Diabetes Mellitus is defined as condition that occurs due to absence of insulin or presence of factors that oppose insulin resulting in elevated glucose levels in blood and urine.

1. Juvenile (onset) diabetes or insulin-dependent diabetes (IDDM) or Type I diabetes

It occurs early in life. It accounts for about 10-20% of diabetic cases. Affected individuals are usually thin or lean or under nourished. It appears usually in childhood or puberty. The age of affected people is always below 30 years.

It is sudden in onset and leads to pathological complications or serious condition. It is due to lack of insulin. The β-cells of affected persons may be destroyed by infections or auto immune diseases. Hence, patients with type I diabetes are treated with insulin injections.

2. Adult (onset) diabetes or non-insulin dependent diabetes (NIDDM) or type II diabetes

It appears late in life usually after 30 years. It accounts for 80-90% of diabetic cases. It occurs gradually and milder condition and pathological complications are less. Affected persons are usually obese. It is a genetic disorder. Insulin production may be normal in the affected persons but numbers of insulin receptors are less.

So, affected individuals are insulin resistant, *i.e., insulin injections are not helpful. Treatment of patients with Type* II diabetes involves use of oral hypoglycemic sulfonyl urea drugs. Further, weight reduction and dietary modifications are helpful in controlling the disease.

In addition to the two types of diabetes other types of diabetes are recognized by WHO. They are

1. Maturity onset diabetes of young (MODY)

2. Malnutrition related diabetes mellitus (MRDM)

3. Gestational diabetes mellitus (GDM)

4. Impaired glucose tolerance diabetes mellitus (IGTDM)

5. Diabetes mellitus associated with other conditions like pancreatic disease, genetic diseases, drug or chemicals induced.

Chronic effects of diabetes mellitus

- In long standing or chronic cases of diabetes in addition to the above symptoms atherosclerosis, coronary artery disease, diabetic neuropathy, diabetic nephropathy and diabetic cataract (retinopathy) develops. Hypertension may also develop in some diabetic cases. Because of involvement of many diseases, diabetes is called as *syndrome*.

- *In* diabetic neuropathy, there is general loss of peripheral sensation particularly of lower limbs. The delayed wound healing and loss of sensation in lower limbs are responsible for development of diabetic foot and may lead to amputation.

- Diabetic nephropathy is due to thickening of capillary basement membrane and increased permeability of capillaries. It is responsible for renal failure in diabetic cases.

- Diabetic cataract is the leading cause of blindness in diabetics. It occurs due to accumulation of sorbitol in lens. Sorbitol is formed from glucose by reduction catalyzed by aldose reductase. Inhibitors of this enzyme may be helpful in preventing development of cataract.

- How hyperglycemia leads to other diseases in diabetes is unclear.

Metabolic changes in diabetes mellitus

Some of metabolic changes in diabetes are similar to starvation. Main differences between diabetes and starvation are blood glucose and insulin levels.

In starvation, blood glucose level remains normal whereas in diabetes it is elevated. The insulin level is normal in starvation and in diabetes insulin action is minimal.

Since insulin is antagonist to glucagon, in diabetes glucagon actions are unopposed. Initially glucagon level in the blood raises and returns to normal later.

Carbohydrate metabolism

In diabetes the blood glucose level increases because of decreased utilization of glucose by peripheral tissues. Due to lack of insulin peripheral tissues like adipose tissue and skeletal

muscle are unable to take up glucose. So glucose conversion to fat and glycogen is block in adipose tissue and skeletal muscle respectively.

In addition, glucagon stimulates gluconeogenesis and glycogenolysis in liver which contributes to blood glucose. Therefore, blood glucose level raises (hyperglycemia) and when the blood sugar level exceeds renal threshold value glucose is excreted in urine (glycosuria).

GLYCOSURIA

Glycosuria refers to sugar in the urine. Less than 0.1% of glucose normally filtered by the glomeruli appears in the urine, and less than 130 mg should appear in the urine over a 24-hour period. Glucose is present in glomerular filtrate but is reabsorbed by the kidney's proximal tubule. If the blood glucose level exceeds the capacity of the tubules to reabsorb all the glucose present in the glomerular filtrate, the renal threshold is reached and glucose spills into the urine. A finding of glycosuria indicates that the person is hyperglycemic or has a lowered renal threshold for glucose. The renal threshold for glucose is approximately 160 to 190mg/dl of blood; glucose does not appear in the urine until the blood glucose rises above this level.

Occasionally, glycosuria may be a normal finding, such as after eating a heavy meal or during times of emotional stress. Some individuals have a benign condition in which they have a lower than usual renal threshold for glucose, but have normal blood glucose levels. In pregnancy, the renal threshold for glucose may be lowered so that small amounts of glycosuria may be present. If the RTG is so low that even normal blood glucose levels produce the condition, it is referred to as *renal glycosuria.*

 Patients on hyperalimentation may have glycosuria if the carbohydrate solution is being infused faster than the pancreas can produce insulin. The most common reason for glycosuria is diabetes mellitus. Urine glucose tests are used to screen for diabetes, to confirm a diagnosis of diabetes, or to monitor diabetic control.

GALACTOSEMIA

A genetic deficiency of any one of the enzymes of the pathway of galactose metabolism-galactokinase, uridyltransferase and galactose epimerase-will impede galactose metabolism and will result in galactosemia if the affected infant ingests lactose. However, if a deficiency of one of these enzymes is identified in the first few days of life through a genetic-disease

screening program, the potentially devastating effects of the mutation can be prevented by eliminating milk and other lactose-containing foods from the diet.

The classic and most severe form of galactosemia is caused by a deficiency of galactose 1 - phosphate uridyltransferase. The resulting accumulation of galactose 1-phosphate in tissues leads to multiple-organ-system pathology, including neurological damage, cataracts, coma, and eventually death. By contrast, deficiency of galactokinase causes cataract formation but is otherwise less severe than classic galactosemia. The enzyme aldose reductase plays a role in the cataract formation associated with galactosemia by reducing galactose to galactitol and trapping this polyol inside cells of the lens. High intracellular concentrations of galactitol draw water into the tissue, thereby promoting osmotic damage to the lens.

Deficiencies of UDP- 1 -galactose 4-epimerase prevent both utilization of exogenous galactose and endogenous galactose synthesis. For this reason, patients are usually placed on a galactose-restricted rather than a galactose-free diet. Patients may also benefit from supplementation with N-acetylgalactosamine, which is needed for the synthesis of glycolipids and other glycoconjugates.

FRUCTOSURIA:

Fructose, the second most common sugar in the adult diet, is ingested principally as the monosaccharide or as part of **sucrose** . It is metabolized principally in the liver (and to a lesser extent in the small intestine and kidney) by phosphorylation at the 1-position to form **fructose 1-P**, followed by conversion to intermediates of the glycolytic pathway. The major products of its metabolism in liver are, therefore, the same as glucose (including lactate, blood glucose, and glycogen).

 Essential fructosuria (**fructokinase deficiency**) and **hereditary fructose intolerance** (a deficiency of the fructose 1-phosphate cleavage by **aldolase B**) are inherited disorders of fructose metabolism.

Fructose synthesis from glucose in the **polyol pathway** occurs in seminal vesicles and other tissues. **Aldose reductase** converts glucose to the sugar alcohol sorbitol (a polyol), which is then oxidized to fructose. In the lens of the eye, elevated levels of **sorbitol** in diabetes mellitus may contribute to **cataract** formation.

When individuals with defects of aldolase B ingest fructose, the extremely high levels of fructose 1-phosphate that accumulate in the liver and kidney cause a number of adverse effects. Hypoglycemia results from inhibition of glycogenolysis and gluconeogenesis. Glycogen phosphorylase (and possibly phosphoglucomutase and other enzymes of glycogen metabolism) are inhibited by the accumulated fructose 1-phosphate. Aldolase B is required for glucose synthesis from glyceraldehydes 3-phosphate and dihydroxyacetone phosphate, and its low activity in aldolase B–deficient individuals is further decreased by the accumulated fructose 1-phosphate.

The inhibition of gluconeogenesis results in lactic acidosis. The accumulation of fructose 1-phosphate also substantially depletes the phosphate pools. The fructokinase reaction uses ATP at a rapid rate such that the mitochondria regenerate ATP rapidly, which leads to a drop in free phosphate levels. The low levels of phosphate release inhibition of AMP deaminase, which converts AMP to inosine monophosphate (IMP). The nitrogenous base of IMP (hypoxanthine) is degraded to uric acid. The lack of phosphate and depletion of adenine nucleotides lead to a loss of ATP, further contributing to the inhibition of biosynthetic pathways, including gluconeogenesis.

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