

Introduction of Diabetes Mellitus and Insulin

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Abstract: Diabetes mellitus is the one of the chronic metabolic disorder, which is lead of cause other health complication. The different types of diabetes mellitus are present and they are classified on the bases of their causes. Insulin is the most effective drug for the treatment of Type I diabetes mellitus. In this article we discussed about basic aspect of diabetes mellitus and insulin like its development, structure, mechanism of action and adverse effect.

Keywords: Diabetes Mellitus, Glucose, Insulin, Islet of Langerhan's.

INTRODUCTION

DIABETES MELLITUS [Udaykumar, P; Paradkar and chenewal; medicalnewstoday.com; everydayhealth.com]

Definition

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and altered metabolism of carbohydrates, lipids and proteins.

Types of Diabetes

Diabetes Mellitus is classified into 4 types

Type I- It is also called as Insulin dependent diabetes mellitus (IDDM).

Type II- It is also called as Non- Insulin dependent diabetes mellitus (NIDDM).

Type III-

Type IV- Gestational Diabetes

In following section we discuss about the different types of diabetes, sign and symptoms diabetes complications and about the insulin like its development, structure, its actions on the body and adverse effects.

Type I or Insulin Dependent Diabetes Mellitus

It is an auto immune disorder where antibodies destroy the beta cells of the islet of langerhans leading to insulin deficiency. It usually occurs in the young children and adolescents. Adolescent is nothing but an irreversible onset diabetes mellitus. The incidence of this type of diabetes mellitus is fortunately low.

Sign and Symptoms

Type I shows the following sign and symptoms

1. Polyuria,
2. Polyphagia,
3. Polydispia,
4. Weight loss
5. Polydispia

6. Decreased muscle strength and irritability
7. Blurred Vision
8. Ketoacidosis
9. Nausea and vomiting
10. Frequent infections
11. Headache
12. Fast heart rate, Etc.

Type II or Non- Insulin dependent Diabetes Mellitus

It is maturity onset. Most of patients are obese. There is both reduced sensitivity of tissues to utilize the insulin and converts the glucose into glycogen and also impaired regulation of insulin secretion by beta cells of langerhans in pancreas by that decrease in circulating concentration of insulin. Diabetes is discovered only when sugar appears in the urine¹.

Sign and Symptoms

- Increased Thirst
- Frequent urination
- Blurred vision

Type III

It is due to causes like pancreatectomy drugs and non pancreatic disease. Type III occurs when neurons in the brain become unable to respond to insulin¹, which is essential for basic functions including memory and learning¹. Some researchers believe insulin deficiency is central to the cognitive decline of Alzheimer's disease³.

Sign and Symptoms

- Memory loss that interfere daily living and social interactions.
- Difficulty in completing familiar tasks.
- Misplacing things.
- Decreased ability to make judgments.

- Sudden changes in personality or demeanor.

Type IV or Gestational Diabetes:

This may be due to placental hormones that are effect insulin resistance¹. Yet for many pregnant women, gestational diabetes does not cause any recognizable symptoms.

That is why screening tests for the conditions are recommended for all pregnant women.

Sign and Symptoms [Paradkar and chenewal]

1. Frequent urination
2. Increased Thirst
3. Extreme tiredness
4. Nausea and vomiting
5. Weight loss even with increased appetite
6. Blurred vision.

Complication of Diabetes [Deshpande, A.D, 2008; www.mayoclinic.org; www.mayoclinic.org]

- Heart and blood vessel disease- complications include cardiovascular disease, stroke, and peripheral vascular disease. Peripheral vascular disease may lead to bruises or injuries that do not heal, gangrene, and, ultimately, amputation.
- Diabetic Neuropathy- caused by damage to the nerves and the small blood vessels that nourish your nerves with oxygen and nutrients.
- Diabetic Nephropathy- is defined as persistent proteinuria in patients without urinary tract infection or other diseases causing the proteinuria. In patients with type 1 diabetes, development of clinical nephropathy is a relatively late event; however, in patients with type 2 diabetes, diabetic proteinuria may be present at diagnosis. Many people with diabetes develop high blood pressure. That can also damage your kidneys.
- Diabetic Retinopathy- damage of retina. Diabetic retinopathy is the most common micro vascular complication among people with diabetes.
- Foot problems-caused by damage to the nerves and reduced blood flow to your feet.
- Gum disease and other dental problems- because a high amount of blood sugar in your saliva helps harmful bacteria grow in your mouth. The bacteria combine with food to form a soft, sticky film called plaque. Plaque also comes from eating foods that contain sugars or starches. Some types of plaque cause gum disease and bad breath. Other types cause tooth decay and cavities.

- Sexual and bladder problems-caused by damage to the nerves and reduced blood flow in the genitals and bladder
- Skin conditions- some of which are caused by changes in the small blood vessels and reduced circulation.
- People with diabetes are also more likely to have infections, including skin infections.
- Pregnancy complication
- Alzheimer disease
- Hearing impairment
- Dementia

INSULIN

Insulin Development History

The discovery of insulin is a breakthrough for the treatment of diabetic and the care of diabetic patients. The development of proper purifying and modifying method for obtain insulin took 30 more years. In 1889 the scientist gives the insulin. In Germany Oskar Minkowski and Joseph von Mering notice that pancreatectomy in experimental animal causes the severe diabetes mellitus and begun the speculation that a mysterious secretion produced by the pancreas is responsible for metabolic control. In the first ten years of Twentieth Century it was broadly hypothesized that an internal solution secreted by pancreas controls carbohydrate metabolism. In 1907 Belgian Investigator J de Meyer proposed that islet cell of pancreatic secret internal secretion and it to be Insulin and in 1916 Sharpey Schafer in Britain suggest same name⁸.

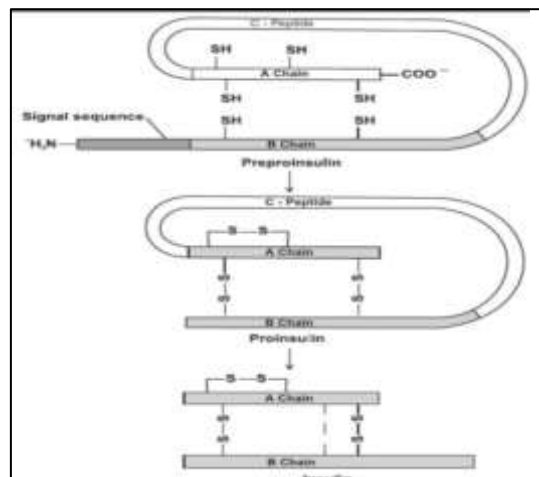
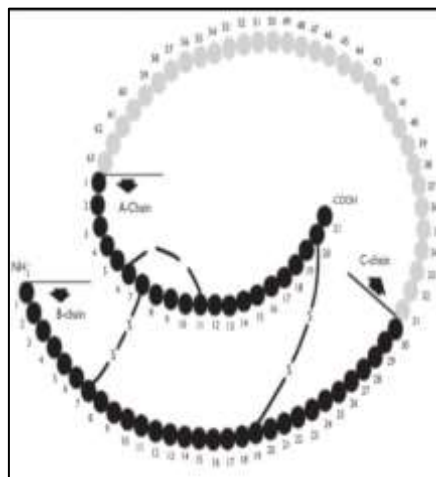
In 1921 two young physician Frederick Banting and forth year medical student Charles Best along with the Prof. McLeod in the Toronto University found final link in a series of studies that guessed the pancreas secretion of substance capable of to decrease blood glucose concentrations. The isolated insulin cured the hyperglycemia in diabetic dogs. In 1922 Leonard Thompson in 14 year diabetic patient first time successfully admistered. In 1928 study proved that the hormone is nothing but protein. Banting and Best identified insulin is short acting that 6hours effective, so repeated dosing is required. To overcome this problem many scientist involve developing the better insulin. In 1936 Hans Christian Hagedorn and colleagues developed the first clinically useful protracted intermediate acting insulin in the form of neutral suspension of protamine insulin but it is chemically unstable. So further preparation is prepared by adding excess amount of protamine and small amount of zinc and it is known as protamine zinc insulin. It shows prolonged

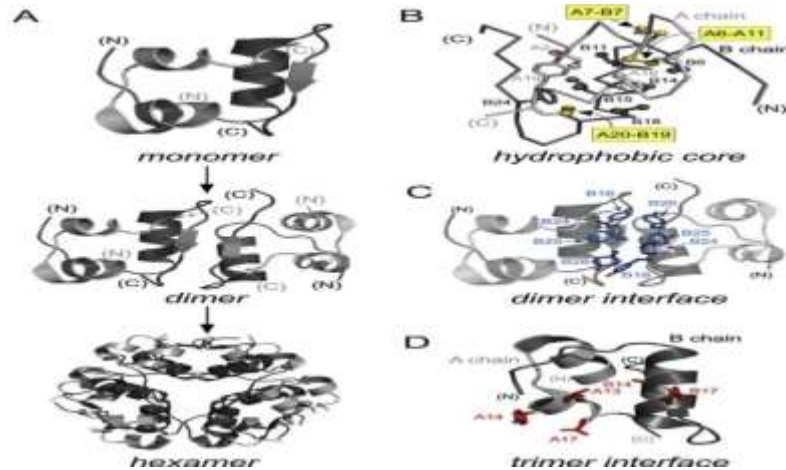
hypoglycemic effect of up to 24 hrs. But it cause hypoglycemia with reports of sudden and severe attacks and also onset of action slow that is 1-3hrs. To form the intermediate insulin by using PZI. The PZI is admixture with the soluble insulin. It act up to 16-18hrs, but it is unstable and had to be administered as separate injections, causing inconvenience to patients. Finally, in 1946, Hagedorn and colleagues introduced crystalline neutral protamine Hagedorn (NPH) insulin, which was a more stable PZI modification combining insulin and protamine in isophane proportions at neutral pH in the presence of a small amount of zinc and phenol and/or phenol derivatives to generate tetragonal oblong-shaped crystals. Unlike

PZI, NPH insulin preparation could be premixed with an intermediate acting insulin and administered, once or twice daily, used alone or in combination with soluble insulin as patient requirement⁹.

Structure of Insulin

Like most of the other hormones insulin is a made of protein comprising of 2 polypeptide chains-chain A- containing 21 amino acids residue, Chain B containing the 30 amino acids residues. The A& B chains are linked by disulphide bridges. In addition A chain contains an intra-chain disulphide bridge linking residue 6 and 11. The structure of insulin as follows¹⁰.





C- Chain, which connects A & B, chains is liberated along with insulin after breakdown of proinsulin. Insulin monomer aggregate to form dimers and hexamers. Although insulin is active as a monomer during its biosynthesis and storage it assembles to dimers and in the presence of zinc to hexamers. X-ray analysis has revealed the 3-dimensional structure of the insulin molecule in its hexameric, dimeric, and monomeric states. Two main conformations of insulin which differ in the extent of helix in the B chain at B9-B20 and B1-B20 respectively have been identified. Other variations are seen in insulin when dimeric or monomeric. Reagents such as chlorides and phenol govern the conformation present in the insulin hexamers and this can influence the behavior and properties of insulin preparations¹¹.

Biosynthesis of Insulin

Insulin is synthesized in the beta cells of pancreas in the form of proinsulin which is the ultimate precursor and gene for the same is located on chromosome 11 close to that for insulin like growth factor 2(IGF-2)¹².

Within a minute after synthesis it is discharged into cisternal space of rough endoplasmic reticulum where it is cleaved into proinsulin by proteolytic enzymes. Proinsulin with a C-chain linking A and B chains is then transported micro vesicle to the Golgi apparatus. Proinsulin is released in vesicles. Conversion of proinsulin to insulin continues to maturing granules through the action of prochrome conversate 2&3 and carboxy peptidase¹³.

Insulin Pharmacology

Insulin Effect on Glucose Uptake: Binding of insulin to the alpha-subunits leads to autophosphorylation and activation of the enzyme tyrosine kinase in the beta unit and physiological effect of insulin. Insulin stimulates glucose

transport across cell membrane by ATP dependent translocation of glucose transporters like GLUT4. GLUT4 has channels; through that glucose enter from extra cellular fluid to Intra cellular fluid. Then glucose metabolize. Insulin also inhibits some DNA transcription, which reduces gluconeogenesis¹⁴.

Role of Insulin in Metabolism 15: The insulin is hormone which is involved in many catabolism processes like glycogen, triglyceride, protein, DNA synthesis.

Some actions are direct and some actions are indirect. In following sections we discuss the functions of insulin in detail.

- **Glycogen Synthesis:** Insulin increases the glucose uptake by activating the GLUT4 transport system in the liver. The absorb glucose converted into glycogen.
- **Glycogenolysis and Gluconeogenesis:** It prevents the conversion of glycogen into glucose in the liver by inhibiting the phosphorylase and cyclic AMP enzyme. By inhibiting gluconeogenesis enzyme it prevent the formation of glucose from non carbohydrate sources (protein and lipids).
- **Protein and DNA Synthesis:** Insulin increase the glucose uptake in the skeletal muscles and also amino acids uptake by that it increases the DNA replication and protein synthesis and it is anabolic reaction.
- **Proteolysis:** Insulin decreases the protein breakdown.
- **Fatty acid Synthesis and Esterification:** Increase the absorption of blood glucose in the adipose tissue and converted into glycerol, alpha glycerophosphate and fatty acid and its synthesis into triglyceride (fat).
- **Lipolysis:** Reduce the conversion of triglycerides into glycerol and fatty acids in

adipose tissues by that Gluconeogenesis is reduced.

- Autophagy: Postprandial level inhibits the autophagy completely and decreases the level of degradation of damaged organelles.
- Sodium renal excretion decrease.
- Entry of insulin in the brain increases the verbal memory, learning and memory.
- Insulin stimulates the gonadotropin releasing hormone in the hypothalamus reason in the brain thus it favors the fertility.

Adverse Effect [Tripathi, K.D, 2019, Murgesh, N, Dandiya, P.C, 2008]

Hypoglycemia: It is most frequent and most serious reaction. Hypoglycemic episodes are more common. It is common in all type of diabetic patients. Common reason for hypoglycemia are inadvertent injection of large dose or by missing of meal after injection or performing vigorous exercise.

Allergy Reaction: Some allergic reaction causes at the site of injection like itching, redness and swelling.

Weight gain: Increase in body weight.

Lipodystrophy: Atrophy of subcutaneous fat at the site of injection takes place.

Presbyopia: It is a loss visual accommodation due to alterations in the physical properties of the lens occurring due to rapidly controlled diabetes with insulin.

Somogyi Effect: Some patients who take insulin before bed wake up with high blood sugar levels. This effect occurs when the insulin causes a hypoglycemic condition in the body, by that activates the antihyperglycemic hormones like cortisol and adrenaline, resulting in rebound hyperglycemia. This can be corrected by reducing the dose of bedtime insulin or changing the time of insulin dosing.

Dawn Phenomenon: It is the presence of high blood glucose levels in the body in the early hours of the day due to inadequate insulin concentration in the body. To correct this phenomenon, the dose of bedtime insulin needs to increase to be able to keep the blood glucose levels under normal condition throughout the night and the early hours of the morning.

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