INTRODUCTION

DIABETES MELLITUS

A disease of all age-groups particularly in all parts of the world: the Diabetes/Diabetes mellitus (Madhumeha) has been well known as a wasting disease due to insulin deficiency in human beings. The pancreas secretes insulin. Carbohydrate metabolism is primarily under the control of insulin. Insulin deficiency occurs in a person due to the functional disorder of the pancreas.

Diabetes mellitus is a clinical syndrome characterized by inappropriate hyperglycemia caused by a relative or absolute deficiency of insulin or by a resistance to the action of insulin at the cellular level. It is the most common endocrine disorder, affecting 16 million individuals in the United States and as many as 200 million worldwide. Diabetes has been a clinical model for general medicine. The primary defect in fuel metabolism results in widespread, multi-organ complications that ultimately encompass virtually every system of the body and every specialty of medicine. It has been said that to know diabetes is to know medicine and health care. Although from a clinical standpoint this may be true, our increasing knowledge of the pathophysiology of the syndrome, together with the mechanisms of long-term complications, has placed diabetes research at the frontier of immunology and molecular biology (Debra-Haire, 1991).

Diabetes mellitus has been known since ages and the sweetness of diabetic urine has been mentioned in Ayurveda by Sushruta. Its pharmacotherapy however is over 80 years old. The word diabetes was coined by the Greek physician Aeretaeus in the first century A.D. In the 17th century, Willis observed that the urine of diabetics as wonderfully sweet as if imbued with honey or sugar. The presence of sugar in the urine of diabetics was demonstrated by Dobson in 1755 (Satoskar, 1999).

History of Diabetes:

Our understanding of diabetes today is due to the work of many prominent physicians and scientists. This is a brief summary of the history of diabetes mellitus from the 15th century BC to the early 20th century when insulin was extracted.
### Table 1: Summary of the history of Diabetes mellitus: (Harmel, 2002).

<table>
<thead>
<tr>
<th><strong>Date</strong></th>
<th><strong>Source</strong></th>
<th><strong>Observation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>15(^{th}) century</td>
<td>Ebers Papyrus (Egypt)</td>
<td>Clinical description of polyuric condition resembling <em>Diabetes mellitus</em>.</td>
</tr>
<tr>
<td>17(^{th}) century</td>
<td>Thomas Willis (England)</td>
<td>Diabetic urine contains sugar.</td>
</tr>
<tr>
<td>18(^{th}) century</td>
<td>Mathew Dobson (England)</td>
<td>Diabetes may follow pancreatic damage.</td>
</tr>
<tr>
<td>1797</td>
<td>John Rolo (England)</td>
<td>One of the first to coin term ‘mellitus’. (honey from Greek and Latin Roots)</td>
</tr>
<tr>
<td>1815</td>
<td>Michel Chevreul (France)</td>
<td>Excess sugar in <em>Diabetes mellitus</em> is glucose.</td>
</tr>
<tr>
<td>1857</td>
<td>Wilhelm Petters (Germany)</td>
<td>Acetone found in Diabetic urine.</td>
</tr>
<tr>
<td>1850 – 60</td>
<td>Claude Bernard (France)</td>
<td>Pancreatic islets identified.</td>
</tr>
<tr>
<td>1869</td>
<td>Paul Langerhans (Germany)</td>
<td>Pancreatectomy causes diabetes.</td>
</tr>
<tr>
<td>1874</td>
<td>Adolf Kussmaul (Germany)</td>
<td>Acidotic breathing in Diabetic Coma.</td>
</tr>
<tr>
<td>1889</td>
<td>Minkowski and von Mering (Germany)</td>
<td>Pancreatectomy causes <em>Diabetes mellitus</em> in Dogs.</td>
</tr>
<tr>
<td>1907</td>
<td>Jean de Meyer (Belgium)</td>
<td>Hypothetical glucose lowering hormone named insulin.</td>
</tr>
<tr>
<td>1922</td>
<td>Frederick Banting, Charles Best, JB Collip, JJR Macleod (Canada)</td>
<td>Isolation and first clinical use of hypoglycemic extracts on patients.</td>
</tr>
<tr>
<td>1971</td>
<td>Roth et al</td>
<td>Discovered insulin receptor.</td>
</tr>
<tr>
<td>1977</td>
<td>Ulrich et al</td>
<td>Insulin gene cloned.</td>
</tr>
</tbody>
</table>

World Health Organization (WHO), projects a 170% growth in the number of people with diabetes in developing countries by 2025.

Between 1995 and 2025 the number of the adult population affect by DM in developing countries is projected to grow by 170%, from 84 to 228 million people. By 2025, these countries will be home to 76% of all persons with diabetes, as compared with 62% in 1995. In the same period, the developed world will see a 41% increase, from 51 to 72 million people.

Worldwide, a 122% rise is projected, from the total of 135 to 300 million. This more than twofold global increase will occur because of population ageing and growth, as well as from obesity, unhealthy diets and a sedentary lifestyle. These latter factors are closely associated with urbanization and industrialization.

A study containing these estimates was published by diabetes care, a most authoritative professional publication on the subject. The WHO in cooperation with the US-based Prudential Centre has undertaken the study for Health Care Research in Atlanta (Georgia) and the University of Michigan. The study linked data from a WHO developed global database on diabetes with UN demographic projections in order to estimate the number of people with diabetes in all countries of the world for three points in time – the years 1995, 2000 and 2025. In 1995, the countries with the largest number of people with diabetes were and are projected to be in the year 2025, are respectively as, India (19 and 57 million), China (16 and 38 million) and the USA (14 and 22 million). The greatest increase between 1995 and 2025 is expected to occur in India (195%).

For 1995, others in the "top 10" countries were the Russian Federation (9 million), Japan (6 million), Brazil (5 million), Indonesia (5 million), Pakistan (4 million), Mexico (4 million) and the Ukraine (4 million).

For 2025, the others in the top 10, if current demographic projections hold, would include Pakistan (15 million), the Russian Federation (12 million), Mexico (12 million), Brazil (around 11 million), Egypt (9 million) and Japan (around 9 million). The projections for the Russian federation are complicated by the continuing social change there.

The WHO study also contains estimates of sex ratio, urban-rural ratio and the age structure of the diabetic population. In 1995, for the world as a whole, there were more women than men with diabetes (73 million vs. 62 million). The female excess was pronounced in the developed countries (31 million vs. 20 million), but for the developing
countries, these figures are surprisingly equal (42 million in each case). WHO estimates that by 2025 the worldwide female/male excess will decrease (159 million vs. 141 million). For developing countries as a whole, a considerable excess of people affected with diabetes in the urban areas is predicted.

Of special interest to health economists and planners are WHO’s projections of the age structure of the diabetic population. If the present trends persist, by 2025 most people with diabetes in developed countries will be aged 65 years or more, while the majority of diabetic persons in developing countries will be in the 45-64 year age group. This means that some 170 million men and women, who will reside in the developing regions of the world in less than 30 years from now, will be suffering from diabetes in their most productive years of life.

**Classification of Diabetes mellitus:** (Davidson's, 1987; Smith, 1995; Kanh, 1995).

On the basis of etiology three main categories of diabetes are recognized, viz.

1. Primary diabetes.

1. **Primary diabetes:**

Majority of the cases belong to this class which is further of two clinical types:

a) **Juvenile onset diabetes which is also referred as Type I or Insulin dependent diabetes mellitus (IDDM).**

In juvenile onset diabetes there is a profound decrease in the number of β-cells in the islets of Langerhans and thus there is absolute deficiency of insulin. The main treatment for this type is insulin.

A viral aetiology is proposed for some severe forms of this condition. Impaired counterregulation by catecholamines, glucocorticoids and growth hormones are also features of this type of diabetes especially in long standing cases. Genetic or aetiological factors and islet cell antibodies to protein such as glutamic acid decarboxylase (GAD) may contribute to the onset of disease.

Type I Diabetes mellitus which is characterised by:-

- Immunologically mediated destruction of pancreatic islet β-cells.
- Absolute or near absolute absence of insulin secretion.
- Tendency to occur at younger age.
• Propensity to develop ketoacidosis due to insulin deficiency.
• Necessity to administer insulin exogeneously in order to ensure survival.

b. Maturity onset diabetes which is also referred as Type II/ Non-insulin dependent diabetes mellitus (NIDDM).

The patients are usually obese and the treatment is usually dietary, through supplementary oral hypoglycaemic drugs. It is diagnosed by blood or urinary glucose measurement. Insulin resistance as well as loss of insulin secretion sensitivity to glucose contributes to the onset of disease.

Type II Diabetes mellitus characterised by:-
• Normal or near normal $\beta$-cell mass and insulin secretion.
• Tendency to develop at greater heterogeneity; i.e.
  - Relatively older age.
  - Low prevalence of ketoacidosis.
  - Lack of insulin requirement for survival.

2. Secondary diabetes mellitus:
The symptoms result from the following:
1. Pancreatic dysfunction (pancreatitis, pancreatectomy).
3. Drugs or chemical induced reactions (eg: glucocorticoids, anticancer agents, streptozotocin or diazoxide, thiazide, some psychoactive agents).
4. Insulin receptor abnormalities.
5. Certain genetic syndromes (hyperlipidemia and muscular dystrophy).

3. Gestational diabetes mellitus:
Gestational diabetes mellitus is diabetes discovered during pregnancy. Pregnancy is a diabetogenic stage because of hormonal changes and stress associated with it.
Diagnosis of early Diabetes mellitus:
In moderately severe early diabetes, following symptoms are present.
1. Hyperglycemia.
2. Glycosuria.
3. Loss of weight due to increased breakdown of fat and tissue protein.
4. Increased production of ketone bodies by liver and their incomplete utilization by the tissue leading to their accumulation in blood (Ketosis) and elimination in urine (Ketonuria).
5. Lowering of pH of blood due to circulating keto acids (acidosis).
6. Dehydration due to elimination of large amounts of water with glucose in urine.
7. Increased levels of lipid, fatty acids and cholesterol in blood (lipemia).
8. Increased tendency to develop cataract in the eye and atheromatous and arteriosclerotic lesions of blood vessels.

Glucose- tolerance test:
Currently the presence of abnormally high glucose levels in the blood is the only criterion on which diagnosis of diabetes mellitus is based.

A sensitive diagnostic criterion is provided by glucose-tolerance test. After a night without food, the patient drinks a test dose of 100g of glucose dissolved in a glass of water. The blood glucose concentration is measured before the test dose and at 30 min. intervals for several hours thereafter. A normal individual assimilates glucose readily, the blood glucose rising to no more than about 9 or 10mM; little or no glucose appears in urine. Diabetic individuals assimilate the test dose of glucose poorly; their glucose level far exceeds the kidney threshold (about 10 mM) causing glucose to appear in their urine (David, 2000).
Table.2: The results of glucose analysis in glucose tolerance test (Deb, 1998).

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Normal Persons</th>
<th>Prediabetic Persons</th>
<th>Mild Diabetes</th>
<th>Severe Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar</td>
<td>80-120 mg/100ml</td>
<td>105-110 mg/100ml</td>
<td>115-125 mg/100ml</td>
<td>150-160 mg/100ml</td>
</tr>
<tr>
<td>Blood Sugar reaches its peak to</td>
<td>In 1hr. 130 mg/100ml</td>
<td>In 1hr. 150-160 mg/100ml</td>
<td>In 1hr. 190-200 mg/100ml</td>
<td>In 1hr. 320-350 mg/100ml</td>
</tr>
<tr>
<td>Returns to the fasting level</td>
<td>At the end of 2-2½ hr.</td>
<td>At the end of 3 hrs.</td>
<td>At the end of 3½ hrs.</td>
<td>At the end of 4hrs</td>
</tr>
<tr>
<td>Urine</td>
<td>No glucose</td>
<td>No glucose</td>
<td>1-2% glucose</td>
<td>More than 2%</td>
</tr>
</tbody>
</table>

Treatment of diabetes mellitus:

1) Insulin
2) Oral hypoglycaemic drugs
3) Herbal drugs.

I) Insulin:

Insulin is the main hormone controlling intermediary metabolism i.e. glucose utilization, protein synthesis (promotes it). Insulin is the peptide hormone secreted by β-cells of the islet of Langerhans of pancreas. Carbohydrate metabolism is primarily under the control of insulin. Reduced secretion of insulin causes diabetes mellitus. Insulin deficiency occurs in a person due to the functional disorder of the pancreas. Insulin is used parenterally in the treatment of diabetes mellitus (Brunton, 2006).

The endocrine part of the islets of Langerhans:

The normal human adult pancreas contains on an average some 500,000 islets of Langerhans, distributed in scattered manner within the gland, comprising 1 to 3% of the total tissue. Each group of cells of the endocrine part is surrounded by the acini of the exocrine part, they look like islands and are hence termed as islets. The distribution of islets is maximum in the tail and minimum in the head of the gland. Different types of
cells are found in the islets. These are called the alpha (α), beta (β), delta (δ) and F cell types. The α cells are fewer in number (about 20%) and they exist peripherally in the islet, while the most numerous β cells (about 75% to 80%) are situated centrally in the form of lumps (Robbins, 2005).

Table 3: Pancreatic islets house have four major cell types (Robbins, 2005).

<table>
<thead>
<tr>
<th>Cell types</th>
<th>Secretary Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha cells (A cells)</td>
<td>Glucagon.</td>
</tr>
<tr>
<td>Beta cells (B cells)</td>
<td>Insulin, C-peptide, Proinsulin</td>
</tr>
<tr>
<td>Delta cells (D cells)</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>F cell</td>
<td>Pancreatic polypeptide (PP)</td>
</tr>
</tbody>
</table>

Chemistry:

The Molecular mass of insulin is about 5734 Daltons. The β-cells of pancreatic islets synthesize insulin from a single chain precursor of 110 Amino acids (A.A), termed as preproinsulin. After the translocation through the membrane of the rough endoplasmic reticulum, the 24- amino acids N-terminal single peptide of preproinsulin is cleaved rapidly to form proinsulin. Thereafter proinsulin folds & the disulphide bond are formed. During conversion of proinsulin to insulin four basic A.A. and the remaining connector or C-peptide are removed by proteolysis. This gives rise to A & B peptide chain of the insulin molecule, which contains one intrasubunit and two intersubunit disulphide bonds. The A chain usually is composed of 21 amino acid residue and B chain has 30 amino acids.

In most cases the affinity of insulin for insulin-receptor correlates closely with its potency for eliciting effect on glucose metabolism. Human, bovine & porcine insulin are equipotent. Insulin is member of family of related peptides termed as Insulin like growth factor (IGF₁ & IGF₂) having molecular masses 7500 Daltons and structures are homologous to proinsulin. These peptides particularly are the presumed mediator of the action of growth hormone. (Brunton, 2006).
Fig.1: Structure of proinsulin. with removal of connecting peptide(C-peptide), proinsulin is converted into insulin.

**Mode of action of insulin:**

Insulin receptor present in the membrane of target cell has 2α-subunit (out of the cell membrane) & 2β-subunits (within the cell membrane). Insulin the ligand binds with α-subunit this leads to activation of β-subunit (and on being activated the β-subunit behaves like the activated enzyme tyrosine kinase) this ultimately causes either phosphorylation of some enzymes (e.g. Acetyl co-A carboxylase) or dephosphorylation of other enzyme (e.g. glycogen synthetase) within the cytosol. Phosphorylation & dephosphorylation of some enzymes leads to activation of the corresponding enzyme & gives biological effect.

Liver: Insulin is an anabolic hormone causing increased carbohydrate metabolism, glycogen formation, lipid synthesis and amino acid uptake and protein synthesis (William, 2005).
**Effects of insulin deficiency:** (Ganong, 1995)

*Insulin deficiency* (*Glucagon excess*)

- **Decreased glucose uptake**
- **Increased protein catabolism**
- **Increased lipolysis**

- **Hyperglycemia**
- **glycosuria**
- **osmotic diuresis**
- **electrolyte depletion**

- **Increased plasma amino acid N₂ loss of urine**

- **Dehydration acidosis**

- **Coma, Death.**
Fig. 2: Sequence of metabolic derangements leading to diabetic coma in type 1 Diabetes mellitus (Robbins, 2005).
FUNCTION OF INSULIN:-

- **Action on cell membrane permeability:**

  Insulin promotes the entry of glucose into all cells of the body excepting the cells of liver, brain & the RBCs. In the brain, however, cells of some special areas (like the hypothalamus), requires the presence of insulin for glucose entry, inside them. Insulin also promotes the entry of amino acids and fatty acid within the cells. Entry of K⁺ inside the cell is facilitated by insulin. Insulin increases Na⁺ K⁺ ATPase activity of the cells and this probably explains the rise of intracellular K⁺ with insulin.

- **Action on metabolism:**

  **Carbohydrate:**

  Insulin inhibits gluconeogenesis (synthesis of glucose from sources other than carbohydrates). These actions cause reduction of blood sugar level. Insulin promotes glycogenesis (synthesis of glycogen from glucose). Blood sugar level falls as a result.

  Insulin enhances peripheral utilization (oxidation) of glucose causing blood sugar level falls. Insulin inhibits glycogenolysis (breakdown of glycogen).

  **Fat:**

  Insulin promotes lipogenesis (synthesis of triglyceride) & inhibits lipolysis (hydrolysis of triglyceride). Thus a diabetic, on receiving insulin begins to put on fat in his adipose tissue. It also inhibits formation of ketone bodies in the body.

  **Protein metabolism:**

  Insulin promotes protein synthesis. Further it facilitates the action of several enzymes, e.g. Hexokinase.

  **Nucleic acid:**

  Insulin promotes synthesis of DNA & RNA (Choudhuri, 2001).
Types of insulin preparation:

1. Soluble insulin / Regular insulin:
   It is rapidly absorbed from the site of injection, circulates quickly and acts strongly.
   It is insulin of choice for coma, precoma and severe ketosis.

2. Long acting insulins:
   a. Protamine zinc insulin: It was the first long acting insulin. It is given as a depot in the subcutaneous tissue. From the site of injection it slowly enters the general circulation and does not provide high concentration in the tissue and hence it has prolonged alteration but it is weak in burning carbohydrates.
   b. Ultra lente / Insulin zinc suspension: Phosphate buffer is replaced with acetate without the use of protamine, globin other added proteins to produce crystalline form ultra-lente insulin having large crystals of about 30-40µ. It has prolonged but weak action.

3. Intermediate acting insulins:
   a. Globin
   b. N.P.H. Isophane
   c. Semi lente insulin (amorphous)

4. Mixtures of insulin:
   a. Soluble insulin + Protamine zinc insulin.
   b. Lente insulin / Insulin zinc suspension.
   A mixture of 30% semi lente and 70% ultra lente insulin gives lente/ insulin zinc suspension. It provides quick and long acting insulin (Lawrence, 1965; Marble, 1971).

Glucagon:
It is hyperglycemic factor of pancreas which is one of the contributory factors in the etiology of diabetes mellitus. It is secreted by α cells of pancreas. Its blood levels are elevated in severe diabetes with ketoacidosis.

   It is a polypeptide with a molecular weight of 3485. The polypeptide consists of 29 amino acid residues arranged in a straight chain. Unlike insulin, glucagon is free from zinc.

   In addition to α cells of pancreas, gastric and duodenal mucosa also secrets glucagon like substance. Ingestion of carbohydrates in food stimulates the release of intestinal
glucagon which in turn stimulates the pancreatic β cells to secrete insulin. The stimulus to glucagon production is lowering of blood glucose levels (Rama, 1994).

**Insulin secretion can be regulated by following factors**-

**Chemical:**

β-Cells have glucose sensing mechanism dependant on entry of glucose in to β-cells & it’s phosphorylation by glucokinase. Activation of glucoreceptor indirectly causes partial depolarization of β-cells & increases intracellular Ca⁺ availability it causes exocytic release of insulin. Other nutrients evoke insulin release are Amino acids, Fatty acids, Ketone bodies but glucose is the principle regulator & it stimulates synthesis of insulin as well.

**Hormonal:**

- Somatostatin inhibits release of both insulin & glucagon.
- Glucagon evokes release of insulin as well as somatostatin.
- Insulin inhibits glucagon secretion.

**Neural:**

- Adrenergic α₂ receptor activation decreases insulin secretion by inhibiting β-cell.
- adenylyl cyclase.
- β- adrenergic stimulation increases insulin secretion.
- Cholinergic muscarinic activation by Ach increases insulin secretion (Rang, 2003).

**B. Oral hypoglycemic agents**-

These drugs lower blood glucose level and are effective orally. The chief drawback of insulin is, it must be given by injection. Hence, the search for orally active drugs is demanded.

**Classification:**

1) Sulfonylureas:

<table>
<thead>
<tr>
<th>First generation</th>
<th>Second generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolbutamide</td>
<td>Glibenclamide</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>(Glyburide)</td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>Glipizide</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>Gliclazide</td>
</tr>
</tbody>
</table>
ii) Biguanides:
   Phenformin
   Metformin

iii) Miscellaneous
   Acarbose
   Guar gum

i) Sulfonylureas: (Mode of Action)
   Sulphonylureas activate receptors on the β islet cells of the pancreas to release more stored insulin in response to glucose. They do not increase insulin formation. They are ineffective in totally insulin deficient patients and for successful therapy probably requires about 30% of normal β cells function to be present. They cause hypoglycemia in normal subjects as well as diabetes (Chatterjee, 1997).

ii) Biguanides: (Mode of Action)
   They do not cause insulin release but presence of some insulin is essential for their action.
   • Suppress hepatic gluconeogenesis and glucose output from liver, probably the major action.
   • Enhance binding of insulin to its receptors and stimulate insulin mediated glucose disposal.
   • Interfere with mitochondrial respiratory chain-promote peripheral glucose utilisation by enhancing anaerobic glycolysis.
   • Inhibit intestinal absorption of glucose, other hexose, amino acids and vit. B₁₂.
     (Chatterjee, 1997).

Acarbose: It is complex oligosaccharide which reversibly inhibits α-glucosidases, the final enzymes in the digestion of carbohydrates in the brush border of small intestinal mucosa. It is mild hypoglycaemic; may be used as an adjuvant to diet in obese diabetics.

Guar gum: It is a dietary fibre (polysaccharide), from Indian cluster beans (Guar) which forms a viscous gel on contact with water. Administered just before or mixed with food, it slows gastric emptying, intestinal transit and carbohydrate absorption.

Guar gum can be used to supplement diet and to lower sulfonylurea dose and as a hypocholesterolemic (Tripathi, 1994).
PRECAUTIONS WITH ORAL HYPOGLYCEMIC AGENTS

Hypoglycemia occurs with sulphonylurea compounds, but occurrences are much more fewer than with insulin therapy.

A biguanide should not be used in patients with renal disease.

Herbal remedies for diabetes have been recorded in ancient medical literatures. In the last few decades, the search for newer antidiabetic agents from natural sources has intensified. Plants hold definite promises in the management of diabetes mellitus (Chatterjee, 1997).

MEDICINAL PLANTS USED AS ANTI-DIABETIC AGENTS:

Diabetes mellitus is a common chronic endocrine disorder. Since ancient times, number of herbal medicines has been used in the treatment of this disease. Many studies have been carried out in search of a suitable plant drug that would be effective in diabetes mellitus.

Table. 4: Some plants having hypoglycemic activity (Nahar, 1993).

<table>
<thead>
<tr>
<th>Plant</th>
<th>Plant part</th>
<th>type of test sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigonella foenum-graecum</td>
<td>seed</td>
<td>Alcohol, water extract</td>
</tr>
<tr>
<td>Nephoelepsis tuberose</td>
<td>bulb</td>
<td>juice</td>
</tr>
<tr>
<td>Costus specious</td>
<td>rhizome</td>
<td>juice</td>
</tr>
<tr>
<td>Plantago ovata</td>
<td>husk</td>
<td>Powder</td>
</tr>
<tr>
<td>Allium sativum</td>
<td>bulb</td>
<td>juice</td>
</tr>
<tr>
<td>Hemidesmus indicus</td>
<td>root</td>
<td>alcoholic extract</td>
</tr>
<tr>
<td>Allium cepa</td>
<td>bulb</td>
<td>juice</td>
</tr>
</tbody>
</table>

Herbal medicines for diabetes can be classified into four categories according to their mode of action:

i) Drugs acting like insulin.
ii) Drugs acting on insulin secreting beta cells.
iii) Drugs acting by modifying glucose utilization.
iv) Drugs acting by miscellaneous mechanisms.
i) **Herbal drugs acting like insulin:**
   
a) **Momordica charantia:**
   
   Fruits of *Momordica charantia* have been successfully used by diabetic patients and their crude extract has shown to possess hypoglycemic activity. Khanna and Jain isolated a hypoglycemic peptide (polypeptide-P) from seeds and other tissues of *Momordica charantia*. They reported that polypeptide-P is a very effective hypoglycemic agent when administered subcutaneously to gebrils, langurs and humans. Singh et al. have reported hypoglycemic effect of acetone extract of whole fruit powder of *Momordica charantia*.

ii) **Drugs acting on insulin secreting beta cells:**
   
a) **Allium cepa:**
   
   *Allium cepa* (onion) was investigated for its hypoglycemic activity by Collip and Janet, Laurin Brahmachari and Augusti reported that the petroleum ether extract of dried onion has hypoglycemic activity and suggested that it can be a useful substitute for tolbutamide in controlling alloxan diabetes in rats.

b) **Pterocarpus marsupium:**
   
   Rajasekharan and Tuli carried out clinical trial and found that *Pterocarpus marsupium* bark is effective in Type 1 diabetes mellitus. Later Charkravarthy et al. reported epicatechin to be the active hypoglycemic constituent.

c) **Aloes:**
   
   Ghannam et al. carried out their study on 5 patients with NIDDM and also on alloxan treated diabetic mice. They reported that oral administration of *aloes* lowers the fasting serum glucose levels in normal and diabetic subjects.

d) **Ficus bengalensis:**
   
   Brahmachari and Augusti reported that the ethanol extract of the bark of *Ficus bengalensis* is effective in alloxan-induced diabetes in rats and rabbits.

- **Plant drugs acting by modifying glucose utilisation:**
   
   *Zingiber officinale* (ginger), *Cyamopsis tetragonolobus* (Gowar Plant) and *Grewia asiatica* (phalsa) are reported to produce hypoglycemia by modifying glucose utilisation.

   Sharma and Shukla reported that ginger juice has glucose lowering effect in normal fasting animals and in alloxan diabetic animals.
Jenkins et al. reported that the hypoglycemic effect of *Cyamopsis tetragonolobus* in diabetic and normal subjects.

Gowar plant and the seeds at a dose of 40g/kg showed hypoglycemic activity similar to that of tolbutamide. The mechanism of action of gowar is probably related to its ability to increase the viscosity of gastrointestinal contents, slow gastric emptying and also act as a barrier to diffusion. The workers concluded that gowar produces its hypoglycemic action by acting at an extrapancreatic site.

The aqueous extract of *Grewia asiatica* was tested in diabetic cats and rabbits of both sexes by Pakrashi and Mukherjee. These workers reported that the fasting blood sugar levels come down to normal after the treatment and remain as such after discontinuation of treatment for another 15 days.

**Drugs acting by miscellaneous mechanisms:**

*a) Leguminous plants:*

Hypoglycemic activity of some leguminous plants was studied by Singh et al. and reported that legumes in diet could reduce glucose levels in normal rats than could a normal diet. Chopra (1955) reported that leguminous plants in diet could reduce blood sugar levels and cholesterol levels because of their dietary fibre content.

*b) Salvia lavandulifolia:*

The flowering species of *Salvia lavandulifolia* are used in the treatment of diabetes mellitus in Spain. Jamenex et al. studied its effect and reported its hypoglycemic activity in normal as well as alloxan diabetic rabbits. The hypoglycemic effect is slight and independent.

*c) Euphorbia prostrata & Fumaria parviflora:*

Aktar et al. reported extracts from these plants reduce blood sugar levels in normal rabbits but not in diabetic rabbits.

*A few other plants with hypoglycemic activity:*

*Panax ginseng,* *Dioscorea dumatorum,* *Cuminum nigrum,* *Ocimum sanctum,* *Curcuma longa,* *Phyllanthus emblica* (Hakim, 1995).
I. Few other plants with hypoglycemic activity (William, 2005).

   a. *Coccinia indica*:

   Bimba et al. reported ethanolic extract of this plant is hypoglycemic, orally active and comparable with Tolbutamide.

   b. *Ficus racemosa*:

   It is reported that the bark extract contains hypoglycemic property.

   c. *Tinospora Cordifolia*:

   Its efficiency was proved by N.N. Sirchar on prescribing its Juice with honey in diabetics, which substantiated the Ayurvedic advocacy.

   Gupta et al. has proved its hypoglycemic property in diabetics “marked reduction of rise in blood sugar level after glucose meal. The hypoglycemic effect may be related partly to the direct metabolic effect and party due to endogenous insulin secretion.

Complications of Diabetes mellitus:

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycemia is associated with long-term damage and dysfunction of small and large blood vessels resulting in failure of various organs. Common complications resulting from uncontrolled diabetes include heart disease, stroke, blindness, nervous system damage and kidney dysfunction (King, 2005).
Fig. 3: Long term complications of diabetes

At the time of diagnosis, most patients with type 2 diabetes will have some symptoms of elevated glucose (i.e., polyuria, polydipsia, polyphagia), microvascular symptoms (i.e., blurred vision, numbness or tingling in hands or feet) and macrovascular complications (i.e., cardiovascular disease).

I) Microvascular complications:

Over 200,000 people die each year because of diabetes related complications. Underlying diabetic complications such as nephropathy, neuropathy, retinopathy, cardiovascular disease and peripheral vascular disease can be present for many years before an actual diagnosis is made.

a) Nephropathy:

Diabetic nephropathy is a clinical syndrome characterized by excessive urinary albumin excretion, hypertension and renal insufficiency. In the United States, diabetic
nephropathy accounts for about 40% of new cases of end-stage renal disease (ESRD). Nephropathy is a frequent complication of type 1 and type 2 diabetes mellitus.

Not all diabetic patients will develop overt nephropathy; however, there are some factors that affect the progression of nephropathy such as cigarette smoking, poor glycaemic control, urinary albumin excretion rate, hyperlipidemia, hypertension and genetics.

The natural history of diabetic nephropathy has 5 stages, which includes hyperfiltration with normal renal function; histological changes without clinically evident disease; incipient diabetic nephropathy or microalbuminuria; overt diabetic nephropathy (macroalbuminuria, reduced renal function) and renal failure requiring dialysis.

b) Neuropathy:

Diabetic peripheral neuropathy (DPN) is one of the most prevalent and complicated conditions to manage among diabetic patients. About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage; resulting in impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, precursor for foot ulcers and other nerve problems. Diabetes is the major contributing reason for non-traumatic lower extremity amputations (more than 60% of cases).

c) Retinopathy:

Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20-74 years. By the end of the first 2 decades of disease, nearly all patients with type 1 diabetes will have evidence of retinopathy. Nearly 20% of patients with type 2 diabetes will have retinopathy at the time of diagnosis of diabetes. Diabetic retinopathy can progress from mild nonproliferative abnormalities, to moderate and severe nonproliferative diabetic retinopathy and finally to proliferative diabetic retinopathy. The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. However, adequate control of blood glucose, blood pressure and lipid levels can significantly decrease the progression and morbidity of diabetic retinopathy.

II) Macrovascular Complications:

Diabetes exerts a heavy toll on the vascular system. The hallmark of diabetic macrovascular disease is accelerated by atherosclerosis involving the aorta and large and medium-sized arteries. Macrovascular disease causes accelerated atherosclerosis among diabetics resulting in increased risk of myocardial infarction stroke and lower-extremity
gangrene. Macrovascular complications associated with diabetes include cardiovascular, cerebrovascular and peripheral arterial diseases.

a) Cardiovascular:

People with diabetes are 2 to 4 times more likely to develop cardiovascular disease (CVD) than those without diabetes. However, the risk of coronary artery disease is increased in patients with poor glycaemic control. In patients with insulin resistance, the disease tends to accelerate to atherogenesis long before the onset of hyperglycemia. Additional mechanisms that contribute to the increased risk of CHD and worse outcomes in persons with diabetes include endothelial dysfunction, hypercoagulability, impaired fibrinolysis, platelet hyperaggregability, oxidative stress, sympathovagal imbalance and glucose toxicity.

b) Cerebrovascular:

Cerebrovascular disease is a term encompassing many disorders that affect the blood vessels of the central nervous system. These disorders result from either inadequate blood flow to the brain (i.e. cerebral ischemia) or from haemorrhages into the parenchyma or subarachnoid space of the central nervous system.

c) Peripheral arterial disease:

Peripheral arterial disease (PAD) is an atherosclerotic occlusive disease. It is the major risk factor for lower extremity amputations. The abnormal metabolic state accompanying diabetes results in changes in the state of arterial structure and function predisposing people to PAD. The risk of development of PAD increases threefold to fourfold in patient with diabetes mellitus (King, 2005).

**AYURVEDA & DIABETES** *(http://ekikrat.in/ayurveda-diabetes)*

According to ayurveda, diabetes is a metabolic kapha type of disorder that disrupts the proper functioning of agni. As a result of this the disease of high blood sugar takes place in a human body. This disease is a slow and silent killer and many people on this planet are suffering from this disease.

**Ayurvedic concept of diabetes mellitus**

According to ayurveda, an imbalance in one of the three doshas is the reason behind the cause of this disease. Every people on the planet are born with three main doshas and any imbalance in it is the main reason for the cause of diseases. Proper balance in the doshas is a must for the normal functioning of the human body.
To many people diabetes can be cured with the help of medicines or by following strict routine diet. But ayurveda’s approach regarding the treatment of this disease is completely different. They believe that the treatment of this disease is based on complete change in the lifestyle of an individual. People suffering from this disease are advised to do medication as well since it offers peace and relaxation to the mind.

Diabetes mellitus is a very complicated disease and is capable of affecting various organs of the human body like eye, kidney and heart. Sometimes it often leads to paralysis as well. The conventional treatment of diabetes is to reduce the level of blood sugar. But in ayurveda, every possible complications of this disease are taken into account. Here in such a case, the entire human body is taken into consideration and then it is treated accordingly.

**Ayurvedic treatment of diabetes.**

With the help of multiprong approach, ayurvedic practitioners proceed forward with the treatment of this killer disease. The basic treatments of this disease are as follows:

- Diabetic patients are first advised to make certain modification in their diet. Here they are told to stay away from the foodstuffs that are rich in carbohydrate.
- Protein rich diet can have adverse effect on the kidneys and for this reason patients are also advised to not to take heavy protein diet.
- Like protein, diabetic patients are also advised to avoid fat rich diet mainly because of the deficiency of the pancreatic enzymes.
REFERENCES:
Chatterjee TK. *Herbal Options*. Eastern traders, Calcutta;1997; 9-16.
Hakim ZS. Potential antidiabetic agents from plant sources; Pharmacological aspects. *Indian J. natural product* 1995; 11(1); 3.
Harmel AP, Davidson MR, *Diabetes mellitus: Diagnosis and Treatment*. Pennsylvania: Saunders; 2002;01-17.
Lawrence RD. *The Diabetic Life*; 17th Edn. 1965; 59.