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SITAGLIPTIN- A COMPREHENSIVE REVIEW

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ABSTRACT

Sitagliptin is an orally administered, potent, and highly selective inhibitor of dipeptidyl peptidase-4 (DPP-4) and was the first agent of its class to be approved for use in the management of adults with type 2 diabetes. Numerous randomized placebo- or active comparator-controlled trials have demonstrated the efficacy of sitagliptin in terms of improving glycaemic control in patients with type 2 diabetes, including its use as monotherapy, initial combination therapy (usually with fixed-dose combinations ofsitagliptin/metformin), or add-on therapy to metformin or other antihyperglycaemic drugs, with or without metformin. Sitagliptin was generally well tolerated in clinical trials, had a low risk of hypoglycemia (although this depends on background therapy), and had a neutral effect on body weight.It stimulates insulin secretion when hyperglycemia is present and inhibits glucagon secretion. In clinical studies, it is weight neutral. This article gives an overview of the mechanism of action, the pharmacology, and the clinical efficacy and safety of sitagliptin in type 2 diabetes therapy.

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INTRODUCTION

Type 2 diabetes (non-insulin dependent)-This type of diabetes is also known as maturity-onset diabetes mellitus. In this type of diabetes, the person is not dependent on an external source of insulin to control his or her blood glucose level, although there is either a low level of insulin in his blood or any type of resistance in the insulin receptor, which is why the glucose is not properly metabolized, and then he has to take medicine that will either increase the secretion of insulin or reduce the resistance in insulin binding with its respective receptors. In this type, there is no loss or only a small reduction in beta cells, and although the insulin circulation level is a little low, normal, or even high, there is also no anti-beta cell antibody. This type of diabetes have very powerful chances to carry forward to the next generation or may show family history episode. In type 2 diabetes mellitus (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. In addition, there is the decreased incretin effect due to impairment in secretion and action of incretin hormones glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP-1). Objective of Review Article is to summarise the details and recent update of sitagliptin in treatment of type-2 Diabetes Mellitus.[12]

MOLECULAR MECHANISM

One of the major mechanisms for the development of diabetes complications is oxidative stress. Oxidative stress develops when the rate of free radical generation exceeds the antioxidant defence systems, resulting in the toxic effects of free radicals. Free radical species are important physiological components in biological homeostasis, but when their production increases excessively and is greater than the body's antioxidant capacity, oxidative stress results. Oxidative stress is a major upstream event for diabetes complications as well as insulin resistance development, inducing pathophysiologic molecular mechanisms and initiating a cascade of deleterious pathways leading to insulin resistance and DM. In this review, we discuss the potential roles of oxidative stress in the development of insulin resistance and DM. Oxidative stress plays key roles in the pathophysiology of insulin resistance and DM. It can reduce peripheral insulin sensitivity via at least five major molecular mechanisms through β-cell dysfunction, inflammatory responses, GLUT-4 downregulation and/or localization, mitochondrial dysfunction, and impairment of the normal insulin signaling pathways.[15,19,20,27]

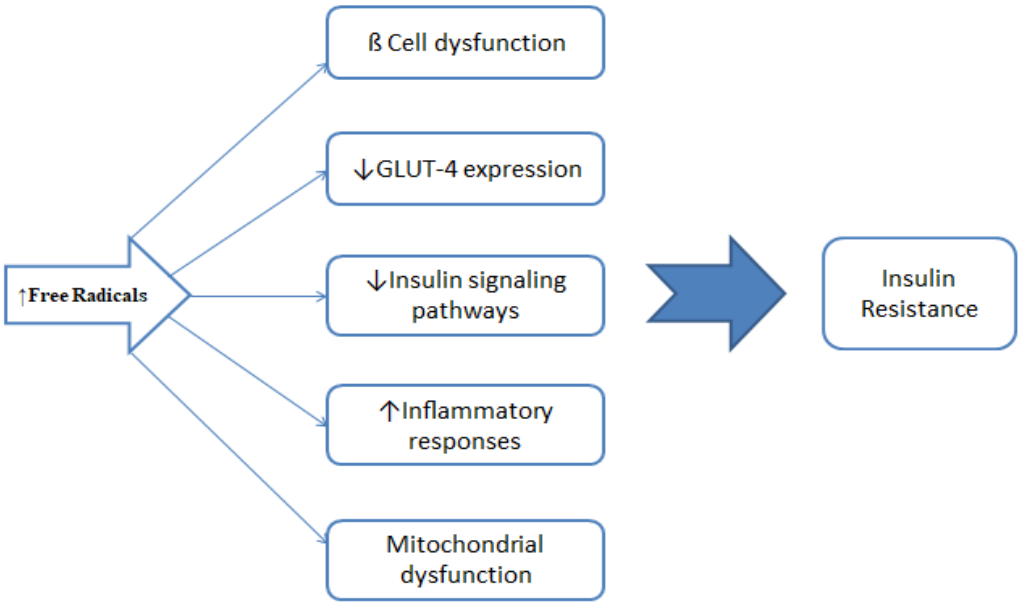

Figure. 1- Oxidative stress induces insulin resistance via five major molecular pathways.

Pharmacological Profile of Sitagliptin

Mechanism of action

Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolises metabolily occurring incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1 enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPP-IV activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma. Sitagliptin reduces hemoglobin A1c (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion . GLP-1 has other widespread effects, including delaying gastric emptying, significantly reducing glucagon levels, and possible central effects on the appetite. Sitagliptin is a potent, orally active DPP-4 inhibitor with excellent selectivity over other proline-selective peptidases. After a standard meal, active GLP-1 concentrations are significantly increased twofold by sitagliptin, coinciding with near-maximal acute glucose-lowering in preclinical studies.[10,11]

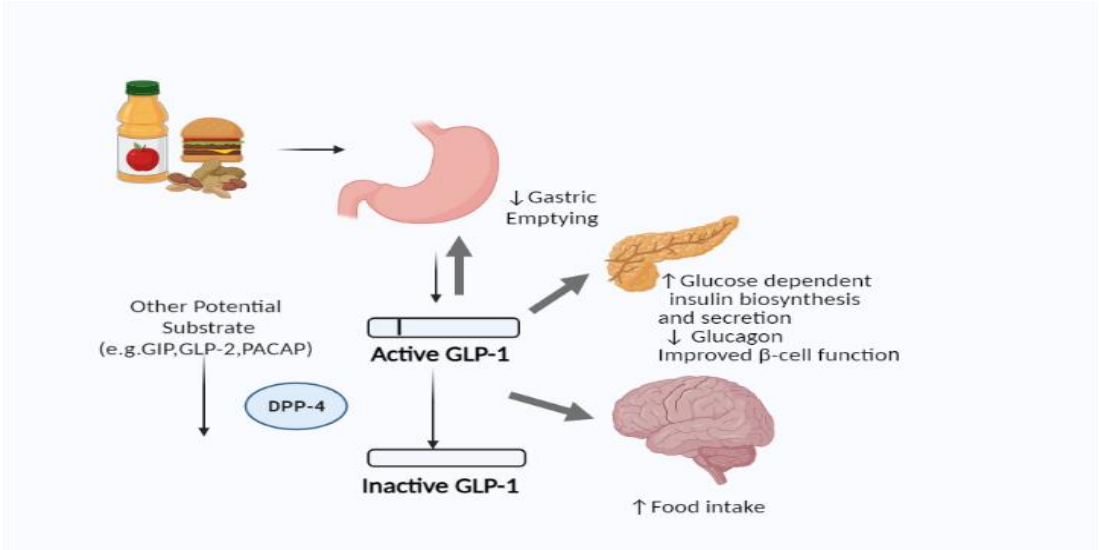

Figure. 2 -The Role of glucagon like peptidase-1in Glucose homeostasis.DPP- 4=dipeptidyl peptidase-4; GIP=glucose – dependent insulinotropic peptide; PACAP=pituitaryadenylatecyclase activating polypeptide.

Pharmacokinetics

The pharmacokinetics of sitagliptinare similar in healthy individuals and in T2DM patients. It is well absorbed orally, with an 87% bioavailability. In human beings, the protein binding of sitagliptin, as determined by ultracentrifugation, is 34–46%. In healthy volunteers and in patients with T2DM of different ethnic backgrounds, the tolerability of different doses taken once or twice daily is good. The main pharmacokinetic parameters (Tmax, Cmax, and t1/2) measured in studies were similar at baseline and in the steady state after longer administration. Steady-state plasma concentrations of sitagliptin are reached after 3 days, with a terminal half-life of 10–12 hours at doses of 25–100 mg. The elimination and excretion are mainly renal (75–80% of an oral drug is found in urine as unchanged drug), and the rest is metabolised via cytochromes CYP3A4 and CYP2C8.[3]

Clinical study:

The DPP-4 inhibitors available demonstrate a high efficacy in inhibiting DPP-4, and under clinical conditions, DPP-4 is inhibited by >80–90%. This inhibition causes a 2- to 3-fold increase in post-prandial GLP-1 plasma concentrations, which mediate the glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion. In addition to this "endocrine" action, the local inhibitory effect of DPP-4 inhibitors on GLP-1 degradation in the intestinal mucosa may contribute to favourable metabolic regulation by stimulating the autonomic afferent nervous system. The bioavailability of DPP-4 inhibitors is very good, and the pharmacodynamic and pharmacokinetic properties lead to clinically sufficient DPP-4 inhibition with once-daily dosing (only vildagliptin requires twice-daily dosing). Omarigliptin is a long-acting DPP-4 inhibitor for once-weekly dosing that is presently approved in Japan but not in Europe or the United States.

In the clinical development programmes and later in broad use after approval, no drug-drug interactions of DPP-4 inhibitors were observed with other antidiabetic drugs or with common medications like antihypertensives, lipid-lowering agents, diuretics, or anticoagulants. DPP-4 inhibitors can lower HbA1c levels by 0.5–1 units. The HbA1c reduction, as with other antihyperglycemic agents, depends largely on the patient population studied, the baseline glycemic situation at the beginning of the observation, and the concomitant therapy, including lifestyle intervention. Non-inferiority to sulfonylureas was demonstrated in phase III clinical development programmes for DPP-4 inhibitors after 1 and 2 years in terms of the glycemic parameters HbA1c as well as fasting and postprandial plasma glucose concentrations. Similar efficacy of DPP-4 inhibitors to either metformin or pioglitazone was also shown in formerly drug-native patients who did not reach glycemic goals with non-pharmacological interventions. DPP-4 inhibitors are body weight neutral, and they are generally well tolerated without side effects. Table 1 gives a summary of the clinical phase III studies with at least a 52-week duration on the efficacy of DPP-4 inhibitors compared to sulfonylureas as add-on therapy to metformin, respectively, in patients not reaching their glycemic goals with a monotherapy of metformin.[22,24]

Table: 1- Efficacy of DPP-4 inhibitors in the clinical phase III programmes with at least 52 weeks duration as add on therapy to metformin compared to sulfonylureas.

Substance/ Study	Observation time (weeks)	Intervention	Change in HbA1c (%)	Change in body weight (kg)	Hypoglycemic episode (%pat.)
Alogliptin Del Prato (23)	104	Alogliptin 12.5mg Alogliptin 25mg Glipizide>5mg	-0.68 -0.72 -0.59	-0.68 -0.89 +0.95	1.4 1.4 23.2
Linagliptin Gallwitz(24)	104	Linagliptin 5mg Glimepiride>1mg	-0.16 -0.36	-1.4 +1.3	7.0 36.0
Saxagliptin Goke(25)	104	Saxagliptin 5mg Glipizide 5-20mg	-0.41 -0.35	-1.5 +1.3	3.5 38.4
Vildagliptin Filozof(27)	52	Vildagliptin 2×50mg	-0.81 -0.85	+0.08 +1.36	n.a
Vildagliptin Matthews(28)	104	Vildagliptin 2×50mg Glimepiride<6mg	-0.10 -0.10	-0.3 +1.2	2.0 18.0

Adverse Effects

In phase III clinical study programmes, DPP-4 inhibitors demonstrated favourable safety and tolerability profiles. Nasopharyngitis and skin lesions were the most common side effects noted. The majority of studies found that adverse events did not result in treatment stopping. The efficacy and safety profile of DPP-4 inhibitors reveals a positive profile, particularly for individuals with renal impairment and older people with type-2 diabetes. No significant abnormalities in safety signals were found throughout long-term cardiovascular safety investigations and clinical use under post-marketing surveillance. A comprehensive analysis of non-clinical and clinical evidence has been conducted by the European Medicines Agency as a result of an extensive discussion on the pancreatic safety of incretin-based medicines that was sparked by publications of a single group.[29]

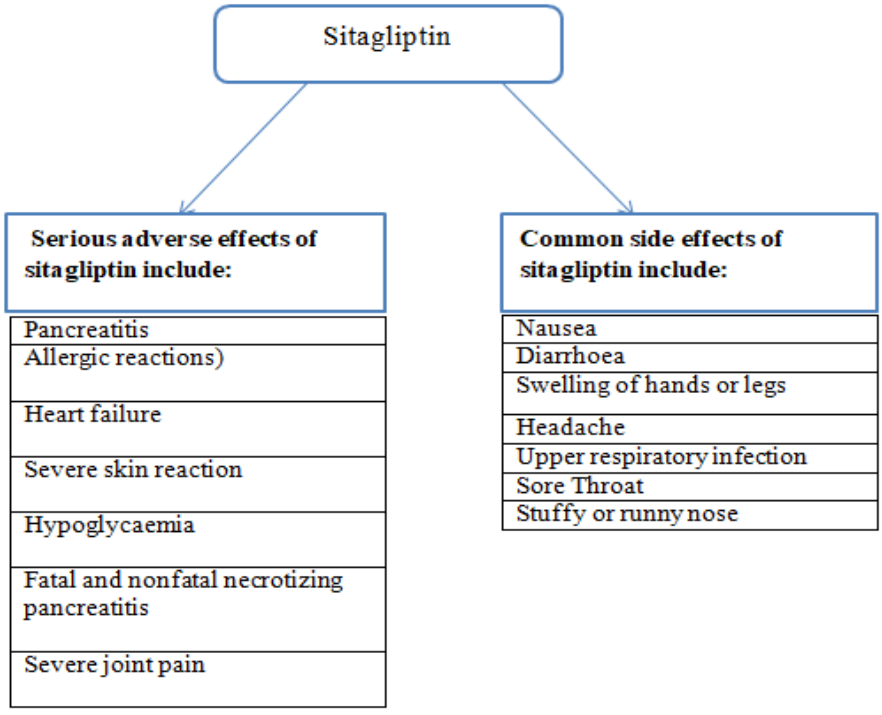

Figure.3- Adverse effects of sitagliptin.

Drug Interactions:

Due to a lack of safety and efficacy data, Sitagliptin is not recommended for use in children under 18 years of age and caution is advised in patients > 75 years old. 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.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. Clinically important CYP3A4 inhibitors mainly include macrolide antibiotics (e.g. clarithromycin, and erythromycin),anti-HIV agents (e.g., ritonavir and delavirdine), antidepressants (e.g. fluoxetine and fluvoxamine), calcium channel blockers(e.g. verapamil and diltiazem), steroids and their modulators(e.g., gestodene and mifepristone), and several herbal and dietary components. A small number of drugs such as rifampin,phenytoin and ritonavir are identified as inducers of CYP3A4. [29]

Table: 2- Sitagliptin Drug Interactions.

Primary drug	Secondary drug	Clinical Outcomes
Sitagliptin	Insulin	May increase risk of low blood sugar level
Sitagliptin	Carbonic anhydrase inhibitor	May increase risk of lactic acidosis
Sitagliptin	Alcohol	May increase risk of hypoglycemia and lactic acidosis
Sitagliptin	Metformin	Nasopharyngitis , upper respiratory tract infection
Sitagliptin	Ivacaftor	Cause lunges and digestive tract dysfunction

DOSE

The maximum approved and recommended dose for Sitagliptin is 100 mg daily and this is the most effective dose for various glycaemic parameters. The administration of Sitagliptin
is independent of meals.[3,10]

CLINICAL USE

Sitagliptin phosphate was approved by the United States FDA for the treatment in October 2006 as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM either as mono therapy or in combination with metformin or thiazolidinediones, when the single agent does not provide adequate glycaemic control. [4]

CONCLUSION

It has been observed from various clinical studies (Table 1) that sitagliptin is effective, well tolerated, and safe in the treatment of T2DM as mono therapy. Assessment of the safety of investigational and marketed drugs is an ongoing process that incorporates a variety of distinct, yet complementary, approaches. Sitagliptin, when used as mono therapy, produces a dose-dependent reduction in PPG levels, but its effect on HbA1C is independent of dose.

Sitagliptin and other DPP-4 inhibitors in general present a novel multimodal approach in the treatment of T2DM. By preserving stimulated circulating plasma levels of in cretin hormones, insulin secretion is stimulated under hyperglycaemic conditions and glucagon secretion is suppressed and glucagon secretion is suppressed. Therefore, not only insulin secretion and insulin resistance are altered, as by previously used oral anti hyperglycaemic agents, but also unmet needs of T2DM are covered by this novel therapeutic principle.[30]

CONFLICT AND INTREST

None

ABBRIVATIONS

Dpp-4 - Dipeptidyl Peptidase-4 Inhibitor
T2DM - Type 2 Diabetes Mellitus
GLP-1 - Glucagon like peptidase- 1
GIP-1 - Glucose dependent insulinotropic Peptide
GLUT-4 - Glucose Transporter protein type-4
HbA1c - Haemoglobin A1c
PACAP - PitutaryAdenylateCyclase Activating Polypeptide
CYP3A4 - Cytochrome P450 family 3 subfamily A member 4
CYP2PC8 - Cytochrome P450 family 2 subfamily C member 8
FDA - Food and Drug administration

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