The review of literature pertaining to the study “Diagnostic approaches and interventional strategies of type 1, type 1.5 and type 2 diabetes” is discussed under the following headings:

2.1 DIABETES IN THE THIRD WORLD

2.2 TYPES OF DIABETES

2.3 DIAGNOSTIC APPROACHES FOR DIABETES

2.4 COMPLICATIONS OF DIABETES

2.5 INTERVENTIONS FOR DIABETES

2.1 DIABETES IN THE THIRD WORLD

Diabetes, for the whole world is not an epidemic anymore but has turned into pandemic (Lal et al., 2009). The worldwide survey reported that diabetes is affecting nearly 10% of the population (Doss et al., 2009). According to the World Health Organization (WHO) projections, the prevalence of diabetes is likely to increase by 35% by the year 2025 (Asaduzzaman et al., 2010). India has a high prevalence of diabetes and the numbers are increasing at an alarming rate. In India alone, diabetes is expected to increase from 40.6 million in 2006 to 79.4 million by 2030 (Mehta et al., 2009).

2.2 TYPES OF DIABETES

The global rise in diabetes is due to population growth, ageing, increasing trends towards an unhealthy diet, obesity and sedentary lifestyles (Ahmed et al., 2010).
2.2.1 Type 1 diabetes

2.2.1.1 Prevalence

Type 1 insulin-dependent diabetes is present in 5–10 percent of all diabetics, but is increasing in adolescent minority groups (Maiese et al., 2007). The prevalence of type 1 diabetes increases with age and the overall incidence of the disease may be increasing (Lueder and Silverstein, 2005).

2.2.1.2 Etiology

Genetic predisposition, autoimmunity and viral infection are the main etiological factors implicated in the pathogenesis of type 1 diabetes mellitus (Muthukrishnan et al., 2007). Type 1 diabetes, which may develop at any age is a chronic autoimmune disease, characterized by irreversible autoimmune destruction of the insulin secreting β-cells of the islets in the pancreas. There is hepatic overproduction of glucose by glycogenolysis and gluconeogenesis and decreased cellular uptake of glucose from the circulation. Type 1 diabetes requires life long treatment with exogenous insulin for survival (Mehra et al., 2007).

2.2.2 Type 1.5 diabetes

2.2.2.1 Prevalence

Type 1.5 diabetes is usually diagnosed after 35 years of age and there is no immediate need for insulin (Goel et al., 2007). Type 1.5 diabetics are phenotypically similar to type 2 diabetic patients but they are also positive for the autoantibody commonly seen in type 1 diabetes. Approximately 10% to 30% of adults with type 2 diabetes test positive for autoantibodies, depending on the age and ethnicity of the study group (Stenstrom et al., 2005). This group of phenotypic adult type 2 diabetic patients (approximately 10%) are said to have latent autoimmune diabetes in adults (LADA) or type 1.5 diabetes or type 1½ diabetes (Palmer et al., 2005).
2.2.2.2 Etiology

Patients with type 1.5 diabetes have an autoimmune process similar to that found with type 1 diabetes. Though patients with type 1.5 diabetes possess genes such as HLA DR2, DQB1*0602, which appear to protect an individual from developing diabetes, the beta-cells become so inflamed by repetitive environmental insults that they begin to succumb to autoimmune destruction within the beta-cells. This immune-mediated destruction of beta-cells in type 1.5 diabetics leads to insulin dependency more rapidly than in type 2 diabetes, but the more attenuated genetic and immune factors associated with type 1.5 diabetes as compared with type 1 diabetes lead to an older age at onset and a slower progression to insulin dependency (Unger, 2008a).

2.2.3 Type 2 diabetes

2.2.3.1 Prevalence

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95% of all diagnosed cases of diabetes. In type 2 diabetes, the body does not produce enough insulin or the cells ignore the insulin (Badyal and Kaur, 2008). The incidence of type 2 diabetes is increasing among all age groups, including adolescents, among whom type 2 diabetes was formerly very rare (Metzger, 2006).

2.2.3.2 Etiology

Type 2 diabetes occurs usually in individuals over 40 years of age and dramatically increases as a result of changes in human behavior and increased body mass index (Elmer et al., 2004). The increasing proportion of the aging population, consumption of calorie rich diet, obesity and sedentary lifestyle have led to a tremendous increase in the number of diabetics worldwide (El-Shenawy and Abdel-Nabi, 2006). This form of diabetes, previously referred to as non–insulin dependent diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin
resistance and usually have relative (rather than absolute) insulin deficiency. At least initially and often throughout their lifetime, these individuals do not need insulin treatment to survive. Most patients with this form of diabetes are obese and obesity itself causes some degree of insulin resistance. This form of diabetes frequently goes undiagnosed for many years (American Diabetes Association, 2010a). Impaired intrauterine growth / nutrition results in the programming of systems that regulate insulin sensitivity, insulin secretion and energy storage and utilization throughout the lifetime of the individual (Metzger, 2006). The familial predisposition to type 2 diabetes is mediated by both genetic and intrauterine environmental factors (Seshiah et al., 2008). The effect of insulin resistance on the endothelial cells is shown in Figure 1.

FIGURE 1

OVERPRODUCTION OF MITOCHONDRIAL REACTIVE OXYGEN SPECIES IN INSULIN RESISTANCE

<table>
<thead>
<tr>
<th>Adipocyte</th>
<th>Endothelial Cell</th>
</tr>
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<tbody>
<tr>
<td>IR</td>
<td></td>
</tr>
<tr>
<td>FFA</td>
<td>FFA Oxidation</td>
</tr>
<tr>
<td>AGE</td>
<td></td>
</tr>
<tr>
<td>GlcNAc</td>
<td></td>
</tr>
<tr>
<td>NFκB</td>
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</tbody>
</table>

FFA - Free fatty acid  
ROS - Reactive oxygen species  
AGE - Advanced glycation end products  
PKC - Protein kinase C  
GlcNAc - N-acetylglucosamine  
IR - Insulin resistance  
NFκB - Nuclear Factor-KappaB
### Clinical features of type 1, type 1.5 and type 2 diabetes

#### TABLE 1

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>TYPE 1 DIABETES</th>
<th>TYPE 1.5 DIABETES</th>
<th>TYPE 2 DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoacidosis</td>
<td>Will develop rapidly unless patient receives insulin replacement therapy</td>
<td>Absent at diagnosis, but may be present when patient becomes severely insulinopenic</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>Increased risk of cardiovascular morbidity and mortality. High incidence rates compared with euglycemic individuals</td>
<td>Risk 2–4 times higher than individuals who are euglycemic</td>
<td>Risk 2–4 times higher than individuals who are euglycemic</td>
</tr>
<tr>
<td>Microvascular complications</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Autoimmune destruction of pancreatic beta-cells</td>
<td>Latent autoimmune destruction of pancreatic beta-cells</td>
<td>Peripheral insulin resistance, reduced pancreatic beta-cell mass and function and reduced insulin secretion</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Glutamic acid decarboxylase (GAD)-65 autoantibodies, Islet-cell antigen-2 and insulin autoantibodies. Typically are positive for all three autoantibodies.</td>
<td>GAD-65 autoantibody is typically the only one detected</td>
<td>Negative</td>
</tr>
<tr>
<td>Insulin requirements for treatment</td>
<td>Insulin is required from the time of diagnosis</td>
<td>Insulin should be initiated as soon as the patient develops autoantibodies</td>
<td>Usually late in the disease when the remaining beta-cell mass and function can no longer support acceptable glycemic control achieved by oral agents or incretin mimetics</td>
</tr>
</tbody>
</table>

(Unger, 2008b)
The clinical features of type 1, type 1.5 and type 2 diabetes are presented in Table 1.

2.3 DIAGNOSTIC APPROACHES FOR DIABETES

Diagnosis of diabetes at an earlier stage is important in preventing diabetes related complications. The tests commonly used to diagnose diabetes are fasting blood glucose, postprandial blood glucose and HbA1c. Recent clinical studies have shown that acute glucose swings in addition to chronic hyperglycemia can trigger oxidative stress mechanisms in type 2 diabetes, demonstrating the importance for therapeutic interventions during acute and sustained hyperglycemic episodes (Monnier et al., 2006). Numerous experimental and clinical observations have indicated that hyperglycemia may directly or indirectly contribute to excess formation of free radicals (El-Shenawy and Abdel-Nabi, 2006).

2.3.1 Blood sugar as a biomarker for diabetes

The criteria for the diagnosis of diabetes mellitus in clinical practice is fasting plasma glucose that is equal or greater than 126 mg/dL or two-hours post prandial plasma glucose greater than 200 mg/dL (Nwankwo et al., 2008). With good glycemic control, several long-term, life-threatening complications of diabetes can be prevented (Shabbidar et al., 2006).

2.3.2 HbA1c as a biomarker for glycemic control

Glycated hemoglobin (HbA1c) is the best measure of long-term glycemic control, since it represents the average blood glucose levels over several months (Thomas and Elliott, 2009). Glycemic control is defined as excellent if the measured HbA1c is < 6.5 %, very good if HbA1c is 6.5 to 7.0 %, good if HbA1c is 7.1 to 7.5 %, acceptable if HbA1c is 7.6 to 8.0 % and poor if HbA1c is > 8.0 % (Al-Shoumer et al., 2008).
2.3.3 C-peptide as a biomarker for differential diagnosis of type 1 and type 2 diabetes

Type 1 diabetes is distinguished from type 2 diabetes on the basis of the need for exogenous insulin for survival (Maghsoudi et al., 2008). C-peptide level may be used to distinguish people with new-onset type 2 diabetes from those with type 1 diabetes in addition to obesity, family history of type 2 diabetes and absence of glutamic acid decarboxylase (GAD)-65 antibodies (Aggarwal et al., 2010).

**FIGURE 2**

**SCHEMATIC REPRESENTATION OF THE MOLECULAR MECHANISM OF C-PEPTIDE ACTIVITY**

Vascular muscle cell | Blood
---|---
- Increases cyclic GMP
- Vasodilatation
- Reduction of microvascular resistance
- Increase in erythrocyte flexibility
- Decrease in cell rigidity
- Decrease in cell adhesions

G-protein - guanine nucleotide-binding proteins | PKC - Protein kinase C
---|---
eNOS - endothelial nitric oxide synthase | NO - nitric oxide

(Forst et al., 2008)
C-peptide has been widely accepted as the most appropriate measure of residual β-cell function because it is secreted on a basis equimolar to insulin and unlike the latter, is not removed in the first pass through the liver (Panero et al., 2009). Because C-peptide is secreted from islet cells into the circulation in equimolar concentrations with insulin and is not extracted by the liver, many investigators have used C-peptide levels as a biomarker of β-cell function (Ko et al., 2009). Fasting C-peptide level < 0.6 ng/ml is considered as an indicator of poor insulin reserve. Hence, C-peptide is a useful guide in initiating therapy to prevent complications (Abdullah et al., 2010). The cellular signaling effects of C-peptide is depicted in Figure 2.

2.3.4 LADA risk score for identifying susceptible type 1.5 diabetes

The clinical characteristics predictive of type 1.5 diabetes are shown in Table 2.

**TABLE 2**

**CLINICAL CHARACTERISTICS PREDICTIVE OF TYPE 1.5 DIABETES**

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50 years</td>
</tr>
<tr>
<td>Acute symptoms of hyperglycemia (polydypsia, polyuria, or unintentional weight loss)</td>
</tr>
<tr>
<td>Body mass index &lt; 25 kg per m²</td>
</tr>
<tr>
<td>Family history of autoimmune disease (thyroid disorders, celiac disease, type 1 diabetes, rheumatoid arthritis or any other form of autoimmune disorder)</td>
</tr>
<tr>
<td>Personal history of autoimmune disease (thyroid disorders, celiac disease, type 1 diabetes, rheumatoid arthritis or any other form of autoimmune disorder)</td>
</tr>
</tbody>
</table>

The presence of at least two of these clinical features (LADA risk score ≥ 2) was found to have 90 % sensitivity and 71 % specificity for identifying diabetic patients affected by type 1.5 diabetes. According to Fourlanos et al. (2006), at diagnosis of diabetes, 63 % of type 1.5 diabetics...
and 19% of type 2 diabetics were found to be below 50 years of age, 66% of type 1.5 diabetics and 24% of type 2 diabetics were found to have acute symptoms of hyperglycemia, 33% of type 1.5 diabetics and 13% of type 2 diabetics were found to have a body mass index < 25 kg per m$^2$, 46% of type 1.5 diabetics and 35% of type 2 diabetics were found to have a family history of autoimmune disease and 27% of type 1.5 diabetics and 12% of type 2 diabetics were found to have a personal history of autoimmune disease. The presence of two or more of the five features at diagnosis had a 90 percent sensitivity and a 71 percent specificity for detecting LADA via autoantibody testing. Patients with one or no feature were unlikely to have LADA (99 percent negative predictive value).

2.3.5 GADA positivity as a biomarker for differential diagnosis of type 1.5 and type 2 diabetes

Type 1.5 diabetes and type 2 diabetes populations can be distinguished from each other based on clinical features, but a large degree of overlap exists between the two types of diabetes. Hence, the use of immunogenetic markers, in particular the measurement of autoantibodies, remains the gold standard for identifying type 1.5 diabetic patients. Identification of these patients is clinically relevant to their management as the early use of insulin resulted in β-cell preservation in several pilot studies (Gilliam and Palmer, 2006). Type 1.5 diabetes can be distinguished from type 2 diabetes by blood tests for antibodies. Type 1.5 diabetes is diagnosed by the presence of pancreatic auto-antibodies, such as glutamic acid decarboxylase (GAD) antibodies in an adult initially presenting with non-insulin dependent diabetes (Brophy et al., 2008).

2.4 COMPLICATIONS OF DIABETES

Severe long term abnormalities can result such as eye complications, heart disease, kidney and foot problems if blood sugar levels are poorly controlled (Brophy et al., 2007). These complications are of two types-
microvascular complications that include retinopathy, nephropathy, neuropathy and peripheral vascular disorders and macrovascular complications that include cardiovascular and cerebrovascular disorders.

The complications of diabetes can involve multiple systems throughout the body that are susceptible to the detrimental effects of oxidative stress and apoptotic cell injury (Maiese et al., 2010). Innovative strategies are necessary for the implementation of new treatments for diabetes that are generated by further understanding the cellular pathways that govern the pathological consequences of diabetes. Furthermore, a significant portion of the population has undiagnosed diabetes, illustrating the need for improved early diagnosis (Rebecchi et al., 2009). Diabetes also leads to long-term complications throughout the body involving cardiovascular, renal and nervous disorders (Daneman, 2006). Plasma C-peptide concentrations provide an indirect measure of the insulin secretory reserve. Low serum level of C-peptide is a possible factor of the progression of diabetic angiopathies (Sari and Balci, 2005). Accumulated clinical experience indicates that there is an inverse association between beta-cell function and chronic complications of autoimmune diabetes—higher the C-peptide levels (an indirect measure of viable beta-cell function), lower the incidence of microvascular complications of autoimmune diabetes (Couri et al., 2009). The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vessels (Chandramohan et al., 2009).

The importance of protecting the body from hyperglycemia cannot be overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both type 1 and type 2 diabetes. Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) (Fowler, 2008).
2.4.1 Causes of diabetic complications

The complications of diabetes are the result of multiple factors in particular, cellular pathways that lead to diabetes. The complications of diabetes have been tied to oxidant stress (Szabo, 2009). Studies with diabetic animals have shown that oxidative stress leads to DNA damage in renal cortical cells (Simone et al., 2008). Although early effects of elevated glucose may increase the presence of potentially protective pathways, more prolonged exposure of elevated glucose with the rise in insulin levels can lead to reactive oxygen species (ROS) and can be detrimental even if glucose levels are controlled (Barbosa et al., 2008).

2.4.2 Mechanisms leading to complications

Oxidative stress may promote the onset of diabetes by decreasing insulin sensitivity and destroying the insulin-producing cells. ROS can penetrate through cell membranes and cause damage to β-cells of pancreas (Chen et al., 2005). A high fat diet or free fatty acids also has been shown to release ROS and contribute to mitochondrial DNA damage and impaired pancreatic β-cell function (Rachek et al., 2006). Oxidant stress and ROS exposure can result in the opening of the mitochondrial membrane permeability transition pore, reduce mitochondrial NAD⁺ stores and result in apoptotic cell injury (Chong and Maiese, 2005). Free fatty acids also can lead to ROS release, mitochondrial DNA damage and impaired pancreatic β-cell function (Li et al., 2008). The development of diabetes has been associated with a decrease in the levels of mitochondrial proteins and mitochondrial DNA (Choo et al., 2006).

Long standing diabetes mellitus is associated with an increased prevalence of microvascular and macrovascular diseases (Mehta et al., 2009). Cellular pathways in diabetes are closely associated to cellular energy maintenance and intact mitochondrial function (Newsholme et al., 2007).
Figure 3 presents the protein kinase C (PKC) pathway and polyol pathway in the pathogenesis of diabetic complications.

**FIGURE 3**

SCHEMATIC REPRESENTATION OF PROTEIN KINASE C AND POLYOL PATHWAYS IN THE PATHOGENESIS OF DIABETIC COMPLICATIONS

**Protein Kinase C Pathway**

- Glucose
- Glyceraldehyde-3-phosphate (GAP)
- Diacylglycerol (DAG)
- Fructose-3-phosphate
- 3-Deoxyglucosone

**Polyol Pathway**

- Glucose
- Aldose reductase (AR)
- Sorbitol dehydrogenase (SDH)
- Fructose-3-phosphate
- 3-Deoxyglucosone

**Diagram Labels**

- GAP - glyceraldehyde-3-phosphate
- AR - aldose reductase
- DAG - diacylglycerol
- SDH - sorbitol dehydrogenase
- PKC - protein kinase C
The pathologic consequences of increased advanced glycation end products (AGE) precursors and increased flux through hexosamine pathway are depicted in Figure 4 and Figure 5 respectively.
The DNA damage induced by ROS through Poly (ADP-ribose) polymerase (PARP) and Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is depicted in figure 6.
2.5 INTERVENTIONS FOR DIABETES

Patients with type 2 diabetes and type 1.5 diabetes are frequently confused with each other and as usually sulfonylureas which are prescribed to type 2 diabetics without overweight or obesity are also prescribed to patients with type 1.5 diabetes. This treatment can cause depletion of still remaining endogenous insulin reserves showing poor basal and postprandial glycemic control when compared with those controlled with insulin therapy (Fielding et al., 2007). With an accurate diagnosis of type 1.5 diabetes, the administration of oral antidiabetic drugs could be avoided (Bermudez et al., 2010). Metformin treatment for one year was found to improve HbA1c in type 1.5 diabetics, but the decrease in insulin one year later was greater in these patients.
According to Kirk and Namak (2009), the need for insulin is linked to the degree of autoimmunity and β-cell failure.

Innovative strategies are necessary for the implementation of new treatments for diabetes that are generated after the understanding of cellular pathways that govern the pathological consequences of diabetes. Furthermore, a significant portion of the population has undiagnosed diabetes, illustrating the need for improved early diagnosis (Rebecchi et al., 2009). Once diabetes is diagnosed, adequate treatment requires a significant amount of resources for patients i.e. access to glucometers, medications, regular access to health care and referral to specialists for management of complications. Life style changes/interventions and drugs are the current strategies that exist to prevent or reduce the onset of diabetes (Mehta et al., 2009). These complications of diabetes are the result of multiple factors, but argue for the implementation of novel drug development strategies (Szabo, 2009). Type 1 diabetes is the classical form of diabetes and these subjects cannot survive without insulin treatment. Type 2 diabetes is a group of genetically determined diseases which may be controlled by diet, hypoglycemic agents and/or exogenous insulin (Ahmed et al., 2010).

2.5.1 Diet

Diet therapy is the cornerstone of treatment in diabetes, especially for type 2 diabetes patients. It is difficult to maintain dietary control for long periods, but dietary control is important and necessary (Shabbidar et al., 2006).

With more sedentary lives and more available food, our waistlines are growing and chronic diseases related to nutrition – like diabetes and cardiovascular disease are on the rise. Our diets, although abundant, are relatively less healthy than in the past (Livesey and Taylor, 2008). Nutrition therapy is an essential component of successful diabetes management and carbohydrate accounts for the largest percentage of energy intake.
Improvement in glycemic control achieved through dietary interventions would lessen the risk of diabetic complications, improve quality of life for people with diabetes, increase their life expectancy and minimise, or even avoid, the necessity for expensive medications and diabetic health care. Different carbohydrate foods have different effects on blood glucose and can be ranked by the overall effect on the blood glucose levels using the glycemic index (Thomas and Elliott, 2009). The glycemic index (GI) is a system for ranking carbohydrates according to their effects on postprandial glucose concentrations. Although low-GI foods are known to produce less postprandial hyperglycemia and hyperinsulinemia than are high-GI foods, the role of low-GI foods in the prevention and treatment of diabetes remains unclear (Miles, 2008). The glycemic index reflects the glycemic response for a fixed amount of carbohydrate, while the glycemic load reflects the total glycemic response by accounting for the quantity and type of carbohydrate consumed. Glycemic index may be beneficial in improving weight regulation, postprandial glucose level, insulin action and risk for cardiovascular disease (Miller et al., 2009). Both the amount and the type of carbohydrate induce distinct plasma glucose and insulin responses that are quantified by the glycemic index (Bove et al., 2006).

In the past, diabetic patients were advised to avoid carbohydrates, but it is now accepted and recommended by diabetic associations that 60-70% of the calories in a diabetic diet should be provided by carbohydrate and that carbohydrate should be in the form of complex polysaccharides (starch) and nonstarch polysaccharide (dietary fiber). Intake of food high in dietary fiber (such as whole grain, unrefined cereals and legumes) instead of more rapidly digested forms of carbohydrates improve glycemic control because of the slow release of carbohydrate due to the high fiber content (Weickert et al., 2006). Fiber, particularly soluble fiber, has repeatedly been shown to decrease postprandial blood glucose and insulin response, both in persons with diabetes and in those without the disease.
Carbohydrate from test food

\[
GI = \frac{\text{Area under blood glucose increment for 50 g glucose}}{\text{Area under blood glucose increment for 50 g glucose}} \times 100
\]

(Gopalpura et al., 2007).

### 2.5.2 Physical activity

During the past 50 years several studies have underlined the central role of physical exercise in the management of patients with both type 1 and type 2 diabetes mellitus. Children, adolescents and young adults with diabetes must be educated on the metabolic changes occurring during physical activity in order to acquire the ability to individually modulate their diet and insulin therapy before and after exercise (Giannini et al., 2007). Physical activity has acute and chronic effects on glucose, lipid and protein metabolism. In type 1 diabetic subjects, the lack of physiological inhibition of insulin secretion during exercise results in a potential risk of hypoglycemia. On the other hand, exercise-induced activation of counter regulatory hormones might trigger an acute metabolic derangement in severe insulin-deficient subjects. Long-term effects of regular exercise are particularly advantageous for type 2 diabetic patients. Regular aerobic exercise reduces visceral fat mass and body weight without decreasing lean body mass, ameliorates insulin sensitivity, glucose and blood pressure control, lipid profile and reduces the cardiovascular risk (Feo et al., 2006).

### 2.5.3 Oral antidiabetic drugs

Pharmacologic treatment of type 2 diabetes to improve glycemic control, to control hypertension and to reduce blood lipid concentrations reduces the occurrence and progression of diabetes complications (Wolever et al., 2008). With a better understanding of the molecular mechanisms of diabetes, patients with genetic defects encoding the β-cell pathways were found to be more responsive to sulphonylurea therapy than to metformin treatment. Phenotyping and targeted therapy can minimize risk and maximize efficacy (Ko et al., 2009).
2.5.3.1 α- Glucosidase inhibitors

Alpha- glucosidase inhibitors (AGIs) such as voglibose are known to inhibit disaccharide hydrolysis in intestinal mucosa, thereby reducing the hydrolysis of disaccharides to monosaccharides. This impedes absorption of carbohydrate and therefore reduces glucose levels in type 2 diabetes patients. Voglibose treatment was found to prevent the increase in body weight (Negishi et al., 2008). Alpha- glucosidase inhibitors (acarbose, miglitol, voglibose) are widely used in the treatment of patients with type 2 diabetes that have a lowering effect on postprandial blood glucose and insulin levels (Van de Laar et al., 2005).

2.5.3.2 Biguanides

Metformin, a biguanide, is one of the most commonly used first-line antihyperglycemic agents in the treatment of type 2 diabetes, which acts primarily by lowering hepatic glucose production and may also improve insulin resistance (Charbonnel et al., 2006). Metformin has been approved for use in the treatment of type 2 diabetes for nearly three decades in many countries. Numerous studies have shown metformin to be highly effective and safe in the treatment of type 2 diabetes. Metformin is the only antidiabetic agent that has been shown to reduce mortality in patients newly diagnosed with type 2 diabetes and the only antidiabetic agent not shown to be associated with increased morbidity and mortality in patients with cardiac disease, including heart failure (Eurich et al., 2009).

2.5.3.3 Third generation sulphonylurea drug

The sulfonylureas stimulate insulin release from pancreatic β cells and have been a cornerstone of type 2 diabetes pharmacotherapy for over 50 years. Although sulfonylureas are effective antihyperglycemic agents, interindividual variability exists in drug response namely pharmacodynamics, disposition namely pharmacokinetics and adverse effects (Aquilante, 2010). The third generation of sulphonylurea, glimepiride stimulates nitric oxide
production and thereby inhibits cytokine-induced nuclear factor (NF)-κB activation in endothelial cells and confers protective effects on vascular endothelial cells. They are preferable sulphonylurea agents in the treatment of type 2 diabetes and vascular diseases (Jojima et al., 2009).

2.5.3.4 Thiazolidinediones

Pioglitazone, a member of the thiazolidinedione drug family, is widely used for the treatment of type 2 diabetic patients. This antihyperglycemic drug is a selective ligand of the nuclear transcription factor, peroxisome proliferator-activated receptor (PPAR-γ). It interacts with PPAR-γ receptors that are located predominantly in adipose, hepatic and skeletal muscle cells. Modulation of these receptors adjusts the regulation of genes involved in metabolic control and also reduces insulin resistance (Smith et al., 2005). PPAR-γ receptor activation increases glucose and lipid uptake, increases glucose oxidation, decreases free fatty acid concentration and decreases insulin resistance. PPAR-γ receptor activation also stimulates adipocyte differentiation resulting in more and smaller fat cells. Hepatic fat is significantly decreased with improvements in glycemic control and correction of dyslipidemia. Insulin action is improved by various mechanisms: increasing expression, synthesis and release of adiponectin from fat cells; increasing expression of genes that increase glucose oxidation and lowering plasma free-fatty acid levels (Gupta et al., 2009).

2.5.3.5 Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors offer a new therapeutic approach for the management of patients with type 2 diabetes (Charbonnel et al., 2006). Sitagliptin is a once-daily, orally active, competitive and fully reversible inhibitor of dipeptidyl peptidase-4, the enzyme that is responsible for the rapid degradation of the incretin hormone glucagon-like peptide-1. It is the first in this new class of antihyperglycemic agents to gain regulatory approval for the treatment of type 2 diabetes, both as a monotherapy and for use in combination with metformin
or a thiazolidinedione. Sitagliptin improves glycemic control by reducing both fasting and postprandial glucose concentrations, leading to clinically meaningful reductions in glycosylated hemoglobin levels (Deacon, 2007).

2.5.4 Insulin

Insulin is the primary treatment for all patients with type 1 diabetes and for type 2 diabetic patients who cannot adequately control their blood sugar by diet and exercise or by oral hypoglycemic agents (Nathan et al., 2006).

2.5.4.1 Newer Insulins

Novel long and short acting insulin analogues, the so-called ‘designer insulins’, developed through genetic engineering in the 1990s, paved the way for more physiological insulin therapy. Newer insulins are faster acting preprandial insulin or longer acting basal insulin which provide a constant concentration with no peak increase in insulin level. Newer analogues exist as monomers and are absorbed much faster (insulin aspart or lispro) or absorbed very slowly (insulin glargine or detemir). The newer analogues have increased the stability, less variability and selective action which will help in developing individualized treatment suitable to specific patient characteristics and will improve glycemic control (Kaur and Badyal, 2008).

Short-acting analogues

These have rapid onset and shorter duration of action. The peak of onset corresponds more closely with the postprandial glucose peak. Therefore, they can be administered immediately before meals. This avoids postprandial hypoglycemia that occurs due to long duration of action of soluble insulin. The shorter duration of action of these analogues leads to lower incidence of hypoglycemia. The agents are insulin lispro, insulin aspart and insulin glulisine (Mannucci et al., 2009).

Long-acting analogues

Ideal basal insulin has long duration of action and provides 24 hour control with minimum variation in absorption and has to be given once a day.
Two long acting insulin analogues have been developed—insulin glargine and insulin detemir. They have made significant improvements in the management of type 1 diabetes both in terms of improvement in glycemic control and in reducing hypoglycemia rates (Philips and Scheen, 2006).

**Other newer insulins**

Albulin is the newest insulin analogue. Albulin displays characteristics of a potent long acting insulin analogue that can be evaluated for use as a novel insulin therapy for patients with insulin-dependent diabetes (Duttaroy et al., 2005). Inhaled insulin drugs have faster onset of action, even faster than intravenous route and large surface area of lungs causes more systemic absorption. If long-term safety and efficacy are confirmed, inhalation will become the first non-subcutaneous route of insulin administration for widespread clinical use. Exubera, an insulin product for pulmonary delivery in powder form is the first inhalational drug to be approved by food and drug administration (Mandal, 2005).

2.5.5 **Plant compounds as antidiabetic agents**

The use of plant by man for the treatment of diseases is an age long practice (Prohp et al., 2008). Diabetes mellitus was known in ancient times and some medicinal plants have been used for its control in traditional medicine (Mukherjee et al., 2006). The oral antihyperglycemic agents currently used in clinical practice have characteristic profiles of serious side effects. This leads to increasing demand for herbal products with antidiabetic activity and less side effects (Doss et al., 2009). The efficacy of plants for the management of diabetes requires confirmation and WHO has recommended the assessment of traditional plant