Metabolic Disorders

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Definition

- Inborn errors of metabolism (IEMs) are rare genetic or inherited disorders resulting from an enzyme defect in biochemical and metabolic pathways.
- Affecting proteins, fats, carbohydrates metabolism or impaired organelle function
- Presenting as complicated medical conditions involving several human organ systems.

- They involve great complexity of the underlying pathophysiology and molecular analysis, and have complicated therapeutic options for management.
- In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds.

- Majority of the IEMs are inherited in an autosomal recessive manner.
- While individually they are rare, collectively they are common

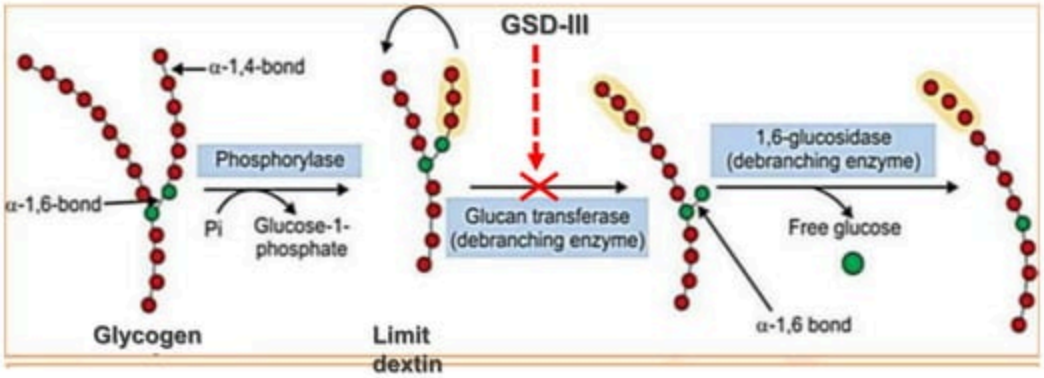
Classification

1. Disorders of carbohydrate metabolism
2. Disorders of amino acid metabolism
3. Disorders of lipid metabolism
4. Disorders of nucleic acid metabolism
5. Disorders of organic acid metabolism

Errors of carbohydrate metabolism

Cori disease

- Also known as Glycogen storage disease type III, Forbes disease, Cori's disease, limit dextrinosis
- Characterized by a deficiency in enzyme amylo-1,6 glucosidase, or debrancher enzyme.
- Presents during infancy
- Inherited in an autosomal recessive pattern
- Occurs in about 1:100,000 live births


GSD-III
α-1,4-bond
α-1,6-bond
Phosphorylase
Pi
Glucose-1-phosphate
Glycogen
Limit dextin
Glucan transferase (debranching enzyme)
1,6-glucosidase (debranching enzyme)
Free glucose
α-1,6 bond

Types

Types	Organs involved
GSD IIIa	liver and muscles
GSD IIIb	liver
GSD IIIc	liver and muscles
GSD IIId	liver

Signs and symptoms

- Fasting hypoglycemia
- Hyperlipidemia
- Elevated blood levels of liver enzymes (AST, ALT)
- Failure to thrive
- Hepatomegaly (usually returns to normal during adolescence)
- Noncancerous (benign) tumors called adenomas may form in the liver

- Occasional seizures in some individuals due to hypoglycemia.
- Muscular disease, including hypotonia and cardiomyopathy (usually occurs late)
- Poor muscle tone (hypotonia) and mild myopathy in early childhood

Causes

- Mutations in the *AGL* gene cause GSDIII.
- Codes for glycogen debranching enzyme
- Most *AGL* gene mutations lead to the production of a nonfunctional glycogen debranching enzyme (IIIa and IIIb)
- The mutations that cause GSD types IIIc and IIId are thought to lead to the production of an enzyme with reduced function.
- All *AGL* gene mutations lead to storage of abnormal, partially broken down glycogen molecules within cells. A buildup of abnormal glycogen damages organs and tissues throughout the body, particularly the liver and muscles

Diagnosis

- Presence of hepatomegaly, ketotic hypoglycemia, elevated liver enzymes in serum and creatine kinase
- Debranching enzyme activity (which is deficient in individuals with the condition) can be measured in a liver biopsy.
- Genetic testing of the AGL gene, confirms the diagnosis

Treatment

- No cure
- In some cases, diet therapy is helpful.
- Strict adherence to a dietary regimen may reduce liver size, prevent hypoglycemia (low blood sugar), help to reduce symptoms, and allow for growth and development.
- Management typically includes a high-protein diet with cornstarch supplementation to maintain a normal level of glucose in the blood.

- Skeletal and cardiac myopathies may be improved with high-protein diet and avoiding excessive carbohydrate intake.
- Liver transplantation may be indicated for patients with hepatic cancers.

Blood glucose regulation

- Glucose is the most important source of energy in all organisms.
- The levels of glucose in the blood are monitored by many tissues, but the cells in the pancreatic islets are among the most well understood and important.
- Factors involved in the homeostasis (regulation) of blood glucose are:

❑ Hormones

❑ Metabolic processes

❑ Renal mechanism

Normal blood glucose concentration

- Fasting blood glucose – 70-110 mg/dL
- Postprandial (PP) blood glucose – 120-140 mg/dL
- Random blood glucose – 70-140 mg/dL
- Hypoglycemia- Lower than the lower range for fasting, PP and Random
- Hyperglycemia – Higher than the upper range for fasting, PP and Random

Hypoglycemia

- Hypoglycemia is a condition in which your blood sugar (glucose) level is lower than normal.
- Hypoglycemia is often related to diabetes treatment.
- But other drugs and a variety of conditions can cause low blood sugar in people who don't have diabetes
- Hypoglycemia needs immediate treatment when blood sugar levels are low.
- Treatment involves quickly getting the blood sugar back to normal either with high-sugar foods or drinks or with medications.

Symptoms

- Anxiety
- Sweating
- Hunger
- Nausea, vomiting
- Irritability
- Tingling or numbness of the lips, tongue or cheek
- Visual disturbances, such as blurred vision, Dilated pupils
- Seizures
- Fatigue
- Loss of consciousness

Causes

- Dose of insulin or other diabetes medications more than required
- Eating less than usual or exercised more than usual after taking diabetes medication
- Excessive alcohol drinking
- Some critical illnesses like, kidney failure, certain tumors, liver disease
- Inborn errors of metabolism
- Hormone deficiencies- deficiency of growth hormone,

Diagnosis

- The glucose level that defines hypoglycemia is variable.
- In diabetics a level below 70 mg/dl is diagnostic.
- A level below 50 mg/dl after not eating or following exercise may be used for a normal individual
- In newborns, a level below 40 mg/dl or less than 60 mg/dl (if symptoms are present) indicates hypoglycemia.
- Other tests that may be useful in determining the cause include insulin and C peptide levels in the blood.

Treatment

- Treatment of some forms of hypoglycemia, such as in diabetes, involves immediately raising the blood sugar to normal through the eating of carbohydrates
- Determining the cause, and taking measures to hopefully prevent future episodes.

- The following are the findings in a patient brought to the hospital in a coma state.

Findings	*Patient*
Blood sugar (Fasting)	270 mg%
Urine Benedict's test	Positive
Urine Rothera's test	Positive
Plasma pH	7.20

a. Name the disorder.

b. Why is patient's plasma pH lower than normal?

c. What does positive Rothera's test indicate?

d. What is the renal threshold value for glucose?

Hyperglycemia

- High blood sugar (hyperglycemia) mainly affects people who have diabetes.
- It can be also seen during stress, severe infection, chronic illness, taking some medications etc.

Blood glucose levels

- Hyperglycemia doesn't cause symptoms until glucose values are significantly elevated — usually above 180 to 200 mg/dL
- Impaired fasting glucose: Fasting glucose- 110-125 mg/dL
- Impaired glucose tolerance: Post prandial glucose- 140-200 mg/dL

Glucose is not high enough to be called as diabetes

- Diabetes: if FBG >125mg/dL and PPBG> 200 mg/dL

Diabetes mellitus

- Syndrome of impaired carbohydrate,fat and protein metabolism, caused by either:

✓ Lack of insulin secretion

or

✓ Decreased sensitivity of tissues to insulin.

Classification

- Type I diabetes mellitus or insulin dependent diabetes mellitus (IDDM) or juvenile diabetes.
- Type II diabetes mellites or non insulin dependent diabetes mellitus (NIDDM) or adult diabetes mellitus.

Type l diabetes mellitus

Cause

Lack of insulin secretion due to destruction of pancreatic beta cells. The destructions of beta cells may be due to:

1. Viral infection
2. Autoimmune disorder
3. Hereditary tendency of beta cell degeneration

Onset

- At about 14 years of age and for this reason it is called juvenile diabetes mellitus.
- Juvenile' means teenage in Latin.

Symptoms

- It develops symptoms very abruptly with:
  - Polyuria (frequent urination)
  - Polydypsia (excessive thirst)
  - Polyphagia (excessive hunger).
- Loss of body weight, weakness, and tiredness.
- Hyperglycemia with glycosuria and ketoacidosis
- The patients of type-I diabetes mellitus are not obese.