**The Endocrine System**

The development, structure and functions of human body are governed and maintained by 2 mutually interlinked systems—*the endocrine system* and *the nervous system*; a third system combining features of both these systems is appropriately called *neuroendocrine system*.

**NEUROENDOCRINE SYSTEM**

This system forms a link between the endocrine and nervous systems. The cells of this system elaborate polypeptide hormones and are widely distributed in the body in different anatomic areas and hence are currently called *dispersed neuroendocrine system*. Cells comprising this system are as under:

*1. Neuroendocrine cells* are present in the gastric and intestinal mucosa and elaborate peptide hormones.

*2. Neuroganglia cells* lie in the ganglia cells in the sympathetic chain and elaborate amines.

*3. Adrenal medulla* elaborates epinephrine and norepinephrine.

*4. Parafollicular C cells* of the thyroid secrete calcitonin.

*5. Islets of Langerhans* in the pancreas (included in both endocrine and neuroendocrine systems) secrete insulin.

*6. Isolated cells in the left atrium* of the heart secrete atrial natriuretic (salt losing) peptide hormone.

 **THE ENDOCRINE SYSTEM**

Anatomically, the endocrine system consists of 6 distinct organs: pituitary, adrenals, thyroid, parathyroids, gonads, and pancreatic islets; the last one is included in neuroendocrine system also.

In general, pathologic processes affecting endocrine glands with resultant hormonal abnormalities may occur from following processes:

**Hyperfunction:** This results from excess of hormone secreting tissues e.g. hyperplasia, tumours (adenoma, carcinoma), ectopic hormone production, excessive stimulation from inflammation (often autoimmune), infections, iatrogenic (drugs-induced, hormonal administration).

**Hypofunction:** Deficiency of hormones occurs from destruction of hormoneforming tissues from inflammations (often autoimmune), infections, iatrogenic (e.g. surgical removal, radiation damage), developmental defects (e.g. Turner’s syndrome, hypoplasia), enzyme deficiency, haemorrhage and infarction (e.g. Sheehan’s syndrome), nutritional deficiency (e.g. iodine deficiency).

**Hormone resistance:** There may be adequate or excessive production of a hormone but there is peripheral resistance, often from inherited mutations in receptors (e.g. defect in membrane receptors, nuclear receptors or receptor for signal transduction).

**DIABETES MELLITUS**

Diabetes mellitus (DM) is defined as a heterogeneous metabolic disorder characterised by common feature of chronic hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism. DM is a leading cause of morbidity and mortality world over. It is estimated that approximately 1% of population suffers from DM.

The actions of insulin are

(1) Promotes glucose uptake by target cells and provides for glucose storage as glycogen

(2) Prevents fat and glycogen breakdown and inhibits gluconeogenesis

(3) Increases protein synthesis

 Insulin acts to promote fat storage by increasing the transport of glucose into fat cells. It also facilitates triglyceride synthesis from glucose in fat cells and inhibits the intracellular breakdown of stored triglycerides. Insulin also inhibits protein breakdown and increases protein synthesis by increasing the active transport of amino acids into body cells. Insulin inhibits gluconeogenesis, or the building of glucose from new sources, mainly amino acids. When sufficient glucose and insulin are present, protein breakdown is minimal because the body is able to use glucose and fatty acids as a fuel source.

The term *diabetes* is derived from a Greek word meaning “going through” and *mellitus* from the Latin word for “honey” or sweet.

**Classification and Etiology**

**I// TYPE 1 DM.** It constitutes about 10% cases of DM. It was previously termed as juvenile-onset diabetes (JOD) due to its occurrence in younger age, and was called insulin-dependent DM (IDDM). Based on underlying etiology,

type 1 DM is further divided into 2 subtypes:

* **Subtype 1A (immune-mediated) DM** characterized by autoimmune destruction of β-cells which usually leads to insulin deficiency.
* **Subtype 1B (idiopathic) DM** characterized by insulin deficiency with tendency to develop ketosis but these patients are negative for autoimmune markers.

**II. Type 2 DM**: Type 2 diabetes mellitus describes a condition of hyperglycemia that occurs despite the availability of insulin. In contrast to type 1 diabetes, type 2 diabetes is not associated with autoantibodies. Most people with type 2 diabetes are older and overweight. The metabolic abnormalities that contribute to hyperglycemia in people with type 2 diabetes include (1) impaired insulin secretion, (2) peripheral insulin resistance, and (3) increased hepatic glucose production.

 Insulin resistance initially stimulates insulin secretion from the beta cells in the pancreas to overcome the increased demand to maintain a normoglycemic state. In time, the insulin response by the beta cells declines because of exhaustion. This results in elevated postprandial blood glucose levels. Because people with type 2 diabetes do not have an absolute insulin deficiency, they are less prone to ketoacidosis than are people with type 1 diabetes.

There also is evidence to suggest that insulin resistance not only contributes to the hyperglycemia in persons with type 2 diabetes, but also may play a role in other metabolic abnormalities. These include high levels of plasma triglycerides, low levels of high-density lipoproteins, hypertension, abnormal fibrinolysis, and coronary heart disease. This constellation of abnormalities often is referred to as the *insulin resistance syndrome,* *syndrome X,* or *the metabolic syndrome.*

Obese people have increased resistance to the action of insulin on its receptors and impaired suppression of glucose production by the liver resulting in both hyperglycemia and hyperinsulinemia. The increased insulin resistance has been attributed to increased visceral (intraabdominal) fat detected on computed tomography scan.

***III// secondary diabetes***, describes diabetes that is associated with certain other conditions and syndromes. about 10% cases of DM have a known specific etiologic defect. One important subtype in this group is *maturity-onset diabetes of the young* *(MODY)* which has autosomal dominant inheritance with genetic defects of beta cell function or insulin function, patient present with hyperglycaemia and impaired insulin secretion just like type 2 DM. other causes that may cause secondary diabetes are

* Endocrine disorders, *e.g.,* acromegaly, Cushing’s syndrome
* Drug or chemical-induced, *e.g.,* Vacor, glucocorticoids, thiazide diuretics, α-Interferon
* Infections, *e.g.,* congenital rubella, cytomegalovirus
* Other genetic syndromes sometimes associated with diabetes, *e.g.,* Down syndrome, Klinefelter’s syndrome, Turner’s syndrome

**IV// Gestational diabetes mellitus** **GDM** refers to glucose intolerance that is detected first during pregnancy. It occurs to various degrees in 2% to 5% of pregnancies. It most frequently predicted in women with a family history of diabetes; with glycosuria; with a history of stillbirth or spontaneous abortion, fetal anomalies in a previous pregnancies or a previous large- or heavy-for-date infant; and those who are obese, of advanced maternal age, or have had five or more pregnancies.

Diagnosis and careful medical management are essential because women with GDM are at higher risk for complications of pregnancy, mortality, and fetal abnormalities. Fetal abnormalities include, caudal regression and neural tube defect. The infant of diabetic mother more prone to had macrosomia (*i.e.*, large body size), hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia, RDS after delivery. The American Diabetes Association (ADA) Clinical Practice Recommendations suggest that pregnant women who have hyperglycemia or have glucose intolerance after 24th week of pregnancy.

**Diagnosis of DM:**

1. If the fasting plasma glucose level is higher than 126 mg/dL on two occasions, diabetes is diagnosed
2. Random blood glucose is one that is done without regard to meals or time of day. A random blood glucose concentration that is unequivocally elevated (>200 mg/dL) in the presence of classic symptoms of diabetes such as polydipsia, polyphagia, polyuria, and blurred vision is diagnostic of diabetes mellitus at any age.
3. *Glycosylated hemoglobin* measures the amount of HbA1c (*i.e.*, hemoglobin into which glucose has been incorporated) in the blood. When hemoglobin is released from the bone marrow, it normally does not contain glucose. During its 120-day life span in the red blood cell, hemoglobin normally becomes glycosylated to form glycohemoglobins A1a and A1b (2% to 4%) and A1c (4% to 6%). Because glucose entry into the red blood cell is not insulin dependent, the rate at which glucose becomes attached to the hemoglobin molecule depends on blood glucose. Glycosylation is essentially irreversible, and the level of HbA1c present in the blood provides an index of blood glucose levels during the previous 2 to 3 months.
* **Normal**: HbA1c below 5.7%
* **Prediabetes**: HbA1c between 5.7% and 6.4
* **Diabetes**: HbA1c of 6.5% or higher

1. **Acute Complications of DM**

The three major acute complications of diabetes are diabetic

ketoacidosis, the Hyperglycemic Hyperosmolar Nonketotic Syndrome HHNS,

and hypoglycemia.

**I// Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) occurs when ketone production by the liver exceeds cellular use and renal excretion. DKA most commonly occurs in a person with type 1 diabetes, in whom the lack of insulin leads to mobilization of fatty acids from adipose tissue because of the unsuppressed adipose cell lipase activity that breaks down triglycerides into fatty acids and glycerol. The increase in fatty acid levels leads to ketone production by the liver. The three major metabolic derangements in DKA are hyperglycemia, ketosis, and metabolic acidosis. The definitive diagnosis of DKA consists of hyperglycemia (blood glucose levels >250 mg/dL), low bicarbonate (<15 mEq/L), and low pH (<7.3), with ketonemia (positive at 1:2 dilution) and moderate ketonuria.

Hyperglycemia leads to osmotic diuresis, dehydration, and a critical loss of electrolytes. Hyperosmolality of extracellular fluids from hyperglycemia leads to a shift of water and potassium from the intracellular to the extracellular compartment. Extracellular sodium concentration frequently is low or normal despite enteric water losses because of the intracellular-extracellular fluid shift. This dilutional effect is referred to as *pseudohyponatremia*. Serum potassium levels may be normal or elevated, despite total potassium depletion resulting from protracted polyuria and vomiting. Metabolic acidosis is caused by the excess ketoacids that require buffering by bicarbonate ions; this leads to a marked decrease in serum bicarbonate levels.

**II//Hyperglycemic Hyperosmolar Nonketotic SyndromeHHNS:**

The hyperglycemic hyperosmolar nonketotic (HHNK) syndrome is characterized by hyperglycemia (blood glucose >600 mg/ dL), hyperosmolarity (plasma osmolarity >310 mOsm/L) and dehydration with the absence of ketoacidosis. HHNK syndrome may occur in various conditions including type 2 diabetes, acute pancreatitis, severe infection, myocardial infarction, and treatment with oral or parenteral nutrition solutions. It is seen most frequently in people with type 2 diabetes. Two factors appear to contribute to the hyperglycemia that precipitates the condition:

1. an increased resistance to the effects of insulin
2. an excessive carbohydrate intake.

In hyperosmolar states, the increased serum osmolarity has the effect of pulling water out of body cells, including brain cells. The condition may be complicated by thromboembolic events arising because of the high serum osmolality. The most prominent manifestations are dehydration, neurologic signs and symptoms, and excessive thirst. The neurologic signs include grand mal seizures, hemiparesis, aphasia, muscle fasciculations, hyperthermia, visual field loss, nystagmus, and visual hallucinations. The onset of HHNK syndrome often is insidious, and because it occurs most frequently in older people, it may be mistaken for a stroke.

**III// Hypoglycemia**

Hypoglycemia, sometimes referred to as an **insulin reaction**, occurs from a relative excess of insulin in the blood and is characterized by below-normal blood glucose levels. It occurs most commonly in people treated with insulin injections, but prolonged hypoglycemia also can result from some oral hypoglycemic agents (*i.e.*, beta cell stimulators). Many factors **precipitate** an insulin reaction in a person with type 1 diabetes, including:

1. error in insulin dose,
2. failure to eat,
3. increased exercise,
4. decreased insulin need after removal of a stress situation.
5. medication changes, and a change in insulin site.

Hypoglycemia usually has a rapid onset and progression of symptoms. Because the brain relies on blood glucose as its main energy source, hypoglycemia produces behaviors related to altered cerebral function. Headache, difficulty in problem solving, disturbed or altered behavior, coma, and seizures may occur. At the onset of the hypoglycemic episode, activation of the parasympathetic nervous system often causes hunger. The initial parasympathetic response is followed by activation of the sympathetic nervous system; this causes anxiety, tachycardia, sweating, and constriction of the skin vessels (*i.e.*, the skin is cool and clammy).

**IV// The Somogyi Effect and Dawn Phenomenon**

**Somogyi Effect** is insulin-associated hypoglycemia can cause hyperglycemia in diabetic patients. insulin-induced hypoglycemia produces a compensatory increase in blood levels of catecholamines, glucagon, cortisol, and growth hormone. These counter regulatory hormones cause blood glucose to become elevated and produce some degree of insulin resistance. The cycle begins when the increase in blood glucose and insulin resistance is treated with larger insulin doses. The hypoglycemic episode often occurs during the night or at a time when it is not recognized, rendering the diagnosis of the phenomenon more difficult. Research suggests that even rather mild insulin-associated hypoglycemia, which may be asymptomatic, can cause hyperglycemia in those with type 1diabetes through the recruitment of counter-regulatory mechanisms.

**The dawn phenomenon** is characterized by increased levels of fasting blood glucose or insulin requirements, or both, between 5 and 9 AM without preceding hypoglycemia. It occurs in people with type 1 or type 2 diabetes. It has been suggested that a change in the normal circadian rhythm for glucose tolerance, which usually is higher during the later part of the morning, is altered in people with diabetes. Growth hormone has been suggested as a possible factor.

**Chronic Complications**

The chronic complications of diabetes include neuropathies, disorders of the microcirculation (*i.e.*, neuropathies, nephropathies, and retinopathies), macrovascular complications, and foot ulcers. These disorders occur in the insulin-independent tissues of the body—tissues that do not require insulin for glucose entry into the cell. This probably means that intracellular glucose concentrations in many of these tissues approach or equal those in the blood.

**I// Diabetic peripheral neuropathies** which affect both the somatic and autonomic nervous systems. Two types of pathologic changes have been observed in connection with diabetic peripheral neuropathies. The first is a thickening of the walls of the nutrient vessels that supply the nerve. The second finding is a segmental demyelinization process that affects the Schwann cell. This demyelinization process is accompanied by a slowing of nerve conduction.

**II// Diabetic nephropathy** which is a leading cause of end-stage renal disease, is associated with the increased work demands and microalbuminemia imposed

by poorly controlled blood glucose levels. The most common kidney lesions in people with diabetes are those that affect the glomeruli. Various glomerular changes may occur, including capillary basement membrane thickening, diffuse glomerular sclerosis, and nodular glomerulosclerosis

**III// Diabetic retinopathy** Diabetes is the leading cause of acquired blindness in the

United States. Although people with diabetes are at increased risk for the development of cataracts and glaucoma, retinopathy is the most common pattern of eye disease. Diabetic retinopathy is characterized by abnormal retinal vascular permeability, microaneurysm formation, neovascularization and associated hemorrhage, scarring, and retinal detachment. Twenty years after the onset of diabetes, nearly all people with type 1 diabetes and more than 60% of people with type 2 diabetes have some degree of retinopathy. Pregnancy, puberty, and cataract surgery can accelerate these changes.

**IV// Diabetic Foot Ulcers** Foot problems have been reported as the most common complication leading to hospitalization among people with diabetes. Distal symmetric neuropathy is a major risk factor for foot ulcers. People with sensory neuropathies have impaired pain sensation and often are unaware of the constant trauma to the feet caused by poorly fitting shoes, improper weight bearing, hard objects or pebbles in the shoes, or infections such as athlete’s foot. When the abnormal focus of pressure is coupled with loss of sensation, a foot ulcer can occur. Common sites of trauma are the back of the heel, the plantar metatarsal area, or the great toe, where weight is borne during walking