A Key Role of Insulin in Diabetes Mellitus.
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ABSTRACT
Diabetes mellitus is a major endocrine metabolic disorder with the characteristic feature of hyperglycemia i.e. increased glucose levels. It usually occurs due to the imbalances in carbohydrate metabolism. Glucose is an important aldohexose sugar whose level gets raised during diabetes. Normally in the body glucose is acted upon by the hormone Insulin which is secreted by the beta islet cells of the pancreas. However during diabetes either the level of insulin decreases or the cells become insensitive to the action of insulin. Diabetes mellitus is associated with a number of complications affecting eyes, kidney, heart, nerves etc. A lot of research is done or is still going on, but diabetes mellitus still is the leading cause of death worldwide. The number of diabetic cases in developing countries is increasing day by day and no huge effort has been put into action to stop this sweet but deadly disease. Diabetes mellitus can be controlled by diet, lifestyle, exercise, oral hypoglycemic agents or insulin (pharmacological). Diabetes mellitus selectively damages cells (endothelial cells and mesangial cells) because in these cells the rate of glucose transport does not decline rapidly as a result of hyperglycemia, leading to high glucose inside the cell. Diabetes mellitus not only affects small blood vessels but also large blood vessels, so the complications of diabetes are divided into two classes i.e microvascular (small blood vessels) and macrovascular (large blood vessels). These complications affect and cause severe damage not only to the organs but to the nerves as well. So such medications should be developed that at least should minimize these adverse damages. At the moment insulin is widely used in diabetes in combination with other medicines. Not only drugs but products obtained from natural sources which could act as a protective agent should be looked upon to reverse and decrease such adverse damages. In this review main focus has been given on insulin molecule (synthesis, secretion, action, etc) and its role in diabetes mellitus.

Keywords: Diabetes Mellitus, Prevalence, Insulin, Oxidative Stress, Complications.

I. INTRODUCTION
According to the World Health Organization, Diabetes mellitus (DM), is a group of metabolic diseases in which a person has high levels of sugar in the blood. The raised level of sugar (glucose) is due to the impaired disturbance in carbohydrate metabolism. The elevated levels of glucose in the produce symptoms of frequent urination, increased thirst, and increased hunger. A person with diabetes does suffer from these symptoms. Diabetes mellitus itself is not dangerous but the complications of diabetes do classify it as one of the leading causes of death. A number of complications whether acute or serious are associated with diabetes. Acute complications include diabetic keto-acidosis and nonketotic hyperosmolar coma, while as serious long-term complications include heart disease, kidney failure (nephropathy), and damage to the eyes (retinopathy). Diabetes mellitus is caused
either due to the destruction of the beta islet cells of the pancreas which in turn do not produce enough insulin or the body does not respond to the insulin. World health day is celebrated every year on 7 April to mark the anniversary of the founding of WHO in 1948 and a theme is selected every year to highlight a priority area of public health. In 2016 the theme for World Health Day 2016 was “Diabetes” and the Goal of World Health Day was “Scale up prevention, strengthen care, and enhance surveillance of diabetes”. According to the studies carried out by Ahmed et al., 2010, factors like population growth, aging, increasing trends towards an unhealthy diet, obesity and sedentary lifestyles are responsible for the global rise in diabetes. It has been reported that the increase in the prevalence is thought to be higher appear in India, China, and other developing countries. As the number continues to be soaring high, diabetes mellitus as a metabolic disease is turning out into a deadly lethal disease, necessary steps need to be taken out as quickly as possible and as soon as possible.

II. Classification of Diabetes
As per World Health Organisation reports of 2013, there are three main types of Diabetes mellitus

**TYPE 1 DIABETES**
- In type 1 diabetes mellitus the body does not produce enough insulin as a result of which the levels of glucose raise in the body.

**TYPE 2 DIABETES**
- In this form of diabetes the cells in the body fails to utilise the insulin properly due to insensitivity to the action of insulin.

**GESTATIONAL DIABETES**
- This form of diabetes occurs when a pregnant women without a previous diagnosis of diabetes develop a high blood glucose level.

III. Insulin
Insulin is a protein secreted by the beta islet cells of the pancreas and consists of 2 polypeptide chains with 51 amino acids. In insulin molecule, the chain A consists of 21 amino acid residues and chain B of 30 amino acid residues linked by disulfide bridges. Also in A chain the residues 6 and 11 are linked by an intra-chain disulfide bridge. A and B chain are connected by C-chain, which is liberated along with insulin after the breakdown of proinsulin. The monomers of insulin molecule aggregate to form dimers and hexamers. The hexamer of Zn consists of three insulin dimers which are arranged in a threefold symmetrical pattern.

**Biosynthesis of Insulin**
The beta islet cells of the pancreas help in the synthesis of insulin from the ultimate precursor molecule which is preproinsulin. The gene for this is located on chromosome 11. This inactive precursor molecule is released into cisternal space of rough endoplasmic reticulum where it is acted upon by proteolytic enzymes and is cleaved into proinsulin. This proinsulin molecule is then transported by microvesicles to the Golgi apparatus, with a C (connecting) chain which links A and B chains. In the vesicles, proinsulin is released. In the maturing granules by the action of prohormone convertase 2 and 3 and carboxy peptidase H, the conversion of proinsulin to insulin continues. With the help of microtubules and microfilaments, the translocation of the maturing granules occurs. During the secretion of mature granules into the circulation by the process of exocytosis, an equimolar ratio of insulin and C-peptide are released. In the islet cell secretion, about 6% composition is of proinsulin and zinc.

**Insulin Secretion**
As a result of different stimuli like glucose, arginine, sulphonylureas, the beta cells of pancreas respond by secreting insulin. Besides these stimuli, other factors which include neural, endocrine and pharmacological can also exert a stimulatory effect. The beta cells take glucose through GLUT-2
receptors. During the entry of glucose into the beta cells, it is oxidized by glucokinase, which acts as a glucose sensor. Glucose is phosphorylated to glucose-6-phosphate (G6P) by the enzyme glucokinase generating ATP (5). If the levels of glucose are less than 90 mg/dl no secretion of insulin occurs that time. At such instances when the concentration of glucose is at sub stimulatory level, the efflux of K\(^+\) through open K- ATP channels keeps the β cell membrane at a negative potential at which voltage-gated Ca\(^{2+}\) channels are closed. However, the uptake and metabolism of glucose by the β cell is enhanced as soon as plasma glucose levels rise. Due to the increase in the concentration of ATP, membrane depolarization occurs and as a result voltage gated Ca\(^{2+}\) opens. Due to the influx of Ca\(^{2+}\) the intracellular concentration of calcium increases and as a result of that exocytosis of insulin granules occurs.

**Factors Influencing Insulin Biosynthesis and Release.**

The secretion of insulin may be affected by alterations in the synthesis at the levels of gene transcription, translation, and post-translational modification that occur in the Golgi body as well as other factors that influence the release of insulin from secretory granules. Modifications which are long term occur by influencing beta cell mass and differentiation (6). Due to the key role of insulin in the metabolism and utilization of glucose, it is very clear that in the synthesis and secretion of insulin, glucose does have a multiple influences. Not only these but other factors that in combination do influence these processes include amino acids, fatty acids, acetylcholine, pituitary adenylate cyclase-activating polypeptide (PACAP), glucose-dependent insulino tropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and several other agonists (7).

**Production of Insulin**

As in recent years, a tremendous development has occurred in the field of medical sciences and a number of life-saving drugs have been synthesized artificially by using newer technologies. One of the recent techniques that have been developed is the recombinant DNA technology. Now a days by using this technique human insulin is also produced. In recombinant DNA technology organisms like E.coli and Yeast are used to produce insulin. The insulin is produced by inserting human insulin the proinsulin gene into organisms like E coli or Yeast. When these organisms multiply they keep on producing insulin or proinsulin which is then enzymatically cleaved to produce insulin. The molecular weight of insulin is 5808 and its isoelectric pH is 5.5 (8). Insulin is a micro crystalline powder and is soluble at a pH of 2-3. When insulin is injected its half life is about 40 min.

**THE INSULIN RECEPTOR**

The insulin is a dimer consists of two alpha and two beta subunits respectively. The alpha subunit has the binding sites for insulin while as the beta subunits traverse the cell membrane. Binding of the insulin molecule to the alpha subunit induces a conformational change in the beta-subunits, resulting in activation of tyrosine kinase pathway and ultimately initiation of a cascade of events. As a result of this translocation GLUT-4 glucose transporter moves to the cell surface and transport of glucose is increased in the cell. The insulin–receptor complex which is formed in due course of time is then internalized by the cell and insulin is degraded. Finally, the receptor is recycled to the cell surface.

**Physiological Role of Insulin**

As a hormone insulin plays a significant role in regulating the supply of cellular energy, balancing macro nutrient and by directing the anabolic processes in the fed state (9). In insulin-dependent tissues (muscle and adipose) requires insulin for the intracellular transport of glucose in them. In muscle cells, insulin stimulates the synthesis of glycogen and lipid, while suppressing the process of lipolysis and gluconeogenesis. In the muscle cells when there is surplus supply of amino acids, at that time insulin is anabolic (10).
IV. Prevention and Treatment

It is very important that people with diabetes need to maintain a proper healthy diet, do regular physical exercises, reduce intake of alcohol, curb carbohydrate intake maintain body weight and blood pressure. Besides these facts management of diabetes can also be done by medications whether oral or injections.

As diabetes mellitus is associated with various complications which in due course of time cause severe damage to the vital organs of the body like pancreas, eyes, kidney, foot, heart, and nerves. As the main origin of occurrence of this disorder is damage to the pancreas and whether at present scenario is it possible at a large scale to transplant pancreas or grow in vivo the organ by using stem cells so that the burden of this metabolic disorder decreases. Possible efforts should be made by all of those who are associated with this area of study. Highly developed labs, scientists, research scholars, government agencies, funding agencies should put enormous efforts towards the growth of this field.

According to the studies carried out by American Diabetes Association, 2014 people with type 1 diabetes do occasionally need pancreas transplant. As per recent reports of International Diabetes Federation titled “Diabetes Atlas 2006” stated that the number of people with diabetes in India currently is around 40.9 million and expected to rise to 69.9 million by the year 2025. According to recent reports of WHO 2016, about 422 million people are suffering from diabetes. The number of diabetic patients is found to be higher in developing countries.

Risk factors of Diabetes:
A number of factors whether genetic or non genetic are considered as a risk factor for developing diabetes.

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<thead>
<tr>
<th>Modifiable Risk Factors</th>
<th>Non-Modifiable Risk Factors</th>
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<tbody>
<tr>
<td>Obesity</td>
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<td>Dietary Habits</td>
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<td>Hypertension</td>
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V. Complication & Cause of Diabetes

If the levels of the blood sugar are not maintained or controlled properly it leads to severe long term complications, involving vital organs such as eye, heart, kidney and foot (12). Multiple systems are involved in the body due to the complications which makes them susceptible to the detrimental effects of oxidative stress and apoptotic cell injury (13). Due to a large portion of population having...
undiagnosed diabetes there is a significant need to provide improved early diagnosis (14). Due to the severe damage that occurs in diabetes, the injurious effects of hyperglycemia is divided into macrovascular complications (coronary artery disease, peripheral arterial disease and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) (15).

In the body long term complications are associated with diabetes involving cardiovascular, renal and nervous disorders (16). This long term damage due to chronic hyperglycemia diabetes causes dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vessels (17). The onset of diabetes mellitus is promoted by oxidative stress which decreases insulin sensitivity and destroys the insulin-producing cells. In the development and progression of diabetes and its complications, increase in oxidative stress is believed to be a major driving force [18-20]. Oxidative stress results in the generation of free radicals and impairs antioxidant defenses [21]. The role of oxidative stress in the development of diabetic complications involves a number of mechanisms including activation of transcription factors, advanced glycated end products (AGEs) [22] and protein kinase C [23]. The key promoters of diabetes dysmetabolism are hyperglycaemia and hyperlipidaemia which cause damage to the cell and insulin resistance through the formation of reactive oxygen species (ROS) and advanced glycation end products (AGEs) [24-26]. ROS causes damage to the β-cells of pancreas by penetrating through the cell membranes (27). A diet that is rich in fat or free fatty acids causes mitochondrial DNA damage and impaired pancreatic β-cell function through the formation of ROS (28). According to the studies carried out by Choo et al., 2006 there is a association between the development of diabetes and a decrease in the levels of mitochondrial proteins and mitochondrial DNA.

VI. References


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