JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Diabetes Mellitus A Silent Killer: Role of DPP4 Inhibitors in Treatment

V. Jakhmola*, P. Tangri

1GRD(PG)IMT, Dept. of Pharmacy, Dehradun, India

ABSTRACT:

Diabetes mellitus is rapidly becoming the world's largest silent killer. World Health Organization says that in 2000, approx 2.8% of the world population was suffering from diabetes (~180 million people), and estimate will be almost double, by the year 2030. Treatment should aim to normalizing the basic defects in the disease, which are islet dysfunction in combination with insulin resistance and should also, directly or indirectly target the diabetes induced complications. Conventional treatments have been the use of Antidiabetic drugs like sulphonylureas and Biguanides. , a new class of antidiabetic drug DPP4 inhibitors (vildagliptin, sitagliptin & saxagliptin etc.) targeted to extrapancreattic cells. DPP-IV inactivates incretin hormone. There are two incretins, known as glucose- dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), which share many common actions in the pancreas but have distinct actions outside of the pancreas. DPP-4 inhibitors are a new class of agents that improve long-term, 24-hour control of HbA1c, FPG (before meal) levels, and PPG (after meal) levels through decreased DPP-4–mediated degradation of incretin hormones. DPP-4 inhibitors provide a complementary mechanism of action to existing OADs and demonstrate significant efficacy when added to MET, an SU, or a TZD, with a well-tolerated profile, including a low risk for hypoglycemia and weight neutrality.

KEY WORDS: diabetes mellitus, DPP4 inhibitors, type II, glucose metabolism

Article history:
Received 05 Mach 2012
Revised 11 march, 2012
Accepted 21 March 2012
Available online 13 April 2012

For Correspondence:

Mr. Vikas Jakhmola,

[1]GRD (PG) IMT, Dept. of Pharmacy, Dehradun, India

Contact no: +91 8126009620

Email: vikas_mpharm@rediffmail.com

Introduction:

Diabetes mellitus is rapidly becoming the world's largest silent killer. World Health Organization says that in 2000, approx 2.8% of the world population was suffering from diabetes (~180 million people), and estimate will be almost double, by the year 2030.[1-3] In India diabetes prevalence increasing rapidly parallel with the fast urbanization. The World Health Organization has predicted that the major diabetic burden will occur in the developing countries. India, China and United States are top 3 countries with the largest number of diabetic people. India in the last decade has highlighted with high prevalence rate of type 2 diabetes high, especially in urban population. India leading the top ten countries with most diabetic people, 66.58 million estimated from 2004, will be rise to 79.4 million from 2030. Diabetes mellitus is a condition of metabolic disorder in which the body either does not produce enough, or does not properly respond to, insulin.[3-5] Diabetes mellitus may be describe as a metabolic disorder of multiple aetiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Insulin is a 51 amino acids polypeptide, and secretes from the islets of Langerhans region of the pancreas and play a major role in decreasing the blood glucose level and regulating the metabolism of carbohydrate, fat, and protein.[6-8] Elevated blood glucose level stimulates insulin release, and insulin stimulates uptake, utilization and storage of glucose. Insulin facilitates entry of glucose into muscle, adipose and several other tissues via GLUT4 glucose transporters. Insulin also stimulates the liver to synthesis glycogen (storage polymer). In lipid

metabolism, insulin promotes fatty acid synthesis in the liver, which is exported from the liver as lipoproteins. In diabetes mellitus impaired insulin secretion and variable degrees of peripheral insulin resistance leading to sustained hyperglycemia.[6-11] Diabetes mellitus may be classified to 3 main categories, depending upon characteristics and cause.

TYPES OF DIABETES

Type 1 diabetes mellitus is insulin-dependent diabetes mellitus (IDDM) found in 10% of diabetic people; it formerly known as Juvenile Onset Diabetes. T1DM is characterized by immune-mediated loss of insulin-producing pancreatic beta cells of the islets of Langerhans, leading to insulin deficiency.[12] Type 2 diabetes mellitus is the most common form of diabetes and is due to defective insulin action and insulin secretion, either of which may be the predominant feature. According to the World Health Organization, over 90% of diabetic cases worldwide are Type 2. Gestational diabetes mellitus is carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy. The factors that cause gestational diabetes to develop are not completely known.[12-15]

SYMPTOMS OF DIABETES:

Along with hyperglycemia, early symptoms of diabetes mellitus are polydipsia, polyphagia, and polyuria. Later complications include vascular disease, peripheral neuropathy, and predisposition to infection. The effect of diabetes mellitus include long-term damage, dysfunction and failure of various organs.[13,14] Years of poorly controlled hyperglycemia lead to multiple, primarily vascular complications that affect small (microvascular) large (macrovascular) vessels or both. Long-term complications include cardiovascular disease, peripheral neuropathy, chronic renal failure (diabetic nephropathy), and retinal damage (diabetic retinopathy). Finally, Diabetes Mellitus is a group of disorders characterized by hyperglycemia and associated with microvascular (i.e., retinal, renal, possibly neuropathic), macrovascular (i.e., coronary, peripheral vascular), and neuropathic (i.e., autonomic, peripheral) complications. [14-18]

PATHOPHYSIOLOGY OF DIABETES

Diabetes mellitus recognized as a “metabolic disorder” with multifaceted clinical entity produced through the interaction of genetic, hormonal and lifestyle factors. The basic elements of this metabolic disorder (syndrome) have already been started many years before the onset of T2DM diabetes mellitus. Pre-diabetes is a condition in which individuals have blood glucose levels higher than normal but not high enough to be termed as diabetes mellitus.[17,18] People with pre-diabetes have an increased risk of developing T2DM, heart disease, and stroke. Metabolic disorder is a clustering of defects like abdominal obesity, elevated triglycerides, reduced HDLC level, hypertension and impaired fasting glucose and these all greatly increases individual’s probability of developing T2DM, atherosclerotic cardiovascular disease and chronic kidney disease.[19-21] Metabolic disorder associated with hyperglycemia, increases expression of many adipocytokines (macrophage proteins) such as TNF-α, IL-6, and MMPs. These proinflammatory cytokines induces insulin resistance. Hyperglycemia mediates its damaging effects through a series of secondary transducers, like ROS, AGE, PKC, PARP enzyme overactivation and no. of proinflammatory cytokines.[22-25] Insulin resistance and hyperglycemia induced cascade, target the vital organ of the body, & arouse the insurgency of diabetic complications. In heart, insulin resistance induced cardiomyopathy is closely linked with hyperglycemia induced endothelial dysfunctioning. Experimental studies suggest that Hyperglycemia and insulin resistance both cause endothelial dysfunction which diminishes the anti-atherogenic role of vascular endothelium. Endothelial dysfunction has been known as an initiating, critical factor, and main pathological change during the development of diabetic vascular disease.[26-29] The incident of heart failure is vastly higher in diabetic patient (39%) and mortality from cardiovascular complications is almost 3–5 fold higher compared with non-diabetic individual. In liver, insulin resistance is key pathogenic factor for Non Alcoholic Fatty Liver Disease (NAFLD).[30] Insulin resistance (hyperinsulinemia) increases serum fatty acid level, which taken up by liver and drive triglyceride production. TG hepatic accumulation causes Non Alcoholic Hepatic Steatosis (NASH). Hyperglycemis induced TNF- α promotes liver inflammation and ROS exacerbate the NASH conditions by ultrastructural mitochondrial lesion, which impair respiratory chain function, ultimately leading to liver fibrosis and cirrhosis.[30-34] Diabetic retinopathy is the result of microvascular retinal changes. Hyperglycemia-induced intramural pericyte death and thickening of the basement membrane lead to incompetence of the vascular walls. These damages change the formation of the blood-retinal barrier and the retinal blood vessels become more permeable.[34,35] An overaccumulation of glucose and/or fructose damages the tiny blood vessels in the retina. During the initial stage, called Nonproliferative Diabetic Retinopathy (NPDR), most people do not notice any change in their vision. Diabetic kidney, depict increased perfusion, GFR and intraglomerular capillary pressure.[36] T2DM show the modification in glomerular components (largely the basement membrane), due to nonenzymatic glycation and accumulation of advanced glycation end products. These combined mechanisms result in renal endothelial dysfunctioning and pathologic changes in the glomerular structure. Diabetes mellitus causes sensorimotor and autonomic neuropathy, both (Diabetic neuropathy). Circulating hyperglycemic blood and hyperglycemia induced secondary transducers, decrease the neuronal blood flow & nerve conduction velocity and affects all peripheral nerves: pain fibers, motor neurons, autonomic nerves.[36-39]

TREATMENT OF DIABETES

From pharmacological treatment side, availability of insulin from 1921 insures that all forms of diabetes are treatable but

a cure is difficult. Insulin is effective in all forms of diabetes mellitus. Most T1DM patient requires 0.4-0.8 UI/kg/day insulin. Pancreas transplants have been tried with limited success in T1DM. In T2DM, insulin dose varies 0.2-1.6 UI/kg/day depending upon severity and body weight of individual.[39-43] No. of oral hypoglycemic drugs act via different mechanism, are more effective T2DM than T1DM diabetes. Sulphonylureas servers as insulin secretion stimulant, act on the "Sulphonylurea Receptors" on the pancreactic β cells membrane causes depolarization, and increase the Ca^{2+} influx that increase the rate of exocytosis of insulin vesicles.[44,45] Thiazolidinediones are novel oral antidiabetic agents (Insulin sensitizer). Thiazolidinediones are selective agonist of nuclear peroxisome proliferatore-activated receptors γ (PPARγ) which enhances the transcription of several insulin responsive genes and deluge the insulin resistance.[46] Biguanides reduce gluconeogenesis and suppresses Hepatic Glucose Production (HGP). α-glucosidase inhibitors, like acarbose, miglitol reduce postprandial plasma glucose excursion. α–glucosidase is a small intestine mucosal bush border enzyme involved in carbohydrate metabolism.[46-49] A newer class of agent DPP4 inhibitors (Dipeptidyl Peptidase-IV) is Sitagliptin etc. Dipeptidyl Peptidase IV inactivates incretin hormone. Incretin are polypeptide that promotes blood glucose homeostasis by stimulating insulin secretion from pancreatic β cells in a glucose-dependent manner. An inhibitor of DPPIV is likely to lower blood sugar levels by increasing the level of active Incretin. Gastric Bypass Surgery has also been successful in many with morbid obesity and T2 DM. Gestational diabetes usually resolves after delivery. [50-54]

CURRENT TREATMENT SCENARIO

In the current scenario, Diabetic treatment focus to grapple blood glucose level with in limit without any adjuvant treatment for the diabetes induced complications. Antidiabetic drugs like sulphonylureas, targets to increase blood insulin level and/or activity of insulin. Biguanides suppresses Hepatic Glucose Production and α-glucosidase inhibitors reduce inhibits carbohydrate metabolism in intestine mucosal bush border region. Partial glycemic control reduces, but does not eliminate, the development of microvascular/macrovascular complications of diabetes (cardiomyopathy retinopathy, nephropathy, and neuropathy) in T1DM and T2DM diabetes and morality rate with diabetes patients is higher due to hyperglycemia induced diabetic complication especially by diabetic cardiomyopathy. Diabetes is directly responsible for 9% of acute myocardial infraction cases 4% of stroke cases, 2% of neuropathy, and 32% of cataract cases. Moreover diabetic complications, the antidiabetic agents also poses a significant risk of morbidity, mortality, and permanent sequelae secondary to prolonged periods of hypoglycemia.[55] As well as, Antidiabetes drug sulphonylureas has been reported to increase cardiac complications and chronic sulphonylurea treatment causes loss of insulin secretory capacity due to β-cell hyperexcitability. No. of antidiabetic drugs are hepatotoxic, also. Thus, there is a need for new treatment modalities for T2DM in view of the progressive deterioration of metabolic control that occurs in spite of intense treatment with existing modalities. New treatment should aim to normalizing the basic defects in the disease, which are islet dysfunction in combination with insulin resistance and should also, directly or indirectly target the diabetes induced complications.[56]

Among all antidiabetic drugs Thiazolidiendione and newer DPP4 inhibitors are targeted to extrapancreatic cells, to normalize hyperglycemia. Thiazolidinediones (TZD) like, Troglitazone, Pioglitazone & Rosiglitazone etc. are a novel class of antidiabetic agents which decrease blood glucose in T2DM patient, through alleviating insulin resistance. Insulin resistance and/or hyperinsulinemia underlie the pathogenesis of not only diabetes but also of the clustering syndrome called "syndrome X" or "insulin resistance syndrome" which includes hypertension, dislipidemia and hypercoagulation. TZD class of insulin sensitizers seems to have therapeutic potential to improve this clustering syndrome in addition to diabetes. TZD activate the peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear hormone receptor. Although PPARγ is predominantly expressed in adipose tissue, but also present in macrophages, vascular smooth muscle cells (VSMC), endothelial cells and several cancer cell lines.[43-47] PPARγ activation by TZD in these cells modulates functions such as the production of inflammatory cytokine by macrophages, proliferation and migration of VSMC, and growth or differentiation in cancer cells. Thiazolidinediones, regulate endothelial cell growth and secretion of vasoactive peptides. PPARγ-receptors are also found on endothelial progenitor cells and PPARγ-agonists (TZD) stimulate progenitor-mediated renal endothelial repair. Thus since TZD class of insulin sensitizers has many kind of therapeutic effect in addition to lowering blood glucose, these agents expect to have therapeutic potential beyond diabetes.[45-49]

ROLE OF DPP4 INHIBITORS

Like Thiazolidinediones, a new class of antidiabetic drug DPP4 inhibitors (vildagliptin, sitagliptin & saxagliptin etc.) targeted to extrapancreattic cells. DPP-IV inactivates incretin hormone. There are two incretins, known as glucose- dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), which share many common actions in the pancreas but have distinct actions outside of the pancreas. The incretins are insulinotropic and insulin secretory response accounts for at least 50% of the total insulin secreted after oral glucose. Both incretins are rapidly deactivated by an enzyme dipeptidyl peptidase 4 (DPP4). An inhibitor of DPPIV is likely to lower blood sugar levels by increasing the level of active incretin.[34-37]

DPP4, also known as the lymphocyte cell surface marker CD26, is a complex enzyme that exists as a membrane-spanning cell-surface aminopeptidase. Human DPP4 is ubiquitously expressed in epithelial & endothelial cells and

widely expressed in many tissues, such as liver, lung, kidney, intestine, lymphocytes, capillary endothelium and T-cells, B-cells and natural killer cells. DPP4 inhibition increases the circulation incretin level and incretin activity in pancreas. DPP4 inhibition may augment various incretin mediated physiological activities like:-[35-41]

- GLUCAGON-LIKE PEPTIDE-1 (GLP-1) stimulates insulin secretion, inhibits glucagon secretion, delay gastric emptying, and induce satiety. These effects contribute to the antidiabetogenic action of GLP-1.
- GIP increases the insulin gene transcription and biosynthesis, and enhances the glucose-sensing system and replenishes β-cells insulin.
- GLP-1 prevents exhaustion of β-cell reserves via increased insulin mRNA stability, gene transcription, and biosynthesis.
- GIP acts synergistically with glucose as a growth- and antiapoptotic factor for β- cells. GIP potentiates glucose-induced β-cell proliferation and protects β-cell against death induced by various stimuli and reduces islets cell death induced by glucolipotoxicity.
- GLP-1 counteract to abnormalities, including decreased insulin secretion and increased glucagon secretion, caused by excessive islet NO generation and augment islet adaptation to high fat diet-induced insulin resistance.
- GIP phosphorylates several transcription factors such as FoxO1 and $p70^{S6K}$, crucial regulators of translation, and involved in glucose- induced ß-cell mitogenesis.
- GIP increases antiapoptotic bcl-2 gene expression, also. Incretin augment pancreatic β–cells regeneration.
- GLP-1 attenuates TNF-α-induced expression of plasminogen activator inhibitor-1, a regulator of plasminogen activation implicated in endothelial cell dysfunction and ameliorates endothelial dysfunction in patients with T2DM with an established coronary artery disease.
- Pituitary adenylate cyclase-activating polypeptide (PACAP), and gastrin-releasing peptide (GRP) Like GLP-1, are DPP4 substrate and potent insulinotropic peptides that augment glucose-stimulated insulin secretion. PACAP and GRP are neuropeptides being signals of pancreatic nerves and, therefore, involved in the neural regulation of islet function. Prevention of inactivation of these peptides may contribute to the antidiabetic ability of DPP-4 inhibitors.

DPP4 is an “Adenosine Deaminase-Complexing Protein”. Adenosine deaminase (ADA), is a ubiquitous complex enzyme which catalyzes the irreversible hydrolysis of adenosine and deoxyadenosine to inosine and deoxyinosine. Adenosine deaminase-complexing protein (DPP4) plays important role in regulating membrane adenosine deaminase activity. It is widely expressed in many tissues, such as liver, lung, kidney, intestine, lymphocytes. Numerous endocrine peptides, chemokines, and neuropeptides such as bradykinin, endomorphin-2, growth hormone-releasing hormone, interleukin-2 and -1ß, prolactin, neuropeptide Y and substance P are also physiological DPP-4 substrates.

CONCLUSION:

Thus, DPP4 inhibition and incretin activation, a dual mechanism that may works in antidiabetic activity of DPP4 inhibitors and this category may be another class of drug that may act beyond the definition of antidiabetic drugs and may give protection to the patient in a multifunctional way, like thiazolidiendione. DPP-4 inhibitors have been studied in a broad range of patients and have demonstrated similar efficacy, regardless of age, gender, or race/ethnicity. These agents offer an important addition to the treatment of patients with T2D by providing another mechanism to address the multiple pathophysiologic defects present in this disease.

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