The term “Diabetes mellitus” is derived from the Greek words dia (=through), bainein (=to go) and diabetes literally means pass through. The disease causes loss of weight as if the body mass is passed through the urine. Although it was known for centuries that the urine of patients with diabetes was sweet, it was not until 1674 that a physician named Willis coined the term Diabetes Mellitus (DM)(from the Greek word for honey) (D M Vasudevan et al., 2005).

DM is a metabolic disorder of several aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (Kaleem et al., 2008). Diabetes is a chronic illness that requires long-term medical care and patient self-management education to check acute complications and to decrease the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A huge body of data exists that supports a range of interventions to progress diabetes outcomes.

CLASSIFICATION AND DIAGNOSIS

Classification

In 1997 American diabetes association (ADA) issued new diagnostic and classification criteria (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus). In 2003 modifications were made regarding the diagnosis of impaired fasting glucose (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus). The classification of diabetes includes four clinical classes.

1. **Type 1 diabetes** (results from- cell destruction, usually leading to absolute insulin deficiency)

2. **Type 2 diabetes** (results from a progressive insulin secretory defect on the background of insulin resistance)

3. **Other specific types of diabetes** due to other causes, e.g., genetic defects in - cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical induced (such as in the treatment of AIDS or after organ transplantation)

4. **Gestational diabetes mellitus** (GDM) (diabetes diagnosed during pregnancy)
TYPE I DIABETES:
Type 1 diabetes is of two types—immune mediated diabetes and Idiopathic diabetes

Immune-mediated diabetes
This form of diabetes, which accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulin dependent diabetes, type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cells include islet cell auto antibodies, auto antibodies to insulin, auto antibodies to glutamic acid decarboxylase (GAD65), and auto antibodies to the tyrosine phosphatases IA-2 and IA-2β. The disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These HLA-DR/DQ alleles can be either predisposing or protective. Immune mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life. These patients are also prone to other autoimmune disorders such as Graves’ disease, Hashimoto’s thyroiditis, Addison’s disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

Idiopathic diabetes
Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes falls into this category, most are of African or Asian ancestry. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated.

TYPE II DIABETES
This form of diabetes, which accounts for ~90–95% of those with diabetes, previously referred to as non-insulin dependent diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency at least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive.

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight
Introduction

criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Ketoacidosis rarely occurs spontaneously in this type of diabetes. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes. However, the genetics of this form of diabetes are complex and not clearly defined.

OTHER SPECIFIC TYPES OF DIABETES:

Genetic defects of the β-cell:

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α. A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. The less common forms result from mutations in other transcription factors, including HNF-4α, HNF-1β, insulin promoter factor (IPF)-1, and NeuroD1.

Point mutations in mitochondrial DNA have been found to be associated with diabetes mellitus and deafness. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition. An identical lesion occurs in the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome) however; diabetes is not part of this syndrome, suggesting different phenotypic expressions of this genetic lesion.

Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has
also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism.

**Genetic defects in insulin action:**

Mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Women may be virilized and have enlarged, cystic ovaries. In the past, this syndrome was termed type A insulin resistance. Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance. The former has characteristic facial features and is usually fatal in infancy, while the latter is associated with abnormalities of teeth and nails and pineal gland hyperplasia.

**Diseases of the exocrine pancreas:**

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. Cystic fibrosis and hemochromatosis will also damage β-cells and impair insulin secretion. Fibrocalculous pancreatopathy may be accompanied by abdominal pain radiating to the back and pancreatic calcifications identified on X-ray examination. Pancreatic fibrosis and calcium stones in the exocrine ducts have been found at autopsy.

**Endocrinopathies:**

Several hormones (e.g., growth hormone, cortisol, glucagon, and epinephrine) antagonize insulin’s action. Excess amounts of these hormones (e.g., acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. Somatostatinoma- and aldosteronoma- induced hypokalemia can cause diabetes, at least in part, by inhibiting insulin secretion.

**Drug or chemical induced diabetes:**

Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic β-cells. Such drug reactions fortunately are rare. There are also many drugs and hormones that can impair insulin action. Examples include nicotinic acid and glucocorticoids. Patients receiving α-interferon have been reported to develop diabetes associated with islet cell antibodies and in certain instances, severe insulin deficiency.
Introduction

Infections:

Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease.

Uncommon forms of immune mediated diabetes:

In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms. Patients usually have high titers of the GAD auto antibodies, and approximately one-third will develop diabetes.

Anti–insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby blocking the binding of insulin to its receptor in target tissues. However, in some cases, these antibodies can act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia. Anti–insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. As in other states of extreme insulin resistance, patients with anti–insulin receptor antibodies often have Acanthosis nigricans. In the past, this syndrome was termed type B insulin resistance.

Other genetic syndromes sometimes associated with diabetes:

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down’s syndrome, Klinefelter’s syndrome, and Turner’s syndrome. Wolfram’s syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of β-cells at autopsy. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness. Other syndromes are listed in table 1.
GESTATIONAL DIABETES MELLITUS:

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. GDM complicates ~4% of all pregnancies in the U.S. resulting in ~135,000 cases annually. The prevalence may range from 1 to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes. Deterioration of glucose tolerance occurs normally during pregnancy, particularly in the 3rd trimester.

Table 1: Etiologic Classification of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   1. Immune mediated
   2. Idiopathic.

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types

1. Genetic defects of β-cell function
   i. Chromosome 20q, HNF-4α (MODY1)
   ii. Chromosome 7p, glucokinase (MODY2)
   iii. Chromosome 12q, HNF-1α (MODY3)
   iv. Chromosome 13q, insulin promoter factor (MODY4)
   v. Chromosome 17q, HNF-1β (MODY5)
   vi. Chromosome 2q. Neurogenic differentiation 1 / cell e-box transactivator 2 (MODY 6)

2. Genetic defects in insulin action
   vii. Type 1 insulin resistance
   viii. Leprechaunism
   ix. Rabson-Mendenhall syndrome
x. Lipoatrophic diabetes

3. Diseases of the exocrine pancreas
   xi. Pancreatitis
   xii. Trauma/pancreatectomy
   xiii. Neoplasia
   xiv. Cystic fibrosis
   xv. Hemochromatosis
   xvi. Fibrocalculous pancreatopathy

4. Endocrinopathies
   xvii. Acromegaly
   xviii. Cushing's syndrome
   xix. Glucagonoma
   xx. Pheochromocytoma
   xxi. Hyperthyrodism
   xxii. Somatostatinoma
   xxiii. Aldosteronoma

5. Drug- or chemical-induced
   xxiv. Vacor
   xxv. Pentamidine
   xxvi. Nicotinic acid
   xxvii. Glucocorticoids
   xxviii. Thyroid hormone
   xxix. Diazoxide
   xxx. b-adrenergic agonists
   xxxi. Thiazides
   xxxii. Dilantin
   xxxiii. α-interferon

6. Infections
   xxxiv. Congential rubella
   xxxv. Cytomegalovirus

7. Uncommon forms of immune-mediated diabetes
   xxxvi. "Stiff-man" syndrome
   xxxvii. Anti-insulin receptor antibodies
8. Other genetic syndromes sometimes associated with diabetes
   xxxviii. Down's syndrome
   xxxix. Klinefelter's syndrome
   xl. Turner's syndrome
   xli. Wolfram's syndrome
   xlii. Friedreich's ataxia
   xliii. Huntington's chorea
   xliv. Laurence-Moon-Biedel syndrome
   xlv. Myotonic dystrophy
   xlvii. Prader-Willi syndrome

IV. Gestational diabetes-mellitus (GDM)

Diagnosis of diabetes

For decades, the diagnosis of diabetes was based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h value in the 75-g oral glucose tolerance test (OGTT) (American Diabetes Association., 2010).

According to expert committee appointed by ADA in 1997, the criteria for diagnosing the Diabetes include,

FPG (Fasting plasma glucose) <100 mg/dl (5.6 mmol/l) = normal fasting glucose;
FPG 100–125 mg/dl (5.6–6.9 mmol/l) = IFG (impaired fasting glucose);
FPG ≥126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes

The corresponding categories when the OGTT is used are the following:

2-h post load glucose <140 mg/dl (7.8 mmol/l) = normal glucose tolerance;

2-h post load glucose 140–199 mg/dl (7.8 –11.1 mmol/l) = IGT (impaired glucose tolerance);

2-h post load glucose ≥200 mg/dl (11.1 mmol/l) = provisional diagnosis of diabetes
Patients with IFG and/or IGT are now referred to as having “pre-diabetes” indicating the relatively high risk for development of diabetes in these patients. IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and/or low-HDL type, and hypertension. Note that many individuals with IGT are euglycemic in their daily lives. Individuals with IFG or IGT may have normal or near normal glycated hemoglobin levels. Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized OGTT.

New guidelines for the diagnosis of diabetes mellitus

In 2009, an International Expert Committee that included representatives of the ADA, the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended the use of the glycosylated haemoglobin (HbA1C) test to diagnose diabetes, with a threshold of ≥ 6.5% (. International Expert Committee, Diabetes Care., 2009), and ADA adopted this criterion in 2010 (American Diabetes Association., 2010). The diagnostic test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. The HbA1C has several advantages to the FPG and OGTT, including greater convenience, since fasting is not required; evidence to suggest greater pre-analytical stability; and less day-to-day perturbations during periods of stress and illness. These advantages must be balanced by greater cost, the limited availability of HbA1C testing in certain regions of the developing world, and the incomplete correlation between HbA1C and average glucose in certain individuals. In addition, HbA1C levels can vary with patients’ ethnicity (Ziemer et al., 2010) as well as with certain anemia and hemoglobinopathies. For patients with an abnormal haemoglobin but normal red cell turnover, such as sickle cell trait, an HbA1C assay without interference from abnormal hemoglobins should be used. For conditions with abnormal red cell
Introduction

turnover, such as pregnancy, recent blood loss or transfusion, or some anemias, the diagnosis of diabetes must employ glucose criteria exclusively. The established glucose criteria for the diagnosis of diabetes (FPG and 2-h Plasma glucose) remain valid as well (Table 2). Just as there is less than 100% concordance between the FPG and 2-h PG tests, there is not perfect concordance between HbA1C and either glucose-based test. Analyses of National Health and Nutrition Examination Survey (NHANES) data indicate that, assuming universal screening of the undiagnosed, the HbA1C cut point of ≥6.5% identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥126 mg/dl (7.0 mmol/l) (Cowie CC et al., 2010).

Table: 2 Diagnosis of diabetes (International Expert Committee., ADA. 2009)

<table>
<thead>
<tr>
<th>S.NO</th>
<th>New Criteria for the diagnosis of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBA1C ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* Or</td>
</tr>
<tr>
<td>2</td>
<td>FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.* or</td>
</tr>
<tr>
<td>3</td>
<td>2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* or</td>
</tr>
<tr>
<td>4</td>
<td>In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l)</td>
</tr>
</tbody>
</table>

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.
PREVALENCE OF DIABETES

The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. Prevalence of diabetes in adults worldwide was estimated to be 4% in 1995 and to rise to 5.4% by the year 2025. It is higher in developed than developing countries. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in 2025. The countries with the large number of people with diabetes are India, China and the U.S. (King et al., 1998).

The global prevalence of diabetes for all age-groups 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. Diabetes prevalence is higher in men than in women, but there are more women with diabetes than men. In developing Countries, the urban population with diabetes is projected to double between 2000 and 2030. The most important demographic influence on diabetes prevalence across the world appears to be the increase in the proportion of people >65 years of age. (Wild et al., 2004)

In the Americas, the number of people with diabetes mellitus was estimated at 35 million in 2000 and is expected to increase to 64 million by 2025. Where as currently 52% of these people from the Americas live in Latin Americas and the Caribbean; by 2025 the percentage will have reached 62%, representing 40 million persons. The North America, the recent estimate of the prevalence of diagnosed diabetes among adults in Canada was 3.2%. In the United States, the prevalence rate of diabetes increase from 11.4% in 1976-1980 to 14.3% in 1988-1994. Diabetes prevalence rates for Mexican-Americans were twice as high as for non-Hispanic whites. About 20% of non-Hispanic blacks in the United States were affected by diabetes. The prevalence rate in this group was the second highest after that of Mexican-Americans. The Pima Indians from the state of Arizona have shown the highest prevalence of diabetes in the Americas and one of the highest in the world. (Barcelo & Rajpathak., 2001).
Introduction

According to J.E. Shaw et al., 2010 (Table 3), projections are somewhat higher than predictions made only a few years ago (wild et.al., 2004). The current estimate for 2010 of 285 million adults with diabetes is 67% higher than the 2004 published estimate for the year 2000 (wild et.al., 2004), and their 2030 estimate of 439 million is 20% higher than the same studies estimate for 2030 (wild et.al., 2004).

Table: 3 The list of countries with the highest number of diabetic people (in millions) for 2010 and 2030 Courtesy: J.E. Shaw et al., 2010

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of adults with diabetes (millions)</th>
<th>Country</th>
<th>No. of adults with diabetes (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>India</td>
<td>1.0</td>
<td>India</td>
</tr>
<tr>
<td>2</td>
<td>China</td>
<td>43.2</td>
<td>China</td>
</tr>
<tr>
<td>3</td>
<td>USA</td>
<td>26.8</td>
<td>USA</td>
</tr>
<tr>
<td>4</td>
<td>Russian Federation</td>
<td>9.6</td>
<td>Pakistan</td>
</tr>
<tr>
<td>5</td>
<td>Brazil</td>
<td>7.6</td>
<td>Brazil</td>
</tr>
<tr>
<td>6</td>
<td>Germany</td>
<td>7.5</td>
<td>Indonesia</td>
</tr>
<tr>
<td>7</td>
<td>Pakistan</td>
<td>7.1</td>
<td>Mexico</td>
</tr>
<tr>
<td>8</td>
<td>Japan</td>
<td>7.1</td>
<td>Bangladesh</td>
</tr>
<tr>
<td>9</td>
<td>Indonesia</td>
<td>7.0</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>10</td>
<td>Mexico</td>
<td>6.8</td>
<td>Egypt</td>
</tr>
</tbody>
</table>

PREVALENCE IN INDIA

The first national study on the prevalence of type 2 diabetes in India was done between 1972 and 1975 by the Indian Council of Medical Research (ICMR, New Delhi) (Ahuja MMS., 1979). Screening was done in about 35,000 individuals above 14 yr of age, using 50 g glucose load. Capillary blood glucose level >170 mg/dl was used to diagnose diabetes. The prevalence was 2.1 per cent in urban population and 1.5 percent in the rural population while in those above 40 yr of age, the prevalence was 5 percent in urban and 2.8 percent in rural areas. Subsequent studies showed a rising trend in the prevalence of diabetes across different parts of India. According to the World Health Organisation estimates, India had 32 million diabetic subjects in the year 2000 and this number would increase to 80 million by
the year 2030 (Wild et al., 2004). The International Diabetes Federation (IDF) also reported that the total number of diabetic subjects in India is 41 million in 2006 and that this would rise to 70 million by the year 2025 (Sicree et al., 2006). More recent reports from various parts of India showed further increases in diabetes prevalence in urban areas. (Ramachandran and Snehalatha 2009).

**Table 4:** shows the prevalence of diabetes in India as reported by different authors during 2000-2008 (Ramachandran et al., 2010).

**Table: 4: Prevalence of diabetes in India.**

<table>
<thead>
<tr>
<th>Region</th>
<th>Year</th>
<th>Age of the subjects years</th>
<th>Prevalence (%)</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>IGT</td>
<td>IFG</td>
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<td><strong>National</strong></td>
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<td></td>
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<tr>
<td>Ramachandran et al</td>
<td>2000</td>
<td>&gt;20</td>
<td>12.1</td>
<td>14.0</td>
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<td></td>
</tr>
<tr>
<td>Reddy et al.</td>
<td>2003</td>
<td>20-69</td>
<td>8.4</td>
<td>---</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Sadikot et al</td>
<td>2004</td>
<td>&gt;20</td>
<td>5.9</td>
<td>6.3</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td><strong>Northern India</strong></td>
<td></td>
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<tr>
<td>Ramachandran et al</td>
<td>2000</td>
<td>&gt;20</td>
<td>11.6</td>
<td>8.6</td>
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<tr>
<td>Gupta et al</td>
<td>2003</td>
<td>20-59</td>
<td>8.6</td>
<td>----</td>
<td>5.3</td>
<td></td>
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<tr>
<td>Prabhakaran et al†</td>
<td>2005</td>
<td>&gt;20</td>
<td>15</td>
<td>37</td>
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<td></td>
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<tr>
<td><strong>Southern India</strong></td>
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<tr>
<td>Ramachandran et al</td>
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<td>&gt;20</td>
<td>13.5</td>
<td>16.8</td>
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<tr>
<td>Mohan et al</td>
<td>2004</td>
<td>20</td>
<td>14.3</td>
<td>10.2</td>
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<tr>
<td>Menon et al</td>
<td>2005</td>
<td>18-80</td>
<td>19.5</td>
<td>4.1</td>
<td>7.0</td>
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<tr>
<td>Ramachandran et al</td>
<td>2006</td>
<td>&gt;20</td>
<td>18.6</td>
<td>7.4</td>
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<tr>
<td><strong>Multi-centric</strong></td>
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<tr>
<td>Mohan et al.</td>
<td>2008</td>
<td>20-80</td>
<td>7.1</td>
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</tr>
</tbody>
</table>

† This study was conducted in industrial workers (men only).
Introduction

Rapid rise in the prevalence of type 2 diabetes in India (1990 to 2007)

Evidence for the rapid rise in prevalence of type 2 diabetes came from Chennai, as the prevalence of type 2 diabetes had risen to 11.6% in the same urban area which had a prevalence of 8.2% five years earlier (Ramachandran et al., 1997). A study done in Kerala showed a very high (16.3%) prevalence of diabetes in 1999 (Kutty et al., 1999). The Kashmir Valley study done in 2000 recorded a prevalence of 6.3% (Zargar et al., 2000).

A study done in Mumbai in 2001 reported a prevalence of 7.5% according to ADA and 4.6% according to WHO criteria (Iyer et al., 2001). The National Urban Diabetes Survey (NUDS) was a population based study conducted in six large cities from different regions of India. This study was done on 11,216 subjects aged over 20 years from all socio-economic strata. The study showed that the age standardized prevalence of type 2 diabetes was 12.1%. The prevalence was the highest in Hyderabad (16.6%), followed by Chennai (13.5%), Bangalore (12.4%), Kolkata (11.7%), New Delhi (11.6%) and Mumbai (9.3%) (Ramachandran et al., 2001). A study on the camel milk consuming community (Raica) of Rajasthan reported absence of diabetes in the community suggesting a protective effect of camel milk (Agrawal et al., 2004). Another caste based study from Rajasthan reported a prevalence of 16.7% in the Bhargava community (Kothari et al., 2005).

The Chennai Urban Rural Epidemiology Study (CURES) showed a prevalence of diabetes in 15.5% of population (age standardised 14.3%) in Chennai in 2006 (Mohan et al., 2006). The Amrita Diabetes and Endocrine Population Survey (ADEPS), a community based cross-sectional survey done in urban areas of Ernakulam district in Kerala has revealed a very high prevalence of 19.5% (Menon et al., 2006). A high (13.2%) prevalence of diabetes was also reported in a rural population of Andhra Pradesh by Chow et al., 2006).

Animal models for studying diabetes mellitus

The existence of experimental animal model of a disease aids not only the understanding of the pathophysiology of such disease, but also the development of drugs for its treatment.
Over the years, several animal models have been developed for studying diabetes mellitus or testing anti-diabetic agents. These models include chemical, surgical (pancreatectomy) and genetic manipulations in several animal species to induce diabetes mellitus. The diabetogenic drugs used include: alloxan monohydrate, streptozotocin with or without nicotinamide/ferric nitritotriacetate/ditizona. The cytotoxic action of these diabetogenic agents is mediated by reactive oxygen species, but both drugs differ in their mechanism of action (Federiuk et al., 2004; Lei et al., 2005).

Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide with a simultaneous massive increase in cytosolic calcium concentration, which causes rapid destruction of pancreatic β-cells (Szudelski, 2001).

Streptozotocin enters the pancreatic β-cell via a glucose transporter-GLUT2 and causes alkylation of deoxyribonucleic acid (DNA). Furthermore, STZ induces activation of poly adenosine diphosphate ribosylation and nitric oxide release. As a result of STZ action, pancreatic β-cells are destroyed by necrosis (Mythili et al., 2004) (Fig 2). For several decades, the β-cell-specific toxin streptozotocin (STZ), an analogue of GlcNAc (Fig 1), has been used to create animal models of diabetes, despite an incomplete understanding of how STZ actually causes β-cell death (Herr et al., 1967). The ability of STZ to act as a NO donor has led many investigators to postulate that NO is involved (Kroncke et al., 1995), but the diabetogenic effect of STZ in vivo cannot be readily duplicated with N-methyl- N-nitrosourea (MNU, the portion of STZ that actually donates NO) (Voss et al., 1988). Recently, STZ has been shown to inhibit the enzyme O-GlcNAc-selective N-acetyl-β-D-glucosaminidase (OGlcNAcase), which removes O-GlcNAc from protein, and is thus the final enzyme in the pathway of O-glycosylation in the β-cell (Liu et al., 2000).

Pancreatic β-cells have been proposed to be selectively sensitive to STZ because the enzyme responsible for transferring O-GlcNAc to proteins, OGlcnAc transferase (OGT) (Kreppel et al., 1997), is expressed at higher levels in the β-cell than in any other cell (Liu et al., 2000; Hanover et al., 1999). The potential problem with STZ is that its toxic effects are not restricted to pancreatic β-cells since it may cause renal injury (Valentovic et al., 2006), oxidative stress inflammation and endothelial dysfunction (Lin et al., 2005). Vacor, dithizone (diphenylthiocarbazone),
and 8-hydroxyquinol one may also cause experimental diabetes, but their use in research is restricted due to their level of toxicity (Clark et al., 1994).

Fig.1: The chemical structure of GlcNAc and STZ

![Chemical Structure](image)

**N-Acetylglucosamine**  **Streptozotocin**

Fig.2: Proposed mechanism of Streptozotocin-induced β-cell injury (Modified from Okamoto et al., 1985)
COMPLICATIONS OF DIABETES

Diabetes mellitus is associated with serious complications that can impair quality of life and function and lead to premature death. The complications of diabetes mellitus can be divided into 2 major types.

1. Acute metabolic complications
2. Chronic or long-term vascular complications

ACUTE COMPLICATIONS OF DIABETES

The acute metabolic complications of diabetes consist of diabetic ketoacidosis (DKA), hyperosmolar non-ketotic coma (HNC), lactic acidosis (LA), and hypoglycemia. The incidence rate for DKA from population-based studies ranges from 4.6 to 8 per 1,000 diabetic persons per year. Pathogenesis of diabetic ketoacidosis and Hyperglycaemic hyperosmolar state represented in Fig 3.

DKA is one of the major acute diabetic complications. DKA is clinically defined by absolute insulin deficiency with hyperglycemia (glucose levels usually >200 mg/dl) with increased lipolysis, increased ketone production, hyperketonemia (ketone levels positive at 1:4 dilution of serum or greater or beta hydroxybutyrate >0.5 mmol/L), and acidosis (pH ≤7.3 or bicarbonate ≤15 mEq/L).

HNC is clinically defined by the presence of relative insulin deficiency and hyperglycemia, usually >1,000 mg/dl with associated elevated serum osmolality (>300 mosm/kg), dehydration, and stupor, progressing to coma if uncorrected, without the presence of ketosis or acidosis. These patients have sufficient circulating insulin to prevent lipolysis and ketosis. Pathophysiology of DKA and HNC are given in figure 3.

LA consists of elevated lactic acid (lactic acidemia, ≥2.0 mmol/L) with acidosis (pH ≤7.3) and without ketoacidosis. There may be low levels of ketones present (≤1:4 on serum dilution, or beta hydroxybutyrate >0.4 but <0.6 mmol/L).
Hypoglycemia is common in insulin-treated diabetic patients and also occurs occasionally in patients treated with the oral hypoglycemic sulfonylurea agents. Hypoglycemia may range from very mild lowering of glycemia (60-70 mg/dl) with minimal or no symptoms, to severe hypoglycemia with very low levels of glucose (<40 mg/dl) and neurologic impairment.

**Fig.3: Pathogenesis of diabetic ketoacidosis (DKA) and Hyperglycaemic hyperos molar state (HHS) (English and Williams, 2004)**
CHRONIC COMPLICATIONS OF DIABETES

Diabetes is a group of chronic diseases characterized by hyperglycemia. Chronic hyperglycemia is associated with long-term damage and dysfunction of small and large blood vessels resulting in failure of various organs. Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) (Fowler, 2008). Over 200,000 people die each year because of diabetes related complications (Preventing Diabetes and Its Complications, 2005).

MICROVASCULAR COMPLICATIONS

Diabetic retinopathy

Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20-74 years. Diabetic retinopathy can progress from non proliferative abnormalities to pre proliferative and finally to proliferative diabetic retinopathy by Fong et al., 2004).

Non-proliferative (NPDR): Characterized by blood vessel changes within the retina: microaneurysms (weakened blood vessel walls), dot & blot hemorrhages (bleeding), hard exudates or edema (leakage of fluid), loss of circulation and nerve fibre layer infarcts (NFLI). It generally does not interfere with vision (Eye Foundation of Kansas City, 2005).

Pre-proliferative (Severe NPDR): Characterized by increased NFLI and haemorrhage, presence of intra retinal micro vascular abnormalities (IRMA), venous bleeding, and reduplication of vessels. 50% of patients will progress to proliferative disease within two years.

Proliferative (PDR): This is very serious and severe. It occurs when new blood vessels branch out or proliferate in and around the retina. It can cause bleeding into the fluid-filled center of the eye or swelling of the retina (vitreous hemorrhage) and lead to blindness. (Fong et al., 2004). It is Characterized by neovascularization of the optic disc (NVD) or neovascularization of the retina elsewhere (NVE).
DIABETIC NEPHROPATHY

Diabetic nephropathy is a clinical syndrome characterized by excessive urinary albumin excretion, hypertension, and renal insufficiency. Normal urinary albumin excretion is less than 30 mg/24 hr. Abnormal albumin excretion is defined as either microalbuminuria (30-299 mg/24 hr) or macroalbuminuria (>300 mg/24 hr) (American Diabetes Association, 2004). The natural history of diabetic nephropathy has 5 stages which include

Stage 1: Functional changes at the onset of diabetes are marked by hyperfiltration and transient microalbuminuria. These changes may be reversed or attenuated with improved glycemic control.

Stage 2: Clinically silent, though pathological changes of diabetic renal disease are evolving.

Stage 3: Incipient nephropathy-persistent microalbuminuria of 30-300 mg albumin/day or 20-200 µg/min demonstrated in 2 out of 3 samples collected over a 6-month period.

Stage 4: Clinical nephropathy-proteinuria or overt diabetic nephropathy or Macro albuminuria with a decline in glomerular filtration rate (GFR > 150 mls/min) with or without hypertension. This is the stage classically referred to as diabetic nephropathy.

Stage 5: End-stage renal disease (ESRD) requiring renal replacement therapy with dialysis or kidney transplantation.

In the United States, diabetic nephropathy accounts for about 40% of new cases of end-stage renal disease (ESRD) (National Diabetes Fact Sheet, 2005). Nephropathy is a frequent complication of type 1 and type 2 diabetes mellitus. Half of patients with type 1 DM who have overt nephropathy will develop ESRD within 10 years and 75% within 20 years (American Diabetes Association, 2003).
MACROVASCULAR COMPLICATIONS

Macrovascular complications associated with diabetes include cardiovascular, cerebrovascular, and peripheral arterial diseases.

CVD (Cardio vascular disease) is the primary cause of death in people with either type 1 or type 2 diabetes was described by Laing et al., 2003; Paterson et al., 2007). People with diabetes are 2 to 4 times more likely to develop CVD than those without diabetes (National Diabetes Fact Sheet, 2005). Among people with type 2 diabetes, women may be at higher risk for coronary heart disease than men. The presence of microvascular disease is also a predictor of coronary heart events (Avogaro et al., 2007). There are several risk factors that may contribute to the development of CHD, including lifestyle (e.g., cigarette smoking and diet), hyperglycemia, hypertension, and high cholesterol. 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 (Haffner, 2005).

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 hemorrhages into the parenchyma or subarachnoid space of the central nervous system. Various terms have been used to describe cerebrovascular events. For example, the term transient ischemic attack (TIA) describes the clinical condition in which a patient experiences a temporary focal neurologic deficit such as slurred speech, aphasia, weakness or paralysis of a limb, or blindness. These symptoms are rapid in onset, lasting, 24 hours (usually 2 to 15 minutes). Reversible ischemic neurologic deficit is similar to a TIA; however, the deficit improves over no more than 72 hours and may not completely resolve. Cerebral infarction is a neurologic event causing permanent damage. Cerebral hemorrhage is a cerebrovascular disorder that involves escape of blood from blood vessels into the brain and its surrounding structures. There are 700,000 new or recurrent cerebrovascular events per year. The incidence of stroke is significantly greater among blacks compared with whites (Welty, 2001). Sudden confusion, loss of coordination, unilateral weakness, and numbness are warning signs of a
cerebrovascular event. 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 (Creager & Libby, 2001). The risk of development of PAD increases 3 to 4 fold in patients with diabetes mellitus (Murabito et al., 1997). Risk factors for the development of PAD include diabetes, hypertension, hyperlipidemia, cigarette smoking, and age. In people with diabetes, the risk of PAD is increased by age, duration of diabetes, and presence of peripheral neuropathy. Elevated levels of C-reactive protein (CRP), fibrinogen, homocysteine, apolipoprotein B and plasma viscosity are potential risk factors for PAD.

**TREATMENT OF DIABETES MELLITUS**

The aim of the treatment is primarily to save life and alleviate symptoms. Secondary aims are to prevent long term diabetic complications and, by eliminating various risk factors, to increase longevity. The first aim is not difficult to attain and in some elderly patients or those who lack motivation it is the only aim (Watkins PJ. et al., 1990). The care of diabetes on self management is based on the patient’s clinical status and his/her ability to participate in self-care. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM.

**The major components of the treatment of diabetes are:**

1. Diet (combined with exercise)
2. Oral hypoglycaemic therapy
3. Insulin treatment
4. Herbal therapy
Introduction

1. Diet (combined with exercise)

Diet is a basic part of management in every case. Treatment cannot be effective unless adequate attention is given to ensuring appropriate nutrition. Ideally, the initial management of NIDDM should be based on dietary therapy combined with increased physical activity, if possible. However, pharmacologic therapy (oral hypoglycaemic drugs or insulin) may be considered in the presence of marked hyperglycaemia.

**Dietary treatment should aim at:**

- Ensuring weight control
- Providing nutritional requirements
- Allowing good glycaemic control with blood glucose levels as close to normal as possible.
- Correcting any associated blood lipid abnormalities
- Ensuring consistency and compatibility with other forms of treatment if used, for example oral agents or insulin.

**The following principles are recommended as dietary guidelines for people with Diabetes:**

- Dietary fat should provide 25-35% of total intake of calories but saturated fat intake should not exceed 10% of total energy. Cholesterol consumption should be restricted and limited to 300 mg or less daily.
- Protein intake can range between 10-15% total energy (0.8-1 g/kg of desirable body weight). Requirements increase for children and during pregnancy. Protein should be derived from both animal and vegetable sources.
- Carbohydrates provide 50-60% of total caloric content of the diet. Although it has been traditionally recommended that carbohydrates should be complex and high in fibre, more emphasis should be placed on the total amount of carbohydrates consumed than the source of carbohydrate.
- Excessive salt intake is to be avoided. It should be particularly restricted in people with hypertension and those with nephropathy.
- Artificial sweeteners are to be used in moderation. Nutritive sweeteners (sorbital and fructose) should be restricted.
The same precautions regarding alcohol intake that apply to the nondiabetic population also apply to people with diabetes. Additionally, however, alcohol tends to increase the risk of hypoglycemia in those taking antidiabetic drugs and should be particularly avoided in those with lipid abnormalities and patients with neuropathy. Except in special conditions like pregnancy and lactation, routine vitamin and mineral supplementation is generally not needed in people with a well balanced diet. There is, at present, no definite evidence to confirm that such treatment has any benefits.

Exercise

Physical activity promotes weight reduction and improves insulin sensitivity, thus lowering blood glucose levels. Together with dietary treatment, a programme of regular physical activity and exercise should be considered for each person. Such a programme must be tailored to the individual’s health status and fitness. People should, however, be educated about the potential risk of hypoglycaemia and how to avoid it.

2. Oral hypoglycaemic therapy

Oral hypoglycaemic agents (OHA’s) are considered only after a regimen of dietary treatment combined with exercise has failed to achieve the therapy targets set.

Currently, there are five distinct classes of OHAs available

1. Sulfonylureas/sulphonylureas (SUs)
2. Meglitinides
3. Biguanides
4. Thiazolidinediones (TZDs)/glitazone
5. α-glucosidase inhibitors

Each class displays unique pharmacological properties

Mechanism of action of five classes of oral hypoglycaemic agents are summarized in Fig: 5
SULFONYLUREAS

Sulfonylureas are frequently classified as either 1st generation or 2nd generation agents. First generation sulfonylureas (acetohexamide, chlorpropamide, tolaamide and tolbutamide) possess a lower binding affinity for the ATP-sensitive potassium channel, their molecular target, and thus require higher doses to achieve efficacy, increasing the potential for adverse events. In addition, the plasma half-life of 1st generation sulfonylureas is extended compared to the 2nd generation agents. 2nd generation sulfonylureas including glyburide (glibenclamide), glipizide, and glimepiride are now widely used. The 2nd generation sulfonylureas are much more potent compounds (~ 100-fold), with a more rapid onset of action, and generally have shorter plasma half-lives and longer duration of action compared to the 1st generation agents.

Mechanism of action:

Sulfonylureas are insulin secretagogues, since they control blood glucose levels by directly stimulating first-phase insulin secretion in the pancreatic β cells. Mitochondrial glucose metabolism leads to ATP generation and increases the intracellular ratio of ATP/ADP, which results in the closure of the ATP-sensitive potassium channel (K^+–ATP; a 140 kDa membrane protein) on the plasma membrane of β-cells. Closure of this channel depolarizes the membrane and triggers the opening of voltage-sensitive calcium channels, leading to the rapid influx of calcium. Increased intracellular calcium causes an alteration in the cytoskeleton, and stimulates translocation of insulin-containing secretory granules to the plasma membrane and the exocytotic release of insulin (Fig. 4).

The K^+-ATP channel is comprised of two subunits. One subunit contains the cytoplasmic binding sites for both sulfonylureas and ATP, and is designated as the sulfonylurea receptor type 1 (SUR1). The other subunit is the potassium channel, which acts as the pore-forming subunit (Inagaki et al., 1995). Either an increase in the ATP/ADP ratio or ligand binding (by sulfonylureas, meglitinides) to SUR1 results in the closure of the K^+-ATP channel and insulin secretion (Fig. 4). Studies comparing sulfonylureas and non-sulfonylurea insulin secretagogues have identified several distinct binding sites on the SUR1 that cause channel closure.
Introduction

Efficacy

All sulfonylureas are equally effective in terms of their hypoglycemic potency, although a recent trial has indicated that glimepiride (Amaryl) may be slightly more efficacious than the others. (Ahmann & Riddle, 2000).

Fig. 4: Proposed Mechanistic action of SulfonylUreas

Side effects

The most common side effect of sulfonylurea is hypoglycaemia, which though usually mild to moderate, can cause fatal complication (Ferner & Neil, 1988), (Seltzer, 1989). In the United Kingdom Prospective Diabetic Study (UKPDS) group 1998) the rates of any hypoglycaemic symptoms were 11% for chlorpropamide, 17.7% for glibenclamide, 36.5% for insulin, and 1.2% for lifestyle management. Long-lasting and serious hypoglycaemia occurs more often with long acting sulfonylureas, such as glibenclamide and chlorpropamide than with short-acting ones, such as glipizide and tolbutamide (Swedish Board of Health and Welfare, 1985). Weight gain is a frequent complication of sulfonylurea treatment and well-controlled studies have found that the mean yearly increase in body weight was 2.8 kg (Campbell & Howlett, 1995). In UKPDS, patients receiving sulfonylureas had a net increase in weight of 3 kg compared to conventionally treated patients (The UKPDS Group, 1995).
Introduction

Other effects may include gastrointestinal disturbances and headache. Hypersensitivity reactions are uncommon but may occur in the first 6-8 weeks of therapy and include transient rashes, fever, and jaundice. Blood disorders are rare, but include thrombocytopenia, agranulocytosis, and aplastic and haemolytic anaemias. About 10-15% of patients on chlorpropamide develop an alcohol flushing reaction similar to that caused by disulfiram (disulfiram-Antibus reaction). Chlorpropamide may also induce hyponatremia by potentiating the effects of antidiuretic hormone on the renal collecting duct, (Paice et al., 1985) which may occur in about 5% of all patients; it is less frequent with glyburide and glipizide.

MEGLITINIDES

The meglitinides are a new class of drugs developed to improve early-phase insulin secretion, which is one of the earliest pathophysiological manifestations of type 2 DM. These are derived from the meglitinide portion of sulfonylureas. Examples of this group are repaglinide and nateglinide. Another meglitinide known as mitiglinide is undergoing clinical trials. Repaglinide, a benzoic acid derivative introduced in 1998, was the first member of the meglitinide group. Nateglinide is a derivative of the amino acid D-phenylalanine and was introduced to the market in 2001.

Mechanism of action

The meglitinides act on β-cell receptors to stimulate insulin secretion by binding to the sulfonylurea receptor subunit and closing the K⁺-ATP channel (Hu et al., 2000), but probably at a site distinct from that of the sulfonylurea receptor (Fuhlendorff et al., 1988). Repaglinide and Nateglinide do not stimulate insulin secretion in the complete absence of glucose and its action is usually confined to intermediate concentrations of glucose i.e. 180 mg/dl (10 mmol/l). These properties account for the low risk of hypoglycaemia seen with repaglinide in contrast to the sulfonylureas.

Adverse effects

In 1-year trials, the most common adverse events reported in repaglinide recipients (n = 1,228) were hypoglycemia (16%), upper respiratory tract infection (10%), rhinitis (7%), bronchitis (6%) and headache (9%). Weight gain does occur in patients treated with repaglinide, but the magnitude is significantly less compared to treatment with glyburide (Marbury et al., 1999; Damsbo et al., 1999). The most
common adverse effects are nausea, diarrhea, dizziness, and light headedness with nateglinide and incidence of mild hypoglycemia is lower than for repaglinide and no reports of severe hypoglycemia and weight gain. Repaglinide and nateglinide should be used cautiously in patients with hepatic insufficiency. They are contraindicated in severe hepatic impairment, pregnancy and breastfeeding.

**BIGUANIDES**

Metformin (Glucophage) and phenformin were introduced in 1957 and *buphormin* was introduced in 1958. They were widely used in Europe for treating type 2 diabetes for nearly 20 years. The latter two were withdrawn in many countries in the 1970s because of an association with fatal lactic acidosis (Schafer, 1983). Metformin (dimethybiguanide; Glucophage) is a synthetic analog of the natural product guanidine. Metformin has a very low rate of lactic acidosis compared to phenformin and has been widely used in Europe, Canada, Middle East and other countries; it became available in the United States in 1995. Metformin is recommended as a first-line therapy in newly diagnosed individuals, and can be used in combination with an insulin secretagogue (sulfonylurea or meglitinide), thiazolidinedione, α-glucosidase inhibitor, exenatide, DPP-4 inhibitor or insulin (DeFronzo, 2000; Bolen *et al.*, 2007).

**Mechanism of action**

The primary effect of metformin is the suppression of basal hepatic glucose production, thereby reducing fasting plasma glucose. The molecular target of metformin action still awaits identification. Metformin does not stimulate insulin secretion; in contrast, metformin reduces fasting plasma insulin and improves whole-body insulin-stimulated glucose metabolism (insulin sensitivity) (Bailey & Turner, 1996; Cusi & DeFronzo, 1998). Recent in vitro and in vivo evidence has shown that metformin activates the AMP-activated protein kinase (AMPK), a major cellular regulator of lipid and glucose metabolism (Hardie *et al.*, 1998). As a result, acetyl-CoA carboxylase activity was reduced, fatty acid oxidation was induced (due to decreased malonyl-CoA), and the expression of lipogenic enzymes along with SREBP-1, a key lipogenic transcription factor was suppressed (Zhou *et al.*, 2001). The use of a novel AMPK inhibitor indicated that AMPK activation was required for the inhibitory effect of metformin on glucose production in hepatocytes. In isolated rat skeletal muscles, metformin stimulated glucose uptake coincident with AMPK activation.
Adverse effects

Approximately one-third of patients on metformin will have transient nausea, anorexia or diarrhea, abdominal discomfort, and metallic taste. Intestinal absorption of vitamin B$_{12}$ and folate is often decreased during chronic metformin therapy. Calcium supplements reverse the effect of metformin on vitamin B$_{12}$ absorption (Bauman et al., 2000). Other adverse effects reported are headache, agitation, dizziness and tiredness. Lactic acidosis is a rare but serious, and it is estimated to have an incidence of 0.03 per 1000 patient/years (Bailey & Turner, 1996). Metformin is contraindicated in patients with impaired renal, respiratory or hepatic function, cardiac failure, or a history of alcohol abuse.

α-GLUCOSIDASE INHIBITORS

Acarbose, miglitol and voglibose are members of the α-glucosidase inhibitor class of oral anti-hyperglycemic compounds that function by blocking the enzymatic degradation of complex carbohydrates in the small intestine (Magner & Amatruda, 2000) and decrease the postprandial rise in plasma glucose, thus reproducing the effect of a low glycaemic index/high fiber diet. These drugs have an excellent safety profile.

Mechanism of action

Acarbose, the first α-glucosidase inhibitor discovered, is a nitrogen-containing pseudotetrasaccharide of microbial origin, while miglitol is a synthetic analog of 1-deoxy nojirimycin. The mechanism of action of these inhibitors is similar but not identical. They bind competitively to the oligosaccharide binding site of the α-glucosidase enzymes, thereby preventing enzymatic hydrolysis. Acarbose binding affinity for the α-glucosidase enzymes is: glycoamylase > sucrase > maltase > dextranase (Puls, 1996). Acarbose has little affinity for isomaltase and no affinity for the β-glucosidase enzymes, such as lactase. Miglitol is a more potent inhibitor of sucrase and maltase that acarbose, has no effect on α-amylase, but does inhibit intestinal isomaltose (Lebovitz, 1998).
Adverse effects

The major side effects of the α-glucosidase inhibitors are related to gastrointestinal disturbances. These occur in approximately 25-30% of diabetic patients, the delay in carbohydrate digestion and their accumulation in the lower gastrointestinal tract increases the amount of fermentable carbohydrate reaching the colon. This results in dose-related flatulence, diarrhoea, and abdominal bloating. Acarbose is contraindicated in patients with inflammatory bowel disease, cirrhosis, or elevated plasma creatinine (>177 µmol/l). This class of drugs is associated with dose-dependent hepatotoxicity, and serum transaminase levels require monitoring for patients receiving high doses (>200 mg three times daily).

THIAZOLIDINEDIONES

Pioglitazone, rosiglitazone and troglitazone are members of the thiazolidinedione class of insulin sensitizing compounds originally discovered and characterized for their glucose- and lipid-lowering activity (Sohda et al., 1982; 1995). A thiazolidine-2, 4-dione structure is common to all agents. These compounds decrease insulin resistance and enhance the biological response to endogenously produced insulin, as well as insulin administered by injection (Mudaliar & Henry, 2001. Foyt et al., 2000). Troglitazone was withdrawn from use because of its association with severe hepatic toxicity (Bae et al., 2003).

Mechanism of action

Pioglitazone and rosiglitazone are selective agonists for the peroxisome proliferator-activated receptor γ (PPARγ), a member of the superfamily of nuclear hormone receptors that function as ligand-activated transcription factors (Kliewer et al., 1999). In the absence of ligand, PPARs bind as heterodimers with the 9-cis retinoic acid receptor (RXR) and a multi-component co-repressor complex to a specific response element (PPRE) within the promoter region of their target genes (Olefsky & Saltiel, 2000). Once PPAR is activated by ligand, the co-repressor complex dissociates allowing the PPAR-RXR heterodimer to associate with a multi-component co-activator complex resulting in an increased rate of gene transcription. The target genes of PPARγ include those involved in the regulation of lipid and carbohydrate metabolism (Picard & Auwerx, 2002).

PPARγ is expressed chiefly in adipose tissue, and its expression in liver and skeletal muscle is low (Fajas et al., 1997). Thus, it is more likely that the primary effects of these drugs are on adipose tissue, followed by secondary benefits on other
Introduction

target tissues of insulin (Combs et al., 2002). The ability of rosiglitazone and pioglitazone to decrease circulating free fatty acids could lead to an improvement in insulin action in the periphery (de Souza et al., 2001). More recently, PPARγ agonists have been reported to increase the expression and circulating level of adiponectin (Acrp30), an adipocyte-derived protein with insulin sensitizing activity (Berg et al., 2001), in diabetic rodents (Combs et al., 2002) and in patients with type 2 diabetes (Yang et al., 2002).

Adverse effects

The major side effects of this class of drugs are edema, weight gain, decreased hematocrit and hemoglobin, and elevated (but reversible) alanine aminotransferase activity. Weight gain (dose-dependent) of 1-4kg after 6 months of treatment (Aronoff et al., 2000) and fluid retention that may be severe enough to exacerbate or precipitate heart failure (Idris et al., 2003), were observed with TZDs. The drugs also cause gastro-intestinal disturbances, anaemia, headache, visual disturbances, dizziness, haematuria, impotence; less commonly fatigue, insomnia, vertigo, hypoglycaemia and proteinuria. Rosiglitazone has not been shown to be hepatotoxic in premarketing trials; a few case reports have implicated it as a cause of acute hepatocellular injury (Dhawan et al., 2002).

Fig 5: Summary of the mechanisms of action of the oral hypoglycemic agents
Introduction

**Insulin treatment**

When glycemic control worsens or is not adequate despite the use of oral hypoglycaemic agents, often the next step is to add insulin therapy. Insulin treatment can improve and maintain glycemic control, preventing long-term complications in type 2 diabetes (UK Prospective Diabetes Study (UKPDS) 13, 1995, UK Prospective Diabetes Study 16.1995 and Ohkubo et al., 1995). Over time most patients with type 2 diabetes experience progressive β-cell dysfunction and will require insulin therapy either alone or in combination with oral agents for satisfactory glycemic control (UK Prospective Diabetes Study 24., 1994). Attempts to mimic physiologic patterns of basal insulin secretion have been difficult because most currently available insulins have disadvantages, including variable absorption, pronounced peaks after injection, and abbreviated durations of action (Barnett and Owens 1997; Galloway 1995; Galloway and Chance 1994; Bolli et al., 1999).

**Types of Insulin for Diabetes Treatment**

There are many forms of insulin to treat diabetes. They are classified by how fast they start to work and how long their effects last.

The types of insulin include:

- Rapid-acting
- Short-acting
- Intermediate-acting
- Long-acting
- Pre-mixed

Deciding factors for insulin therapy, including:

- Individualized response to insulin (how long it takes insulin to be absorbed in the body and remain active in the body varies slightly from person to person).
- Lifestyle Choices
- Age.
- Blood sugar management goals.
The following chart lists the types of injectable insulin with details about onset (the length of time before insulin reaches the bloodstream and begins to lower blood sugar), peak (the time period when the insulin is the most effective in lowering blood sugar) and duration (how long insulin continues to lower blood sugar). These three factors may vary, depending on your body's response. The final column provides some insight into the "coverage" provided by the different insulin types in relation to meal time (www.anacalifornia.org/insulinissues/MythvsFactrebuttalfinal.pdf)

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular Insulin</td>
<td>30 min</td>
<td>1-2 hours</td>
<td>4-6 hours</td>
<td>Morning, Early Afternoon, Late Afternoon</td>
</tr>
<tr>
<td>Long-Acting Insulin</td>
<td>3-4 hours</td>
<td>1-2 hours</td>
<td>24 hours</td>
<td>Morning, Early Afternoon, Late Afternoon</td>
</tr>
<tr>
<td>Rapid-Acting Insulin</td>
<td>15-30 min</td>
<td>1-2 hours</td>
<td>2-4 hours</td>
<td>Mealtime</td>
</tr>
<tr>
<td>Insulin Glargine</td>
<td>3-4 hours</td>
<td>1-2 hours</td>
<td>24 hours</td>
<td>All Day</td>
</tr>
<tr>
<td>Insulin Aspart</td>
<td>30 min</td>
<td>1-2 hours</td>
<td>4-6 hours</td>
<td>Morning, Early Afternoon, Late Afternoon</td>
</tr>
</tbody>
</table>

*Final column provides insight into the "coverage" provided by the different insulin types in relation to meal time.*
### Table 4.1: Type of Insulin & Brand Names

<table>
<thead>
<tr>
<th>Type of Insulin &amp; Brand Names</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Role in Blood Sugar Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog or lispro</td>
<td>15-30 min.</td>
<td>30-90 min.</td>
<td>3-5 hrs</td>
<td>Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is used with Longer-acting insulin.</td>
</tr>
<tr>
<td>Novolog or aspart</td>
<td>10-20 min.</td>
<td>40-50 min.</td>
<td>3-5 hrs</td>
<td></td>
</tr>
<tr>
<td>Apidra orglulisine</td>
<td>20-30 min.</td>
<td>30-90 min.</td>
<td>1-2½ hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular (R) humulin or novolin</td>
<td>30 min - 1hr</td>
<td>2-5 hrs</td>
<td>5-8 hrs</td>
<td>Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes</td>
</tr>
<tr>
<td>Velosulin (for use in the insulin pump)</td>
<td>30 min - 1hr</td>
<td>2-3 hrs</td>
<td>2-3 hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH (N)</td>
<td>1-2 hrs</td>
<td>4-12 hrs</td>
<td>18-24 hrs</td>
<td>Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with rapid- or short-acting insulin.</td>
</tr>
<tr>
<td>Lente (L)</td>
<td>1-2½ hrs</td>
<td>3-10 hrs</td>
<td>18-24 hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente (U)</td>
<td>30 min - 3hr</td>
<td>10-20 hrs</td>
<td>20-36 hrs</td>
<td>Long-acting insulin covers insulin needs for about one full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.</td>
</tr>
<tr>
<td>Lantus</td>
<td>1-1½ hour</td>
<td>No peaktime; insulin is delivered at a steady level</td>
<td>20-24 hrs</td>
<td></td>
</tr>
<tr>
<td>Levemir or detemir</td>
<td>1-2 hrs</td>
<td>6-8 hours</td>
<td>Up to 2hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-Mixed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin 70/30</td>
<td>30 min.</td>
<td>2-4 hrs</td>
<td>14-24 hrs</td>
<td>These products are generally taken twice a day before mealtime.</td>
</tr>
</tbody>
</table>
Complications of insulin therapy

The most common adverse reactions to insulin are weight gain and hypoglycaemia by Henry et al., 1993 and Kudlacek et al., 1992) Hypoglycaemia may result from an inappropriately large dose, from mismatch between the peak delivery of insulin and food intake or from superimposition of additional factors (adrenal insufficiency, pituitary insufficiency) that increase sensitivity to insulin or that (exercise) increase insulin-independent glucose uptake. The more vigorous the attempt to achieve euglycaemia, the more frequent the episodes of hypoglycaemia. In one clinical trial (DCCT), the incidence of hypoglycaemia reactions were three times higher in the intensive insulin therapy group than in the conventional therapy group. (Diabetes Control and Complications Trial Research Group.,1993) Use of physiological insulin regimens combined with education can actually decrease the frequency of hypoglycaemia(Pampanelli et al.,2002 and Bott et al.,1997) and reduce the risk of hypoglycaemia( Lalli et al.,1999 and Cryer et al.,2002). Weight gain after starting insulin therapy for uncontrolled diabetes is an inevitable consequence and is the result of increased truncal fat and muscle bulk. (Diabetes Control and Complications Trial Research Group, 1993 and Yki-Jarvinen et al., 1999) This is also due to reduced energy losses through glycosuria. In this case physiological insulin regimens can help to minimize weight gain by reducing inappropriate insulinaemia and hypoglycaemia between meals and thus the need for snacks in both adults and children. In type 2 diabetes metformin can help limit weight gain when insulin is started (Yki-Jarvinen et al., 1999).

Insulin allergy and resistance.

There has been a dramatic decrease in the incidence of resistance and allergic reactions to insulin with the use of human insulin or highly purified preparations of the hormone. Bovine insulin was especially prone to cause allergic reactions. These reactions still occur as a result of the small amounts of aggregated or denatured insulin in all preparations, to minor contaminants, or because of sensitivity to one of the components added to insulin in its formulation (protamine, $\text{Zn}_2^+$, phenol, etc.). The most frequent allergic reactions were IgE-mediated local urticaria reaction which are extremely rare nowadays. (Kahn CR and Rosenthal AS., 1979).
Herbal Treatment of diabetes mellitus:

The recorded use of herbal remedies for the treatment of diabetes mellitus goes back as far as the Ebrus Papyrus 1550 BC (Day, 1990). Recognition of the disease in early times is illustrated by an ancient Indian text (6 BC) in which Ayurvedic Physician Susruta described two forms of madhumeha or sweet urine – an “inherited” type which causes emaciation and a second type which affects individuals with sedentary habits and a tendency to over eat (Shanmugasundaram et al., 1983). Traditional medicine systems from around the world, particularly Arabia, China and the Indian subcontinent, have evolved a range of herbal treatments for diabetes (Nadkarni, 1982; Bailey & Day, 1989; Zhang & Xiao, 1993). Diabetes affects about 5% of the global population (Chakraborty & Rajagopalan, 2002) and management of diabetes without any side effects is still a challenge to the medical system (Kameswara Rao et al., 2003a). Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost (Venkatesh et al., 2003). In recent years, herbal medicines have started to gain importance as a source of hypoglycemic agents. Therefore, investigation on such agents from traditional medicinal plants has become more important (Suba et al., 2004a; WHO, 1980). India has a rich history of using various potent herbs and herbal components for treating diabetes. Many Indian plants have been investigated for their beneficial use in different types of diabetes and reported in numerous scientific journals.

Several pharmacopoeias have provided parameters to maintain quality and standardize procedures in identification/ authentication of herbal inputs and their products. The European Pharmacopoeia 2002 has 174 monographs on herbal drugs and preparations. British Herbal Pharmacopoeia has 233 monographs, British Herbal Compendium has 84 monographs, United States Pharmacopoeia and the National Formulary has 28 official monographs of the most commonly used plants in the country. The countries with strong background of traditional medicine as China and India are leading. Chinese Pharmacopoeia 2000 has 992 monographs and Ayurvedic pharmacopoeia of India [API] has about 1000 single drugs and 8000 compound formulations of recognized merit used in India (Inamdar et al., 2007). The World
Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as botanical garden of the world (Seth & Sharma, 2004).


The glycosides isolated from the species belonging to the families Caesalpinaceae, Compositae, Convolvulaceae, Ericaceae, Moraceae, Mytaceae, Papavaraecae, Ranunculaceae, Rhamnaceae and Scrophulaceae afforded active principles which lowered blood sugar in test animals. Similarly glycans and triterpenes of species of Ranunculaceae and glycans of Graminae exhibited similar activity (Oliver- Bever, 1986). In plants of Liliaceae this property was attributed to various types of sulfide molecules. Polysacharides, oils and vitamins from the family
Graminae also showed pharmacological activity by decreasing blood sugar level in animals (Kameswarao et al., 1997). Alkaloids of Apocyanaceae, Papaveraceae, Rhamnaceae and Zygophyllaceae were particularly effective in diabetes. Saponin from Araliaceae, glycoproteins from Malvaceae, peptides, amino acids and proteins from papilionaceae and Rubiaceae families also showed beneficial effects in reducing the blood sugar (Oliver- Bever, 1986). Three alkaloids leurosine, Vindoline and Vindolinine which were isolated from Catharanthus roseus showed good hypoglycemic activity. Trigonelline is a hypoglycemic principle isolated from Trigonella foenumgraecum (fenugreek) seeds. S-methyl cysteine sulphoxide and S-allyl cysteine sulphoxide are antihyperglycemic agents isolated from the bulbs of Allium cepa and Allium sativam respectively. Epicatechine from the bark of Pterocarpus marsupium showed insulin mimetic activity (Chakravarthy et al., 1981a and Chakravarthy et al., 1985). Hexane fraction of Swertia chirata (swerchirin, 1,8-dihydroxy -3,5-dimethoxy Xanthone ) is potent to reduce blood glucose levels (Saxena AM et al., 1991). Aqueous extract of tender leaves of Neem (Azadirachta indica) neem oil, nimbin and acetyl nimbin and nimbolid from the leaves of Azadirachta indica have shown antidiabetic activity. Gymnemic acid isolated from the leaves of Gymnema sylvestre which are chewed in India reduce glycosuria and normalize the blood sugar in diabetic patients in about 3- 4 weeks (Oliver-Bever, 1986 and Kameswarao, B et al.,1997 . (Patel et al., 2012) have listed some plants which have shown insulin secretagogue activity (Table 5). Earlier studies from our laboratory have reported the insulin secretagogue activities of Momordica cymbalaria, Terminalia pallida and Syzygium alternifolium in experimental diabetic animals (Kameswar rao et al., 2003, M.T. Sampath.,2008 and Ramesh babu kasetti et al.,2010).
### Table 5: List of the some plants having insulin mimetic or insulin secretagogue activity

<table>
<thead>
<tr>
<th>S.No</th>
<th>Plant botanical name</th>
<th>Common name</th>
<th>Family</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abies pindrow</td>
<td>Morinda</td>
<td>Pinaceae</td>
<td>Insulin secretagogue activity</td>
</tr>
<tr>
<td>2</td>
<td>Acacia arabica</td>
<td>Babool</td>
<td>Leguminosae</td>
<td>Release of insulin from pancreas</td>
</tr>
<tr>
<td>3</td>
<td>Agrimony eupatoria</td>
<td>Rosaceae</td>
<td>Leaves</td>
<td>Insulin releasing and insulin like activity</td>
</tr>
<tr>
<td>4</td>
<td>Aloe barbadensis</td>
<td>Gheequar</td>
<td>Liliaceae</td>
<td>Stimulating synthesis and release of insulin</td>
</tr>
<tr>
<td>5</td>
<td>Annona squamosa</td>
<td>Sharifa</td>
<td>Annonaceae</td>
<td>Increased plasma insulin level</td>
</tr>
<tr>
<td>6</td>
<td>Averrhoa bilimbi</td>
<td>Bilimbi</td>
<td>Oxalidaceae</td>
<td>Increase serum insulin level</td>
</tr>
<tr>
<td>7</td>
<td>Bixa orellana</td>
<td>Annota</td>
<td>Bixaceae</td>
<td>Increase plasma insulin concentration and increase insulin binding on insulin receptor</td>
</tr>
<tr>
<td>8</td>
<td>Boerhaavia difusa</td>
<td>Punamava</td>
<td>Nyctaginaceae</td>
<td>Increase plasma insulin concentration</td>
</tr>
<tr>
<td>9</td>
<td>Camellia sinensis</td>
<td>Green tea</td>
<td>Theaceae</td>
<td>Increase insulin secretion</td>
</tr>
<tr>
<td>10</td>
<td>Capsicum frutescens</td>
<td>Mirch</td>
<td>Solanaceae</td>
<td>Increase insulin secretion and reduction of insulin binding on the insulin receptor</td>
</tr>
<tr>
<td>11</td>
<td>Cinnamomum zeylanicum</td>
<td>Dalchini</td>
<td>Lauraceae</td>
<td>Elevation in plasma insulin level</td>
</tr>
<tr>
<td>12</td>
<td>Clausena anisata</td>
<td>-</td>
<td>Rutaceae</td>
<td>Stimulate secretion of insulin</td>
</tr>
<tr>
<td>13</td>
<td>Eucalyptus globulus</td>
<td>Eucalyptus</td>
<td>Myrtaceae</td>
<td>Increase insulin secretion from clonal pancreatic beta line (BRIN- BD 11)</td>
</tr>
<tr>
<td>14</td>
<td>Ficus religiosa</td>
<td>Peepal</td>
<td>Moraceae</td>
<td>Initiating release of insulin</td>
</tr>
<tr>
<td>15</td>
<td>Hibiscus rosa</td>
<td>Gudhal</td>
<td>Malvaceae</td>
<td>Stimulate insulin secretion from beta cells</td>
</tr>
<tr>
<td>16</td>
<td>Helicteres isora</td>
<td>Indian screw tree</td>
<td>Sterculiaceae</td>
<td>Decrease plasma triglyceride level and insulin sensitizing activity</td>
</tr>
<tr>
<td>17</td>
<td>Ipomoea batata</td>
<td>Shakarkand</td>
<td>Convolvulaceae</td>
<td>Reduce insulin resistance and blood glucose level</td>
</tr>
<tr>
<td>18</td>
<td>Juniperus communis</td>
<td>Hauber</td>
<td>Pinaceae</td>
<td>Increase peripheral glucose consumption and induce insulin secretion</td>
</tr>
<tr>
<td>19</td>
<td>Olea europia</td>
<td>Olive</td>
<td>Oleaceae</td>
<td>Increase insulin release and increase peripheral uptake of glucose</td>
</tr>
<tr>
<td>20</td>
<td>Swertia chirayata</td>
<td>Chirayata</td>
<td>Gentianaceae</td>
<td>Stimulates insulin release from islets</td>
</tr>
<tr>
<td>21</td>
<td>Scoparia dulcis</td>
<td>Mithi patti</td>
<td>Scrophulariaceae</td>
<td>Insulin-secretagogue activity</td>
</tr>
<tr>
<td>22</td>
<td>Tinospora crispa</td>
<td>Giloe</td>
<td>Menispermaceae</td>
<td>Anti-hyperglycemic, stimulates insulin release from islets</td>
</tr>
<tr>
<td>23</td>
<td>Urtica dioica</td>
<td>Bichhu booti</td>
<td>Urticaceae</td>
<td>Increase insulin secretion</td>
</tr>
<tr>
<td>24</td>
<td>Vinca rosea</td>
<td>Sadabahar</td>
<td>Apocynaceae</td>
<td>Beta cell rejuvenation, regeneration and stimulation</td>
</tr>
<tr>
<td>25</td>
<td>Zingiber oficinale</td>
<td>Adrak</td>
<td>Zingiberaceae</td>
<td>Increase insulin level and decrease fasting glucose level</td>
</tr>
</tbody>
</table>
Scope of the Study:

The main scope review that the research carried out with species of the genus *Sapindus*, in order to organize the data produced. The use of species of *Sapindus* in folk medicine worldwide is validated by scientific studies that have demonstrated the efficacy of the extracts in various experimental models like rats. This review allowed finding many biological and pharmacological studies with fractions of crude extracts and isolated substances that show antihyperglycemic, antiulcer, molluscicidal and anti-inflammatory activities. The main bioactive substances found in the genus *Sapindus* are saponins and acyclic sesquiterpene oligoglycosides. These species produce a complex mixture of glycosidic compounds with diverse biological effects. It is difficult to establish clear functionality and structure-activity relationships regarding the effects of saponins and OGSAs, because there are many saponins with similar chemical structures, and also because of the complexity of cellular physiological reactions, which are often differently influenced by differences in stereo-structures of effector ligands. Species of *Sapindus saponaria* have wide and long-term traditional uses in the local folk medicine. All the pharmacological studies carried out with *S. saponaria* extracts suggest its potential as an appropriate material to be used in the development of a topical medicine product, as a good phytotherapeutic agent. In spite of the several existing chemical and pharmacological studies with different *Sapindus* extracts, and although the properties of several isolated substances suggest their potential as suitable natural resources for developing new compounds for the pharmaceutical industry. Folk medicine for diabetes reports around 35 plants with anti-diabetic activity in Andhra Pradesh. Among them the studies related to the activity of *Sapindus saponaria* plant has best natural chemical composition like saponin, sesquiterpene, oligoglycosids and cytotoxicity nature for choosing the particular Sapindaceae family in connection with anti-diabetic activity are scanty.

Diabetes mellitus has been shown to be a state of increased free radical formation. The increased production of reactive oxygen species has been attributed to protein glycation and (or) glucose auto-oxidation due to a hyperglycemic environment. Lipid peroxidation of cellular structures; a free radical-induced activity is thought to play an important role in ageing, atherosclerosis and late complications of diabetes mellitus. An impaired radical scavenger function has been linked to altered activity of
Introduction

enzymatic and non enzymatic free radical scavengers. Diabetes is also associated with characteristic histological changes of organs like pancreas, liver etc., resulting in the alterations of their functions. To understand the mechanism of action of leaf extract having biological activity and having the perpertuies of pharmacological activity of the selected medicinal plant, an insight into the biochemical and histological changes that occur in the blood serum and some other parts of animal during the treatment, is mandatory. Hence, this study was undertaken up with the following objectives.

Objectives of the Study:

To determine the different doses of selected plant (Sapindus saponaria) leaf extract by administration significantly, through examination of antihyperglycemic activity and other biochemical studies in rats through the following parameters.

- To Screen and identify the chemical properties of the selected medicinal plant extract of Sapindus saponaria (SS) by Phytochemical screening test.
- To investigate the biochemical changes in carbohydrate metabolism in STZ induced diabetic rats on dosage administration of leaf extract of Sapindus saponaria (SS).
- To elucidate and evaluate the changes on lipid metabolism, lipid peroxidation and antioxidant enzyme activity in diabetic rats.
- To examine the different parts like Pancreas and liver in rats by administration of Sapindus saponaria leaves extract by histopathological method.