# Endocrine Functions of the Pancreas & Regulation of Carbohydrate Metabolism

CHAPTER 24

## First Part

**OBJECTIVES**

*After reading this chapter, you should be able to:*

- List the hormones that affect the plasma glucose concentration and briefly describe the action of each.
- Describe the structure of the pancreatic islets and name the hormones secreted by each of the cell types in the islets.
- Describe the structure of insulin and outline the steps involved in its biosynthesis and release into the bloodstream.
- List the consequences of insulin deficiency and explain how each of these abnormalities is produced.
- Describe insulin receptors, the way they mediate the effects of insulin, and the way they are regulated.
- Describe the types of glucose transporters found in the body and the function of each.
- List the major factors that affect the secretion of insulin.
- Describe the structure of glucagon and other physiologically active peptides produced from its precursor.
- List the physiologically significant effects of glucagon and the factors that regulate glucagon secretion.
- Describe the physiologic effects of somatostatin in the pancreas.
- Outline the mechanisms by which thyroid hormones, adrenal glucocorticoids, catecholamines, and growth hormone affect carbohydrate metabolism.
- Understand the major differences between type 1 and type 2 diabetes.

| | |
|---|---|
| Endocrine Functions of the Pancreas & Regulation of Carbohydrate Metabolism | • structure, biosynthesis, & secretion of insulin<br>• fate of secreted insulin<br>• mechanism of action<br>• consequences of insulin deficiency<br>• regulation of insulin secretion<br>• glucagon<br>• other islet cell hormones<br>• hypoglycemia & diabetes mellitus in humans |

**Islets of Langerhans secrete**:

1. **Insulin** and **glucagon**: Regulate **Carbohydrates**, **Proteins** and **fats** intermediary **metabolism**
2. **Somatostatin**: regulation of **islet** cell **secretion**
3. **Pancreatic polypeptide**: regulation of **ion transport** in the **intestine**

**Islets cells**:

1. **B (beta, β , 60-75%)**: located in the center of the islet; secrete insulin
2. **A (alpha, α, 20%)**: surround B cells; secrete glucagon
3. **D (delta, δ, less common)**: surround B cells; secrete somatostatin
4. **F (gamma, γ, less common)**: surround B cells; secrete pancreatic polypeptide

- Size of **endocrine** glands (islet cells): **2%**
- Size of **exocrine** glands: **80%**
- **Ducts** and **blood vessels**: **18%**
- Total number of **islets** in human: **1-2 Million** islets.

# INTRODUCTION

At least four polypeptides with regulatory activity are secreted by the islets of Langerhans in the pancreas. Two of these, **insulin** and **glucagon**, are hormones and have important functions in the regulation of the intermediary metabolism of carbohydrates, proteins, and fats. The third polypeptide, **somatostatin**, plays a role in the regulation of islet cell secretion, and the fourth, **pancreatic polypeptide**, is probably concerned primarily with the regulation of ion transport in the intestine.

# ISLET CELL STRUCTURE

The islets of Langerhans are collections of cells.

The cells in the islets can be divided into types on the basis of their staining properties and morphology. Humans have at least four distinct cell types: A, B, D, and F cells. A, B, and D cells are also called α, β, and δ cells.

β-Islets make up about 2% of the volume of the gland, whereas the exocrine portion of the pancreas makes up 80%, and ducts and blood vessels make up the remainder. Humans have 1 to 2 million islets.

The A cells secrete glucagon, the B cells secrete insulin, the D cells secrete somatostatin, and the F cells secrete pancreatic polypeptide. The B cells, which are the most common and account for 60–75% of the cells in the islets, are generally located in the center of each islet. They tend to be surrounded by the A cells, which make up 20% of the total, and the less common D and F cells.

**Insulin**:
**Structure**: heterodimer (**αβ bridged by S-S bond**) **polypeptide;** (51 a.a. nonglycosylated)
**Synthesis**: by translation by ribosomes in REP
**Storage:** in secretory granules
**Excretion**: by exocytosis
**Half-life: 5min** (insulin-receptor internalization and degradation by proteases
**Action**: net **storage** of **carbohydrates**, **proteins** and **fats** (act on **skeletal muscles**, **cardiac muscles**, **liver** and **adipose tissue**)
**See NEXT page**

# STRUCTURE, BIOSYNTHESIS, & SECRETION OF INSULIN

## STRUCTURE & SPECIES SPECIFICITY

Insulin is a polypeptide containing two chains of amino acids linked by disulfide bridges.

## BIOSYNTHESIS & SECRETION

Insulin is synthesized in the rough endoplasmic reticulum of the B cells . It is then transported to the Golgi apparatus, where it is packaged into membrane-bound granules. These granules move to the plasma membrane by a process involving microtubules, and their contents are expelled by exocytosis .

## EFFECTS OF INSULIN

The physiologic effects of insulin are far-reaching and complex. They are conveniently divided into rapid, intermediate, and delayed actions (Table ).

The actions of insulin on adipose tissue; skeletal, cardiac, and smooth muscle; and the liver are summarized by the net effect of the storage of carbohydrate, protein, and fat.

Therefore, insulin is appropriately called the "hormone of abundance."

# FATE OF SECRETED INSULIN

## METABOLISM

The half-life of insulin in the circulation in humans is about 5 min. Insulin binds to insulin receptors, and some is internalized. It is destroyed by proteases in the endosomes formed by the endocytotic process.

# Effects of insulin on various tissues

**Adipose tissue**

- Increased glucose entry
- Increased fatty acid synthesis
- Increased glycerol phosphate synthesis
- Increased triglyceride deposition
- Activation of lipoprotein lipase
- Inhibition of hormone-sensitive lipase
- Increased $K^+$ uptake

**Muscle**

- Increased glucose entry
- Increased glycogen synthesis
- Increased amino acid uptake
- Increased protein synthesis in ribosomes
- Decreased protein catabolism
- Decreased release of gluconeogenic amino acids
- Increased ketone uptake
- Increased $K^+$ uptake

**Liver**

- Decreased ketogenesis
- Increased protein synthesis
- Increased lipid synthesis
- Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis, and increased glycolysis

**General**

- Increased cell growth

Important table

## TABLE Principal actions of insulin.

| |
|---|
| **Rapid (seconds)** |
| Increased transport of glucose, amino acids, and $K^+$ into insulin-sensitive cells |
| **Intermediate (minutes)** |
| Stimulation of protein synthesis |
| Inhibition of protein degradation |
| Activation of glycolytic enzymes and glycogen synthase |
| Inhibition of phosphorylase and gluconeogenic enzymes |
| **Delayed (hours)** |
| Increase in mRNAs for lipogenic and other enzymes |

**Glucose entry across cell membrane – Stimulation by insulin**:

- **Entry in intestinal and renal tubular cells**: by Secondary active transport with $Na^+$ "i.e.; by SGLUT".
- **Entry in other cells:** by facilitated diffusion using GLUTs. **Insulin increase** the **number** of **GLUTs.** In **muscle** and **adipose** tissues insulin **increase** the number of **GLUT2**
- **Entry in liver:** Glucose enters by **GLUT2**. **THEN** **phosphorylated** by glucokinase. **When** free intracellular glucose reduced the entry by facilitated diffusion continue. **Insulin induces glucokinase**

MCQ: Insulin increases the entry of glucose into

A. All tissues
B. Renal tubular cells
C. The mucosa of the small intestine
D. Most neurons in the cerebral cortex
**E. Skeletal muscle**

# GLUCOSE TRANSPORTERS

Glucose enters cells by **facilitated diffusion** or, in the intestine and kidneys, by secondary active transport with $Na^+$. In muscle, adipose, and some other tissues, insulin stimulates glucose entry into cells by increasing the number of glucose transporters (GLUTs) in the cell membranes.

The GLUTs that are responsible for facilitated diffusion of glucose across cell membranes are a family of closely related proteins that span the cell membrane 12 times and have their amino and carboxyl terminals inside the cell.

Insulin also increases the entry of glucose into liver cells, but it does not exert this effect by increasing the number of GLUT-4 transporters in the cell membranes. Instead, it induces glucokinase, and this increases the phosphorylation of glucose, so that the intracellular free glucose concentration stays low, facilitating the entry of glucose into the cell.

MCQ: β islets make up about 2% of the volume of pancreas. Which of the followings is not a feature of these cells?

A. They account 60-75% of the cells in the islets of Langerhans
B. They are located in the center of each islet
C. They are surrounded by A, D and F cells
D. **They secrete glucagon**
E. They respond to increased plasma levels of arginine

MCQ: Insulin is a polypeptide secreted by pancreas containing two chains of amino acids. Which of the followings is not related to insulin ?

A. It is a heterodimer of αβ chains linked by S-S bonds
B. **It is synthesized by cytoplasmic ribosomes**
C. It has a half-life of 5min
D. Has a net storage effects on carbohydrates, proteins and fats
E. Its action is terminated by cells on which it is act

MCQ: At least 4 polypeptides with regulatory activity are secreted by the islets of Langerhans in the pancreas. Which of the following are incorrectly paired?

A. B cells: insulin
B. D cells: somatostatin
C. A cells: glucagon
D. Pancreatic exocrine cells: chymotrypsinogen
E. **F cells: gastrin**

MCQ: Insulin is considered as a growth hormone secreted by pancreas c. Which of the followings is not an action of insulin ?

A. It increase glucose entry in all tissues except RBCs, brain and heart
B. It increase K+ entry into skeletal muscle and fat cells
C. **It stimulate hormone-sensitive lipase in adipose tissues**
D. It decrease protein catabolism and reduce plasma amino acids
E. It inhibits gluconeogenesis in liver cells

MCQ: Glucose enters cells by facilitated diffusion or by secondary active transport with Na+. Which of the followings is not correct for glucose transporters?

A. SGLUTs are present in renal tubules and are not regulated by insulin
B. GLUT2 are present in enterocytes and are not regulated by insulin
C. GLUT4 are resent in skeletal muscle cells and are regulated by insulin
D. Entry of glucose into cardiac cells is not largely regulated by insulin
E. **GLUT2 are resent in hepatic cells and are regulated by insulin**

**Insulin and $K^+$ plasma level**:

- **Infusion of glucose and insulin:** lower plasma K+ in patients with renal failure (use for temporary management)
- **Hypokalemia:** developed in patients with diabetic acidosis who are treated with insulin
- **Mechanism:** possibly due to increase the activity of $Na^+$-$K^+$/ATPase pump (pumping more $K^+$ into the cell)

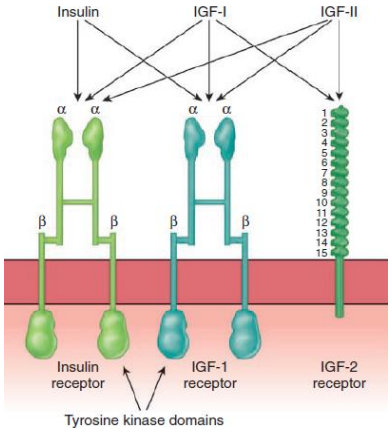
## RELATION TO POTASSIUM

Insulin causes $K^+$ to enter cells, with a resultant lowering of the extracellular $K^+$ concentration. Infusions of insulin and glucose significantly lower the plasma $K^+$ level in normal individuals and are very effective for the temporary relief of hyperkalemia in patients with renal failure.

**Hypokalemia** often develops when patients with diabetic acidosis are treated with insulin. The reason for the intracellular migration of $K^+$ is still uncertain. However, insulin increases the activity of Na, K ATPase in cell membranes, so that more $K^+$ is pumped into cells.

**Insulin receptor– Stimulation by insulin**:

- **Tetramer:** 4 glycoprotein subunits (2α2β)
- **Type: Tyrosine kinase**
- **Insulin binding site: the α subunits**
- **Catalytic site: β subunits**
- **Signal transduction: Phosphorylation** of several proteins and **dephosphorylation** of others
- **Effect: Protein synthesis** and cellular **regulation**




MCQ: Insulin receptors are found on many different cells in the body. Which of the followings is not correct about these receptors?

A. They are tyrosine kinase receptors
B. They can bind IGF-I as swell
C. They are heterodimers glycoproteins
D. When activated they induce phosphorylation of some cellular proteins
E. **When activated in liver cells they increase the number of GLUT2 transporters**

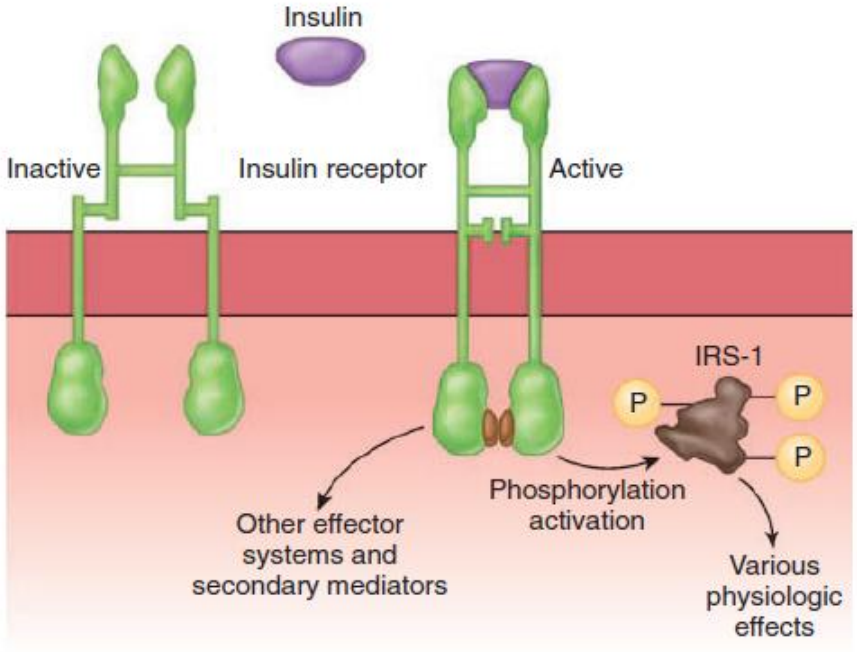
# MECHANISM OF ACTION

## INSULIN RECEPTORS

Insulin receptors are found on many different cells in the body, The insulin receptor, is a tetramer made up of two α and two β glycoprotein subunits (Figure ).

The α subunits bind insulin and are extracellular, whereas the β subunits span the membrane. The intracellular portions of the β subunits have tyrosine kinase activity.

Binding of insulin triggers the tyrosine kinase activity of the β subunits, producing autophosphorylation of the β subunits on tyrosine residues.



**Causes of insulin deficiency** :

- **Pancreatectomy**
- **Destruction** of **B cells** by toxins
- Drugs that **inhibit** insulin **secretion**
- **Anti-insulin** antibodies

**Insulin deficiency causes hyperglycemia which has consequences of:**

1. **Polyuria** (excreted glucose osmosing water - **water diuresis**)
2. **Dehydration** (**water loss** due water diuresis)
3. **Polydipsia** (Thirst due to dehydration and **increase plasma osmolality**)
4. **Polyphagia**: feeling of **hunger**

**Diabetic control is indexed by level of $HbA_{1c}$ (glycated Hb A)**

**Normal** : below 5.7%
**Prediabetes**: 5.7 - 6.4%
**Diabetes**: 6.5% or higher.

# CONSEQUENCES OF INSULIN DEFICIENCY

In humans, insulin deficiency is a common pathologic condition. In animals, it can be produced by pancreatectomy; by administration of toxins that in appropriate doses cause selective destruction of the B cells of the pancreatic islets; by administration of drugs that inhibit insulin secretion; and by administration of anti-insulin antibodies.

# EFFECTS OF HYPERGLYCEMIA

Hyperglycemia by itself can cause symptoms resulting from the hyperosmolality of the blood. In addition, there is glycosuria because the renal capacity for glucose reabsorption is exceeded. Excretion of the osmotically active glucose molecules entails the loss of large amounts of water (osmotic diuresis . The resultant dehydration activates the mechanisms regulating water intake, leading to polydipsia

When plasma glucose is episodically elevated over time, small amounts of hemoglobin A are nonenzymatically glycated to form $HbA_{Ic}$ . Careful control of the diabetes with insulin reduces the amount formed and consequently $HbA_{Ic}$ concentration is measured clinically as an integrated index of diabetic control for the 4- to 6-weeks period before the measurement.

**Decreased intracellular glucose affect proteins**:

- **Protein catabolize** to **supply amino acids** for **gluconeogenesis (hence** blood amino acids **increase)**
- **Liver convert amino acids** into **glucose** (first step is deamination)
- Deamination of amino acids **increases** blood **$CO_2$** (predispose to **acidosis**)
- Glucagon and **adrenal glucocorticoids** also **stimulate gluconeogenesis**
- In uncontrolled DM **muscles** are **poorly developed**

## CHANGES IN PROTEIN METABOLISM

In diabetes, the rate at which amino acids are catabolized to $CO_2$ and $H_2O$ is increased. In addition, more amino acids are converted to glucose in the liver. The increased gluconeogenesis has many causes. Glucagon stimulates gluconeogenesis, and hyperglucagonemia is generally present in diabetes. Adrenal glucocorticoids also contribute to increased gluconeogenesis when they are elevated in severely ill diabetics. The supply of amino acids is increased for gluconeogenesis because, in the absence of insulin, less protein synthesis occurs in muscle and hence blood amino acid levels rise.

**Insulin deficiency** :

- **Normally insulin inhibits** the **hormone-sensitive lipase** in **adipose tissue** (**inhibit lipolysis** and **promote adipogenesis**)
- **Lipid catabolism** thus **accelerated** causes **increased ketone bodies** formation ( and **decrease** synthesis of **TG**)
- **Plasma FFA** is more than **doubled**
- Glucagon also increase plasma FFA

**Intracellular glucose deficiency**

- Conversion of glucose to fatty acids decrease in the depots

**FFA parallel** plasma **glucose** in **DM** and is better **indicator** of the diabetic state

## FAT METABOLISM IN DIABETES

The principal abnormalities of fat metabolism in diabetes are accelerated lipid catabolism, with increased formation of ketone bodies, and decreased synthesis of fatty acids and triglycerides.

In diabetes, conversion of glucose to fatty acids in the depots is decreased because of the intracellular glucose deficiency. Insulin inhibits the hormone-sensitive lipase in adipose tissue, and, in the absence of this hormone, the plasma level of **free fatty acids** ( FFA ) is more than doubled. The increased glucagon also contributes to the mobilization of FFA. Thus, the FFA level parallels the plasma glucose level in diabetes and in some ways is a better indicator of the severity of the diabetic state.

**In uncontrolled diabetes**:

- **The plasma is lipemic** (increased FFA, TG and chylomicrons due to decrease removal of TGs into the fat depots "i.e.; decrease TG synthesis in adipose tissues")

- **VLDL** and **LDL** (hence **plasma cholesterol**) **elevated** that **accelerate** the development of **atherosclerotic** vascular disease.
- The increase in VLDL or LDL is **due** to **increase hepatic production** or **decrease removal** of these lipoproteins

In uncontrolled diabetes, the plasma concentration of triglycerides and chylomicrons as well as FFA is increased, and the plasma is often lipemic. The rise in these constituents is mainly due to decreased removal of triglycerides into the fat depots. The decreased activity of lipoprotein lipase contributes to this decreased removal.

## CHOLESTEROL METABOLISM

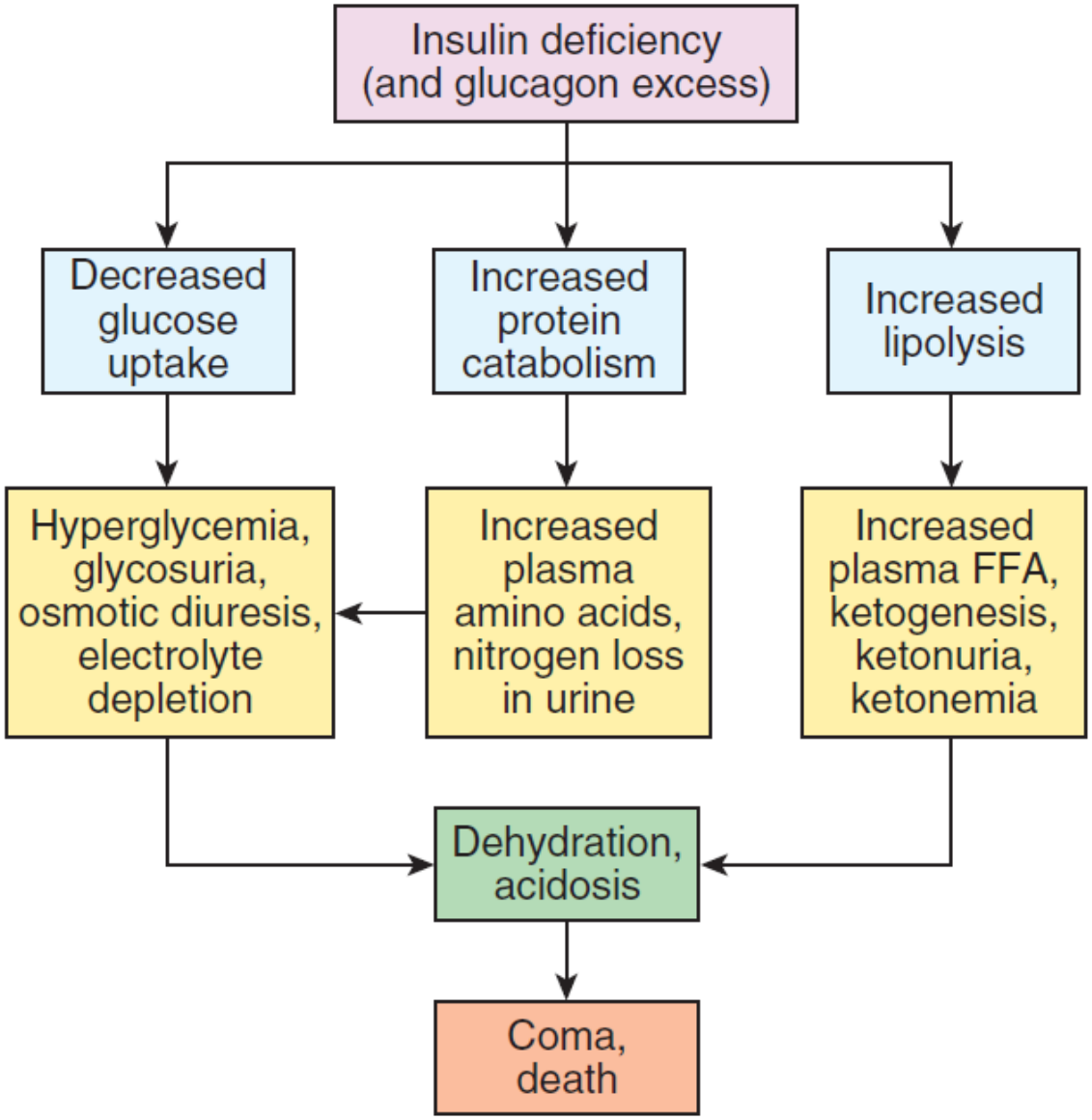
In diabetes, the plasma cholesterol level is usually elevated and this plays a role in the accelerated development of the atherosclerotic vascular disease that is a major long-term complication of diabetes in humans. The rise in plasma cholesterol level is due to an increase in the plasma concentration of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) . These in turn may be due to increased hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation.

**Causes of coma**:

1. Acidosis (acetoacetate, β-hydroxybutyrate)
2. Dehydration (due to water diuresis)
3. Hyperosmolarity (due to high plasma glucose)
4. Lactic acidosis (in hypoxic conditions)

## COMA

Coma in diabetes can be due to acidosis and dehydration. However, the plasma glucose can be elevated to such a degree that independent of plasma pH, the hyperosmolarity of the plasma causes unconsciousness (**hyperosmolar coma**). Accumulation of lactate in the blood (**lactic acidosis**) may also complicate diabetic ketoacidosis if the tissues become hypoxic, and lactic acidosis may itself cause coma.


Insulin deficiency
(and glucagon excess)
Decreased
glucose
uptake
Increased
protein
catabolism
Increased
lipolysis
Hyperglycemia,
glycosuria,
osmotic diuresis,
electrolyte
depletion
Increased
plasma
amino acids,
nitrogen loss
in urine
Increased
plasma FFA,
ketogenesis,
ketonuria,
ketonemia
Dehydration,
acidosis
Coma,
death

MCQ: In humans, insulin deficiency is a common pathologic condition. Which of the followings is not correct about insulin deficiency?

A. It can leads to body weight reduction
B. It can lead to hyperglucagonemia
C. **It is common in old individuals**
D. It can raise plasma osmolality
E. It can be assessed by measuring the C-peptide in plasma

MCQ: Hyperglycemia refers to raised in plasma glucose level. Which of the followings is not of the marks of hyperglycemia?

A. Water diuresis
B. High need for drinking water
C. Feeling of hunger
D. Glycation of hemoglobin
E. **Comma**

MCQ: Changes in carbohydrates metabolism is common in insulin deficient patients. Which of the followings is incorrect in those patients?

A. **There will be an increase in blood pH**
B. There will be an increase in protein catabolism
C. There will be an increase in plasma glucagon level
D. There will be a rise in cortisol secretion
E. There will be an increase in blood urea nitrogen

MCQ: Changes in lipid metabolism is common in insulin deficient patients. Which of the followings is incorrect in those patients?

A. There will be an decrease in blood pH
B. There will be an increase in lipid catabolism
C. There will be an increase in plasma fatty acids
D. **There will be a rise HDL-cholesterol**
E. There will be an increase in acetoacetate blood levels

MCQ: Metabolic changes in diabetic patients are either due to deficiency of intracellular glucose or deficiency of insulin action. Which of the followings is not related to deficiency of insulin action?

A. Hyperglucagonemia
B. Lipolysis
C. Hyperglycemia
**D. Lactic acidosis**
E. None of the above

MCQ: Coma in diabetics can be due to many causes. Which of the followings is not a cause of coma in diabetic patients?

A. Ketoacidosis
B. Hypovolemia
C. Hyperosmolarity
**D. Hyperammonemia**
E. All above are causes of coma in diabetics