Chapter-1

Introduction
CHAPTER-I

DIABETES MELLITUS (DM)

Diabetes Mellitus has been known since ancient times. References of the symptoms of this disease are seen in ancient text of Orient and Occident. "Charaka" and "Sushruta", the two great men of Indian medicine described the disease as "Madhumeha", a condition in which large quantities of sugar is lost from the body through urine.

In modern era, the word diabetes is derived from the Greek word 'diabainien' which means "to pass through". This disease is characterized by an excess of sugar in the blood and urine, hunger, thirst and gradual loss of weight. Diabetes mellitus (sometimes called "sugar diabetes") is a condition that occurs when the body is not able to use glucose normally, which is the main source of energy for the body's cells.

Diabetes mellitus, long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century. The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity (Wild et al., 2004). Pronounced changes in the human environment, and in human behavior and lifestyle, have accompanied globalization, and these have resulted in escalation rates of both obesity and diabetes (Zimmet et al., 2001). These two conditions collectively termed as 'diabesity', this terminology was first suggested by Shafrir (Astrup et al., 2000; Shafrir et al., 1997). There are approximately 110 million people having diabetes from worldwide, the majority of them have type 2 diabetes; this number is predicted to be doubled by the year 2010. In USA the prevalence of diabetes increased by 33 % overall, and by 76% in people aged 30-39 years during last decade (Mokdad et al., 2000).
The World Health Organization Expert Committee defined the diabetic state as one of chronic hyperglycemia that result from many environmental and genetic factors, often acting jointly. A hormone called insulin, which is synthesized in pancreas and allows glucose to enter into the cell and convert this into energy, this insulin controls the levels of glucose in the blood. The insulin molecule consists of two peptide chains, A and B linked by two-disulfide bridge. A chain consists of 21 amino acid residues, containing intra-chain disulfide bridge linking residues 6 and 11, and the B chain of 30 amino acid residues.

Several processes are involved in the development of diabetes. These include the destruction of the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. Insulin is an anabolic hormone, this is discovered by Banting and Best in 1920's. The action of insulin is countered by the catabolic hormones glucagons, adrenaline, noradrenaline, and growth hormone. Figure 1.2
glucagons, adrenaline, noradrenaline, and growth hormone. Figure 1.2 summarized the action of insulin. The active receptor speeds uptake of amino acid and glucose, which activates protein synthesis from amino acid and glycogen and triglyceride synthesis from glucose. Insulin inhibits breakdown of triglycerides in adipose tissue and gluconeogenesis in the liver, a whole series of intracellular signal substances seemed to be responsible for many action of insulin. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient actions of insulin on target tissues that results from insensitivity or lack of insulin. In uncontrolled diabetes, glucose and lipids remain in the blood, resulting in hyperglycemia, or high blood sugar.

The major physiological determinant of insulin secretion in mammals is glucose availability, but various physiological and pharmacological agents also act as secretagogues.

Insulin secretagogues either may be initiators (effective alone such as glucose and some amino acids) or potentiators (such as glucagon). Glucose stimulates insulin release in biphasic way, comprising of a rapid first phase lasting for 5-10 min. and a prolonged second phase lasting for the duration of the stimulus.

The loss of effective insulin action directly leads to unrestrained hepatic glucose production and inefficient peripheral glucose utilization (Figure 1.2). Excessive hepatic glucose output accounts for elevated fasting plasma glucose (FPG) levels. Resistance to the antilipolytic action of insulin in adipose tissue leads to elevated plasma free fatty acid (FFA) levels and increased FFA delivery to the liver. In liver the oxidation of FFA generates energy (ATP) needed to sustain gluconeogenesis. In addition, the latter process is stimulated by FFA metabolites such as acyl coenzyme A (Eppenberger et al., 1994). In this indirect manner, insulin resistance also
Moreover, the elevation of FFA levels also contributes to insulin resistance in muscle (Shulman et al., 2000).

Figure 1.2: Regulation of Energy Metabolism by Insulin
CLASSIFICATION OF DIABETES MELLITUS

Historically, diabetes has been broken down into two main categories: type 1 diabetes, previously called juvenile diabetes, and type 2 diabetes, previously called adult onset diabetes (WHO, 1999). Much has been learned about the underlying nature of diabetes in recent years and the classification and diagnosis of diabetes has changed to reflect this new knowledge. Doctors no longer refer to just two types of diabetes, and though most people with diabetes have type 1 or type-2 diabetes. Diabetes comes in many forms; the two main types of diabetes -- type 1 and type 2 -- are fundamentally different conditions that can require very different treatments to achieve the common goal of keeping blood glucose levels as close to normal as possible. Virtually all forms of diabetes are caused by decreased in the circulating concentration of insulin (insulin deficiency) and a decrease in the response of peripheral tissue to insulin (insulin resistance).

In both types of diabetes, glucagon opposed the effect of insulin on the liver by stimulating glycogenolysis and gluconeogenesis, but it has relatively little effect on peripheral utilization of glucose. There are many other types of diabetes listed below.

A. Type 1 diabetes mellitus

Type 1 diabetes accounts for 5-10% of people with diabetes. Type 1 diabetes is an autoimmune disease resulting from specific destruction of the insulin-producing β-cells, of the islet of langerhans of the pancreas (Tisch and Mc Devitt, 1996). It has two distinct phases: insulitis, when a mixed population of leukocyte invades the islets; and diabetes when most β-cells have been killed off, and there is no longer sufficient production of insulin to regulate blood glucose levels, resulting in hyperglycemia. Individuals can have convert insulitis for long time (years in humans, months in rodent models) before it finally progresses to overt diabetes, and
sometimes it never does. Diabetes progresses when most islets have been killed and there is no longer sufficient insulin production to regulate blood glucose levels. Patients inject insulin to compensate for insulin deficiency, but the effort and practice needed to mimic the normal β-cell function, which precisely adjusts the rate of insulin secretion to the actual circulating blood glucose level, is enormous.

Type 1 diabetes is an old disorder and it appears in ancient Egyptian and Greek writings. It is also a common disease, currently affecting about 0.5% of the population in developed countries and increasing in incident. There are evidences to that a fraction (5-15%) of people originally diagnosed as type 2 diabetic may actually have progress to a less severe form of type (Mathis et al., 2001). Markers of immune destruction, including islet cell autoantibodies, and/or autoantibodies to insulin, and autoantibodies to glutamic acid decarboxylase (GAD) are present in 85–90% of individuals with Type 1 diabetes mellitus (Cavaghan et al., 2000). The peak incidence of this form of Type 1 diabetes occurs in childhood and adolescence, but the onset may occur at any age, ranging from childhood to the ninth decade of life. There is a genetic predisposition to autoimmune destruction of beta cells, and it is also related to environmental factors that are still poorly defined. Although patients are usually not obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients may also have other autoimmune disorders such as Graves’ disease, Hashimoto’s thyroiditis and Addison’s disease.

Diabetes is primarily mediated by T-lymphocytes. T-cells with diabetogenic properties fall into both the CD4+ helper and the CD8+ killer classes. The disease results from T-cell activation by recognition of islet β-cell antigens of the major histocompatibility complex (MHC) molecules presented on β-cells. Detection of apoptotic β-cells in vivo and the study of
their characteristics in animal models are very difficult due to the asynchronism of the apoptotic process (Kurrer et al., 1997; O'Brien et al., 1997).

Type 1 is usually characterized by the presence of anti–GAD, islet cell or insulin antibodies that identify the autoimmune processes and lead to beta–cell destruction. It has two forms:

1. **Immune-mediated diabetes mellitus**
   It results from a cellular mediated autoimmune destruction of the beta cells of the pancreas. One or more key antibodies are found in 85-90% of people with this form of type 1 diabetes. People with this form of type 1 diabetes always require insulin to survive. This is the most common form of type 1 diabetes and is also referred to as type 1A diabetes."

2. **Idiopathic diabetes mellitus**
   Refers to forms of the disease that have no known etiologies. These forms are much less common than immune-mediated type 1 and are mostly found in people with African or Asian ancestry. People with this form of type 1 diabetes often lack antibodies found in immune-mediated type 1 diabetes, and may be able to go without insulin therapy for some periods of time. This form of type 1 diabetes is also referred to as "Type 1B diabetes."

B. **Type 2 diabetes mellitus**
Type 2 is the most common form of diabetes and is characterized by disorders of insulin action and insulin secretion, either, of which may be the predominant feature. This type of diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance. Many people have type 2 diabetes for years before being diagnosed. Most people with type 2 diabetes are obese. Treatment usually includes advice to lose weight and increase exercise, as well as oral medications. In type 2 or non-insulin-dependent
diabetes mellitus, muscle and fat cells are 'resistant' to the action of insulin and compensatory mechanism that are activated in the β-cell to secrete more insulin are not sufficient to maintain blood glucose levels within a normal physiological range (Khan et al., 2001). Type 2 diabetes is made up of different forms, each of which is characterized by variable degrees of insulin resistance and β-cell dysfunction, and which together lead to hyperglycemia (American Diabetes Association report of the expert committee on the diagnosis and classification of diabetes mellitus, 2000). At each end of this spectrum a single gene disorders are involved that affect the ability of the pancreatic β-cell to secrete insulin or the ability of muscle, fat and liver cells to respond to insulin's action (Fajans et al., 2001; Tylor et al., 1999). Type 2 diabetes is a multifactorial disease that shows heterogeneity in many respects (Grap, 1997).

C. Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) constitutes a separate category for cases of diabetes, first detected during pregnancy. When diabetes is detected early in pregnancy, it is likely to be type 1 or type 2 diabetes mellitus that is presenting symptomatically and was probably precipitated or worsened by the pregnant state. Some women with gestational diabetes require only changes to their diet, while some women require insulin injections. The American Diabetes Association estimates that 4% of pregnancies in the United States are complicated by gestational diabetes.

Diabetes is commonly detected in the second and third trimester and is likely to be specific for the pregnant state, to be transient, and to reverse to normal glucose tolerance or to IGT on follow-up oral glucose tolerance testing 6 weeks after delivery. However, GDM is associated with a high risk of future diabetes, especially in women who have IGT post partum or obese (Kjos and Buchanan, 1999). Permanent diabetes will develop in about 50% of patients within 10 years of GDM. The greatest importance of
any single episode of GDM lies in the risks it poses to the fetus. These risks include intrauterine mortality, neonatal mortality, respiratory distress syndrome, hypoglycemia, hypocalcemia, jaundice, and acrosomia, which can cause trauma such as shoulder dystopia during passage through the birth canal.

D. **Maturity onset diabetes of the young (MODY)**

This is a clinically heterogeneous group of disorders characterized by non-ketotic diabetes mellitus, an autosomal dominant mode of inheritance. Onset occurs usually before 25 years of age and frequently in childhood or adolescence, and occurs mainly due to primary defect in pancreatic \( \beta \)-cell function (Tylor et al., 1999). The abnormality lies in the glucose sensing mechanism of the \( \beta \)-cell, which does not detect capillary glucose concentration until they are 1-2 mmol/L higher than normal (Owen et al., 1992; Glasgow, 1991).

E. **Other specific types of diabetes**

Diabetes caused by other identifiable etiologies.

1. **Genetic defects of beta cell function (e.g., MODY 1, 2, 3)**
   a. Chromosome 20q, HNF-4 (MODY1)
   b. Chromosome 7p, Glucokinase (MODY2)
   c. Chromosome 12q, HNF-1 (MODY3)
   d. Chromosome 13q, Insulin Promoter Factor (MODY4)
   e. Chromosome 17q, HNF-1 (MODY5)
   f. Chromosome 2q, Neurogenic Differentiation 1/\( \beta \)-Cell e-Box transactivator 2 (MODY 6)
   g. Mitochondrial DNA

2. **Genetic defects in insulin action**
   a. Type 1 insulin resistance
   b. Leprechaunism
c. Rabson-Mendenhall syndrome
d. Lipoatrophic diabetes
e. Others

3. Diseases of the exocrine pancreas
   a. Pancreatitis
   b. Trauma/pancreatectomy
   c. Neoplasia
d. Cystic fibrosis
e. Hemochromatosis
   f. Fibrocalculous pancreatopathy
g. Others

4. Endocrinopathies
   a. Acromegaly
   b. Cushing's syndrome
c. Glucagonoma
d. Pheochromocytoma
e. Hyperthyroidism
   f. Somatostatinoma
g. Aldosteronoma
   h. Others

5. Drug or chemical induced (e.g., steroids)
   a. Vacor
   b. Pentamidine
c. Nicotinic acid
d. Glucocorticoids
e. Thyroid hormone
   f. Diazoxide
g. α-adrenergic agonists
6. Infection
   a. Congenital rubella
   b. Cytomegalovirus
   c. Others

7. Uncommon forms of immune-mediated diabetes
   a. "Stiff-man" syndrome
   b. Anti-insulin receptor antibodies
   c. Others

8. Other genetic syndromes sometimes associated with diabetes
   a. Down's syndrome
   b. Klinefelter's syndrome
   c. Turner's syndrome
   d. Wolfram's syndrome
   e. Friedreich's ataxia
   f. Huntington's chorea
   g. Laurence-Moon-Biedel syndrome
   h. Myotonic dystrophy
   i. Porphyria
   j. Prader-Willi syndrome
   k. Others

DIAGNOSIS OF DIABETES MELLITUS

Differentiation of diabetes type 1, type 2 and MODY in childhood can be difficult. Factor that would make diagnosis of type 1 diabetes more likely includes young age at presentation, short duration of symptoms.
ketoacidosis, auto antibodies and history of weight loss. The World Health Organization criteria for the diagnosis of diabetes are fasting venous plasma glucose value greater than or equal to 7.0 mmol/L, or a value greater than or equal to 11.1 mmol/L 2h after a glucose load, figure 1.3 shows a systematic approach for diagnosis to diabetes in children and young people. An alternative to blood glucose estimation or the OGTT has long been sought to simplify the diagnosis of diabetes, glycated hemoglobin, which reflect an average glycaemia over a period of weeks, was thought to provide such a test. The diagnosis should not be based on a single glucose determination but requires confirmatory symptoms or blood/plasma determination. Diagnosis requires the identification of people at risk for development of complications (Boccuzzi et al., 2001; Brown et al., 1999).

To determine gestational diabetes in pregnant women, a standard oral glucose tolerance tests should be performed after overnight fasting (8–14 hours) by giving 75 g anhydrous glucose in 250–300 ml water. The plasma glucose level should be measured fasting and two hrs after meal. The fasting blood sugar levels above 126 mg/dl (7.0 mmol/l) in diabetes indicates that the risk of microvascular complications.
Figure 1.3: Diagnostic approach to diabetes in children and young people. WHO, World Health Organization; GAD, glutamate decarboxylase; MODY, maturity-onset diabetes of the young.
Test for diagnosis of diabetes

a. Urine Test

This test is carried for ketone bodies and reducing sugar like glucose, galactose, lactose, sucrose etc. It can be used as an initial screening test. The principal involved in sugar testing in urine is reduction of cupric ions in alkaline solution by reducing sugars to reddish orange insoluble cuprous oxide. The intensity of color change depends upon the amount of reducing sugars present in urine (Alfonso et al, 1985).

The ketone bodies like acetoacetic acid, acetone are tested based on the principal that they produce a distinctive purple color when treated with a mixture of sodium nitropruside, ammonium sulphate and concentrated ammonium hydroxide. The color intensity indicates the concentration of ketones.

b. Fasting Blood Glucose

WHO experts' committee report states that fasting blood glucose value of 140 mg/100 ml of blood or more is of diagnostic of diabetes. The principal involves conversion of blood sugar to gluconic acid and hydrogenperoxide (H$_2$O$_2$) by glucose peroxidase. The H$_2$O$_2$ level is then estimated by iodometric procedures or by oxidation of chromogen in the presence of peroxidase to form a colored product. (Alfonso et al., 1985).

c. Insulin Assay

The development of radioimmunoassy has produced a sensitive and specific method for measuring plasma insulin level (Tripathi et al, 2000).

d. Glycosylated hemoglobin (HbA$_1$C)

Monitoring HbA$_1$C is another way to follow patients with hyperglycemia. Normal HbA$_1$C accounts for 3%-6% of the total hemoglobin
while in diabetics it is more then 6%. HbA1C assay give an estimate of diabetic control for the proceeding 6-10 weeks (Kar and Chakrabarti, 1999).

**e. C- Peptide Assay**

C-peptide (Connecting peptide) measurement is superior to insulin assay because its levels are not affected by insulin therapy and patients may be maintained on insulin therapy while assessing their β-cells function (Mohan H, 1995).

**f. HOMA analysis**

HOMA analysis is done using a computer program that utilizes fasting glucose and insulin or C-peptide values to model β-cell function (%B) and insulin sensitivity (%S), which is then expressed in relation to values in a ‘Standard individual’ in which they are accorded the value 100%. Hence values for %S less than 100 % indicate a degree of insulin resistance compared to the reference population. As HOMA is designed to compare values in two groups or in a single group under different conditions, using the same biochemical assays for each group, it is more appropriate for population studies than for the assessment of individuals (Ehtisham and Barrett, 2004).

**g. The oral glucose tolerance test (OGTT)**

In this procedure a standard 75 mg oral glucose is given with venous sampling. It is shown in the table 1.1 (Sims et al., 1979).

In a subsequent revision by the WHO, the mid test criteria were deleted and the normal fasting blood glucose value was increased < 140 with the two hrs test < 140. A fasting value of ≥140, preferably repeated is considered as diagnostic of diabetes.
Table 1.1: Who criteria for diagnosis of diabetes mellitus

<table>
<thead>
<tr>
<th>Class</th>
<th>Plasma glucose level (mg/dl)</th>
<th>Fasting</th>
<th>Mid test</th>
<th>2 Hrs test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>&lt;115</td>
<td>&lt;200</td>
<td>&lt;140</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td></td>
<td>&lt;140</td>
<td>≥ 200</td>
<td>140-199</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>≥140</td>
<td>≥200</td>
<td>≥200</td>
</tr>
</tbody>
</table>

COMPLICATIONS OF DIABETES

The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death.

In type 1 diabetes, the major risk is microvascular complications, although macrovascular complications are also increased. In contrast, type 2 diabetes is usually part of “metabolic syndrome”, which is associated with other risk factors from early in the disease process, including abdominal obesity, hypertension, dyslipidaemia, a prothrombotic state and insulin resistance. Although macrovascular disease is the major cause of morbidity in type 2 diabetes.

Many of the complications of diabetes are strongly related to high blood sugar levels. It is believed that keeping blood sugar levels within target range is the best defense against the complications of diabetes. In recent studies on the pathogenesis of diabetic complications, it has been
proposed that cellular injury caused by intracellular alterations in the metabolism of defense system against oxidative stress results in diabetic complications (Wolf, 1987; Lyons et al., 1991)

All forms of diabetes are characterized by chronic hyperglycaemia and the development of diabetic-specific microvascular pathology in the retina, renal glomerulus and peripheral nerve. As a consequence of its microvascular pathology, diabetes is a leading cause of blindness, end stage renal disease and a verity of debilitating neuropathies. Diabetes is also associated with accelerated atherosclerotic macrovascular disease affecting arteries that supplies blood to the heart, brain and lower extremities. Advanced glycation product formed due to hypeglycaemia cross linked with collagen and leads to arterial stiffness. As a result, patients with diabetes have much higher risk of myocardial infraction, stroke and limb amputation. Large prospective clinical studies show a strong relationship between glycaemia and diabetic microvascular complication in both type 1 and type 2 diabetes (Btownlee, 2001). Some of the complications of diabetes are described below.

A. Heart disease

Cardiovascular disease is the leading cause of diabetes-related deaths. Adults with diabetes have heart disease death rates that are two to four times higher than those of adults without diabetes. Diabetes is associated with significant morbidity and mortality due to end-organ damage and the associated risk of cardiovascular disease (Centers for Disease control and prevention of diabetes and impaired fasting glucose in adults- United states, 1999-2000. MMVR 2003; Third report of the National Cholesterol Education 2002; Eppenberger and Hertig, 1994).
B. Stroke

The risk for stroke is also two to four times higher among people with diabetes.

C. High blood pressure

About 73 percent of adults with diabetes have high blood pressure (130/80 mm Hg or higher) or use prescription medications for hypertension.

D. Blindness

Diabetes is the leading cause of new cases of blindness among adults between the ages of 20 to 74.

E. Retinopathy

Diabetic retinopathy (any of various non inflammatory disorders of the retina) causes between 12,000 to 24,000 new cases of blindness each year. In the earliest stage of diabetic retinopathy, the characteristic abnormality is increased vascular permeability. Without treatment, microvascular occlusions occur, resulting in retinal ischemia and, eventually, the growth of new vessels, termed proliferative retinopathy.

F. Kidney Disease

Diabetes is the leading cause of end-stage renal disease, accounting for 43 percent of new cases. Glomerular capillary basement thickening associated with diffuse or nodular expansion of the glomerular mesangium is a characteristic histopathological feature of diabetic nephropathy.

G. Nervous system damage

About 60 percent to 70 percent of people with diabetes have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome and other nerve problems.
H. Amputations

More than 60 percent of nontraumatic lower-limb amputations in the United States occur among people with diabetes. Severe forms of diabetic nerve disease are a major contributing cause of lower-extremity amputations.

I. Pregnancy complications

Diabetes can cause several pregnancy complications. Poorly controlled diabetes before conception and during the first trimester of pregnancy can cause major birth defects in 5 percent to 10 percent of pregnancies and spontaneous abortions in 15 percent to 20 percent of pregnancies. Poorly controlled diabetes during the second and third trimesters of pregnancy can result in excessively large babies, posing a risk to the mother and the child.

Interventions for both types of diabetes, the frequency will escalate worldwide, with the main impact being seen in developing nations (Amoa et al., 1997; King et al., 1998; Astrup et al., 2000). Thus prevention of diabetes and its micro-and macrovascular complications should be an essential component of future public health strategies for all nations.

MANAGEMENT OF DIABETES MELLITUS

Diabetes mellitus is a complex disorder that requires constant attention to diet, exercise, glucose monitoring, and medication to achieve good glycaemic control. Factors contributing to optimum disease management included age, complexity of treatment, duration of disease, depression, and psychological issues (Glasgow, 1991). Several studies suggest that a large proportion of people with diabetes have difficulty in managing their medication regimens (oral hypoglycemic agents [OHAs] and insulin) as well as other aspects of self-management (Pugh et al., 2003).
The goals of therapy for DM are -

- To eliminate symptoms related to hyperglycemia
- To reduce or eliminate long term microvascular and macrovascular complication of DM
- To allow the patient to achieve a normal life style as possible

Methods of treatment available for diabetics

1. Diet alone
2. Diet and insulin
3. Diet and an oral hypoglycemic

1. Diet

Approximately 50% of new cases of diabetes can be controlled adequately by diet alone. Dietary measures are required in the treatment of all diabetic patients to achieve the overall therapeutic goal i.e. normal metabolism (Catalan et al., 2001). Aims of dietary management are:

- To abolish symptoms of hyperglycemia
- To avoid hypoglycemia associated with therapeutic agents (insulin, sulphonylureas)
- To reduce overall blood glucose and minimize fluctuations
- Patient should avoid atherogenic diets or those that may aggravate diabetic complications.
- Controlled diet should be taken, that can activate weight reduction in obese patients to reduce insulin resistant, hyperglycemia and dyslipidaemia.
CHAPTER-1

Two basic types of diet are used in the treatment of diabetes, low energy weight reducing diets and weight maintenance diet. Diabetics' diet should meet the following requirements-

- The diet should be based on the nutritional assessment and treatment goals for the individual patient.
- The diet should have 50% of the daily caloric intake derived from carbohydrate.
- There should be restricted consumption of mono and disaccharides (fructose, sucrose and glucose).
- Sugar free drinks should be used and confectionary, pudding, biscuits and cakes should be limited.
- Intake of fat should be restricted to 30-35% of energy.
- Reduced sodium intake should not more than 6 g daily.

2. Insulin therapy

Insulin is the mainstay for the treatment of virtually all IDDM and many NIDDM patients. Insulin was discovered in 1921. Until 1980's insulin was obtained by extraction and purification from bovine and porcine pancreas. The use of recombinant DNA technology has enabled large-scale production of human insulin (Pugh et al., 2003).

The goals of insulin therapy differ between type 1 and type 2 DM. In type 1 DM insulin therapy is designed to mimic physiological daily fluctuation of serum insulin concentrations and provide basal regulation of hepatic glucose production and glucose uptake after meal. The aim of therapy in type 2 DM is to restrain hepatic glucose over production. The liver and skeletal muscles are insulin resistant in type 2 DM, the dose-of
exogenous insulin differs and thus multi-injection regimen is used to control preprandial and postprandial glucose.

The factor that determines the type and amount of insulin in an individual depends on the patients' sensitivity to the action of insulin and various combinations of the numerous insulin preparations are available, that can be tried. Doses can be altered on the basis of results of blood glucose estimation at different times of the day until good metabolic control is achieved over 24 hrs (Table 1.2).

A. Insulin regimen

There is considerable patient to patient variation in the peak and duration of insulin action. In all regimen, long acting insulin supplies basal insulin, whereas prandial insulin is provided by either regular or lispro insulin.

1. Conventional therapy

One commonly used regimen consists of twice daily injections of intermediate insulin (NPH or lente) mixed with short acting insulin before the morning or evening meal. Here 2/3 of the total insulin dose, in the preparation of 2:1 (Intermediate short acting), is administered in the morning and the regimen 1/3 before the evening meal in proportion of 1:1.

The drawback of each regimen is that it enforces a rigid schedule on the patient. Hyperglycemia/ hypoglycemia may occur as a result of variation in the patient's meal pattern.

2. Multiple subcutaneous insulin injection technique (MSI)

This involves the combination of basal insulin, preprandial short acting insulin, and changes in short-acting insulin doses, to accommodate the result of frequent SMBG (Self monitoring blood glucose), anticipated food intake, and physical activity. Such regimen offers the patients maximal
flexibility in terms of lifestyle and the best chance for achieving near normoglycemia.

3. Continuous subcutaneous insulin infusion (CSII)

Here sophisticated insulin infusion devices are now available that can accurately deliver small dose of insulin (μl/ hrs). Multiple basal infusion rates can be programmed to –

➢ Accommodate nocturnal versus day time basal insulin requirement.
➢ Alter infusion rate periods of exercise.
➢ Select different waveforms of insulin infusion.

Table 1.2: Type of Insulin (Skyler et al., 1998)

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Onset</th>
<th>Peak Time of action</th>
<th>Effective duration</th>
<th>Maximum duration</th>
</tr>
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<tr>
<td><strong>Short acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>&lt;0.25</td>
<td>0.5-1.5</td>
<td>3-4</td>
<td>4-6</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5-1.0</td>
<td>2-3</td>
<td>3-6</td>
<td>6-8</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>2-4</td>
<td>6-10</td>
<td>10-16</td>
<td>14-18</td>
</tr>
<tr>
<td>Lente</td>
<td>3-4</td>
<td>6-12</td>
<td>12-18</td>
<td>16-20</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td>6-10</td>
<td>10-16</td>
<td>18-20</td>
<td>20-24</td>
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<tr>
<td>Glargine</td>
<td>4</td>
<td>24</td>
<td>&gt;24</td>
<td></td>
</tr>
</tbody>
</table>

B. Insulin delivery

Many factors affect the rate of absorption of insulin like insulin formulation, site, depth, volume of injection, skin temperature, local massage and exercise.
Insulin commonly administered by using disposable tubeculin plastic syringe with 29G and ½ inch needle. Several other delivery systems are used for insulin administration, includes pen injector, open loop systems with a battery, powdered-portable pumps providing continuous subcutaneous or intravenous infusion of insulin.

3. Oral hypoglycemic agent

These drugs lower blood glucose level and are effective orally. The treatment of type 2 DM has been revolutionized by the availability of several new classes of oral hypoglycemic agents. Most of them depend upon a supply of endogenous insulin. The oral hypoglycemic agents are classified on the basis of mechanism of action.

a. Sulfonylureas

Stimulate pancreas to make more insulin. They act on the ‘sulphonyl urea receptors’ on the pancreatic β cell membrane and cause depolarization by reducing conductance of ATP sensitive K⁺ channels. They do not cause hypoglycemia in pancreatetomised animal and in type 1 diabetics, presence of at least 30% functional β cells is essential for their action. Hypoglycemia is commonest adverse effect of sulphonyl ureas this may occasionally be sever and rarely fatal.

b. Biguanides

Mechanism of action is not clearly understood. Explanation offered for their hypoglycemia action are-

- Supress hepatic gluconeogenesis and glucose output from liver.
- Enhance binding of insulin to its receptor and stimulate insulin mediated glucose disposal.
- Interfere with mitochondrial respiratory chain- promote peripheral glucose utilization.
- Inhibit intestinal absorption of glucose.
c. **Alpha-glucosidase inhibitors**
   It slows down the absorption of the starches produced due to food. Such as acarbose decrease the absorption of carbohydrates from the digestive tract, thereby lowering the after-meal glucose levels.

d. **Thiazolidinediones**
   This helps insulin to work better at the cell site. In essence, they increase the cell's sensitivity (responsiveness) to insulin.

e. **Meglitinides**
   including repaglinide and nateglinide, they trigger the pancreas to make more insulin in response to amount of glucose is in the blood.

f. **D-phenylalanine derivatives**
   Nateglinide (nah-TAG-lin-ide) is the first medicine in a new group of diabetes pills called D-phenylalanine derivatives, it acts by helping pancreas to make more insulin quickly.

**Combination oral medicines.** Put together different kinds of pills depending on the blood glucose level and activity of pancreas to insulin. Combination therapy may very person to person,

**4. Emerging therapies**
   Over time, the β-cells of patients with type 2 diabetes lose the ability to produce insulin, therefore, control of blood glucose with current oral agents becomes difficult. These agents also produce undesirable side effects such as edema, weight gain, and gastrointestinal intolerance which may result in noncompliance with therapy. Because of these problems, investigators have focused on new agents with novel mechanisms of action (e.g., glucagon-like peptide-1 agonists, dipeptidyl peptidase-IV inhibitors, and amylin analogs) to control blood glucose.
a. **Glucagon-Like Peptide-1 (GLP-1) Agonists**

   In response to the intake of food, GLP-1 is produced and secreted in the gastrointestinal tract. The increase of GLP-1 results in additional insulin secretion from β-cells of the pancreas by increasing β-cell differentiation, growth, and lifespan. It also contributes to additional glucose control by delaying gastric emptying, decreasing appetite, and increasing the feeling of fullness while ingesting a meal (Parkes et al., 2001; Nauck et al., 1997). The overall effect of GLP-1 is to assist in the control of blood glucose, especially after the ingestion of a meal. The half-life of GLP-1 in the body is less than 2 minutes and degraded by the enzyme dipeptidyl peptidase-IV (DPP-IV). To increase the effects of GLP-1 different analogues, that are not as susceptible to DPP-IV, have been developed. Agents such as exenatide and liraglutide have a longer half-life than endogenous GLP-1 and prolonged glucose-lowering effects.

b. **Amylin analogs**

   The hormone amylin is secreted from the β-cells of the pancreas in combination with endogenous insulin. Both hormones are secreted in equal molar amounts and have a secretion pattern that is increased with food intake and reduced during periods of fasting. Amylin decreases the release of glucagon, slows the rate of gastric emptying, and increases satiety, which in conjunction with insulin leads to a reduction in blood glucose values. Blood glucose reductions are greater with the combination of amylin and insulin compared to insulin alone. In patients with insulin insufficiency, there is reduced amylin secretion. Exogenous amylin has been investigated in patients requiring insulin to obtain better glucose control than with insulin administration alone (Kruger et al., 2006).

   Synthetic hypoglycemic agents can produce serious side effects and in addition, they are not suitable for use during pregnancy (Lamar, 1985). Therefore, the search for more effective and safer hypoglycemic
agent has continued to be an important area of active research. Furthermore, after the recommendations made by WHO on diabetes mellitus investigation on hypoglycemic agents become more important (WHO, 1999).

4. Herbal based antidiabetic drugs

The high cost and poor availability of current therapies for many of the rural population in India necessitates the need for the development of indigenous, inexpensive herbal remedies used as antidiabetic and antihyperlipidemic crude or purified drugs. Herbal medicines are being used by 80% of the world population for primary health care. The natural products shall be considered as the best in primary health care because of better cultural acceptability, safety, efficacy, potent, inexpensive and lesser side effects. Several herbal medicines and supplements have been studied as potential therapeutic agents in the management of diabetes and its related complications. Hundreds of plants have been studied for their potential blood glucose lowering properties and antioxidant properties. A scientific investigation of traditional herbal remedies for diabetes may provide valuable leads for the development of alternate drugs and therapeutic strategies. Even the discovery of widely used hypoglycemic drug, metformin came from the traditional approach of using Galega officinalis. The bioactive extracts and compounds need to be standardized on the basis of active principle along with chromatographic fingerprinting pattern. This can be achieved by judicious and rationally designed interdisciplinary research programmes. Cost efficient, potent and less or no side effect of drugs of plant origin have been achieved through compound formulations either in their natural or semi processed forms. The herbal remedies can act as good adjuvant drug to reduce the requirement of insulin/sulfonylurea derivatives (Pullaiah and Naidu, 2003).
OBJECTIVE OF PRESENT RESEARCH WORK

1. To assess antioxidant potential of aqueous extracts of *Clitoria ternatea* and *Aloe vera gel* in diabetic rats and to find out the LD$_{50}$ of both the drugs.

2. To assess the antihyperglycaemic effects of aqueous extracts of *Clitoria ternatea* and *Aloe vera gel* in diabetic rats.

3. Induction of myocardial infraction by isoproterenol in rats and assessment of cardioprotective effect of both the test drugs.

4. Induction of cardiomyopathy by isoproterenol in diabetic rats and evaluation of all antioxidant and cardioprotective parameters in cardiomyopathic diabetic rats by using effective doses of aqueous extract *Clitoria ternatea* and *Aloe vera gel*.

5. Development of chromatographic markers for the *Aloe vera gel* and alcoholic extract of *Clitoria ternatea*. 