CHAPTER-V

Diabetes and its Treatment
5.1. Introduction

‘Diabetes’ or ‘Madhumeha’ is a growing disease, which is the leading cause of death and disability in the world. It has affected nearly 10% of the global population above 20 years of age contributing to death of almost 2,00,000 persons per year. The direct consequence of the increase in the number of diabetic patients during the last few years has increased the cost of healthcare. The cost of lost productivity and medical treatment for the U.S.A. in 1997 was estimated to be 44 Billion US $ and 132 Billion US $ in 2002.\textsuperscript{1} Diabetes mellitus is the disorder of metabolism i.e. the way our body uses digestive food for growth and energy. Most of the food, we eat is broken up into glucose in form of sugar in blood, which is the main source of fuel for the body. After digestion this glucose passes into blood stream and used up by cells for growth and energy. For glucose to get into cells, insulin (a hormone produced by endocrine gland i.e. pancreas) must be present. When we take our meal, the β Cells of pancreatic islets of langerhance, automatically produce right amount of insulin from blood to body cells. If pancreas does not produce enough insulin or the cells do not respond appropriately to the insulin produced, glucose stays in the blood.\textsuperscript{2-4} This makes high blood sugar which overflows in the urine. In this way body loses its main source of fuel even though blood contains large amount of glucose. Such condition is called as ‘Glycosurea’, which is the main symptom of diabetes mellitus. The normal level of blood sugar is 100mg/100ml in the human body, which increases after each intake of carbohydrate rich meal. When the percentage of glucose in the blood or urine increases up to 300-500 mg/100 ml, the person is called Diabetic.
A diabetic person has an increased risk of heart-attack, stroke as well as kidney failure, various diseases related with eyes and nervous systems. Therefore DM is a group of metabolic disorders characterized by hyperglycemia arising as a consequence of relative or severe deficiency of insulin secretion and resistance along with metabolic derangements of carbohydrates, fat and proteins. There are numerous pathogenic processes involved in the development of diabetes but most of the class fall into two categories- Type 1 DM and Type 2 DM that leads to serious complications and premature death.

### 5.2. Types of Diabetes

DM can be categorised into following classes:
5.2.1. Type -1 Diabetes (IDDM)

It is also called ‘Insulin-dependent diabetes mellitus’ or ‘Juvenile-onset diabetes’. About 5-10% of total diagnosed diabetic persons are suffering from IIDM or T₁DM. It is an auto immune disease in which immune system of the body attacks and destroys the insulin producing β-cells of pancreas. Therefore pancreas produces little or no insulin. In fact it is unknown, what exactly causes the body’s immune system to attack the β-cells, but it is believed that autoimmune, genetic or environmental factors are probably responsible. T₁DM usually strikes children and young adults although disease onset can occur at any age. Someone with T₁DM needs insulin injections daily to live. There is no other proper way known to prevent T₁DM. Now a days several clinical trials or preventive methodologies are currently in progress and planned.⁵,⁶

5.2.2. Type-2 Diabetes (NIDDM)

It is also called ‘Non-Insulin-dependent diabetes mellitus’ or ‘adult-onset diabetes’. It accounts for nearly 90-95% of total diagnosed diabetic persons. T₂DM is frequently associated with obesity, older age, family history of diabetes or history of gestational diabetes, impaired glucose metabolism, physical inactivity and certain ethnicities. It is observed that 80% of people with T₂DM are overweight.⁷,⁸

In NIDDM or T₂DM, the pancreas is usually producing enough insulin, but body cannot use the insulin effectively. Thus it is the condition of insulin-resistance in the body. As the insulin needs rise, the pancreas gradually loses its ability to produce it. The result is same as T₁DM, that glucose builds up in the blood and body cannot make effective use of its main source of fuel i.e. Glucose.
5.2.3. Gastational Diabetes

Such type of diabetes develops in certain women in their late pregnancy period and symptoms usually disappear when pregnancy is over. It is believed that gestational diabetes is caused either by hormones of pregnancy or a shortage of insulin during pregnancy period. Such women’s have a greater risk (20-50%) of developing T2DM within next 5 to 10 years. Gestational diabetes requires treatment to normalize maternal blood glucose level to avoid the complications in infant.⁹,¹⁰
5.2.4. Diabetes associated with drug administration

A large number of drugs can cause hyperglycemia or hypoglycemia of diabetic patient to their existing therapeutic regimens. Some common drugs such as Thiazides, Glucocorticoides, Furosemides and Solbutamol etc. tend to raise the blood sugar & reduce the effectiveness of insulin.

Some other types of diabetes results from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections or other illness. But such diabetes accounts for only 1-5% of all diagnosed diabetic persons.

5.3. Symptoms of Diabetes-Mellitus

The symptoms of Diabetes mellitus are more or less common in both T₁DM as well as T₂DM, but differ in onset of the disease.¹¹

- **Type-1 DM** – Symptoms usually develop over a short period, although, β-cell destruction can begin years earlier. The symptoms of T₁DM include increased thirst or urination, constant hunger, weight loss, blurred vision and extreme fatigue. A person with type-1 DM, if not diagnosed and treated with insulin, can lapse into a life threatening coma, also known as ‘diabetic ketoacidosis’.

- **Type-2 DM** - Symptoms of T₂DM develop gradually and their onset is not as sudden in T₁DM. The symptoms are similar to T₁DM including slow healing of wounds or sores as an observable symptom.

The overall symptoms of diabetes mellitus can be classified as:

**Primary Symptoms**
1. ‘Loss of weight’ is an important primary symptom of DM. It is mainly due to water loss as well as loss of other body substances through urine.

2. ‘Frequent urination’ in diabetic patient is second major symptom, which causes irritation in bladder.

3. ‘Dryness of mouth’ which causes marked thirst of diabetes.

4. ‘Weakness’ and ‘fatigue’.

5. ‘Hunger’ due to need for food because of loss of sugar through extracted urine, and

6. Other symptoms like shortness of breath, itching of skin, falling of hairs and nails, swelling of extremities etc.

Secondary Symptoms

1. ‘Disturbance of visual activity’ due to effects of excessive blood sugar and altered media on the nerve and muscle structure of eye.

2. ‘Deterioration and Infection of teeth and gums’ in which gums become swollen and bleed.

3. ‘Enlargement of Tonsils’.

4. ‘Depression of the reproductive symptoms’ in male and female both.

5. ‘Lowering of blood Pressure’, and

6. ‘Irregular menstrual cycle’ in women.

Beside these, diabetics show various problems related to cardiovascular system, nervous system, muscular system, eyes, joints etc.

5.4. Diagnosis of Diabetes
5.4.1. Serum glucose level Test

ADA (American Diabetes Association), provided the guideline that-
“Fasting plasma glucose (FPG) test level of 140 mg/dl or higher constitutes presumptive diagnosis of diabetes.” or “a classical serum glucose level in excess of 200 mg/dl, taken without regard to timing of caloric intake is also diagnostic for Diabetes.”12

* If FPG test yields result between 110-120 mg/dl, the patient is said to suffer from Impaired Fasting Glucose (IFG) disorder which is a precursor condition of diabetes.

5.4.2. Oral glucose tolerance test (OGTT)

75 gm of glucose is taken orally and glucose serum level, followed for a few hours. If the serum glucose level is 200 mg/dl or more, after the two hours of ingesting glucose, the patient is said to be diabetic.13

5.4.3. Glycosylated Haemoglobin (HbA1c)

It is found in blood and formed when serum glucose level is high. The half-life of HbA1c is about 120 days in erythrocytes. Thus it gives a useful account of serum glucose spikes over last eight weeks. HbA1c expresses a percentage of total haemoglobin. In non-diabetic patient, the HbA1c level is 5-8% while in totally diabetic person it will be about 12%. HbA1c level can also be used as index of success in diabetes therapy. There is a direct correlation between serum glucose level and HbA1c.
In view of rapid increase in diabetic cases, WHO and ADA have reduced the level of blood sugar concentration from 140 mg/dl to 126 mg/dl for the risk of diabetes. Estimation of glycosylated hemoglobin (HbA$^1$c) which is the marker of average plasma glucose concentration is still valid for diagnosis of T$_2$DM.

**5.4.4. Laboratory diagnosis of Diabetes**

Determination of sugar in blood and urine sample can be performed by different laboratory techniques. These are:

(A) **Urine sugar test** – Benedict’s test

(B) **Clinitest** – Modification of Benedict's test

(C) **Quantitative Urine sugar Analysis**

(D) **Examination of Urine for Acetone** - *Ingram, Cardiff and Wale’s Method,*

(E) **Blood sugar Determination.**
   - **Macro determination** – Benedict’s Method.
   - **Micro determination** – Folin-Malmros’s Method

**5.5. Role of Insulin in Diabetes$^{15,16}$**
“Banting and Best” in 1921 first discovered the Insulin hormone. They demonstrated that pancreatic extract, after degeneration of exocrine part due to ligation of pancreatic duct, shows hypoglycemic action. They named this hormone as ‘Insulin’. Insulin is a two chain polypeptide (joined by two disulfide bond), having 51 amino acids with molecular weight about 6000. It is secreted by pancreatic islets of ß-cells and its secretion is regulated by chemical, hormonal as well as neural mechanism. Under basal condition nearly one unit of Insulin (1U) is secreted per hour (*1 mg. of International standard of Insulin = 24 U). The overall effects of insulin are to favours storage of fuel i.e. glucose. The action of insulin and results of its deficiency can be summarized as:

1. Insulin facilitates the glucose transport across the cell membrane, however glucose entry in liver, RBC, WBC and brain cells is largely independent of insulin.

2. Insulin facilitates the glycogen synthesis from glucose as enhanced by the production of ‘glucokinase’ enzyme, necessary for the phosphorelation of glucose.

3. Insulin inhibits gluconeogenesis from protein, FFA and glycerol in liver by decreased synthesis of ‘phosphoenol pyruvate carboxykinase’ enzyme. In case of insulin deficiency, proteins and amino acids are funneled in peripheral tissues to liver where these are converted to carbohydrate.

   Thus diabetes is underutilization and overproduction of glucose which causes hyperglycemia and ultimately glycosurea.

4. Insulin inhibits lipolysis in adipose tissue and favour triglyceride synthesis. In diabetics excess fat is broken down due to unchecked action of lipolytic hormones which cause the production of ‘Actyl Coenzyme-A’ from liver. Normally Actyl Co-A resynthesized to fatty
acid and triglycerides, but in diabetes this process is reduced and *Acetyl Co-A* is diverted to produce ketone bodies such as actone, acetoacetates, β-hydroxy butyrates etc. and thus causes, ‘**ketoacidosis**’.

5. Insulin facilitates amino acids entry and their synthesis into process and inhibits protein breakdown in muscles and other cells.

5.5.1. **Adverse Reaction to Insulin**

**A. Insulin Resistance**: When the insulin requirement of body is increased (conventionally > 200U/day but physiologically > 100U/day) it causes the development of insulin resistance, which may be acute or chronic. Insulin resistance is very common because of sedentary lifestyle and aging, resulting in high blood pressure, dyslipidemia and diabetes.\(^\text{17}\)

Figure 5.3 : **Complexities of Insulin Resistance**
T₂DM does not always occur with insulin resistance but defect in insulin secretion is associated with microvascular complications viz. blindness, neuropathy, and nephropathy atherosclerosis and limb amputation. In these situations presence of C-peptide and absence of the markers of autoimmunity such as antibodies to ‘glutamic acid decarboxylase’ may help to diagnose the disease.

Figure 5.4. : Essential dual defect for manifestation of T₂DM

B. Diabetic coma (β-Ketoacidosis)

This is associated with complications of insulin therapy. When insulin medicated glucose uptake into fat and liver cell is inadequate, these cells attempt to obtain energy by oxidizing fatty acids. It results in overproduction of ketoacids which spill into the blood. Since β-ketoacid is much more acidic than normal fatty acids; it disturbs the buffer capacity of the blood. It causes life threatening acidosis in the patient i.e. Diabetic coma. Such acidosis is only treated by emergency
C. Hypoglycemia or Insulin-shock

The only systemic difficulty with insulin therapy is hypoglycemia, in which excess of insulin causes an excessive fall in serum glucose level. It results in dizziness, headache, behavioural changes, confusions, visual disturbance, fatigue, weakness and sometimes coma. The symptoms of hypoglycemia differ from patient to patient and also depend in the rate of fall of serum glucose level.

The symptoms of Hypoglycemia are promptly relieved by oral administration of sugars. Thus it is necessary to a diabetic patient to carry hard candy.

D. Hyperosmolar (Nonketonic-hyperglycaemic) coma

It frequently occurs in elderly type-2 DM patients. In these patients, uncontrolled, glycosurea causes diuresis resulting into the dehydration and haemoconcentration over several days. Thus urine output is finally reduced and glucose rapidly accumulates into body (up to 800 mg/dl), which increases the plasma osmolarity resulting into coma. In general the hyperosmolar coma is treated in the same way as diabetic coma. Sometimes prophylactic heparin therapy is also recommended to such patients.
INSULIN LACK

- Hyperglycaemia
  - Glycosuria
  - Osmotic diuresis
  - Loss of electrolytes (Na⁺, K⁺, Ca²⁺, Mg²⁺)
  - Intracellular K⁺ depletion

- Acidosis
  - Ketonuria
  - Impairment of glucose entry into brain

- Ketosis
  - Vomiting
  - Hyperventilation

- Impairment of glucose entry into brain

- Loss of fixed cations in urine
  - Loss of water
  - Dehydration

- Hyperosmolarity of blood

- Intracellular dehydration
  - Impairment of consciousness

- Hypotension
  - Shock
  - Tachycardia

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**Figure 5.5**: Schematic depiction of the development of Diabetic Ketoacidosis due to insulin lack. Symptoms produced are shown within boxes.

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### 5.5.2. Complications of Insulin Therapy

Besides insulin resistance, diabetic coma and hypoglycemia there are certain sudden developing complications which occur during long time insulin medicated therapy. These are:

- **Edema and Allergy**
  
  Sometimes patient develops a short lived dependent edema due to Na⁺ retention during insulin therapy. It causes weight gain of 0.5-2.5 Kg. But symptoms usually disappear simultaneously within weeks.

- **Lipoatrophy and Lipohypertrophy**
  
  It has been observed that repeated injections of insulin at the same site, especially in females, cause atrophy of subcutaneous fatty tissues. It produces unsightly depression in the tissues. Lipoatrophy is probably a variance of an immune response to insulin.
Enlargement of subcutaneous fat depots, due to the lipogenetic action of high local concentration of insulin is called lipohypertrophy. Both problems may be related to contaminated insulin preparations and mode of insulin administration. They cause irregular absorption of insulin as well as cosmetic problems.

5.5.3. Types of Insulin

Today several insulin preparations are available for treatment of DM. viz.-Human, beef or pork insulin. There are minor differences between them

<table>
<thead>
<tr>
<th>Species</th>
<th>A-Chain</th>
<th>B-Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8th AA</td>
<td>10th AA</td>
</tr>
<tr>
<td>Human</td>
<td>THR</td>
<td>ILEU</td>
</tr>
<tr>
<td>Pork</td>
<td>THR</td>
<td>ILEU</td>
</tr>
<tr>
<td>Beef</td>
<td>ALA</td>
<td>VAL</td>
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</tbody>
</table>

The insulin derived from beef or pork is precipitated under varying conditions of P_H and Zn ion concentration to control the formation of insulin.19,20

- Large crystal and high Zn content leads to such insulin preparations with a slow onset with a long duration of activity.
- Amorphous insulin which is rapid in onset of activity but short acting in nature.
- Insulin preparation complexed with protamin and Zn (PZI Insulin) act as a depot of hormone after injection.
- Regular Insulin which has an intermediate onset of action which may be acidic or neutral.
The use of PZI insulin with regular insulin is more common for treatment of IDDM.

**Insulin delivery devices:** Number of innovations have been made to improve ease and accuracy of insulin administration as well as to achieve tight glycemic control. Some common insulin delivery devices are insulin syringes, pen-devices, jet injectors, insulin pumps, artificial external pancreas etc.

### 5.6. Treatment of Diabetes –Mellitus

DM is a worldwide health problem which is associated with our changing lifestyle manner. Today DM becomes a dreadful cause of death and disability in human race. Current therapeutic strategies for treatment of DM are based on reduction of hyperglycemia by increasing plasma insulin level or decreasing insulin resistance.\(^{21}\)

Current therapies for T\(_2\)DM include suitable balanced diet, exercise and variety of pharmacological agents including insulin and insulin secretagogues viz. sulfonylureas and non sulfonylureas agent. These agents act by different mechanisms to normalize blood glucose levels and avoid serious complications that affect the kidney, cardiovascular, ophthalmic and nervous system.\(^{18}\)
5.6.1. Dietary treatment of Diabetes Mellitus

Dietary management is an essential preventive step in treatment of DM. Experiments show that dietary treatment along with insulin therapy causes marked health improvements in diabetic patients. ‘Leukens and Dohan’\textsuperscript{14} showed that fasting and fat-feeding as well as insulin administration, allowed the islets to rest and decreased the amount of insulin produced along with complete recovery of island cells in cats. Thus therapy makes possible the complete cure of diabetes in early cases if treatment is carried out before permanent changes have taken place.\textsuperscript{22}

5.6.2. Insulin and Insulin secretagogues

5.6.2.1. Insulin

Insulin is effective in all forms of DM. But for T\textsubscript{1}DM or ‘Juvenile diabetes’, there are no treatment alternatives to diet and exogenously administrated insulin. The only consideration is the form of insulin to be used. The chief purpose of insulin therapy in DM is to restore metabolism to normal, avoid symptoms due to hyperglycemia and glucosurea, and prevent short term complications (infection, ketoacidosis etc) and long term sequels such as cardiovascular, retinal, renal complications. Insulin therapy is needed in such cases where –

1. DM is not controlled by diet and exercise alone or when these are not practicable.
2. Primary and secondary failure of oral hypoglycemic agents or when these drugs are not tolerated.
3. Underweight diabetic patients.
4. Temporarily to tide over infections, trauma surgery, pregnancy etc.
5. Any complication of diabetes e.g. ketoacidosis, gangrene of extremities etc.

Insulin therapy is generally started with regular insulin given before each major meal. The requirement of insulin is assessed by testing urine or
blood sugar levels. *Mostly type-1 patients require 0.4-0.8 U/Kg/day while type-2 patients require 0.2 – 1.6 U/Kg/day.* Obese patients require proportionally higher dose due to relative insulin resistance. Very recently a new chemical substance “**Hepatic Insulin sensitizing substance (HISS)**” has been discovered which is yet to be identified chemically.\(^{23}\)

HISS is secreted form liver in response to insulin injection that brings about 50-60 % disposal of glucose in a dose dependent manner. Subcutaneous administered insulin is not a convenient mode of drug administration. More ever exogenous insulin does not replicate the normal pattern of nutrient related basal insulin secretion. The difference in the action of injected and endogenously secreted insulin is due to difference in their pharmacokinetic pathway. These short comings have been minimized by developing rapid acting insulin analogues, *Insulin lyspro* and *Insulin aspartate*. Now long action insulin analogue *Insulin glargine* and *Insulin detemir* are available for the treatment of T2DM.\(^{24}\)Another analogue of Insulin is *glulisine* which is currently advanced in clinical trials.

### 5.6.2.2. Insulin secretagogues

Oral agents that increase pancreatic insulin secretions are called secretagogues. These are orally effective drugs that help a person with diabetes to control their blood sugar level. These oral hypoglycemic agents are found to be useful alternatives of painful insulin injection remedy. There use is based on patient –specific factor to optimize the blood sugar. Several factors are taken into consideration while choosing a medication region including desired glycemic control i.e. weight and lipid profile, contradictions and costs etc.

This class of therapeutics can be divided into sulfonylureas and non-sulfonylureas subgroups. Both act via similar molecular mechanism but latter displays, shorter half life, which theoretically decreases the risk for hypoglycemia. The binding to the sulfonylurea receptor on the plasma
membrane of pancreatic β-cells leads to facilitated insulin secretion and improved control. However through sulfonylureas improve β-cells function of diabetic patients in the 1\textsuperscript{st} year of therapy, their effect decline after several years of therapy.\textsuperscript{25} Furthermore insulin secretagogues could trigger hyperinslinaemia leading to the hypoglycemia and may provoke weight gain. These are classified as:

<table>
<thead>
<tr>
<th>Classes</th>
<th>Ist –Generation</th>
<th>IIInd-Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Sulfonylureas</strong></td>
<td>Tolbutamide</td>
<td>Glyburide</td>
</tr>
<tr>
<td></td>
<td>Tolazamide</td>
<td>Glipizide</td>
</tr>
<tr>
<td></td>
<td>Acetoheaxamide</td>
<td>Glimepiride</td>
</tr>
<tr>
<td></td>
<td>Chloropropramide</td>
<td>Gliclazide</td>
</tr>
<tr>
<td><strong>2. Non-Sulfonylureas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Biguanides</td>
<td>Phenformin</td>
<td>Metformin, Buformin</td>
</tr>
<tr>
<td>B. Meglitinides</td>
<td>Repaglinide</td>
<td>Nateglinide</td>
</tr>
<tr>
<td>C. Thiazolidinediones</td>
<td>Rosiglitazone</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>D. Glucosidase Inhibitors</td>
<td>Acarbose</td>
<td>Miglitol</td>
</tr>
<tr>
<td>E. Aldose - Reductose</td>
<td>Sorbinil</td>
<td>Tolerstate</td>
</tr>
<tr>
<td>Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. Thiazolidinediones (TZDs)</td>
<td></td>
<td>Sodium Palmoxirat,</td>
</tr>
<tr>
<td>G. Miscellaneous (Future</td>
<td></td>
<td>Ciglitazone, Lingolised Fumarate</td>
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<tr>
<td>Trends)</td>
<td></td>
<td>etc.</td>
</tr>
</tbody>
</table>


5.6.2.2.1. Sulfonylureas\textsuperscript{26,27}

Chemically, all the members of this class of insulin secretagogues are substituted ‘Arlysulfonlureas’. They differ by the substitution at the para position on the benzene ring, and at one nitrogen residue of the urea moiety. The aliphatic group R confers the lipophilicity to the molecule whereas the substitution in the arylsulfonyl group R’ influences primarily the duration of action. The generic formula of sulfonylurea is:

![Generic formula of sulfonylurea](image)

Traditionally these agents are divided into 1st and 2nd generation sulfonylureas. 2nd generation agents are more potent than 1st one. They have large range of options and cause fewer side effects. In most diabetic cases, it has been observed that those patients, who do not response to 1st generation sulfonylureas, may respond to newer agents. Sulfonylureas are used in the treatment of patients suffering from T2DM, who cannot be treated with diteropathy alone or who are unwilling to take insulin if dietary control fails. Combination of sulfonylureas with suboptimal insulin regimen in patient with T2DM may provide better glycemic control than that of treatment of suboptimal insulin regimen alone.
# 1st GENERATION SULFONYLUREAS

<table>
<thead>
<tr>
<th>Sulfonylurea</th>
<th>Brand Name</th>
<th>Chemical Structure</th>
<th>Daily Dose</th>
<th>Duration of Action (In hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tolbutamide</td>
<td>Otinase</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>0.5-2 gm in divided dose</td>
<td>6-12</td>
</tr>
<tr>
<td>2. Tolazamide</td>
<td>Tolinase</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>0.1-1 gm as single or divided dose</td>
<td>10-14</td>
</tr>
<tr>
<td>3. Acetohexamide</td>
<td>Dymelor</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>0.25-1.5 gm as single or divided dose</td>
<td>12-24</td>
</tr>
<tr>
<td>4. Chloropropamide</td>
<td>Diabinese</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>0.1-0.5 gm as single dose</td>
<td>Up to 60</td>
</tr>
</tbody>
</table>
2\textsuperscript{nd} GENERATION SULFONYLUREAS

<table>
<thead>
<tr>
<th>5. Glyburide</th>
<th>Diabeta, Micronase</th>
<th>0.00125-0.02 gm as single dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Glibenclamide)</td>
<td></td>
<td>10-2</td>
</tr>
<tr>
<td>6. Glipizide</td>
<td>Glucotrol, Glucotrol\textsuperscript{c1}</td>
<td>0.005-0.03 gm as single dose</td>
</tr>
<tr>
<td>(Glydiazinamide)</td>
<td></td>
<td>10-2</td>
</tr>
<tr>
<td>7. Gliclazide</td>
<td>Diamicron</td>
<td>----</td>
</tr>
<tr>
<td>8. Glimepiride</td>
<td>Amaryl</td>
<td>0.001-0.008 gm as single dose</td>
</tr>
</tbody>
</table>

➤ **Mechanism of Action**

A single dose of sulfonylureas may provoke a brisk release of insulin from pancreas. They act on so called ‘sulfonylurea receptors’ on pancreatic β-cell membrane and cause depolarization by reducing conductance of ATP sensitive K\textsuperscript{+} channels. This enhances Ca\textsuperscript{++} influx to cause degranulation. The sulfonylurea primarily augments the II\textsuperscript{nd} phase insulin secretion with little effect on the I\textsuperscript{st} phase. They do not cause hypoglycemia in T\textsubscript{1}DM, because presence of at least 30\% functional β-cells is essential for their action. It confirms their indirect action through pancreas.

➤ **Therapeutic Application**

Sulfonylureas are used to control hypoglycemia in T\textsubscript{2}DM patients who can not achieve appropriate control with change in diet alone. In all
patients, however, continued dietary restrictions are essential to maximize the efficacy of sulfonylureas. Patients with T2DM whose disease is controlled by relatively low dose of insulin (less than 40 U/day) are most likely to respond to sulfonylureas as those who are obese and/or older than 40 years of age. The drugs are not preferred for those, suffering from T1DM with pregnancy, lactation and significant hepatic or renal insufficiency.

> **Combination Therapy with Sulfonylurea and Insulin**

Since sulfonylurea drugs commonly increase the pancreatic β-cells secretion of insulin but also might restore peripheral tissues sensitivity to insulin, their use with insulin has been advocated to reduce the total insulin dose, required to control hyperglycemia.

The combination therapy of sulfonylureas and NPH insulin in T2DM patients, who fail to respond to monotherapy of sulfonylureas, is found to be more effective to control hyperglycemia.

### 5.6.2.2.2 Biguanides

It is another class of oral hypoglycemic drugs. They differ with sulfonylurea drugs in two ways—as they cause little or no hypoglycemic effects in non-diabetic patients and they do not stimulate pancreatic β-cells. Biguanides have been used in T2DM or NIIDM as adjunct in insulin therapy and they are active only in patients with some endogenous insulin secretion. The generic formula of Biguanides is -

![Generic formula of Biguanides](image)

Mainly there are three members of this group which are frequently used for the treatment of T2DM. These are:
<table>
<thead>
<tr>
<th>Biguanides</th>
<th>Chemical Structure</th>
<th>Daily Dose</th>
<th>Duration of Action (In hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Phenformin</td>
<td><img src="image" alt="Phenformin Structure" /></td>
<td>0.025-0.15 gm as single or divided dose</td>
<td>4-6</td>
</tr>
<tr>
<td>2. Buformin</td>
<td><img src="image" alt="Buformin Structure" /></td>
<td>1.0-2.5 gm in divided dose</td>
<td>10-12</td>
</tr>
<tr>
<td>3. Metformin (Glucophage)</td>
<td><img src="image" alt="Metformin Structure" /></td>
<td>0.05-0.3 gm in divided dose</td>
<td>10-12</td>
</tr>
</tbody>
</table>

**Metformin Hydrochloride (Glucophage<sup>XR</sup>)**

* A combination of *Metformin hydrochloride* and *Glyburide* is available for the treatment of NIIDM under brand name-“Glucovance”.

**Mechanism of Action**

It has been observed that Biguanides do not cause insulin release, but presence of some insulin is essential for their action. The mechanism of their hypoglycemic action is summarized as they cause:
1. Direct stimulation of glycolysis in tissues, with increased glucose removal from blood.
2. Reduces hepatic glyconeogenesis.
3. Slowing of glucose absorption form the gastrointestinal tract, and
4. Reduction of plasma glucose level.

**Therapeutic Applications**

Biguanides have been most often prescribed for patients with refractory obesity, whose hyperglycemia is due to ineffective insulin action i.e.
Insulin resistant syndrome”. As it do not increase weight or provoke hypoglycemia, it is preferred over insulin or sulfonylureas in the treatment of NIIDM. This is why; these agents are more appropriately termed as “Euglycemics” rather than “Hypoglycemics”

Biguanides are widely used in combination with sulfonylureas in NIIDM patients, in whom sulfonylurea monotherapy is inadequate. Both “Phenformin” and “Metformin” are used for “maternity onset Diabetes (NIIDM)” but Metformin is safer than Phenformin because former drug do not causes lactic acidosis which is more common with Phenformin treatment.31

- **Adverse effects**
  - The most common adverse effects are abdominal pain, Arorexia, nausea, metallic taste, mild diarrhoea & tiredness.
  - “Lactic Acidosis” is the most serious complication associated with Phenfomin.
  - Metformin does not cause hypoglycemia except in overdose. Its high dose is responsible for vitamin B12 deficiency due to its interference with absorption of drug.
  - In addition to general restriction for use of oral hypoglycemic agents, Biguanides are contradicted in hypotensive stage, Cardiovascular, Respiratory, hepatic & renal disease and in alcoholic patients because of increase risk of lactic acidosis.

5.6.2.2.3. Meglitinide

This group of oral-hypoglycemic agents including two members, “Repaglinide” and “Nateglinide”.

- **Repaglinide (Brand name-Prandin)**

  It is fast acting, short-acting non sulfonylurea, and oral hypoglycemic agent. It belongs to a new chemical class of insulinotropic agents
(secretagogues) called as Meglitinide analogues. It was approved by FDA in 1998 for the treatment of T2DM.

It is the first β-cell medicated prandial glucose regulator. It allows the rapid release of insulin from pancreatic β-cells followed by a rapid lowering of blood glucose. Although it produces fewer side effects such as weight gain, and serious hypoglycemia, it is at least five times more potent than glyburide on intravenous administration; however difference in oral administration is about ten fold.\textsuperscript{32}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

**Therapeutic Applications**

It is used in the management of T2DM around meal time as alternative to sulfonylureas, or to supplement, reforming or long acting insulin. It should be avoided for the diabetic patients suffering from liver complications.

➢ **Nateglinide (Brand-name-Starlix)\textsuperscript{33}**

It is another non-sulfonylurea drug which principally stimulates the 1st phase insulin secretion resulting in rapid onset and shorter duration of hypoglycemic action than Repaglinide. It prevents postprandial hyperglycemia in T2DM without producing late phase hypoglycemia. It lowers the blood glucose by stimulating release of insulin from pancreatic β-cells by binding to receptors that block K\textsuperscript{+}-ATP channels which cause depolarization of cells, which therefore activate voltage dependent L-type
Ca\textsuperscript{++} channels and increase intracellular calcium, thus leading to insulin release. It causes side effects such as dizziness, nausea, flue-like symptoms, joint pain etc.

\[
\text{(R)-2-(4-isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid)}
\]

- **Therapeutic Applications**
  
  It is used as monotherapy or in combination with other antidiabetic agents like Metformin to control post prandial T\textsubscript{2}DM.

5.6.2.2.4. **Glucosidase Inhibitors**

Glucosidase enzyme is found in the brush boarder of the small intestinal mucosa, and is responsible for breaking down the complex polysaccharides and sucrose to monosaccharides which are then absorbed. *Alpha-Glucosidase inhibitors* reduce the intestinal absorption of starch, dextrin and disaccharides by inhibiting the action of intestinal brush boarder. Glucosidase inhibition of the enzyme slows the absorption of carbohydrates; therefore post prandial rise in plasma glucose is reduced in both normal and diabetic persons. Thus these inhibitors are useful adjuncts to insulin in the treatment of both T\textsubscript{1}DM and T\textsubscript{2}DM. There are two \(\alpha\)-d-glucose inhibitors, “Acarbose” and “Miglitol” available for diabetes management.
> **Acarbose (Brand Name- Precose)**

It is a complex oligosaccharide of microbial origin which reversibly inhibits glucosidase enzyme during the digestion of carbohydrates. With treatment of Acarbose, postprandial glycaemia is reduced without increasing insulin levels. Regular use of it tends to lower HbA\(^1\)c, body weight and serum triglyceride. It shows limiting side effects such as production of intestinal gas. Acarbose is initially dosed as 50 mg chewed with 1\(^{st}\) mouthful of a meal and given three times in a day.

![Structure of Acarbose](image)

**Structure of Acarbose**

* Combination therapy of Acarbose is not recommended with Metformin because it interferes with absorption of Metformin.

> **Miglitol (Brand name -Glyset)**

It is desoxynojirimycin derivative of Acarbose. It was introduced in 1998 and seems to produce therapeutic results similar to Acarbose. It causes significant lowering of HbA\(^1\)c and of postprandial and fasting serum glucose. Unlike Acarbose, Miglitol is rapidly absorbed in the blood stream following oral administration. It is distributed primarily to the extra cellular space and is rapidly cleared through kidney.
*Guargum –(Brand Name- DIATAID, CAROTARD)

It is dietary fiber (polysaccharides) obtained from Indian cluster bean (Guar), which forms a viscous gel on contact with water. When administrated just before or mixed with meal, it slows gastric emptying, intestinal transit and carbohydrate absorption. Thus postprandial glycmeia is suppressed but overall lowering of blood glucose is marginal. It also reduces serum cholesterol about 10%. Absorption of other drugs administered with it may reduce to give 2 to 3 gaps. It can be used to supplement diet and to lower sulfonylurea dose. The administered dose starts form 2.5 gm/d and increases gradually to 5gm TDS. Its side effects are flatulence, feeling of fullness, loss of appetite, gastric discomfort and nausea.

5.6.2.2.5. Aldose-Reductose Inhibitors

Chronic DM causes the development of microvascular and neurological complications like retinopathy and neuropathy. The Aldose-reductose inhibitors are designed to reduce glucose toxicity in tissues such as eye, kidney and nerve trunks. They act by inhibiting the cellular enzymes that convert glucose to fructose and subsequently to sorbitol. Both of them may contribute to the toxic effects in hyperglycemia. Thus these are very useful in diabetic retinopathy as well as neuropathy. There are two important drugs for DM, which belong to this class as given below;
➢ Sorbinil

It has been tried mainly in the treatment of diabetic neuropathy. It is rapidly absorbed after oral administration but slowly eliminated. The suitable dose for once a day is 250 mg/day.

![Chemical structure of Sorbinil](image)

(5)-6-fluorospiro (chroman-4,4’ imidazolidine)-2,5’-dione

➢ Tolerstate (Brand Name-Alderase)

It is a naphthoylglycine derivative. It is a long acting aldose-reductose inhibitor, useful in prophylaxis of diabetic neuropathy and cataracts.

![Chemical structure of Tolerstate](image)

N-[6-Methoxy -5- trifluoromethyl-] -1- naphthyl -(Thiocarbonyl)-N-methylglycine

5.6.2.2.6. Thiazolidinediones

This class of new drug was approved by FDA in late 1990s, commonly known as “Glitazones”, for the treatment of DM. All the members of this group are similar in having a common partial chemical
structure i.e. Thiazolidine 2, 4 Dione (TZD). They correct the hyperglycemia by enhancing the insulin sensitivity of adipose, hepatic and skeletal muscle tissues. Because of this mode of action, glitazone treatment is not associated with dangerous hypoglycemic incidents that are common in conventional sulfonylurea as well as insulin therapy.\textsuperscript{35} There are three main members of this group, these are:

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Generic Name</th>
<th>Brand-Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Troglitazone</td>
<td>Rezulin</td>
</tr>
<tr>
<td>2.</td>
<td>Pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>3.</td>
<td>Rosiglitazone</td>
<td>Avandia</td>
</tr>
</tbody>
</table>

Out of these, Troglitazone (Rezulin) was withdrawn from the market in march 2000 because it has been observed that it causes hepatic and cardiac toxicity in diabetic patients.

![Troglitazone (Rezulin)](image1)

![Rosiglitazone (Avandia)](image2)
This novel class of oral antidiabetic drugs is selective agonist for the nuclear “Peroxisome-proliferator activated receptor-γ (PPARγ)” which enhances the transcription of several insulin responsive genes. They tend to reverse insulin resistance by stimulating GLUT-4 expression and translocation, entry of glucose into muscle and fat is improved. Hepatic gluconeogenesis is also suppressed.

Both Pioglitazone and Rosiglitazone are useful in the treatment of T2DM. It is also observed that Thiazolidine-diones do not cause any clinically significant interaction with other drug classes, as they are metabolized in liver by specific cytochrome P450 enzyme.\(^{36,37}\)

Both are taken once a day, absorbed in 2 hours, but maximum clinical effect is observed after 6-12 weeks. During treatment with Thiazolidinediones, it is necessary to have regular monitoring of liver function in patients who have active hepatic disease. These are used either alone with diet and exercise in monotherapy or in combination with insulin, Metformin or sulfonylurea, in the treatment of T2DM. Certain slide effects of TZD\(_5\) are anemia, weight gain, edema and plasma volume expansion etc.

5.6.2.2.7. Other hyperglycemics

- **Diazoxide**

  It inhibits insulin release from β-cells and causes hyperglycemia lasting 4-8 hrs. Its action on ATP sensitive K\(^+\) channels is opposite to that
of sulfonylureas. Other actions which may contribute to hyperglycemia are decreased peripheral utilization of glucose and release of catecholamine. It has been used to prevent hypoglycemia in insulinomas.

- **Thiazide diuretics and Phenytoin**
  
  These are also mild hyperglycaemics.

- **Somatostatin**
  
  It causes hyperglycemia primarily by inhibiting insulin release.

- **Streptozocin**
  
  It is obtained from *streptomyces achromogenus*, causes selective damage to insulin secreting β-cells. It has been used to produce experimental diabetes in animals and to treat insulin secreting tumors of pancreas.

### 5.7. Status of Oral hypoglycemics in Diabetes Mellitus

In spite of several contradictions and side effects in their use, no doubt oral hyperglycemic are found to be milestones in the treatment of diabetes. These are however; control symptoms caused due to hypoglycemia and glycosurea and are much more convenient than insulin therapy. Generally oral hypoglycemic are medicated only in T2DM, when not controlled by diet and exercise.³⁸ They are best used in patients with:

1. Age above 40 years at onset of disease.
2. Obesity of the time of presentation.
3. Duration of disease is greater than 5 years when starting treatment.
4. Fasting plasm sugar is greater than 200mg/dl.
5. Insulin requirement of body is greater than 40 U/day patients have no ketoacidosis history or any other complications.

Oral hypoglycemics should be used to supplement dietary management and not to replace it. Their mono therapy as well as combination therapy is sufficient to control the diabetic symptoms also in those patients which
switch over to insulin therapy. The role of oral hypoglycemic in diabetes management may be summarized as –

In fact 50% patients of T2DM initially treated with oral hypoglycemic ultimately need insulin. Despite their limitations, oral hypoglycemic drugs are suitable therapy for majority of T2DM patients. The important features of oral hypoglycemic drugs are.

5.7.1. Combination Therapy of Diabetes Mellitus

Oral hypoglycemic drugs are used in monotherapy as well as in combination therapy of the treatment of DM. These combination pills contain two different types of diabetes pill. “Bicon” offers Indian and International generic manufacturing of a wide variety ocombination pills, such as:
<table>
<thead>
<tr>
<th></th>
<th>pharmaceutical</th>
<th>(or combination)</th>
<th>Effect on FPG and HbA(^1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Glucovance</td>
<td>Glyburide+Metformin</td>
<td>Decreases FPG by 50-60 mg/dl and HbA(^1c) by 1.7-1.9%</td>
</tr>
<tr>
<td>2.</td>
<td>Actoplus-Met</td>
<td>Pioglitazone+Metformin</td>
<td>Decrease FPG by 45-60 mg/dl and HbA(^1c) by 1.5-2.0%</td>
</tr>
<tr>
<td>3.</td>
<td>Avandamet</td>
<td>Rosiglitazone+Metformin</td>
<td>Decreases FPG by 48-65 mg/dl and HbA(^1c) by 0.9-1.9%</td>
</tr>
<tr>
<td>4.</td>
<td>Avandaryl</td>
<td>Rosiglitazone+glimepiride</td>
<td>Lowers the amount of glucose made by liver and helps insulin to work in proper way.</td>
</tr>
<tr>
<td>5.</td>
<td>Duetact</td>
<td>Pioglitazone+glimepiride</td>
<td>Decreases FPG by 60-65 mg/dl and HbA(^1c) by 1.2-2.0%</td>
</tr>
<tr>
<td>6.</td>
<td>Janumet</td>
<td>Sitagliptin + Metformin (A DPP-4 inhibitor)</td>
<td>Make more insulin in body, especially after meal and lower glucose mode by liver.</td>
</tr>
<tr>
<td>7.</td>
<td>Metaglip</td>
<td>Glipizide+Metformin</td>
<td>Helps to keep liver form putting stored glucose into blood.</td>
</tr>
<tr>
<td>8.</td>
<td>Trigulin</td>
<td>S.U. + Metformin + TZD</td>
<td>Decreases FPG by 65-70 mg/dl and HbA(^1c) by 2-3%</td>
</tr>
</tbody>
</table>
References

Alexandria, VA, ADA, 2005


44. UK Prospective Diabetes Study Group, ‘Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type-2 diabetes’, (UKPDS 33), 352, 837-853 (1998a)