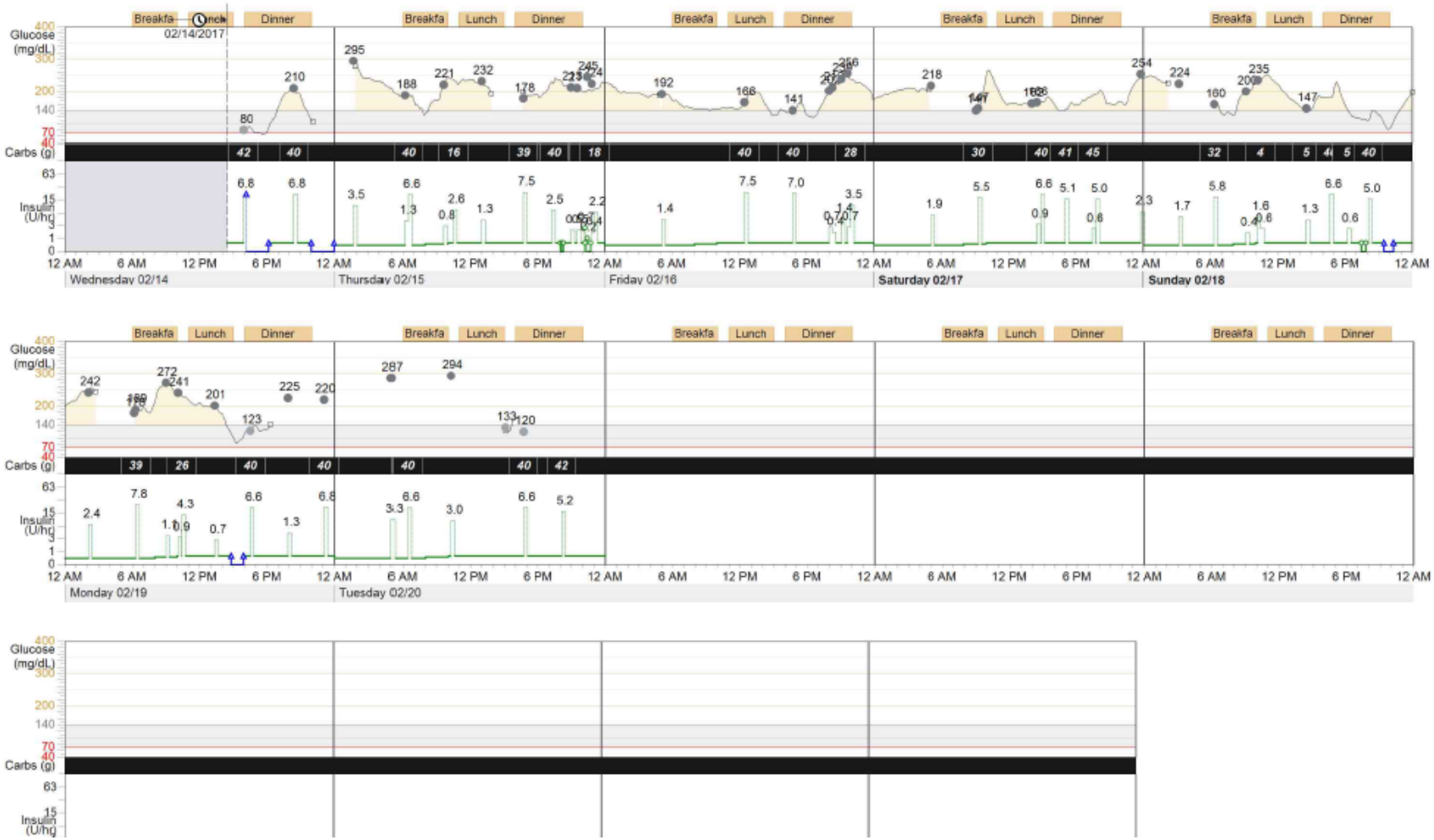
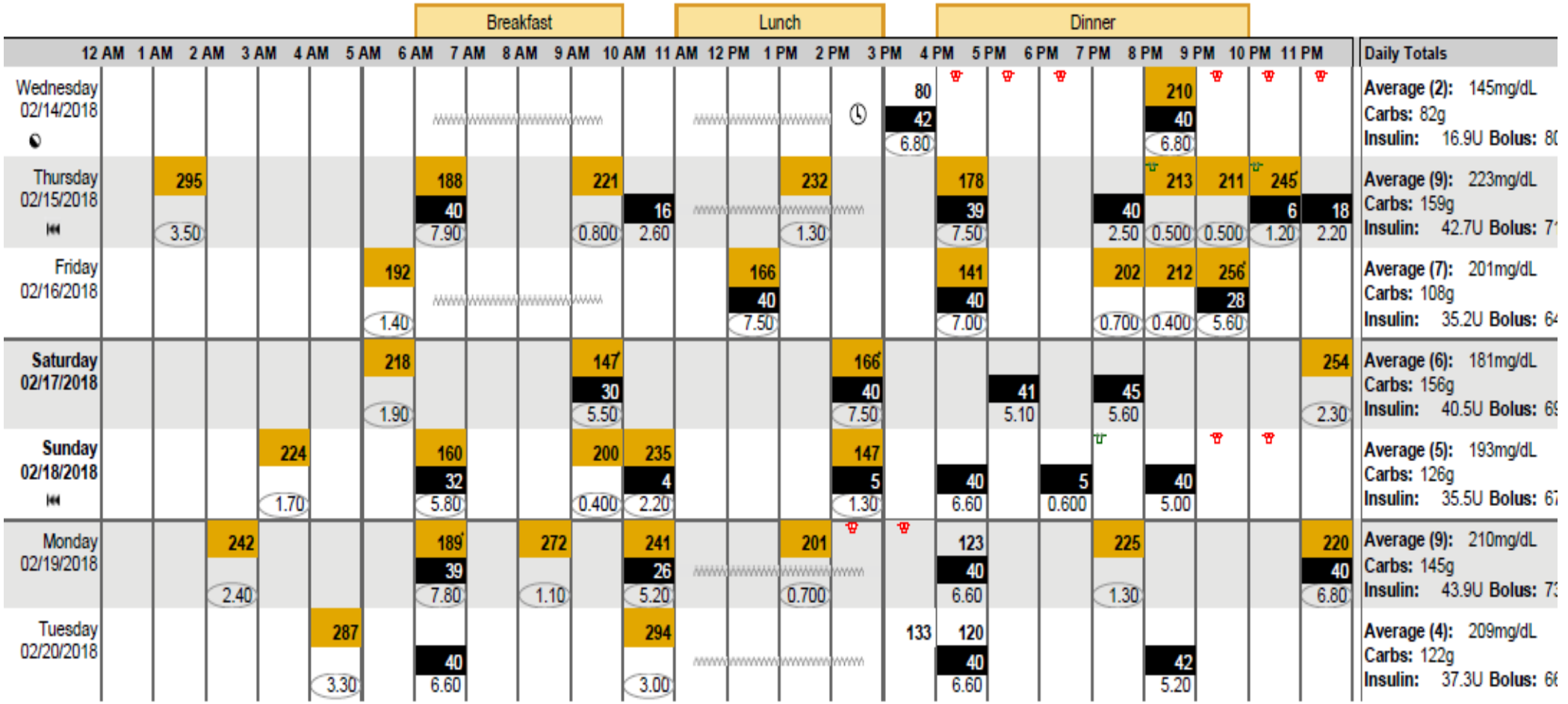



Breakfa
Lunch
Dinner
02/14/2017
Glucose (mg/dL)
Carbs (g)
Insulin (U/hg)
12 AM
6 AM
12 PM
6 PM
Wednesday 02/14
Thursday 02/15
Friday 02/16
Saturday 02/17
Sunday 02/18
Monday 02/19
Tuesday 02/20


Breakfast
Lunch
Dinner
12 AM 1 AM 2 AM 3 AM 4 AM 5 AM 6 AM 7 AM 8 AM 9 AM 10 AM 11 AM 12 PM 1 PM 2 PM 3 PM 4 PM 5 PM 6 PM 7 PM 8 PM 9 PM 10 PM 11 PM
Daily Totals
Wednesday 02/14/2018
80 42 6.80
210 40 6.80
Average (2): 145mg/dL
Carbs: 82g
Insulin: 16.9U Bolus: 8
Thursday 02/15/2018
295 3.50
188 40 7.90
221 0.800
16 2.60
232 1.30
178 39 7.50
213
211
245 6 1.20
40 2.50 0.500 0.500
18 2.20
Average (9): 223mg/dL
Carbs: 159g
Insulin: 42.7U Bolus: 7
Friday 02/16/2018
192 1.40
166 40 7.50
141 40 7.00
202 0.700
212 0.400
256 28 5.60
Average (7): 201mg/dL
Carbs: 108g
Insulin: 35.2U Bolus: 6
Saturday 02/17/2018
218 1.90
147 30 5.50
166 40 7.50
41 5.10
45 5.60
254 2.30
Average (6): 181mg/dL
Carbs: 156g
Insulin: 40.5U Bolus: 6
Sunday 02/18/2018
224 1.70
160 32 5.80
200 0.400
235 4 2.20
147 5 1.30
40 6.60
5 0.600
40 5.00
Average (5): 193mg/dL
Carbs: 126g
Insulin: 35.5U Bolus: 6
Monday 02/19/2018
242 2.40
189 39 7.80
272 1.10
241 26 5.20
201 0.700
123 40 6.60
225 1.30
220 40 6.80
Average (9): 210mg/dL
Carbs: 145g
Insulin: 43.9U Bolus: 7
Tuesday 02/20/2018
287 3.30
294 3.00
133
120 40 6.60
42 5.20
Average (4): 209mg/dL
Carbs: 122g
Insulin: 37.3U Bolus: 6

Glucose monitoring system

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

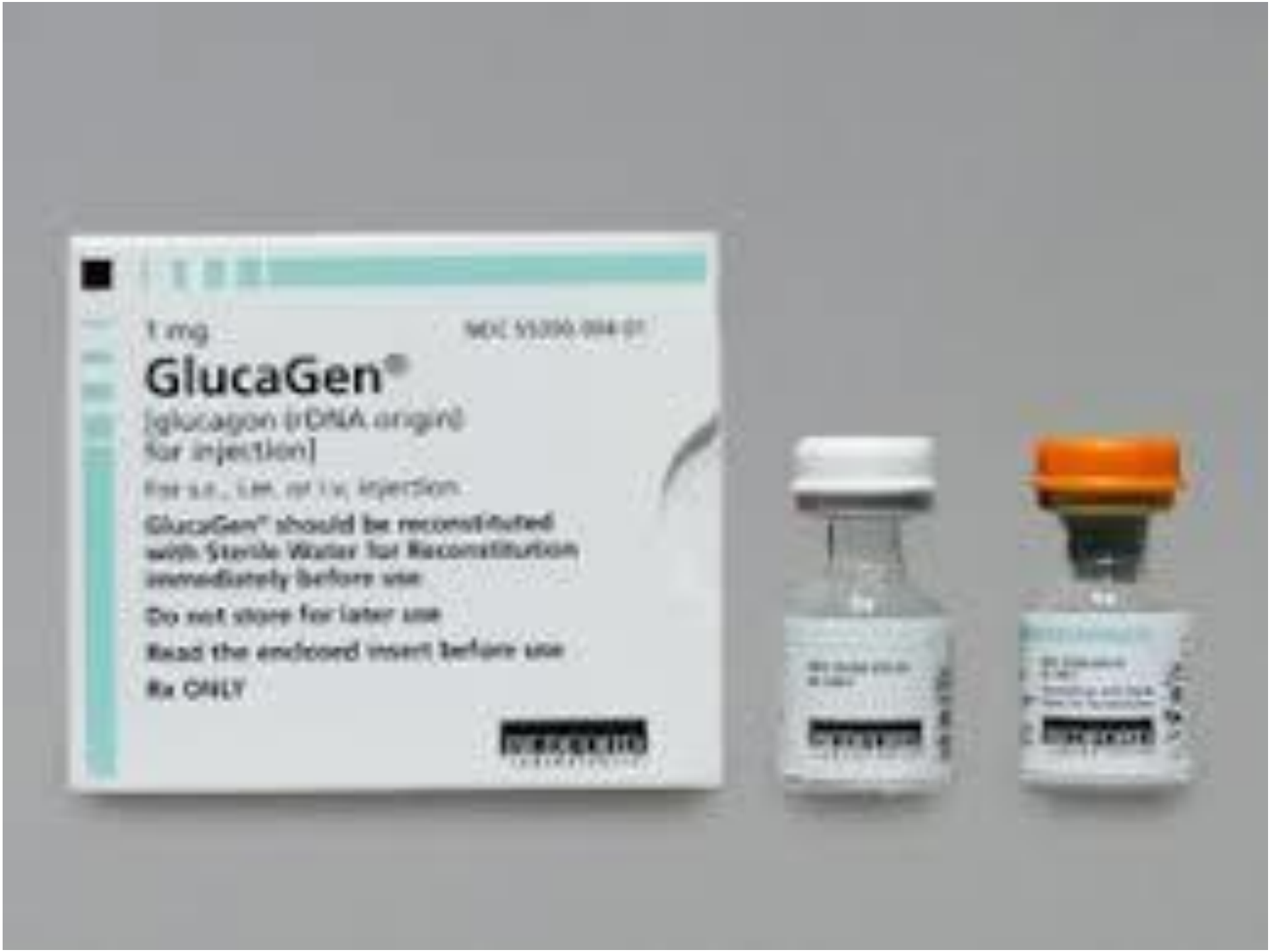
Hypoglycemia

- 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 | sth that cause rapid response like juices not chocolate for example because it has fat that will prolong the digestion process)

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
℞ ONLY

- On 10/Sep./2019:

FDA approved the Gvoke HypoPen, an emergency glucagon rescue treatment for severe hypoglycemia.

- **In July/2019:**

FDA approved the first non-injectable form of glucagon, BAQSIMI. The rescue device from Eli Lilly is a powder form of glucagon administered into the nose, and comes in a single-use dispenser.

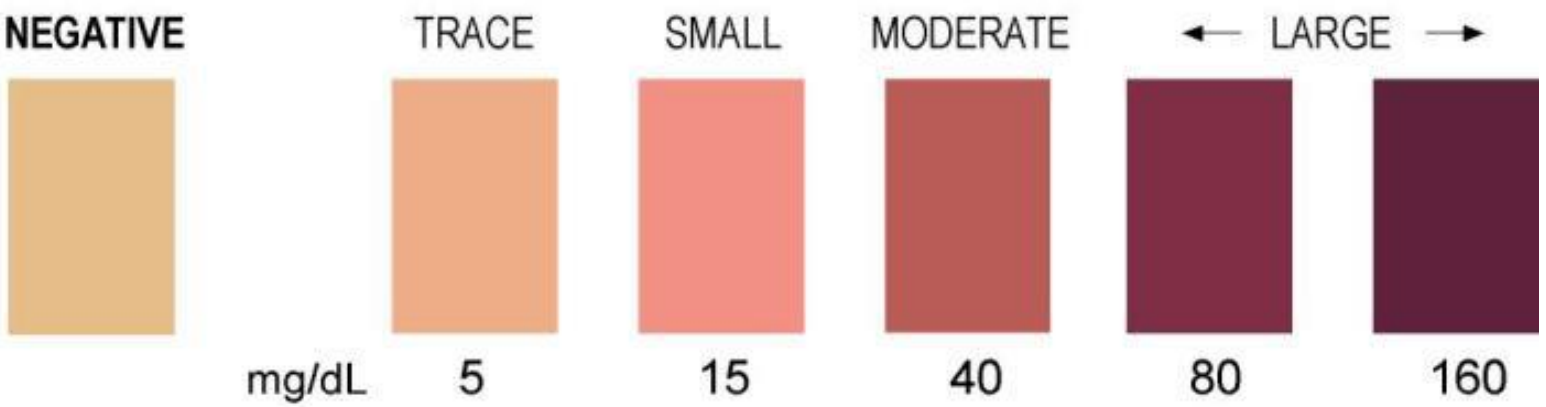
Sick Day Management

- 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.**



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.

- Defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol accounts for more than 95 percent of cases of congenital adrenal hyperplasia. This conversion is mediated by 21-hydroxylase, deficiency of which is caused by mutations in the CYP21A2 gene.

- The initial goals are treatment of hypotension and dehydration, reversal of electrolyte and glucose abnormalities, and correction of cortisol deficiency.
- 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.

- An initial dose of hydrocortisone of 50 to 100 mg/m^2 should be administered as an IV bolus (typical neonatal dose is 25 mg), followed by hydrocortisone at a dose of 50 to 100 mg/m^2 IV per day divided every six hours. Stress doses of hydrocortisone should be continued until the patient is stable and feeding normally.
- During treatment with stress doses of hydrocortisone. mineralocorticoid replacement is unnecessary.
- If the diagnosis of classic 21-hydroxylase deficiency is confirmed, infants should receive glucocorticoid and mineralocorticoid therapy and salt supplementation

Congenital Hypothyroidism

- The detection and treatment of neonates with hypothyroidism should be considered a pediatric emergency. If therapy is not begun soon after birth , developmental delay will result within few weeks to few months.
- Neonatal screening is essential because of the difficulty in making a clinical diagnosis early enough.

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 .

- If congenital hypothyroidism goes undetected, these manifestations progress. Retardation of physical and mental development becomes greater over the following months and by 3-6 months of age the clinical picture is fully developed.
- 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 :

A.a. Permanent primary hypothyroidism.

↓ T_4 ,↑ TSH .

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

most common cause of congenital hypothyroidism

- ectopy - agenesis. –hypoplasia. – hemiagenesis.

2. Thyroid dyshormogenesis :

-Goiter .

-TPO M/C.

3. TSH resistance due to TSH receptor mutation: Rare.

A.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.

B. 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

Levothyroxine

THANK YOU