Problem 1 – Unit 4 – Biochemistry: Hypoglycemia and Type-I Diabetes

Hypoglycemia

- **It is characterized by:**
  - Central nervous system symptoms (confusion, aberrant behavior, coma)
  - Blood glucose level equal or less than 40 mg/dl (2.2mmol)
  - Symptoms being resolved within minutes following administration of glucose (IV dextrose, juice… etc).
- Severe prolonged hypoglycemia causes brain death.
- **Hormones combating hypoglycemia are**: glucagon & epinephrine combined with diminished release of insulin.

A. Symptoms of hypoglycemia:

- **Classified into two categories:**
  - Adrenergic symptoms: anxiety, palpitation, tremor & sweating (when blood glucose level falls abruptly).
  - Neuroglycopenic symptoms: headache, confusion, slurred speech, seizures, coma & death (occurs with a gradual decline in blood glucose).

B. Glucoregulatory systems:

- **Two overlapping glucose regulating systems:**
  - Glucagon from α-cells of islets of Langerhans.
  - Receptors in the hypothalamus secreting epinephrine & ACTH (for cortisol release from adrenal cortex).
- **Glucagon & epinephrine:**
  - They are for acute short-term regulation of blood glucose levels.
  - Glucagon stimulates glycogenolysis & gluconeogenesis.
  - Epinephrine promotes glycogenolysis, lipolysis, inhibits insulin secretion & the insulin-mediated uptake of glucose by peripheral tissues.
- **Cortisol & growth hormone:**
  - They are for long-term management of glucose metabolism.

C. Types of hypoglycemia:

- **Insulin-induced hypoglycemia**: patients with diabetes who are receiving insulin treatment. For treatment of this type:
  - Oral administration of carbohydrate in conscious patients.
  - Subcutaneously or intramuscularly administration of glucagon in unconscious patients.
- **Postprandial hypoglycemia**: it is caused by exaggerated insulin release following a meal, prompting transient hypoglycemia with mild adrenergic symptoms. For treatment:
  - Eat frequent small meals.
- **Fasting hypoglycemia**: produces neuroglycopenic symptoms, may result from a reduction in the rate of glucose production by hepatic glycogenolysis or gluconeogenesis.
- **Hypoglycemia & alcohol intoxication:**
  - Ethanol is first converted to acetylaldehyde by alcohol dehydrogenase.
  - Acetylaldehyde is oxidized to acetate by aldehyde dehydrogenase.
  - Electrons are transferred to NAD resulting in a massive increase in NADH.
  - NADH favors the reduction of pyruvate to lactate & of oxaloacetate to malate.
  - Decrease in synthesis of glucose.

Type I diabetes:

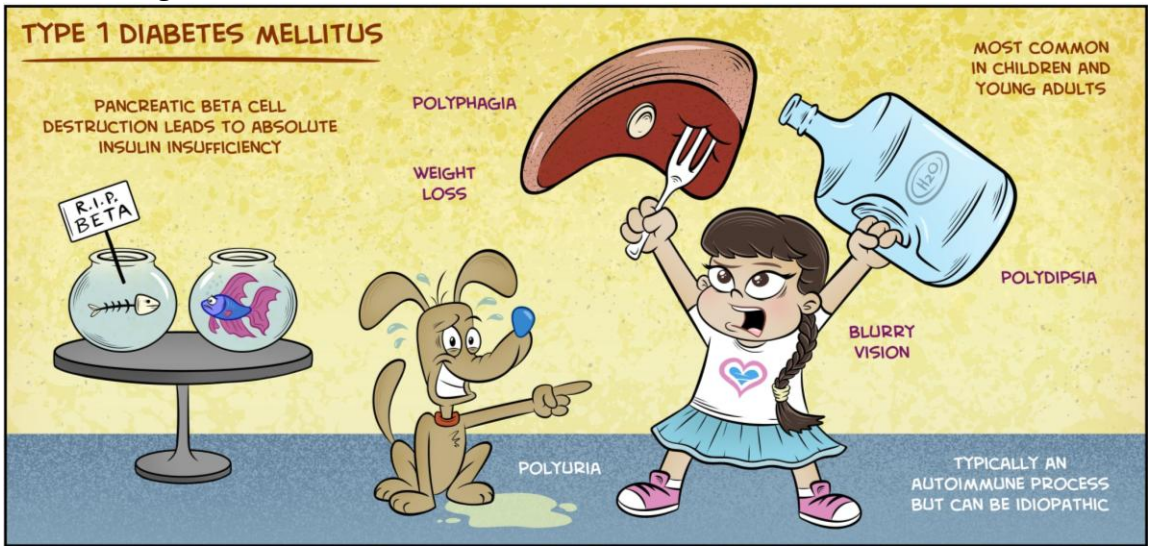
- It is an absolute deficiency of insulin caused by an autoimmune attack of β-cells –with infiltration of T lymphocytes- of the pancreas resulting in a condition called insulitis.
- **Stimulation of β-cells destruction from:**
  - **Environment**: ex. Viral infection.
  - **Genetic**: allows the β-cells to be recognized as "nonself". In type II, genetic influence is stronger.

A. Diagnosis of type 1 diabetes:

- **Onset**: during childhood or puberty.
- **Symptoms**: develop suddenly:
  - Polyuria.
  - Polydipsia.
  - Polyphagia.
  - Weight loss.
  - Fatigue & weakness.
- It is confirmed by a fasting blood glucose (FBG) greater than or equal to 126 mg/dl (7mmol). Commonly accompanied by ketoacidosis.

B. Metabolic changes in type I diabetes:

- **Hyperglycemia & ketoacidosis:**
  - It is cause by increased hepatic production of glucose & diminished peripheral utilization (muscle & adipose have the insulin-sensitive GLUT-4).
  - Ketosis is cause by accelerated hepatic fatty acid β-oxidation & synthesis of 3-hydroxybutyrate & acetoacetate.
  - **Diabetic ketoacidosis is treated by**: replacing fluid & electrolytes and administering short-acting insulin.
- **Hypertriacylglycerolemia:**
  - Excess fatty acids are converted to TAG packaged & secreted by VLDL.
  - Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal.



C. Treatment of type I diabetes:

- Insulin injected subcutaneously by two therapeutic regimens: standard & intensive.
- **Standard treatment versus intensive treatment:**
  - Standard treatment consists of one or two daily injections of recombinant human insulin.
  - The rate of formation of HbA_{1c} (normally < 6.5%) is proportional to the average blood glucose concentration over the previous 3 months. Thus, HbA_{1c} provides a measure of how well treatment has normalized blood glucose in the diabetic over that time.
  - Intensive treatment consists of three injections or more times a day.
- **Hypoglycemia in type I diabetes:**
  - Patients with type I diabetes also develop a deficiency of glucagon secretion. The combined deficiency of glucagon and epinephrine secretion (because of neuropathy) creates a condition sometimes called “hypoglycemia unawareness”.
- **Contraindication for tight control:**
  - Children are not put on a program of tight control for blood glucose because of the risk that episodes of hypoglycemia may adversely affect brain development.
  - Elderly people typically do not go on tight control because hypoglycemia can cause strokes & heart attacks in this population.