**Metabolic disorders of carbohydrate metabolism**

1. Diseases associated with impaired digestion and absorption

Lactose intolerance.

1. Disease associated with impaired glycolysis
2. Lactic acidosis.
3. Pyruvate kinase deficiency (Hemolytic anemia).
4. Hexokinase deficiency.
5. Diseases associated with impaired HMP shunt:-

Hemolytic anemia due to glucose -6- phosphate dehydrogenase deficiency (Favism).

1. Diseases associated impaired uronic acid pathway:-

Essential pentosuria.

1. Diseases associated with impaired glycogen metabolism (Glycogen storage diseases ):-

Type I : Von Gierke’s disease.

Type II : Pompe’s disease.

Type III : Cori’s disease or Forbe’s disease or limit dextrosis.

Type IV : Andersen's disease.

Type V : McArdle’s disease.

Type VI :Her’s disease.

Type VD : Tarui’s disease.

Type VI.

1. Diseases associated with impaired fructose metabolism
2. Essential fructosuria.
3. Hereditary fructose intolerance.
4. Diseases associated with impaired galactose intolerance: Galactose Intolerance (Galactosemia).
5. Variations in normal blood glucose
6. Hyperglycemia.
7. Hypoglycemia.
8. Glucosuria.
9. Diabetes mellitus.

Diseases associated with impaired digestion and
absorption

Lactose intolerance (Lactase deficiency)

-Defect :

Deficiency of lactase enzyme which digest lactose into glucose and galactose

-Effect:

Presence of undigested lactose in intestine causes:

a. Increased osmotic pressure in the intestine.

b. Increased fermentation of lactose by intestinal bacteria with subsequent production ofCO2 gas.

- Clinically

Vomiting, abdominal cramps, flatulence, watery diahrrea, dehydration on eating fresh and non-fermented milk products.

-Treatment

1. Removing lactose (milk) from diet. Milk and its products are replaced by live culture yogurt.
2. B-galactosidase therapy.

Disease associated with impaired glycolysis
1) lactic acidosis

- Defect:

- lowered blood PH (acidosis) due to increased blood lactate above normal.

Causes of hyperlactemia

1. Severe muscular exercises increases lactate production.
2. Anoxia increases lactate production and decreases its utilization as in :

Myocardial infarction, respiratory disorders and severe anemia

1. Liver diseases that decrease lactate utiiization.
2. Hypoglycemic drugs e.g.Phenformin that increases lactate production by anaerobic oxidation of glucose.

**-Pathophysiology**:

Increased lactic acid leads to depletion of the blood alkali reserve (sodium bicarbonate)

- Clinically

- Fatigue after muscular exercise is caused in part by lactate.

-Uncontrolled lactic acidosis could cause coma.

1. Pyruvate kinase deficiency (Hemolytic anemia)

- Defect:

Genetic reduction in pyruvate kinase activity to 5% - 25% of its normal level.

* Pathopbysioiogy:-
* This defect causes decreased rate of glycolysis and leads to deficiency of ATP produced in RBCs.

• This leads to stoppage of the ATP - dependant membrane pumps (e.g.Na - k ATPase), so the RBCs can’t control its contents, swell and lysis occurs.

* **Clinically**

It is the second most common genetic deficiency that causes haemolytic anaemia (G6PD is the most common).

**3) Hexokinase deficiency**

**-Defect:**

Genetic deficiency of hexokinase.

* **Pathophysiology:-**

Decreased rate of glycolysis leading to :

1. Decreased ATP — RBCs haemolysis .
2. Low 2,3DPG level — high hemoglobin affinity to O; that will be less available for tissues.
* **Clinically**
1. Hemolytic anemia.
2. Tissue hypoxia.

**Diseases associated with impaired HMP shunt
Hemolytic anemia due to glucose -6- phosphate
dehydrogenase deficiency
(Favism)**

**-Defect :**

Inherited deficiency of G6PD, the disease is sex linked recessive.

* **Pathophysiology:-**
1. Deficiency of G6PD — decreased NADPH.H+ production which is essential for RBCs to reduce glutathione in the presence of glutathione reductase.

Glutathione reductase

G-S-S-G + NADPH.H+ ► 2 GSH + NADP

Oxidized Reduced

glutathione glutathione

1. Reduced glutathione (GSH) is needed to remove hydrogen peroxide H202 which is toxic if not destroyed:-
2. Oxidize hemoglobin of red cells to methemoglobin and precipitate it (Heinz bodies).
3. Oxidize lipids of RBCs membranes, damaging them and causing hemolysis.

Glutathione peroxidase

H2O2 + 2 GSH ► GSSG + H2O

So, deficiency of G6PD **⇒⇒⇒** decrease NADPH.H+ **⇒⇒⇒** decrease reduced Glutathione **⇒⇒⇒**accumulation of H202 **⇒⇒⇒** hemolysis of RBCs.

**-Clinically**

1) The mutation causing such deficiency occurs in many individuals without any symptoms under normal conditions.

2) Patients with enzyme deficiency show acute attacks of hemolytic anemia in the form of severe jaundice and decreased hemoglobin concentration when exposed to certain oxidizing agents (leading to increased H2O2:-

1. Fava beans.
2. Antimalrial drugs.
3. Antibiotics as streptomycin and sulfonamides.
4. Under stress conditions.

**-Treatment:**

1. When hemolysis occurs, life saving measures should be taken to save the life of the baby and prevent renal failure.
2. Many individuals having this defect are cured spontaneously during adult life.

**Diseases associated impaired uronic acid pathway
Essential pentosuria.**

**-Defect:**

Hereditary absence of L-xylitol dehydrogenase.

**-Pathophysiology:**

-Failure of conversion of L-xylulose (produced from uronic acid pathway not from diet) to D-xyLulose.

-L-xylulose will accumulate and will be excreted in urine.

**Diseases associated with impaired glycogen metabolism
(Glycogen storage diseases )**

**-Definition:**

Glvcogen storage diseases (or glycogenosis) are groups of inherited disorders characterized by deposition (over-storage) of an abnormal type or quantitv of glycogen.

**-Type I: Von Gierke's disease:**

It is the commonest type of this group.

**-Defect *:***

Genetic deficiency of glucose-6-phosphatase in liver and kidney.

* **Pathophysiology:-**

Accumuiation of large amounts of glycogen in liver and kidney.

* **Clinically**
1. disturbance in liver functions.
2. Hepatomegaly and nephromegaly.
3. Fasting hvpogiycemia.
4. ketosis and hyperlipidemia.
5. Hyperuricemia:

Deficiency of glucose-6-phospnatase leads to accumulation of glucose-6- phosphate that is utilized through HMP shunt to give large amount ofpentose-5- phosphate that enters in purine synthesis that is cataboiized into large amount of uric acid, i.e., hyperuricemia.

1. Lactic acidosis and failure to thrive.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Disease Name** | **Number** | **Defective Enzyme** | **Organ** | **Symptoms** |
| **Von Gierke’s**  | Type I | Glucose-6-phosphatase | Liver & kidney | 1. Enlarged liver & kidney.
2. Fasting ketotic hypoglycemia.
3. Hyperlipidemia.
4. Hyperuricemia.
5. Lactic acidosis.
6. Failure to thrive.
 |
| **Pompe’s**  | Type II | Lysosomal α-1,4 and α-1,6-glycosidase | All tissues,e.g., heart | Cardiomegaly, heart failure & death before age 2 |
| **Forbe's**  | Type III | Debranching enzyme | Muscle & liver | Like type **I** but milder. |
| **Andersen’s**  | Type IV | Branching enzyme | Liver & spleen | Cirrhosis, liver failure & death before age 2. |
| **McArdle’s**  | Type V | Glycogen phosphorylase | Muscles | Muscle cramps & damage. |
| **Hers'**  | Type VI | Glycogen phosphorylase (50% of normal activity) | Liver | Hepatomegaly, Mild hypoglycemia & acidosis (Mild Type **I**). |
| **Tarui’s**  | Type VII | Phosphofructokinase | Muscles & RBCs. | Like type **V** |
|  | Type VIII | Phosphorylase kinase | Liver | Like type **I** but milder |

 **Diseases associated with impaired fructose metabolism**

1. **Essential fructosuria.**

**-Defect:**

Hereditary deficiency of fructokinase enzyme.

* Pathophysiology:-

The excess accumulated fructose in biood lead to fructosemia and lost in urine (fructosuria).

* Clinically

it is not a serious condition.

1. **Hereditary fructose intolerance**

**-Defect:** Deficiency of Aldolase B enzyme.

-Pathophysiology:-

Accumulation of fructose-1-phosphate leading to

1. Damage of the liver ; iiver failure.
2. Inhibition of glycogen phosphrylase enzyme — inhibition of glycogenolysis —- this leads to fructose induced fasting hypoglycemia.

**Diseases associated with impaired galactose intolerance
Galactose Intolerance (Galactosemia).**

-Defect :

 Inherited deficiency of

1. galactokinase,
2. and/or galactose-1-phosphate-uridyl transferase
3. and/or UDP-galactose epimerase.

**-**Pathophysiology:-

* Accumulation of galactose in blood, i.e., galactosemia because the body cannot metabolize galactose taken in the diet.
* Thus, the levels of galactose are increased in tissues, blood and urine, i.e., galactosuria.
* The increased tissue galactose is reduced to galacticol by aldose reductase.
* galacticol causes hyperosmotic damage to cells.

Clinically:-

1. Fatty liver, liver cirrhosis.
2. Mental retardation.
3. Cataract (opacity of eye lens).

**Variations in normal blood glucose**

**Hyperglycemia:**

* It is the rise of blood glucose level above 140 mg/dl.

 **Causes:**

1. **Deficiency of insulin in:**
* Diabetes mellitus (commonest cause).
* Experimental or surgical pancreatectomy (removal of pancreas).
* Alloxan injection that destroy β-cells.
* Pancreatitis and pancreatic cancer.
1. **Increased anti-insulin hormones:**

- ACTH and glucocorticoids: as in adrenal cortical tumors and Cushing's syndrome. Also, other stresses, e.g., sepsis, some infectious diseases, anesthesia, asphyxia and convulsions.

- Adrenaline: as in emotions, stress and pheochromocytoma.

- TSH and thyroxine as in hyperthyroidism.

- Pituitary growth hormone: as in Acromegaly.

1. **Dietary or Alimentary**, high carbohydrate diet especially rich in simple sugars.
2. **Drug-induced**, e.g., chronic use of corticosteroids.

**Hypoglycemia:**

* It is the decrease of blood sugar level below 40 mg/dl.

 **Causes:**

1. **Glycogen storage diseases:** Causes fasting hypoglycemia.
2. **Excess of insulin as in:**
* Over dose of insulin during treatment of diabetes mellitus lead to hypoglycemia.
* Missing a meal during treatment with insulin.
* Insulinoma, a tumor of β-cells.
1. **Decrease of anti-insulin hormones in cases of:**
* Glucocorticoids as in Addison’s disease.
* Pituitary hormones as in panhypopituitarism.
* Thyroxine as in hypothyroidism.
* Liver diseases, sever exercises, alcoholism, tumors secreting IGFs and leucine sensitivity.

**Effect of hypoglycemia: Hypoglycemia** is a very dangerous condition because glucose is the major fuel of the brain. Hypoglycemia causes confusion and dizziness. If blood glucose level is decreased below 40 mg/dl hypoglycemic coma will occur. Clinically the condition has a picture similar to that of sympathetic over stimulation.

**Glycosuria (Glucosuria)**

**Definition:**

- The presence of any reducing sugar in urine is called glycosuria, whereas, presence of glucose in a detectable amount by qualitative Benedict's test is called glucosuria. However, glycosuria is inter-exchangeable with glucosuria. - Glucose starts to appear in urine when its blood level exceeds that maximum renal reabsorption limit, i.e., renal threshold that is 160 - 180 mg/dL. .

**Causes of glucosuria:**

 **A-Hyperglycemic glucosuria:**

 Its Causes are (types):

1. Diabetes mellitus .
2. Alimentary glucosuria due to intake of high carbohydrate diet. It will never cause glucosuria except when there is a mild impairment of glucose utilization
3. Emotional glucosuria: due to stimulation of adrenal medulla to secrete excess catecholamines.
4. Surgical and experimental diabetes mellitus induced by:
* Total or subtotal pancreatectomy and alloxan or streptozotocin injection.
* Injection of high doses of cortisone, anterior pituitary or thyroid hormones.
* Hyperfunction of anterior pituitary leading to GH, TSH and ACTH, hyperfunction of thyroid gland and increased glucagon secretion.
1. **Normoglycemic glucosuria:**

 Its causes are

1. Renal diabetes: It is a congenital decrease in renal threshold due to inefficient reabsorption of glucose (diabetes innocence).

2. Experimental renal diabetes induced by injection of phloridzin which inhibits reabsorption of glucose in renal tubules.

3. Pregnancy leads to decreased carbohydrate tolerance and renal threshold in the later months of pregnancy.

4. Renal diseases and toxicity by mercury, lead and cadmium.

**Diabetes mellitus**

**Definition:**

- It is a chronic syndrome with impaired carbohydrate metabolism due to deficiency or ineffectiveness of insulin or decreased insulin/anti-insulin ratio leading to chronic hyperglycemia and glycosuria along with secondary changes in metabolism of protein, lipids, water and electrolytes. It has grave consequences if not treated.

**Types of Diabetes mellitus:**

|  |  |
| --- | --- |
| **Type I, IDDM, Juvenile Onset** | **Type II, NIDDM, Maturity Onset** |
|  Less frequent (about 20%). |  More frequent (about 80%). |
|  Before age 15 and males are more affected. | Middle age and females are more affected. |
|  Abrupt onset. |  Gradual onset. |
|  Severe, ketoacidosis and coma are frequent. |  Mild, ketoacidosis and coma are rare. |
|  Recent weight loss. |  2/3 of cases are obese.  |
|  No insulin due to atrophy of β-cells.  |  Impaired insulin secretion and resistance to its action (there may be higher insulin than normal). |
| Treated with insulin. |  Treated with diet and weight control and hypoglycemics. |
|  Positive autoimmune markers. |  No autoimmune markers. |
|  No C-peptide |  Detectable C-peptide.  |

**Diagnosis and monitoring of diabetes mellitus:**

1. **Random plasma glucose level** ≥200 mg/dL (≥11.1 mM/L) with classical diabetic symptoms (thirst, polyuria and weight loss) is diagnostic.
2. **Fasting plasma glucose level** (type 2) ≥126 mg/dL (≥7 mM/L) is diagnostic.

1. **Two hours post-prandial plasma glucose level** ≥ 200 mg/dL (≥11.1 mM/L) is diagnostic.
2. **Serum C-peptide level:**

- It is co-secreted in an equimolar concentration with insulin.

 - It is used to differentiate between endogenous and exogenous insulin and between type 1 diabetes where no detectable plasma C-peptide and type 2 diabetes where there C-peptide is detectable.

- Normal serum insulin level is 29-181 pM/L, whereas, C-peptide is 0.9 - 4.2 ng/mL.

1. **Glycosylated hemoglobin (HbA1C):**

- Glycosylated hemoglobin is a glycated protein which results from the slow non-enzymatic attachment of glucose to N-terminal valine of β-globin chain.

-It is measured by HPLC, affinity chromatography, gel electrophoresis and immunoassay.

- Its level in the RBCs directly proportionates with the blood glucose level at the time of formation of such cell. This level remains as it is for the whole life span of red cells (120 days).

- Therefore, it is useful for monitoring the degree of control of diabetes mellitus over the preceding 2-3 months before the test.

-Normal glycosylated hemoglobin A1C is 4.0 – 6.5% and uncontrolled diabetic patients is more 7.2%.

1. **Glycated albumin(fructosamine level):**

- Albumin is another protein, which undergoes glycation in a similar way as hemoglobin,

-Where Amadori's rearrangement transforms glucose into fructosamine.

- As albumin has a half-life of about 17 days, fructosamine assay gives an indication about the degree of control of diabetes over the preceding 2-3 weeks.

- Normal value in males is 205-285 μM/L and in females is 199-279 μM/L.

- Fructosamine assay is affected by many factors, which makes it less sensitive than glycosylated hemoglobin A1C.

1. **Urinary Ketone bodies:** indicates insulin deficiency and warns of diabetic ketoacidosis.
2. **Glucose tolerance test (or curve):** The test is used for detection of symptomless, early diabetes, differentiation of different types and severity of diabetes, and help adjusting and following up treatment

**Oral procedure of glucose tolerance curve:**

- The patient must stop smoking, eat normal carbohydrate diet for a few days, and comes overnight fasted (10 – 12 hours).

-A blood sample is taken for blood glucose (collected on fluoride) measurement (fasting glucose) and sample of urine for glucose and ketone bodies detection.

- The patient is given 50-100 gm glucose dissolved in about 250 mL water and blood and urine samples are taken every half hour for two and half hours.

- The blood glucose level is plotted against time to draw glucose tolerance curve.

Interpretation of the results of glucose tolerance test:

**A. Normal curve:**

- The fasting **plasma glucose** level is 70 – 110 mg/dL.

-It increases to a maximum of 130 – 150 mg/dL within one hour after glucose intake.

This ascending limb represents absorptive stage of glucose.

- The blood glucose returns slightly below fasting level after 2 hours due to over utilization of glucose by insulin secretion this called **hypoglycemic response or insulin shock**.

-Insulin secretion continues till the blood glucose level decreases to normal fasting level then it stops.

- All urine samples contain no glucose as the blood glucose level is below renal threshold.

**B. Diabetic curves:**

- It is characterized by diminished glucose tol­erance as:

* Fasting plasma glucose level is higher than normal, ≥126 mg/dL.

* Maximum level of plasma glucose is greater than normal, hence glucose appears in urine.
* Slow return to fasting level
* **Glucosuria**, it is detected by **the strip and reduction tests.**
* **The strip test** (glucose oxidase, peroxidase and chromogen)is also used for self-monitoring of capillary blood glucose.



**Other conditions with impaired glucose tolerance:**

- Hyperactivity of pituitary gland, hyperactivity of adrenal cortex and obesity and atherosclerosis.

**- Hypoglycemic curve:** It indicates increased glucose tolerance due to excessive insulin secretion (Insulinoma) and deficiency of anti-insulin hormones as glucocorticoids (Addison’s disease), anterior pituitary hormones (cretinism), etc. It is characterized by:

1. Fasting level is below normal.
2. Maximum rise is below normal.
3. The return to fasting level is rapid.