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# REVIEW ON DIABETES MELLITUS

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**ABSTRACT**

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high levels of glucose in blood due to non-secretion of insulin or insulin insensitivity. However, different types of DM are available. Out of these, type 1 diabetes mellitus (Type 1 DM) and type 2 diabetes mellitus (Type 2 DM) are now recognized as serious global health problem, growing rapidly worldwide and taking its place as one of the main threats to human health in the 21st century. The International Diabetes Federation (IDF) estimated that, the developing countries like India, already top of the diabetic league. Now a day, more than 90% of diabetic patients suffer from type 2 DM, which is characterized by insulin resistance and hyperglycemia. Several epidemiological and clinical studies indicate a direct relationship between hyperglycemia and long term microvascular and macrovascular complications, which develop as the disease progresses, gradually decrease quality of life of diabetic patients. Therefore, it is essential to control blood glucose levels during the early stages of the disease. Therapy for DM primarily has been aimed at improving glycemic control via a combination of diet, exercise and current therapeutic agents such as insulin formulations, sulfonylureas, metformin, acarbose, thiazolidine-2,4-diones, glucagon like peptide-1 analog and dipeptidyl peptidase-4 or IV inhibitors.

**Key words:** Diabetes mellitus, International Diabetes Federation, Hyperglycemia.

## INTRODUCTION

In our daily life energy is necessary to do any work and a carbohydrate, particularly glucose is required for the production of energy in the living body. Here, the blood acts as vehicle to provide glucose to all the different types of cells. When glucose enters into the cell, insulin acts like key for entrance through the cell membranes. Due to deficiency of insulin, enough glucose cannot enter the cells from the blood in circulation and thereby causing higher glucose (or sugar) level in blood, and when this situation persists for longer period of time over days, months or even years, a complex pathological condition develops and this condition is called as diabetes [1].

The term diabetes was coined by ‘Aretaeus of Cappadocia, (81-138 A.D.). Which is derived from the Greek “diabainein” that literally means “passing through” or “syphon”, a reference to one of major symptoms of diabetes-excessive urine production. In 1674 Thomas Willis added the word, “mellitus” to the disease, a word from Latin meaning “honey”, a reference to the sweet taste of urine due to presence of glucose [2,3]. In Vedic medical treatises from ancient India identified and classified it as Madhumeha or honey urine. The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment " sweet urine disease[4].

DM is a chronic metabolic disorder characterized by high levels of glucose in blood due to non-secretion of insulin or insulin insensitivity. Either of the factors causes disturbances in carbohydrate, lipid and protein metabolism [5]. Moreover, type 1 DM and type 2 DM are now recognized as serious global health problem, growing rapidly worldwide and taking its place as one of the main threats to human health in the 21st century [6,7].

## GLOBAL PREVALENCE OF DM

The global increase in the prevalence of DM is due to population growth, aging, urbanisation and an

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increase of obesity and physical inactivity. The IDF estimated that the number of people living with diabetes has soared to 366 million, representing 8.3% of the global adult population. This number is projected to increase to 552 million people by 2030, or 9.9% of adults. Literature review reported that, the top ten countries in the world, in terms of the number of peoples with diabetes, for 2010 and 2030 (Table 1).

Developing countries like India, already top of the diabetic league [8,9]. It is estimated that every fifth person with diabetes will be an Indian. Due to these sheer numbers, the economic burden due to diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications, which lead to increased morbidity and mortality [10].

## ETIOLOGY AND CLASSIFICATION OF DM

The older classification systems of DM are dividing into, primary (idiopathic) and secondary types, juvenile-onset and maturity-onset types, and insulin-dependent and non-insulin dependent types have become outdated [11]. However, based on widespread understanding of etiology of DM, DM are classified into different types (Table 2) [12,13].

## TYPE 1 DM

Type 1 DM constitutes about 10% cases of DM. It is characterized by loss of the insulin producing β-cells of the islets of langerhans in the pancreas leading to deficiency of insulin. It was previously termed as juvenile onset diabetes (JOD) or insulin dependent diabetes mellitus (IDDM). However, in the new classification, neither age nor insulin-dependence, based on underlying etiology, type 1 DM is further divided into two subtypes;

Type 1A DM: It is characterised by autoimmune destruction of β-cells which usually leads to insulin deficiency. Though type 1 DM occurs commonly in patients under 30 years of age. But, autoimmune destruction of β-cells can occurs at any age and hence the term JOD has become outdated. In fact, 5-10% patients who develop DM above 30 years of age are of type 1A DM.

Type 1B DM: It is characterised by insulin deficiency with tendency to develop ketosis but these patients are negative for autoimmune markers. For persons with type 1 DM, insulin replacement therapy is necessary to sustain life.

### Pathogenesis of Type 1 DM

The pathogenesis of type 1A DM is immune-mediated and has been extensively studied. While type 1B DM remains idiopathic.

**Genetic susceptibility:** Type 1A DM involves inheritance of multiple genes to confer susceptibility to the disorder;

(i) It has been observed in identical twins that if one twin has type 1A DM, there is about 50% chance of the second twin developing it, but not all.
(ii) About half the cases with genetic predisposition to type 1A DM have the susceptibility gene located in the human leukocyte antigen (HLA) region of chromosome 6 particularly HLADR3, HLADR4 and HLADQ locus. It appears that in HLA- associated susceptibility individual, β-cells acts as autoantigens and activates $CD4^{+}$T lymphocytes, bringing about immune destruction of pancreatic β-cells.

**Autoimmune factors:** Type 1A DM have shown several immunologic abnormalities;
(i) Presences of islet cell antibodies against glutamic acid decarboxylose and insulin.
(ii) Occurrence of lymphocytic infiltrate in and around the pancreatic islets termed insulitis.
(iii) Role of T cell-mediated autoimmunity is further supported by transfer of type 1A DM from diseased animal by infusing T lymphocytes to a healthy animal.
(iv) Selective destruction of the β-cell while other islet cell types remain unaffected. This is mediated by T-cell mediated cytotoxicity or apoptosis.
(v) Association of type 1A DM with other autoimmune diseases such as Graves' disease, Addison's disease, Hashimoto's thyroiditis and Pernicious anemia.
(vi) Remission of type 1A DM in response to immuno-suppressive therapy such as administration of cyclosporin A.

**Environmental factors:** Involvement of certain environmental factors in type 1A DM pathogenesis;
(i) Certain viral infections preceding the onset of disease e.g. mumps, measles, coxsackie B virus, cytomegalo virus and infectious mononucleosis.
(ii) Experimental induction of type 1A DM with certain chemicals such as alloxan, streptozotocin and pentamidine.
(iii) Geographic and seasonal variations in its incidence suggest some common environmental factors.
(iv) Possible relationship of early exposure to bovine milk proteins and occurrence of autoimmune process in type 1A DM is being studied.

## TYPE 2 DM

Type 2 DM was previously called maturity onset diabetes (MOD) or non-insulin dependent diabetes mellitus (NIDDM) of obese and non-obese type. Accordingly MOD, type 2 DM predominantly occurs in older individuals. But, now a day, it also occurs in obese adolescent children. Hence, the term MOD is inappropriate. Moreover, many type 2 DM patients also require insulin therapy to control hyperglycemia and thus are not truly NIDDM [11,12]. In type 2 DM, there is no loss or moderate reduction in β-cell mass; insulin in

circulation is low, normal or even high and no anti-β cell antibody is demonstrable [14].

More than 90% of diabetic patients suffer from type 2 DM, which is characterized by insulin resistance and hyperglycemia. Now a day, several epidemiological and clinical studies indicate a direct relationship between hyperglycemia and long term microvascular and macrovascular complications such as neuropathy, retinopathy, nephropathy, myocardial infarction, atherosclerosis, coronary artery disease, stroke and lower limb amputation, which develop as the disease progresses, gradually decrease quality of life of diabetic patients. Therefore, it is essential to control blood glucose levels during the early stages of the disease [15,16]. Furthermore, this metabolic disease is also linked to a wide spectrum of other pathophysiologic conditions including dyslipidemia, hypertension, hyperuricemia, increased plasminogen activator inhibitor type-1 (PAI-1), abnormal fibrinolytic system and abdominal obesity [17].

Therapy for type 2 DM primarily has been aimed at improving glycemic control via a combination of diet, exercise, and current therapeutic agents such as insulin formulations, sulfonylureas, metformin, acarbose, TZDs, GLP-1 analog and DPP-4 or IV inhibitors [18,19].

**Pathogenesis of Type 2 DM**

A number of factors have been implicated in the pathogenesis of type 2 DM. But, HLA association and autoimmune phenomena are not implicated.

**Genetic factors:** Genetic component has a stronger basis for type 2 DM than type 1 DM. Although no definite and consistent genes have been identified, multifcatorial inheritance is the most important factor in development of type 2 DM. There is approximately 80% chance of developing diabetes in other identical twin, if one twin has the disease. A person with one parent having type 2 DM is at an increased risk of getting diabetes. But, if both parents have type 2 DM the risk in the offspring rises to 40%.

**Constitutional factors:** Certain environmental factors such as obesity, hypertension and level of physical activity play contributory role and modulate the phenotyping of the disease [11].

**Insulin resistance:** Insulin resistance, the decreased ability of insulin to act effectively on target tissues (especially liver, muscle and fat). It is one of the most prominent metabolic features of type 2 DM and results from a combination of genetic susceptibility and obesity. In obese subjects, insulin levels typically increase to maintain normal glucose tolerance. Because, basal and total 24 hrs rates of insulin secretion are three to four times higher in obese insulin-resistant subjects than in lean controls. The hyperinsulinemia associated with insulin resistance results from a combination of an increase in insulin secretion and a reduction in insulin clearance rates. However, insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output (or synthesis); both effects contribute to the hyperglycemia. The precise underlying molecular defect responsible for insulin resistance in type 2 DM has yet not been fully identified [13,20].

Insulin resistance syndrome: It is a cluster of interrelated risk factors for cardiovascular disease (CVD) and diabetes. Therefore, a wide variety of new names have been applied to the cluster such as metabolic syndrome, metabolic syndrome X, cardiovascular metabolic syndrome, chronic cardiovascular risk factor clustering syndrome, plurimetabolic syndrome, dysmetabolic syndrome, cardiometabolic syndrome and "deadly quartet" as well as insulin resistance syndrome [21]. The insulin resistance syndrome is containing a number of metabolic and clinical abnormalities such as obesity, atherosclerosis, coronary artery disease, vascular endothelial dysfunction, hyperinsulinemia relative to glucose levels (at least initially in type 2 DM), hyperuricemia (raised serum uric acid concentrations), hypercoaguability (increased levels of PAI-1 and fibrinogen) hypertension (raised blood pressure) and dyslipidemia [Increased concentrations of both very low-density lipoprotein (VLDL)-triglycerides (TG) and small, dense low-density lipoprotein (LDL)-cholesterol; decreased concentrations of high-density lipoprotein (HDL)- cholesterol] [22]

**Impaired insulin secretion:** The different pathogenetic factors are implicated in the progressive impairment of insulin secretion in type 2 DM (Figure 1).

(i) Genetics: In twins have provided strong evidence for the genetic basis of β-cell dysfunction. Impaired insulin secretion also has been shown to be an inherited trait in Finnish families with type 2 DM with evidence for a susceptibility locus on chromosome 12.

(ii) Insulin resistance: Early in the course of disease, in response to insulin resistance there is compensatory increased secretion of insulin in an attempt to maintain normal blood glucose level. Finally, however, there is failure of β-cell function to secrete sufficient insulin. Although there is some secretion of insulin i.e. case of type 2 DM have mild to moderate deficiency of insulin (which is much less severe than that in type 1 DM) but not its total absence.

(iii) Glucose toxicity: Metabolic environment of chronic hyperglycemia surrounding the islets may paradoxically impair β-cell function.

(iv) Lipotoxicity: Short-term exposure of β-cell to physiologic increases in free fatty acid (FFA) stimulates insulin secretion. Inside the β-cell, long-chain fatty acids are converted to their fatty acyl coenzyme-A derivatives, which lead to increased formation of phosphatidic acid and diacylglycerol. These lipid intermediates activate

specific protein kinase C isoforms, which enhances the exocytosis of insulin. In addition, fatty acyl coenzyme-A also stimulates exocytosis, cause closure of the $K^+$-ATPase (Adenosine Triphosphate) channel, stimulate $Ca^{2+}$-ATPase and increase intracellular calcium. As a result, augment of insulin secretion. In contrast to acute effects, chronic β-cell exposure to elevated fatty acyl coenzyme-A inhibits insulin secretion through operation of the Randle cycle.

(v) Tumor necrosis factor-α (TNF-α): Increased fatty acyl coenzyme-A levels within the β-cell stimulate ceramide synthesis, which augments inducible nitric oxide synthase. As a result, increases the expression of inflammatory cytokines such as interleukin-1 (IL-1) and TNF-α, which impair β-cell function and promote β-cell apoptosis.

(vi) Incretins effects: Deficiency of or resistance to incretins have been implicated in the pathogenesis of β-cell dysfunction in type 2 DM.

(vii) Islet amyloid polypeptide (amylin): This amylin in the form of fibrillar protein, which is deposits in pancreatic islets in longstanding cases of type 2 DM may be responsible for impaired function of β-cells islet cells.

(viii) Age, gender and obesity: Recent studies with well-matched controls (age, gender and obesity) suggest that β-cell mass is reduced, even during the early stages of the development of type 2 DM. It seems likely that factors in addition to β-cell loss must be responsible for the impairment in insulin secretion [23].

**Increased hepatic glucose synthesis:** One of the normal roles played by insulin is to promote hepatic storage of glucose as glycogen and suppress gluconeogenesis. In type 2 DM, as a part of insulin resistance by peripheral tissues, liver also shows insulin resistance i.e. in spite of hyperinsulinaemia in the early stage of disease, gluconeogenesis in the liver is not suppressed. This results in increased hepatic synthesis of glucose which contributes to hyperglycemia in this case.

**TYPE 3 DM**

Besides the two main types of DM, about 10% cases of type 3 DM have a known specific etiologic defect. Therefore, it is also called other specific types of diabetes. From these known specific etiologic defects, one of the most important in this group is MODY, which is characterised by autosomal dominant inheritance, early onset of hyperglycemia (usually < 25 years) and impaired insulin secretion. Mutations in the insulin receptor cause a group of rare disorders characterised by severe insulin resistance [11-13].

**TYPE 4 DM**

Gestational DM (GDM) refers to the onset or initial recognition of glucose intolerance during pregnancy usually observed in the third trimester. It occurs in about 4% of all pregnancies. The risk factors associated with GDM are obesity, glycosuria and family history that includes diabetes. If the GDM develops during pregnancy, the women has a 50% risk of developing type 2 diabetes in the future and a 50% risk of experiencing GDM in subsequent pregnancy. Babies born to women with pre-existing diabetes that is poorly controlled are two to four folds more likely to have a serious birth defect (e.g. eye defects, respiratory tract defects, cleft palate, anal atresia/stenosis, urinary tract defects and positional defect of foot). Whether the mother has pre-existing diabetes maintain tight blood glucose control for three to six months before conception and insulin therapy replace all oral hypoglycemic medications during pregnancy [12,24].

**SIGNS AND SYMPTOMS OF DM**

The classical triads of diabetes symptoms are glycosuria, polyuria, polydipsia and polyphagia, which are respectively, glucose remains in the urine, frequent urination, increased thirst and consequent increased fluid intake, and increased appetite. Symptoms may be developing quite rapidly (weeks or months) in type 1 DM, particular in children. However, in type 2 DM the symptoms develop much more slowly and may be subtle or completely absent. Type 1 DM may also cause a rapid yet significant weight loss and irreducible fatigue. All of these symptoms except weight loss can also manifest in type 2 DM patients whose diabetes is poorly controlled [25].

**COMPLICATIONS OF DM**

Complications of DM are mainly divided into two main types are given in layout format (Figure 2);

**Diabetic Ketoacidosis (DKA):** It can develop in patient with severe lack of insulin causes lipolysis in the adipose tissues, resulting in release of FFA into the plasma. These FFA are taken up by the liver where they are oxidized through acetyl coenzyme-A to ketone bodies such as acetoacetic acid and β-hydroxybutyric acid. Such FFA oxidation to ketone bodies is accelerated in the presence of elevated level of glucagon. Once the rate of ketogenesis exceeds the rate at which the ketone bodies can be utilized by the muscles and other tissues, ketonaemia and ketonuria occurs. If urinary excretion of ketone bodies is prevented due to dehydration, systemic metabolic ketoacidosis occurs. DKA usually occurs in type 1 DM and rarely occurs in type 2 DM. Clinically, DKA condition is characterised by anorexia, nausea, vomiting, deep and fast breathing, mental confusion, coma and death.

**Hyperosmolar Nonketotic Coma (HNC):** The HNC shows many symptoms in common with DKA, but an entirely different cause. This condition is sometimes called non-ketotic hyperglycemia coma. This is usually occurs in elderly type 2 DM cases. In person with very

high blood glucose levels (usually considered to be above 300mg/dl), water is drawn out of cells into the blood by osmosis and the kidneys dump glucose into the urine. This results in loss of water and an increase in blood osmolality. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels combined with the loss of water will eventually lead to dehydration. Furthermore, the body cells become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common and dangerous. The important features here are the relative absence of ketones and the frequent occurrence of hypernatraemia.

**Hypoglycemia:** Hypoglycemia episode may develop in patients of type 1 DM. it may result from excessive administration of insulin, missing a meal and stress. The symptoms of hypoglycemia are dizziness, indecision, clumsiness, slow thinking, sweating, palpitation, a feeling of hunger and tingling around the mouth. Hypoglycemic episodes are harmful as they produce permanent brain damage [11,26].

**Diabetic Retinopathy (DR):** Diabetic retinopathy occurs in 3/4 of all persons having diabetes for more than fifteen years and is the most common cause of blindness [25]. Furthermore, DR is classified into two stages such as non-proliferative and proliferative stages.

Non-proliferative retinopathy stage: Appears late in the first decade or early in the second decade of DM disease. It is marked by retinal vascular microaneurysms, blot haemorrhages and cotton-wool spots. The pathophysiologic mechanisms involved in non-proliferative retinopathy includes loss of retinal pericytes, increased retinal vascular permeability, alterations in regional blood flow and abnormal retinal microvasculature, all of which lead to retinal ischemia. In this case, mild non-proliferative retinopathy progresses to more extensive disease, which is characterised by changes in venous vessel caliber, intraretinal microvascular abnormalities, more numerous microaneurysms and hemorrhage.

Proliferative retinopathy stage: Appearance of neovascularization in response to retinal hypoxia. These newly formed vessels may appear at the optic nerve (or macula) and rupture easily, leading to vitreous haemorrhage, fibrosis and ultimately retinal detachment [13,27,28].

**Diabetic Neuropathy:** DM can harm nerves all over the body. About half of all people with diabetes have some degree of neuropathy, which can be mononeuropathy, polyneuropathy and autonomic neuropathy.

Diabetic mononeuropathy: It is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve (dysfunction of isolated cranial or peripheral nerves).

Diabetic polyneuropathy: There is loss of peripheral sensation which, when coupled with impaired microvascular and macrovascular junction in the periphery. Furthermore, it can contribute to non-healing ulcers, the leading cause of non-traumatic amputation.

Diabetic autonomic neuropathy (DAN): Individuals with long-standing type 1 DM or type 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic and peptidergic systems. It can also involve multiple systems such as cardiovascular, gastrointestinal, genitourinary, sudomotor and metabolic systems. Finally, sudden death has also been attributed to autonomic neuropathy [13,20,29].

**Diabetic Nephropathy:** It is a major cause of end stage renal disease. There are glomerular hemodynamic abnormalities resulting in glomerular hyperfiltration, leading to glomerular damage as evidenced by microalbuminurea. There is overt proteinuria, decreased glomerular filtration rate and end-stage renal failure. Dysfunction of the glomerular filtration apparatus is manifested by microalbuminurea and is attributed to changes in synthesis and catabolism of various glomerular basement membrane macromolecules such as collagen and proteoglycans, leading to an increase in glomerular basement thickening. The nephropathy that develops in type 2 DM differs from that of type 1 DM. Because, microalbuminurea or macroalbuminurea may be present in when type 2 DM is diagnosed. Lastly, it should note that albumin urea in type 2 DM may be responsible for hypertension, congestive heart failure (CHF), prostate disease and infection in type 2 DM. Another possible mechanism to explain the increase in permeability of the glomerulus is the increase in renal vascular epidermal growth factor (VEGF) levels observed in preclinical models of diabetes, since VEGF is both an angiogenic and a permeability factor.

**Cardiovascular Morbidity and Mortality:** In DM there is marked increase in several CVD, including coronary artery disease, CHF, myocardial infarction (heart attack), peripheral artery disease and sudden death. The absence of chest pain (silent ischemia- bloodlessness of a part of the body due to contraction, spasm and blocking of the arteries) is common in individuals with DM. The increases in cardiovascular morbidity and mortality appear too related to the synergism of hyperglycemia with other cardiovascular risk factors such as dyslipidemia, hypertension, poor diet, obesity, reduced physical activity and cigarette smoking. Additional risk factors more widespread in the diabetic population include microalbuminurea, macroalbuminurea, an elevation of serum creatinine and abnormal platelet function. Moreover, insulin resistance is also associated with increased risk of cardiovascular complications in individuals with and without DM. Individuals with insulin resistance and type 2 DM have elevated levels of PAI-1

and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis [13,20,28].

**Gastrointestinal / Genitourinary Dysfunction:** Long-standing type 1DM and type 2 DM may affect the motility and function of gastrointestinal and genitourinary system.

Gastrointestinal dysfunction: Gastrointestinal disturbances (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea and fecal incontinence) are common and any section of the gastrointestinal tract may be affected. The most prominent gastrointestinal dysfunction are delayed gastric emptying (Gastroparesis) may present with symptoms of anorexia, nausea, vomiting, early satiety and abdominal bloating. Upper-gastrointestinal symptoms should lead to consideration of all possible causes, including autonomic dysfunction. However, constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea.

Genitourinary dysfunction: DAN may lead to genitourinary dysfunction including bladder and sexual dysfunction. In men, DAN may cause loss of penile erection (Erectile dysfunction) and retrograde ejaculation. However, in female sexual dysfunction such as reduced sexual desire, dyspareunia and reduced vaginal lubrication (vaginal dryness) [29].

**Infections:** Individuals with DM exhibit a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization secondary to long-standing diabetes. Hyperglycemia aids the colonization and growth of a variety of organisms (Candida and other fungal species).

Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population (e.g. rhinocerebral mucormycosis and malignant or invasive otitis externa, which is usually secondary to Pseudomonas aeruginosa infection in the soft tissue surrounding the external auditory canal). Pneumonia, urinary tract infection, skin and soft tissue infections are all more common in the DM population. Gram-negative organisms, e.g. Staphylocous aureus and mycobacterium tuberculosis, are more frequent pathogens in patients of DM. Diabetic individuals have an increased rate of colonization of staphylocous aureus in skin folds and nares. Diabetic patients also have a greater risk of postoperative wound infections.

## DIAGNOSIS OF DM

Hyperglycemia and symptoms remains the fundamental basis for the diagnosis of DM via;

**Symptomatic Cases:** Symptoms of diabetes plus random plasma glucose concentration above 200 mg/dl (>11.1 mmol/L). The severity of clinical symptoms of polyuria and polydipsia are directly related to the degree of hyperglycemia.

**Asymptomatic Cases:** The problem arises in asymptomatic patients who have normal fasting glucose level in the plasma but are suspected to have diabetes on other grounds and are thus subjected to oral glucose tolerance test (OGTT). The World Health Organization (WHO)-American Diabetes Association (ADA) has suggested definite diagnostic criteria for early diagnosis of DM (Table 3).

## EXAMINATIONS OF DM

Urine testing (Glucosuria and Ketonuria test), single blood sugar estimation (Folin-Wu, O-toludine, Somogy-Nelson and glucose oxidase methods), oral glucose tolerance test (OGTT) and other tests such as glycosylated haemoglobin ($HbA_{1C}$), extended glucose tolerance test (GTT), intravenous GTT, cortisone-primed GTT, insulin assay and C-peptide assay are helpful in establishing the diagnosis of DM. Out of these available tests, currently OGTT and $HbA_{1C}$ are used.

**OGTT:** In diabetic condition and other cases like during pregnancy, OGTT is performed. The patient who is scheduled for OGTT is instructed to eat a high carbohydrate diet for at least 3 days prior to the test and come after an overnight fast on the day of the test (for at least 8 hours). A fasting blood sugar sample is first drawn. The 75gm of glucose dissolved in 300ml of water is given. Blood and urine specimen are collected at half-hourly intervals for at least 2 hours. Blood or plasma glucose content is measured and urine is tested for glucosuria to determine the approximate renal threshold for glucose.

**$HbA_{1C}$:** Long-term objective assessment of degree of diabetic control is better done by measurement of $HbA_{1C}$, a minor haemoglobin component present in normal persons. This is because the non-enzymatic glycosylation of haemoglobin takes place over 120 days, life span of red blood cells. $HbA_{1C}$ assay, therefore, gives an estimate of diabetic control for the previous 6-10 weeks. $HbA_{1C}$ of 6.5% is recommended as the cut point for diagnosing DM [11,20].

## CLINICAL MANAGEMENT OF DM

The layout of clinical management of DM is shown given below (Figure 3);

**Patient Education about DM:** The diabetes educator is a health care professional [nurse, dietician or pharmacist] with specialized patient education skills who certified in diabetes education. Education topics important for optimal diabetes care include self monitoring of blood glucose, urine ketone monitoring, insulin administration,

guidelines for diabetes management during illnesses, management of hypoglycemia, foot and skin care, diabetes management before, during and after exercise, and risk factor-modifying activities.

**Nutrition:** Medical nutrition therapy (MNT) is a term used by the ADA to describe the optimal co-ordination of caloric intake with other aspects of diabetic therapy. ADA has issued recommendations for three types of MNT;
(i) MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals (obese or with pre-diabetes) by promoting weight reduction.
(ii) MNT is directed at preventing or delaying diabetes-related complications in diabetic individuals by improving glycemic control.
(iii) MNT is directed at managing diabetes-related complications in diabetic individuals. For example, in individuals with diabetes and chronic kidney disease, protein intake should limited to 0.8g/kg of body weight per day.

**Physical Activity:** Individuals with type 1 or type 2 DM, exercise has multiple positive benefits including lowering plasma glucose, increasing insulin sensitivity, cardiovascular risk reduction, reduced in blood pressure, maintenance of muscle mass, reduction in body fat and weight loss. If patient with DM, the ADA recommends 150min/week (distributed over at least 3 days) of aerobic physical activity. But, to avoid exercise-related hyperglycemia or hypoglycemia, individuals with type 1 DM should;
(i) Monitor blood glucose before, during and after exercise.
(ii) Delay exercise if blood glucose is 250mg/dl and ketones are present.
(iii) If the blood glucose is 100 mg/dl, ingest carbohydrate before exercising.
(iv) Monitor glucose level during exercise and ingest carbohydrate to prevent hypoglycemia.
(v) Decrease insulin doses (based on previous experience) before exercise.
(vi) Learn individual glucose responses to different type of exercise and increase food intake for up to 24 hrs after exercise, depending on intensity and duration of exercise.
(vii) In individuals with type 2 DM, exercise-related hypoglycemia is less common but can occur in individuals taking either insulin or insulin secretagogues [13].

**INSULIN**

Insulin was discovered in 1921 by Banting and Best. It was obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger. The pancreatic islet of langerhans containing β-cells, which synthesize insulin from a single-chain precursor of 110 amino acids termed preproinsulin in the rough endoplasmic reticulum. Preproinsulin is transported to the Golgi apparatus, where it undergoes proteolytic cleavage to proinsulin and then to insulin plus a fragment of uncertain function called C peptide. Both insulin and C peptide are stored in granules within the β-cell. The C peptide is secreted in the blood along with insulin. The prohormone convertases, PC2 and PC3, convert proinsulin to insulin by proteolytic cleavage of four basic amino acids (residue 31, 32, 64 and 65) and removal of the C peptide. Insulin is a two chain polypeptide having 51 amino acids and molecular weight about 6000. The A peptide chain has 21 amino acids while B peptide chain has 30 amino acids, linked by one intrasubunit and two intersubunit disulfide bonds (Figure 4). Insulin secretion is tightly regulated to maintain stable concentrations of glucose in blood during both fasting and feeding. This regulation is achieved by the coordinated interplay of various nutrients, gastrointestinal hormones, pancreatic hormones and autonomic neurotransmitters [30,31].

**Mode of action:** Insulin acts on specific receptors located on the cell membrane. The insulin receptor is a heterotetrameric glycoprotein consisting of two extracellular α-subunits (135 kDa) and two transmembrane β-subunits (95 kDa) linked together by disulfide bonds. The α-subunits carry insulin binding sites, while the β-subunits have tyrosine protein kinase activity. Binding of insulin to α-subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β-subunits, pairs of β-subunits phosphorylate tyrosine residues (T-PO) on each other, expose the catalytic site to phosphorylate tyrosine residues of IRS1-4. In turn, a cascade of phosphorylation and dephosphorylation reactions is set into motion resulting in stimulation or inhibition of enzymes involved in the rapid metabolic actions of insulin. Certain second messengers like phosphatidyl inositol triphosphate ($PIP_3$) who are generated through activation of a specific $PI_3$-kinase also mediate the action of insulin on metabolic enzymes. Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporter 4 (GLUT4) and GLUT1 to the plasma membrane as well as by increasing its activity. Activation of transcription factors also promotes proliferation and differentiation of specific cells (Figure 5) [14,30].

**Effects of insulin:** Insulin has important effect on several transport molecules (GLUT 1 to 5) that facilitate glucose movement across cell membranes (Table 4). Moreover, insulin is the main hormone controlling intermediary metabolism, having actions on liver, fats and muscle (Table 5).

**Pharmacokinetic:** Insulin circulates in blood as a monomer and its volume of distribution approximates the volume of extracellular fluid. Under fasting conditions, the pancreas secretes about 40μg (1unit) of insulin/h into

the portal vein to achieve a concentration of insulin in portal blood of 2–4 ng/mL (50–100 μunits/mL) and in the peripheral circulation of 0.5ng/mL (12μunits/mL). After ingestion of a meal, there is a rapid rise in the concentration of insulin in portal blood, followed by a parallel but smaller rise in the peripheral circulation.

The liver and kidney are the two main organs that remove insulin from the circulation, presumably by hydrolysis of the disulfide connections between the A and B chains through the action of glutathione insulin transhydrogenase (insulinase). After this reductive cleavage further degradation by proteolysis occurs. The liver normally clears the blood of approximately 60% of the insulin released from the pancreas and kidney removing 35-40% of the endogenous hormone. However, in insulin-treated diabetics receiving subcutaneous insulin injections, this ratio is reversed, 60% of exogenous insulin being cleared by the kidney and the liver removing no more than 30-40%. The half-life of circulating insulin is 3-5 minutes.

**Adverse effects**

Hypoglycemia: If insulin dose level is high during treatment, the hypoglycemia condition occurs in diabetes patients.

Insulin allergy: Hypersensitivity is a rare condition in which local or systemic urticaria results from histamine release from tissue mast cells sensitized by anti-insulin IgE antibodies. In severe cases an anaphylaxis result occurs. Immune insulin resistance: Insulin-treated patients develop a low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a small extent. Rarely, the titer of insulin antibodies leads to insulin resistance and may be associated with other systemic autoimmune processes such as lupus erythematosus.

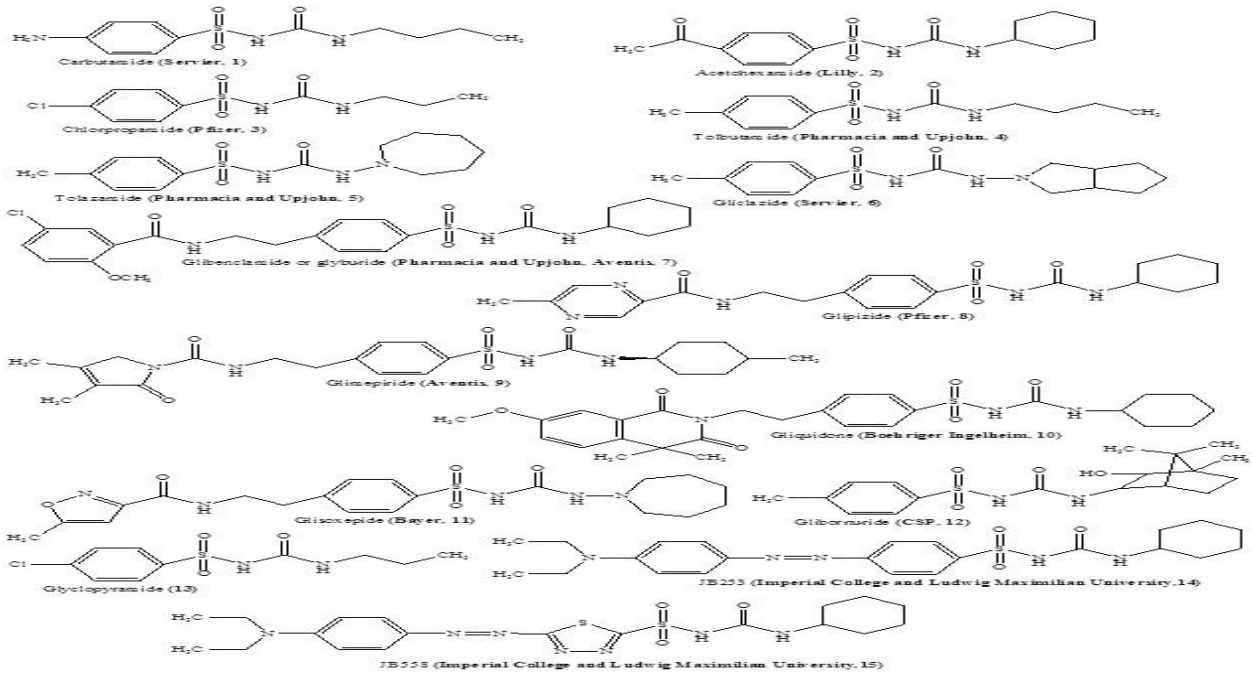
Lipoatrophy and lipohypertrophy: Atrophy of subcutaneous fat at the site of insulin injection is probably an immune response to insulin (lipoatrophy). Lipohypertrophy (enlargement of subcutaneous fat depots) is ascribed to the lipogenic action of high local concentrations of insulin. Both problems are rare with more purified preparations. However, hypertrophy may occur with human insulin if patients inject themselves repeatedly in the same site

Insulin edema: Edema, abdominal bloating and blurred vision develop in many diabetic patients with severe hyperglycemia or ketoacidosis [12,30,31].

**Sulfonylureas**

Sulfonylureas have been used hypoglycemic agents since the mid-1950. The sulfonylurea derivatives are divided into four generations. First generation drugs include carbutamide (1), acetohexamide (2), chlorpropamide (3), tolbutamide (4), tolazamide (5) and gliclazide (6). Second generation drugs include gliclazide (6), glibenclamide or glyburide (7), glipizide (8), glimepiride (9), gliquidone (10), glisoxepide (11), glibornuride (12) and glyclopyramide (13) [32-36]. Third generation drugs include gliclazide (6) and glimepiride (9). Fourth generation (light-dependent) drugs include JB253 (14) and JB558 (15) [37-39].

Out of these sulphonylureas, carbutamide (1) was demarketed in 1960 due to toxicities, especially to bone marrow [32]. Acetohexamide (2) has been discontinued in the US market due to its extensively metabolized in the liver to the active metabolite hydroxyhexamide, which exhibits greater hypoglycemic potency than acetohexamide [40]. Glibornuride (12) is also withdrawn from the market [41]. Remaining sulphonylureas such as chlorpropamide (3), tolbutamide (4), tolazamide (5), glibenclamide or glyburide (7), glipizide (8), glimepiride (9), gliquidone (10), glisoxepide (11) and glyclopyramide (13) are still in market [42-44].



**Mode of action:** Sulphonylureas are directly stimulating the release of insulin from pancreatic β-cells and maintain elevated blood glucose level in the body. The sulfonylureas are produce their hypoglycemic actions via several mechanisms that can be broadly sub-classified as pancreatic, extra-pancreatic [45] and optical control of insulin release using a photoswitchable sulfonylurea [39]

Pancreatic mechanism: The primary action of the all **(1-15)** sulfonylurea is to stimulate the release of insulin from β-cells. They act by affecting the ATP-sensitive potassium ($K_{ATP}$) channel. This channel is a hetero-octameric complex of two subunits like a sulfonylurea receptor (SUR1) and an inwardly rectifying potassium channel (Kir6.2). On binding to SUR1, potassium efflux is blocked, leading to depolarization of the membrane. This depolarization opens voltage-dependent calcium channels, resulting in an influx of calcium. At higher intracellular calcium concentrations, calcium-sensitive proteins act to promote the release of stored insulin from the β-cells (Figure 6).

Extra-pancreatic mechanism: The sulfonylureas also reduce serum glucagon levels possibly contributing to its hypoglycemic effects. The precise mechanism by which this occurs remains unclear but may result from indirect (secondary) inhibition due to enhanced release of both somatostatin and insulin. These sulfonylureas may also potentiate insulin action at target tissues (drug-dependent characteristic). Glimepiride **(8)** show extrapancreatic effects for a greater proportion of its hypoglycemic effect. It is possible because of this that it is considered less likely to produce unwanted hypoglycemia. Glimepiride **(8)** binds well to not only SUR1 in β-cells but also binds to SUR2A (as found in cardiac smooth muscle) and SUR2B (brain and smooth muscle) [12,24,45].

Optical control of insulin release using a photoswitchable sulfonylurea: The main action of sulphonylureas (1-15) on $K_{ATP}$ channels, sulfonylureas boost of insulin release from the pancreatic β-cell mass to restore glucose homeostasis. Limitations of these compounds (1-13) are elevated risk of developing hypoglycemia and cardiovascular disease, both potentially fatal complications. Therefore, now a day, design and development of a photoswitchable sulfonylurea such as JB253 **(14)** and JB558 **(15)**, which are reversibly and repeatedly blocks $K_{ATP}$ channel activity subsequent exposure to light [39,46].

**Pharmacokinetics:** All sulfonylureas are effectively absorbed from the gastrointestinal tract, although food and hyperglycemia can reduce the absorption. In view of the time required for absorption, sulfonylureas with short half-lives may be more effective when given 30 minutes before eating. Sulfonylureas in plasma are largely bound to protein, especially serum albumin. The second-generation agents are approximately hundred times more potent than those in the first generation. Because, their half-lives are 3–5 hrs, their hypoglycemic effects persist for 12–24 hrs and they often can be administered once daily. All sulfonylureas are metabolized by the liver and the metabolites are excreted in the urine [30].

**Adverse effects and side effects**

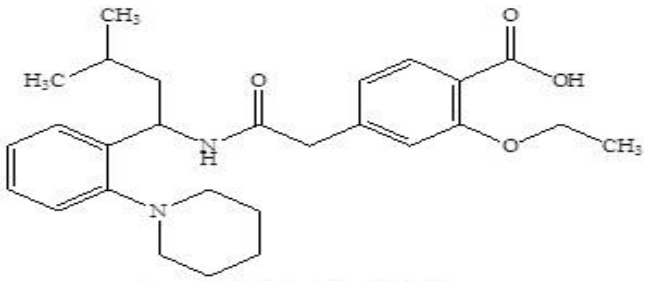
Nonspecific side effects: Nausea, vomiting, flatulence, diarrhea or constipation, headache, paresthesias and weight gain.

**Hypoglycemia**

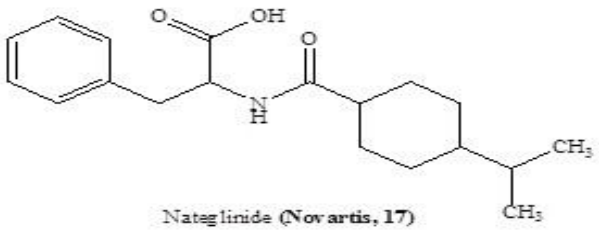
Hypersensitivity: Rashes, photosensitivity, purpura, transient leukopenia and infrequently agranulocytosis [14].

**Glinides (Non-sulfonylureas)**

The glinides such as meglitinide [e.g. Repaglinide (16), it was introduce in the United States in 1998] and D-phenylalanine [e.g. Nateglinide (17), it was approved in the United State in late 2000] analogues. These are quick developed and short acting insulin releases.




Repaglinide (**Novo Nordisk, 16**)




Nateglinide (**Novartis, 17**)

**Mode of action:** The mechanism of action of glinides (16 and 17) is similar with glimepiride (9). It is well binding to SUR1, SUR2A and SUR2B, to block $K_{ATP}$ channels, resulting in insulin secretion from β-cells in addition to having extrapancreatic effects [24,25].

**Pharmacokinetics:** Repaglinide (16) has a rapid onset of action with a peak concentration and peak effects within approximately 1 hr after ingestion. But the duration of action is 5-8 hrs. It is hepatically cleared by CYP3A4 with a plasma half-life of 1 hr. It is administered before each major meal to control postprandial hyperglycemia.

Nateglinide (17) is ingested just before meals. It is absorbed within 20 minutes after oral administration with a time to peak concentration of less than 1 hr and is metabolized in the liver by CYP2C9 and CYP3A4 with a half-life of 1.5 hrs. The overall duration of action is less than 4 hrs. Nateglinide (17) may have a special role in the treatment of individuals with isolated postprandial

hyperglycemia, but it has minimal effect on overnight or fasting glucose levels [12].

**Side effects:** Repaglinide (16) shows mild headache, dyspepsia, arthralgia and weight gain. Whereas, nateglinide (17) shows dizziness, nausea, flu likes symptoms and joint pain [14].

**α-Glucosidase Inhibitors**

The α-glucosidase inhibitors are the inhibitors, which delay glucose absorption by temporarily inhibiting one or more of these digestive enzymes. The α-glucosidase inhibitors like acarbose (18), validamine (19), valienamine (20), valiolamine (21), α-methylacarviosin (22) and voglibose (23) are moderate to highly potent inhibitors of intestinal sucrase and maltase and fall into the category of inhibitor type I pseudoglucosylamines related to high energy intermediate I. However, miglitol (24) is an inhibitor type II derivative of 1-deoxynorjirimycin related to high energy intermediate II. The parent compound (1-deoxynorjirimycin) has potent inhibitory effects in porcine intestinal mucosal preparations on α-glucosidase enzymes. Concentrations in narrow range inhibited 50% of the sucrase, maltase, isomaltase and glucoamylase activity. Many derivatives of 1-deoxynorjirimycin have been prepared and tested. Out of these derivatives, emiglitate (25) produces long lasting inhibition [25,47]. Now a day, Acarbose (18) and miglitol (24) were marketed in the United States in 1998 and several other countries. Voglibose (23) was marketed in Japan in 1994 and several other countries.

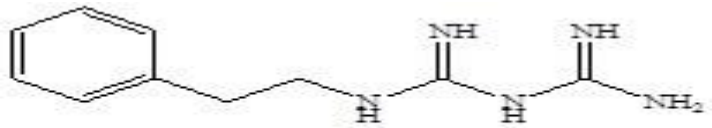
**Mode of action:** The complex carbohydrate that we ingest (i.e. starch) as part of our diet must first be hydrolyzed to monosaccharide. Starch normally is digested by salivary and pancreatic α-amylase to yield disaccharides (maltose), trisaccharides (maltotriose) and oligosaccharides (dextrin). The oligosaccharides responsible for final hydrolysis of these materials are all located in the brush border of the small intestine and consist of two classes. The β-galactosidases hydrolyze β-disaccharides such as lactose, whereas the α-glucosidases act on α-disaccharides such as maltose, iso-maltose and sucrose. Therefore, the enzyme α-glucosidase is present in the brush border of the small intestine and is responsible for cleaving dietary carbohydrates and facilitating their absorption into the body. Inhibition of α-glucosidase enzyme allows less dietary carbohydrate to be available for absorption and in turn, less available in the blood following a meal [24,32].

**Pharmacokinetics:** α-glucosidase inhibitors are a mild antihyperglycemic and not a hypoglycemic. It may be used as an adjuvant to diet (with or without a sulfonylurea) in obese diabetics. It is minimally absorbed, but produce loose stool in about 50% patients due to fermentation of unabsorbed carbohydrates. These drugs are excreted by the kidneys.

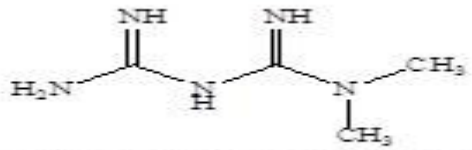
**Adverse effects and side effects:** Gastrointestinal disturbances in the form of flatulence, abdominal pain, distension, diarrhea and nausea. Vomiting is common side effects of therapy with α-glucosidase inhibitors [12,14].

**Biguanides**

Biguanides introduced in the late 1950, phenformin (26) was found to have antidiabetic properties and was used in the United State until 1977. When it was removed from the market in many countries and has been banned in India since 2003. Because of patients deaths associated with higher risk of lactic acidosis. Metformin (27) was introduced in 1995 in the united state after a track record of safe and effective use decades overseas and it is currently in wide use.




Phenformin (26)




Metformin (Bristol-Meyers Squibb, 27)

**Mode of action:** Biguanides are described as insulin sensitizers but their complete mechanism of action has not been fully elucidated. Biguanides act in the liver by decreasing excessive glucose production, most likely via reduced gluconeogenesis resulting from an increased sensitivity to insulin. They also improve glucose utilization by restoring tissue sensitivity to insulin. Biguanides appear to have their main action in the liver mitochondria via activation of adenosine 5'-monophosphate-activated protein kinase. Additional favorable effects of metformin (27) therapy such as an improved lipid profile, retard intestinal absorption of glucose, other hexoses, amino acids and vitamin $B_{12}$ have been reported [14,24].

**Pharmacokinetics:** Metformin (27) is quickly absorbed from the small intestine. Metformin (27) has a half-life of approximately 2 to 4 hrs. Metformin (27) does not bind to plasma proteins, but does partition into erythrocytes. Metformin (27) is not metabolized and is excreted by the kidneys as the active compound [12,25].

**Adverse effects and side effects:**

The side effects of Metformin **(27)** are abdominal pain, anorexia, nausea, vomiting and mild diarrhea. Hypoglycemia: Metformin **(27)** does not cause hypoglycemia except in overdose.

Lactic acidosis: Small increase in blood lactate occurs with metformin **(27)**. But lactic acidosis is rare (<1 per 10,000 patient years) because it is poorly concentrated in hepatic cells.

Vitamin $B_{12}$ deficiency: Due to interference with its absorption can occur with high dose of metformin **(27)** [12,14].

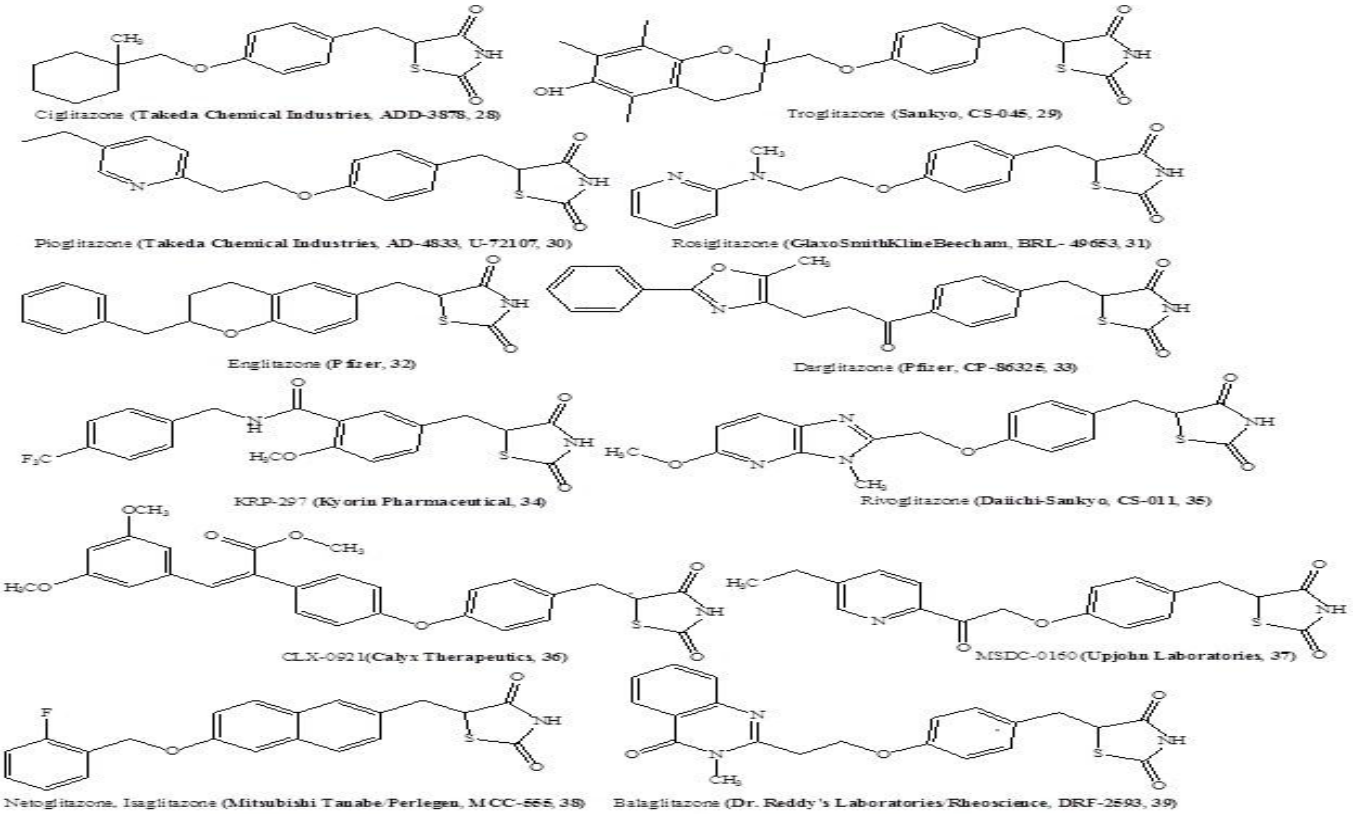
**Thiazolidine-2,4-dione (TZD)**

TZD's have become a pharmacologically important class of heterocyclic compounds since their introduction in the form of glitazones into clinical use for the treatment of type 2 DM and its complications. TZDs are known to be selective agonists of peroxisome proliferator-activated receptor-gamma (PPAR-γ), thereby increasing insulin sensitivity at adipose, muscle and hepatic tissues [48-49].

Of the TZD compounds, ciglitazone (28), troglitazone (29), pioglitazone (30), rosiglitazone (31), englitazone (32), darglitazone (33), KRP-297 (34), rivoglitazone (35) and CLX-0921(36) have been clinically examined. Unfortunately, ciglitazone (28), englitazone (29) [50], darglitazone (33) [51,52], KRP-297 (34) [53], rivoglitazone (35) [54,55] and CLX-0921 (36) [56] were discontinued in clinical development. Troglitazone (29), the first available glitazone, after launching in 1997 was subsequently withdrawn from the market due to its hepatotoxicity [50,57,58]. However, between 1997 and 1999, food drug administration (FDA) approved, second and third marketed TZDs such as rosiglitazone (31) and pioglitazone (30), respectively [58,59,60]. Both drugs pioglitazone (30) and rosiglitazone (31) have been approved for monotherapy and combination therapy with metformin, sulfonylureas, or insulin [61].

The current marketed status of pioglitazone (30) and rosiglitazone (31) reveals that, rosiglitazone (31) was withdrawn from the market in the United Kingdom and India in 2010, and in New Zealand, South Africa and United State of America in 2011 [58,62]. Because of rosiglitazone (31) associated with a significantly increased the risk of myocardial infarction, heart failure and death, as a result of cardiovascular complications [63]. Next to drug-induced liver injury is the second largest cause for the withdrawal of rosiglitazone (31) from the market. The mechanisms of drug-induced liver injury are not fully clear, especially the mechanism by which rosiglitazone (31) caused liver toxicity [64].

In contrast to rosiglitazone (31), pioglitazone (30) is banned in France in 2011, can cause heart failure and increases risk of bladder cancer. It is sold in the United State, United Kingdom, Japan, Canada, Europe and India with a boxed warning on the packet [65-67]. Currently, MSDC-0160 (37) [68], isaglitazone (38) [7, 55] and balaglitazone (39) [69,70] are included in an ongoing clinical trial examinations.




**Mode of action:** PPARγ regulate gene expression through two mechanisms, transactivation (DNA-dependent) and transrepression (DNA-independent) [37]. PPAR-γ binds to co-repressors in the absence of ligand and inhibits transcriptional activity in a DNA-independent manner. Whereas, in transactivation process TZD class containing potent synthetic ligand binding to the PPAR-γ. Ligand binding to the PPAR-γ, causing a conformational change in the AF-2 domain found in the ligand binding domain and forms a heterodimeric complex with RXR, another nuclear receptor with its own ligand (e.g., 9-cis-retinoic acids). Ligand binding to either PPAR-γ or RXR induces conformational changes in the PPARγ–RXR heterodimer, favouring release of co-repressor molecules and recruitment of co-activator proteins, which facilitate access and assembly of a transcriptional regulatory complex

[71,72]. This complex binds to specific consensus DNA sequences, termed peroxisome proliferator responsive element (PPRE), which are located in the regulatory regions of the target gene and result in an increase in gene transcription via replication of messanger ribonucleic acid (Figure 7). These targets suggest that, proteins are involved in lipid and glucose metabolism [11,61].

**Pharmacokinetics:** Pioglitazone **(**30) is well absorbed and reaching maximum blood levels in about 2 hrs. Binding to plasma proteins is greater than 99% with a single dose volume of distribution of 0.63L/kg. Pioglitazone (30) is metabolized by CYP3A4 and CYP2C8 to active metabolites. Serum half-life of the pioglitazone (30) is 3-7hrs, whereas that for total pioglitazone (30)-related species is 16-24 hrs. From 15 to 30% of an oral dose is excreted in the urine, primarily as metabolites and their conjugates. The balance is presumable excreted in the bile.

Rosiglitazone (31) is also well absorbed with absolute bioavailability of 99%. After oral dosing, peak blood levels are observed in about 1h. Rosiglitazone (31) is highly bound to plasma protein (99.8%) with a steady-state volume of distribution of approximately 17.6 L. Rosiglitazone (31) is metabolized in the liver to minimally active metabolites, predominantly by CYP2C8 and to lesser extent by CYP2C9. Rosiglitazone (31) is eliminated with half-life 3 to 4 hrs, primarily in the urine (64%) and lesser amounts in the feces (23%) [12,25].

**Effects of TZDs:** Literature review reported that, the summary of the different effects of TZDs treatment on pancreas, adipose tissue, liver, skeletal muscle and vascular wall-endothelium (Table 6) [24,61]. However, TZDs treatment also reported different effects on well-known and emerging CVD risk factors (Table 7) [48].

**Benefits and risk:** The literature review reported that, confirmed and potential benefits and risks of TZDs are depicted in Table 8[48,73].

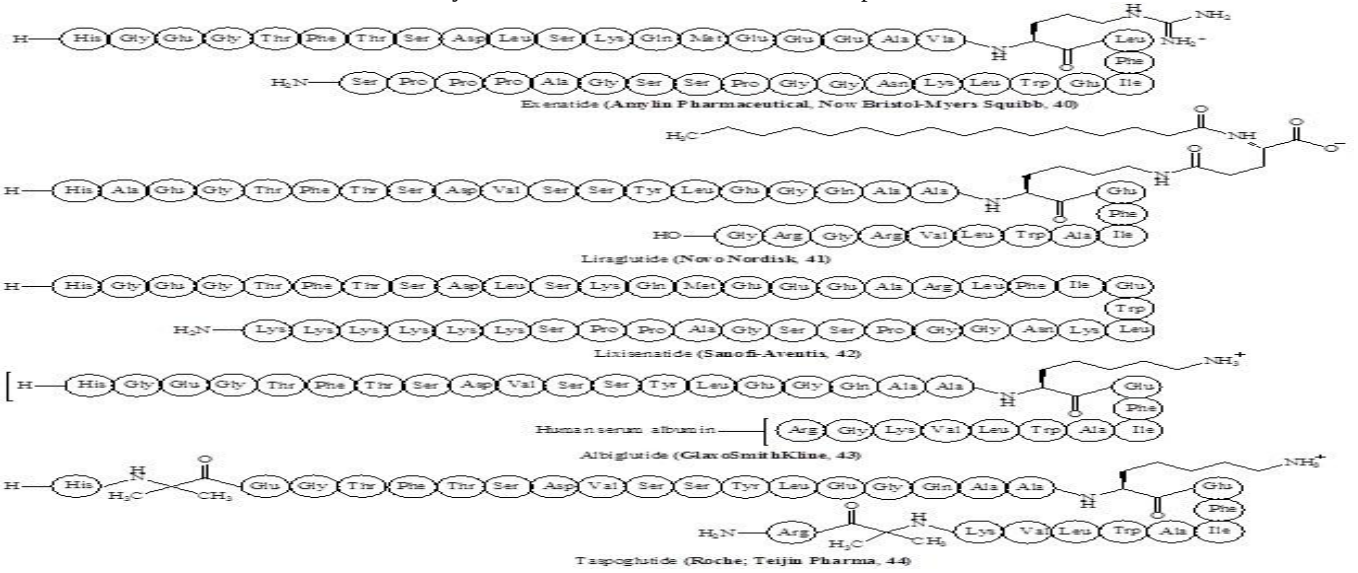
**Glucagon like Peptide-1 (GLP-1)**

The incretins term was first coined by La Barre in 1932. The "incretin effects" refers to insulin stimulated by orally administered glucose independent of any increase in blood glucose. Eventually, two incretins were identified, in 1971 and 1985, respectively: glucose-dependent Insulinotropic peptide (GIP) and GLP-1 (Figure 8).

Initially, GIP was believed to neutralize stomach acid to protect the small intestine from acid damage, reduce the rate at which food is transferred through the stomach, and inhibit the gastrointestinal motility and secretion of acid. Later, it was established that like GLP-1, GIP also plays a key role in glucose homeostasis. GIP, a 42 amino acid peptide is secreted by K cells from the upper small intestine within minutes of nutrient ingestion, facilitates the rapid disposal of ingested nutrients. After the discovery of its insulin secretion properties, GIP has been evaluated as a potential antidiabetic agent. However, in human subjects with type 2 DM exhibit relative resistance to the actions of GIP and therefore GIP is not an effective blood glucose lowering agent in type 2 DM subjects.

GLP-1 is a secreted by intestinal L-cells of the distal small intestine (predominantly in the ileum and caecum) in response to food intake. GLP (1-37) is further shortened, apparently also by PC1/3, to GLP-1(7-37) or GLP-1(7-36) amide (Figure 8). At least 80% of GLP-1 is release into the bloodstream. Both bioactive forms of GLP-1 are very short-lived (Plasma $t_{1/2}$~ 1-2min). Because, dipeptidyl peptidase type 4 (DPP-4 or DPP-IV) rapidly cleaves two residues from the amino terminus and generating GLP-1(9-37) and GLP (9-36) amide, respectively. Therefore, continuous administration of GLP-1, development of DPP-4 resistant GLP-1 agonists (peptide based) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs, non-peptide based) for the treatment of T2DM [19,32].

The GLP-1 RAs are exenatide (40), liraglutide (41), lixisenatide (42), albiglutide (43), taspoglutide (44) and dulaglutide (45). A schematic diagram of dulaglutide (45) is shown in Figure 9. Out of these GLP-1 RAs, in September 2010 Roche halted phase III clinical trials of taspoglutide (44) due to incidences of serious hypersensitivity reactions and gastrointestinal side effects [32, 74-77]. The approval statuses of remaining GLP-1 RAs were reported in Table 9[78].



**Mode of action:** The GLP-1 is a peptide hormone acts via specific GPCRs in the portal vein to trigger vagal afferents that, mediated by neuronal pathways within the brain, generate efferent signals stimulating pancreatic insulin release and inhibiting glucagon release. GPCRs for GLP-1 (GLP-1Rs) are also expressed in pancreatic islet β-cells, as well as in the GI tract, kidney, vagus nerves and neurons in areas of the brain such as hypothalamus and hindbrain. In pancreatic islet β-cells, GLP-1RAs binding to GLP-1Rs increases the biosynthesis of insulin, as well as of glucokinase and GLUT2 glucose transporter [19,32].

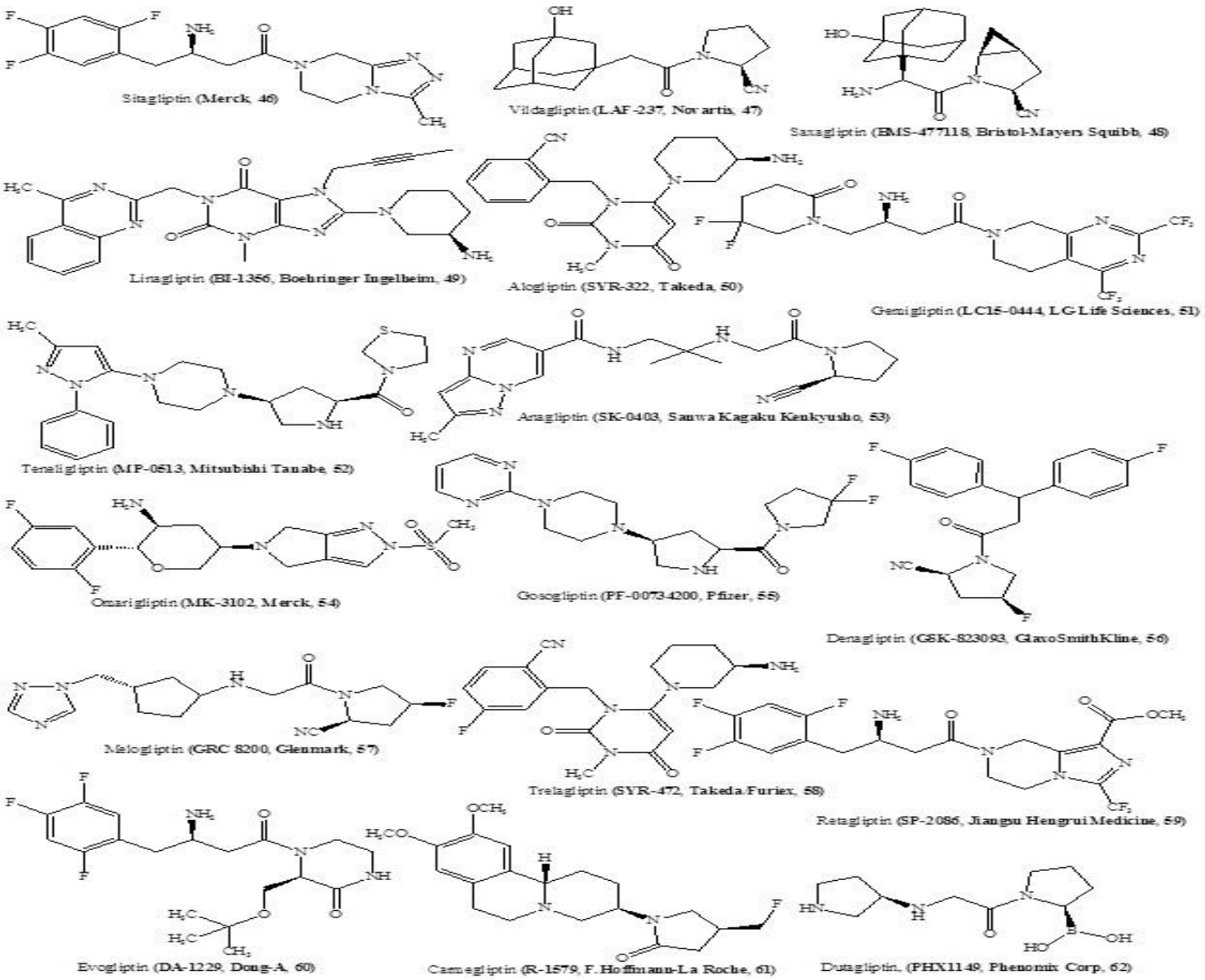
The GLP-1 is a peptide hormone that increases insulin secretion and decreases glucagon secretion from the pancreas in a glucose-dependent manner. GLP-1RAs provide pharmacologic levels of GLP-1, which reduces glucose and weight by increasing glucose-dependent insulin secretion and decreasing glucagon secretion, delaying gastric emptying and increasing satiety (Figure 10).

**Pharmacokinetics and adverse effects:** All GLP-1RAs **(40-45)** are administered as subcutaneous injections and modified human serum albumin. The most common adverse effects with the GLP-1 RAs are gastrointestinal related (nausea, vomiting, and diarrhea), weight loss and injection-site reactions [32,78].

**Dipeptidyl Peptidase Type 4 (DPP-4 or DPP-IV) Inhibitors (Gliptin)**

Various clinically feasible approaches for the use of GLP-1 to treat Type 2 DM have been reported. Out of these approaches, DPP-4 inhibitors are of considerable interest to the pharmaceutical industry. DDP-4 was first identified in1967 and early inhibitors were created by relatively simple modifications of proline-based structures. Now a day, structurally, two distinctive classes such as peptidomimetic and non-peptidomimetic DPP-4 inhibitors have been reported.

The peptidomimetic DPP-4 inhibitors class can be subdivided into glycine-based (α-series) and β-alanine-based (β-series). However, a number of non-peptidomimetic DPP-4 inhibitors class are structurally different from traditional α- or β-series. The non-peptidomimetic DPP-4 inhibitors class including fused imidazole, cyclohexylamine, aminopiperidine, quinazolinone, pyrimidinedione, isoquinolone and fluoroolefin derivatives [19,24]. The inhibitors of these derivatives and their approval and clinical trial status are reported in Table 10 [79].



**Mode of action:** Gliptin, which exert their action by increasing incretin levels such as GLP-1 and GIP. These two hormones are contributed to the physiological regulation of glucose homeostasis via increase the production and release of insulin by pancreatic β-cells (Figure 11). Approximately 60% of the postprandial insulin release is promoted by these two hormones. In addition, GLP-1 also reduces the secretion of glucagon by pancreatic β-cells, resulting in a decreased hepatic glucose production. These effects are glucose-dependent; GLP-1 stimulates insulin secretion and reduces glucagon production only at a higher blood glucose level. However, the effects of GLP-1 and GIP last only for a few minutes as they are inactivated due to DPP-4 [80].

**Pharmacokinetics:** The DPP-4 inhibitors are all orally available. These all are rapidly absorbed and significant inhibition of plasma DPP-4 activity being seen within 5 min of administration. The available data indicate that, the volume of distribution of the various inhibitors in humans is greater than the total body water. However, in the plasma, most of the inhibitors display low, negligible, extensively and reversible protein binding in a concentration-dependent manner. The major metabolic pathway of gliptins is liver. Generally, the gliptins are eliminated primarily via the kidney with the rate of renal clearance exceeding glomerular filtration and suggesting that active transport is involved [81].

**Adverse effects and side effects:** Common adverse effects include nasopharyngitis, upper respiratory infections and headaches. Rarely, severe allergic reactions have been reported [12].

**Table 1. Top 10 Countries for Estimated Numbers of Adults with Diabetes**

| Rank | Country | 2010 (millions) | Country | 2030 (millions) |
|---|---|---|---|---|
| 1 | India | 50.8 | India | 87.0 |
| 2 | China | 43.2 | China | 62.6 |
| 3 | U.S. | 26.8 | U.S. | 36.6 |
| 4 | Russian Federation | 9.6 | Pakistan | 13.8 |
| 5 | Brazil | 7.6 | Brazil | 12.7 |
| 6 | Germany | 7.5 | Indonesia | 12.0 |
| 7 | Pakistan | 7.1 | Mexico | 11.9 |
| 8 | Japan | 7.1 | Bangladesh | 10.4 |
| 9 | Indonesia | 7.0 | Russian Federation | 10.3 |
| 10 | Mexico | 6.8 | Egypt | 8.6 |

**Table 2. Etiology and Classification of DM**

| Types and Subtypes | Etiology |
|---|---|
| (1) Type 1 DM<br>(a) Type 1A DM<br>(b) Type 1B DM | <br>Immune-mediated<br>Idiopathic |
| (2) Type 2 DM | Genetic factor, Insulin resistance and Impaired insulin secretion. |
| (3) Type 3 DM | Genetic defects of β-cell function due to mutations in various enzymes [earlier called maturity-onset diabetes of the young (MODY)], genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug or chemical-induced, infections, uncommon forms of immune-mediated diabetes and other genetic syndrome sometimes associated with diabetes. |
| Type 4 DM | Glucose intolerance during pregnancy |

**Table 3. Revised Criteria for Diagnosis of DM**

| Patient Status | Plasma glucose value* mg/dl (mmol/L) | Diagnosis |
|---|---|---|
| Fasting value | Below 110 | Normal fasting value |
| | 110-126 (6.1-7.0) | Impaired fasting glucose (IGF)** |
| | 126 (7.0) or more | DM |
| Two-hour after 75g oral glucose load | 140-200 (7.8-11.1) | Impaired glucose tolerance (IGT)** |
| | 200 (11.1) or more | DM |
| Random value | 200 (7.8-11.1) in a symptomatic patient | DM |

*plasma glucose values are 15% higher than whole blood glucose value.
**individuals with IFG and IGT are at increased risk for development of type 2 DM later.

**Table 4. Insulin Effects on Various Glucose Transporters**

| Transporter | Glucose Km* (mmol/L) | Tissues |
|---|---|---|
| GLUT 1 | 1-2 | All tissues, especially red cells and brain. |
| GLUT 2 | 15-20 | B-cells of pancreas, liver, kidney and gut |

| | | |
|---|---|---|
| GLUT 3 | <1 | Brain, kidney, placenta and tissues |
| GLUT 4 | ≈5 | Muscle and adipose tissue |
| GLUT 5 | 1-2 | Gut and kidney |

*The Km value an indicator of the affinity of the transporter protein for glucose molecules.

**Table 5. Effects of Insulin on Carbohydrate, Fat and Protein Metabolism**

| ***Metabolism*** | **Liver cells** | **Fat cells** | **Muscle** |
|---|---|---|---|
| Carbohydrate | ↓ Gluconeogenesis<br>↓Glycogenolysis<br>↑Glycolysis<br>↑ Glycogenesis | ↑ Glucose uptake<br>↑ Glycerol synthesis | ↑ Glucose uptake<br>↑ Glycolysis<br>↑ Glycogenesis |
| Fat | ↑Lipogenesis<br>↓ Lipolysis | ↑ Synthesis of triglycerides<br>↑ Fatty acid synthesis<br>↓ Lipolysis | |
| Protein | ↓ Protein breakdown | | ↑ Amino acid uptake<br>↑ Protein synthesis |

Up (↑) arrow indicates increases and down (↓) arrow indicates decreases.

**Table 6. Effects of TZDs treatment on Pancreas, Adipose Tissue, Pancreas, Liver, Skeletal Muscle and Vascular Wall-Endothelium**

| **Body parts** | **Effects of TZDs** |
|---|---|
| Pancreas | Improves pancreatic β-cell function |
| Adipose tissue | Increase of subcutaneous adipose tissue<br>Proliferation of small size adipocytes<br>Increases in glucose uptake, lipogenesis, fatty acid uptake and pre-adipocyte differentiation |
| Liver | Reduction of visceral adipose tissue<br>Increase in insulin sensitivity, glucose uptake and lipogenesis<br>Decreases in gluconeogenesis and glycogenolysis |
| Skeletal muscle | Increase in insulin sensitivity, glucose uptake, glycolysis and glucose oxidation |
| Vascular wall-endothelium | Reduction of PAI-1, fibrinogen, HbA1c, plasma insulin concentration, TNF-α, matrix metalloproteinase-9 (MMP-9), endothelin-1, intracellular adhesion molecule-1, vascular cell adhesion molecule-1 and inflammatory markers such as C-RP (C-Reactive Protein), IL-6, E-selectin, serum amyloid A and sCD40L.<br>Improvement in markers such as intima media thickness (IMT), flow-mediated vasodilation and pulse wave velocity |

**Table 7. Effects of TZDs Treatment on Established and Emerging CVD Risk Factors**

| **CVD risk factor** | **Impact of TZDs treatment** |
|---|---|
| Hyperglycemia | Reduction in HbA1c (0.5 to 1.5%) |
| Hypertension | Reduction in blood pressure |
| Dyslipidemia | Reduction in triglycerides<br>Increase in HDL cholesterol and LDL particle size<br>Decrease in FFA and postprandial lipemia |
| Markers of endothelial inflammation | Decreased CRP, white blood cell count, fibrinogen, MMP-9, TNF-α and microalbuminuria<br>Increased adiponectin |
| Markers of elevated thrombotic risk | Decreased PAI-1 and platelet aggregation |

**Table 8. Proven and Potential Benefits and Risks of TZDs**

| **Benefits** |
|---|
| Improved glycemic control, pancreatic β-cell function and endothelial function |
| Lower insulin resistance and blood pressure |
| Fat redistribution/decreased visceral fat and IMT |
| Reduced cardiovascular morbidity and mortality |
| Induction of ovulation in polycystic ovary syndrome |
| Less bone turnover |
| Treatment for neoplasms |
| Decreased alanine aminotransferase, suggesting decreased liver fat |
| **Risks** |

| |
|---|
| Hepatotoxicity/potential for liver failure<br>Weight gain/increased total body fat (subcutaneous)<br>Edema/fluid retention<br>Pulmonary edema<br>Increased lipoprotein levels<br>Bone fracture |

**Table 9. Currently Available GLP-1 RAs**

| Drug/ Dosing frequency | US FDA approval status | EMA approval status |
|---|---|---|
| Exenatide **(40)**/ Twice daily | Approved 28 April 2005 | Approved 20 November 2006 |
| Exenatide **(40)**/ Weekly | Approved 26 January 2012 | Approved 17 June 2011 |
| Liraglutide **(41)**/ Daily | Approved 25 January 2010 | Approved 30 June 2009 |
| Lixisenatide **(42)**/ Daily | Submitted Withdrawn 12 September 2013 | Approved 1 February 2013 |
| Albiglutide **(43)**/ Weekly | Approved 15 April 2014 | Approved 23 January 2014 |
| Dulaglutide **(45)**/ Weekly | Submitted | Submitted |

**Table 10. The DPP-4 inhibitors Approval and Clinical Trial Status Reports**

| Drugs and its Approval status | Drugs and its clinical trials status |
|---|---|
| Sitagliptin **(46):** Approved by USFDA in 2006 and is used as either a monotherapy or in combination with metformin. | Omarigliptin **(54):** In phase-III clinical trials. |
| | Gosogliptin **(55):** In the clinical trial study |
| Vildagliptin **(47):** Approved by EMA in 2008 for use within the EU. It is still waiting for FDA approval for use in the US. | Denagliptin **(56):** In the clinical trial study |
| | Melogliptin **(57):** In phase-III clinical trials. |
| Saxagliptin **(48):** Approved by USFDA in 2009 and is used as either a monotherapy or in combination with metformin, TZDs and sulfonylurea. | Trelagliptin **(58):** In phase-III clinical trials in Japan and has been submitted to New Drug Application (NDA). |
| Linagliptin **(49):** Approved by USFDA in May 2011. | Retagliptin **(59):** In phase-III clinical trials. |
| Alogliptin **(50):** Approved by USFDA in January 2013. | Evogliptin **(60):** Completed phase-II clinical trial. |
| Gemigliptin **(51):** Approved by Korean FDA in June 2012. | Carmegliptin **(61):** The clinical trial result shows that it was efficacious and safe inhibitor |
| Teneligliptin **(52):** Approved by Japan.<br>Anagliptin **(53):** Approved by Japan. | Dutagliptin **(62):** Currently in phase-III clinical trial and shows excellent safety profile |

**Fig 1. Pathogenetic factors affecting impairment insulin secretion**

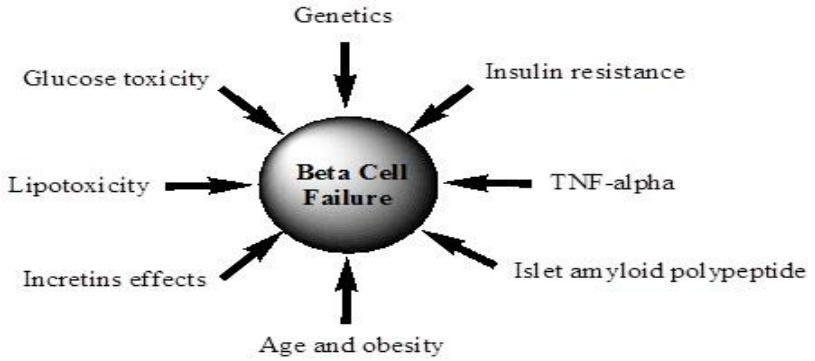



**Fig 2. Layout figure of complications of DM**

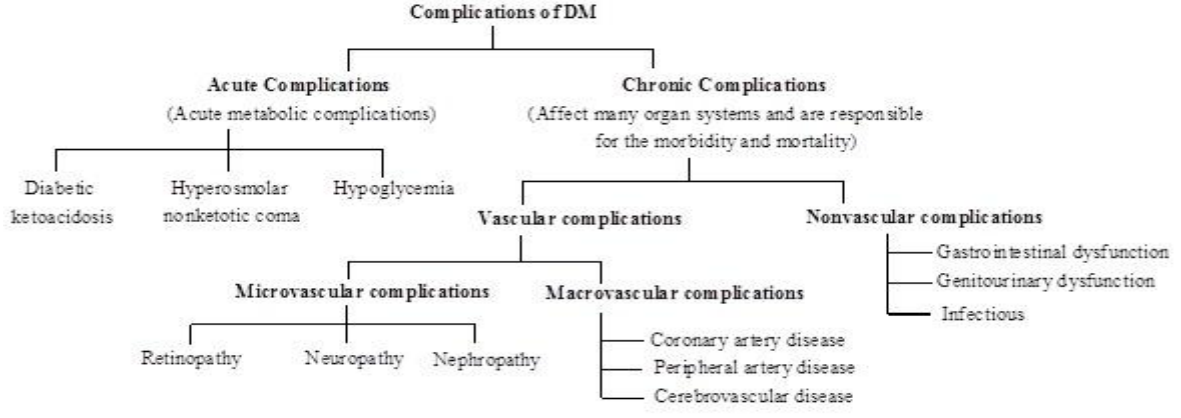


**Fig 3. Layout figure of complications of DM**

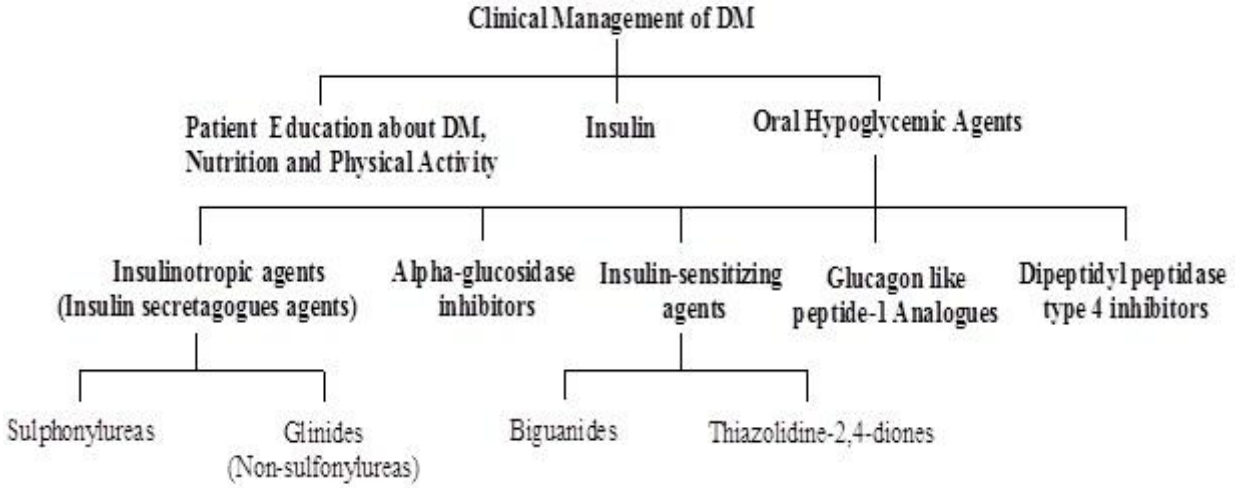



**Fig 4. Human proinsulin and its conversion to insulin**

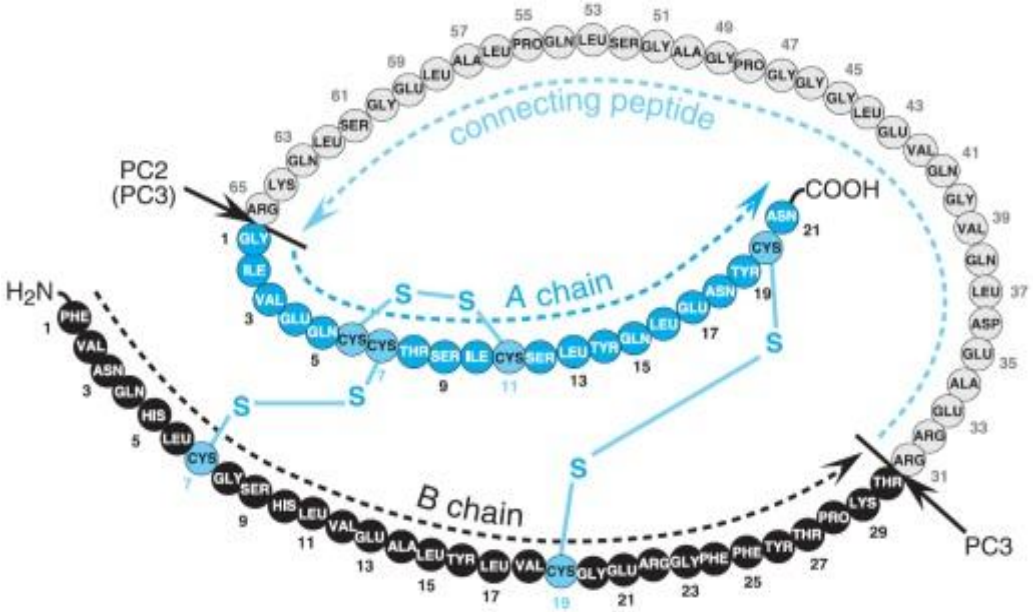



**Fig 5. A model of insulin receptor and mediation of its metabolic and cellular actions**

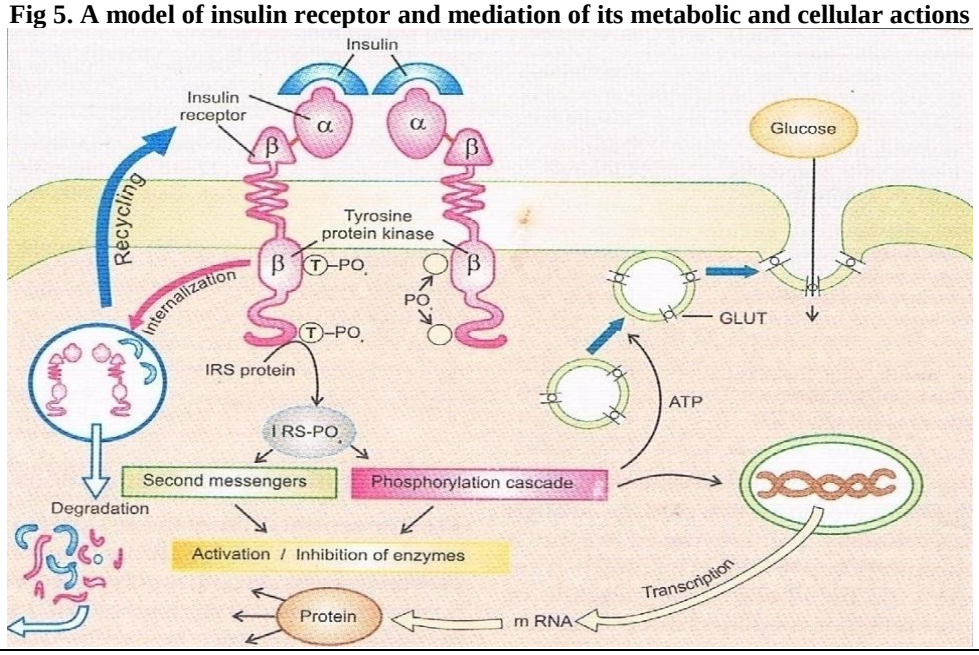


**Fig 6. Mechanism action of sulfonylurea on pancreatic β-cells**

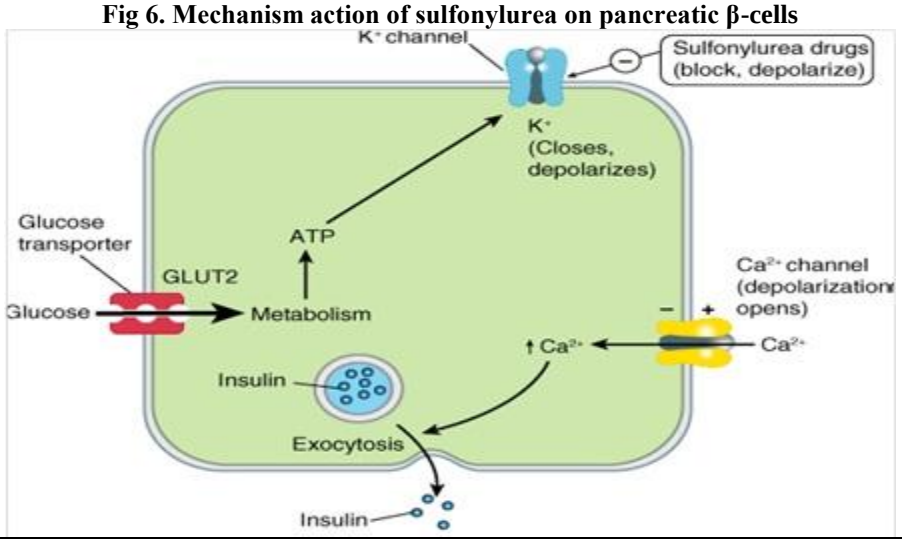



**Fig 7. Action of transcriptional regulation of PPARγ via TZD**

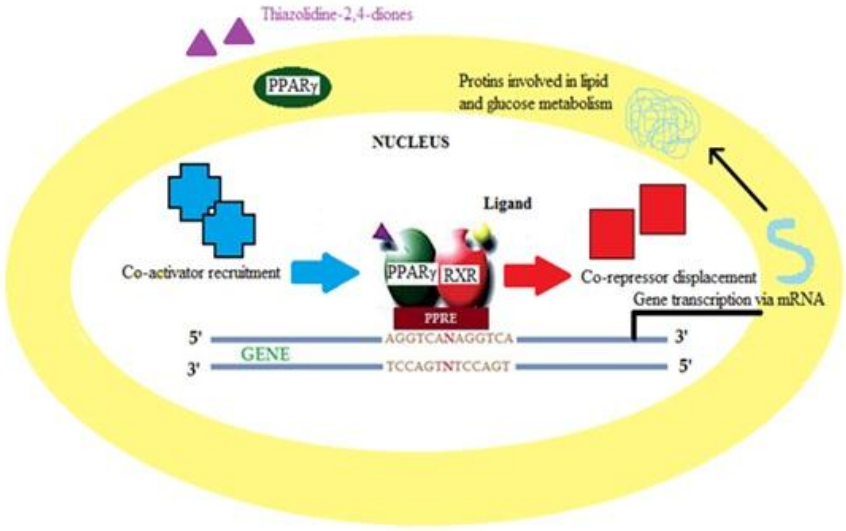



**Fig 8. The incretin hormones**

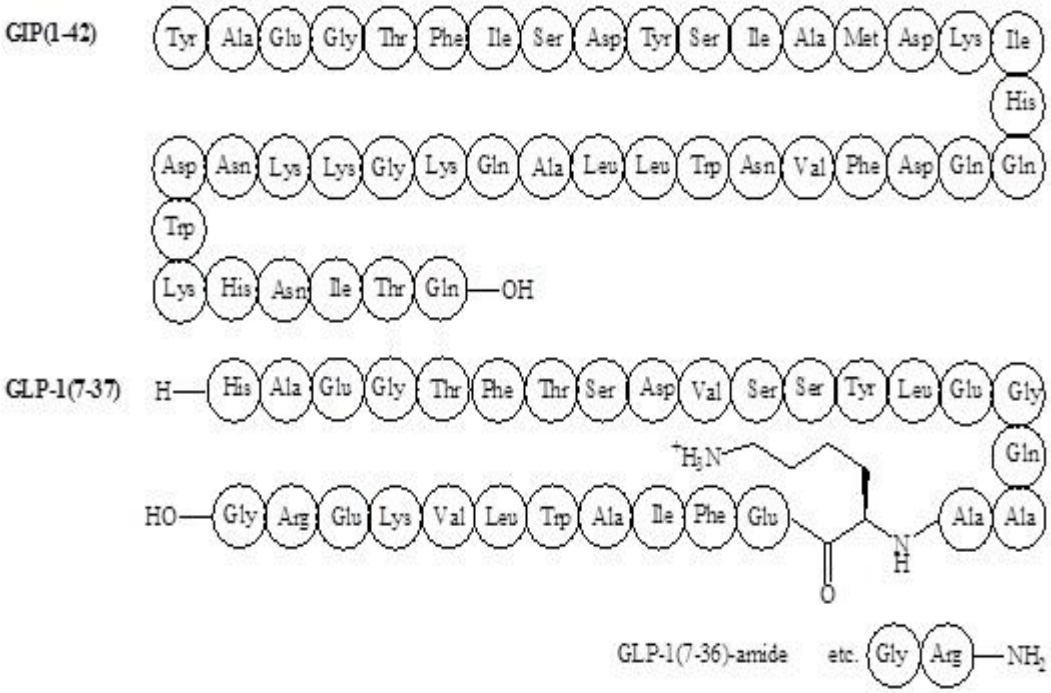


**Fig 9. A schematic diagram of dulaglutide**

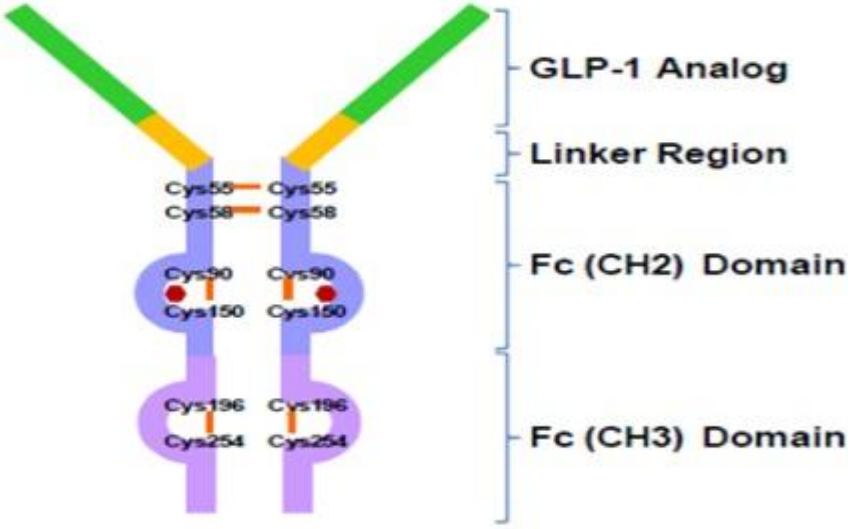



**Fig 10. Physiological effects of GLP-1 analogue**

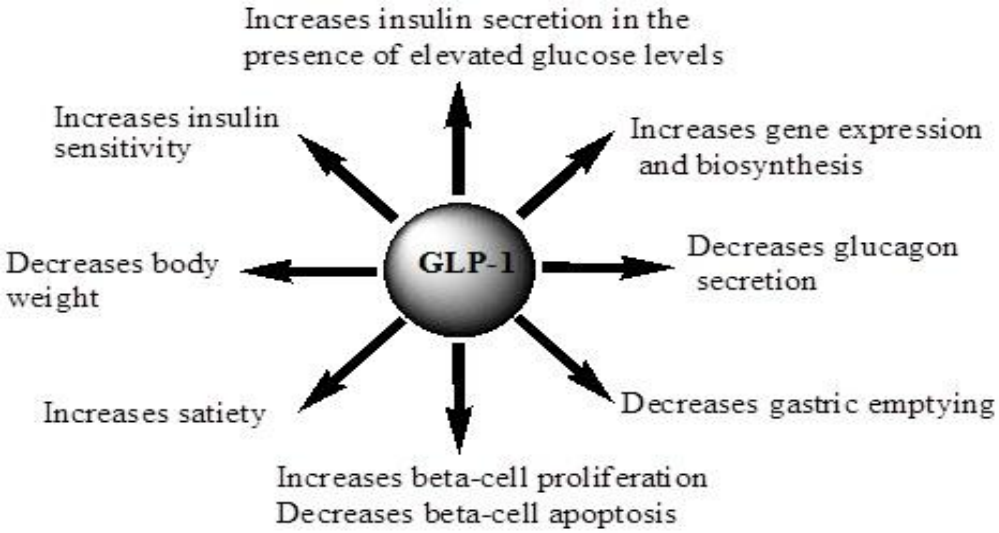
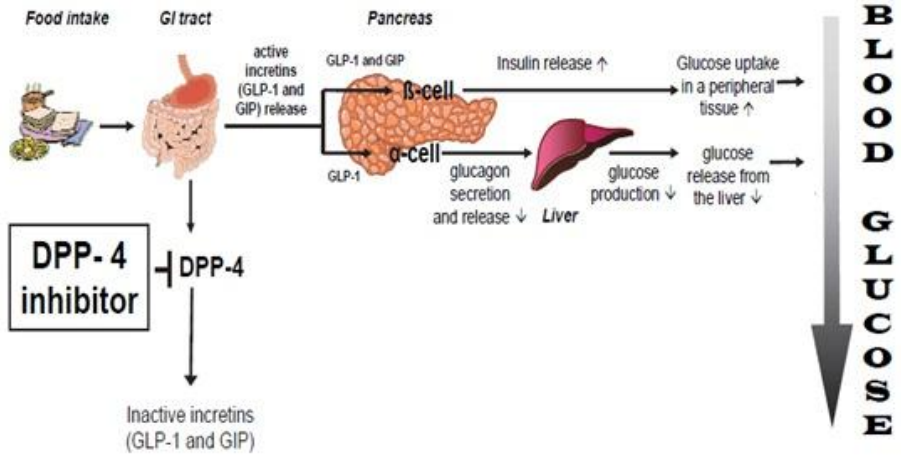



**Fig 11. Mode of Action of DDP-4 Inhibitors**

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