



A Review On Role Of Insulin In Diabetes Mellitus

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Abstract: Diabetes is caused by combined abnormalities in insulin production and action. The pathophysiology of these defects has been studied extensively and is reasonably well understood. The discovery of insulin represents an authentic breakthrough, characterized, at the same time, by contrasts, controversies and disputes among scholars, as well as by great disappointments, failures and hopes. The prevalence of this disease is increasing at a very fast and alarming rate and by 2035; 592 million people will be diabetic worldwide. Majority of diabetic people live in low and middle income countries and India is at second position in diabetes prevalence. There is an increase in the prevalence of type-1 diabetes also, but main cause of diabetic epidemic is type-2 diabetes mellitus, which accounts for more than 90 percent of all diabetes cases. Type2 diabetes is a serious and common chronic disease resulting from a complex inheritance- environment interaction along with other risk factors such as obesity and sedentary lifestyle.

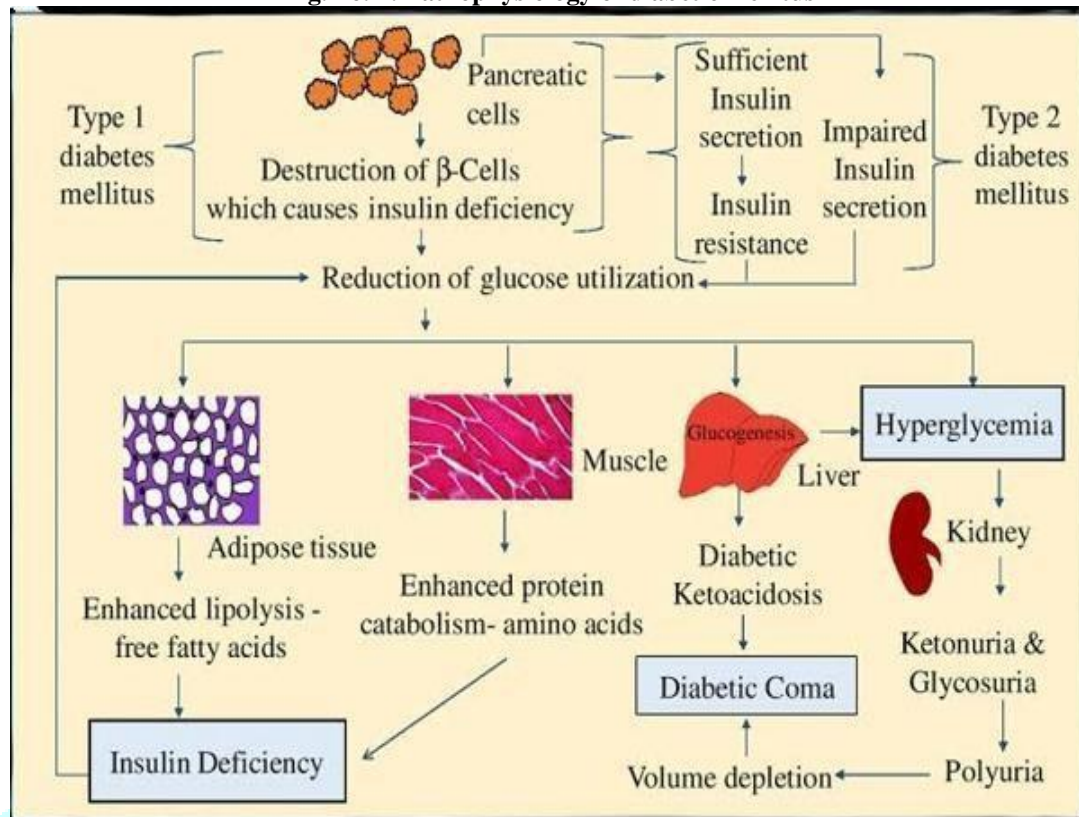
Keywords: Diabetes mellitus, Insulin, pancreas, Glucose

INTRODUCTION:

Diabetes mellitus:-It is group of metabolic disease characterized by increased level of glucose in the blood (hyperglycemia) resulting from defects insulin secretion, insulin action. Diabetes is due to either the pancreas not producing enough insulin or the cell of body not responding properly to the Insulin produced.

Clinical features similar to diabetes mellitus were described 3000 years ago by the ancient Egyptians. The term "diabetes" was first coined by Aretus of Cappodocia (81-133AD). Later, the word mellitus (honey sweet) was added by Thomas Willis (Britain) in 1675 after rediscovering the sweetness of urine and blood of patients (first noticed by the ancient Indians). It was only in 1776 that Dobson (Britain) firstly confirmed the presence of excess sugar in urine and blood as a cause of their sweetness. In modern time, the history of diabetes coincided with the emergence of experimental medicine. An important milestone in the history of diabetes is the establishment of the role of the liver in glycogenesis, and the concept that diabetes is due to excess glucose production Claude Bernard (France) in 1857. The role of the pancreas in pathogenesis of diabetes was discovered by Mering and Minkowski (Austria) 1889. Later, this discovery constituted the basis of insulin isolation and clinical use by Banting and Best (Canada) in 1921. Trials to prepare an orally administrated hypoglycemic agent ended successfully by first marketing of tolbutamide and carbutamide in 1955. This report will also discuss the history of dietary management and acute and chronic complications of diabetes.

Fig. no. 1: Pathophysiology of diabetic mellitus



Types of diabetes mellitus:-

A) Types 1 Diabetes mellitus / Insulin dependent diabetes mellitus/ juvenile onset diabetes mellitus:-

Type 1 diabetes mellitus is a condition in which the body can no longer produce sufficient amount of its own insulin. In this body sugar (glucose) Level increase and in the options of supplement insulin, diabetic, and death will be occur. Only 5% of people have this Type 1 diabetes mellitus. In all type 1 causes circulating level are low or very low and patient are more prone or ketosis. This type is less common and a low degree of genetic predisposition. If blood glucose level are not properly regulated and are not corrected overtime, heart disease, kidney disease, blindness and nerve damage occurs as a result.

B) Type 2 diabetes mellitus /Non-insulin- dependent diabetes / Maturity onset diabetes mellitus:-

Type 2 diabetes mellitus, cell does not respond insulin it's called insulin resistance. The glucose then stay in your body add not enough goes into your cell, overtime having too much glucose in your body can causes health problems. About 90% of people cause this type 2 diabetes mellitus. Type 2 diabetes mellitus causes genetics, obesity, stress, lack of exercise. Type 2 diabetes mellitus causes reduced the sensitivity of peripheral tissue to insulin, reduce the numbers of insulin receptor, down regulates of insulin receptors.

Diabetes mellitus effects on organs:-

A) The cardiovascular system:-

According to the Centers for Disease Control and Prevention (CDCP), cardiovascular disease is the leading cause of early death among people with diabetes. The people with diabetes are two to three times more likely to have a stroke or die of some form of heart disease than those without diabetes.

B) Blood vessels:-

Excess blood sugar decreases the elasticity of blood vessels and causes them to narrow, impeding blood flow. This can lead to a reduced supply of blood and oxygen, increasing the risk of high blood pressure and damage to large and small blood vessels. High blood pressure is a risk factor for heart disease. Nearly 74% Trusted Source of adults with diabetes have hypertension.

C) WOUNDS AND INFECTIONS:-

Poor circulation affects trusted source the body's ability to heal when there is a wound or an infection. This is due to a low supply of blood, oxygen, and nutrients. A person with diabetes should check their skin regularly for wounds and see their doctor if they have any signs of an infection, including redness, swelling, or fever.

D) The nervous system:-

Neuropathy, or nerve damage, is a common complication of diabetes.

About 10–20% Trusted Source of people with an initial diagnosis of diabetes will have nerve damage. The longer a person is living with diabetes, the higher their chance of getting neuropathy. More than half of people living with diabetes will eventually get the condition.

E) The kidneys and urinary system:-

Over time, high blood sugar levels can damage blood vessels in the kidneys. This damage prevents the kidneys from filtering waste out of the blood. In time, kidney failure can result. Diabetic nephropathy is a kidney disease that affects people with diabetes. The NIDDK describes diabetes as one of the main causes of kidney disease. It affects 1 in 3 people trusted source with diabetes.

F) VISION:-

Diabetes increases the risk trustedsource of a number of eye problems, some of which can lead to vision loss. Short-term problems include blurred vision due to high blood sugar. Long-term complications include:

- a. Glaucoma
- b. Diabetic retinopathy
- c. Macular edema

G) Digestive system: -Damage to the nervous system can affect autonomic body functions, including digestion. Gastro paresis can happen when nerve damage interferes with Trusted Source the ability of the digestive system to move food from the stomach into the small intestine.

The condition can result in:

- Nausea
- Vomiting
- Acid reflux
- Bloating
- Abdominal pain
- Loss in severe cases

H) Skin:-

There are links between diabetes and various skin conditions. Symptoms can range from mild to severe.

Problems include a higher chance of:

- Dry skin
- Dark patches of skin, known as acanthosis nigricans
- Bacterial infections, such as sties or boils
- Fungal infections, such as thrush or athlete's foot
- Itching
- Blisters
- Dermopathy, which involves harmless but potentially bothersome roundish, brown, scaly patches

I) Bladder and sex organs:-

Uncontrolled blood sugar forces your bladder to handle a lot of urine because your body retains more fluid. You may wake often at night to use the bathroom. The interrupted sleep can be one reason diabetes leaves you tired. Or diabetes can damage your nerves so you won't feel that your bladder is full. You could leak pee. Weakened urinary muscles can make it harder for you to empty your bladder fully. Or you may pee too much. Poor bladder control, plus high blood sugar and immune system problems, can lead to urinary tract infections (UTIs). When it comes to sex, men with diabetes are three times more likely to have trouble getting or keeping an erection (called erectile dysfunction). For women, their sex drive could drop, lubrication drops, and sex may hurt. Lowered blood flow or nerve problems could make it harder to have an orgasm.

Insulin: -The insulin was discord in 1921 byBunting and Best. It was first obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger. Sanger established amino acid Sequence Of insulin in 1960 and it was synthesized in 1963. Hodgkin and co- workers ha elucidated Insulin's three dimensional structure 1972. Insulin is two chain polypeptide having 51 amino acid And molecular weight about 5742 Dalton .The A chain has 21 amino acid While B chain has 30 amino acid .The beta cells Of pancreatic islets Synthesize insulin from a single chain precursor of 110 amino acid termed preproinsulin (110AA) from which 24AA are first removed first produce pro-insulin. The C peptide is split off by proteolysis in Golgi apparatus; both Insulin and c peptide are stored in granules within the cell. The c peptide is secreted in the blood along with insulin.

The first-phase release is rapidly triggered in response to increased blood glucose levels, and lasts about 10 minutes. The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar, peaking in 2 to 3 hours. The two phases of the insulin release suggest that insulin granules are present in diverse stated populations or "pools". During the first phase of insulin exocytosis, most of the granules predispose for exocytosis are released after the calcium internalization. This pool is known as Readily Releasable Pool (RRP). The RRP granules represent 0.3-0.7% of the total insulin-containing granule population, and they are found immediately adjacent to the plasma membrane. During the second phase of exocytosis, insulin granules require mobilization of granules to the plasma membrane and a previous preparation to undergo their release. Thus, the second phase of

insulin release is governed by the rate at which granules get ready for release. This pool is known as a Reserve Pool (RP). The RP is released slower than the RRP (RRP: 18 granules/min; RP: 6 granules/min). Reduced first-phase insulin release may be the earliest detectable beta cell defect predicting onset of type 2 diabetes. First-phase release and insulin sensitivity are independent predictors of diabetes.

Actions of insulin:-

The overall effects of insulin are to dispose meal derived glucose, amino acids, fatty acids and favour storage of fuel. It is a major anabolic hormone: promotes synthesis of glycogen, lipids and protein. The actions of insulin and the results of its deficiency can be summarized as:

1. Insulin facilitates glucose transport across cell membrane; skeletal muscle and fat are highly sensitive. The availability of glucose intracellularly is the limiting factor for its utilization in these and some other tissues. However, glucose entry in liver, brain, RBC, WBC and renal medullary cells is largely independent of insulin. Ketoacidosis interferes with glucose utilization by brain and contributes to diabetic coma. Muscular activity induces glucose entry in muscle cells without the need for insulin. As such, exercise has insulin sparing effect. The intracellular pool of vesicles containing glucose transporter glycoproteins GLUT4 (insulin activated) and GLUT1 is in dynamic equilibrium, Paracrine modulation of hormone secretion within the pancreatic islets of Langerhans with the GLUT vesicles inserted into the membrane. This equilibrium is regulated by insulin to favour translocation to the membrane. Moreover, on a long-term basis, synthesis of GLUT4 is upregulated by insulin.

2. The first step in intracellular utilization of glucose is its phosphorylation to form glucose-6-phosphate. This is enhanced by insulin through increased production of glucokinase. Insulin facilitates glycogen synthesis from glucose in liver, muscle and fat by stimulating the enzyme glycogen synthase. It also inhibits glycogen degrading enzyme phosphorylase → decreased glycogenolysis in liver.

3. Insulin inhibits gluconeogenesis (from protein, FFA and glycerol) in liver by gene mediated decreased synthesis of phosphoenolpyruvate carboxykinase. In insulin deficiency, proteins and amino acids are funneled from peripheral tissues to liver where these substances are converted to carbohydrate and urea. Thus, in diabetes there is underutilization and over production of glucose → hyperglycaemia → glycosuria.

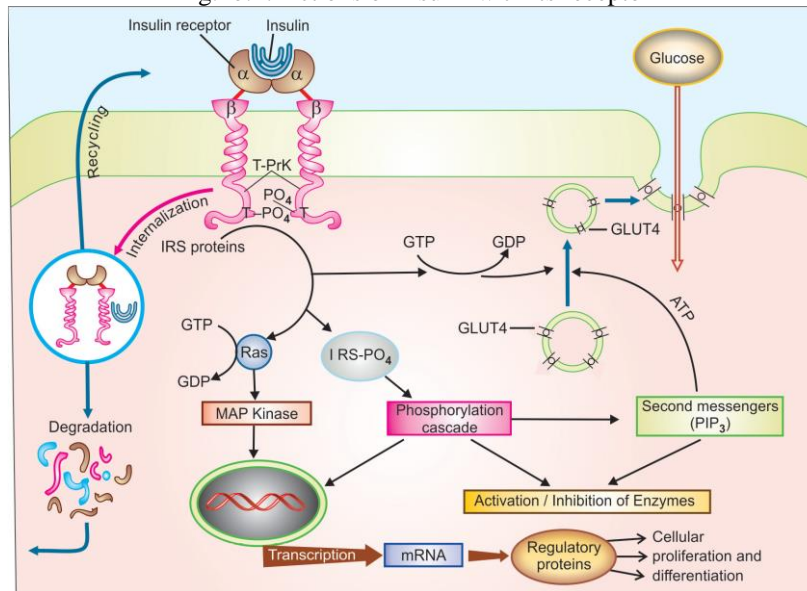
4. Insulin inhibits lipolysis in adipose tissue and favours triglyceride synthesis. In diabetes increased amount of fat is broken down due to unchecked action of lipolytic hormones (glucagon, Adr, thyroxine, etc.) → increased FFA and glycerol in blood → taken up by liver to produce acetyl-CoA. Normally acetyl-CoA is resynthesized to fatty acids and triglycerides, but this process is reduced in diabetics and acetyl CoA is diverted to produce ketone bodies (acetone, acetoacetate, β-hydroxy-butyrate). The ketone bodies are released in blood—partly used up by muscle and heart as energy source, but when their capacity is exceeded, ketonaemia and ketonuria result.

5. Insulin enhances transcription of vascular endothelial lipoprotein lipase and thus increases clearance of VLDL and chylomicrons.

6. Insulin facilitates AA entry and their synthesis into proteins, as well as inhibits protein breakdown in muscle and most other cells. Insulin deficiency leads to protein breakdown → AAs are released in blood → taken up by liver and converted to pyruvate, glucose and urea. The excess urea produced is excreted in urine resulting in negative nitrogen balance. Thus, catabolism takes the upper hand over anabolism in the diabetic state. Most of the above metabolic actions of insulin are exerted within seconds or minutes and are called the rapid actions. Others involving DNA mediated synthesis of glucose transporter and some enzymes of amino acid metabolism have a latency of few hours—the intermediate actions. In addition insulin exerts major long-term effects on multiplication and differentiation of many types of cells.

Mechanism of action Insulin acts on specific receptors located on the cell membrane of practically every cell, but their density depends on the cell type: liver and fat cells are very rich. The insulin receptor is a receptor tyrosine kinase (RTK) which is heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds. It is oriented across the cell membrane as a heterodimer. The subunits carry insulin binding sites, while the β subunits have tyrosine protein kinase activity. Binding of insulin to α subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β subunits → pairs of β subunits phosphorylate tyrosine residues. Insulin enhances glucose uptake and metabolism in the cells, thereby reducing blood sugar level. Their neighboring alpha cells, by taking their cues from the beta cells, secrete glucagon into the blood in the opposite manner: increased secretion when blood glucose is low, and decreased secretion when glucose concentrations are high. Glucagon increases blood glucose level by stimulating glycogenolysis and gluconeogenesis in the liver. The secretion of insulin and glucagon into the blood in response to the blood glucose concentration is the primary mechanism of glucose homeostasis.

Fig.no.2: Actions of insulin with its receptor



Type of insulin depending upon duration of action

A) Rapid acting insulin: -

Rapid acting insulin are usually taken just before or with a meal. They act very quickly to minimize the rise in blood sugar Level in the body .Rapid acting insulin's are commonly prescribed to People type one diabetes and type 2 diabetes Miletus. As the rapid acting insulin active very quickly they can lead to an increased chances of hyperglycemia care should be therefore taken when dosing. Rapid acting insulin begins to work about 15 minutes after injection, peaksin about one to two hours after an injection and last between two to four hours.

Insulin lispro: - insulin lisprois produced by reversing proline and lysine add the carboxy terminus B28 and B29 position, each forms vary weak hexamers that dissociate rapidly S.C. Injection. Resulting a quick and more defined peak as well as shorter duration of action. Unlike regular insulin, it needs to be injected immediately before or even after the meal, a slightly greater reduction in HbA1c compared to regular insulin has been reported.

HUMALOG 100 U/ml, 3ml cartridge, 10ml vial

Insulin aspart:- The Proline at B28 of human insulin Is replaced by aspartic acid .this change reduces the tendency for self – aggregation, and a time action profile similar to insulin lispro is obtained. Glucose escape is less pronounced.IGf-1 receptor affinity and mutagenic potential are similar to those of human insulin.it more closely mimics the physiological insulin release pattern after a meal.

NOVOLOG; NOVORAPID 100U/ml injection. Biphasic insulin aspart – novo MiX 30 FEXPEN injector

B) Short acting insulin: -Short acting insulin Collider regular or neutral insulin. It is oh buffered neutral PH solution of unmodified insulin stabilized buy a small amount of zinc. add the concentration of the injectable solution, the insulin molecules self-aggregate go form examiners around zinc ions, after S.C Injection, insulin monomers are released gradually by dilution, so that absorption occur slowly. The peak action is produced only after two to three hours and action continues up to 6 to 8 hours. The absorption pattern He is also affected by those higher dose act longer not as quickly to act as rapid acting insulin and therefore may be more appropriate in certain people

C) Intermediate acting:-Intermediate acting insulin is a basal, or background insulin that help to prevent high blood sugar in people with diabetes. As the name suggests, it has a duration between rapid add ultra-long acting insulin. Insulin helps to more glucose out of your bloodstream and into your cell, where it's needed for energy. Intermediate acting insulin works by providing the body with a steady source of insulin. intermediate acting insulin generally riches the blurred stream about two to four hours after injection, peaks 4 to 12 hours later, and is effective what 12 to 18 hours. Intermediate acting insulin is used to prevent hyperglycemia.

Isophane (neutral protamine Hagedorn or NPH) insulin: -Protamine added in a quantity just sufficient too complex all insulin molecule neither of the two is present in free form and pH is neutral. On S.C. Injection, the complex dissociate slowly twilled and intermediate duration. It is mostly combined with regular insulin (70:30 or 50:50) and injected S.C twice daily before breakfast and before dinner

D) Long acting insulin: -Manipulating varied aspect chains and/or amino Acids within the hypoglycemic agent molecule has allowable convenience of long hypoglycemic agent (e.g., detemir, glargine, anddegludec), permitting slower absorption, “peak less” concentrations, and long period of Action. This higher replicates traditional basal secretion or constant hypoglycemic agent secretion providing a comparatively steady level of dailyhypoglycemic agent (GururajSettyEal., 2016). For several patients,

initiation of hypoglycemic agent Therapy begins with basal or long hypoglycemic agent. Basal hypoglycemic agent slows viscous aldohexose production and is needed in a very fast state to keep up aldohexose physiological condition and provides a lot of consistent, Background level of hypoglycemic agent. In general, basal hypoglycemic agent is run once daily, each twenty four hours at the same time every day. It's vital to notice that basal hypoglycemic agent (e.g., glargine) ought to nearly always be administered in spite of food intake as this is the constant background hypoglycemic agent normally secreted by the duct gland to keep up Normal aldohexose levels freelance of food intake. Patients with polygenic disease UN agency have traditional aldohexose Values ought to still receive their basal hypoglycemic agent doses even within the absence of caloric intake. NPH hypoglycemic agent may be administered as basal insulin; however, it needs twice-daily administration. The primary advantage of NPH as a basal hypoglycemic agent is Financial, because it is often more cost effective than long acting hypoglycemic agent analogs.

Insulin glargine :- This long acting biosynthetic insulin had two additional arginine reduce add the carboxyl terminus of B chain and glycine replace asparagine at A 21 .8 remain soluble at PH4 of the formulation, but precipitates At neutral encountered on S.C Injection. A depot it's created from which monomeric insulin dissociates slowly to enter the circulation. Onset of action delayed but relatively low blood level on insulin are maintained for up to. 24 hours a smooth Peak less effect is obtained. Fasting and interdigestive blood glucose level are effectively lowered irrespective of time of the day when injected or the site of S.C. injection. It is mostly injected at bedtime.

LANTUS OPTISET 100 U/ml vial and 3 ml prefilled pen injector

Insulin detemir:- myristoyl (a fatty acid) radical is attached to the amino acid of lysine at B29 of insulin chain. As a result, it blinds to albumin after s.c. injection from which the free from become available slowly. A pattern of insulin action almost similar to that of insulin glargine is obtained, but twice daily dosing may be needed.

Uses of insulin:-

- Human insulin is used to control blood sugar level in Diabetes mellitus patient
- Insulin is mostly used to treat type 1 and type 2 diabetes mellitus
- Restore metabolism to normal
- Prevent acute & chronic complications
- Achieve the biochemical control

Adverse effects of insulin:-

- Redness, swelling, and itching at the injection site.
- Weight gain.
- Constipation.
- Swelling of your arms and legs.
- Low blood sugar (hypoglycemia).
- Injection site reactions.
- Skin changes at the injection site (lip dystrophy).
- Changes in the feel of your skin, skin thickening (fat build-up), or a little depression in the skin (fat breakdown)

Conclusion: -

Insulin is one of the modes of treatment for diabetes. It means that, the role of insulin is most important in the management of sugar or glucose level in the blood. A wide variety of insulin delivery devices are available today. Each delivery device is directed to deliver the desired dose of insulin. Diabetes is a serious life-threatening disease and must be constantly monitored and effectively subdued with proper medication and by adapting to a healthy lifestyle. This review provides the information regarding the importance of insulin in diabetes mellitus.

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