Chapter 1
INTRODUCTION

1.0 Introduction

Diabetes Mellitus is a metabolic-cum-vascular syndrome of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrates, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. This disorder is frequently associated with long term damage, which can lead to failure of organs like eyes, kidneys, nerves heart and blood vessels. Diabetes mellitus contributes to a considerable increase in morbidity and mortality rates, which can be reduced by early diagnosis and treatment.

Globally as of 2010, it was estimated that there were 285 million people with type 2 diabetes making up about 90% of diabetes cases. This is equivalent to about 6% of the world's adult population. Diabetes is common both in the developed and the developing world. It remains uncommon, however, in the underdeveloped world. Rates of diabetes in 1985 were estimated at 30 million, increasing to 135 million in 1995 and 217 million in 2005. This increase is believed to be primarily due to the global population aging, a decrease in exercise, and increasing rates of obesity. The five countries with the greatest number of people with diabetes as of 2000 are India having 31.7 million, China 20.8 million, the United States 17.7 million, Indonesia 8.4 million, and Japan 6.8 million. It is recognized as a global epidemic by the World Health Organization.

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the “diabetes capital of the world”. According to the Diabetes Atlas (2006) published by the international Diabetes Federation, the number of people with Diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. The so called “Asian Indian Phenotype” refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e. higher waist circumference despite lower body mass index, lower adiponectin and
higher high sensitive C-reactive protein levels. This phenotype makes Asian Indian more prone to diabetes and premature coronary artery disease. At least a part of this is due to genetic factors. However, the primary driver of the epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary pattern and decreased physical activity as evident from the higher prevalence of diabetes in the urban population. Even though the prevalence of micro vascular complications of diabetes like retinopathy and nephropathy are comparatively lower in Indians, the prevalence of premature coronary artery disease is much higher in Indians compared to other ethnic groups. The most disturbing trend is the shift in age of onset of diabetes to a younger age in the recent years. This could have long lasting adverse effects on nation’s health and economy.

Diabetes has been known since antiquity, and treatments were known since the middle age, the elucidation of the pathogenesis of diabetes occurred mainly in the 20th century. Until 1922, when insulin was first discovered and made clinically available, a clinical diagnosis of diabetes was an invariable death sentence, more or less quickly. Non progressing Type 2 diabetics almost certainly often went undiagnosed then; many still do. The discovery of the role of the pancreas in diabetes is generally credited to Joseph Von Mering and Oskar Minkowski, two European researchers who, in 1889, found that when they completely removed the pancreas of dogs, the dogs developed all the signs and symptoms of diabetes and died shortly afterward.

Diabetes can be due to failure in the formation of insulin or liberation or action. There are four types of cells in the pancreatic islets:

1. The insulin secreting beta cell.
2. Glucagons secreting alpha cell.
3. Somatostatin secreting delta cell.
4. Pancreatic polypeptide secreting PP cell.

Beta cells constitute about 60% of the islets that are predominant in the tail of pancreas. Since insulin is produced by the beta cells of islets of langerhans, any receding in the number of functioning cells will decrease the amount of insulin that can be synthesized. This can be due to deformity of any kind in the islets of langerhans, either inflammations, infections, or damaged cells.
Introduction

1.1 Types of Diabetes:

The older classification system dividing diabetes into primary and secondary types, juvenile onset and maturity onset types, and insulin- dependent (IDDM) and non insulin dependent (NIDDM) types, have become obsolete and undergone major revision due to extensive understanding of etiology and pathogenesis of DM in recent times.

World Health Organization (1999) study group in diabetes mellitus has recognized the following major clinical types of diabetes:

1. Type 1, Insulin Dependent Diabetes Mellitus (IDDM)
2. Type 2, Non-Insulin Dependent Diabetes Mellitus (NIDDM)
3. Gestational Diabetes Mellitus (GDM)
4. Impaired Glucose Tolerance

1.1.1 Type 1, Insulin Dependent Diabetes Mellitus (IDDM),

Various genetic and environmental or acquired factors have been implicated in the etiology, altered frequency of certain human lymphocyte antigens (HLA) on chromosome 6, abnormal immune responses, autoimmunity, and islet cell antibodies. In some cases viral infectious disease such as measles or mumps may trigger the autoimmune response.

Type1 diabetes develops rapidly. It is more severe because of its lack of indigenous insulin to control blood glucose level and the subsequent metabolic imbalances, and thus it is more unstable because of the difficulty in controlling blood glucose level smoothly with exogenous insulin injection. Type 1 diabetes accounts 5% to 10% of all diagnosed cases of diabetes. People with type1 diabetes are dependent on exogenous insulin to prevent ketoacidosis and death. Although it may occur at any age, even in the eighth and ninth decades of life, most cases are diagnosed in people younger than 30 years of age, with a peak incidence at around ages 10 to 12 years in girls and ages 12 to 14 years in boys. (Fig 1.1).
Figure 1.1: Pathogenesis algorithm, Type 1 diabetes mellitus (developed by John Anderson and Sanford Games)
1.1.2 Type 2, Non-Insulin Dependent Diabetes Mellitus (NIDDM)

Type 2 diabetes may account for 90% to 95% of all diagnosed cases of diabetes and is a progressive disease that, in many cases, is present long before it is diagnosed. Hyperglycemia develops gradually and is often not severe enough in the early states for the patient to notice any of the classic symptoms of diabetes. Although undiagnosed, these individuals are at increased risk of developing macro vascular and micro vascular complications.

In NIDDM genetic factors include familial aggregation of cases and autosomal dominant inheritance in some cases. Environmental factors, such as obesity, super imposed on a genetic susceptibility, may precipitate the disease. Type 2 Diabetes secondary to other conditions, such as acromegaly, Cushing’s syndrome, primary aldosteronism and others; certain drug therapy including diuretics, oral contraceptives, thyroid hormones, antidepressants or catecholamines. This subtype may also be associated with abnormalities in insulin receptors or certain genetic syndromes.

Risk factors for type 2 diabetes include genetic and environmental factors, including a family history of diabetes, older age, and obesity, particularly intraabdominal obesity, physical inactivity, a prior history of gestational diabetes, impaired glucose homeostasis, and race or ethnicity. Total adiposity and a longer duration of obesity are established risk factors for type 2 diabetes. Nevertheless, type 2 diabetes is found in persons who are not obese, and many obese persons never develop type 2 diabetes. Obesity combined with a genetic predisposition may be necessary for type 2 diabetes to occur. Another possibility is that a similar genetic predisposition leads independently to both obesity and insulin resistance, which increases the risk for type 2 diabetes. (Fig.1.2)
FIG 1.2: Pathogenesis algorithm, type 2 diabetes mellitus (developed by John Anderson and Sanford Games)
In most cases, type 2 diabetes results from a combination of insulin resistance and β cell failure, but the extent to which each of these factors contributes to the development of the disease is unclear (Ferrannini, 1998). Endogenous insulin levels may be normal, depressed, or elevated, but they are inadequate to overcome concomitant insulin resistance (decreased tissue sensitivity or responsiveness to insulin); as a result, hyperglycemia ensues. Insulin resistance is first demonstrated in target tissue, mainly muscle and the liver. Initially, there is a compensatory increase in insulin secretion, which maintains normal glucose concentrations, but as the disease progresses insulin production gradually decreases. Hyperglycemia is first exhibited as an elevation of postprandial (after a meal) blood glucose caused by insulin resistance at the cellular level and is followed by an elevation in fasting glucose concentrations. As insulin secretion decreases, hepatic glucose production increases, causing the increase in preprandial (fasting) blood glucose level. Compounding the problem is the deleterious affect of hyperglycemia itself—glucotoxicity—on both insulin sensitivity and insulin secretion (Yki Jajrvinen 1997), hence the importance of achieving near-euglycemia in persons with type 2 diabetes.

Insulin resistance is also demonstrated at the adipocyte level, leading to lipolysis and an elevation in circulating free fatty acids. Increased fatty acid causes a further decrease in insulin sensitivity at the cellular level, impair pancreatic insulin secretion and augment hepatic glucose production (lipotoxicity) (Bergman et al. 2000). The above defects contribute to the development and progressions of type 2 diabetes and are also primary targets for pharmacologic therapy.

Person with type 2 diabetes may or may not experience the classic symptoms of uncontrolled diabetes and they are not prone to develop ketoacidosis. Although persons with type 2 diabetes do not require exogenous insulin for survival, about 40% or more will eventually require exogenous insulin for adequate blood glucose control. Insulin may also be required for control during periods of stress induced hyperglycemia, such as during illness of surgery.

Differentiating Features of Type I and Type 2 Diabetes are shown in Table 1.1
### Table 1.1: Differentiating Features of Type I and Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other names</strong></td>
<td>IDDM Ketosis–onset diabetes, Brittle diabetes, Jureivle – onset diabetes</td>
<td>NIDDM Ketosis--resistant diabetes, Lipo plethoric diabetes, Stable diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult –onset diabetes</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Little or no insulin produced by the pancreas (absolute insulin deficiency)</td>
<td>Pancreas doesn’t make enough insulin or body doesn’t use insulin correctly</td>
</tr>
<tr>
<td><strong>Frequency of DM</strong></td>
<td>5 - 10%</td>
<td>90-95%</td>
</tr>
<tr>
<td><strong>Usual age of onset</strong></td>
<td>&lt;20 years old (mean age- 12)</td>
<td>Above 40 years but recently occurring more frequently in children or young adults</td>
</tr>
<tr>
<td><strong>Associated conditions</strong></td>
<td>Viral infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td><strong>Control by oral medication</strong></td>
<td>(oral hypoglycemic agents) No</td>
<td>Yes (at beginning)</td>
</tr>
<tr>
<td><strong>Requires Insulin</strong></td>
<td>Yes</td>
<td>Not usually in the beginning; however, as the disease progresses, insulin is sometimes needed to control blood glucose level</td>
</tr>
<tr>
<td><strong>Cell response to Insulin</strong></td>
<td>Normal</td>
<td>Usually resistant</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Symptoms are often dramatic and appear suddenly relatively severe.</td>
<td>Symptoms may appear slowly and relatively moderate</td>
</tr>
</tbody>
</table>

**Source:** India Diabetes Educator Project Manual Aug (2008)

### 1.1.3 Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It occurs in about 7% of all pregnancies resulting in more than 2,00,000 cases annually ADA, (2001). Women with known diabetes mellitus before pregnancy are not classified as having GDM. GDM is usually diagnosed during the second or third trimester of pregnancy. At this point, insulin- antagonist hormone levels increases, and insulin resistance normally occurs.
1.1.4 Impaired Glucose Tolerance

In this class hyperglycemia occurs but the fasting plasma glucose level is less than that seen in classical diabetes (140mg per deci litre) and the plasma glucose level during an oral glucose tolerance test is intermediate between normal and diabetic. This type may be a stage in the development of Type 1 or Type 2 diabetes, although many do not go on to develop clinical diabetes.

1.2 Aetiology / Causes

In the great majority of patients diabetes is a primary disorder, but it may arise secondary to other diseases that impair the function of the pancreas or destroy its structure. Genetic and dietary factors, infections and possibly stress may each increase the risk of an individual developing diabetes.

1.2.1 Genetic Factors

Many genetic mechanisms increase the risk of diabetes and its various manifestations and these differ in type 1 and type 2 diabetes. All communities with a low prevalence have also a low prevalence of obesity. Obesity is common in all racial and ethnic groups with a high prevalence of type 2 diabetes, but not all type 2 diabetes are obese. Many attempts have been made to identify genetic markers, but as yet the result are of no practical value either in epidemiological studies or in identifying potential patients.

1.2.2 Obesity

A close association between obesity and diabetes has long been recognized. Although most type 2 diabetics are obese, only a minority of obese patients develop diabetes. Whether or not an obese individual develops diabetes probably depends on genetic factor.

The view that obesity is diabetogenic in those genetically predisposed to the disease is based on the fact that in simple obesity there is insulin resistance, particularly in muscles, and hyperinsulinaemia. The mechanisms which induce this increased secretion of insulin and resistance to its action are being investigated. It is postulated that there is impaired insulin uptake by receptors in target tissues.
Introduction

Table 1.2: MDRF-Indian diabetes risk score
(Score > 60 : High risk, 30-50: Medium risk, < 30 Low risk)

<table>
<thead>
<tr>
<th>Categorized risk factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 35 years</td>
<td>0</td>
</tr>
<tr>
<td>35-49 years</td>
<td>20</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>30</td>
</tr>
<tr>
<td><strong>Abdominal obesity</strong></td>
<td></td>
</tr>
<tr>
<td>Waist circumference female&lt;80 cm, Male &lt; 90 cm (Reference)</td>
<td>0</td>
</tr>
<tr>
<td>Female 80-89 cm, Male 90-99 cm</td>
<td>10</td>
</tr>
<tr>
<td>Female ≥ 90 cm, Male ≥ 100 cm</td>
<td>20</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
</tr>
<tr>
<td>Vigorous exercise of strenuous at work</td>
<td>0</td>
</tr>
<tr>
<td>Moderate exercise at work/home</td>
<td>10</td>
</tr>
<tr>
<td>Mild exercise at work/home</td>
<td>20</td>
</tr>
<tr>
<td>No exercise and sedentary at work/home</td>
<td>30</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>Both non-diabetic parents</td>
<td>0</td>
</tr>
<tr>
<td>Either parent diabetic</td>
<td>10</td>
</tr>
<tr>
<td>Both parents diabetic</td>
<td>20</td>
</tr>
<tr>
<td>Maximum score</td>
<td>100</td>
</tr>
</tbody>
</table>

Estimate of Plasma insulin in patients with symptoms of diabetes immediately after diagnosis support this concept. Although some of those who are obese have abnormally high plasma insulin, most show some degree of insulin deficiency. In general, the more carbohydrate tolerance is impaired in obese diabetics, the more deficient the insulin secretory response to various stimuli. Obese people in general are less physically active than those whose weight is normal. It is possible that physical exercise may reduce the risk of diabetes in susceptible individuals.
Introduction

1.2.3 Dietary Fiber

In many African countries the fiber content of the diet is high and prevalence of diabetes is low. In prosperous communities this relationship tends to be reserved. This led to the hypothesis that a low fiber diet was part of the aetiology of diabetes, but it is difficult to see how a deficiency of fiber could cause the disorder. Most diets now recommended for diabetics are high in fiber but this is for the general benefits from such diets and not for a specific effect on the disorder.

1.2.4 Infection

Diabetes is frequently first diagnosed by finding glucose in the urine of patient with an acute staphylococcal or other infection. Type 1 and 2 diabetes both present in this way. Infections cause a non specific outpouring of catabolic hormones which antagonize insulin action and this may trigger the onset of the disorder.

There is now increasing evidence that type 1 diabetes especially in younger patients follows a Coxsackie or other virus infection. There is sometimes a long interval between the infection and the onset of symptoms. The virus may trigger an autoimmune reaction in the pancreatic islets and this impaired insulin secretion and ultimately destroys the beta cells.

1.2.5 Stress

Physical injury, surgery and emotional distress some time precede the first symptoms of diabetes. Like infection, this each causes a sudden increase in secretion of catabolic hormones which may precipitate the disorder. However, stress probably does not cause diabetes in people who otherwise would never have developed it.

There is no single cause of primary diabetes. The disorder follows impaired secretion by pancreatic islet cells or utilization of insulin by peripheral tissues. Many environmental factors may lead to such impairment in susceptible individuals. Genetic factors appear as main determinant of susceptibility to such environmental factors, those leading to overweight and obesity being the most important in type 2 diabetes and viral infections in type 1.
1.2.6 Secondary Diabetes

A minority of cases of diabetes occur as the result of diseases which destroy the pancreas and lead to impaired secretion of insulin. e.g. pancreatitis, haemochromatosis, carcinoma of the pancreas and pancreatectomy. Diabetes may also accompany endocrine disorders which increase concentration of catabolic hormones or modify the regulation of insulin receptors.

1.2.7 Hormones

a. Growth Hormone
This, if administered to dogs, produces permanent diabetes and about 30 percent of patients with acromegaly are diabetic.

b. Adrenocortical Hormones
Cortisol and other corticosteroids raise the blood glucose by increasing protein breakdown and by inhibition utilization of glucose by peripheral tissues. Thus many patients with Cushing’s syndrome show impaired carbohydrate tolerance conversely increased sensitivity to insulin is an important feature of Addison’s disease and hypopituitarism and this can be corrected by corticosteroids.

c. Adrenaline
This raises blood glucose by increasing breakdown of liver glycogen and by suppressing secretion of insulin. Patients with a phaeochromocytoma frequently show a diabetic glucose tolerance test and the incidence of these rare tumours is relatively high among diabetic patients.

d. Thyroid Hormones
Thyroxin if given in excess aggravates the diabetic state and some patients with hyperthyroidism show impaired glucose tolerance.

1.2.8 Gestational Diabetes

This refers to the hyperglycemia which may occur temporarily during pregnancy in women with an inherited predisposition to type 1 or type 2 diabetes. During normal
Introduction

pregnancy there is an increased production of hormonal antagonists to insulin which lead to increased rates of secretion and release of insulin. A failing pancreas may be unable to meet this demand.

1.2.9 Drugs

For example the adrenocortical steroids and thiazide diuretics, may precipitate diabetes, especially in those genetically susceptible.

1.2.10 Liver Disease

Liver disease, particularly cirrhosis and hepatitis, may be associated with impaired glucose tolerance.

1.3 Other Risk Factors

Two additional classes identify those who are known to be at increased risk for diabetes.

a. Previous abnormality of glucose tolerance

Individuals who now have normal glucose tolerance but who have a history of impaired glucose tolerance are included. Such persons were formerly described as being prediabetic or latent diabetics. Woman who have had gestational diabetes and formerly obese diabetics whose weight has returned to normal are included in this group.

b. Potential abnormality of glucose tolerance

Persons in this group have never had abnormal glucose tolerance but are at greatly increased risk for development of diabetes. They include persons who are identical twins, siblings or children of diabetes; mothers of infants weighing more than 9 ponds at birth; obese individuals; or certain racial or ethnic groups with a high prevalence of diabetes, such as American Indians. The Pima tribe has an especially high incidence.

1.4 Signs and Symptoms:

There are many signs and symptoms which points that the person might be suffering from diabetes. They are
Introduction

1.4.1 Hyperglycemia

A deficient supply of functioning insulin affects the metabolism of carbohydrates, fats, proteins, electrolytes and water and the consequences of the impairments are complex. When Insulin is not being produced or is ineffective, the formation of glycogen is decreased and the utilization of glucose in the peripheral tissues reduces. As a consequence the glucose that enters the blood circulation from various sources is removed more slowly hyperglycemia follows. This is further accentuated by gluconeogenesis.

1.4.2 Glycosuria:

When the blood glucose level exceeds the renal threshold (about increase 160 to 180 mg/100 ml) glycosuria occurs.

1.4.3 Fluid and Electrolyte Imbalance:

The loss of glucose in the urine represents wastage of energy and entails an increased elimination of water and sodium from bodies.

1.4.4 Acidosis:

With a deficiency of insulin, lipogenesis decreases and lipolysis is greatly increased, these has both immediate and long range consequences. The liver forms “ketone bodies” including acetoacetic acid oxidizes the fatty acids released from adipose tissue or available by adsorption from the intestinal tract, beta-hydroxybutyric acid and acetone. The liver utilizes only limited quantities of the ketones and releases them to the circulation

In diabetes mellitus the ketoses are produced at a rate that for exceeds the ability of the tissues to utilizes them and the concentration in the blood is greatly increased. Acetone is excreted by the lungs and gives the characteristic fruity odour to the breath. Acetoacetic acid and beta- hydroxy butyric acid are excreted in the urine (ketoneuria). Being fairly strong organic acids these ketones combine with base so that the alkaline reserve is depleted and acidosis results.
1.4.5 Polyuria and Nocturia
Glycosuria occurs when the blood glucose levels are above 180 mg/dl. Glucose increases the osmotability of the glomerular filtrate and thus prevents the reabsorption of water as the filtrate passes down the renal tubules. In this way the volume of urine is markedly increased in diabetes and polyuria and nocturia occurs.

1.4.6 Polydipsia
Thirst develops because of osmotic effects sufficiently high glucose (above the ‘renal threshold’) in the blood is excreted by the kidneys but this requires water to carry it and causes increased fluid loss, which must be replaced. The lost blood volume will be replaced from water held inside body cells, causing dehydration. This in turn leads to loss of water and electrolytes, which results in thirst and polydipsia.

1.4.7 Dehydration
As the blood glucose rises, the extra cellular fluids become hyper tonic and water leaves the cells, if the loss of water and electrolytes continue depletion of extra cellular fluid leads to the clinical features of severe dehydration.

1.4.8 Fatigue and Loss of Weight
Impaired utilization of carbohydrates results in a sense of fatigue and two compensatory mechanisms operate to provide alternative metabolic substrate. Both lead to loss of body tissue and wasting may occur in spite of a normal or even increased intake of food. This is added to any loss of weight resulting from loss of fluid.

1.4.9 Increased Excretion of Potassium, Magnesium and phosphorous: Glycogen and protein are present in cells associated with water and intracellular electrolytes. As glycogen and protein are catabolised, glucose and electrolytes, particularly potassium is released into the extra cellular space. An increased urinary excretion of potassium, magnesium and phosphorous therefore occurs in uncontrolled diabetes.
1.5 Diagnostic and Screening Criteria

According to WHO 1999, Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level $\geq 7.0$ mmol/l (126mg/dl)
- Plasma glucose $\geq 11.1$ mmol/l (200mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of hyperglycemia and causal plasma glucose $\geq 11.1$ mmol/l (200mg/dl)
Table 1.3 diabetes diagnostic criteria

<table>
<thead>
<tr>
<th>Condition</th>
<th>2 hour glucose</th>
<th>Fasting glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit</td>
<td>mmol/l(mg/dl)</td>
<td>mmol/l(mg/dl)</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;7.8 (&lt;140)</td>
<td>&lt;6.1 (&lt;110)</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>≥7.8 (≥140)</td>
<td>&lt;7.0 (&lt;126)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥11.1 (≥200)</td>
<td>≥7.0 (≥126)</td>
</tr>
</tbody>
</table>

Source: WHO (1999)

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) is considered diagnostic for diabetes mellitus.

Impaired fasting glucose: People with fasting glucose levels from 100 to 125 mg/dl (5.6 to 6.9mmol/l) are considered to have impaired fasting glucose. Patient with plasma glucose at or above 140 mg/dl (7.8mmol/l), but not over 200 mg/dl (11.1mmol/l), two hours after a 75g oral glucose load are considered to have impaired glucose tolerance.

**1.6 Morbid Anatomy**

The pancreas- Abnormalities in the islets of Langerhans are found at autopsy in most cases of clinical diabetes. However, these are mostly of a quantitative nature and nearly all the types of lesion in the islets in diabetes also occur in non diabetics, although they are much less common.
Introduction

In type 1 diabetes there are marked changes in the islet tissue. The abnormality consists essentially of degeneration of the islets tissue, from which the β cells have largely disappeared, leaving behind α cells and small undifferentiated cells. The remaining β cells show evidence of excessive activity; the nuclei are commonly enlarged with deregulation of the cytoplasm, Antibodies to islet cells are usually found in the blood of young diabetics soon after the onset of their disease.

In type 2 diabetics a moderate reduction in the mass of islet tissue is commonly seen which does not appear to account for the degree of impaired carbohydrate tolerance. On the other hand, in many cases the β cells, despite prolonged hyperglycemia and their reduced number, fail to develop cytological signs of hyper-activity, which suggests that in these diabetics the β cell may be insensitive to the stimulus of a rise in blood glucose.

1.7 Complications

1.7.1 Acute Complications

Hypoglycemia, diabetic ketoacidosis and hyperglycemic hyperosmolar state (HSS) are acute complications related to diabetes.

a. Hypoglycemia

Hypoglycemia (or insulin reaction) is a common side effect of insulin therapy. Autonomic symptoms are often the first signs of mild, hypoglycemia and include shakiness, sweating, palpitation and hunger. Neuroglycopenic symptoms can also occur at similar glucose levels as autonomic symptoms but with different manifestations. The earliest signs of neuroglycopenia include a slowing down in performance and difficulty concentrating and reading. As blood glucose levels drop further, the following symptoms occur, frank mental confusion and disorientation, slurred or rambling speech, irrational or unusual behaviors, extreme fatigue and lethargy, seizures and unconsciousness.
Common Causes of Hypoglycemia

- Medication errors
- Excessive insulin or oral medicines
- Improper timing, doses of insulin or oral medication in relation to food intake
- Intensive insulin therapy
- Inadequate food intake
- Omitted or inadequate meals or snacks
- Delayed meals or snacks
- Increased exercise or activity
- Unplanned activity
- Prolonged duration or increased intensity of exercise

b. Hyperglycemia and Diabetes Ketoacidosis

Hyperglycemia can lead to diabetic ketoacidosis (DKA), a life threatening but reversible complication characterized by severe disturbances in carbohydrate, protein and fat metabolism. DKA is always the result of inadequate insulin for glucose utilization. As a result the body depends on fat for energy and ketones are formed. Acidosis results from increased production and decreased utilization of acetoacetic acid and 3 β hydroxybutyric acid from fatty acids. These ketones spill into the urine, hence the reliance on testing for ketones.

Diabetic ketoacidosis is characterized by elevated blood glucose level (≥250 mg/dl but generally < 600 mg/dl) and the presence of ketones in the blood and urine. Symptoms include Polyuria, polydipsia, hyperventilation, dehydration, the fruity odor of ketones, and fatigue. If DKA left untreated, it can lead to coma and death.

c. Fasting Hyperglycemia

The possible reasons for fasting hyperglycemia include waning of insulin action, the dawn phenomenon and the Somogyi (rebound) effect (phenomenon). The first situation is due to an inadequate insulin doses overnight and requires an adjustment in insulin doses. [Hypoglycemia followed by “rebound” hyperglycemia is called the Somogyi effect.]
Introduction

d. Hyperosmolar Hyperglycemic State

Hyperosmolar hyperglycemic state is defined as an extremely high blood glucose level, the absence of or the presence of only small amounts of ketones, and profound dehydration. Glucose levels generally range from greater than 600 to 2000 mg/dl. Patients who have HHS have sufficient insulin to prevent lipolysis and ketosis. This condition occurs rarely, usually in older patients with type 2 diabetes. Treatment consists of hydration and small doses of insulin to correct the hyperglycemia.

1.7.2 Long Term Complication

Long term complications of diabetes include macro vascular disease, micro vascular disease and neuropathy. Macro vascular disease involves diseases of large blood vessels; micro vascular diseases associated with diabetes involve the small blood vessels and include nephropathy and retinopathy. In contrast diabetic neuropathy is condition characterized by damage to the nerves.

a. Macro vascular Disease

Insulin resistance, which may precede the development of type 2 diabetes and macro vascular disease by many years, induces numerous metabolic changes, “known as the metabolic syndrome or the insulin resistance syndrome.” It is characterized by intra abdominal obesity or the android distribution of adipose tissue (waist circumference greater than 102 cm (>40 in) men and greater than 88 (>35 inches) in women) and is associated with dyslipidemia, hypertension, glucose intolerance, and increased prevalence of macro vascular complications. Other risk factors include genetics, smoking, sedentary lifestyle, high-fat diet, renal failure, and microalbuminuria.

Macro vascular disease including, coronary heart disease (CHD), peripheral vascular disease (PVD) and cerebro vascular disease (CVD) are more common, tend to occur at an earlier age and are more extensive and severe in people with diabetes. Furthermore, in women with diabetes, the increased risk of mortality from heart disease is greater than in men in contrast to the nondiabetic population, in which heart disease mortality is greater in men than in women. (ADA, 2001)
(i) Dyslipidemia
Lipid abnormalities occur in 11% to 44% of adult in United State with deadbeats. In type 2 diabetes the prevalence of an elevated cholesterol level is about 28% to 34% and about 5% to 14% have high triglyceride levels; also lower HDL cholesterol levels are common. Furthermore, patients with type 2 diabetes typically have smaller, denser LDL particles, which increases atherogenicity even if the total LDL cholesterol level is not significantly elevated. Primary therapy is directed first at lowering LDL cholesterol levels with goal being to reduce LDL cholesterol concentrations to 100 mg/dl or lower. Lifestyle interventions should be intensified at LDL cholesterol concentration greater than 100mg/dl and pharmacologic therapy with a stain (HMG-CoA reductase inhibitors) should be initiated at LDL cholesterol concentration of 130 mg/dl or greater. In addition, if the HDL cholesterol is less than 40 mg/dl, a fibric acid such as fenofibrate can use used (ADA, 2002g) Aspirin therapy should be used in all adult patients with diabetes and macrovascular disease and for primary prevention in patients 40 years of age or older with diabetes and one or more cardiovascular risk factors (ADA 2002a).

(ii) Hypertension
Hypertension is a common comorbidity of diabetes, affecting 20% to 60% of persons with diabetes depending on the person’s age, obesity and ethnicity. Treatment of hypertension in person with diabetes should also be vigorous to reduce the risk of macrovascular and microvascular disease Blood Pressure should be measured at every routine visit with a goal for blood pressure control of less than 130/80 mm Hg.

b. Microvascular Disease
(i)Nephropathy
In the United State, diabetic nephropathy accounts for about 40% of new cases of end-stage renal disease (ESRD). About 20% to 30% of patients with type 1 or type II diabetes develop evidence of nephropathy, but in type 2 diabetes, a considerably smaller number will progress to ESRD; however, because of the greater prevalence of type 2 diabetes, such patients constitute more than half of the patients with diabetes currently starting on dialysis (ADA, 2002h).
The earliest clinical evidence of neuropathy is the appearance of low but abnormal urine albumin level (>30 mg daily or 20 μg per minute), referred to as microalbuminuria or incipient nephropathy. Although diabetic nephropathy cannot be cured, persuasive data indicate that the clinical course of the disease can be modified. To reduce the risk or slow the progression of nephropathy, glucose and blood pressure control should be optimized.

**(ii) Retinopathy**

Diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults 20 to 74 years of age. After 20 years of diabetes, nearly all patients with type 1 diabetes and more than 60% of patients with type 2 diabetes have some degree of retinopathy (ADA 2002i).

**(iii) Neuropathy**

Chronic high levels of blood glucose are also associated with nerve damage and affects 60% to 70% of patients with both type 1 and type 2 diabetes (ADA 2001). Peripheral neuropathy usually affects the nerves that control sensation in the feet and hands. Autonomic neuropathy affects nerve function controlling various organ systems. Cardiovascular effect include postural hypotension and decreased responsivness to cardiac nerve impulses, leading to painless or silent ischemic heart desease. Sexual function may be affected, with importance the most common mainfestation. Damage to nerves innervating the gastrointestinal tract can cause a variety of problems. Neuropathy can be manifested in the esophagus as nausea and esophagitis in the stomach as unpredictable emptying, in the small bowel as loss of nutrients and in the large bowel as diarrhea or constipation. Intensive treatment of hyperglycemia reduces the risk of developing diabetic neuropathy.

**(iv) Gastro paresis**

Gastro paresis (impaired gastric motility) affects about 25% of this population and is perhaps the most frustrating condition that patients and dietitians; experience. It results in delayed or irregular contractions of the stomach, leading to various gastrointestinal symptoms, such as feelings of fullness, bloating, nausea, vomiting, diarrhea or constipation. It can cause detrimental effects on blood glucose control.
1.8 Treatment

1.8.1 Conventional Therapies

The general consensus on treatment of type 2 diabetes is that lifestyle management is at the forefront of therapy options. In addition to exercise, weight control, and medical nutrition therapy, oral glucose-lowering drugs and injections of insulin are the conventional therapies. Since the most important pathological process during the development of diabetes involves three key organs, i.e., pancreatic islets, liver, and skeletal muscle, almost all anti-diabetic therapies are aimed at these organs. Pharmacological treatment is indicated when fasting glucose level exceeds 140 mg/dl, the postprandial glucose level exceeds 160 mg/dl or HbA1c exceeds 8.0 percent.

**a. Oral Glucose-Lowering Drugs**

There are several types of glucose-lowering drugs (Modi, 2007), including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones), α-glucosidase inhibitors (miglitol, acarbose). New peptide analogs, such as exenatide, liraglutide and DPP-4 inhibitors, increase GLP-1 serum concentration and slow down the gastric emptying (Hui et al., 2005; Garber et al., 2008). Most glucose-lowering drugs, however, may have side effects, such as severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness and even death (Neustadt et al., 2008).

By conventional standards, oral therapy is indicated in any patient with type 2 diabetes in whom diet and exercise fail to achieve acceptable glycemic control. Although initial responses may be good, oral hypoglycemic drugs may lose their effectiveness in a significant percentage of patients. The drug categories include sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides. Sulfonylureas, including first generation (e.g., tolbutamide) and second generation (e.g. glyburide) sulfonylureas, enhance insulin secretion from the pancreatic beta-cells. A significant side effect is hypoglycemia. Sulfonylurea therapy is also usually associated with weight gain due to hyperinsulinemia, which has been implicated as a cause of secondary drug failure. Biguanides include the drug metformin, which was originally derived from a medicinal plant, Galega officinalis.
Metformin reduces plasma glucose via inhibition of hepatic glucose production and increase of muscle glucose uptake. It also reduces plasma triglyceride and LDL-cholesterol levels. Side effects include weakness, fatigue, shortness of breath, nausea, dizziness, lactic acidosis, and kidney toxicity. Alpha-glucosidase inhibitors include the drug acarbose. This drug category decreases postprandial glucose levels by interfering with carbohydrate digestion and delaying gastrointestinal absorption of glucose. The major side effects are gas, bloating, and diarrhea.

Thiazolidinediones are represented by troglitazone, rosiglitazone and pioglitazone. These expensive oral agents work by improving insulin sensitivity in muscle and, to a much lesser extent, in the liver. These drugs decrease plasma triglyceride levels, but such decrease may be associated with weight gain and an increase in LDL-cholesterol levels. Liver toxicity is a concern requiring monthly monitoring of liver function. Since troglitazone (Rezulinâ) is more toxic to the liver than rosiglitazone and pioglitazone (having resulted in dozens of deaths from liver failure), in March 2000 the FDA asked the manufacturer of Rezulin to remove the product from the market. Meglitinides (drug name Repaglinide) augment insulin secretion, but weight gain, gastrointestinal disturbances, and hypoglycemia are possible side effects.

b. Insulin Therapy:
Insulin is usually added to an oral agent when glycemic control is suboptimal at maximal doses of oral medications. Some diabetologists prefer to initiate insulin therapy in patients with newly diagnosed type 2 diabetes. Weight gain and hypoglycemia are common side effects of insulin therapy. Vigorous insulin treatment may also carry an increased risk of atherogenesis.

c. Exercise
Any exercise prescription should be individualized to account for patient interests, physical status, capacity, and motivation. Exercising five or six times per week enhances weight reduction. Because many people with diabetes have not been active, exercise should start at a low level and gradually increase to avoid adverse effects such as injury, hypoglycemia, or cardiac problems.
Introduction

d. Dietary approach
Given the heterogeneous nature of type 2 diabetes, no single dietary approach is appropriate for all patients. Meal plans and diet modifications are generally individualized by a registered dietitian to meet patient needs and lifestyle. A typical conventional approach would recommend a diet composed of 60-65 percent carbohydrate, 25-30 percent fat, and 10-20 percent protein.

1.8.2 Alternative Therapies for Type 2 Diabetes
Type 2 diabetes is a chronic metabolic disease that has a significant impact on the health, quality of life, and life expectancy of patients, as well as on the health care system. Exercise, diet, and weight control continue to be essential and effective means of improving glucose homeostasis.

Type 2 diabetes is treated with tablets and regulated diet. In spite of this, in most diabetic patient, it is not possible to achieve and maintain completely normal blood glucose level throughout the entire day with these conventional therapies. Lifestyle management measures may be insufficient or patient compliance difficult, rendering conventional drug therapies (i.e., oral glucose-lowering agents and insulin injection) necessary in many patients. In addition to adverse effects, drug treatments are not always satisfactory in maintaining euglycemia and avoiding late stage diabetic complications.

Many people take help of other therapies like natural therapy or Homeopathy or Ayurvedic. Amongst them naturopathy is the most commonly used. Naturopathy is the combination of both exercise in the form of yoga, body massage, diet and some of the natural herbs used in ayurveda. Plants are wondrous chemists. They can easily synthesize chiral specific compounds which can longer time to be synthesized in the laboratory. India is endowed with forest reserves with its rich varieties of flora.

Alternative therapies with anti-diabetic activity have been researched relatively extensively, particularly in India. Ideal therapies should have a similar degree of efficacy without the troublesome side effects associated with conventional treatments. Alternative treatments for diabetes have become increasingly popular the last several years, including medicinal herbs, nutritional supplementation, acupuncture, and hot
tub therapy. As an alternative approach, medicinal herbs with antihyperglycemic activities are increasingly sought by diabetic patients and health care professionals. Commonly used herbs and other alternative therapies, less likely to have the side effects of conventional approaches for type 2 diabetes, are reviewed.

1.8.2 Medicinal Herbs

Anti-diabetes herbs: Certain herbs may lower blood glucose (Yin et al., 2008; Kuriyan et al., 2008); however, their test results are subject to several factors. Firstly, each herb contains thousands of components, only a few of which may be therapeutically effective (Angelova et al., 2008). Secondly, different parts of an herb have different ingredient profiles. Moreover, different extraction methods may yield different active ingredients (Shan et al., 2007). There are many herbal remedies suggested for diabetes and diabetic complications. Medicinal plants form the main ingredients of these formulations. A list of medicinal plants with antidiabetic and related beneficial effects is given in Table 1.4 (Dixit et al., 2006).

Herbs for Diabetes treatment are not new. Since ancient times, plants and plant extracts were used to combat diabetes. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter. 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 Zohary et al., (2000). India is the largest producer of medicinal herbs and is called as botanical garden of the world. At last even the World Health Organization (WHO) expert committee on diabetes has recommended that traditional medicinal herbs be further investigated. Covered here are medicinal herbs in India that have been confirmed by scientific investigation, which appear to be most effective, relatively non-toxic and have substantial documentation of efficiency.

Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin exemplifies an efficacious oral glucose-lowering agent. Its development was based on the use of Galega officinalis to treat diabetes. Galega officinalis is rich in guanidine, the hypoglycemic component. Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued
after insulin became more widely available. However, experience with guanidine and biguanides prompted the development of metformin. To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated. The following is a summary of several of the most studied and commonly used medicinal herbs.

**Acacia arabica (Babhul):** It is found all over India mainly in the wild habitat. The plant extract acts as an antidiabetic agent by acting as secretagogue to release insulin.

**Aegle marmelos (Bengal Quince, Bel or Bilva):** Administration of aqueous extract of leaves improves digestion and reduces blood sugar and urea, serum cholesterol in alloxanized rats as compared to control. Along with exhibiting hypoglycemic activity, this extract also prevented peak rise in blood sugar at 1h in oral glucose tolerance test.

**Allium cepa (onion):** *Allium cepa* is also known to have antioxidant and hypolipidaemic activity. When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels.

**Allium sativum (garlic):** This is a perennial herb cultivated throughout India. Allicin, a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypoglycemic activity. This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect.

**Aloe vera and Aloe barbadensis:** Aloe, a popular houseplant, has a long history as a multipurpose folk remedy. The plant can be separated into two basic products: gel and latex. Aloe vera gel is the leaf pulp or mucilage, aloe latex, commonly referred to as “aloe juice,” is a bitter yellow exudate from the pericyclic tubules just beneath the outer skin of the leaves. Extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats.
**Introduction**

*Azadirachta indica (Neem):* Hydroalcoholic extracts of this plant showed anti-hyperglycemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm. Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects.

*Eugenia jambolana (Indian gooseberry, jamun):* In India decoction of kernels of *Eugenia jambolana* is used as household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Anti-hyperglycemic effect of aqueous and alcoholic extract as well as lyophilized powder shows reduction in blood glucose level. This varies with different level of diabetes.

*Mangifera indica (Mango):* The leaves of this plant are used as an antidiabetic agent in Nigerian folk medicine, although when aqueous extract given orally did not alter blood glucose level in either normoglycemic or streptozotocin induced diabetic rats. However, antidiabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose. The results indicate that aqueous extract of *Mangifera indica* possess hypoglycemic activity. This may be due to an intestinal reduction of the absorption of glucose.

*Momordica charantia (bitter gourd):* It is commonly used as an antidiabetic and antihyperglycemic agent in India as well as other Asian countries. Extracts of fruit pulp, seed, leaves and whole plant was shown to have hypoglycemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of *M. charantia* showed significant hypoglycemic effect when administered subcutaneously to langurs and humans.

*Ocimum sanctum (holy basil):* It is commonly known as Tulsi. Since ancient times, this plant is known for its medicinal properties. The aqueous extract of leaves of *Ocimum sanctum* showed the significant reduction in blood sugar level in both normal and alloxan induced diabetic rats.
**Introduction**

**Panax ginseng (Ginseng):** It has been shown to enhance the release of Insulin from the pancreas and to increase the number of Insulin receptors. It also has a direct blood sugar-lowering effect. Therapeutic dosage is 100-200 mg daily. The anti hyperglycemic and antiobese effects of Panax ginseng berry extract and its major constituent, ginsenoside Re, in obese diabetic mice and their lean littermates was evaluated (Attele et al., 2002)

**Phaseolus vulgaris (Kidney bean):** In addition to lowering cholesterol, kidney bean’s high fiber content prevents blood sugar levels from rising too rapidly after a meal, making these beans an especially good choice for individuals with diabetes, Insulin resistance or hypoglycemia. It seems that Phaseolus preparations should not be considered the first choice in phytopharmaceutical treatment of diabetes or lead structure research. To be effective, fairly high doses of aqueous extracts need to be given. Because of their fibre content and an α-amylase inhibitory effect, beans might be more useful as food components in preventing or ameliorating type 2 diabetes (Heknstadtermk, 2010).

**Phyllanthus amarus (bhuiawala):** It is a herb of height up to 60 cm. from family Euphorbiaceae. It is commonly known as Bhuiamala .It is scattered throughout the hotter parts of India, mainly Deccan, Konkan and south Indian states. Traditionally it is used in diabetes therapeutics. Methanolic extract of Phyllanthus amarus was found to have potent antioxidant activity. This extract, also reduced the blood sugar in alloxanised diabetic rats (Raphael et.al., 2002). The plant also shows anti-inflammatory, antimutagenic, anticarcinogenic, antidiarrhoeal activity.

**Plantago ovate (Ispaghula):** It can be taken in the form of seeds/husk (Freitas et al., 2002). In case of diabetics, it controls blood sugar by inhibiting the excessive absorption of sugar from the intestine.

**Prunuis decos (Almond):** The fixed Oil of Almonds is extracted from both Bitter and sweet Almonds (Singh, 2002). They have a special dietary value (containing about 20% of proteins): they contain practically no starch, and are therefore often made into flour for cakes and biscuits for patients suffering from diabetes.
Introduction

**Pterocarpus marsupium (Indian Kino):** It is a deciduous moderate to large tree found in India mainly in hilly region. Pterostilbene, a constituent derived from wood of this plant caused hypoglycemia in dogs (Harannath et al., 1958; Joglekar et al., 1959) showed that the hypoglycemic activity of this extract is because of presence of tannates in the extracts. Flavonoid fraction from Pterocarpus marasupium has been shown to cause pancreatic beta cell regranulation (Chakravarty et al., 1980). Marsupin, pterosupin and liquiritigenin obtained from this plant showed anti hyperlipidemic activity (Jahhromi et al., 1993). Epicatechin, its active principle, has been found to be insulinoenic, enhancing insulin release and conversion of proinsulin to insulin in vitro. Like insulin, epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dose-dependent manner (Ahmad et al., 1989). The role of Pterocarpus marsupium as anti-diabetic has been very well established (Devgun et al., 2009). The antidiabetic activity of various subtraction of the alcohol extract of the bark of Pterocarpus marsupium Roxb was evaluated in alloxan-induced diabetic rats (Dhanabal et al., 2006)

**Stevia rebaudiana (Stevia):** Steviosides, the principle sugar molecule of Stevia, which is 400 times sweeter than Sucrose, neither absorbed nor metabolized in digestive processes (Parasons et al., 2001). As a result, the steviosides, molecules pass unchanged through the human gastrointestinal tract and are not absorbed into the blood, producing no calories.

**Syzygium jambolanum (Jambul Seeds):** Practioners of ayurvedic medicine report that jambul fruit pulp lowers blood-sugar levels in approximately thirty minutes, while jambul seed lowers blood sugar levels (Matsui et al., 1996) in about twenty four hours. The maximum hypoglycemic effect of the herb requires ten days of treatment. This Ayurvedic herb has long been used to reduce the level of sugar in the blood and urine. Over a period of several weeks it can diminish the thirst associated with diabetes and decrease the quantity of urine output, and in some cases can lower the need for medical Insulin. The anti-diabetic potential of Syzygium jambolanum fruit was studied by analyzing the effect of its crude and fractions on key glucose transport mediators such as IRTK, GLUT4, PI3K and PPAR (Rajasekar and Kirubanandan, 2010).
**Introduction**

*Tinospora cordifolia (Guduchi):* It is a large, glabrous deciduous climbing shrub belonging to the family Menispermaceae. It is widely distributed throughout India and commonly known as Guduchi. Oral administration of the extract of Tinospora cordifolila (T. cordifolia) roots for 6 weeks resulted in a significant reduction in; blood and urine glucose and in lipids in serum and tissues in; alloxan diabeatic rats. The extracts also prevented a decrease in body weight (Prince *et al.*, 2001). T. cordifolia is widely used in Indian ayurvedic medicine for treating diabetes mellitus (Prince *et al.*, 1999), Mathew *et al.*, 1997). Oral administration of an aqueous T. cordifolia root extract to alloxan diabeatic rats caused a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg kg could elicit significant antihyperglycemic effect in different animals models, its effect was equivalent; to only one unit/kg of insulin (Khosla *et al.*. 1995.). It is reported that the daily administration of either alcoholic or aqueous extract of T. cordifolila decreases the blood glucose level and increases glucose tolerance in rodents (Gupta *et al.*, 1967)

**Table 1.4: Indian medicinal plants with anti diabetic and relateds beneficial properties**

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Ayurvedic/common name of herbal formulation</th>
<th>Antidiabetic and other beneficial effects in traditional medicine</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annona squamosa</td>
<td>Sugar Apple</td>
<td>Hypoglycemic and anti hyperglycemic activities of ethanolic leaf extract, Increased plasma insulin level</td>
<td>Kaleem <em>et al.</em>, (2006) and Gupta <em>et al.</em> (2005 a,b)</td>
</tr>
<tr>
<td>Artemisia pallens</td>
<td>Davana</td>
<td>Hypoglycemic, increases peripheral glucose utilization or inhabits glucose reabsorption</td>
<td>Subramonian <em>et al.</em>, (1996)</td>
</tr>
<tr>
<td>Areca catechu</td>
<td>Supari</td>
<td>Hypoglycemic</td>
<td>Chempakam (1993)</td>
</tr>
<tr>
<td>Beta vulgaris</td>
<td>Chukkander</td>
<td>Increase glucose tolerance in OGTT</td>
<td>Yoshikawa <em>et al.</em>, (1996)</td>
</tr>
<tr>
<td>Boerhavia diffusa</td>
<td>Punarnava</td>
<td>Increase in hexokinase activity, decrease in glucose-6-Phosphate and fructose bis-phosphates</td>
<td>Pari and Sathees (2004a,b) and Satheesh and Pari (2004)</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Common Name</td>
<td>Activity Type</td>
<td>Authors</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Bombax ceiba</td>
<td>Semul</td>
<td>Hypoglycemic</td>
<td>Saleem et al. (1999)</td>
</tr>
<tr>
<td>Butea monosperma</td>
<td>Palasa</td>
<td>Antihyperglycemic</td>
<td>Saleem et al. (2006)</td>
</tr>
<tr>
<td>Capparis decidua</td>
<td>Karir or Pinju</td>
<td>Hypoglycemic, antioxidant, hypolipidaemic</td>
<td>Agrawal and Chouhan (1998)</td>
</tr>
<tr>
<td>Coccinia indica</td>
<td>Bimb or Kanturi</td>
<td>Hypoglycemic</td>
<td>Kamble et al. (1998)</td>
</tr>
<tr>
<td>Emblica officinalis</td>
<td>Amla, Dhatriphala, a constituent of herbal formulation Triphala</td>
<td>Decreases lipid peroxidation Anti oxidant, hypoglycemic</td>
<td>Bhattacaharya et al. (1999) Kumar and Muller (1999) and Devasagayam et al. (1995)</td>
</tr>
<tr>
<td>Eugenia uniflora</td>
<td>Pitanga</td>
<td>Hypoglycemic, inhibits lipase activity</td>
<td>Rai et al. (1999)</td>
</tr>
<tr>
<td>Enicostema littorale</td>
<td>Krimiharita</td>
<td>Increase hexokinase activity, Decrease glucose 6-phosphate and fructose 1, 6 bisphosphatase activity. Dose dependent hypoglycemic activity</td>
<td>Maroo et al. (20030) Ravi et al. (2000) And Augusti et al. (1994)</td>
</tr>
<tr>
<td>Ficus bengalenessis</td>
<td>Bur</td>
<td>Hypoglycemic, antioxidant</td>
<td>Chaattopadhyay(1999) and Preuss et al. (1998)</td>
</tr>
<tr>
<td>Gymnema sylvestre</td>
<td>Gudmar or Merasingi</td>
<td>Anti hyperglycemic effect, hypolipidemic</td>
<td>Schadeve and Khemani (1999)</td>
</tr>
<tr>
<td>Hibiscus rosa sinensis</td>
<td>Gudhal or Jasson</td>
<td>Initiate insulin release from pancreatic beta cells</td>
<td>Kusano and Abe (2000)</td>
</tr>
<tr>
<td>Ipomoea batatas</td>
<td>Ipomoea batatas</td>
<td>Reduce insulin resistance</td>
<td>Nagarjun (1992) and Roa et al, (1999)</td>
</tr>
<tr>
<td>Momordica cymbalalria</td>
<td>Kadavancahi</td>
<td>Hypoglycemic, hypolipidemic</td>
<td>Singh et al. (2008)</td>
</tr>
<tr>
<td>Momordica charntia</td>
<td>Bitter gourd</td>
<td>Hypoglycemic</td>
<td>Khan et al. (1995)</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Common Name</td>
<td>Activity</td>
<td>Reference(s)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Musa sapientum</td>
<td>Banana</td>
<td>Anti hyperglycemic, antioxidant</td>
<td>Dhanabal et al. (2005), Pari and Umamaheswari, (2000) and Pari and Maheshwari (1999)</td>
</tr>
<tr>
<td>Punica granatum</td>
<td>Anar</td>
<td>Inhibitory activity against sucrose, α glucosidase inhibitor</td>
<td>Jafri et al. (2000)</td>
</tr>
<tr>
<td>Salacia Retriculata</td>
<td>Vairi</td>
<td>Inhibitory activity against sucrose, α glucosidase inhibitor</td>
<td>Yoshikawa et al. (1998)</td>
</tr>
<tr>
<td>Swertia Chirayita</td>
<td>Chirata</td>
<td>Stimulates insulin release from islets</td>
<td>Saxena et al. (1993)</td>
</tr>
<tr>
<td>Syzygium alternifolium</td>
<td>Shahajire</td>
<td>Hypoglycemic and anti hyperglycemic</td>
<td>Rao and Rao (2001)</td>
</tr>
<tr>
<td>Terminalia belerica</td>
<td>Baheda, a constituent of Triphala</td>
<td>Antibacterial, hypoglycemic</td>
<td>Sabu and Kuttan (2002)</td>
</tr>
<tr>
<td>Terminalia chebula</td>
<td>Hirda</td>
<td>Antibacterial, hypoglycemic</td>
<td>Sabu and Kuttan (2002)</td>
</tr>
<tr>
<td>Tinospora crispa</td>
<td>Hirda</td>
<td>Anti hyperglycemic, stimulates insulin release from islets</td>
<td>Noor and Ashcroft (1998)</td>
</tr>
<tr>
<td>Vinca rosea</td>
<td>Sadabahar</td>
<td>Anti hyperglycemic,</td>
<td>Chattopadhyay et al. (1991)</td>
</tr>
<tr>
<td>Withania somnifera</td>
<td>Ashvagandha Winter cherry</td>
<td>Hypoglycemic, diuretic and hypocholesterolemic</td>
<td>Adallu and Radhika (2000)</td>
</tr>
</tbody>
</table>

(Source: Research journal of medicinal plants 2011)
1.9 Introduction to MKK (Methidana, Kali jiri, Kale til)

*a. Methidana (Trigonella foenum graecum / fenugreek)*

It is found all over India and the fenugreek seeds are usually used as one of the major constituents of Indian spices. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in both rats and humans. Administration of fenugreek seeds also improved glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduced hepatic and renal glucose-6-phosphatase and fructose 1, 6-biphosphatase activity. This plant also shows antioxidant activity.

Arti Gupta, 2014 noted that Fenugreek has drawn much attention as a potential functional food and natural health product or ingredient therein. Medicinal properties attributed to fenugreek have been reported to be associated with its unique phytochemicals such as polysaccharides, complex carbohydrates, galactomannans, steroidal sapogenins, amino acids: 4-hydroxyisoleucine L-tryptophan, lysine; fibre, protein, fatty acids, vitamin C, niacin and potassium. It is rich source of calcium, iron, carotene and other vitamins.

Researches show that fenugreek contains steroidal saponins, occurring mainly as furostanol 3,26-diglycosides such as trigofoenosides A-G. On hydrolysis the saponins yield 0.6-1.7% of spirostanol, sapogenins consisting mainly (about 95%) of diosgenin and its 25β-epimeryamogenin in a 3:2 ratio, together with tigogenin and others. Steroidal saponin peptide esters such as fenugreekine are also present. Mucilage polysaccharide consisting mainly of galactomannan (25-45%) with a backbone of β-(1→4) linked manose residues, branches of α-(1→6) galactosyl residues and a small portions of xylose. Other constituents include: trigonelline (coffearine, the N-methyl betaine of nicotinic acid) protein (rich in tryptophan and lysine), saponin hydrolyzing enzymes, proteinase inhibitors which act on human trypsin and chymotrypsin, scopoletin and other coumarins, flavone glycosides, sterols (cholesterol, β-sitosterol), lecithin and choline. A small amount (<0.01%) of volatile oil is present, in which alkanes, terpenes, oxygenated and aromatic compounds have been identified. The dominant and characteristic aroma compound in fenugreek is 3-hydroxy-4-5-dimethyl-2(5H)-furanone (sotalone) of which 3-25mg/kg is present in the seeds.
Arti Gupta (2014), the hypoglycemic effects of fenugreek have been reported that amino acid 4-hydroxyisoleucine in fenugreek seeds increased glucose induced insulin release in human. It was observed that 4-hydroxyisoleucine extracted from fenugreek seeds has insulin tropic activity. This amino acid appeared to act only on pancreatic beta cells and the levels of somatostatin and glucagon were not altered. In human studies, fenugreek reduced the area under the plasma glucose curve and increased the number of insulin receptors, although the mechanism for this effect needs more study. Fenugreek seeds exert hypoglycemic effects by stimulating glucose dependent insulin secretion from pancreatic beta cells, as well as by inhibiting the activities of alpha-amylase. It is considered that the hypoglycemic effect of fenugreek is thought to be largely due to its high content of soluble fiber, which acts to decrease the rate of gastric emptying thereby delaying the absorption of glucose from the small intestine. The cases suggest fenugreek reduced post-prandial hyperglycemia in the case of diabetics, but less so in case of non-diabetics. It has proved that galactomannan blocks intestinal absorption of glucose. Water soluble fiber increases the viscosity inside the intestine and inhibits absorption of glucose.

b. Kali jiri (Centratherum anthelminticum / Kuntze)

It is highly reputed in Hindu medicines remedy for leucoderma and other skin diseases. The seeds have a hot sharp taste, acrid, astringent to the bowels, anthelmintic and cure ulcers. The seeds are used as purgative, for asthma, kidney troubles and hiccough, applied in inflammatory swelling, remove blood from liver, good for sores and itching of the eyes. In Punjab, it is considered as antipyretic. The seeds are also credited with tonic, stomachic, and diuretic properties. Different organic solvent and aqueous extracts of these seeds were scientifically evaluated for antifilarial, antibacterial, larvicidal, antiviral, antifungal, anticancer, anthelmintic, antidiabetic, antioxidant, analgesic, antipyretic, anti-inflammatory, diuretic, wound healing activities.

Centratherum anthelminticum Kuntz (Hindi- Kali jiri) previously known as Vernonia anthelmintica belongs to family compositae. It has a good anthelmintic property and used for the treatment of various skin infections. It is also reported to be used in asthma, kidney troubles, cough and also used to remove blood from liver. But no
work has been done up till now to establish its antidiabetic potential. The major classes of chemical constituent present in this plant are glycosides, carbohydrates, phenolic compounds and tannins, flavanoids, proteins, saponins, sterolslipids and fats.

The effect of *C. anthelminticum* was studied for the management of diabetes mellitus. Alloxan has been observed to cause a massive reduction of the β– cell of the islets of langerhans and induce hyperglycemia. The perusal of literature shows that studies were carried out on this plant with regards to other pharmacological properties and phytochemistry but there is no scientific evidence for antidiabetic activity. The plant is credited with flavoneglycosides, which in general believed to be responsible for antidiabetic activity. The possible mechanism by which *C. anthelminticum* brings about its hypoglycemic action may be potentiating Pharmacologyonline 3: 1-5 (2008) Bhatia et al. the insulin effect of plasma by increasing either the pancreatic secretion of the insulin from the β cell of islets of langerhan s or its release from bound insulin. In this context a number of other plants have also been observed to have hypoglycemic effect.

Yadava and Barsainya,1997 reported two novel compounds a flavone glycoside and 8,5′-methoxy 3′,4′-methylenedioxy 3,7-dihydroxy flavone from theseeds C. anthelminticum Verma et al.,2004 identified from the seeds of *C. anthelminticum* six new compounds hexatetracontan-16-ol, 6,9-eicosadiene, Butyl 11-hydroxy octadecanoate, hexyl 3-hydroxynonanoate, hexyl 9-hydroxyheptatriacontanoate and heptadecyl nonadecanoate along with the known stigmasterol 14. Mehta et al.,2010 reported from the seeds of C.anthelminticum a novel saponin 3-O-[β-Dglucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-β-D-glucuronopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-Dglucopyranosyl]-hederagenin.

The study by Ani and Naidu 2008 suggested that the *C. anthelminticum* exhibit antihyperglycemic effect by reducing postprandial glucose in rats through the modulation of α-amylase and glucosidases (sucrase and maltase) activity and thus may be valuable in the management of diabetes mellitus.
Introduction

c. Kale til (Black Sesame Seeds)

For thousands of years, sesame seeds have been a source of food and oil. Sesame has one of the highest oil content of any seed, some varietals exceeding 50 per cent oil content compared to soybean's 20 per cent. Sesame seeds contain the lignans pinoresinol and lariciresinol. Sesame seeds a very good source of manganese and copper, but they are also a good source of calcium, magnesium, iron, phosphorus, vitamin B1, zinc and dietary fibre. In addition to these important nutrients, sesame seeds contain two unique substances: sesamin and sesamoline.

Sesame (Sesamum indicum L.), otherwise known as sesamum or benniseed, member of the family Pedaliaceae, is one of the most ancient oilseeds crop. The seed is rich in protein and the protein has disable amino acid profile with good nutritional value similar to soybean (NAERLS, 2010). The chemical composition of sesame shows that the seed is an important source of oil (44-58%), protein (18-25%), carbohydrate (~13.5%) and ash (~5%) (Borchani et al., 2010). Sesame seed is approximately 50 percent oil (out of which 35% is monounsaturated fatty acids and 44% polyunsaturated fatty acids) and 45 percent meal (out of which 20% is protein) (Ghandi, 2009; Hansen, 2011).

Lower blood sugar: It can affect the endocrine system by lowering blood sugar levels, thus reducing the concentration of glucose (sugar) in the bloodstream. This makes it a beneficial dietary inclusion for persons living with diabetes, in conjunction with other lifestyle adjustments geared toward lowering blood glucose. Two grams of black seed a day resulted in reduced fasting glucose, decreased insulin resistance, increased beta-cell function, and reduced glycosylated hemoglobin (HbA1c) in human subjects.

Kamal-Eldin et al., have reviewed patent literature claiming beneficial effects of sesame seed. They note that these health claims are based on the very high levels (up to 2.5%) of furofuran lignans with beneficial physiological activities, mainly sesamin, sesamolin, and sesaminol glucosides. Among edible oils from six plants, sesame oil had the highest Ferric Reducing/Antioxidant Power (FRAP) value, which means the herbs and additives are better preserved in sesame oil. To the extent these herbs have health benefits, the study proposes that it may be possible that ingestion of these herbs
preserved in sesame oil could increase resistance of polyunsaturated fatty acids of cell membranes and lipoproteins to oxidation within the body.

### 1.10 The Rationale of the Study

Diabetes mellitus is a chronic metabolic disorder, with a strong hereditary basis. According to the Diabetes Atlas 2006 published by the international Diabetes Federation, the number of people with Diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025. Diet plays an important role in the management of diabetes. Many people try pills, herbs and infusions recommended.

Most of the research done in the past has addressed the issue of ideal macronutrient percentage in the diet for people with Diabetes. Today there is no longer one insulin regimen or hypoglycemic drug or a fixed prescription that can be applied to all people with diabetes. Based on recent advances in finding alternative treatments efforts are on to find suitable anti diabetic therapy. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, medicinal plants, herbs and spices are preferred due to lesser side effects and low cost. Many conventional drugs have been derived from prototypic molecules in medicinal plants. To date over 400 traditional herbs and spices have been tried for the treatment of diabetes, especially Type 2 diabetes. The World Health Organization Expert committee on diabetes has also recommended that traditional medicinal herbs be further investigated. To support this view of WHO the basic objective of this study is to see the effect of combination of Methidana, Kale til and Kali jiri on control of type 2 diabetes.

### 1.11 Objectives of the study

1. To compare the effect of MKK and MKK + Hypoglycemic drugs on blood glucose level of NIDDM patient.
2. To compare the change in weight of NIDDM patient taking MKK and MKK+ Hypoglycemic drugs.
3. To study the Dietary pattern of NIDDM patient taking MKK and MKK+Hypoglycemic drugs.
4. To study the Nutrient intake of NIDDM patient taking MKK and MKK + Hypoglycemic drugs.