1. INTRODUCTION

The word **diabetes** derived from the Greek means to siphon and refers to the marked loss of water by urination, polyuria. The word **mellitus** derived from the Latin means sweet and thus diabetes mellitus is known as sweet urine disease. It is regarded as a metabolic disease of unknown cause resulting from a deficiency of the pancreatic hormone insulin and an irregularity in the release of glucagon, a polypeptide hormone. Often, the sufferer of this disease has been consuming large amounts of refined sweets such as cakes, pies, ice cream, candies, pastries etc. Under these conditions, the pancreas is continually stressed to secrete its hormone in order to eliminate the excess glucose from the blood. This results in enervation of the gland and exhaustion leads to decreased insulin output. The fact is other organs are involved as observed in many other symptoms manifested by the diabetic such as arteriosclerosis, blindness etc. One problem with refined sugar is that it goes immediately into the blood without digestion. This flood of sugar is very enervating to the pancreas.

Diabetes is a disease characterized by abnormal metabolism of blood sugar and defective insulin production. Blood sugar level is an important parameter for the diagnosis, treatment and prognosis of diabetes. Blood sugar level is the level of sugar circulating in blood at a given time. Blood glucose levels vary with time and some factors that affect **blood sugar levels** are body composition, age, physical activity and sex.

1.1. Definition

Diabetes mellitus (DM), often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). In other words, DM is a set of related diseases in which the body cannot regulate the amount of sugar (specifically, glucose) in the blood. The blood delivers glucose to provide the body with energy to perform all of a person's daily activities.

1.2. History

Diabetes was one of the first diseases described, with an Egyptian manuscript from 1500 BCE mentioning ‘too great emptying of the urine’. Indian physicians around the same
time identified the disease and classified it as *madhumeha* or "honey urine", noting the urine would attract ants. The word *diabetes* comes from Latin ‘*diabētēs*’, which in turn comes from Ancient Greek ‘*diabētēs*’ which literally means ‘a passer through; a siphon.’ The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Appollonius of Memphis. Ancient Greek physician Aretaeus of Cappadocia (1st century CE) used that word, with the intended meaning "excessive discharge of urine", as the name for the disease. Ultimately, the word comes from Greek ‘*diabainein*’, meaning "to pass through," which is composed of ‘*dia*-’, meaning "through" and ‘*bainein*’, meaning "to go". The word "diabetes" is first recorded in English, in the form *diabete*, in a medical text written around 1425. The word *mellitus* comes from the classical Latin word *mellitus*, meaning "mellite" (i.e. sweetened with honey; honey-sweet). The Latin word comes from *mell-*, which comes from *mel*, meaning ‘honey’; sweetness; pleasant thing, and the suffix -*ītus*, whose meaning is the same as that of the English suffix"-ite". It was Thomas Willis who in 1675 added "mellitus" to the word ‘diabetes’ as a designation for the disease, when he noticed the urine of a diabetic had a sweet taste (glycosuria).

1.3. Classification

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes and "other specific types". The "other specific types" are a collection of a few dozen individual causes. The term "diabetes", without qualification, usually refers to diabetes mellitus. The rare disease diabetes insipidus has similar symptoms as diabetes mellitus, but without disturbances in the sugar metabolism (insipidus means "without taste" in Latin).

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and noninsulin-dependent diabetes mellitus (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as: gestational diabetes, insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes).
The three main types of diabetes mellitus (DM) are:

- Type 1 DM results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as insulin-dependent diabetes mellitus (IDDM) or "juvenile" diabetes)

- Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as noninsulin-dependent diabetes mellitus (NIDDM) or "adult-onset" diabetes)

- Gestational diabetes is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

1.3.1. Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. The body stops producing insulin or produces too little insulin to regulate blood glucose level. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which beta cell loss is a T-cell-mediated autoimmune attack. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of DM cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.

- Type 1 diabetes is typically diagnosed during childhood or adolescence. It used to be referred to as juvenile-onset diabetes or insulin-dependent diabetes mellitus.

- Type 1 diabetes can occur in an older individual due to destruction of the pancreas by alcohol, disease, or removal by surgery. It also results from progressive failure of the pancreatic beta cells, the only cell type that produces significant amounts of insulin.
- People with type 1 diabetes require insulin treatment daily to sustain life. "Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe to dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes.13, 14

1.3.2. Type 2 diabetes
Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.9 Although the pancreas still secretes insulin, the body of someone with type 2 diabetes is partially or completely unable to use this insulin. This is sometimes referred to as insulin resistance. The pancreas tries to overcome this resistance by secreting more and more insulin. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type.
In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.
People with insulin resistance develop type 2 diabetes when they fail to secrete enough insulin to cope with their higher demands.
- At least 90% of adult individuals with diabetes have type 2 diabetes.
- Type 2 diabetes is typically diagnosed in adulthood, usually after age 45 years. It used to be called adult-onset diabetes mellitus, or non-insulin-dependent diabetes mellitus. These names are no longer used because type 2 diabetes does occur in younger people, and some people with type 2 diabetes require insulin therapy.
Type 2 diabetes is usually controlled with diet, weight loss, exercise, and oral medications. However, more than half of all people with type 2 diabetes require insulin to control their blood sugar levels at some point in the course of their illness.

1.3.3. Metabolic syndrome
Metabolic syndrome (also referred to as syndrome X) is a set of abnormalities in which insulin-resistant diabetes (type 2 diabetes) is almost always present along with hypertension (high blood pressure), high fat levels in the blood (increased serum lipids, predominant elevation of LDL cholesterol, decreased HDL cholesterol, and elevated triglycerides), central obesity, and abnormalities in blood clotting (fibrinolysis,
procoagulation) and inflammatory responses. A high rate of cardiovascular disease is associated with metabolic syndrome.

Metabolic syndrome is defined by the National Cholesterol Education Program\textsuperscript{15} as the presence of any three of the following conditions (Table I1).

**Table I1: Limiting conditions of the metabolic syndrome**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess weight around the waist</td>
<td>waist measurement of more than 40 inches for men and more than 35 inches for women</td>
</tr>
<tr>
<td>High levels of triglycerides</td>
<td>150mg/dL or higher</td>
</tr>
<tr>
<td>Low levels of HDL or ‘good’</td>
<td>below 40mg/dL for men and below 50mg/dL for women</td>
</tr>
<tr>
<td>cholesterol</td>
<td></td>
</tr>
<tr>
<td>High blood pressure (Hypertension)</td>
<td>130/85 mmHg or higher</td>
</tr>
<tr>
<td>High fasting blood glucose level</td>
<td>110mg/dL or higher</td>
</tr>
</tbody>
</table>

Although the metabolic syndrome is not exclusively associate with T2D and the associated insulin resistance, the increasing prevalence of obesity and associated development of T2D places insulin resistance as a major contributor to the syndrome. The role of adipose tissue stems from the fact that the organs active at secretion of cytokines, termed adipocytokines. These include tumor necrosis factor-\(\alpha\) (TNF\(\alpha\)), interleukin-6 (IL6), leptin, adiponectin and resistin. Leptin has received particular attention of late due to its role in obesity in addition to the fact that recent data indicates that plasma leptin levels are found to be predictive of the potential for cardiovascular pathology.

Many clinicians and researchers believe that insulin resistance underlies the cardiovascular pathogenesis of the metabolic syndrome. One primary reason for this is the role of insulin in fat homeostasis. As discussed above, the major role of insulin is to induce the storage of fuel. This can be as fat (triacylglycerides, TGs) in adipose tissue or as carbohydrate in the form of glycogen in liver and skeletal muscle. The effect of insulin resistance at the level of fat homeostasis is an increase in circulating TGs, referred to as dyslipidemia. Due to insulin resistance there is an increase in the delivery of peripheral fatty acids to the liver which in turn drives hepatic TG synthesis. These TGs are then packaged into lipoprotein particles termed VLDLs (very low density lipoproteins) which are returned to the circulation. Taken together, the insulin resistance and its associated negative effects on metabolism, the increased levels of circulating TGs, the reduced levels of HDLs and
hypertension, all contribute to the progression of atherosclerosis. With associated coagulation and fibrinolysis pathogenesis, the cardiovascular events of the metabolic syndrome can be devastating.

Since many of these pathogeneses can be reversed with proper diet and exercise, it is in a person’s best interest to take responsibility for the role their lifestyle choices play in the development of the metabolic syndrome.\textsuperscript{16}

\textbf{1.3.4. Prediabetes}

It is a common condition related to diabetes. In people with prediabetes, the blood sugar level is higher than normal but not yet high enough to be considered diagnostic of diabetes.

- Prediabetes increases a person's risk of developing type 2 diabetes, heart disease, or stroke.
- Prediabetes can typically be reversed (without insulin or medication) with lifestyle changes such as losing a modest amount of weight and increasing physical activity levels. Weight loss can prevent, or at least delay, the onset of type 2 diabetes.
- An international expert committee of the American Diabetes Association redefined the criteria for prediabetes, lowering the blood sugar level cut-off point for prediabetes. Approximately 20\% more adults are now believed to have this condition and may develop diabetes within 10 years if they do make lifestyle changes such as exercising more and maintaining a healthy weight.

About 17 million Americans (6.2\% of adults in North America) are believed to have diabetes. It has been estimated that about one third of adults with diabetes do not know they have diabetes.

- About 1 million new cases of diabetes is diagnosed occur each year, and diabetes is the direct or indirect cause of at least 200,000 deaths each year.
- The incidence of diabetes is increasing rapidly. This increase is due to many factors, but the most significant are the increasing incidence of obesity associated with the prevalence of a sedentary lifestyle.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically
determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, *malnutrition-related diabetes mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.17

1.4. Relation among Insulin Resistance, Pre-diabetes and T2DM
If someone has insulin resistance his/her muscle, fat and liver cells do not use insulin properly. The pancreas tries to keep up with the demand for insulin by producing more. Eventually, the pancreas cannot keep up with the body’s need for insulin, and excess glucose builds up in the bloodstream. Many people with insulin resistance have high level of blood glucose and high levels of insulin circulating in their blood at the same time. People with blood glucose levels that are higher than normal but not yet in the diabetic range have “pre-diabetic”. Doctors sometimes call this condition impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on the test used to diagnose it.
If someone has pre-diabetes, he/she has a higher risk of developing type 2 diabetes, formerly called adult-onset diabetes or non insulin dependent diabetes. Studies have shown that that most people with pre-diabetes go on to develop type 2 diabetes within 10 years, unless they loose 5 to 7 percent of their body weight – which is about 10 to 15 pounds for someone who weighs 200 pounds – by making modest changes in their diet and level of physical activity. People with pre-diabetes also have a higher risk of heart disease. Type 2 diabetes is sometimes defined as the form of diabetes that develops when the body does not respond properly to insulin, as opposed to type 1 diabetes, in which the pancreas makes no insulin at all. At first, the pancreas keeps up with the added demand by producing more insulin. In times, however, it loses the ability to secrete enough insulin in response to meals. Insulin resistance can also occur in people who have type 1 diabetes, especially if they are overweight.15
Also Latent Autoimmune Diabetes of Adults (LADA) is another condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology.17
1.5. Causes

The cause of diabetes depends on the type.

Type 1 diabetes is believed to be an autoimmune disease. The body's immune system specifically attacks the cells in the pancreas that produce insulin.

- A predisposition to develop type 1 diabetes may run in families, but genetic causes (a positive family history) are much more common for type 2 diabetes.
- Environmental factors, including common unavoidable viral infections, may also contribute to type 1 diabetes.
- Type 1 diabetes is most common in people of non-Hispanic, Northern European descent (especially Finland and Sardinia), followed by African Americans, and Hispanic Americans. It is relatively rare in those of Asian descent.
- Type 1 diabetes is slightly more common in men than in women.

Type 1 diabetes is partly inherited, and then triggered by certain infections, with some evidence pointing at Coxsackie B4 virus. A genetic element in individual susceptibility to some of these triggers has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, T1DM seems to require an environmental trigger.

Type 2 diabetes is due primarily to lifestyle factors and genetics. T2DM as a common and complex disease has been characterized by the following causes:

- Obesity: obesity is also considered a key risk factor for T2DM. The association between increasing body mass index (BMI) and greater weight gain and risk of diabetes is most pronounced among Asians, suggesting that lower cut off BMI values are needed to identify. Asians at a higher risk of diabetes. BMI cut point for Indians for any cardiometabolic risk factors is 23 kg/m2 in both sexes.

- Abdominal adiposity: there is also a probable indication that there is a preferential abdominal adiposity in Indians irrespective of the degree of general adiposity.
- Imbalance of human metabolism is associated with T2DM: Changes in work patterns from heavy labour to sedentary, the increase in computerization and mechanization, and
improved transport are just a few of the changes that have had an impact on human metabolism.

• Genes: since 2007, genome-wide association studies has catalogued around 20 genes (like TCF7L2, HHEX, CDKAL1, SLC30A8 etc.) showing a strong association (with modest odds ratio ranges between 1.2 and 1.5) with T2DM.

• Ethnicity: the interethnic differences (like differences in prevalence of T2DM among Europeans, Americans, Chinese, and Asian Indians) in insulin resistance may have an environmental or genetic explanation. The main acquired factors that seemingly increase insulin resistance in all ethnic groups include obesity, sedentary lifestyle, diet rich in animal products, and aging.21

The following table 2 give is a comprehensive list of other causes of diabetes.22

Table 2: Causes of DM

<table>
<thead>
<tr>
<th>Genetic defects of β-cell function</th>
<th>Endocrinopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maturity onset diabetes of the young</td>
<td>• Growth hormone excess (acromegaly)</td>
</tr>
<tr>
<td>• Mitochondrial DNA mutations</td>
<td>• Cushing syndrome</td>
</tr>
<tr>
<td>Genetic defects in insulin processing or insulin action</td>
<td>• Hyperthyroidism</td>
</tr>
<tr>
<td>• Defects in proinsulin conversion</td>
<td>• Pheochromocytoma</td>
</tr>
<tr>
<td>• Insulin gene mutations</td>
<td>• Glucagonoma</td>
</tr>
<tr>
<td>• Insulin receptor mutations</td>
<td>Infections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exocrine pancreatic defects</th>
<th>• Cytomegalovirus infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic pancreatitis</td>
<td>• Coxsackievirus B</td>
</tr>
<tr>
<td>• Pancreatectomy</td>
<td>Drugs</td>
</tr>
<tr>
<td>• Pancreatic neoplasia</td>
<td>• Glucocorticoids</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
<td>• Thyroid hormone</td>
</tr>
<tr>
<td>• Hemochromatosis</td>
<td>• β-adrenergic agonists</td>
</tr>
<tr>
<td>• Fibrocalculous pancreatopathy</td>
<td>• Statins23</td>
</tr>
</tbody>
</table>
Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.

Humans are capable of digesting some carbohydrates, in particular those most common in food; starch, and some disaccharides such as sucrose, are converted within a few hours to simpler forms, most notably the monosaccharide glucose, the principal carbohydrate energy source used by the body. The rest are passed on for processing by gut flora largely in the colon. Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage.

Insulin is also the principal control signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels result both in the reduced release of insulin from the β-cells and in the reverse conversion of glycogen to glucose when glucose levels fall. This is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin. Glucose thus forcibly produced from internal liver cell stores (as glycogen) re-enters the bloodstream; muscle cells lack the necessary export mechanism. Normally, liver cells do this when the level of insulin is low (which normally correlates with low levels of blood glucose).

Higher insulin levels increase some anabolic ("building up") processes, such as cell growth and duplication, protein synthesis, and fat storage. Insulin (or its lack) is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis (the fat-burning metabolic phase).

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not have its usual effect, so it will not be absorbed properly by those body cells that
require it, nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

When the glucose concentration in the blood is raised beyond its renal threshold (about 10 mmol/L, although this may be altered in certain conditions, such as pregnancy), reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria) (Figure II). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst.

Figure II: Glucose levels in blood of Renal Threshold and Glucosuria

1.6. Diabetes Symptoms

Symptoms of type 1 diabetes are often dramatic and come on very suddenly.

- Type 1 diabetes is usually recognized in childhood or early adolescence, often in association with an illness (such as a virus or urinary tract infection) or injury.
The extra stress can cause diabetic ketoacidosis.
- Symptoms of ketoacidosis include nausea and vomiting. Dehydration and often-serious disturbances in blood levels of potassium follow.
- Without treatment, ketoacidosis can lead to coma and death.

Symptoms of type 2 diabetes are often subtle and may be attributed to aging or obesity.
- A person may have type 2 diabetes for many years without knowing it.
- People with type 2 diabetes can develop hyperglycemic hyperosmolar nonketotic syndrome.
- Type 2 diabetes can be precipitated by steroids and stress.
- If not properly treated, type 2 diabetes can lead to complications such as blindness, kidney failure, heart disease, and nerve damage.

**Common symptoms of both type 1 and type 2 diabetes include:**

- **Fatigue, constantly tired:** In diabetes, the body is inefficient and sometimes unable to use glucose for fuel. The body switches over to metabolizing fat, partially or completely, as a fuel source. This process requires the body to use more energy. The end result is feeling fatigued or constantly tired.

- **Unexplained weight loss:** People with diabetes are unable to process many of the calories in the foods they eat. Thus, they may lose weight even though they eat an apparently appropriate or even an excessive amount of food. Losing sugar and water in the urine and the accompanying dehydration also contributes to weight loss.

- **Excessive thirst (polydipsia):** A person with diabetes develops high blood sugar levels, which overwhelms the kidney's ability to reabsorb the sugar as the blood is filtered to make urine. Excessive urine is made as the kidney spills the excess sugar. The body tries to counteract this by sending a signal to the brain to dilute the blood, which translates into thirst. The body encourages more water consumption to dilute the high blood sugar back to normal levels and to compensate for the water lost by excessive urination.

- **Excessive urination (polyuria):** Another way the body tries to rid the body of the extra sugar in the blood is to excrete it in the urine. This can also lead to dehydration because a large amount of water is necessary to excrete the sugar.
- **Excessive eating (polyphagia):** If the body is able, it will secrete more insulin in order to try to manage the excessive blood sugar levels. Moreover, the body is resistant to the action of insulin in type 2 diabetes. One of the functions of insulin is to stimulate hunger. Therefore, higher insulin levels lead to increased hunger. Despite increased caloric intake, the person may gain very little weight and may even lose weight.

- **Poor wound healing:** High blood sugar levels prevent white blood cells, which are important in defending the body against bacteria and also in cleaning up dead tissue and cells, from functioning normally. When these cells do not function properly, wounds take much longer to heal and become infected more frequently. Long-standing diabetes also is associated with thickening of blood vessels, which prevents good circulation, including the delivery of enough oxygen and other nutrients to body tissues.

- **Infections:** Certain infections, such as frequent yeast infections of the genitals, skin infections, and frequent urinary tract infections, may result from suppression of the immune system by diabetes and by the presence of glucose in the tissues which allow bacteria to grow. These infections can also be an indicator of poor blood sugar control in a person known to have diabetes.

- **Altered mental status:** Agitation, unexplained irritability, inattention, extreme lethargy, or confusion can all be signs of very high blood sugar, ketoacidosis, hyperosmolar hyperglycemia nonketotic syndrome, or hypoglycemia (low sugar). Thus, any of these merit the immediate attention of a medical professional.

- **Blurry vision:** Blurry vision is not specific for diabetes but is frequently present with high blood sugar levels.

A pictorial representation of the organs (with their location in our body) involved with the symptoms of diabetes in given in figure 12.
1.7. Diagnosis of Diabetes

Physicians prescribe special tests in diagnosing diabetes and also in monitoring blood sugar level control in known diabetics.

A number of laboratory tests are available to confirm the diagnosis of diabetes.

**Finger stick blood glucose:** This is a rapid screening test that may be performed anywhere, including community-based screening programs.

- Although a not as accurate as testing the patient's blood in the hospital laboratory, a fingerstick blood glucose test but is easy to perform, and the result is available right away.
- The test involves sticking the patient's finger for a blood sample, which is then placed on a strip. The strip goes into a machine that reads the blood sugar level. These machines are only accurate to within about 10%-20% of true laboratory values.
• Fingerstick blood glucose values tend to be most inaccurate at very high or very low levels, so this test is only a preliminary screening study. Fingerstick is the way most people with diabetes monitor their blood sugar levels at home.

**Fasting plasma glucose:** The patient will be asked to eat or drink nothing for 8 hours before having blood drawn (usually first thing in the morning). If the blood glucose level is greater than or equal to 126 mg/dL (without eating anything), they probably have diabetes.

- If the result is abnormal, the fasting plasma glucose test may be repeated on a different day to confirm the result, or the patient may undergo an oral glucose tolerance test or a glycosylated hemoglobin test (often called "hemoglobin A1c") as a confirmatory test.

- If fasting plasma glucose level is greater than 100 but less than 126 mg/dL, then the patient has what is called impaired fasting glucose, or IFG. This is considered to be prediabetes. These patients do not have diabetes, but they are at high risk of developing diabetes in the near future.

**Oral glucose tolerance test:** This test involves drawing blood for a fasting plasma glucose test, then drawing blood for a second test at two hours after drinking a very sweet drink containing up to 75 grams of sugar.

- If the blood sugar level after the sugar drink is greater than or equal to 200 mg/dL, the patient has diabetes.

- If the blood glucose level is between 140 and 199, then the patient has impaired glucose tolerance (IGT), which is also a prediabetic condition.

**Glycosylated hemoglobin or hemoglobin A1c:** This test is a measurement of how high the blood sugar levels have been over approximately the last 120 days (the average life-span of the red blood cells on which the test is based). Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.

- Excess blood glucose hooks itself on to the hemoglobin in red blood cells and stays there for the life of the red blood cell.

- The percentage of hemoglobin that has had excess blood sugar attached to it can be measured in the blood. The test involves having a small amount of blood drawn.
A hemoglobin A1c test is the best measurement of blood sugar control in people known to have diabetes. A hemoglobin A1c result of 7% or less indicates good glucose control. A result of 8% or greater indicates that blood sugar levels are too high, too much of the time.

The hemoglobin A1c test is the best test for diabetes follow-up care, than to diagnose diabetes. Still, a hemoglobin A1c result greater than 6.1% is highly suggestive of diabetes. Generally, a confirmatory test would be needed before diagnosing diabetes.

The hemoglobin A1c test is generally measured about every 3 to 6 months for people with known diabetes, although it may be done more frequently for people who are having difficulty achieving and maintaining good blood sugar control.

This test is not used for people who do not have diabetes or are not at increased risk of diabetes.

Normal values may vary from laboratory to laboratory, although an effort is under way to standardize how measurements are performed.

Special attention is paid to history including information about the patient's symptoms, risk factors for diabetes, past medical problems, current medications, allergies to medications, family history of diabetes, or other medical problems such as high cholesterol or heart disease, and personal habits and lifestyle.

The limiting values of the parameters of the pathological tests for the diagnosis of DM are listed in table I3.

**Table I3: Diagnosis criteria for Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Condition</th>
<th>2 hour glucose mmol/l(mg/dl)</th>
<th>Fasting glucose mmol/l(mg/dl)</th>
<th>HbA1c %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;7.8 (&lt;140)</td>
<td>&lt;6.1 (&lt;110)</td>
<td>&lt;6.0</td>
</tr>
<tr>
<td>Prediabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glycaemia</td>
<td>&lt;7.8 (&lt;140)</td>
<td>≥6.1(≥110) &amp; &lt;7.0(&lt;126)</td>
<td>6.0-6.4</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>≥7.8 (≥140)</td>
<td>&lt;7.0 (&lt;126)</td>
<td>6.0-6.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥11.1 (≥200)</td>
<td>≥7.0 (≥126)</td>
<td>≥6.5</td>
</tr>
</tbody>
</table>
1.8. Complications of diabetes

Both type 1 and type 2 diabetes ultimately lead to high blood sugar levels, a condition called hyperglycemia. Over a long period of time, hyperglycemia damages the retina of the eye, the blood vessels of the kidneys, the nerves, and other blood vessels.

- Damage to the retina from diabetes (diabetic retinopathy) is a leading cause of blindness.
- Damage to the kidneys from diabetes (diabetic nephropathy) is a leading cause of kidney failure.
- Damage to the nerves from diabetes (diabetic neuropathy) is a leading cause of foot wounds and ulcers, which frequently lead to foot and leg amputations.
- Damage to the nerves in the autonomic nervous system can lead to paralysis of the stomach (gastroparesis), chronic diarrhea, and an inability to control heart rate and blood pressure during postural changes.
- Diabetes accelerates atherosclerosis, (the formation of fatty plaques inside the arteries), which can lead to blockages or a clot (thrombus). Such changes can then lead to heart attack, stroke, and decreased circulation in the arms and legs (peripheral vascular disease).
- Diabetes predisposes people to elevated blood pressure, high levels of cholesterol and triglycerides. These conditions both independently and together with hyperglycemia, increase the risk of heart disease, kidney disease, and other blood vessel complications.

Diabetes can contribute to a number of acute (short-lived) medical problems.

- Many infections are associated with diabetes, and infections are frequently more dangerous in someone with diabetes because the body's normal ability to fight infections is impaired. To compound the problem, infections may worsen glucose control, which further delays recovery from infection.
- Hypoglycemia or low blood sugar, occurs intermittently in most people with diabetes. It can result from taking too much diabetes medication or insulin (sometimes called an insulin reaction), missing a meal, exercising more than usual, drinking too much alcohol, or taking certain medications for other conditions. It is very important to recognize hypoglycemia and be prepared to treat it at all times. Headache, feeling dizzy, poor concentration, tremor of the hands, and sweating are common symptoms of hypoglycemia. A person can faint or have a seizure if blood sugar level becomes too low.
• **Diabetic ketoacidosis (DKA)** is a serious condition in which uncontrolled hyperglycemia (usually due to complete lack of insulin or a relative deficiency of insulin) over time creates a buildup of ketones (acidic waste products) in the blood. High levels of ketones can be very harmful. This typically happens to people with type 1 diabetes who do not have good blood glucose control. Diabetic ketoacidosis can be precipitated by infection, stress, trauma, missing medications like insulin, or medical emergencies such as a stroke and heart attack.

• **Hyperosmolar hyperglycemic nonketotic syndrome** is a serious condition in which the blood sugar level gets very high. The body tries to get rid of the excess blood sugar by eliminating it in the urine. This increases the amount of urine significantly, and often leads to dehydration so severe that it can cause seizures, coma, and even death. This syndrome typically occurs in people with type 2 diabetes who are not controlling their blood sugar levels, who have become dehydrated, or who have stress, injury, stroke, or are taking certain medications, like steroids.

### 1.9. Diabetes Prognosis

Diabetes is a leading cause of death in all industrialized nations. Overall, the risk of premature death of people with diabetes is twice that of people who do not have diabetes. Prognosis depends on the type of diabetes, degree of blood sugar control, and development of complications.

With India having the highest number of diabetic patients in the world, the sugar disease is posing an enormous health problem in the country.\textsuperscript{23,24,25} Calling India the ‘diabetes capital of the world’, the International Journal of Diabetes in Developing Countries has said that there is alarming rise in prevalence of diabetes, which has gone beyond epidemic form to a pandemic one.

The International Diabetes Federation estimates that the number of diabetic patients in India more than doubled from 19 million in 1995 to 40.9 million in 2007. It is projected to increase to 69.9 million by 2025. Currently, up to 11 per cent of India’s urban population and 3 per cent of rural population above the age of 15 has diabetes. Diabetes affects all people in the society, not just those who live with it. The World Health Organization estimates that mortality from diabetes and heart disease cost India about $210 billion every year and is expected to increase to $335 billion in the next ten years. These estimates are based on lost productivity, resulting primarily from premature death.
The most prevalent is the Type 2 diabetes, which constitutes 95 per cent of the diabetic population in the country.  

The estimated global burden of type 2 diabetes mellitus (T2DM) for 2010 was 285 million people and was projected to increase to 438 million in 2030 (Figure I3); a 65% increase. Similarly, for India this increase was estimated to be 58%, from 51 million people in 2010 to 87 million in 2030. The impacts of T2DM are considerable: as a lifelong disease, it increases morbidity and mortality and decreases the quality of life.

![Figure I3: Estimated number of diabetic population in India](image)

### 1.10. Prevalence of T2DM

**Global Prevalence**

The number of cases of diabetes worldwide in the year 2000 among adults (more than or equal to 20 years) was estimated to be 171 million and will rise to 366 million by 2030. In terms of rank of countries for T2DM prevalence, Ukraine (3.2 million) is at the bottom of the list, Pakistan (5.2 million) comes at number six, China is second with 20.8 million people and India has the highest number (31.7 million) of people with rate of 3% for T2DM (Table I4). The Pima Indians of Arizona in the United States (US) and have the highest prevalence rates (21%) of T2DM. A study by compared the prevalence of T2DM in Pima Indians living in Arizona to members of a population of Pima ancestry living in northwestern Mexico. In association with marked lifestyle differences, the two genetically related populations had very different prevalence of diabetes. The Pima Indians living in Mexico were found to have a prevalence of 6% and 11%, for men and women, respectively, as compared to the frequency of 54% and 37% reported in the Pima
Indians living in Arizona. According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20–79 year age group have diabetes and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes. The largest increases will take place in the regions dominated by developing economies. The ten countries with largest diabetic population are listed in table I4.

**Table I4: Top ten countries for number of persons with type 2 Diabetes**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Year 2000 People with T2DM (million)</th>
<th>Year 2030 (projected) Country</th>
<th>People with T2DM (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>India</td>
<td>37.1</td>
<td>1</td>
<td>India</td>
</tr>
<tr>
<td>2</td>
<td>China</td>
<td>20.8</td>
<td>2</td>
<td>China</td>
</tr>
<tr>
<td>3</td>
<td>USA</td>
<td>17.7</td>
<td>3</td>
<td>USA</td>
</tr>
<tr>
<td>4</td>
<td>Indonesia</td>
<td>8.4</td>
<td>4</td>
<td>Indonesia</td>
</tr>
<tr>
<td>5</td>
<td>Japan</td>
<td>6.8</td>
<td>5</td>
<td>Pakistan</td>
</tr>
<tr>
<td>6</td>
<td>Pakistan</td>
<td>5.2</td>
<td>6</td>
<td>Brazil</td>
</tr>
<tr>
<td>7</td>
<td>Russia Fed.</td>
<td>4.6</td>
<td>7</td>
<td>Bangladesh</td>
</tr>
<tr>
<td>8</td>
<td>Brazil</td>
<td>4.6</td>
<td>8</td>
<td>Japan</td>
</tr>
<tr>
<td>9</td>
<td>Italy</td>
<td>4.3</td>
<td>9</td>
<td>Philippines</td>
</tr>
<tr>
<td>10</td>
<td>Ukraine</td>
<td>3.2</td>
<td>10</td>
<td>Egypt</td>
</tr>
</tbody>
</table>

**Prevalence in India**

Mohan et al. found that the incidence of:

1. T2DM in the urban south Indian population was 20.2 per 1,000 person years,
2. Pre-T2DM was 13.1 per 1,000 person years,
3. T2DM among subjects with impaired glucose tolerance (IGT) at baseline was higher compared to those with normal glucose tolerance (NGT).

This research team recommended that Indian Diabetes Risk Score (IDRS) was best predictive tool of estimating incidence of T2DM in Asian Indians.
Figure I4 shows the recent prevalence of T2DM of diabetic population in different parts of India. \(^{37-44}\)

**Figure I4:** Recent population based studies showings the prevalence of type 2 diabetes in different parts of India

**Urban India:** In the urban population, an Indian Council of Medical Research (ICMR) study in 1972 reported a prevalence of 2.3\(^{45}\) which rose to 12.1\(^{\%}\) in the year 2000.\(^{46}\) More recently, estimates were provided from a nationwide surveillance study\(^{47}\) of T2DM that in urban areas there was a prevalence 7.3\(^{\%}\) of known T2DM and a prevalence of 3.2\(^{\%}\) in peri-urban/slum areas (urban fringes).
Prevalence rates vary according to measuring criteria used e.g. using the American diabetes association criteria, it has recently been estimated to be 1.9% in the rural areas; but with using the WHO criteria the estimate increased to 2.7%. Other studies indicate higher rates. Data from a large-scale survey on 4,535 individuals aged more than or equal to 30 years from 20 villages of Godavari, a developing rural area of Andhra Pradesh, suggests that rural India may soon experience the urban epidemic of T2DM. Estimates of T2DM prevalence were calculated by applying sampling weights derived from the 2004 census where T2DM was defined by disease history and/or fasting glucose of 7.0 mmol or over. The results indicated that the prevalence for known T2DM was of 6.4%, for undiagnosed T2DM 6.8%, and that 15.5% had impaired fasting glucose. While these data are by no means representative of rural India as a whole, they imply increases of T2DM. Figures based on National Family Health Survey (NFHS) in 2005-06 suggest the prevalence of T2DM in rural India are highest in Kerala, Tripura, West Bengal, Goa and Sikkim, (1500 to >2000 individuals per 100,000 individuals) and least in central India (<500 individuals per 100,000 individuals) (Figure 15).
1.11. Economic Burden of Diabetes in India

Despite diabetes being a life-long disorder and is expensive to manage and treat for the large proportion of subjects in developing societies, there is lack of data on its economic burden in India. In the Indian context the financial burden is often shared by relatives of the patients. The health care budget of the government in India is a meager 2% compared to 14% to defense. The total amount needed for India to treat T2DM is estimated to around 2.2 billion USD. In India the direct medical cost to identify one subject with insulin glucose tolerance is INR 5,278. The cost of insulin amounts to 350.00 USD (16,000 Indian Rupees) per year, while medication for non-insulin-requiring patients costs about 70.00 USD per year. In the Indian context these costs are prohibitive: 75.5% of the Indian population is earning less than $2 per day and 41.6% less than $1.25 per day. To determine the direct cost of ambulatory diabetes care, to evaluate the socio-demographic associates of spending, and to ascertain the relationship of spending with the delivered quality of diabetes care; the community based data available from the middle and high income groups in Delhi (DEDICOM survey) was analyzed and it was concluded from the study that a majority of diabetes patients spend a significant proportion of their family income on diabetes related expenditure (~Rs. 6000 i.e. ~US$ 150) per year. The cost is higher for subjects with longer duration since diagnosis, those with higher education or income, those with co-morbidities and those requiring oral hypoglycemic agents or insulin. In developing countries like India, the brunt of diabetes and cardiovascular disease occurs among the economically productive age group (20-45 year olds). Diabetes mellitus is responsible for 1157 thousand years of life lost due to the disease, and for 2263 thousand DALYs during 2004. The World Health Organization estimates that mortality from diabetes and heart disease cost India about $210 billion every year and is expected to increase to $335 billion in the next ten years. These estimates are based on lost productivity, resulting primarily from premature death.

Overall cost during the course of treatment of T2DM borne by in and out-patient subjects and subjects needing surgical care is cited in table 15.
Table 15: Cost of diabetes borne by in and out-patient subjects and subjects needing surgical care

<table>
<thead>
<tr>
<th>Variables</th>
<th>Inpatient Care N=122 (1)</th>
<th>Outpatient care N=122 (2)</th>
<th>Patients needing surgical Care, N= 40 (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Family Income</td>
<td>48,000 (3,600-6,00,000)</td>
<td>48,000 (2,400-10,80,000)</td>
<td>45,000 (2,400-6,00,000)</td>
</tr>
<tr>
<td>Money spent on DM*</td>
<td>6,725 (620-41,000)</td>
<td>3,050 (364-48,450)</td>
<td>5,395 (350-73,700)</td>
</tr>
<tr>
<td>Expenditure on Hospitalization</td>
<td>5,000 (300-30,000)</td>
<td>Nil</td>
<td>9,000 (2,800-3,10,000)</td>
</tr>
<tr>
<td>Expenditure on Transport</td>
<td>300 (3-30,000)</td>
<td>200 (4-12,000)</td>
<td>200 (5-50,000)</td>
</tr>
<tr>
<td>Average expenditure**</td>
<td>7,505 (400-75,200)</td>
<td>3,310 (360-48,600)</td>
<td>13,880 (550-75,200)</td>
</tr>
<tr>
<td>Proportion of Income spent on DM#</td>
<td>17.5%</td>
<td>7.7%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

*1 vs 2 P= 0.0001; 2 vs 3 P= 0.01; 3 vs 1 P= 0.36  **1 vs 2 P= 0.0001; 2 vs 3 P= 0.10# 1 vs 2 P= 0.0001; 2 vs 3 P= 0.0013; 3 vs 1 P= 0.86

Data are median values of Indian rupees-range given in brackets.

1.12. Morbidity and Mortality associated with Diabetes

*Global Morbidity and Mortality associated with Diabetes*
- Close to four million deaths in the age group of 20-79 years in 2010.\(^{59}\)
- Accounting for 6.8% of global all-cause mortality in this age group in 2010.\(^{59}\) IDF 2006 reported >50 million diabetes people in South East Asia.
- 7.97 million disability adjusted life years (DALYs) were lost because of diabetes.\(^{60}\)

*Diabetes Morbidity and Mortality in India*
- Responsible for 109 thousand deaths in 2004.\(^{61}\)
- 1.157 million years of life lost in 2004.\(^{61}\)
- 2.263 million DALYs in India during 2004.\(^{58}\)

The bar diagram in figure 16 gives a comparative account of mortality rates among diabetic and non-diabetic individuals.\(^{62}\)
1.13. Treatment of Diabetes

While many measures were tried, effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Best developed insulin in 1921 and 1922. This was followed by the development of the long-acting insulin NPH in the 1940s.

The treatment of diabetes is highly individualized, depending on the type of diabetes, whether the patient has other active medical problems, whether the patient has complications of diabetes, and age and general health of the patient at time of diagnosis.

- A health care professional will set goals for lifestyle changes, blood sugar control, and treatment.
- Together, the patient and the health care professional will formulate a plan to help meet those goals.

Education about diabetes and its treatment is essential in all types of diabetes.

- When the patient is first diagnosed with diabetes, the diabetes care team will spend a lot of time with the patient, teaching them about their condition,
treatment, and everything they need to know to care for themselves on a daily basis.

- The diabetes care team includes the health care professional and his or her staff. It may include specialists in foot care, neurology, kidney diseases, and eye diseases. A professional dietitian and a diabetes educator also may be part of the team.

### 1.13.1. Type 1 diabetes

Treatment of diabetes almost always involves the daily injection of insulin, usually a combination of short-acting insulin (for example, lispro [Humalog] or aspart [NovoLog]) and longer acting insulin (for example, NPH, Lente, glargine [Lantus], detemir [Levemir]).

- Insulin must be given as an injection just under the skin. If taken by mouth, insulin would be destroyed in the stomach before it could get into the blood where it is needed.
- Most people with type 1 diabetes give these injections to themselves. Even if someone else usually gives the patient injections, it is important that the patient knows how to do it in case the other person is unavailable.
- The patient should be trained to store and inject the insulin. Insulin is usually given in two or three injections per day, generally around mealtimes. Dosage is individualized and is tailored to the patient's specific needs by the health care professional. Longer acting insulins are typically administered one or two times per day.
- Some people have their insulin administered by continuous infusion pumps to provide adequate blood glucose control. Supplemental mealtime insulin is programmed into the pump by the individual as recommended by his or her health care professionals.
- It is very important to eat after the taking insulin, as the insulin will lower blood sugar regardless of whether the person has eaten. If insulin is taken without eating, the result may be hypoglycemia. This is called an insulin reaction.
- There is an adjustment period while the patient learns how insulin affects them, and how to time meals and exercise with insulin injections to keep blood sugar levels as even as possible.
• Keeping accurate records of blood sugar levels and insulin dosages is crucial for the patient's diabetes management.
• Eating a consistent, healthy diet appropriate for the patient's size and weight is essential in controlling blood sugar level.

1.13.2. Type 2 diabetes
Depending on how elevated the patient's blood sugar and glycosylated hemoglobin (HbA1c) are at the time of diagnosis, they may be given a chance to lower blood sugar levels through lifestyle changes, without medication.
• The best way to do this is to lose weight if the patient is obese, and begin an exercise program.
• This will generally be tried for 3 to 6 months, then blood sugar and glycosylated hemoglobin will be rechecked. If they remain high, the patient will be started on an oral medication, usually a sulfonylurea or biguanide (metformin [Glucophage]), to help control blood sugar levels.
• Even if the patient is on medication, it is still important to eat a healthy diet, lose weight if they are overweight, and engage in moderate physical activity as often as possible.
• The health care professional will initially monitor the patient's progress on medication very carefully. It is important to receive just the right dose of the right medication, to regulate blood sugar levels in the recommended range with the fewest side effects.
• The doctor may decide to combine two types of medications to achieve blood sugar levels control.
• Gradually, even people with type 2 diabetes may require insulin injections to control their blood sugar levels.
• It is becoming more common for people with type 2 diabetes to take a combination of oral medication and insulin injections to control blood sugar levels.

1.14. Diabetic Medications (Therapeutic Intervention for Hyperglycemia)
Many, if not all, of the vascular consequences of insulin resistance are due to the persistent hyperglycemia seen in T2D. For these reason a major goal of therapeutic
intervention in T2D is to reduce circulating glucose levels. Many different types of medications are available to help lower blood sugar levels in people with type 2 diabetes. Each type works in a different way. There are many pharmacologic strategies to accomplish these goals. It is very common to combine two or more types to get the best effect with fewest side effects.

- **Sulfonylureas**: They are oral hypoglycemic drugs and are referred to as endogenous insulin secretagogues because they induce pancreatic release of endogenous insulin. The first generation sulfonylureas (tolbutamide, acetohexamide, chlorpropamide and tolazamide) are not routinely prescribed in the US. The second generation sulfonylureas include glipizide, glimipiride and glyburide. Because all of these drugs can induce pronounced hypoglycemia, treatment is initiated with the lowest possible dose and carefully monitored until the dose is found that results in a fasting plasma glucose (FPG) of 110-140 mg/dL. Sulfonylureas function by binding to and inhibiting the pancreatic ATP-dependent potassium channel that is normally involved in glucose mediated insulin secretion. They have no significant effects on circulating triglycerides lipoproteins or cholesterol.

- **Biguanides**: They are a class of oral hypoglycemic drugs that function to lower serum glucose levels by enhancing insulin-mediated suppression of hepatic glucose production and enhancing insulin-stimulated glucose uptake by skeletal muscle. Metformin (Glucophage) is a member of this class and is currently the most widely prescribed insulin-sensitizing drug in current clinical use. Metformin administration does not lead to increased insulin release from the pancreas and as such the risk of hypoglycemia is minimal. Because the major site of action for metformin is the liver, its use can be contraindicated in patients with liver dysfunction. The drug is ideal for obese patients and for younger T2 diabetics. Evidence on the mode of action (MOA) of metformin shows that it improves insulin sensitivity by increasing insulin receptor tyrosine kinase activity, enhancing glycogen synthesis and increasing recruitment and transport of GLUT4 transporters to the plasma membrane. Additionally, it has been shown that metformin affects mitochondrial activities dependent upon the model system studies. Metformin has a mild inhibitory effect on complex I of oxidative phosphorylation, has antioxidant
properties, and activates both glucose 6-phosphate dehydrogenase (G6PDH) and AMP-activated protein kinase (AMPK). The importance of AMPK metformin action stems from the role of AMPK in the regulation of both lipid and carbohydrate metabolism. In adipose tissue, metformin inhibits lipolysis while enhancing re-esterification of fatty acids.

In adolescent females with T2D, the use if metformin is highly recommended to reduce the incidence of as well as the potential for polycystic ovarian syndrome, (PCOS). PCOS is brought on by the hyperinsulinemia if T2D. insulin effects on the ovary drive conversion of progesterone to testosterone and a reduction in serum hormone globulin (SHBG). Taken together, the effects of hyperinsulinemia leads to a hyperandrogenic state in the ovary resulting in follicular atresis and ovulatory dysfunction.

- **Alpha-glucosidase inhibitors:** These oral hypoglycemic agents slow absorption of the starches a person eats. This slows down glucose production. Alpha-glucosidase inhibitors like acarbose (Precose) and miglitol (Glyset) function by interfering with the action of the α-glucosidases present in the small intestinal brush border. The consequence of this inhibition is a reduction in digestion and the consequent absorption of glucose into the systemic circulation. The reduction in glucose uptake allows the pancreatic β-cells to more effectively regulate insulin secretion. The advantage to the use of the α-glucosidase inhibitors is that they function locally in the intestine and have no major systemic action. Hypoglycemia does not usually occur with the use of α-glucosidase inhibitors but they are effective at reducing fasting plasma glucose (FPG) levels and levels of glycosylated haemoglobin (HbA1c). The adverse side effects of these inhibitors are abdominal bloating and discomfort, diarrhea and flatulence.16

- **Thiazolidinediones (TZDs):** These oral hypoglycemic agents increase sensitivity to insulin. The TZDs such as troglitazone (Rezulin: Warner Lambert Co. but this drug was voluntarily removed from the market due to liver damage risk64), rosiglitazone (Avandia: Glaxo Smithkline) and pioglitazone (Actos: Eli Lilly and Co.) have been proven useful in treating the hyperglycemia associated with insulin-resistance in both T2D and nondiabetic conditions (though these have also been withdrawn in many
countries owing to their cardiovascular adverse effects. The TZDs function as agonist for the nuclear receptor peroxisome proliferator activated receptor-γ (PPARγ). The net effect of the TZDs is a potentiation of the actions of insulin in liver, adipose tissue and skeletal muscle, increased peripheral glucose disposal and a decrease in glucose output by the liver.

- **Meglitinides:** These oral hypoglycemic agents stimulate the pancreas to make more insulin. The meglitinides repaglinide (Prandin) and nateglinide (Starlix) are non sulfonylurea insulin secretagogues that are both fast acting and of short duration. Like the sulfonylureas meglitinide therapy results in significant reduction in FPG as well as HbA₁c. The MOA of meglitinide is initiated by binding to a receptor on the pancreatic β-cell that is distinct from the receptors for the sulfonylureas. However, meglitinides do exert effects on potassium conductance like the sulfonylureas, the meglitinides have no direct effects on the circulating levels of plasma lipids.

- **D-phenylalanine derivatives:** These agents stimulate the pancreas to produce more insulin more quickly.

- **Amylin synthetic derivatives:** Amylin is a naturally occurring hormone secreted by the pancreas along with insulin. An amylin derivative, such as pramlintide (Symlin), is indicated when blood sugar control is not achieved despite optimal insulin therapy. Pramlintide is administered as a subcutaneous injection along with insulin and helps achieve lower blood sugar levels after meals, helps reduce fluctuation of blood sugar levels throughout the day, and improves hemoglobin A1C levels.

- **Insulins:** Synthetic human insulin is now the only type of insulin available in the United States; it is less likely to cause allergic reactions than animal-derived varieties of insulin used in the past. The type of insulin chosen to customize treatment for an individual is based on the goal of providing optimal blood sugar control. Different types of insulin are available and categorized according to their times of action onset and duration. Commercially prepared mixtures of insulin may also be used to provide constant (basal) control and immediate control.
Examples of rapid-acting insulins
- Regular insulin (Humulin R, Novolin R)
- Insulin lispro (Humalog)
- Insulin aspart (Novolog)
- Insulin glulisine (Apidra)
- Prompt insulin zinc (Semilente, slightly slower acting)

Examples of intermediate-acting insulins
- Isophane insulin, neutral protamine Hagedorn(NPH) (HumulinN, NovolinN)
- Insulin zinc (Lente)

Examples of long-acting insulins
- Extended insulin zinc insulin (Ultralente)
- Insulin glargine (Lantus)
- Insulin detemir (Levemir)

The sites of action of the therapeutic agents for T2DM are depicted in figure 17.

**Incretin mimetics:** Incretin mimetics promote insulin secretion by the pancreas and mimics other blood sugar level lowering actions that naturally occur in the body. Exenatide (Byetta) was the first incretin mimetic agent approved in the United States.
It is indicated for diabetes mellitus type 2 in addition to metformin or a sulfonylurea when these agents have not attained blood sugar level control alone.

**DPP IV Inhibitors:** DPP-IV inhibitors are compounds that increase the concentration of endogenous incretins, including glucagon like peptide-1 (GLP-1), by limiting the proteolytic cleavage by dipeptidyl peptidase-IV (DPP-IV). The clinical effect is to
stimulate insulin secretion in a glucose-specific manner and suppress glucagon secretion. DPP4 inhibitors such as sitagliptin and vildagliptin are novel agents for treatment of type 2 diabetes. They target both prandial and fasting glucose concentrations, and work by improving β-cell sensitivity to glucose, whereby it increases glucose-dependent insulin secretion. Gliptins can be used as monotherapy or combined with metformin or SUs. Gliptins are largely weight neutral. No serious adverse events were noted during the clinical trials. Vildagliptin is not recommended in patients with hepatic impairment. Long-term safety regarding cardiovascular outcomes needs to be assessed.67

A flowchart of the currently available stepwise clinical therapy for T2DM is given in figure I8.68

1.15. Peroxisome Proleferator Activated Receptors and T2DM
Type 2 diabetes is characterized by hyperglycemia, insulin resistance, and defects in insulin secretion and is usually associated with dyslipidemia, hypertension, and obesity. Although the detailed pathophysiology of this disease remains incompletely understood, metabolic defects in the liver, pancreatic β-cells, adipose tissue, and skeletal muscle all contribute to the development of type 2 diabetes. Though long thought to be mainly a disorder of carbohydrate metabolism, today a great deal of evidence suggests that abnormalities in fat metabolism play a central role in the pathogenesis of this disease.69-71 Perxisome proliferator-activated receptors (PPARs) are orphan receptors belonging to the steroid/thyroid/retinoid receptor superfamily of ligand-activated transcription factors. Although cloned only a few decade ago,72,73 the rapid progress in functional analysis of these receptors has established that the PPARs play a central role in regulating the storage and catabolism of lipids in both animals and humans (Figure I9). Therefore, much attention has been paid in the research of structural determination and ligand activation of these receptors. There are three PPAR subtypes, which are the products of distinct genes and are commonly designated PPARα [NR1C1], PPARγ [NR1C3], and PPARδ [NR1C2].74 The PPARs have a protein domain structure (Figure I9) common to other members of the nuclear receptor gene family. This consists of a variable N-terminal region that contains the transcriptional activation function 1 domain (AF-1), a highly conserved DNA-binding domain (DBD), and a ligand-binding domain (LBD) within which lies a C-terminal region that contains the transcriptional activation function 2
domain (AF-2). The LBD contains certain conserved amino acids that have been mapped to critical receptor functions involved in signal transduction. However, there is significant sequence variation in the residues that line the ligand-binding pocket, which is reflected in the fact that each receptor subtype is pharmacologically distinct. The PPARs form functionally active heterodimers with another nuclear receptor, the 9-cis-retinoic acid receptor (RXR). These heterodimers regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements (PPREs, Figure I10). PPREs have been identified in the regulatory regions of a large number of genes, including many that encode proteins involved in lipid metabolism and energy balance, such as aP2, phosphoenolpyruvate carboxykinase (PEPCK), acyl-CoA synthetase, and lipoprotein lipase (LPL).

Figure 19: PPAR family of nuclear receptors. Top: comparison of human PPARs is shown. Numbers represent percent homology with PPARα: AF-1= activation function 1; DBD= DNA binding domain; LBD= ligand-binding domain; AF-2= activation function 2. Bottom: the PPARs bind to DNA response elements in the regulatory regions of target genes as heterodimers with RXR. When an agonist binds to the PPAR receptor, recruitment of coactivator proteins (not shown) leads to transcriptional modulation: PPRE= PPAR response element.
The various beneficial effects of PPAR ligands\textsuperscript{77} are depicted pictorially in figure I10.

\textbf{Figure I10:} The beneficial metabolic effects of PPAR ligands. PPAR\textsubscript{γ} agonists are effective in treating T2DM. They modulate the expression of numerous genes in adipocytes, which results in improved insulin sensitivity, increased fatty acid uptake and decreased lipolysis. As a result, circulating FFA levels are diminished. Activation of PPAR\textsubscript{γ} also results in changes in adipokine production, remodeling of adipose tissue, and the concurrent repartitioning of lipids from lipolytic visceral fat into subcutaneous fat that contains newly generated, small insulin-sensitive adipocytes. PPAR\textsubscript{γ} agonists also decrease the inflammation of adipose tissue that is induced by obesity and contributes to increased insulin resistance. As a result of these multiple adipocentric actions (pale orange), PPAR\textsubscript{γ} activation improves insulin sensitivity in skeletal muscle and liver, and reduces hyperglycemia. In dyslipidemic subjects, PPAR\textsubscript{α} agonists induce lipid uptake and catabolism and the production of apolipoproteins A-I and A-II, thereby diminishing circulating TG and increasing HDL-C levels (cream). In addition to their anti-dyslipidemic activities, recent in vitro and preclinical data indicate that PPAR\textsubscript{α} agonists also have direct vasoprotective effects (brown). Activation of PPAR-\textdelta increases fatty acid oxidation and uncouples energy metabolism in skeletal muscle. Thus, PPAR\textsubscript{δ} agonists lower triglycerides, increase HDL-C and protect against obesity in preclinical species (dark red). Dotted lines represent activities observed only in preclinical experiments and in vitro.
PPARα plays a pivotal role in the uptake and oxidation of fatty acids and also in lipoprotein metabolism. PPARα is expressed highly in liver, heart and skeletal muscle, tissues that extract a high level of their energy requirements from lipids. During prolonged fasting that results in hypoglycemia, fatty acids are released from fat depots and travel to the liver where they are taken up, oxidized and metabolized into ketone bodies to provide fuel for peripheral tissues. The crucial role of PPARα in mediating these metabolic processes and, ultimately, energy homeostasis is demonstrated by the phenotype of PPARα null mice, which, on fasting, are characterized by hypoglycemia, hypoketonemia, hyperlipidemia and hepatic steatosis. Dyslipidemia, characterized by elevated circulating levels of triglycerides (TGs) in combination with decreased levels of high-density lipoprotein cholesterol (HDL-C), is often a forerunner of cardiovascular disease. PPARα agonists decrease plasma TG levels and increase HDL-C levels. The former action is mediated by increasing lipid uptake, activation and catabolism through the transcriptional modulation of numerous genes that control these processes. The latter is mediated, in part, by augmenting hepatic production of apolipoprotein A-I (apoA-I) and apoA-II, which are major proteinaceous components of HDL-C. Additionally, PPARα agonists cause favorable changes in the particle size and subclass distribution of lipoproteins.

The effects of PPARα agonists (Figure I11) on circulating lipid parameters and, perhaps, vascular cells are beneficial because these ligands reduce the progression of atherosclerosis and the incidence of coronary events in major clinical studies, including the Helsinki Heart Study and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT). The antiatherosclerotic efficacy of PPARα agonists is particularly pronounced in diabetic patients, as demonstrated in the VA-HIT and the Diabetes Atherosclerosis Intervention Study. Such results are noteworthy because cardiovascular disease is the major cause of mortality in T2DM patients, a cohort in which the prevalence of dyslipidemia is 2–3 times higher than in the general population.
1.15.2. PPARγ

PPARγ is present in high concentrations in adipocytes. Seminal studies in vitro have demonstrated that this receptor is both necessary and sufficient for adipocyte differentiation, and that it promotes lipid accumulation by adipocytes. The importance of PPARγ in adipocyte biology is underscored further by studies in vivo in which adipose-specific ablation of PPARγ expression in mice results in adipocyte hypocellularity, and heterozygous PPARγ knockout mice have reduced adiposity.

Consonant with the idea that PPARγ ligands mediate their effects primarily through adipose tissue, it has been demonstrated that they alter the expression of genes that are involved in lipid uptake, lipid metabolism and insulin action in adipocytes. As a result, they enhance adipocyte insulin signaling, lipid uptake and anabolic lipid metabolism, and attenuate lipolysis and free fatty acid (FFA) release. Consequently, lipid levels in adipose tissue rise whereas circulating FFAs diminish. It has been proposed that by repartitioning lipids away from liver and muscle, the two primary tissues that are responsible for insulin-mediated glucose disposal and metabolism, PPARγ agonists ameliorate hyperglycemia by reversing lipotoxicity-induced insulin resistance. Thus far, TZD treatment has been shown to diminish the lipid content of liver but not skeletal muscle. Data from patients with type 2 diabetes mellitus (T2DM) and preclinical species also demonstrate that PPARγ agonists function as ‘adipose remodeling factors’ that redistribute lipids from insulin-resistant, lipolytic visceral-fat depots into subcutaneous fat that contains small, newly differentiated, insulin-responsive adipocytes. Because fatty acids that are released from visceral adipose tissue drain into the portal vein and can serve as gluconeogenic substrates in the liver, such anatomical changes are thought to decrease their availability, thereby reducing the hepatic production of glucose and further improving glucose homeostasis. In support of this
hypothesis, human probands with inhibitory PPARγ mutations suffer from partial lipodystrophy, which is characterized by decreased subcutaneous fat, increased visceral fat, hyperglycemia and insulin resistance. In addition to altering fat deposition, PPARγ agonists modulate the endocrine activity of adipose tissue by regulating the synthesis of secreted adipocyte proteins (‘adipokines’) that affect insulin signaling in hepatic and peripheral tissue. For example, adiponectin, which potentiates insulin sensitivity in liver and skeletal muscle, is upregulated in response to PPARγ activation. Other studies reveal that PPARγ agonists reduce elevated levels of pro-inflammatory cytokines and chemokines that result from the excessive accumulation of macrophages in adipose tissue of obese, insulin-resistant rodents. Because pro-inflammatory cytokines derived from adipocytes and macrophages can inhibit insulin-stimulated signal transduction and, thereby, induce insulin resistance, PPARγ agonists might also improve insulin sensitivity through this immunosuppressant mechanism.

![Figure I12: Two well known and popular PPARγ agonists](image)

1.15.3. PPARδ
Because of its ubiquitous expression and the paucity of selective ligands, PPARδ is the least understood PPAR subtype. Nevertheless, early PPARδ selective agonists were found to elevate HDL-C levels in diabetic mice, a seminal observation that indicated that PPARδ ligands might have beneficial effects on dyslipidemia. Subsequently, the potent PPARδ agonist GW501516 [[2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl)methyl]thio]phenoxy] acetic acid] was shown to increase HDL-C while decreasing elevated TG and insulin levels in obese rhesus monkeys. GW501516 also attenuates weight gain and insulin resistance in mice fed high-fat diets by increasing the expression in skeletal muscle of genes that promote lipid catabolism and mitochondrial uncoupling, thereby increasing β-oxidation of fatty acids in skeletal muscle.
The α-helices of PPARγ and PPARδ LBDs, represented by tubes are shown in figure I13.

Figure I13: Crystal structures of the apo-PPAR LBDs. The α-helices are represented by tubes. Helix 2′, helix 3, and the AF-2 helix are designated as H2′, H3, and AF-2, respectively. The solvent-accessible ligand-binding site is indicated by the white shaded surface: (A) PPARγ LBD; (B) PPARδ LBD.

1.16. Role of PPAR Agonists in the therapy of Type 2 Diabetes

1.16.1. PPARα and PPARγ Agonists

The role of PPARα and PPARγ activation in ameliorating the hyperglycemia and hyperlipidemia associated with type 2 diabetes originates with two classes of compounds, the fibrates and the glitazones or thiazolidinediones (TZDs), which were empirically discovered via rodent pharmacology to have antihyperlipidemic and antihyperglycemic activity, respectively. The fibrates [e.g., clofibrate (1), fenofibrate (2), and bezafibrate (3); Figure I11] are drugs that have long been shown to effectively reduce triglycerides (TG) and free fatty acids (FFA) and increase high-density lipoprotein cholesterol (HDL) in both rodents and man. The discovery that these compounds are weak activators of PPARα, suggested that this receptor may be the primary molecular target of this class of drugs. This hypothesis has been reinforced by the discovery of more potent and
selective ligands for PPARR that display improved lipid-lowering activity compared to the fibrates. In addition, fibrates have also been shown to improve glucose tolerance in type 2 diabetic patients, although this activity may not be attributable to activation of PPARα because some of these compounds also have appreciable PPARγ activity. Fibrates are generally well-tolerated drugs; however, they are associated with a number of side effects, the most common of which are gastrointestinal side effects such as nausea and diarrhea, and elevations in liver enzymes. Skeletal myopathy and acute rhabdomyolysis have also been reported during treatment with all the currently marketed fibrates. It is not clear whether the effects on muscle are mediated by PPARα, but it will be important to carefully monitor these side effects with the more potent, selective PPARα agonists currently in clinical development. In addition, fibrates are excreted via the kidneys and thus should be avoided in patients with renal failure. Finally, fibrates have a propensity to cause drug-drug interactions because of their inhibition of cytochrome P450 enzymes and thus must be used with great caution in combination with other lipid-lowering drugs, particularly statins. While the combination of stains and fibrates has shown improved control of lipoprotein risk factors relative to either agent alone, this combination has shown an increase in renal failure, myopathy, and severe rhabdomyolysis.

The TZDs have been shown to enhance the sensitivity of target tissues to insulin and to reduce plasma glucose, lipid, and insulin levels in animal models of type 2 diabetes and in humans. The TZDs pioglitazone [Actos (4)] and rosiglitazone [Avandia (5)] (Figure I12) are currently marketed for the treatment of type 2 diabetes and represent important agents in the treatment of this disease both as monotherapy or in combination with existing therapies. These drugs display significant glucose-lowering efficacy, generally achieving mean decreases in haemoglobin A1C (HbA1C) of approximately 1-1.5% and mean decreases in fasting glucose of 60-80 mg/dL in type 2 diabetic patients. These drugs also display modest beneficial effects on TGs, FFAs, and HDL cholesterol. As was the case with fibrates and PPARR, the discovery that the TZDs are potent, selective agonists of PPARγ provided a key link to understanding the molecular mechanism of these drugs. These discoveries have alsoin the effort to optimize selective PPARγ agonists as effective antidiabetic agents and selective PPARα agonists as antihyperlipidemic agents.

While rosiglitazone and pioglitazone have many beneficial effects in type 2 diabetics, they also have some undesirable effects. A gain in weight of 3-5 kg is seen in most patients, with a minority gaining an inordinate amount of weight. This weight gain is
accompanied by an increase in subcutaneous fat mass. The clinical significance of this weight gain requires further evaluation, but in a treatment population that generally is already overweight this can minimally lead to negative psychological effects. In some patients this weight gain is accompanied by an increase in plasma volume leading to edema that is often resistant to diuretic therapy. This plasma volume expansion may precipitate or exacerbate congestive heart failure, and hence the currently marketed TZDs are not recommended in diabetic patients with NYHA class III and class IV cardiac status and should be used with caution in class I and class II patients. While the mechanism of the fluid retention seen with the marketed TZDs has not been elucidated, it is likely to be a PPARγ mediated effect because structurally unrelated selective PPARγ agonists also promote fluid retention.

Given the importance of controlling both glucose and lipid levels in type 2 diabetes, the concept of identifying ligands that bind and activate both PPARα and PPARγ represents a logical continuation in the field of PPAR research. In addition to their benefit on lipids, reports in the literature that fibrates reduce body weight gain in rodents without affecting food intake offer hope that activation of PPARα may mitigate the weight gain induced by PPARγ activation seen in humans. The hypothesis that PPARα/γ dual agonism should provide additive, and possibly synergistic, pharmacology has resulted in an intensive effort within the pharmaceutical industry to develop and evaluate these agents (Figure II4).

1.16.2. The PPAR dual agonists

PPARα/γ dual agonists

PPARα/γ dual agonists have been postulated as a combination strategy to achieve a broad spectrum of metabolic effects and reduce mortality rates associated with type 2 diabetes by improving insulin resistance, hyperglycemia and alleviating atherogenic dyslipidemia. In addition, PPARα agonists stimulate lipid oxidation and decrease adiposity in rodent obesity models. Thus, the propensity of PPARγ activation to induce weight gain through its adipogenic affects may be offset by the ability of PPARα activation to stimulate lipid catabolism thereby providing a compound with reduced propensity for inducing undesired weight gain. In recent years, a number of structurally diverse PPARα/γ dual agonists have been reported. Many of these have been evaluated in the clinic and some have advanced into late stage development. The clinical efficacy of the initially discovered
dual PPARα/γ agonists has been encouraging. However, the discontinuation of the development of the most promising PPARα/γ dual agonists, including muraglitazar, tesaglitazar, ragaglitazar, TAK559 and KRP297 due to various safety liability issues has been disconcerting. Other dual agonists are advancing through different stages of development. However, growing concerns regarding toxicities, as well as the recent requirement by the FDA to include 2-year rodent carcinogenicity studies prior to advancing any PPAR compound into any clinical study of greater than 6 months in duration, has tempered enthusiasm.

Figure I14: PPARα/γ dual agonists
The activities of the discussed PPARα agonists, PPARγ agonists and PPARα/γ dual agonists in terms of binding and cell-based functional assays are listed in table I6.

**Table I6: Activity of PPARα/γ Agonists in Binding and Cell-Based Functional Assays**

<table>
<thead>
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\(^a\)All data were generated using hPPAR LBD.\(^{132}\) Data reported are either K\(_i\) or IC\(_{50}\) values in which K\(_i\) = IC\(_{50}\)/ (1 + [L]/K\(_d\)) (where IC\(_{50}\) is the concentration of test compound required to inhibit 50% of the specific binding of the radioligand, [L] is the concentration of the radioligand used, and K\(_d\) is the dissociation constant for the radioligand at the receptor). Refer to the original reference to determine whether reported values is K\(_i\) or IC\(_{50}\); nr = not reported. \(^b\)All data were generated using the hPPAR-GAL4 transactivation assay\(^{110}\); ia = inactive at 10 µM or the highest concentration tested; nr ) not reported. \(^c\)Data are for active metabolites. \(^d\)Data are for murine receptors.

**PPARγ/δ dual agonists**

Based upon the central roles that both PPARγ and PPARδ play in lipid metabolism, PPARγ/β(δ) dual agonists have been postulated as a beneficial combination therapy for type 2 diabetes. Such a combination is predicted to effectively lower glucose and improve insulin sensitivity while simultaneously improving the dyslipidemia common in diabetic patients.\(^{139-141}\) The beneficial effects on lipid homeostasis and ability to stimulate reverse cholesterol transport are anticipated to significantly impede the progression of atherosclerosis which should contribute to lowering the mortality rates of type 2 diabetic patients. Furthermore, the propensity of PPARδ activation to improve insulin sensitivity
and increase fatty acid oxidation suggests that a dual PPARγ/δ agonist could attenuate the undesired weight gain realized with selective PPARγ agonists.

Reports of PPARγ/β(δ) dual agonists have been limited. The design and characterization of a ligand (Compound A, Figure I15) with predominately dual PPARγ/β(δ) activity has been described by GlaxoSmithKline.\textsuperscript{142} Dosing compound 23 in male ZDF rats at 30 mg/kg for 7 days successfully reduced plasma glucose levels (47%) and serum triglycerides (51%) and elevated HDLc (24%). However, no data regarding other key endpoints such as effects on body weight or inflammation markers was reported.

![Compound A (GlaxoSmithKline)](image)

**Figure I15:** PPARγ/δ dual agonists, A and B

More recently, researchers at Eli Lilly and Co. have described a dual PPARγ/β(δ) agonist (Compound B, Figure I15) with approximately 17-fold greater functional PPARβ(δ) potency in cell based transactivation assays compared to PPARγ.\textsuperscript{143} This dual agonist improves insulin sensitivity and reverses hyperglycemia with minimized weight gain in preclinical models of type 2 diabetes. In ZDF rats, compound 20, lowered plasma glucose levels in a dose-dependent manner and reduced plasma free fatty acids. Further studies demonstrated that compound 20 significantly enhanced whole body insulin sensitivity in response to a glucose challenge comparable to rosiglitazone. Animals treated with compound 20 and rosiglitazone at equivalent glycemic efficacy doses significantly gained weight but those animals receiving compound 20 showed ~50% less weight gain and a markedly smaller increase in fat mass. These pre-clinical studies provide evidence supporting the hypothesis that a dual PPARγ/β(δ) agonist can attenuate the undesired weight gain side effect prevalent with marketed TZDs. It remains to identify the appropriate γ/β(δ) ratios that will deliver optimal glucose control with minimized adverse side effects.
1.16.3. PPAR pan agonists

The development of dual PPARα/γ and PPARγ/β(δ) agonists has highlighted the potential therapeutic benefits gained from targeting multiple PPAR receptors in a single molecule. Combining the agonist activity of all three PPAR subtypes, the so called PPARpan agonist, into a single chemical entity could potentially deliver a drug that treats a broad spectrum of metabolic diseases by improving insulin sensitization, obesity, dyslipidemia and hypertension as well as providing beneficial effects on inflammatory markers. Improved management of overall adverse safety events may be realized through the synergistic effects of PPARα and PPARβ(δ) on fatty acid oxidation to sequester the undesired weight gain induced through PPARγ activation as well as improved cardiovascular health through the beneficial anti-atherogenic effects of PPARβ(δ). This strategy has led several pharmaceutical companies to pursue the design and development of PPARpan agonists for the treatment of type 2 diabetes and metabolic syndrome.

The development of PPARpan agonists is in its early stages and only a few compounds have progressed into clinical trials. GlaxoSmithKline's PPARpan agonist GW677954 (Figure I16) is currently being investigated in Phase II trials for the treatment of insulin resistance, hyperglycemia and dyslipidemia associated with type 2 diabetes and metabolic syndrome. Preclinical results in primates showed administration of GW677954 at 2.5 mg/kg/day for 14 days achieved greater than 30% reductions in blood glucose, insulin and triglycerides, a 25% decrease in LDLc and a 20% elevation in HDLc levels without weight gain or fluid retention.

![Figure I16: PPAR pan agonist compounds](image)

Plexxikon's compound PLX-204 is a distinct PPARpan agonist in that it is a partial agonist of PPARγ which is believed to influence the compound's overall pharmacological profile. In rodent models of type 2 diabetes, PLX-204 has shown promising results with the simultaneous lowering of serum glucose (N50%), hemoglobin A1c (∼50%), and triglycerides (4-fold) while raising HDLc levels (N25%) compared to placebo without
significant changes in body weight or hematocrit. Phase II clinical trials with PLX-204 are in progress. LY465608 (Figure 116) was originally reported as a dual PPARα/γ agonist by researchers at Eli Lilly Pharmaceuticals. Further detailed studies demonstrated that this compound also possesses significant PPARδ activity and now LY465608 is classified as a PPARpan agonist. Data compiled from various preclinical studies in rodent models of type 2 diabetes shows that LY465608 effectively lowers plasma glucose levels, improves insulin sensitivity and exerts a positive effect on lipid and cholesterol homeostasis by reducing serum triglycerides and elevating HDL cholesterol. Weight gain was observed in long term treatment of ZDF rats with LY465608, but the increase was significantly less than observed with the full PPARγ agonist rosiglitazone despite equivalent levels of glycemic control.

The prospect of PPARpan agonists to combat multiple aspects of the diabetic phenotype has high expectations. The key issue for the development of PPARpan agonists, as well as PPAR dual agonist combinations, is whether they can deliver an improved therapeutic index compared to the existing PPAR subtype selective agonists. More clinical information on these PPARpan agonists is eagerly anticipated and will be closely scrutinized as the first generation of these compounds advance through development.

1.17. Partial Agonism to the Rescue

Disappointingly, full PPAR agonists are plagued by certain adverse side effects. On the up side, partial PPAR agonists have the potential to retain the desired efficacy and beneficial effects of full PPAR agonists while diminishing the unwanted effects. Especially in case of PPARγ; partial agonists are being developed with the goal of retaining the beneficial effects of this class of agents, while diminishing their adverse effects (For example metaglidasen by Metabolex). Studies with partial agonists of PPARγ suggests that a focus on partial PPAR agonists may be a way of developing agents that have the desired efficacy of PPAR agonists and are devoid of, at least, some of their potential adverse effects.

The hypothesis “Partial agonism at both PPARα and PPARγ receptors by dual partial activators may provide a solution - resulting in the desirable responses and reducing the adverse effects” caused by the individual agonists for the treatment of T2DM attracted
our attention and prompted us to develop a research protocol to design, predict, select and synthesise such new chemical entities. Development of such agents is a very challenging endeavor, as the molecules should have affinity simultaneously for all the aimed macromolecular targets with similar binding pockets and also the fine tuning of the substituents required to obtain the optimum potency, which may finally result in desired activity profile and lesser or no adverse effects as compared to the selective ligands.

1.18. Computational methods in the design of multiple receptor activating ligands

Computational methods which has emerged as very useful and money saving tool in drug design, can be effectively employed in designing multiple receptor activating ligands. The design of multiple receptor activating ligands is very challenging as it requires structural fine tuning so that the designed molecule should bind to and activate the targeted receptors of structural similarity. The x-ray crystal structural information of the 3D-geometry of targeted receptors is advantageous for this special effort. 3D-QSAR (three dimensional structure activity relationship) techniques are applied to derive indirect binding information from the correlation between the biological activity of a training set of molecules and their 3D structures which could facilitate in designing newer molecules ‘yet to be synthesized’ as novel agents having desired therapeutic potential and safety profile. The importance of steric and electrophilic characteristics is revealed by aligning structurally similar analogues using pharmacophoric features as structural superimposition guides. The comparative molecular field analysis (CoMFA) calculates steric and electrostatic properties in the space surrounding each of the aligned molecules in a data set according to Lennard-Jones and Coulomb potentials, respectively. CoMFA develops the 3D QSAR model based on the relationship between the steric/electrostatic properties and biological activities. Comparative Molecular Similarity Indices Analysis (CoMSIA) calculates similarity indices around the molecules, with the similarity expressed in the terms of different physicochemical properties, such as steric occupancy, partial atomic charges, local hydrophobicity and hydrogen bond donor and acceptor properties. The similarities are calculated using much smoother potentials that are not as steep as the Lennard-Jones and Coulombic functions and have a finite value even at the atomic positions. Docking of designed molecules into the x-ray crystal structure of the active site of the target protein may reveal valuable approximation regarding binding of the molecules to the protein in biological system. Finally the analysis of the results
obtained from 3D QSAR and Docking experiments enable us to screen and select the best target molecules with optimum efficacies to be taken forward for synthesis and characterization.

AIM AND OBJECTIVES

The aim is to work on the hypothesis that partial PPARα/γ dual agonism may provide additive and positive synergistic pharmacology with less or no adverse effects so as to meet and overcome the issues facing with the development of dual acting agonists. Accordingly it was planned to synthesize and validate computationally heterocyclyl linked acyclic analogs of isoxazolidinediones i.e. 1,3-dicarbonyl compounds in general and β-ketoesters in particular, after designing on the basis of 3D-QSAR studies, which have almost all the structural features to act as effective insulin sensitizer and are expected to bind and activate PPARα and PPARγ, but to partial extent relative to full agonists which will eventually lead to Partial PPARα and PPARγ dual agonists for the management of hyperglycemia and hyperlipidemia.

- To build robust and significantly good predictive 3D QSAR (Comparative Molecular Field Analysis- CoMFA) models for prediction of PPAR α, γ activities.
- Design of New Chemical Entities based on the contour analysis resulted from the generated CoMFA models.
- To predict the activities and binding affinities (Docking studies) of the designed NCEs computationally.
- Final selection of the molecules for synthesis on the basis of prediction of activities and binding affinities obtained computationally with an aim to achieve partial agonism.
- Devising new synthetic strategies, which meet the requirement of “Ideal Synthesis” and also take into consideration the concept of connectivity analysis, thereby, providing new insights towards the skeletal and functionality requirement of these molecules.
- Synthesis and structural characterization of the final selected molecules.

Dual PPARα/γ agonists (tyrosine and α-aryl/alkoxy propanoic acid based molecules for which the PPARα and PPARγ activities are reported for single enantiomer) were taken from the literature to obtain a dataset which was divided into training and test set to develop 3D QSAR models. The energy optimized conformation of the crystal structure of farglitazar (a potent PPARα/γ dual agonist) extracted from the crystal structure of PPARγ
(farglitazar bound to ligand binding domain of PPARγ) was used as a template for molecular modeling. Three significant CoMFA models namely; PPARα, PPARγ and PPAR dual were developed with the training set. These were validated using the test set and can be employed to predict activities of novel PPAR agonists. The generated contours indicate steric and electrostatic features for design of novel PPAR agonists. Three CoMSIA models were also developed in a similar way. Benzimidazolyl, indolyl and acridonyl linked β-ketoester based partial PPARα/γ dual agonists were designed based on structure analysis of the known PPAR agonists and optimization of the requirements of the steric and electrostatic features of the contours of the developed CoMFA models and hydrogen bond donor and acceptor features of the contours of the developed CoMSIA models (Figure I17). All the designed benzyl and benzylidene β-ketoester based molecules were subjected to prediction of activities by the developed CoMFA models and prediction of binding affinities to the receptor active sites by docking studies at PPARα and PPARγ. Two criteria were set taking into account the predicted PPARα, PPARγ and PPAR dual activities and, the total docking scores and Gold scores resulting from the docking studies performed at the two receptors (PPARα: 1k7l, PPARγ: 1fm9) to select four best partial agonists from each series of designed NCEs. Acridonyl linked molecules were rejected by the selection processes and, benzimidazolyl/indolyl linked benzylidene/benzyl β-ketoester based NCEs were selected as best partial PPARα/γ dual activators which were put forward for synthesis (Table I7).

Table I7: The designed NCEs selected as PPARα/γ partial agonists for synthesis

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The hypothesis “Partial agonism at both PPARα and PPARγ receptors by dual partial activators may provide a solution - resulting in the desirable responses and reducing the adverse effects” caused by the individual agonists for the treatment of T2DM attracted our attention and prompted us to develop a research protocol to design, predict, select and synthesise such new chemical entities. Development of such agents is a very challenging endeavor, as the molecules should have affinity simultaneously for all the aimed macromolecular targets with similar binding pockets and also the fine tuning of the substituents required to obtain the optimum potency, which may finally result in desired activity profile and lesser or no adverse effects as compared to the selective ligands.

1.18. Computational methods in the design of multiple receptor activating ligands

Computational methods which has emerged as very useful and money saving tool in drug design, can be effectively employed in designing multiple receptor activating ligands. The design of multiple receptor activating ligands is very challenging as it requires structural fine tuning so that the designed molecule should bind to and activate the targeted receptors of structural similarity. The x-ray crystal structural information of the 3D-geometry of targeted receptors is advantageous for this special effort. 3D-QSAR (three dimensional structure activity relationship) techniques are applied to derive indirect binding information from the correlation between the biological activity of a training set of molecules and their 3D structures which could facilitate in designing newer molecules ‘yet to be synthesized’ as novel agents having desired therapeutic potential and safety profile. The importance of steric and electrophilic characteristics is revealed by aligning
structurally similar analogues using pharmacophoric features as structural superimposition guides.\textsuperscript{148} The comparative molecular field analysis (CoMFA) calculates steric and electrostatic properties in the space surrounding each of the aligned molecules in a data set according to Lennard-Jones and Coulomb potentials, respectively.\textsuperscript{149} CoMFA develops the 3D QSAR model based on the relationship between the steric/electrostatic properties and biological activities. Comparative Molecular Similarity Indices Analysis (CoMSIA) calculates similarity indices around the molecules, with the similarity expressed in terms of different physicochemical properties, such as steric occupancy, partial atomic charges, local hydrophobicity and hydrogen bond donor and acceptor properties. The similarities are calculated using much smoother potentials that are not as steep as the Lennard-Jones and Coulombic functions and have a finite value even at the atomic positions. Docking of designed molecules into the X-ray crystal structure of the active site of the target protein may reveal valuable approximation regarding binding of the molecules to the protein in biological system. Finally the analysis of the results obtained from 3D QSAR and Docking experiments enable us to screen and select the best target molecules with optimum efficacies to be taken forward for synthesis and characterization.

AIM AND OBJECTIVES

The aim is to work on the hypothesis that partial PPAR\(\alpha/\gamma\) dual agonism may provide additive and positive synergistic pharmacology with less or no adverse effects so as to meet and overcome the issues facing with the development of dual acting agonists. Accordingly it was planned to synthesize and validate computationally heterocyclyl linked acyclic analogs of oxazolidinediones \textit{i.e.} \(\alpha\)-alkoxy carboxylic acids, after designing on the basis of 3D-QSAR studies, which have almost all the structural features to act as effective insulin sensitizer and are expected to bind and activate PPAR\(\alpha\) and PPAR\(\gamma\), but to partial extent relative to full agonists which will eventually lead to \textbf{Partial PPAR\(\alpha\) and PPAR\(\gamma\) dual agonists} for the management of hyperglycemia and hyperlipidemia.

- To build robust and significantly good predictive 3D QSAR (Comparative Molecular Similarity Field Analysis- CoMSIA) models for prediction of PPAR \(\alpha, \gamma\) activities.
- Design of New Chemical Entities based on the contour analysis resulted from the generated CoMSIA models.
To predict the activities and binding affinities (Docking studies) of the designed NCEs computationally.

Final selection of the molecules for synthesis on the basis of prediction of activities and binding affinities obtained computationally with an aim to achieve partial agonism.

Devising new synthetic strategies, which meet the requirement of “Ideal Synthesis” and also take into consideration the concept of connectivity analysis, thereby, providing new insights towards the skeletal and functionality requirement of these molecules.

Synthesis and structural characterization of the final selected molecules.

Dual PPARα/γ agonists (tyrosine and α-aryl/alkoxy propanoic acid based molecules for which the PPARα and PPARγ activities are reported for single enantiomer) were taken from the literature to obtain a dataset which was divided into training and test set to develop 3D QSAR models. The energy optimized conformation of the crystal structure of farglitazar (a potent PPARα/γ dual agonist) extracted from the crystal structure of PPARγ (farglitazar bound to ligand binding domain of PPARγ) was used as a template for molecular modeling. Three significant CoMSIA models namely; PPARα, PPARγ and PPAR dual were developed with the training set. These were validated using the test set and can be employed to predict activities of novel PPAR agonists. The generated contours indicate steric and electrostatic features for design of novel PPAR agonists. Three CoMSIA models were also developed in a similar way. Benzimidazolyl, indolyl and acridonyl linked α-alkoxy carboxylic acids based partial PPARα/γ dual agonists were designed based on structure analysis of the known PPAR agonists and optimization of the requirements of the steric and electrostatic features of the contours of the developed CoMFA models and hydrogen bond donor and acceptor features of the contours of the developed CoMSIA models (Figure I17). All the designed benzyl and benzylidene Heterocyclyl linked TZD’s (Thiazolidinedione) and DEM(Diethyl malonate) based molecules were subjected to prediction of activities by the developed CoMSIA models and prediction of binding affinities to the receptor active sites by docking studies at PPARα and PPARγ. Two criteria were set taking into account the predicted PPARα, PPARγ and PPAR dual activities and, the total docking scores resulting from the docking studies performed at the two receptors (PPARα: 1k7l, PPARγ: 1fm9) to select four best partial agonists from each series of designed NCEs. (Table I7a and b).
**Table I7a:** The designed NCEs selected as PPARα/γ partial agonists for synthesis

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**Table I7b:** The Other NCEs selected as PPARα/γ partial agonists for synthesis

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Figure 117: a) Steric and electrostatic solid contours (CoMFA) of the PPARα model. b) Steric and electrostatic solid contours (CoMFA) of the PPARγ model. c) Hydrogen bond donor and acceptor solid contours (CoMSIA) of the PPAR dual model.

Farglitazar shown as the standard ligand, special features taken into account for the design of the NCEs as partial agonists have been indicated. Green (contribution level 80%) and yellow (contribution level 20%) polyhedra indicate regions where more steric bulk or less steric bulk, respectively, will enhance the activity. Positive potential favoured areas for the activity are shown in blue (contribution level 80%) and disfavoured areas are shown in red (contribution level 20%). Magenta polyhedra (contribution level 80%) indicate regions where hydrogen bond donor groups are favourable for the activity and yellow-brown regions disfavour (contribution level 20%) the character. Orange polyhedra (contribution level 80%) indicate regions where hydrogen bond acceptor groups are favourable for the activity and cyan regions (contribution level 20%) indicate areas where the character is disfavored.
A common rational synthetic route with easily available starting materials and using routinely used chemistry was followed to synthesize the selected benzimidazolyl, indolyl and acridonyl linked α-alkoxy carboxylic acids based NCEs is reported in the present work. In addition to this benzimidazolyl and indolyl linked benzylidene and benzyl containing TZD’s (Thiazolidinediones) and DEM (Diethylmalonates) based ONCEs were also prepared in the present work. N-methyl benzimidazolyl linked aldehyde (L1), N-methyl indolyl aldehyde (L2) and Acridinyl linked aldehyde (L3) were prepared as an important intermediates for the synthesis of benzimidazolyl, indolyl and acridinyl linked α-alkoxy carboxylic acids based final selected molecules. Also these intermediate aldehydes in case of benzimidazole and indole were also converted into benzimidazolyl and indolyl linked benzylidene TZD’s and DEM based compounds. Further indolyl linked benzylidene DEM were reduced catalytically to indolyl linked benzyl DEM based compounds. Another α-bromoester route opted to synthesize benzimidazolyl and indolyl linked benzyl TZD’s based compounds.

**Figure I18:** General Scheme for the Synthesis of Designed and Selected NCEs
The series of heterocyclyl linked α-alkoxy carboxylic acids was obtained from the aldehyde by Wittig reaction to form the homologated vinyl ether followed by acetal formation with different suitable alcohol, conversion of acetal to α-alkoxy cyano by reaction with trimethylsilyl cyanide and on hydrolysis gives the final heterocyclyl linked α-alkoxy carboxylic acids, (F1a-d) in case of benzimidazole, (F2c-d) in case of indole and (F3c-d) in case of acridone (Figure I18). Other series of heterocyclyl linked TZD’s were prepared by two different routes, heterocyclyl linked benzylidine TZD’s, (F4a) in case of benzimidazole and (F5a) in case of indole were prepared by the Knovenagel type condensation of aldehyde with TZD's using piperidinium acetate in toluene as solvent under reflux condition (Figure I19). Another route used to prepared heterocyclyl linked benzyl TZD’s from heterocyclyl linked α-bromoester. Meerwein arylation of the aniline derivatives gave α-bromoester, which were treated with thiourea to afford the heterocyclyl linked iminothiazolidindiones. Acid hydrolysis of iminothiazolidindiones gave the desired heterocyclyl linked benzyl TZD’s (F4b) in case of benzimidazole and (F5b) in case of indole via Mitsunobu coupling, in good yield.

The series of heterocyclyl linked DEM ethyl ester were prepared by Knovenagel condensation between aldehyde and DEM gave the heterocyclyl linked benzildine DEM ethyl ester (F6a) in case of benzimidazole and (F7a) in case of indole, which on catalytic hydrogenation with 10% Palladium on carbon gave the heterocyclyl linked benzyl DEM ethyl ester (F6b) in case of benzimidazole and (F7b) in case of indole (Figure I19).