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# Insulin and Diabetes Mellitus: Review

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**Abstract:** Diabetes is the disease or disorder of pancreas by which pancreas stop the secretion of insulin in the body. Insulin allows the glucose enter in to the cells which provide energy to every cells of the body without insulin, glucose cannot enter in to the cell. Those parts which help to secrete insulin, the part which are defective which is known as diabetes type 1. In the type of diabetes mellitus the overall diabetes cases 10%. The type-1 diabetes which is most occurring in children. About 90% of incidence of type-2 diabetes mellitus. It is mainly occurring after the age 40s. In this case insulin secreted but only in low amount and it is co-related of our life style such as overeating, physical activity etc. There are following symptoms which are associated in diabetes like-increase urination, thirst, appetite and so on. The patients are between normal and diabetic that is called pre-diabetic patients. There are various treatment and preventions help to cure from diabetes like exercise, drinking water, implement portion control etc. Insulin plays a vital role in the treatment of diabetes which helps to lower the production of glucose level.

**Keywords:** Introduction, Epidemiology, Glucose, metabolism, Insulin, Complication, Diabetes

## 1. Historic Background of Diabetes Mellitus

Clinical description cited in an Egyptian papyrus (1500BC) as well as Charaka and Sushruta recognizing the increased carbohydrate content of urine can be considered as leading milestones in diabetes literature. The remarks made by Charaka and Sushruta that the disease was most prevalent in those who were indolent, overweight, gluttonous, indulged in sweet and fatty foods; turned out of the perfect description of diabetic. Considering the sweet taste of urine, the disorder was named Madhumeha.<sup>1</sup> Recognizable description of polyuria was given by Aretaeus of Cappadocia in the 2<sup>nd</sup> century AD and he was the first to coin the term diabetes, referring to Greek word for a syphon.<sup>2</sup>

The knowledge acquired during the Ancient Era was lost sight of and progress was tardy and indiscrete during the medieval period (600-1500 AD).<sup>3</sup> With the advent of modern age (1500-1750 AD) and its progression through renaissance to industrial revolution (1750-1850 AD), cardinal features of diabetes were identified. John Rollo was the first to apply the adjective mellitus (from Greek and Latin words meaning honey). In the early 19<sup>th</sup> century, glucose metabolism was clarified and in the middle of the century, tasting the urine to make the diagnosis was superseded by chemical tests for glucose.<sup>2</sup> It was the end of the 19<sup>th</sup> century when islets of Langerhans was identified as putative internal secretory portion of the pancreas and in 1909, insulin was recognized as the glucose lowering internal secretion of the islets.<sup>1</sup> Doctors in the era played important role as taxonomists and narrated complications associated with diabetes. DM is now a field with constant ongoing investigation and its future is in hands of genetic factors.

### Epidemiology:

Epidemiology plays an eye opening role in developing prevention strategies for T2DM. The ever expanding blue circle of diabetes has encased 350 million population of the world.<sup>4</sup> The total number of people suffering by diabetes is prophesized to boost to about 438 million by 2030, with one-third of affected individuals living in India and china.

The gloomily increased prevalence gives the impression that these predictions will prove to be an underestimate. The majority of this increase will, however, occur in the developing world. According to the International Diabetes Federation (IDF), India stands second in prevalence of diabetes, for which earned the dubious title of diabetes capital of the world.<sup>5</sup>

Epidemiological studies exhibit perturbing increase in number of cases of T2DM in younger age groups, particularly in developing countries where the peak age at diagnostics is 45 to 64 years and prevalence rates are rising sharply in under 30s. Sequential surveys from India indicate that the prevalence of T2DM has given steadily since the 1970s. The most recent study (National Urban Survey), carried out in six cities, found age-standardized prevalence rates of 12% for diabetes and of 14% for impaired glucose tolerance (IGT); subjects under 40 years of age had prevalence of 5% diabetes and 13% IGT.<sup>1</sup>

### Normal Glucose Metabolism:

Structurally monomer, biologically monosaccharide and chemically organic carbon, glucose, is a ubiquitous fuel for the cell.<sup>15</sup> Blood glucose is tightly regulated and maintained within a narrow range as hyperglycemia may cause cellular dehydration, impart deleterious effect on vascular endothelium whereas hypoglycemia may deprive brain its sole energy source as it cannot oxidize free fatty acids and relies upon glucose as its principle metabolic fuel.<sup>7</sup>

Insulin lowers blood glucose by suppressing hepatic glucose production and stimulating glucose uptake in skeletal muscle and fat, mediated by the glucose transporter, GLUT4. Breach in this cascade may be contributed hepatic glucose output, pancreatic endocrine function and peripheral tissue glucose uptake.

### Insulin:

A part from producing and releasing digestive enzymes, pancreas is committed to synthesis of two major hormone accountable for glucose metabolism, insulin and glucagon. The name insulin is derived from Latin insula, meaning

island. Insulin plays a vital role in regulation of carbohydrate, fat and protein metabolism and in turn, contributes significantly to the energy homeostasis in humans.<sup>1, 3, 6</sup>

Although history of insulin is entrenched in 1880s a seminal event of introducing Insulin as a pharmaceutical agent took place in 1920s.<sup>8</sup> Insulin constitutes 51 amino acids and has a 5808Da molecular weight. It is a dimer, composed of A-chain and B-chain consisting 21 and 30 amino acid residues respectively, which are linked together by disulphide bonds. Additionally A-chain contains an intra-chain disulphide bridge connecting 6<sup>th</sup> and 11<sup>th</sup> amino acid residue. Typical structure of insulin differs among species, thwarting the research work for employing insulin from other species as a therapeutic agent.<sup>1</sup>

Endocrine pancreas, consisting only 2% of the total mass of the pancreas, is composed of small groups of cells distributed throughout the organ, called islets of Langerhans. Beta cells constitute 65-80% of all the cells of the islets and are accountable for synthesis of insulin.<sup>7</sup> INS gene, residing at chromosome 11, signals for proinsulin, and a precursor of insulin. Proinsulin is discharged into cisternal space of rough endoplasmic reticulum within a minute after synthesis and cleaved into proinsulin by the action of proteolytic enzymes. Proinsulin encompasses C (connecting) chain, containing 33 amino acids residues, linking A and B chains. Over the next 30 minutes, it is transported into the Golgi apparatus through the microvesicles. It is converted to insulin by the action of prohormone convertase 2 and 3, and carboxy peptidase H. Microtubules and microfilaments helps in translocation of maturing granules.<sup>8</sup>

The insulin, packed within the mature granules, is liberated from the beta cells. In two phases. The first phase release is rapidly triggered in response to heightened blood pressure levels where as second phase is slow, sustained release of newly formed vesicles triggered independently of sugar. The first phase release can be abridged as follows.<sup>7, 8</sup>

Through glucose transporter GLUT2, glucose enters the beta cells.

Glucose is admitted to glycolysis and the krebs cycle, and multiple high energy ATP molecules are produced by oxidation.

It leads to upsurge in ATP: ADP ratio and shuts the ATP sensitive K<sup>+</sup> channels and prevents K<sup>+</sup> ions leaving the cell by facilitated diffusion which results in depolarization of cell membrane.

On depolarization, voltage gated Ca<sup>2+</sup> channels open, allowing influx of Ca<sup>2+</sup> ions.

Accumulated Ca<sup>2+</sup> activate phospholipase C, which cleaves plasma membrane phosphatidyl inositol 4, 5-bisphosphate into inositol 1, 4, 5-triphosphate (IP3) and diacylglycerol.

IP3 binds to receptor proteins in the plasma membrane of rER, allowing the release of Ca<sup>2+</sup> ions from rER through IP3 gated channels and rises intracellular concentration of Ca<sup>2+</sup> ions.

Intensified accumulation of Ca<sup>2+</sup> ions substantiates the release of synthesized insulin stored in secretory vesicles.

Each insulin receptor consists of two subunits alpha and beta. Signal generated on binding of insulin molecule to the extracellular alpha-subunit is transmitted across the cell membrane into the internal beta subunit and leads to activation of tyrosine kinase (TK). The activated enzyme induces auto phosphorylations involving more and more of insulin receptor substrates (IRS) that is recruited into the beta subunits. IRS consists of six cloned proteins (IRS 1-6) which on phosphorylation function as adaptors between IRS and Phosphoinositol 3-kinase (PI3K) so as to enable activation of PI3K and lead to formation of PI 3, 4, 5-phosphate (PIP3). PIP3 induces translocation of GLUT4, leading to increase in uptake of glucose into cell. Furthermore PIP3 activates Akt and protein kinase C (PKC) isoforms which mediate insulin effect on various metabolic functions including protein synthesis.<sup>1</sup>

## Diabetes

### Definition

As defined by WHO, the term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from defect in insulin secretion, insulin action or both.<sup>9</sup>

### Blood glucose estimation:

Tests for blood/plasma glucose level are carried out at fasting; randomly at any time of the day, irrespective of food intake or following carbohydrate loads. American Diabetes Association (ADA) recommended the use of fasting blood sugar (FBS) alone for both clinical and epidemiological evaluations except in case of pregnant women. On the other hand, WHO consultation decided to retain use of OGTT for border line cases in clinical practice and particularly surveys because of its greater sensitivity and as fasting state cannot be ensured particularly in field studies.<sup>8</sup> Thus relying on only one test in diverse clinical scenario in contentious.

### Fasting Blood Sugar (FBS):

Overnight fasting for 8-14 hours is considered desirable. In case of exigency, four hours after a modest meal may be taken as fasting but is far from ideal. Frank diabetes was usually diagnosed at 130 mg/dl up to 1979, when National Diabetes Data Group (NDDG) and WHO expert committee recommended diagnosis of diabetes at 120mg /dl of fasting venous whole blood and 140 mg/dl of fasting plasma glucose.<sup>1</sup>

### Random Blood Sugar (RBS):

Samples for test may be collected at any irrespective of prandial status. In the presence of typical symptoms, a sole plasma or capillary blood glucose of 200 mg/dl or venous whole blood of 180 mg/dl is accepted as diagnostic of diabetes. In the absence of frank symptoms a second test is needed to confirm the diagnosis.<sup>1, 3, 10</sup>

### Screening for diabetes:

In the context of ranging epidemic of T2DM all over the world, health authorities have prevention program at the top

of their concerns. Recent observations on success of intervention efforts in subjects with IGT have raised the need of early detection of prediabetic status of impaired fasting glucose and IGT.<sup>11</sup> As screening of the entire adult population is extremely difficult and may not be cost effective, the consensus is to screen subjects at high-risk for the disorder.

### Classification

The first widely accepted classification of diabetes mellitus published by WHO (1980) was modified in 1985.<sup>9</sup> Terms type 1 and type 2 were omitted whereas the terms IDDM and NIDDM were retained and a class of malnutrition-related diabetes mellitus was introduced. Later WHO and ADA modified the classification, although Kuzuya and Matsuda proposed to classify diabetes according to both clinical stages and etiological types.

Understanding of pathogenesis revealed that all forms of diabetes pass through the stages of IGT before progressing to clinical or overt diabetes. In addition to IGT with 2 hour plasma glucose values (140-199 mg/dl), a new class of IFG with FBS value 110-125 mg/dl was introduced in view of the potential of such levels to raise the risk of vascular complications.<sup>9</sup> In 2006 the terms type-1 and type-2 were reintroduced as the terms IDDM and NIDDM were confusing and resulted in patients being classified on the basis of treatment. Also MRDM was removed and kept together with other etiological conditions which are primary and culminate in diabetes.

### Type-1 Diabetes Mellitus (T1DM)

Majority of cases which are primarily due to destruction of pancreatic islet beta cell and are prone to ketoacidosis.<sup>9</sup> T1DM includes only those cases attributable to an autoimmune process and cases for which neither etiology nor pathogenesis is known individuals and sluggish in others. The rapidly progressive form is commonly seen in children, but may also occur in adults. The slowly progressive form that occurs in adults is sometimes referred to as LADA. Most effected people are not obese when onset occurs. Sensitivity and responsiveness to insulin are very usually normal. Especially in the early stages.<sup>11, 12</sup> T1DM can be complemented by unbalanced and impetuous hyperglycemia, and sometimes with life threatening hypoglycemia. Other impairments seen in 1-2% of cases include an impaired counter regulatory response to hypoglycemia, infection, erratic absorption of dietary carbohydrates due to gastroparesis and endocrinopathies.<sup>9</sup> Peak incidence of T1DM occurs in childhood and adolescence, but the onset may occur at any age, extending from childhood to 9<sup>th</sup> decade of life. Idiopathic form, insulinopenia without evidence of autoimmunity, id formed to be more common in individuals of African and Asian origin.<sup>1, 2, 9</sup>

### Type-2 Diabetes Mellitus (T2DM)

T2DM is a more intricate condition than T1DM as it is an amalgamation of resistance to the actions of insulin wit impaired pancreatic beta cell function leading to relative insulin deficiency. Among diagnosed T2DM patients, around 10% may have LADA or maturity onset diabetes in the young (MODY). Currently it is considered that the impaired insulin sensitivity i.e. insulin resistance (IR) and

insulin secretory dysfunction i.e. beta cell dysfunction, are two essential factors operating in concert and are accountable for evaluation of the metabolic disarray that constitutes diabetes.<sup>1</sup> In early stages, the response to progressive insulin resistance is an increase in insulin secretion, causing hyperinsulinemia. Eventually the beta cells are unable to compensate adequately and hyperglycemia is evident. With further beta cell failure, glycaemic control deteriorates and treatment requirements escalate.

### Diagnosis

The diagnosis of patients with diabetes or pre diabetes some test are needed to performed, like oral glucose tolerance testing, HbA1c testing etc. A high risk factor of diabetes mellitus is following such as obesity, hypertension, and family history diabetes [13]. The 1997 American diabetes association (ADA) recommendation for diagnosis of D M factor. Focus on fasting plasma glucose (FPG). While WHO is focus on the OGTT.<sup>14</sup> Diabetes mellitus is diagnosed by any following type of test.<sup>15</sup>

- 1) Fasting plasma glucose level: It should be 8 hour fasting before taking this test. Condition of DM More than 126mg/dl.
- 2) Plasma glucose: More than or equal to 200mg/dl two hours after a 75 gram oral glucose load as in a OGTT.
- 3) Symptoms of high blood sugar and casual plasma glucose: It is greater than or equal to 200 mg/dl.
- 4) Glycated hemoglobin (HbA1c): It is greater than or equal to 48mmol/mol.<sup>16</sup>

Note: According to current definition of D M, two fasting glucose measurement above 126 is considered diagnostic for D M. Per the WHO people with fasting glucose levels from 110 to 125mg/dl are considered to have impaired fasting glucose.<sup>17</sup> HbA1c test is much better than the FGP test for determination risk of cardiovascular disease and death from any cause.<sup>18</sup>

### Prevention

Type 1 diabetes could not preventive because it is due auto immune disease; it should be control by some medication uses (oral hypoglycemic agent). Type 2 diabetes should be preventable or delayed by the maintaining a normal body weight, physical activity, eating a healthy diet. Limiting surgary beverages and eating less red meat and other source of saturated fat can also help the prevent diabetesdiabetes.<sup>19</sup>

Medication used to treat diabetes do so by lowering blood sugar level. There are different classes of oral hypoglycemic agent that are used to treatment of diabetes mellitus. Metformin is the first choice in people with diabetes; generally metformin decreases hepatic glucose output and reduce insulin resistance.<sup>20, 21, 22</sup>

## 2. Conclusion

The type 1 diabetes mellitus occurs due to the destroyed the beta cell and thus it does not produces the sufficient amount of insulin to control the blood sugar level. Type 2 diabetes is occurs due to the insulin resistance, life style such as

excessive body weight and insufficient exercise. The main goal of diabetes management is, as far as possible, to restore carbohydrate metabolism to normal state.

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