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An Overview of Therapeutic and Non Therapeutic Methods of Anti-Diabetic Activitys

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Abstract

Diabetes mellitus and its complications are one of the major health challenges of our time. Currently, more than 400 million adults are affected, a number that is expected to increase to 600 million people within the next two decades. Type 2 diabetes mellitus, or non-insulin dependent diabetes mellitus, is the most common type and its initial stages are treated with oral anti-diabetics. Though anti-hyperglycemic agents with different mechanisms of action are commercially available, their adverse events and hepato-renal toxicity are pronounced. Thus, the discovery of new and safer medicines is urgently warranted. Natural drug products have always been an important source of bio actives and drugs derived from nature still account for half of today's approved therapeutics. This Special Issue, "Anti-diabetic Drugs from Natural Resources", is dedicated to the discovery of new anti-diabetic lead compounds from nature. Research articles and reviews dealing with novel anti-diabetic activities of natural products and/or natural sources of anti-diabetics are therefore very welcome. Additionally, the evaluation of extracts and herbal preparations used for the treatment of diabetes mellitus by modern analytical techniques will be considered.

Keywords

Anti-diabetics • Anti-hyperglycemic agents • Natural resources • Analytical techniques

Introduction

Definition

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels (American Diabetes Association) [1].

Epidemiology

Diabetes is the world's largest endocrine disease and will be the 7th leading cause of death in 2030. According to W.H.O projection, the prevalence of diabetes is likely to increase by 35%. Recent estimates indicate there were 171 million diabetes worldwide in the year 2000 and this would increase to 366 million by the year 2030. The number of diabetic patients will be double in urban population in developing countries between 2000-2030. The low and middle income countries will have more diabetic population and prevalence rate will increase in next coming 22 years. Over the next coming 50 years, rate of diabetes prevalence in USA will increase in US population with higher number of diagnosed diabetic patients. This higher rate results due to population growth (27%), prevalence rate (36%) and change in demographic composition (37%). India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the diabetes capital of the world. Statistical projections about India suggest that the number of diabetics will rise from 31 million in 2000 to 79 million in the year 2030 making the country with the highest number of diabetics in the world followed by China and then USA [2].

According to ICMR Report, diabetes prevalence rate is lower in northern India as compared to Southern India viz., Chandigarh (0.12 million), Jharkand (0.96 million), Maharastra (9.2 million) and Tamilnadu (4.8 million).The national urban survey estimates diabetes prevalence rate in metropolitan's cities viz., Kolkata (11.7%), Kashmir (6.1%), New Delhi (11.6%), Mumbai (9.3%), Chennai (13.5%), Hyderabad (16.6%) and Bangalore (12.4%) [3].

Symptoms

The clinical diagnosis of diabetes is often indicated by the presence of symptoms such as:

- Polyuria.
- Polydipisia.
- Feeling very hungry
- Extreme fatigue.
- Blurry vision.
- Cuts/bruises that are slow to heal.
- Unexplained Weight loss.
- Tingling, pain, or numbness in the hands/feet (type 2).

Classification of Diabetes

Diabetes has been classified as: Diabetes mellitus and Diabetes insipidus

Diabetes Mellitus

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The American Diabetic Association and World Health Organisation time to time issued new diagnostic and classification of diabetes mellitus includes four clinical classes (American Diabetes Association) [4].

• Type-1 diabetes (absolute insulin deficiency resulted from βcell destruction)

• Type-2 diabetes (insulin resistance due to progressive insulin secretory defects)

• Other specific types of diabetes [due to other causes, e.g., genetic defects in βcell function, monogenic diabetes syndromes (neonatal diabetes and maturity onset diabetes of the young), genetic defects in insulin action, diseases of the exocrine pancreas, drug or chemical induced.

• Gestational diabetes mellitus (GDM) (diagnosed during pregnancy)

Type 1 diabetes and pathogenesis: Type 1 diabetes (insulin dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. It is a chronic autoimmune disorder that precipitates in genetically susceptible individuals by environmental factors (Atkinson and Eisenbarth). The body's own immune system attacks the βcells of islets of Langerhans in pancreas, destroying or damaging them sufficiently to reduce and eventually eliminate insulin production [3].

The disease appeared in children and adolescents suddenly, usually presenting with a classic trio of symptoms (Polydypsia, polyphagia and polyuria) alongside of overt hyperglycemia. The risk development of type-1 diabetes in an individual can be assessed by studying family history, e.g., age of onset and sex of member from effected family, immunity, genetic marker profiling. It also varies according to seasonal changes, e.g., higher in winters and lower in summer. In 2020, it has been predicted that new cases of type-1 diabetes will be doubled in number especially in child younger than 5 years and 70% increase in prevalent cases younger than 15 years [5].

Type-2 diabetes and pathogenesis: Insulin maintains homeostasis of energy store levels for growth and normal functioning of biochemical process in the body. In normal individual, an equilibrium balance between insulin secretion and insulin sensitivity maintain glucose levels in narrow range under fasting and non-fasting conditions. Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder associated with mutilation in both insulin action and insulin secretion which results in disturbed glucose homeostasis.

The glucose homeostasis in human body is maintained by glucagon. Glucagon hormone is released from βcells of the islets of Langerhans of pancreas which stimulates hepatic glycogenolysis and gluconeogenesis. In T2DM, hyperglycaemia halt βcell suppression and hepatic glucose production increased in fasting state. The total hepatic glucose maintenance and production controls with glucagon levels along with somatostatin, and its inhibition decreases hepatic glucose production. Incretin hormone (GLP-1) and epinephrine also stimulate glucagon release in the human body. GLP-1 originates from same gene which encodes glucagon and proglucagon [6].

Other Specific Types of Diabetes

Other specific type of diabetes has been associated with diseases of the exocrine pancreas, drug or chemical induced Maturity Onset Diabetes of youth (MODY) (American Diabetic Association) [1]. The pancreas morphology distortion and exocrine pancreas failure has been reported in 5% of diabetic population in Western world. Diabetes due to pancreatic diseases is known as pancreatogenic or type 3c diabetes mellitus. Exocrine pancreas failure also results in both Type 1 and 2 diabetes. The occurrence of exocrine pancreas failure increase with decreasing levels of C-peptides. Pathophysiology of type 3 diabetes is quite different from type 1 and type 2 diabetes and it arises due to chronic inflammation (chronic pancreatitis) which leads to pancreatic carcinoma. In type 3 diabetes, patient's exocrine dysfunction, vitamin D deficiency, alteration in the incretin secretion and fat hydrolysis are commonly [5].

Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus (GDM) or type 4 diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Recent data shows GDM is responsible for total 7% of all complications related to pregnancy (American diabetic Association) during pregnancy woman pancreas unable to control increased levels of glucose and lipids. GDM is associated with other risk factors like prevalence of type-2 diabetes, preeclampsia, and ovarian syndrome and adverse conditions e.g. abortion. It has been postulated that insulin resistance by Pregnancy hormone and other factors which inhibit binding of insulin resistance by pregnancy hormone and other factors which inhibit binding of insulin to the receptors are responsible for GDM. GDM causes lipolysis which results in type 1 diabetes and ketoacidodsis with mild increase in glucose level [6].

Diabetes insipidus

Diabetes insipidus (DI) is a disease occurs due to failure in secretion of vasopression or antidiuretic hormone (ADH) from supraopticohypophysical system. This occurs only when the ADH neurons in the supraoptic and paraventricular nuclei are destroyed and cause frequent urination. Diabetes insipidus patient, due to lack of ADH makes the urine almost always very dilute except in very severe dehydration states. This disorder may be familial, idiopathic or secondary.

Diabetic insipidus is classified on the basis of fundamental defects in human body, i.e, impaired or inadequate secrection of ADH from the posterior pituitary gland known as neurogenic or central diabetes insipidus and insufficient renal response to ADH called nephrogenic diabetes insipidus. Central diabetes insipidus shows symptoms like polyuria, polydipsia, hypovolemia, hypernatrema elevated serum sodium levels, loss of electrolytes (Potassium and Magnesium) and weight loss. Central diabetes inspidus is also known as autoimmune central diabetes insipidus due to its association with autoimmunity in young patient with a clinical history of autoimmune diseases and radiological evidence of pituitary stalk thickening. Nephrogenic diabetes insipidus is a very rare disorder occurs due to response failures in the water retaining action of vasopression in the kidney [3].

Causes of Diabetes

Different causes are associated with each type of diabetes.

Type 1 diabetes

Doctors don't know exactly what causes type 1 diabetes. For some reason, the immune system mistakenly attacks and destroys insulin-producing beta cells in the pancreas. Genes may play a role in some people. It's also possible that a virus sets off the immune system attack.

Type 2 diabetes

Type 2 diabetes occurs from a combination of genetics and lifestyle factors. Being overweight or obese increases the risk too. Carrying extra weight, especially in belly, makes the cells more resistant to the effects of insulin on blood sugar.

This condition runs in families. Family members share genes that make them more likely to get type 2 diabetes and to be overweight [7].

Gestational diabetes

Gestational diabetes is the result of hormonal changes during pregnancy. The placenta produces hormones that make a pregnant

woman's cells less sensitive to the effects of insulin. This can cause high blood sugar during pregnancy.

Women who are overweight when they get pregnant or who gain too much weight during their pregnancy are more likely to get gestational diabetes [8].

Diagnosis of Diabetes

American Diabetic Association has laid down four criteria for diagnosis of diabetes (American Diabetic Association) [4].

Fasting glucose level >126 mg/dL (impaired glucose tolerance) and non-fasting plasma glucose >200 mg/dL

OGTT >200 mg/Dl

Hyperglycaemic symptoms (polyphagia, polyuria, polydipsia)

HbAlc >6.5%.

Treatment of Diabetes

Insulin therapy

Insulin therapy is main course of treatment for both type 1 and type 2 diabetes, specifically for type 1 diabetes. The various insulin delivery systems are available for administration of insulin, e.g., portable pen injectors, inhaled insulin, insulin degludee, insulin syringes and infusion pumps. Insulin is also administered intravenously, intramuscular, and traditionally insulin is administered by subcutaneous route. Insulin therapy is given to control abrupt glucose changes in diabetic state. Thus, insulin administration is similar in pharmacokinetic profile as that of endogenous insulin released from pancreas, i.e., rapid rise in concentration in blood, short duration of action and rapid clearance. Insulin replacement therapy is one of the effective methods for the treatment of type 1 and type 2 diabetes. Type 1 diabetic patients are treated with insulin therapy after confirmation of disease symptoms. Patients counseling is necessary before prescribing insulin therapy, e.g., amount of food intake in terms of carbohydrate, need of physical activity and hypoglycaemia effects [9].

Two types of insulin therapy regimens are usually followed in management of diabetes such as intensive and conventional therapy. Intensive insulin therapy is also known as flexible insulin therapy, in which current glucose levels and amounts of carbohydrate intake in the meal is considered before administration of human regular insulin. Hypoglycaemia is most common reported side effect in the intensive insulin therapy. In conventional insulin therapy, premixed human insulin (30% regularand 70% NPH) is administered before breakfast and dinner which is followed by fixed diet plans. The intensive insulin therapy consisted of daily three or more insulin injections and conventional insulin therapy is designed to control glucose levels with one or two insulin injection daily [6].

Insulin preparations

There are five types of insulin preparations that are most commonly used. They are differentiated by how quickly they start to work, and how long their effects last:

Rapid-acting insulin starts to work within 15 minutes and its effects last for 3 to 4 hours.

Short-acting insulin starts to work within 30 minutes and lasts 6 to 8 hours

Intermediate-acting insulin starts to work within 1 to 2 hours and lasts 12 to 18 hours.

Long-acting insulin starts to work a few hours after injection and lasts 24 hours or longer.

Mixtures of insulin [10].

Rapid acting insulin

Rapid acting insulin is safe and having very fast onset of action, rapid clearance, effective for short duration. Commercially, three injectable forms are available viz., insulin as part and insulin glulisine. A rapid-acting analog does not cause hypoglycaemia or nocturnal hypoglycaemia and show better control on postprandial glucose. These analogs can be administered before or immediately after meals.

Insulin lispro is first marketed insulin preparation in USA. Insulin lispro has alternation in the amino chain-B of insulin, i.e., proline (B-29) and lysine (B-28). This alteration increases dissolution rate of insulin because dimeric form of insulin is converted into monomer and rapidly absorbed but this modification does not change receptor binding affinity. Insulin as part is another commercially available insulin preparation for human use and is made by the substitution of praline (B-28) with aspartic acid. This exchange alters the interaction between monomer-monomer, i.e., aspartic acid (B-28) and glycine (B-23) which cause decrease in insulin self-aggregation [2].

Short acting insulin

Short acting insulin analogues did not show hazard of severe hypoglycaemia these have shown better management of HbAlc, postprandial glucose and diabetic ketoacidosis. Regular insulin is short acting insulin made by DNA recombinant technology. Itexists as hexamer form which is bulky in nature and create depot upon subcutaneous injection which causes delay in transportation through blood. Onset of regular insulin is appearing within 30 min and duration of action is about 2 to 3 hours.

Intermediate acting insulin

Intermediate-acting insulin has delay onset of action and absorption. Three types of intermediate-acting insulin have been used clinically viz., NPH (Neutral protamine Hagedorn or isophane), insulin glargine and insulin detemir. NPH at neutral pH is combined product of insulin and stoichiometric protamine in the isopbane ratio, i.e., neither insulin nor protamine found in large concentration. NPH is poorly soluble insulin product in blood which results in delay in action (onset of action is 2-5 h and duration of action is 4-5 h).NPH insulin shows little improvement in HbAlc level when compared with other intermediate-acting insulins [2].

Insulin glargine, intermediate acting insulin is having two modifications, i.e., addition of two arginine molecules at C-terminus of B-chain of human insulin and replacement of asparagine by glycine. This addition of arginine causes slightly increase in the solubility of insulin glargine towards acidic pH and shift in isoelectric point from pH 5.4 to 6.7. Insulin glargine has shown greater affinity towards insulin like growth factor-I receptors compared to regular insulin. The onset of action of insulin glargine is slow with significant activity maintained for 11-24 hours. Insulin glargine can be administrated any time during a day and significantly reduces HbAlc levels and prevent hypoglycemic shocks during nights.

Insulin detemir is a new long lasting analogue which is created by substitution of myristic acid at B-29 position and removal of threonine from B-30 position. These modifications cause self-aggregation and protein binding with albumin. The duration of action of insulin detemir is more than 12 h and having 1-2 h onset of action. Insulin detemir is considered to be much safer than NPH [2]. It shows better control on glycaemia in type 1 diabetes because it does not precipitate after subcutaneous administration, bind to albumin protein in the blood and form dept which can be easily buffer, if change occur in absorption parameters [11].

Long-acting insulin

This type takes the longest amount of time to start working. The insulin can take up to 4 hours to get into the bloodstream. Long-acting insulins don't peak like short-acting insulins they can control blood sugar for an entire day. This is similar to the action of insulin normally produced by our pancreas to help control blood sugar levels between meals. Long-acting insulins are also called basal or background insulins. They keep working in the background to keep our blood sugar under control throughout our

daily routine.

Mixtures of insulin

Mixture of insulin is a preparation created by mixing rapid and short-acting insulin in same syringe before administration such as insulin lispro, aspart, glulisine with NPH. Other mixtures of insulin are NPL (Neutral Protamine Lispro) and NPA (Neutral Protamine Aspart). Insulin preparation containing 50% of short-acting insulins are termed as high-mix insulins. These mixtures are well-tolerated, provide efficient control over glycaemia, and can be administered once or twice daily. The premixed formulation like 70% NPH and 30% regular insulin improves efficacy, accuracy and gives better control over glycaemia [7].

Oral anti diabetic agents

The oral antidiabetic drugs are used for the treatment of type 2 diabetes which is not controlled with diet restriction and physical exercise. Six categories of oral antidiabetic agents have been available in the market viz., biguanides, alpha-glucosidase inhibitors, sulfonylureas, meglitinides, thiazolidinediones, and dipeptidyl peptidase-IV (DPP-4) inhibitors. The first-line therapy for treatment in T2DM is started with most widely used oral antidiabetic drug, i.e., metformin. Second line of therapy involves sulfonylureas, thiazolidinediones, glucagon-like polypeptide-I (GLP-1) agonists, dipeptidyl peptidase-IV (DPP-4) inhibitors, meglitinides, or insulin in Table 1.

Table 1. Oral anti-diabetic agents

Types of Drug	Mechanism	Examples
Biguanides	Reduce the amount of glucose that liver makes	Metformin (Glucophage)
Alpha-glucosidase inhibitors	Slow our body's breakdown of sugars and starchy foods	Acarbose, Voglibose and miglitol
DPP-4 inhibitors	Improve blood sugar without making it drop too low	Linagliptin, saxagliptin, and sitagliptin
Glucagon-like peptides	Change the way our body produces insulin	Dulaglutide, exenatide, and liraglutide
Meglitinides	Stimulate pancreas to release more insulin	Nateglinide and repaglinide
SGLT2 inhibitors	Release more glucose into the urine	Canagliflozin and dapagliflozin
Sulfonylureas	Stimulate pancreas to release more insulin	Gliclazide, glibenclamide, glipizide, and glimepiride
Thiazolidinediones	Help insulin work better	Pioglitazone and rosiglitazone

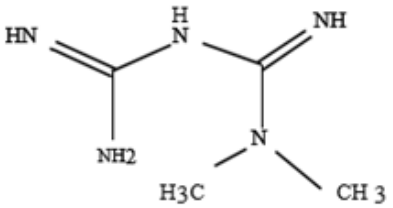

Figure 1. Metformin.

Metformin, a dimethylbiguanide, is used in treatment of T2DM chronically without increase in the risk of hypoglycaemia. Its efficacy, tolerance, safety, improved peripheral insulin sensitivity without increase in insulin secretion, weight gain and other beneficial effects on cardiovascular systems promote this drug as best for treatment of diabetes mellitus. The prediabetic risk development in patients with impaired glucose tolerance in Indian population has been significantly reduced with metformin. American Diabetes Association and American Association of Clinical Endocrinologist recommend monotherapy with metformin for the earlier treatment of hyperglycaemia in adult T2DM patients (American Diabetes Association) in Figure 1.

Sulfonylureas are developed in 1920s and used in the treatment of non-insulin dependent diabetes mellitus. The chronic use of sulfonylurea normalizes insulin levels to baseline with reduced glucose levels. Sulfonylurea is hormone releasing agent. Sulfonylurea acts as insulin secretagogues and stimulates insulin release from βcells of pancreas [3].

Sulfonylureas are classified into two groups' viz., first and second generation agents, e.g., Acetohexamide, Chlorpromazine, Tolazamide and Tolbutamide. The less potent agents are including in first generations agents, e.g., glibenclamide, glimepiride, gliclazide and glipizide and available in the markets for treatment non-insulin dependent diabetes mellitus. They inhibit ATP-senstive K-channels in βcell and initiate cascade of events which result in the release of insulin from granules. ATP-sensitive K-channels is a complex consisting of two subunit proteins Kir6.2 (pore-forming subunit) and SUR1 (drug-binding regulatory subunit) [8].

SUR1 is receptor binding site for sulfonylurea which initiates closing of ATP-K+ channels and decrease efflux of potassium which cause depolarization of plasma membrane of βcell. The chronic use of sulfonylureas significantly increases the risk of coronary heart disease in women in Figures 2-5.

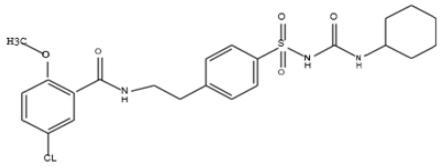

Figure 2. Glibenclamide.

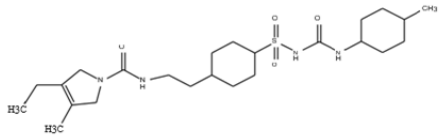

Figure 3. Glimepiride.

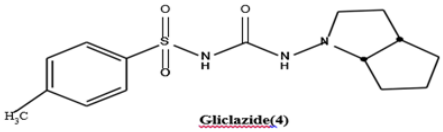

Figure 4. Gliclazide.

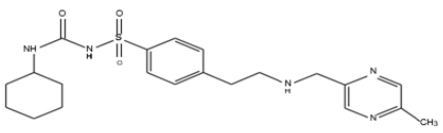

Figure 5. Glipizide.

Meglitinides are nonsulfoilylurea insulin secretagogues and act as rapid-acting postprandial insulin releasers. They too increase insulin secretion similar to sulfonylurea. The two marketed meglitinides are repaglinide and nateglinide. Meglitinides bind to Kir6.2 (pore-forming subunit) of ATP-sensitive K-channels present on plasma membrane of βcells of pancreas. Meglitinides are not effective in patients with dysfunction βcells in Pancreas in Figure 6. The monotherapy with repaglinide proves to be more effective in reducing HbAlc and fasting glucose levels in comparison to nateglinide. Repaglinide shows better tolerance and appear to be safe alternative in

geriatrics diabetic patients. They have rapid and short duration of action due to short half-life and potentiate only first phase insulin release. This contributes towards lower risk of hypoglycaemia. The adverse reactions of meglitinides are similar to sulfonylurea but with mild decrease in body weight in Figure 7 [11].

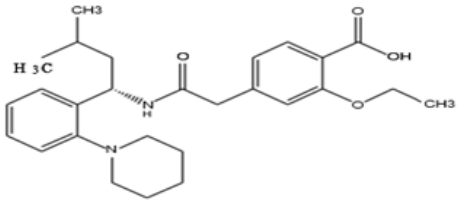

Figure 6. Repaglinide.

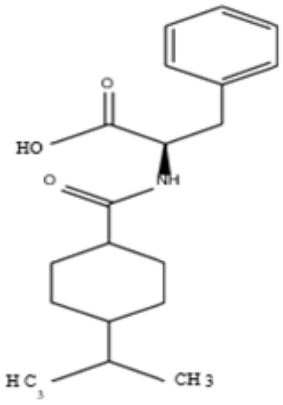

Figure 7. Nateglinide.

Thiazolidinediones or glitazones are new class of oral antidiabetic agents and are FDA approved drugs for type 2 diabetes, e.g., pioglitazone and rosiglitazone in Figures 8 and 9. Thiazolidinediones enhance insulin action, increase glucose muscle uptake and cause suppression of gluconeogensis. They reduce the concentration of circulating free fatty acids, triglycerides and cause rise in the levels of HDL and LDL cholesterol. Thiazolidinediones decrease insulin resistance by reppression of hepatic glucose output and increasing insulin dependent glucose metabolism, thus, used in treatment of type 2 diabetes associated with insulin resistance. Thiazolidinediones enhance insulin sensitivity and alter transcription of genes which modulate carbohydrate and lipid metabolism. They are ligands for peroxisome proliferative activated receptor-β(PPAR-β in muscle, adipose tissue and liver. PPAR-gamma activation causes transcription in genes for lipoprotein enzyme lipase, adipocyte fatty acid binding protein, fatty acyl-CoA synthase, glucokinase and GLUT4. Thiazolidinediones diminish insulin resistance through activation of endocrine signaling in skeletal muscle and liver. Rosiglitazone and other PPAR βactivator agents inhibit activation of c-Jun NH2-terminal kinase (JNK) signaling pathway and enhance survival rate of β-cells of pancreas [12].

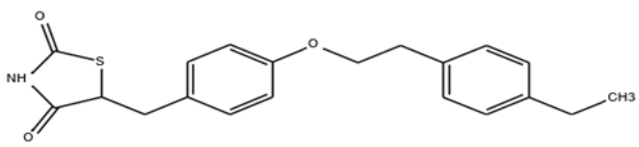

Figure 8. Pioglitazone.

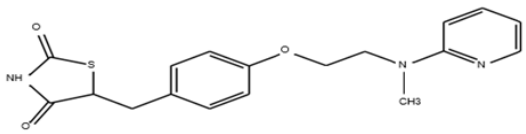

Figure 9. Rosiglitazone.

The reported side effect of thiazolidinediones is edema when used in combination therapy with insulin. Thiazolidinediones also aggravate risk of congestive heart failure in T2DM patient. βGlucosidase is membrane bound enzyme present in small intestine and assists in absorption of carbohydrate after meal. βglucosidase inhibitors (AGIs) have similar mechanism of action, i.e., inhibition of carbohydrates absorption from gastrointestinal tract. AGIs are pseudo-sugars which competitively and reversibly inhibit βglucosidase enzyme and cause delay in the absorption of carbohydrates from gut. These are used in management of type 2 diabetic patients with impaired glucose tolerance. Voglibose, miglitol in Figures 10 and 11, acarbose are most widely used AGIs for the treatment of type 2 diabetes and decrease postprandial plasma glucose and insulin levels.

AGIs are most beneficial T2DM patient's havingpostprandial plasma glucose levels and normal HbAlc. A clinical situation where glucose levels are not controlled with mono-therapy of other oral antidiabetic agent, diet and exercise, AGIs can be used as first line of drug in combination therapy. Acarbose is used as add-on therapy in poorly controlled T2DM patients with diet, sulphonylurea and biguanide. The starting dose of AGI is low and administered after meals. These inhibitors reduce glucose level about 54 mg/dL and HbAlc 0.9%. The common side effects of AGIs are flatulence, gut discomfort, diarrhoea and bloating. Hepatic injury is rare side effect reported with AGIs use [9].

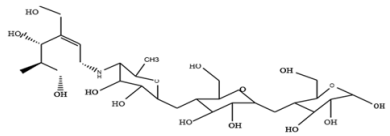

Figure 10. Acarbose.

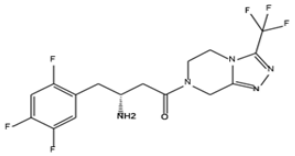

Figure 11. Sitagliption.

The two primary incretin hormones secreted from intestine after post meal are glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Incretin hormones stimulate insulin secretion from βcells of pancreas and regulate glucose homeostasis. In response to elevated glucose concentration after meal, incretin hormones (GLP-1 and GIP) enhance insulin release from βcells, and additionally GLP-1 decreases glucagon production. In hypoglycaemia state, GIP promotes glucagon counter-regulation and increases βcells sensitivity for glucose. Incretin hormones action is meditated through activation of adenylatecyclase and high level of cyclic adenosine monophosphate (cAMP). Incretinmimetics are new class of drugs used in treatment and management of type 2 diabetes, e.g., dipeptidyl peptidase 4 inhibitor (DPP-4 Inhibitor) and GLP-1 receptor agonist. In plasma, dipeptidyl peptidase-4 (DDP-4) cause's cleavage of two NH2-terminal amino acids of both GIP and GLP-1, thus, block the action of incretin hormones which results in reducing insulin level and higher postprandial glucose. DPP-4 Inhibitor effectively decreases HbAlc without causing increase in the body weight. Five DPP-4 inhibitor are available in market viz., sitagliptin, vildagliptin in Figures 11 and 12 [10].

Sitagliptin is a selective and efficacious dipeptidyl peptidase 4 inhibitor used for the management of type 2 diabetes and well tolerated with ongoing metformin therapy. Recent studies reveals sitagliptin monotherapy reduces both fasting and non-fasting glucose level along with improved functioning of βcells in T2DM.

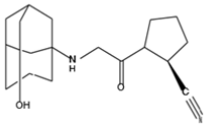

Figure 12. Vildaglipt.

Sitagliptin is also found to be valuable and safe in treatment type 1 diabetes mellitus. It exhibits better control over glycaemia when used in combination with Linagliptin, a xanthine base, is selective towards DPP 4 enzyme. It decreases HbAlc levels in diabetes with good tolerability profile in patient with renal defects. It is well tolerated in obese, geriatric patients and does not require dose adjustment. Linagliptin shows better safety profile over sulfonylurea without causing increase in body weight, stroke and cardiovascular effects. It enhances insulin sensitivity and reduces liver fat inhepatic steatosis [11].

Non-Therapeutic Methods

The higher prevalence of obesity and diabetes in urban population is related to unhealthy lifestyles, i.e., lack of exercise, unhealthy dietary habits and over eating. The diet control and weight reduction have shown advantageous effect on insulin action and sugar level in the mild type 2 diabetes mellitus. It is related in terms of change in macronutrients and abdominal fat. In type 1 diabetes mellitus, variation in dose regime of rapid and short-acting insulin has been made according to carbohydrate content of meal to meal for better control on hyperglycaemia. A similar approach has been recommended for type 2 diabetes mellitus. In obeseT2DM patients, increased unsaturated fat consumption in meal causes decrease in insulin sensitivity and increase in the body weight. Protein metabolism does not increase glucose levels instead protein ingestion causes stimulation of insulin release, C-peptide and glucagon [2].

In day to day lifestyle, lack of physical activities has increased developmental risk of type-2 diabetes mellitus in young, adult and older people. Exercise or burning of extra calories found to be helpful in prevention and control of type 2 diabetes mellitus and weight gain. The eight week long exercise regime exhibit decrease in glycosylated haemoglobin. Physical activities improve insulin sensitivity and decrease elevated glucose level in the body. The risk of diabetes in predictable patient with impaired glucose tolerance is reduced by higher expenditure of energy and weight loss. It also reduces the incidence of cardiovascular diseases associated with type 2 diabetes [9].

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