1. INTRODUCTION

1.1. Diabetes: An Overview

Diabetes mellitus (DM) is a metabolic disorder. This disorder is characterized by polyuria (frequent and abundant urines), glycosuria (presence of glucose in urines) and hyperglycaemia (glucose rate on an empty stomach higher than 1.2 g/l in plasma blood and confirmed in at least two occasions). A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular inefficiency. Diabetes comes with other complications (kidney, eye). Diabetes is a major cause of disability and death. Currently, diabetes therapy is based on the use of hypoglycaemics (sulfonamides, biguanides, insulin), on hygieno-diet measures and exercises (Srivastava Shikha et al. 2012).

Two major types of Diabetes mellitus are: Type 1 Insulin-depandant diabetes mellitus (IDDM), juvenile onset diabetes mellitus. There is β cell destruction in pancreatic islets; majority of cases are autoimmune (type 1A) antibodies that destroy β cells are detectable in blood, but some are idiopathic (type 1B) – no β cell antibody is found. In all type 1 cases circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition. Type 2 Noninsulin-depandent diabetes mellitus (NIDDM), maturity onset diabetes mellitus. There is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal or even high degree of genetic predisposition; generally has a late onset (past middle age). Over 90% cases are type 2 DM. Causes may be: Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration or relatively β cell deficiency. Reduced sensitivity of peripheral tissues
to insulin reduction in number of insulin receptors, “down regulation” of insulin receptors. Many hypertensive are hyperinsulinaemic, but normoglycaemic; exhibit insulin resistance associated with dyslipidaemia (metabolic syndrome). And due to excess of hyperglycaemic hormones glucagon etc. cause relative insulin deficiency (Tripathi KD 2003).

Insulin is a peptide hormone, produced by beta cells of the pancreas, and is central to regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, skeletal muscles, and fat tissue to take up glucose from the blood. In the liver and skeletal muscles, glucose is stored as glycogen, and in adipocytes it is stored as triglycerides. When control of insulin levels fails, diabetes mellitus can result. As a consequence, insulin is used medically to treat some forms of diabetes mellitus. Patients with type 1 diabetes depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type 2 diabetes are often insulin resistant and, because of such resistance, may suffer from a "relative" insulin deficiency. Some patients with type 2 diabetes may eventually require insulin if other medications fail to control blood glucose levels adequately. Over 40% of those with Type 2 diabetes require insulin as part of their diabetes management plan.

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the “diabetes capital of the world”. According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. The incidence and prevalence of type 2 diabetes are rising steadily worldwide. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is
projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people 65 years of age.

Non-insulin diabetes mellitus (NIDDM) is much commoner than IDDM, accounting for 75 to 95% of all diabetics in most populations. It usually only occurs in patients over the age of 40 yrs. In the UK, diabetes affects approximately 750,000 people, of whom 600,000 have NIDDM. The incidence of NIDDM increases with age and with increasing obesity. As with IDDM there are major ethnic and geographical variations. In general, in non obese populations the prevalence is 1 to 3%. In the more obese societies, there is a sharp increase in prevalence with figures of 6 to 8% in the USA increasing to values as high as 30% in Hindu, Tamils, in South Africa. Diabetes is 5 times more common among Asians, Immigrants in the UK, then in the indigenous population. World studies of immigrants have suggested that the chances of developing NIDDM are between 2 and 20 times higher in well fed populations then in lean population on the same race (Tripathi KD 2003, V Mohan 2007).

1.2. Historical Perspective

The signs and symptoms of diabetes have been observed and recorded since the beginnings of civilization. The term “diabetes” was first introduced in the 1st or 2nd century BC by Demetrius of Apameia, descriptions of abnormal polyuria were recorded as early as 1500 BC in the Egyptian Papyrus Ebers (International Diabetes Federation 2006).

The term “diabetes” was based from the Ionic and Latin terms that meant to pass through or to siphon. It was coined by Areteus of Cappadocia (AD 30-90) In addition to coining the term diabetes, Areteus is credited with the first accurate clinical description of
The first test for diabetes was the urine taste test. While the Greek physician Claudius Galen (AD 129-200) believed diabetics’ urine was “unchanged drink” which may have accounted for a different aroma, early Egyptians, Indians, and Asians noted the sweet taste of urine. Chang Chung-Ching (AD 229) noted that the urine was so sweet that dogs liked it. Indeed, animals and insects alike were attracted to the sweet urine. The Hindu medical textbooks from the 5th century described sweet, honey and sugarcane urine amongst 20 varieties of diseased flow of urine. Both Avicenna (AD 980-1037) and Paracelsus (AD 1493-1541) later recommended tasting the urine of diabetics (International Diabetes Federation 2006, World Health Organization 2014).

Theophilos Protospatharios (630 AD) was the first to mention applying heat to urine as a diagnostic test. Paracelsus reported that boiling diabetic urine recovered “4 ounces of salt”. However, it was Thomas Willis (1621-1675) that first described the saccharine nature of urine, describing the sweet taste after evaporation.

In 1776, Matthew Dobson performed a diagnostics experiment that lead to the belief that diabetes was not just a disease of the kidneys, Dobson evaporated the urine of diabetic patients to discover the presence of a substance like brown sugar in taste and appearance, he also went on to observe that diabetic patients had the sweetish taste of sugar in their blood. This confirmed the relationship between the sugars present in the blood and those excreted in the urine. John Rollo established the link between the food consumed by diabetics and the amount of sugar in the urine. Rollo recorded the amount and kind of food eaten by his diabetic patients, and then weighed the "sugar cake" which remained after evaporating their urine. He observed that carbohydrates increased sugar levels, and animal product consumption resulted in less sugar. He promoted the idea that the treatment for diabetes
should be a diet low in carbohydrates and high in fat and protein. This modification of diet became the recommended treatment for diabetes until the discovery of insulin.

The first clinical tests for glycosuria were developed in the nineteenth century. In 1841, Karl Trommer, developed a qualitative test for sugar which involves treating a urine sample with a strong acid which results in the acid hydrolysis of disaccharides into monosaccharides. The solution is then neutralized and a solution of copper sulphate is added, then excess of alkali, followed by boiling, a brick-red cuprous oxide precipitate forms if glucose is present.

In 1850, Hermann von Fehling developed a quantitative test based on Trommer’s work to measure sugar content. Frederick Pavy (1829-1911) established a quantitative relationship between the degree of hyperglycemia and glycosuria based on Fehling’s test. Pavy also improved upon the Fehling’s test for quantitative sugar urinalysis by substituting ammonia for caustic potash and thereby facilitating production of the first urinalysis tablets.

In 1979, the National Diabetes Data Group and the World Health Organization developed diagnostic criteria for the diagnosis of diabetes that involved measuring glucose tolerance using an oral glucose tolerance test (OGTT). An OGTT involves giving a patient 75 gm of glucose by mouth and then measuring their blood sugars two hours later. If a patient’s blood sugars are elevated more than they would be in a normal individual, then that patient has impaired glucose tolerance. Using this test, the following criterion was established for the diagnosis of diabetes: fasting blood glucose 7.8 mmol/L or higher, or an OGTT two-hour blood glucose value of 11.1 mmol/L or higher.

These guidelines were updated in 1997 by the American Diabetes Association (ADA), and then revised in 2003. The new guidelines require meeting one of three criteria in order to diagnose diabetes: a) a fasting blood glucose concentration of 7.0 mmol/L or higher with
symptoms of hyperglycemia, which include polydipsia, polyuria, and weight loss; b) a random blood glucose of 11.1 mmol/L or higher; c) a two hour value in an OGTT of 11.1 mmol/L or higher. The diagnosis must then be confirmed on a different day with any of the three criteria. There has been recent interest in using hemoglobin A1c values to aid in the diagnosis of type 2 diabetes in conjunction with random blood glucose levels. Hemoglobin A1c is the glycosylated form of hemoglobin A, the major adult hemoglobin type. The utility in measuring hemoglobin A1c comes from the fact that its concentration is proportional to blood glucose levels. In non-diabetics, the normal hemoglobin A1c level is less than 5% of the total hemoglobin. In patients with diabetes, chronically elevated blood sugars will lead to a higher than normal percentage of hemoglobin A1c. It has been proposed that to avoid the inconvenience of measuring fasting blood glucose as a means of diagnosis, an abnormal random blood glucose value (11.1 mmol/L or higher) in addition to a hemoglobin A1c value greater than 2 standard deviations above normal could be used.

Since 1999 Japan has been using HbA1c levels over 6.5% as a diagnostic marker for diabetes. It seems clear that there still remains work to be done to standardize the diagnostic tools in the determination of diabetes (Kitabchi, AE 2009, Shoback 2011, RSSDI textbook of diabetes mellitus 2012, Rippe 2010, Picot, J et al. 2009).

1.3. Epidemiology

Diabetes mellitus is one of the most common endocrine disorders affecting almost 6% of the world’s population. The number of diabetic patients will reach 300 million in 2025 (International Diabetes Federation, 2014, Williams textbook of endocrinology 2014).
1.4. Prevalence

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030.

The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people 65 years of age. More than 97% of these patients will have type II diabetes. The projected increase in the number of diabetic patients will strain the capabilities of healthcare providers the world over. Thus it is of paramount importance to revisit the causes and epidemiology of diabetes mellitus. Diabetes mellitus is caused by both environmental and genetic factors. The environmental factors that may lead to the development of diabetes mellitus include physical inactivity, drugs and toxic agents, obesity, viral infection, and location. While type I diabetes is not a genetically predestined disease, an increased susceptibility can be inherited. Genetic susceptibility plays a crucial role in the etiology and manifestation of type II diabetes, with concordance in monozygotic twins approaching 100%. Genetic factors may have to be modified by environmental factors for diabetes mellitus to become overt. An individual with a susceptible gene may become diabetic if environmental factors modify the expression of these genes. Since there is an increase in the trend at which diabetes prevail, it is evident that environmental factors are playing a more increasing role in the cause of diabetes mellitus (Williams textbook of endocrinology 2014).
1.5. Incidence

The incidence of type I diabetes ranged from 1.9 to 7.0/100,000/yr in Africa, 0.13 to 10/100,000/yr in Asia, approximately 4.4/100,000/yr in Australasia, 3.4 to 36/100,000/yr in Europe, 2.62 to 20.18/100,000/yr in the Middle East, 7.61 to 25.7/100,000/yr in North America, and 1.27 to 18/100,000/yr in South America (World Health Organization 2014).

Table 1 —List of countries with the highest numbers of estimated cases of diabetes for 2000 and 2030.

<table>
<thead>
<tr>
<th>Ranking Diabetes</th>
<th>Country</th>
<th>People with Diabetes (Millions)</th>
<th>Country</th>
<th>People with Diabetes (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>India</td>
<td>31.7</td>
<td>India</td>
<td>79.4</td>
</tr>
<tr>
<td>2</td>
<td>China</td>
<td>20.8</td>
<td>China</td>
<td>42.3</td>
</tr>
<tr>
<td>3</td>
<td>U.S.</td>
<td>17.7</td>
<td>U.S.</td>
<td>30.3</td>
</tr>
<tr>
<td>4</td>
<td>Indonesia</td>
<td>8.4</td>
<td>Indonesia</td>
<td>21.3</td>
</tr>
<tr>
<td>5</td>
<td>Japan</td>
<td>6.8</td>
<td>Pakistan</td>
<td>13.9</td>
</tr>
<tr>
<td>6</td>
<td>Pakistan</td>
<td>5.2</td>
<td>Brazil</td>
<td>11.3</td>
</tr>
<tr>
<td>7</td>
<td>Russian Federation</td>
<td>4.6</td>
<td>Bangladesh</td>
<td>11.1</td>
</tr>
<tr>
<td>8</td>
<td>Brazil</td>
<td>4.6</td>
<td>Japan</td>
<td>8.9</td>
</tr>
<tr>
<td>9</td>
<td>Italy</td>
<td>4.3</td>
<td>Philippines</td>
<td>7.8</td>
</tr>
<tr>
<td>10</td>
<td>Bangladesh</td>
<td>3.2</td>
<td>Egypt</td>
<td>6.7</td>
</tr>
</tbody>
</table>
1.6. Types of Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action or both. Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Chronic hyperglycemia is associated with microvascular and macrovascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage, amputations, heart disease, and stroke. The type of diabetes is based on the presumed etiology (Cooke DW 2008, Kitabchi AE 2009, Lambert P 2002, Rother KI 2007, Merck Manual Professional 2010, Alagesaboopathi C 1999, Ambasta SP 1986).


Type 1 Diabetes

- Caused by the immune destruction of the beta cells of the pancreas.
- Antibodies to islet cells and insulin are present at diagnosis.
- Insulin secretion gradually diminishes.
- May present at any age, but most common in childhood and adolescence.
- Insulin by injection is necessary for survival.
- Contributing factors:
  - Genetic predisposition
  - Environmental triggers (infection or other stress)
Type 2 Diabetes

- Caused by insulin resistance in the liver and skeletal muscle, increased glucose production in the liver, over production of free fatty acids by fat cells and relative insulin deficiency.
- Insulin secretion decreases with gradual beta cell failure.
- Reductions in blood glucose levels often can be achieved with changes in food intake and physical activity patterns. Oral medication and/or insulin injections are eventually required.
- Contributing factors:
  - Obesity
  - Age (onset of puberty is associated with increased insulin resistance)
  - Lack of physical activity
  - Genetic predisposition
  - Racial/ethnic background (African American, Native American, Hispanic and Asian/Pacific Islander)
  - Conditions associated with insulin resistance, (e.g., polycystic ovary syndrome).
## Characteristics of two major types of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Type</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Onset &lt; 20 year normal weight decreased&lt;br&gt;blood insulin&lt;br&gt;Anti –islet cell antibodies&lt;br&gt;Ketoacidosis common</td>
<td>Onset &gt; 30 year obesity normal or increased&lt;br&gt;blood insulin&lt;br&gt;no Anti –islet cell antibodies&lt;br&gt;Ketoacidosis rare</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>50% concordance in Twins&lt;br&gt;HLA-D Linked</td>
<td>60 to 80% concordance in Twins&lt;br&gt;No HLA Association</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Autoimmunity&lt;br&gt;immunopathologic mechanism severe insulin deficiency</td>
<td>Relative insulin deficiency</td>
</tr>
<tr>
<td><strong>Islet cell</strong></td>
<td>Insulin early marked atrophy &amp; fibrosis&lt;br&gt;severe beta cell depletion</td>
<td>No insulites focal atrophy &amp; amyloid deposits Mild beta cell depletion</td>
</tr>
</tbody>
</table>

**Fig. 1:** Characteristics of two major types of Diabetes Mellitus
1.7. Pathophysiology of diabetes

Pathophysiology of diabetes rests upon knowledge of the basics of carbohydrate metabolism and insulin action. Following the consumption of food, carbohydrates are broken down into glucose molecules in the gut. Glucose is absorbed into the bloodstream elevating blood glucose levels. This rise in glycemia stimulates the secretion of insulin from the beta cells of the pancreas. Insulin is needed by most cells to allow glucose entry. Insulin binds to specific cellular receptors and facilitates entry of glucose into the cell, which uses the glucose for energy. The increased insulin secretion from the pancreas and the subsequent cellular utilization of glucose results in lowered of blood glucose levels. Lower glucose levels then result in decreased insulin secretion (Aiyer KN 1963, Ansari AA 1993).

If insulin production and secretion are altered by disease, blood glucose dynamics will also change. If insulin production is decreased, glucose entry into cells will be inhibited, resulting in hyperglycemia. The same effect will be seen if insulin is secreted from the pancreas but is not used properly by target cells. If insulin secretion is increased, blood glucose levels may become very low (hypoglycemia) as large amounts of glucose enter tissue cells and little remains in the bloodstream (Asolkar LV et al. 1992, Moos NS 1978).
Fig. 2: Pathogenesis of Type 1DM
Fig. 3: Pathophysiology of hyperglycaemia and increased circulating fatty acids in type 2 diabetes
Fig. 4: Main symptoms of diabetes mellitus
1.8. Need of Natural sources as Anti-diabetic

The astronomic increase in the prevalence of diabetes has made diabetes a major public health challenge for India and is become important human ailment afflicting many from various walks of life in different countries and once again the whole world being looked upon ayurvedic the oldest healing system of medicine for the treatment of diabetes. Although there are many synthetic medicines developed for patients, but it is the fact that it has never been reported that someone had recovered totally from diabetes. The modern oral hypoglycemic agents produce undesirable and side effects. Thus in the recent years considerable attention has been directed towards the antidiabetic potential of medicinal plants and their herbal formulation in the management of disease (Tiwari Vivek et al. 2011, Dwivedi Sumeet 2009, Dwivedi Sumeet et al. 2010).

More than 400 traditional plant treatments for diabetes mellitus have been recorded, but only a small number of these have received scientific and medical evaluation to assess their efficacy. Ancient Indian medicine mentions several indigenous plants and mineral preparations for the treatment of diabetes mellitus. A hypoglycaemic action from some treatments has been confirmed in animal models and non-insulin-dependent diabetic patients, and various hypoglycemic compounds have been identified. A botanical substitute for insulin seems unlikely, but traditional treatments may provide valuable clues for the development of new oral hypoglycaemic agents and simple dietary adjuncts (Colagiuri S. 2010).