Research Article

Role of Sitagliptin- Dipeptidyl Peptidase-4 Inhibitor in Patients with Type 2 Diabetes Mellitus - An Overview

Bhuvaneswari Shanmugasundaram[1], Revathi Pichaipillai[1]*, Sarojini Kaliyaperumal[2], Chinthana Govindarajan[1], Jegan Arokiasamy[1], Sudhananthini Thangam[1], Manickavasagam Subramania Pillai[1]
[1]Department of Pharmacology, Chennai Medical College Hospital and Research Centre, (SRM Group), Tiruchirapalli, India.
[2]Department of Physiology, Ponniah Ramajayam Institute of Medical Sciences, Kancheepuram, India
*Corresponding author's E-mail: reva1923@gmail.com

ABSTRACT

Diabetes mellitus is major health problem and increasing cause of morbidity and mortality. Type 1 diabetes mellitus accounts for 5 to 10% and type 2 diabetes mellitus for 90 to 95% of diabetic population. Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new therapeutic approach for type 2 diabetes mellitus patients. At present, six DPP-4 inhibitors are available in the market – Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Linagliptin and Teneligliptin. Sitagliptin was first approached by 2009 and alogliptin in 2010. DPP4 inhibitors act by enhancing the levels of active incretin hormone. Sitagliptin as monotherapy reduces fasting glucose level and postprandial glucose level and glycosylated haemoglobin (HbA1C) around 0.7%. Studies showed that as add on therapy with biguanides, sulfonylurea and insulin, it significantly reduces the fasting plasma glucose level, Postprandial glucose level and glycosylated haemoglobin levels. Sitagliptin nullifies the side effects produced by oral agents. It reduces the hypoglycemic symptoms produced by sulfonylurea and weight gain produced by biguanides. Combination therapy with insulin improves the metabolic control and lipid profile by reducing low density lipoprotein cholesterol level and decreases the insulin requirements. Regarding safety and efficacy, Sitagliptin is more effective than any other oral hypoglycemic agents. Sitagliptin is safer in type 2 diabetes mellitus patients with cardiovascular disease. It improves the cardiac function and coronary artery perfusion, thereby reduces the cardiovascular risk in type 2 diabetes mellitus patients.

Keywords: Diabetes mellitus, DPP4 inhibitors, Incretin, Sitaglipitin, Efficacy, Safety

INTRODUCTION

In 2030, earning India mentioned as dubious distinction of being called the "diabetes capital of the world". Eating provokes the secretion of multiple gastrointestinal hormones involved in the regulation of gut motility, secretion of gastric acid and pancreatic enzymes, gall bladder contraction, and nutrient absorption. Gut hormones also facilitate the disposal of absorbed glucose through the stimulation of insulin secretion from the endocrine pancreas. Glucose-dependent insulinotropic polypeptide (GIP) was identified first, it is purified from porcine intestinal extracts and had weak effects on gastric acid secretion but more potent insulinotropic actions in human beings. Some study highlighted that 42-aminoacid hormone synthesized in duodenal and jejunal entero endocrine K cells in the proximal small bowel[1]. Glucagon-like peptide-1 (GLP-1) was identified secondly after the cloning of the cDNAs and genes encoding proglucagon. GLP-1 exists in two circulating equipotent molecular forms, GLP-1(7-37) and GLP-1(7-36) amide. Hence a combination of endocrine and neural signals probably promotes the rapid stimulation of GLP-1 secretion. The GIP receptor is predominantly expressed on islet β cells, and to a lesser extent, in adipose tissue and in the central nervous system. By contrast, the GLP-1 receptor (GLP-1R) is expressed in islet α and β cells and in peripheral tissues, including the central and peripheral nervous systems, heart, kidney, lung, and gastrointestinal tract. Activation of both incretin receptors on β cells leads to rapid increases in levels of insulin by exocytosis process, in a glucose-dependent manner[2]. When blood glucose levels are elevated following a meal, GLP-1 is released from the gastrointestinal tract, and it stimulates insulin secretion from the pancreatic β cells, reduces glucagon secretion from the pancreatic α cells, improves β-cell function and slows gastric emptying[3,4]. It promotes enhanced glucose disposal through neural mechanisms[5], actions that also contribute to the control of glucoregulation.

The circulating levels of intact GLP-1 and GIP decrease rapidly because of enzymatic inactivation, mainly dipeptidyl peptidase-4 (DPP-4) and renal clearance[6] and also human neutral endopeptidase. The acquired incretin defect, GIP but not GLP-1 shows noticeably attenuated insulinotropic action in patients with type 2 diabetes. Furthermore, those with type 2 diabetes show a small but significant reduction in meal-stimulated levels of GLP-1[7,8]. The GLP-1 is rapidly degraded by DPP-4[9,10] has fostered the development of specific protease inhibitors that prevent the rapid fall of GLP-1 in circulating plasma after eating.

Pathogenesis and Pathophysiology of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) has a greater genetic association than type 1 diabetes mellitus (T1DM). The pathogenesis of type 2 diabetes mellitus is characterized by impaired insulin secretion and insulin resistance. This
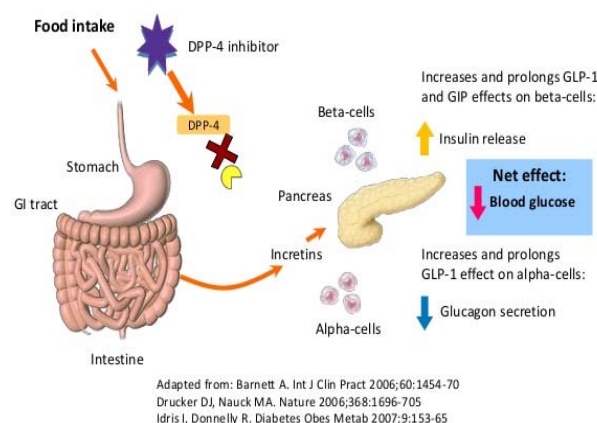
indicates that genetic factors are more important than environmental factors. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes[11]. In T2DM patients, the evident metabolic abnormalities include obesity, insulin resistance, qualitative and quantitative abnormalities in insulin secretion, dysregulated secretion of other islet hormones such as amylin and glucagon and increased endogenous glucose production[12]. The incretin effect of GIP in stimulating insulin secretion is almost lost in T2DM and many studies indicate the existence of a specific defect in GIP action in these patients, may be due to chronic desensitization of GIPRs (Glucose dependent insulinotropic peptide receptors)[13].

DPP 4

DPP-4 is a ubiquitous membrane-spanning cell-surface amino peptidase widely expressed in many tissues, such as liver, lung, kidney, intestinal brush-border membranes, lymphocytes, and endothelial cells[14]. The extracellular domain of DPP-4 can also be cleaved from its membrane-anchored form and circulate in plasma, where it retains its full enzymatic activity. DPP-4 preferentially cleaves peptides with a proline or alanine residue in the second amino terminal position. Many gastrointestinal hormones, neuropeptides, cytokines, and chemokines are substrates for DPP-4, among them both GIP and GLP-1[15,10]. The discovery of defective incretin response in T2DM has led to the development of incretin-based therapies, being the first one approved in 2005. The two classes of incretin-based drugs available include GLP-1 agonists and DPP-4 inhibitors (DPP-4i), which inhibit DPP-4, the enzyme responsible for the short life of endogenous GLP-1 (less than two minutes)[16]. GLP-1 and GIP promote insulin secretion and biosynthesis in a glucose-dependent manner, acting to regulate postprandial glycaemia. In contrast with GIP, GLP-1 inhibits the glucagon and somatostatin release. Many small-molecule DPP-4 inhibitors have been developed that specifically and potently inhibit DPP-4 activity after oral administration. Typically, these agents reduce serum DPP-4 activity by more than 80%, with some inhibition maintained for 24hr after one dose or with once daily treatment[17]. DPP-4 inhibition is accompanied by a rise in postprandial levels of intact GLP-1[18,19]. The inhibition of glucagon secretion might be of particular importance because glucagon is a main determinant of glucose production from the liver[20] and T2DM is associated with hyperglucagonemia and defective suppression of glucagon secretion by glucose[21-23]. The DPP-4i are a newer class of oral drugs for the treatment of T2DM. Newer and safer treatment options for optimal glycaemic control are continuously being investigated and developed. The GLP-1 agonists and DPP-4i are examples of such development. The currently available DPP-4i includes sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin and teneligliptin. The DPP-4 inhibition with these agents generally result in almost complete

inhibition of DPP-4 for 24 hours, increasing circulating GLP-1 and GIP levels in two to three times higher than normal[16]. In addition to the change in lifestyle (diet and exercise), pharmacotherapy is required to maintain glycemic control and minimize chronic complications[24].

DPP-4 Inhibitors Enhance Incretin and Insulin Secretion

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In clinical practice they are associated with significant reductions in HbA_{1c}, no weight gain and a low risk of hypoglycemia. Indeed, the suggestion of possible cardiovascular benefit seen in the safety studies is now being formally examined in large randomized-controlled trials with primary cardiovascular end points. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) developed an algorithm to assist providers in managing T2DM. When developing the algorithm, the AACE and ACE identified minimizing hypoglycemia and weight gain as their top priorities in drug therapy selection. As a result of that, initial recommendations focus on the use of metformin or a thiazolidinedione if metformin is contraindicated, followed by a GLP-1 agonist or a DPP-4i[25]. This article will focus on the sitagliptin inhibitor and its place in therapy in the management of T2DM.

Sitagliptin was the first of the DPP-4i to be approved by the US Food and Drug Administration (FDA) in 2006. This was followed by the approval of vildagliptin in February 2007. Recently, saxagliptin in 2009 and alogliptin in 2010 (presently only in Japan) has been approved by FDA. Compounds such as sitagliptin (β-amino acid based) and vildagliptin are considered as nitrile containing inhibitors.

Absorption

The DPP-4i are all orally available and are rapidly absorbed, with significant inhibition of plasma DPP-4 activity being seen within 5 min of administration. Oral bioavailability in humans is generally high (~87% for sitagliptin[18] and 85% for vildagliptin)[26].

Distribution

The available data indicates that the volume of distribution of the various inhibitors in humans is greater

than the total body water (~70 L for vildagliptin, 198 L for sitagliptin)[27]. There is some indirect evidence that vildagliptin may be able to cross the cell membrane. In the plasma, most of the inhibitors display low, reversible protein binding (38% for sitagliptin[18], 10% for vildagliptin)[27,28]. Preclinical studies have revealed that the highest concentrations of the drugs are found in the intestines, kidney and liver,[27] notably in tissue also have it. Available information indicates that very low levels of the inhibitors are found in the brain (vildagliptin)[27], suggesting that the compound may not cross the blood–brain barrier. However, they do appear to be able to cross the placenta freely (vildagliptin and sitagliptin)[27].

Metabolism

Sitagliptin do not undergo appreciable metabolism *in vivo* in humans; around 80% of the dose is eliminated unchanged as the parent compound[27,29]. The major metabolic pathway for vildagliptin is hydrolysis at its cyano moiety, which occurs in the liver and other tissues via a CYP450-independent mechanism, to produce a carboxylic acid metabolite (M20.7/LAY151) and four minor metabolites[27,28].

Excretion

The elimination and excretion is mainly renal (75-80% of an oral drug is found in urine as unchanged drug) and the rest is metabolised via cytochrome CYP3A4 and CYP2C8. For sitagliptin, around 70% of the dose is excreted as the parent molecule and active transport has been shown to account for around 50% of its clearance[18] the human organic anion transporter (OAT)-3, organic anion transporting polypeptide (OATP)-4C1 and PGP transporters in the proximal tubule have been indicated to be involved[30]. Data for vildagliptin also indicate the kidneys to be the predominant route of elimination, with 22% of the dose appearing in the urine unchanged and 50% appearing as the major metabolite (M20.7); active transport in addition to glomerular filtration was indicated to be involved in the elimination of both compounds[28].

Inhibitory Effect

Thus, sitagliptin form non-covalent interactions with residues in the catalytic site[31]. In contrast, inhibition of DPP-4 by vildagliptin has been described as a two-step process that involves the formation of a reversible covalent enzyme–inhibitor complex in which there is a slow rate of inhibitor binding and a slow rate of inhibitor dissociation, resulting in the enzyme slowly equilibrating between the active and inactive forms[32-34]. This means that the catalytic activity will be inhibited even after the free drug has been cleared from the circulation.

One study in which the inhibitors were directly compared under identical experimental conditions reported that sitagliptin and vildagliptin showed similar efficacy (i.e. maximal effect) for inhibition of DPP-4 *in vitro*, but that there were differences in potency (i.e. amount of compound needed; IC50 = 19 and 62 nm, for sitagliptin and vildagliptin respectively)[35]. With regard to half-life, there are also differences between the various inhibitors. Vildagliptin[27,36] are cleared from the plasma relatively quickly, whereas sitagliptin[27,37] have much longer survival times.

Drug Interaction Profile

DPP-4i does not interfere with cytochrome P450 (CYP) enzymes. They are neither inhibitors nor inducers. The exception is saxagliptin, which is metabolised by the CYP3A4/5 isoform into a primary active metabolite[38].

Trials of Safety and Efficacy

DPP-4i: sitagliptin, linagliptin, vildagliptin and saxagliptin have been pulled together in a useful meta-analysis by Monami and colleagues, published in 2010[39]. In the meta-analysis they included 32 published trials and nine unpublished trials with a duration greater than 12 weeks. They confirmed that, compared with placebo, the DPP-4 inhibitors reduced HbA$_{1c}$ by around 0.7%. The efficacy was similar in monotherapy and in combination with other agents. When comparisons were made with other oral drugs used in T2DM, the reductions in HbA$_{1c}$ were comparable with glitazones, but slightly less than with metformin or sulphonylureas. There was no weight gain and a very low risk of hypoglycemia.

DPP-4i has been generally well-tolerated in short term studies. Common reported adverse effects include nasopharyngitis, urinary tract infections, pancreatitis and headaches. Serious allergic reactions have been reported, including anaphylactic reactions, angioedema and exfoliative dermatological reactions[3,4,40-42]. The incidence of hypoglycaemia is low, but may be increased when DPP-4i are used in combination with other antidiabetic agents. The DPP-4i also appear to be less likely to be associated with weight gain.

Contraindication

DPP-4i are contraindicated when there is Compelling indication for insulin therapy, a history of a serious hypersensitivity reaction to DPP-4i and a patient with a history of acute pancreatitis, chronic or recurring pancreatitis, or pancreatic cancer[40].

In Renal Insufficiency

On the basis of observations, sitagliptin, vildagliptin and saxagliptin have been approved for use in subjects with mild renal insufficiency [creatinine clearance (CrCl) 50–80 ml/min] without dose adjustment, and where the indication is approved, sitagliptin and saxagliptin can be used in patients with moderate (CrCl 30–50 ml/min) or severe renal insufficiency/end-stage renal disease (ESRD) (CrCl <30 ml/min) with appropriate dose adjustment to 50 and 75%, respectively, are required[43].

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In Hepatic Insufficiency

Overall, these studies suggested that no dose adjustment will be necessary in patients with hepatic impairment. Vildagliptin is, however, not recommended for use in patients with hepatic insufficiency or those with pretreatment alanine aminotransferase or aspartate aminotransferase at greater than three times the upper limit of normal and subjects with moderate hepatic impairment, exposure to sitagliptin was slightly, but non significantly increased[44].

## Roleof DPP-4 Inhibitors in Malignancy

DPP-4, the cell surface protease is expressed in various normal tissues and functions as tumor suppressor. DPP-4 expression is lost in many types of human cancers like non small cell lung carcinoma (NSCLC) and prostate cancer. Therefore, DPP-4i is associated with risk of NSCLC and prostate cancer. In a study, DPP-4i have shown to promote already existing intestinal tumors and may support the potential of colon cancer cells to metastasis[45,46].

Management Glycaemic Control with DPP-4 Inhibitors

Management includes a prudent diet, regular exercise and medicine to reduce blood glucose levels. Current pharmacological options for T2DM include sulphonylureas, insulin, thiazolidinediones, α-glucosidase inhibitors and metformin. These treatment options, although highly effective in reducing blood glucose levels, may be associated with an increased risk of hypoglycaemia, weight gain and gastrointestinal intolerance. These unwanted adverse effects may act as barriers to optimal glycemic control[3]. The changes of HbA1c levels on administration of DPP-4i (before initiation of DPP-4i $7.2 \pm 0.7\%$; 4 months after initiation of DPP-4i $6.7 \pm 0.6\%$ [paired t-test, $P < 0.01$ vs before] are associated with estimated intake of fish and estimated intake of dietary n-3 polyunsaturated fatty acids (PUFA), such as serum Eicosapentaenoic acid and (EPA) and Docosahexaenoic acid (DHA) levels. The efficacy of DPP-4 inhibitors can be predicted by serum EPA and DHA levels; and (ii) consuming more fish with diet therapy can enhance the efficacy of DPP-4i. Furthermore, the findings suggest that the differing efficacies of DPP-4i found among different ethnicities might be partly a result of differences in fish consumption[42].

Although EPA and DHA have been shown to prevent excessive adiposity, thereby ameliorating insulin resistance in animal models, the effects of n-3 PUFA on glycemic control in T2DM itself are somewhat controversial[47]. Dietary n-3 PUFA and DPP-4i synergistically increase biologically-active GLP-1 levels to facilitate maintenance of glycemic control, but it remains to be determined whether EPA and DHA enhance GLP-1 secretion in patients with T2DM. An additional recently identified safety concern is an increased risk of fractures, especially in postmenopausal women[48].

Sitagliptin
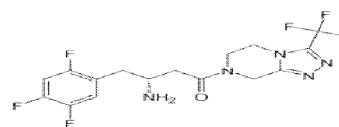
Sitagliptin phosphate

Sitagliptin phosphate, the first DPP-4i provides a new treatment option for patients with T2DM.

Drug Interactions

Sitagliptin have shown to have a few drug-drug interactions. Sitagliptin is metabolised by CYP3A4 but it does not appear to induce or inhibit cytochrome P450 isoenzymes and does not show interactions with inducers or inhibitors of cytochromes. Sitagliptin concomitant administration with digoxin (0.25 mg) for ten days increased plasma digoxin concentration; therefore monitoring is advisable to avoid digoxin toxicity but dose adjustment is not recommended18[49,50,18]. The maximum approved and recommended dose for Sitagliptin is 100 mg daily and this is the most effective dose for various glycemic parameters.

Trials with Monotherapy

Some study demonstrated that Sitagliptin at doses of 100 mg and 200 mg provided clinically meaningful and statistically significant ($p<0.001$) reduction in HbA1c, fasting plasma glucose (FPG) and post prandial glucose (PPG) levels over 18 weeks compared to placebo in patients of T2DM with mild to moderate hyperglycaemia (baseline HbA1c equivalent to 8%) inadequately controlled on diet and exercise[11]. Sitagliptin, at both doses also led to a significantly ($p<0.001$) higher proportion (35.8% with 100 mg and 28.6% with 200 mg) of patients achieving an HbA1C <7% after 18 weeks compared with placebo (15.5%). At doses >or=100 mg QD, DPP-4 activity is inhibited by >80%, with a consequent 2-fold rise in active GLP-1 levels. The reduction in HbA1c observed with 100 mg QD of Sitagliptin in Phase III monotherapy trials ranged from approximately 0.5% to 0.6% ($P<or= 0.001$ vs placebo)[51]. A recent study depicted that after 24 weeks, Sitagliptin 100 and 200 mg significantly ($p<0.001$) reduced HbA1C, FPG and PPG levels as compared with placebo without deterioration in Sitagliptin effect throughout 24 weeks[52]. The percentage of patients achieving HbA1C <7% was 41% with 100 mg and 45% with 200 mg versus 17% for placebo ($p < 0.001$). A significant ($p<0.001$) interaction between baseline HbA1C and treatment was observed with the finding of great efficacy in patients with higher baseline HbA1C[52]. Goldstein demonstrated the effect of Sitagliptin and Metformin as monotherapy and as combination therapies (at different doses) in T2DM patients who had inadequate glycaemic control with diet and exercise. It was found that all active treatment group produced statistically significant ($p < 0.001$) reduction in HbA1c , FPG and PPG levels compared to placebo and the

co-administration groups provided greater reduction relative to the individual monotherapies. Patients with more severe baseline hyperglycaemia (HbA1C ≥ 9%) had the largest reduction with co-administration of Sitagliptin and Metformin[53].

In Cherbonnel 701 patients of type T2DM who had inadequate glycemic control with metformin alone, the addition of Sitagliptin 100 mg once daily was well tolerated and provided effective and sustained improvement in HbA1c, FPG and PPG levels. Nearly half of the patients receiving Sitagliptin 100 mg once daily achieved current American Diabetes Association glycaemic goal of HbA1c < 7% compared with less than one-fifth of placebo treated patients. Treatment with Sitagliptin was associated with low rate of hypoglycemia that was similar to that seen with placebo as well as neutral effect on body weight[54].

Nauck found that Sitagliptin 100 mg once daily was non-inferior to Glipizide 20 mg once daily as an adjunct to Metformin ≥ 1500 mg once daily. 52-week mean reduction in HbA1c of 0.67% were achieved both in patients receiving Sitagliptin and those receiving Glipizide, with the added benefit of small weight losses with Sitagliptin (-1.5 kg) compared to small weight gain with Glipizide (+1.1 kg)[7]. Rosenstock with similar design with an add-on combination of Sitagliptin to an existing Pioglitazone therapy. The glycemic parameters HbA1C, FPG and PPG levels improved. From baseline HbA1C of 7.9%, a significant percentage of patients reached a target HbA1C < 7.0% (45%) in Sitagliptin group compared with placebo (23%)[55].

Research found that Sitagliptin 100 mg once daily significantly improved glycemic control and β-cell function in patients with T2DM, who had inadequate glycaemic control with Glimepiride or Glimepiride plus Metformin therapy[56]. The addition of Sitagliptin was generally well tolerated. In one monotherapy trial, 743 patients (mean baseline hemoglobin A_{1c} [HbA_{1c}], 7.9%) were randomized to receive sitagliptin 5, 12.5, 25, or 50 mg twice daily; glipizide 5 mg (titrated to 20 mg) once daily; or placebo. After 12 weeks of treatment, all doses of sitagliptin yielded a significant reduction in HbA_{1c} ranged from 0.38% to 0.77% (P<.001), with the greatest reduction observed in the group receiving sitagliptin 50 mg twice daily when compared with placebo. In the glipizide group, HbA_{1c} was reduced by 1%. Sitagliptin therapy was well tolerated, with a low incidence of hypoglycemia or weight gain reported[57]. Study showed that sitagliptin 100 or 200 mg once daily or placebo for 18 weeks. The results demonstrated a significant decrease in HbA_{1c} of 0.6% and 0.48% in patients taking sitagliptin 100 or 200 mg, respectively, versus placebo (P<.001). In addition, the incidence of hypoglycemia with sitagliptin treatment was similar to the incidence with placebo treatment; but weight neutral[11]. A recent study also randomized 741 patients (baseline HbA_{1c}, 8.0%) to monotherapy with sitagliptin 100 or 200 mg once daily or

placebo for 24 weeks. The investigators observed that sitagliptin 100 or 200 mg significantly reduced HbA_{1c} by 0.79% and 0.94%, respectively, versus placebo (P<.001). The incidence of hypoglycemia was similar among the groups but neutral effect on body weight and also associated with slightly more gastrointestinal (GI) disturbances than placebo. The authors concluded that sitagliptin was safe and effective as monotherapy for T2DM, with 50 mg twice daily being the most effective dose[51].

Treatment with sitagliptin showed an average decrease in HbA1c levels of 0.65% after 12 weeks of treatment, 0.84% after 18 weeks of treatment, 0.85% after 24 weeks of treatment, 1.0% after 30 weeks of treatment, and 0.67% after 52 weeks of treatment[58]. In diabetic patients who also suffer from coronary heart disease, it was demonstrated that treatment with sitagliptin improved their heart function and coronary artery perfusion, as observed in echo-debutamin tests[59]. Literature showed that sitagliptin produced small but statistically significant reductions of 2–3 mmHg systolic and 1.6–1.8 mmHg diastolic in 24-h ambulatory blood pressure measurements acutely (day 1) and at steady state (day 5), in nondiabetic patients with mild to moderate hypertension[60].

Recently, a study by[61], in metabolic syndrome patients, showed that during placebo and low-dose ACE inhibition (5 mg enalapril), sitagliptin lowered blood pressure. However, this trend was reversed during higher-dose acute ACE inhibition (10 mg enalapril). They hypothesized that the combination of sitagliptin and high-dose ACE inhibition causes activation of the sympathetic tone, hence attenuating blood pressure reduction.

Trials with Combination Therapy

A study was conducted in 28 patients after receiving sitagliptin 50 mg twice daily or placebo to metformin ≥1,500 mg/d for 4 weeks, patients then received the opposite treatment for 4 weeks. The results demonstrated that adding sitagliptin to ongoing metformin therapy reduced FPG by 20.3 mg/dL versus placebo (P<.05). In addition, the investigators observed that adding sitagliptin to metformin therapy had no effect on GI complaints, hypoglycemia, or changes in weight[62].

Two larger trials (N=1,056 and N=701) also examined the effect of adding sitagliptin to ongoing metformin therapy[52,53]. In these trials, the addition of sitagliptin 100 mg to metformin therapy resulted in a 0.65% to 2.07% decrease in HbA_{1c}. The incidence of hypoglycemia and little to no effect on body weight in all groups was similar to the incidence reported in patients taking placebo. In non inferiority trial was to determine whether adding sitagliptin to metformin was as effective as adding glipizide to metformin. A battery of 1,172 patients receive sitagliptin 100 mg once daily or glipizide 5 mg (up to 20 mg) once daily in addition to metformin ≥1,500 mg/d for 52 weeks. Both treatment regimens resulted in a

decrease in HbA_{1c} of 0.67%, thus confirming non-inferiority. As resulted in a significantly lower incidence of hypoglycemia ($P<.001$) and significant weight loss versus glipizide (sitagliptin, –1.5 kg; glipizide, +1.1 kg; between-group difference, –2.5 kg; $P<.001$)[63].

A total of 441 patients (mean HbA_{1c}, 8.3%) were randomized to receive sitagliptin 100 mg once daily or placebo in addition to glimepiride ≥4 mg once daily alone or in combination with metformin ≥1,500 mg/d. After 24 weeks, the investigators observed that the addition of sitagliptin decreased HbA_{1c} by 0.74% ($P<.001$) and FPG by 20.1 mg/dL ($P<.001$). In this trial, the addition of sitagliptin resulted in a greater incidence of hypoglycemia ($P<.001$) and significant weight gain ($P<.001$) versus placebo[55].

In 353 patients (mean baseline HbA_{1c}, 8.1%) received sitagliptin 100 mg once daily or placebo in addition to pioglitazone 30 or 45 mg for 24 weeks. The addition of sitagliptin resulted in a decrease in HbA_{1c} of 0.7% ($P<.001$) and a decrease in FPG of 17.7 mg/dL ($P<.001$). The incidence of hypoglycemia and changes in body weight had shown similar in two groups and also more abdominal pain than patients in the placebo group[64]. At doses >or=100 mg QD, DPP-4 activity is inhibited by >80%, with a consequent 2-fold rise in active GLP-1 levels. In Phase III combination trials of sitagliptin, HbA(1c) was reduced by approximately 0.7% when added to metformin and approximately 0.9% with pioglitazone (P < 0.001 vs placebo)[51].

Out of 25 patients with type I diabetes and 31 insulin treated type II diabetes patients was treated with sitagliptin 100 mg once daily for 21 weeks. After 21 weeks, type I diabetes patients had significant reduction in body mass index, FPG, PPG, HbA1C and daily insulin requirement. In patients with T2DM, improves the metabolic control, reduces the low density cholesterol level and insulin requirements[65].

Role in Atherosclerotic

Recently researches confirmed that Sitagliptin and exendin-4 can not only activate the phosphorylation of activated protein kinase (AMPK) but also inhibit the activation of mitogen-activated protein kinase (MAPK) including p38 and extracellular signal-regulated kinase (ERK)[66-69]. The main findings of this study lie in the effects of sitagliptin in reducing the formation of atherosclerotic lesion area in the aortic root and abdominal aorta and changing the histological composition of atherosclerotic plaques by reducing the content of collagen fiber and tending to reduce smooth muscle cells and macrophages in the aorta In apolipoprotein-E (ApoE) mice, the sitagliptin group showed fewer atherosclerotic plaques than in controls (7.64 ± 1.98% [range 4.62–10.13%] vs 12.91 ± 1.15% [range 11.55–14.37%], p < 0.001; High Density lipoprotein (HDL) has been demonstrated to reduce the risk of atherosclerosis by multiple pathophysiologic mechanisms[70]. And Low Density lipoprotein (LDL) has been regarded as a positive risk for atherosclerosis when they invade the endothelium and become oxidized. It improves not only glycemic control, but also blood pressure and lipid profiles[71]. Sitagliptin can activate the AMPK pathway and inhibit MAPK signaling by increasing the phosphorylation of AMPK and its downstream molecule sitagliptin did significantly reduce the expression of monocyte chemoattractant protein (MCP-1) and interleukin (IL-6) (p = 0.001 and p = 0.033); the serum levels of soluble vascular cell adhesion molecule (VCAM-1) and P-selectin decreased significantly in the sitagliptin group vascular cell adhesion molecule VCAM-1: 1163.16 ± 159.62 ng/ml vs 1365.18 ± 170.26 ng/ml, p < 0.05; P-selectin: 232.71 ± 64.29 ng/ml vs 288 ± 44.46 ng/ml, p < 0.05.

As Sitagliptin is primarily secreted via renal elimination, therefore, the dosage must be adjusted in patients with moderate to severe renal impairment or end stage renal disease. Dose is decreased by two fold in moderate (CrCl 30-50 ml/min) renal insufficiency and four fold in severe (CrCl < 30 ml/min) renal insufficiency patients. There is no need of dose adjustment in patients of mild (CrCl 50-80 ml/min) renal insufficiency[72]. Studies have shown that moderate hepatic insufficiency have no clinical effect on pharmacokinetics of Sitagliptin. The single 100 mg dose of the Sitagliptin was well tolerated with no meaningful changes observed in liver function tests. Therefore, no dosage adjustments of Sitagliptin are required in patients with mild to moderate hepatic insufficiency[73]. There are no clinical studies on humans in literature to demonstrate the effects of Sitagliptin in severe hepatic insufficiency patients. Few adverse effects reported with Sitagliptin are nasopharyngitis, upper respiratory tract infections, headache, back pain, osteoarthritis, and pain in extremities. In Laboratory parameters, small increase in white blood cells, serum uric acid and small decrease in alkaline phosphatase is reported. Treatment with Sitagliptin is having neutral effect on body weight[11,74]. Sitagliptin has shown reproductive toxicity at high doses and has been detected in high amounts in the milk of lactating animals. Because of a lack of human data this drug should not be used during pregnancy or breast feeding[49].

CONCLUSION

Sitagliptin, a first DPP4i, as a monotherapy significantly reduces fasting plasma glucose level, postprandial glucose levels and HbA1C in T2DM patients. Sitagliptin as add on therapy with biguanides and sulfonylurea in T2DM patients produced significant reduction in HbA1C, FPG, PPG. Combination therapy with insulin improves the metabolic control and lipid profile by reducing LDL cholesterol level and decreases the insulin requirements. Sitagliptin has got low rate of hypoglycemic symptoms and neutral effect on body weight. Sitagliptin improves the cardiac function and coronary artery perfusion, thereby reduces the cardiovascular risk in T2DM patients.

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