ISLETS OF LANGERHANS

Endocrine function of pancreas is performed by the islets of Langerhans. Human pancreas contains about 1 to 2 million islets. Islets of Langerhans consist of four types of cells:

1. A cells or α-cells, which secrete glucagon

2. B cells or β-cells, which secrete insulin

3. D cells or δ-cells, which secrete somatostatin

4. F cells or PP cells, which secrete pancreatic polypeptide.

INSULIN: Insulin is a polypeptide with 51 amino acids and a molecular weight of 5,808. It has two amino acid chains called α and β chains, which are linked by disulfide bridges. The α-chain of insulin contains 21 amino acids and β-chain contains 30 amino acids. The biological half-life of insulin is 5 minutes.

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PLASMA LEVEL: Basal level of insulin in plasma is 10 μU/mL.

SYNTHESIS

Synthesis of insulin occurs in the rough endoplasmic reticulum of β-cells in islets of Langerhans. It is synthesized as pre- nproinsulin that gives rise to proinsulin. Proinsulin is converted into insulin and C peptide through a series of peptic cleavages. C peptide is a connecting peptide that connects α and β chains. At the time of secretion, C peptide is detached.

Pre proinsulin → Proinsulin → Peptic cleavage → Insulin

Binding of insulin to insulin receptor is essential for its removal from circulation and degradation. Insulin is

degraded in liver and kidney by a cellular enzyme called *insulin protease or insulin-degrading enzyme.*

ACTIONS OF INSULIN

Insulin is the important hormone that is concerned with the regulation of carbohydrate metabolism and blood glucose level. It is also concerned with the metabolism of proteins and fats.

1. On Carbohydrate Metabolism: Insulin is the only antidiabetic hormone secreted in the body, i.e. it is the only hormone in the body that lowers blood glucose concentration.

Insulin **decreases the blood glucose** level by:

i. Facilitating transport and uptake of glucose by the cells

ii. Increasing the peripheral utilization of glucose

iii. Increasing the storage of glucose by converting it into glycogen in liver and muscle

iv. Inhibiting glycogenolysis

v. Inhibiting gluconeogenesis.

2. On **Protein Metabolism**

Insulin facilitates the synthesis and storage of proteins and inhibits the cellular utilization of proteins as for energy by the following actions:

i. Facilitating the transport of amino acids into the cell from blood, by increasing the permeability of

cell membrane for amino acids

ii. Accelerating protein synthesis by influencing the transcription of DNA and by increasing the

translation of mRNA

iii. Preventing protein catabolism by decreasing the activity of cellular enzymes which act on

proteins

iv. Preventing conversion of proteins into glucose.

Thus, insulin is responsible for the conservation

and storage of proteins in the body.

3. On **Fat Metabolism**

Insulin stimulates the synthesis of fat. It also increases the storage of fat in the adipose tissue.

Actions of insulin on fat metabolism are:

i. Synthesis of fatty acids and triglycerides. Insulin promotes the transport of excess glucose into

cells, particularly the liver cells. This glucose is utilized for the synthesis of fatty acids and triglycerides. Insulin promotes the synthesis of lipids by activating the enzymes which convert:

a. Glucose into fatty acids

b. Fatty acids into triglycerides.

ii. Transport of fatty acids into adipose tissue

Insulin facilitates the transport of fatty acids into the adipose tissue.

iii. Storage of fat

Insulin promotes the storage of fat in adipose tissue by

inhibiting the enzymes which degrade the triglycerides.

4. On **Growth**

Along with growth hormone, insulin promotes growth of body by its anabolic action on proteins. It reduces blood glucose level. Insulin reduces the blood glucose level by its following actions on carbohydrate

metabolism:

i. Increases transport and uptake of glucose by the cells.

Insulin facilitates the transport of glucose from blood into the cells by increasing the permeability of cell membrane to glucose. Insulin stimulates the rapid uptake of glucose by all the tissues, particularly liver, muscle and adipose tissues. But, it is not required for glucose uptake in some tissues such as brain (except hypothalamus), renal tubules, mucous membrane of intestine and RBCs. Insulin also increases the number of glucose transporters, especially GLUT 4 in the cell membrane. Glucose transporters: Usually, glucose is transported into the cells by sodium-glucose symport pump. In addition to symport pump, most of the cells have another type of transport proteins called glucose transporters (GLUT).

So far, seven types of GLUT are identified (GLUT 1–7). Among these, GLUT4 is insulin sensitive and it is located in cytoplasmic vesicles. It is present in large numbers in muscle fibers and adipose cells. When insulin-receptor complex is formed in the membrane of such cells, the vesicles containing GLUT4 are attracted towards the membrane and GLUT4 is released into the membrane. Now, GLUT4 starts transporting the glucose molecules from extracellular fluid (ECF) into the cell. The advantage of GLUT4 is that

i. it transports glucose at a faster rate.

ii. Promotes peripheral utilization of glucose

In presence of insulin, glucose which enters the cell is oxidized immediately. The rate of utilization depends upon the intake of glucose.

iii. Promotes storage of glucose – glycogenesis

Insulin promotes the rapid conversion of glucose into

glycogen (glycogenesis), which is stored in the muscle

and liver. Thus, glucose is stored in these two organs

in the form of glycogen. Insulin activates the enzymes

which are necessary for glycogenesis. In liver, when

glycogen content increases beyond its storing capacity,

insulin causes conversion of glucose into fatty acids.

iv. Inhibits glycogenolysis

Insulin prevents glycogenolysis, i.e. the breakdown of

glycogen into glucose in muscle and liver.

v. Inhibits gluconeogenesis

Insulin prevents gluconeogenesis, i.e. the formation of

glucose from proteins by inhibiting the release of amino

acids from muscle and by inhibiting the activities of

enzymes involved in gluconeogenesis.

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transport of amino acids into the cell and synthesis of

proteins in the cells. It also has the protein-sparing effect,

i.e. it causes conservation of proteins by increasing the

glucose utilization by the tissues.

Houssay Animal

The importance of insulin and growth hormone in the

growth of the body is demonstrated by Houssay animal.

Houssay animal is one in which both anterior pituitary

and pancreas are removed. Administration of either

insulin or growth hormone alone does not induce growth

in this animal. However, the administration of both

the hormones stimulates the growth. This proves the

synergistic actions of these two hormones on growth.

„ MODE OF ACTION OF INSULIN

On the target cells, insulin binds with the receptor protein

and forms the insulin-receptor complex. This complex

executes the action by activating the intracellular

enzyme system.

Insulin Receptor

Insulin receptor is a glycoprotein with a molecular weight

of 340,000. It is present in almost all the cells of the

body.

Subunits of insulin receptor

Insulin receptor is a tetramer, formed by four glycoprotein

subunits (two α-subunits and two β-subunits). The

α-subunits protrude out of the cell and the β-subunits

protrude inside the cell (Fig. 69.1). The α and β subunits

are linked to each other by disulfide bonds. Intracellular

surfaces of α-subunits have the enzyme activity –

protein kinase (tyrosine kinase) activity.

When insulin binds with α-subunits of the receptor

protein, the tyrosine kinase at the β-subunit (that

protrudes into the cell) is activated by means of

autophosphorylation.

Activated tyrosine kinase acts on many intracellular

enzymes by phosphorylating or dephosphorylating them

so that some of the enzymes are activated while others

are inactivated.

Thus, insulin action is exerted on the target cells by

the activation of some intracellular enzymes and by the

inactivation of other enzymes.

„ REGULATION OF INSULIN SECRETION

Insulin secretion is mainly regulated by blood glucose

level.

FIGURE 69.1: Diagram showing the structure of

insulin receptor. S–S = Disulfide bond.

In addition, other factors like amino acids, lipid

deriva tives, gastrointestinal and endocrine hormones

and autonomic nerve fibers also stimulate insulin

secretion.

1. Role of Blood Glucose Level

When blood glucose level is normal (80 to 100 mg/dL),

the rate of insulin secretion is low (up to 10 μU/minute).

When blood glucose level increases between 100 and

120 mg/dL, the rate of insulin secretion rises rapidly to

100 μU/minute. When blood glucose level rises above

200 mg/dL, the rate of insulin secretion also rises very

rapidly up to 400 μU/minute.

Biphasic effect of glucose

Action of blood glucose on insulin secretion is biphasic.

i. Initially, when blood glucose level increases

after a meal, the release of insulin into

blood increases rapidly. Within few minutes,

concentration of insulin in plasma increases up

to 100 μU/mL from the basal level of 10 μU/mL.

It is because of release of insulin that is stored

in pancreas. Later, within 10 to 15 minutes, the

insulin concentration in the blood reduces to half

the value, i.e. up to 40 to 50 μU/mL of plasma.

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ii. After 15 to 20 minutes, the insulin secretion rises

once again. This time it rises slowly but steadily.

It reaches the maximum between 2 and 2½

hours. The prolonged increase in insulin release

is due to the formation of new insulin molecules

continuously from pancreas (Fig. 69.2).

2. Role of Proteins

Excess amino acids in blood also stimulate insulin

secretion. Potent amino acids are arginine and lysin.

Without any increase in blood glucose level, the amino

acids alone can cause a slight increase in insulin

secretion. However, amino acids potentiate the action

of glucose on insulin secretion so that, in the presence

of amino acids, elevated blood glucose level increases

insulin secretion to a great extent.

3. Role of Lipid Derivatives

The β-ketoacids such as acetoacetate also increase

insulin secretion.

4. Role of Gastrointestinal Hormones

Insulin secretion is increased by some of the

gastrointestinal hormones such as gastrin, secretin,

CCK and GIP.

5. Role of Endocrine Hormones

Diabetogenic hormones like glucagon, growth hormone

and cortisol also stimulate insulin secretion, indirectly.

FIGURE 69.2: Changes in plasma level of insulin after meals.

Increase in blood glucose level after meals produces biphasic

effect on plasma level of insulin.

All these diabetogenic hormones increase the blood

glucose level, which stimulates β-cells of islets of

Langerhans. So insulin secretion is increased.

Prolonged hypersecretion of these hormones causes

exhaustion of β-cells, resulting in diabetes mellitus.

6. Role of Autonomic Nerves

Stimulation of parasympathetic nerve to the pancreas

(right vagus) increases insulin secretion. Chemical

neurotransmitter involved is acetylcholine. Stimulation

of sympathetic nerves inhibits the secretion of insulin

and the neurotransmitter is noradrenaline.

However, the role of these nerves on the regulation

of insulin secretion under physiological conditions is not

clear.

„ GLUCAGON

„ SOURCE OF SECRETION

Glucagon is secreted from A cells or α-cells in the islets

of Langerhans of pancreas. It is also secreted from A

cells of stomach and L cells of intestine.

 CHEMISTRY AND HALF-LIFE

Glucagon is a polypeptide with a molecular weight of

3,485. It contains 29 amino acids. Half-life of glucagon

is 3 to 6 minutes.

 SYNTHESIS

Glucagon is synthesized from the preprohormone

precursor called preproglucagon in the α-cells of islets.

Preproglucagon is converted into proglucagon, which

gives rise to glucagon.

 METABOLISM

About 30% of glucagon is degraded in liver and 20% in

kidney. The cleaved glucagon fragments are excreted

through urine. 50% of the circulating glucagon is

degraded in blood itself by enzymes such as serine and

cysteine proteases.

„ ACTIONS OF GLUCAGON

Actions of glucagon are antagonistic to those of insulin

(Table 69.1). It increases the blood glucose level,

peripheral utilization of lipids and the conversion of

proteins into glucose.

1. On Carbohydrate Metabolism

Glucagon increases the blood glucose level by:

i. Increasing glycogenolysis in liver and releasing

glucose from the liver cells into the blood.

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Glucagon does not induce glycogenolysis in

muscle

ii. Increasing gluconeogenesis in liver by:

a. Activating the enzymes, which convert

pyruvate into phosphoenol pyruvate

b. Increasing the transport of amino acids into

the liver cells. The amino acids are utilized

for glucose formation.

2. On Protein Metabolism

Glucagon increases the transport of amino acids into liver

cells. The amino acids are utilized for gluconeogenesis.

3. On Fat Metabolism

Glucagon shows lipolytic and ketogenic actions. It

increases lipolysis by increasing the release of free fatty

acids from adipose tissue and making them available for

peripheral utilization. The lipolytic activity of glucagon, in

turn promotes ketogenesis (formation of ketone bodies)

in liver.

4. Other Actions

Glucagon:

i. Inhibits the secretion of gastric juice

ii. Increases the secretion of bile from liver.

„ MODE OF ACTION OF GLUCAGON

On the target cells (mostly liver cells), glucagon

combines with receptor and activates adenyl cyclase

via G protein. Adenyl cyclase causes the formation of

cyclic adenosine monophosphate (AMP) which brings

out the actions of glucagon. Glucagon receptor is a

peptide with a molecular weight of 62,000.

„ REGULATION OF GLUCAGON SECRETION

Secretion of glucagon is controlled mainly by glucose

and amino acid levels in the blood.

1. Role of Blood Glucose Level

Important factor that regulates the secretion of glucagon

is the decrease in blood glucose level. When blood

glucose level decreases below 80 mg/dL of blood,

α-cells of islets of Langerhans are stimulated and more

glucagon is released. Glucagon, in turn increases the

blood glucose level. On the other hand, when blood

glucose level increases, α-cells are inhibited and the

secretion of glucagon decreases.

2. Role of Amino Acid Level in Blood

Increase in amino acid level in blood stimulates the

secretion of glucagon. Glucagon, in turn converts the

amino acids into glucose.

3. Role of Other Factors

Factors which increase glucagon secretion:

i. Exercise

ii. Stress

iii. Gastrin

TABLE 69.1: Differences between insulin and glucagon

Features Insulin Glucagon

Source of secretion β-cells of islets of langerhans α-cells of islets of langerhans

Action on carbohydrate

metabolism

Decreases blood glucose level by:

1. Facilitating transport and uptake of glucose

by all cells except liver cells

2. Increasing peripheral utilization of glucose

3. Increasing glycogenesis in liver and muscle

4. Preventing glycogenolysis

5. Preventing gluconeogenesis

Increases blood glucose level by:

1. Facilitating glucose transport into liver cells

2. Increasing glycogenolysis

3. Increasing gluconeogenesis

Action on protein

metabolism

1. Facilitates amino acid transport

2. Accelerates protein synthesis

3. Prevents protein catabolism

4. Prevents conversion of proteins into glucose

1. Increases transport of amino acids into liver

cells

2. Increases utilization of amino acids for

gluconeogenesis

Action on fat

metabolism

1. Increases synthesis and storage of fat

2. No ketogenic effect

1. Increases lipolysis

2. Promotes ketogenesis

Blood fatty acids Decreases Increases

Hypersecretion leads to Hypoglycemia Hyperglycemia

Hyposecretion leads to Diabetes mellitus Hypoglycemia

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iv. Cholecystokinin (CCK)

v. Cortisol.

Factors which inhibit glucagon secretion:

i. Somatostatin

ii. Insulin

iii. Free fatty acids

iv. Ketones.

„

GROWTH HORMONE

SOMATOSTATIN

„ SOURCE OF SECRETION

Somatostatin is secreted from:

1. Hypothalamus

2. D cells (δ-cells) in islets of Langerhans of pancreas

3. D cells in stomach and upper part of small

intestine.

 CHEMISTRY AND HALF-LIFE

Somatostatin is a polypeptide. It is synthesized in two

forms, namely somatostatin-14 (with 14 amino acids)

and somatostatin-28 (with 28 amino acids). Both the

forms have similar actions. Half-life of somatostatin is

2 to 4 minutes.

„ SYNTHESIS

Somatostatin is synthesized from the precursor

prosomatostatin. Prosomatostatin is converted mostly

into somatostatin-14 in the D cells of islets in pancreas.

However, in the intestine, large amount of somatostatin-

28 is produced from prosomatostatin.

„ METABOLISM

Somatostatin is degraded in liver and kidney.

„ ACTIONS OF SOMATOSTATIN

1. Somatostatin acts within islets of Langerhans and,

inhibits β and α cells, i.e. it inhibits the secretion of

both glucagon and insulin

2. It decreases the motility of stomach, duodenum and

gallbladder

3. It reduces the secretion of gastrointestinal hormones

gastrin, CCK, GIP and VIP

4. Hypothalamic somatostatin inhibits the secretion of GH

and TSH from anterior pituitary. That is why, it is also

called growth hormone-inhibitory hormone (GHIH).

„ MODE OF ACTION OF SOMATOSTATIN

Somatostatin brings out its actions through cAMP.

„ REGULATION OF SECRETION

OF SOMATOSTATIN

Pancreatic Somatostatin

Secretion of pancreatic somatostatin is stimulated

by glucose, amino acids and CCK. The tumor of D

cells of islets of Langerhans causes hypersecretion

of somatostatin. It leads to hyperglycemia and other

symptoms of diabetes mellitus.

Gastrointestinal Tract Somatostatin

Secretion of somatostatin in GI tract is increased by the

presence of chyme-containing glucose and proteins in

stomach and small intestine.

„ PANCREATIC POLYPEPTIDE

„ SOURCE OF SECRETION

Pancreatic polypeptide is secreted by F cells or PP cells

in the islets of Langerhans of pancreas. It is also found

in small intestine.

„ CHEMISTRY AND HALF-LIFE

Pancreatic polypeptide is a polypeptide with 36 amino

acids. Its half-life is 5 minutes.

„ SYNTHESIS

Pancreatic polypeptide is synthesized from preprohormone

precursor called prepropancreatic polypeptide

in the PP cells of islets.

„ METABOLISM

Pancreatic polypeptide is degraded and removed from

circulation mainly in kidney.

„ ACTIONS OF PANCREATIC POLYPEPTIDE

Exact physiological action of pancreatic polypeptide is

not known. It is believed to increase the secretion of

glucagon from α-cells in islets of Langerhans.

 MODE OF ACTION OF

PANCREATIC POLYPEPTIDE

Pancreatic polypeptide brings out its actions through

cAMP.

 REGULATION OF SECRETION

Secretion of pancreatic polypeptide is stimulated by

the presence of chyme containing more proteins in the

small intestine.

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„

CORTISOL

THYROID HOMONE

REGULATION OF BLOOD GLUCOSE LEVEL (BLOOD GLUCOSE LEVEL)

„ NORMAL BLOOD GLUCOSE LEVEL

In normal persons, blood glucose level is controlled within a narrow range. In the early morning after

overnight fasting, the blood glucose level is low ranging between 70 and 110 mg/dL of blood. Between first

and second hour after meals (postprandial), the blood glucose level rises to 100 to 140 mg/dL. Glucose level

in blood is brought back to normal at the end of second hour after the meals.Blood glucose regulating mechanism is operated through liver and muscle by the influence of the pancreatic hormones – insulin and glucagon. Many other hormones are also involved in the regulation of blood glucose level. Among all the hormones, insulin is the only hormone that reduces the blood glucose level and it is called the antidiabetogenic hormone. The hormones which increase blood glucose level are called diabetogenic hormones or anti-insulin hormones.

Necessity of Regulation of Blood Glucose Level

Regulation of blood glucose (sugar) level is very essential because, glucose is the only nutrient that is utilized for energy by many tissues such as brain tissues, retina and germinal epithelium of the gonads.

ROLE OF LIVER IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Liver serves as an important glucose buffer system. When blood glucose level increases after a meal, the

excess glucose is converted into glycogen and stored in liver. Afterwards, when blood glucose level falls, the

glycogen in liver is converted into glucose and released into the blood. The storage of glycogen and release of glucose from liver are mainly regulated by insulin and glucagon.

ROLE OF INSULIN IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Insulin decreases the blood glucose level and it is the only antidiabetic hormone available in the body (Refer the actions of insulin on carbohydrate metabolism in this

Chapter).

ROLE OF GLUCAGON IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Glucagon increases the blood glucose level (Refer

actions of glucagon on carbohydrate metabolism in this

Chapter).

ROLE OF OTHER HORMONES IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Other hormones which increase the blood glucose level

are:

1. Growth hormone (Chapter 66)

2. Thyroxine (Chapter 67)

3. Cortisol (Chapter 70)

4. Adrenaline (Chapter 71).

Thus, liver helps to maintain the blood glucose

level by storing glycogen when blood glucose level

is high after meals; and by releasing glucose, when

blood glucose level is low after 2 to 3 hours of food

intake. Insulin helps to control the blood glucose level,

especially after meals, when it increases. Glucagon and

other hormones help to maintain the blood glucose level

by raising it in between the meals.

„ APPLIED PHYSIOLOGY

„ HYPOACTIVITY – DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized

by high blood glucose level, associated with other

manifestations. ‘Diabetes’ means ‘polyuria’ and

‘mellitus’ means ‘honey’. The name ‘diabetes mellitus’

was coined by Thomas Willis, who discovered sweetness

of urine from diabetics in 1675.

In most of the cases, diabetes mellitus develops

due to deficiency of insulin.

Classification of Diabetes Mellitus

There are several forms of diabetes mellitus, which

occur due to different causes. Diabetes may be primary

or secondary. Primary diabetes is unrelated to another

disease. Secondary diabetes occurs due to damage or

disease of pancreas by another disease or factor.

Recent classification divides primary diabetes

mellitus into two types, Type I and Type II. Differences

between the two types are given in Table 69.2.

Type I Diabetes Mellitus

Type I diabetes mellitus is due to deficiency of insulin

because of destruction of β-cells in islets of Langerhans.

This type of diabetes mellitus may occur at any age of

life. But, it usually occurs before 40 years of age and

the persons affected by this require insulin injection.

So it is also called insulin-dependent diabetes mellitus

(IDDM). When it develops at infancy or childhood, it is

called juvenile diabetes.

Type I diabetes mellitus develops rapidly and progresses

at a rapid phase. It is not associated with obesity,

but may be associated with acidosis or ketosis.

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Causes of type I diabetes mellitus

1. Degeneration of β-cells in the islets of Langerhans

of pancreas

2. Destruction of β-cells by viral infection

3. Congenital disorder of β-cells

4. Destruction of β-cells during autoimmune diseases.

It is due to the development of antibodies against

β-cells (Refer Chapter 17 for details).

Other forms of type 1 diabetes mellitus

1. Latent autoimmune diabetes in adults (LADA):

LADA or slow onset diabetes has slow onset and

slow progress than IDDM and it occurs in later life

after 35 years. It may be difficult to distinguish LADA

from type II diabetes mellitus, since pancreas takes

longer period to stop secreting insulin.

2. Maturity onset diabetes in young individuals

(MODY): It is a rare inherited form of diabetes

mellitus that occurs before 25 years. It is due to

hereditary defects in insulin secretion.

Type II Diabetes Mellitus

Type II diabetes mellitus is due to insulin resistance

(failure of insulin receptors to give response to insulin).

So, the body is unable to use insulin. About 90% of

diabetic patients have type II diabetes mellitus. It usually

occurs after 40 years. Only some forms of Type II diabetes

require insulin. In most cases, it can be controlled by

oral hypoglycemic drugs. So it is also called noninsulindependent

diabetes mellitus (NIDDM).

Type II diabetes mellitus may or may not be

associated with ketosis, but often it is associated with

obesity.

Causes for type II diabetes mellitus

In this type of diabetes, the structure and function of

β-cells and blood level of insulin are normal. But insulin

receptors may be less, absent or abnormal, resulting in

insulin resistance.

Common causes of insulin resistance are:

1. Genetic disorders (significant factors causing type II

diabetes mellitus)

2. Lifestyle changes such as bad eating habits and

physical inactivity, leading to obesity

3. Stress.

Other forms of type II diabetes mellitus

1. Gestational diabetes: It occurs during pregnancy. It

is due to many factors such as hormones secreted

during pregnancy, obesity and lifestyle before and

during pregnancy. Usually, diabetes disappears

after delivery of the child. However, the woman

has high risk of development of type II diabetes

later.

2. Pre-diabetes: It is also called chemical, subclinical,

latent or borderline diabetes. It is the stage between

normal condition and diabetes. The person does not

show overt (observable) symptoms of diabetes but

there is an increase in blood glucose level. Though

pre-diabetes is reversible, the affected persons are

at a high risk of developing type II diabetes mellitus.

TABLE 69.2: Differences between type I and type II diabetes mellitus

Features Type I (IDDM) Type II (NIDDM)

Age of onset Usually before 40 year Usually after 40 year

Major cause Lack of insulin Lack of insulin receptor

Insulin deficiency Yes Partial deficiency

Immune destruction of β-cells Yes No

Involvement of other endocrine disorders No Yes

Hereditary cause Yes May or may not be

Need for insulin Always Not in initial stage

May require in later stage

Insulin resistance No Yes

Control by oral hypoglycemic agents No Yes

Symptoms appear Rapidly Slowly

Body weight Usually thin Usually overweight

Stress-induced obesity No Yes

Ketosis Yes May or may not be

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Secondary Diabetes Mellitus

Secondary diabetes mellitus is rare and only about 2%

of diabetic patients have secondary diabetes. It may

be temporary or may become permanent due to the

underlying cause.

Causes of secondary diabetes mellitus

1. Endocrine disorders such as gigantism, acromegaly

and Cushing’s syndrome.

Hyperglycemia in these conditions causes excess

stimulation of β-cells. Constant and excess stimulation,

in turn causes burning out and degeneration of

β-cells. The β-cell exhaustion leads to permanent

diabetes mellitus.

2. Damage of pancreas due to disorders such as chronic

pancreatitis, cystic fibrosis and hemochromatosis

(high iron content in body causing damage of

organs)

3. Pancreatectomy (surgical removal)

4. Liver diseases such as hepatitis C and fatty liver

5. Autoimmune diseases such as celiac disease

6. Excessive use of drugs like antihypertensive

drugs (beta blockers and diuretics), steroids, oral

contraceptives, chemotherapy drugs, etc.

7. Excessive intake of alcohol and opiates.

Signs and Symptoms of Diabetes Mellitus

Various manifestations of diabetes mellitus develop

because of three major setbacks of insulin deficiency.

1. Increased blood glucose level (300 to 400 mg/dL)

due to reduced utilization by tissue

2. Mobilization of fats from adipose tissue for energy

purpose, leading to elevated fatty acid content in

blood. This causes deposition of fat on the wall of

arteries and development of atherosclerosis

3. Depletion of proteins from the tissues.

Following are the signs and symptoms of diabetes

mellitus:

1. Glucosuria

Glucosuria is the loss of glucose in urine. Normally,

glucose does not appear in urine. When glucose level

rises above 180 mg/dL in blood, glucose appears in

urine. It is the renal threshold level for glucose.

2. Osmotic diuresis

Osmotic diuresis is the diuresis caused by osmotic

effects. Excess glucose in the renal tubules develops

osmotic effect. Osmotic effect decreases the reabsorption

of water from renal tubules, resulting in

diuresis. It leads to polyuria and polydipsia.

3. Polyuria

Excess urine formation with increase in the frequency of

voiding urine is called polyuria. It is due to the osmotic

diuresis caused by increase in blood glucose level.

4. Polydipsia

Increase in water intake is called polydipsia. Excess

loss of water decreases the water content and increases

the salt content in the body. This stimulates the thirst

center in hypothalamus. Thirst center, in turn increases

the intake of water.

5. Polyphagia

Polyphagia means the intake of excess food. It is very

common in diabetes mellitus.

6. Asthenia

Loss of strength is called asthenia. Body becomes very

weak because of this. Asthenia occurs due to protein

depletion, which is caused by lack of insulin. Lack of insulin

causes decrease in protein synthesis and increase in

protein breakdown, resulting in protein depletion. Protein

depletion also occurs due to the utilization of proteins for

energy in the absence of glucose utilization.

7. Acidosis

During insulin deficiency, glucose cannot be utilized by

the peripheral tissues for energy. So, a large amount

of fat is broken down to release energy. It causes the

formation of excess ketoacids, leading to acidosis.

One more reason for acidosis is that the ketoacids

are excreted in combination with sodium ions through

urine (ketonuria). Sodium is exchanged for hydrogen

ions, which diffuse from the renal tubules into ECF

adding to acidosis.

8. Acetone breathing

In cases of severe ketoacidosis, acetone is expired in

the expiratory air, giving the characteristic acetone or

fruity breath odor. It is a life-threatening condition of

severe diabetes.

9. Kussmaul breathing

Kussmaul breathing is the increase in rate and depth of

respiration caused by severe acidosis.

10. Circulatory shock

Osmotic diuresis leads to dehydration, which causes

circulatory shock. It occurs only in severe diabetes.

11. Coma

Due to Kussmaul breathing, large amount of carbon

dioxide is lost during expiration. It leads to drastic

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reduction in the concentration of bicarbonate ions

causing severe acidosis and coma. It occurs in severe

cases of diabetes mellitus.

Increase in the blood glucose level develops

hyperosmolarity of plasma which also leads to coma. It

is called hyperosmolar coma.

Complications of Diabetes Mellitus

Prolonged hyperglycemia in diabetes mellitus causes

dysfunction and injury of many tissues, resulting in some

complications. Development of these complications

is directly proportional to the degree and duration

of hyperglycemia. However, the patients with wellcontrolled

diabetes can postpone the onset or reduce

the rate of progression of these complications.

Initially, the untreated chronic hyperglycemia affects

the blood vessels, resulting in vascular complications

like atherosclerosis. Vascular complications are responsible

for the development of most of the complications

of diabetes such as:

1. Cardiovascular complications like:

i. Hypertension

ii. Myocardial infarction

2. Degenerative changes in retina called diabetic

retinopathy

3. Degenerative changes in kidney known as diabetic

nephropathy

4. Degeneration of autonomic and peripheral nerves

called diabetic neuropathy.

Diagnostic Tests for Diabetes Mellitus

Diagnosis of diabetes mellitus includes the determination

of:

1. Fasting blood glucose

2. Postprandial blood glucose

3. Glucose tolerance test (GTT)

4. Glycosylated (glycated) hemoglobin.

Determination of glycosylated hemoglobin is

commonly done to monitor the glycemic control of the

persons already diagnosed with diabetes mellitus.

Abnormal response in diagnostic tests

Abnormal response in diagnostic tests occurs in

conditions like pre-diabetes (see above). There is

an increased fasting blood glucose level or impaired

(decreased) glucose tolerance.

Treatment for Diabetes Mellitus

Type I diabetes mellitus

Type I diabetes mellitus is treated by exogenous insulin.

Since insulin is a polypeptide, it is degraded in GI

tract if taken orally. So, it is generally administered by

subcutaneous injection.

Type II diabetes mellitus

Type II diabetes mellitus is treated by oral hypoglycemic

drugs. Patients with longstanding severe diabetes

mellitus may require a combination of oral hypoglycemic

drugs with insulin to control the hyperglycemia.

Oral hypoglycemic drugs are classified into three

types.

1. Insulin secretagogues: These drugs decrease the

blood glucose level by stimulating insulin secretion

from β-cells. Sulfonylureas (tolbutamide, gluburide,

glipizide, etc.) are the commonly available insulin

secretagogues

2. Insulin sensitizers: These drugs decrease the

blood glucose level by facilitating the insulin action

in the target tissues. Examples are biguanides

(metformin) and thiazolidinediones (pioglitazone

and rosiglitazone)

3. Alpha glucosidase inhibitors: These drugs control

blood glucose level by inhibiting α-glucosidase. This

intestinal enzyme is responsible for the conversion

of dietary and other complex carbohydrates into

glucose and other monosaccharides, which can be

absorbed from intestine. Examples of α-glucosidase

inhibitors are acarbose and meglitol.

 HYPERACTIVITY – HYPERINSULINISM

Hyperinsulinism is the hypersecretion of insulin.

Cause of Hyperinsulinism

Hyperinsulinism occurs due to the tumor of β-cells in the

islets of Langerhans.

Signs and Symptoms of Hyperinsulinism

1. Hypoglycemia

Blood glucose level falls below 50 mg/dL.

2. Manifestations of central nervous system

Manifestations of central nervous system occur when

the blood glucose level decreases. All the manifestations

are together called neuroglycopenic symptoms.

Initially, the activity of neurons increases, resulting

in nervousness, tremor all over the body and sweating.

If not treated immediately, it leads to clonic convulsions

and unconsciousness. Slowly, the convulsions cease

and coma occurs due to the damage of neurons.