



Review Article

DIPEPTIDYL PEPTIDASE - 4 INHIBITORS IN REGALING TYPE 2 DIABETES MELLITUS: A REVIEW

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ABSTRACT

A novel class of antidiabetic drugs which were explicated for the treatment of type 2 diabetes mellitus is the dipeptidyl peptidase (DPP) - 4 inhibitors. The DPP-4 inhibitors foreclose the metabolism of the incretin hormones glucagon-like peptide-1 and gastric inhibitory polypeptide, advancing the combination and discharge of insulin when blood levels of glucose are elevated. There are more or less divergences between them as far as their absorption, distribution, metabolism & excretion and additionally in their strength and span of activity. However, their efficaciousness seems to be alike. They enhance glycemic control, decreasing both fasting and postprandial glucose levels to bring down HbA1c levels, without weight gain. The available DPP-4 inhibitors for the treatment of type 2 diabetes are saxagliptin, sitagliptin linagliptin, alogliptin, and vildagliptin.

Keywords: Diabetes mellitus, DPP-4, incretin, sitagliptin.

INTRODUCTION

Type 2 diabetes which is a non-in reverse ailment is hugely proliferating all through the world. Impairment of the pancreatic β -cells and perverted downsizing of glucagon generation of pancreatic α -cells stipulate the type 2 diabetes by inducing insulin resistance. Various prospects are ought to be claimed for consideration such as present complications, obesity of patient, normal body weight, age, and side effects. The rates of diabetes-linked microvascular and possibly macrovascular ramifications can be brought down by an effective drug control. Intended for minifying the aerobic hazard it is indispensable to modify the consorted risk factors such as consequences related to obesity and dyslipidemia. Medications that can amend glycemia without weight pick up could be an advantage for the hefty patients with type 2 diabetes. Directly, a considerable measure of novel medications are in development for the intercession of diabetes conceding items with a crude component of activity, for example, dipeptidyl peptidase - 4 inhibitors.¹

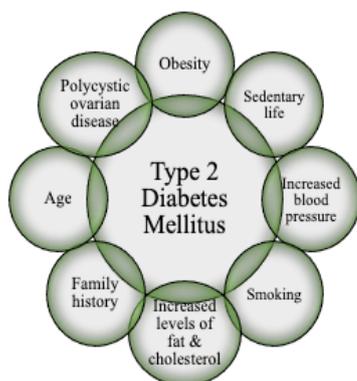


Fig 1: Risk factors of Type 2 diabetes mellitus

To reduce the blood glucose levels, apart from the intake of drugs, patients must execute steady exercises and should follow apprehensive diet. Metformin, α -glucosidase inhibitors, insulin, sulphonylureas, and thiazolidinedione are the current pharmacologically categorized drug of choice in the intervention of type 2 diabetes. Hypoglycemia level ascent was seen with sulphonylurea and insulin, weight pick up caused by insulin, sulphonylurea, and thiazolidinediones, and gastrointestinal bigotry issue was seen with metformin. These above undesirable adverse issues are the barricades to control glycemia optimally. As a result, a novel and secure treatment choices, for example, glucagon-like peptide 1 agonists and dipeptidyl peptidase-4 inhibitors are unendingly being investigated and advanced for ideal glycemic control.²

ABOUT DPP4

The newfangled category in pharmacology for oral antihyperglycemic drugs that pioneer a raw view for handling the type 2 diabetes mellitus is dipeptidyl peptidase-4 inhibitors. The mechanization of DPP-4 inhibitors is newly trenchant from any subsisting division for oral antihyperglycemic agents³. When blood levels of glucose are elevated, the dipeptidyl peptidase-4 inhibitors selectively forbid the metabolism of two major incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide which are boosting the synthesis and secretion of insulin^{4,5}.

Even though they are not more virile, the DPP-4 inhibitors nonetheless offer many clinically pertinent merits in lowering blood glucose concentrations and reducing glycated hemoglobin levels. A substantial merit of DPP-4 is that it lessens the miserable risk than those are ascertained with sulphonylurea. Also, the weight-inert profile in opposition to the weight gain which is ascertained with sulphonylurea and thiazolidinedione is a positive merit of these drugs. These drugs have been assessed in various combinings with other antihyperglycemic agents and as

monotherapy which is equated with a placebo or an agent of some other category³.

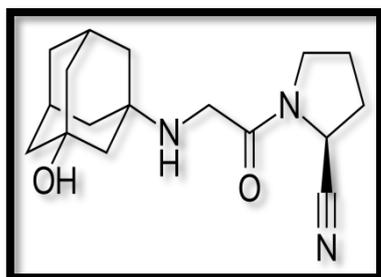


Fig 2: Vildagliptin¹²

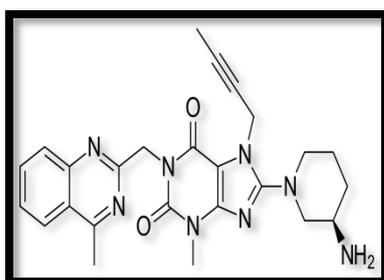


Fig 3: Linagliptin¹²

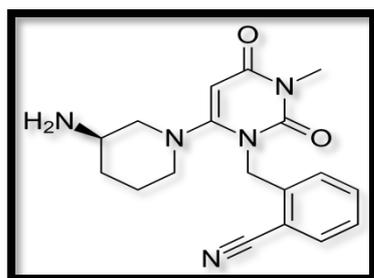


Fig 4: Alogliptin¹²

In 2007, US FDA approved the combined product of sitagliptin and Glucophage. Saxagliptin, the second DPP-4 inhibitor, was recognized both as monotherapy what's more in blend with couple of various cures, for instance, metformin, sulfonylurea, or thiazolidinedione. The use of Vildagliptin 50 mg twice daily was approved in Europe in 2007 and Latin America also as a combination with other drugs. The other two DPP-4 inhibitors are linagliptin and alogliptin. Alogliptin was approved in Japan in 2010 and by the FDA on January 2013. All the DPP-4 inhibitors are typical in their metabolism, excretion, commended dosage which is postulated for efficient glucose management. Whilst comparing their efficacy, patient tolerance, lowering HbA1c levels and safety profile they all appear to be similar^{6, 7}.

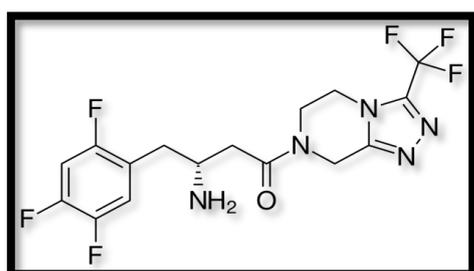


Fig 5: Sitagliptin¹²

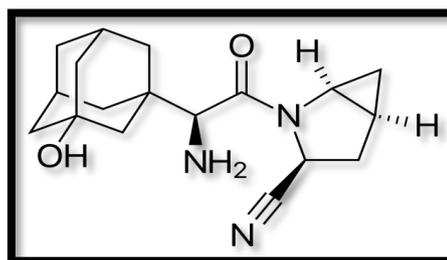


Fig 6: Saxagliptin¹²

The pleiotropic processes of DPP-4 are possibly linked with immune ordinance, cell apoptosis and signal activity since as a transmembrane glycoprotein it is situated on the surface of most cell types. The debasement of endogenous glucagon-like peptide 1 is the enduring and clinically pertinent action of DPP-4. By disrupting this effect, DPP-4 inhibitors raise insulin secretion in a glucose strung-out manner. Anyway, their long-term safety persists indecisive, whilst post-marketing feedback has given rise to issues about particular adverse events such as pancreatitis and hypersensitivity reactions⁷. Other possible side effects of DPP-4 inhibitors include severe joint pain, low blood sugar when this class of medicines is combined with other prescription medicines used to treat diabetes, and allergic reactions⁸.

This review summarizes the evidence regarding the safety profile of the commercially available DPP-4 inhibitors.

MECHANISM OF DPP4 INHIBITION^{1, 9}

As yet, the mediation of type 2 diabetes has been limited predominantly to lift the creation of insulin, raise insulin affectability, to diminish retention of glucose and insulin recharging. The as of late advanced classification for treatment of sort 2 diabetes is DPP-4 inhibitors. These have a place with a crisp gathering of medications which employ their action by upgrading the levels of incretin.

Incretins incorporate glucagon-like peptide 1 and glucose-subordinate insulinotropic polypeptide (GIP) which is emitted in the digestive system and prompts the physiological mandate of glucose homeostasis. Following the admission of nourishment, the immersion of dynamic endogenous GLP-1 and GIP are expanded to 2-3 times. Dynamic GLP-1 and GIP upgrades the yield and release of insulin by 60% because of pancreatic beta cells. Furthermore, GLP-1 additionally lessens the emission of glucagon by pancreatic alpha cells, bringing about a diminished hepatic glucose generation. These impacts are glucose-subordinate; GLP-1 fortifies insulin discharge and diminishes glucagon creation just at a higher blood glucose level. In any case, the impacts of GLP-1 and GIP last just for a couple of minutes as they are inactivated because of DPP-4.

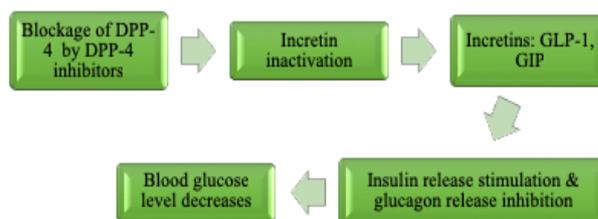


Fig 7: Mechanism of DPP-4 inhibitors

The promising restorative capability of GLP-1 as a pharmacological device for treating type 2 diabetes has been found in the 1990s. Further, it can re-establish the blunted first stage insulin discharge in sort 2 diabetes. Additionally, in this regard, their component of activity varies from that of the sulphonylurea which invigorates insulin emission likewise at low levels of blood glucose and may prompt hypoglycemia. Secured combinings of sitagliptin and after that vildagliptin with metformin have likewise been dove which impacts morbidic components of sort 2 diabetes at more target levels. They chop down the extent of insulin resistance, tweak insulin secretion, cut down glucagon discharge and furthermore reduce hepatic glucose generation. Their results are direct and levels of dynamic GLP-1 are upgraded by DPP-4 inhibitors as well as moreover by metformin.

CHEMISTRY OF DPP4

The DPP-4 inhibitors constitute a flexible gathering of mixes, which is nonexclusively cut up into those that copy the dipeptide structure of DPP-4 substrates, for example, sitagliptin, vildagliptin, and saxagliptin which are nitrile containing inhibitors and those which are non-peptidomimetic, for example, alogliptin and linagliptin. The mixes which have been begun for healing use are on the whole activist reversible inhibitors, which display extravagant liking for DPP-4, bringing about restraint constants (K_i) in the down nanomolar extend. In any case, there are contrasts in the path in which they move with the compound. Subsequently, sitagliptin, alogliptin and linagliptin shape non-covalent communications with balances in the synergist site. In boundary, hindrance of DPP-4 by vildagliptin and saxagliptin has been keyed out as a two-stage process that proposes the molding of a reversible covalent enzyme-inhibitor complex in which there is a moderate rate of inhibitor authoritative and a moderate rate of inhibitor separation. This implies the reactant movement will be repressed even after the free medication has been cleared from the dissemination and may clarify why vildagliptin and saxagliptin restrain DPP-4 action for longer than their moderately short half-lives would propose. This may have repercussions as far as their lengths of activity and dosing frequencies¹⁰.

ABSORPTION

All DPP-4 inhibitors are orally operable and are quickly engrossed with substantial forbiddance of plasma DPP-4 function being seen amongst 5 min of ingestion. Oral bioavailability in human being is broadly extravagant about 87% for sitagliptin, 85% for vildagliptin and 67% for saxagliptin whilst pretty low for linagliptin of about 30%.¹⁰

DISTRIBUTION

Information suggests that the volume of dispersion of the different inhibitors in human being is more prominent than the total body water of 70 L for vildagliptin, 198 L for sitagliptin, 300 L for alogliptin and 2.7 L/kg for saxagliptin, recommending that these drugs circulate broadly into the tissues. There is some collateral manifest that vildagliptin might have the capacity to cross the cell membrane layer. Thence, it has been accounted for that at high portions vildagliptin represses DPP-8/9 *in vivo* in rodents. Linagliptin attaches widely to plasma proteins and it has been computed that at the curative dose majority of the medication will be protein bound. Preclinical investigations have uncovered that the most prominent concentration of the medications are determined in the digestive organs, kidney, and liver. Accessible data demonstrates that low levels of the inhibitors are determined in the cerebrum, recommending that the drugs may not cross the blood-brain barrier. Nonetheless, they do seem to be capable to pass the placenta without any difficulty.¹⁰

METABOLISM

DPP-4 inhibitor such as sitagliptin, alogliptin, and linagliptin do not go through considerable metabolism in human beings. Around 80% of the dosage is eradicated unaltered as the parent drug. The confined metabolism of sitagliptin brings out six metabolites in little quantity *with in vitro* analyses showing that the essential catalyst creditworthy is CYP3A4 with a small commitment from CYP2C8. In the metabolism of alogliptin, the parent compound represents > 80% of alogliptin-related material in plasma and two minor metabolites have been recognized and representing under 1% & 5%. On account of linagliptin, the parent drug is about 70% in plasma. Interestingly, both vildagliptin and saxagliptin experience encompassing metabolism in human beings. For vildagliptin, the major metabolic pathway is hydrolysis at its cyano moiety which happens in the liver. The parent compound and the metabolite which is pharmacologically dormant are represented in the plasma. In liver, saxagliptin is utilized by CYP 3A4/5 to create a noteworthy metabolite, which is additionally an aggressive inhibitor with roughly half of the intensity of the parent compound. The metabolite of saxagliptin-related material is represented by the parent drug and some other unknown modest monohydroxylated metabolites.¹⁰

EXCRETION

Usually, almost all the DPP-4 inhibitors are obviated chiefly through the kidney by glomerular filtration, proposing that active transport is convoluted. For sitagliptin, around 70% of the portion is eliminated as the parent compound. Around 60 – 70% of alogliptin and its minor metabolites are renally eliminated coming out as the parent compound. Likewise, both saxagliptin and its essential metabolite are renally excreted representing 24% and 36% of the drug. The kidneys are the preponderant route of excretion for vildagliptin also with 22% of the drug showing up in the urine unaltered and half showing up as the major metabolite by active transport. Linagliptin is the special case, with <6% of the drug being eliminated in the urine which may be due to high level of protein binding which has been eluded glomerular filtration. Preferably, linagliptin also has a hepatic path of excretion with 78% showing up in the stools unaltered.¹⁰

POTENCY

Since the DPP-4 inhibitors are regulated by many divergences in the assay terms, it so backbreaking to equate them using the information described in individual studies. In any case, the inhibitors were specifically compared under unclear trial conditions announced that each of the five inhibitors demonstrated compatible viability for restraint of DPP-4 *in vitro*, however, that there were deviations in strength. Concerning half-life, there are likewise deviations between the various inhibitors. Vildagliptin and saxagliptin are cleared from the plasma generally rapidly, while sitagliptin, alogliptin, and linagliptin have any longer continuance times. These distinctions are thought about in the medicinal dosages which run from 5 mg for saxagliptin to 100 mg for sitagliptin and in the dosing recurrence. In any case, regardless of the deviations in intensity, when utilized at their medicinal measurements, the impacts of the inhibitors, as far as the degree of DPP-4 restraint *in vivo*, are for the most part compatible.¹⁰

DPP-4 INHIBITORS AND BLOOD GLUCOSE CONTROL⁶

The impact of DPP-4 inhibitors on the blood ranges of HbA1c as monotherapy or in combining with other medicaments was tried in numerous trials enduring 3 – 13 months. The consequences of these trial medications with sitagliptin demonstrated a normal diminishing in HbA1c levels of 0.65% following 3 months of

treatment, 0.84% following 4.5 months of treatment, 0.85% following 6 months of treatment, 1.0% following 7.5 months of treatment, and 0.67% following 13 months of treatment. Intervention with saxagliptin demonstrated a normal reduction in HbA1c levels of 0.43– 1.17%. Intervention with vildagliptin evidenced a normal drop-off in HbA1c levels of 1.4% following 6 months as monotherapy in a subgroup of patients.

In a meta-investigation that admitted data concerning intervention of type 2 diabetes with sitagliptin and vildagliptin for 3 months equated with placebo and other oral antidiabetic medications and it demonstrated a decrease of 0.74% in HbA1c levels. This outcome demonstrated DPP-4 inhibitors were just somewhat less viable than sulfonylureas and as viable as metformin and thiazolidinediones as to decreasing blood glucose. In contemplates with combining treatment of DPP-4 inhibitors and metformin in one tablet, the outcomes were far better in view of two conceivable induces. To start with, metformin has an improved modulating impact on the range of glucagon-like peptide 1 (GLP-1), and hence it improves the incretin impact of the DPP-4 inhibitors. A second conceivable clarification for the enhanced outcomes in the blended medication is the enhanced consistency of patients when taking one oral medication rather than two.

DPP-4 INHIBITORS AND PATIENT WEIGHT

Analyses on the regulation of DPP-4 inhibitors on patient mass exhibited varying outcomes yet are typically believed to be unbiased. Contemplates in regards to intervention with sitagliptin indicated unevenness between 1.5 kg of weight reduction in 13 months of intervention to 1.8 kg of weight benefit in 6 months of intervention. Analyses in regards to intervention with vildagliptin demonstrated unevenness between 1.8 kg of weight reduction to 1.3 kg of weight gain in 6 months of intervention. Interchangeable interventions with respect to saxagliptin indicated unevenness between 1.8 kg of weight reduction to 0.7 kg of weight gain in 6 months of intervention. In higher order of 13 analyzes in regards to the intervention of each of all sitagliptin, saxagliptin, and vildagliptin, the impact of this radical of medications on weight was achromatic.⁶

DPP-4 INHIBITORS AND CARDIOVASCULAR EFFECT

In late years, a few tribulations were promulgated about the safety impact of incretins on the heart. A few analyses were likewise promulgated on the gainful impact of DPP-4 inhibitors. In analyses done on mice without the DPP-4 receptors that were dealt with sitagliptin, the researchers initiated acute myocardial infarction by left anterior descent coronary artery ligation. In these, an up-control of cardio-defensive qualities and their protein items was established. In another examination, it was demonstrated that intervention with sitagliptin can diminish the infarct zone and the defensive impact of sitagliptin was protein kinase A-subordinate. In diabetic patients who likewise endure the ill effects of coronary heart disease, it was shown that intervention with sitagliptin enhanced their heart capacity and coronary artery perfusion, as ascertained in echo-debutamin examinations.⁶

Another investigation promulgated a retrospective contemplate in regard to the impact of intervention with saxagliptin on cardiovascular unwholesomeness and fatality. In this investigation, in spite of the fact that there are numerous impediments, there was no enhanced danger of cardiovascular unwholesomeness and fatality and maybe a negligible nonsignificant reinforcement. An investigation uncovered that in metabolic disorder, patients demonstrated that throughout placebo and low-level ACE suppression sitagliptin brought down the pressure of the blood. Anyway, this pattern was turned around

throughout higher-level of acute ACE suppression. DPP-4 inhibitors have as well been found to have postprandial lipid levels effects. A study demonstrated that intervention with vildagliptin for about a month enhances postprandial plasma triglyceride and apolipoprotein.⁶

Another study proposed that DPP-4 hindrance expands postprandial lipid movement and oxidation by energizing the benevolent arrangement instead of direct impact on metabolic condition. Another part to our knowledge was assessed in a study that evaluated postprandial lipid synthesis and discharge in ordinary and fructose-enriched hamsters and in wild-kind mice that were intervened with or without sitagliptin. These investigations and early comparable progressing analyses are imparting practitioners trust that the DPP-4 inhibitors as a radical of medications will deliver a profitable impact on blood glucose levels as well as on heart and coronary artery subroutine.⁶

There are likewise extra information grounded on retrospective age group analyzes or grouped studies of randomized controlled preliminaries in regards to the impact of individual persons on cardiovascular effects. Utilization of sitagliptin was not related with an expanded danger of cardiovascular-related infirmity accessions or demise in correlation with other antidiabetic medicates in a retrospective populace based age group investigation of around 72,740 recently treated patients with type 2 diabetes.⁷ There is great proof that DPP4 hindrance arbitrates defensive impact on atherosclerosis, hypertension, and myocardial infarction. Various analyses in animal exemplary affirm a good impact of DPP4 hindrance in enhancing endothelial capacity and pressure in blood. Both DPP4 hindrance and GLP-1 agonism decreases postprandial triacylglycerol and ApoB-48 in rodents. Another higher level of investigation with 70 analyses and 41,959 patients also proposed that DPP4 hindrance decreased cardiovascular endangerment and all-cause fatality in diabetic patients.¹¹

MONOTHERAPY OF GLIPTINS³

As metformin is deliberated as the primary choice of intervention for type 2 diabetes mellitus, it is important to think about the adequacy and wellbeing of a DPP-4 inhibitor with that of metformin in drug-primitive type 2 diabetes mellitus patients deficiently ensured with eating routine and physical exercise. Altogether, metformin exhibited marginally but noteworthy diminution in both HbA1c and weight. Nevertheless, the DPP-4 inhibitor indicated hypernomy in gastrointestinal durability when equated with metformin. However, these relative outcomes do not affirm the initiatory consumption of a DPP-4 inhibitor rather than the reference medication metformin excluding the patients for whom metformin is either not substantially endured or is apprised like patients with renal inadequacy.

GLIPTINS IN COMBINATION INTERVENTION³

Due to the ramification of the pathophysiology of type 2 diabetes mellitus and the regularly ascertained chief or subaltern letdown of monotherapy, initial combining intervention possibly deliberated to extend more effectual treatment of type 2 diabetes mellitus. Various clinical tribulations have assessed initial compounding of either metformin & gliptin or thiazolidinediones & gliptin and equated the consequences with the initial monotherapy. Nonetheless, none of these preliminaries assessed an initial combination admitting DPP-4 inhibitor against another initial combination without gliptin in nip and tuck equivalence. The initial combination of sitagliptin or vildagliptin with metformin had predominant adequacy equated with monotherapy interventions with corresponding overall acceptability profiles and low endangerment of hypoglycemia. Interchangeable consequences were observed with the initial combination of

saxagliptin and metformin. These well-disposed consequences were ascertained in short-term of 4.5 – 6 months and long-term of 13.5 - 26 months clinical trials. The likely dose- stunting impact of adding a DPP-4 inhibitor to comparatively low-amount metformin in orientation to metformin uptitration may enable patients to accomplish identical or higher-up HbA1c-bringing down without the gastrointestinal capability problems related with superior dosages of metformin. Alike consequences have been accounted for with the initial combination of thiazolidinediones & gliptin. Diminution in HbA1c of 1-2.4% against baseline have been accounted for and were constantly essential more prominent than those ascertained with monotherapy with either thiazolidinediones or a DPP-4 inhibitor. Also, first-line combining interventions had negligible endangerment of hypoglycemia, directed to alike or just marginally more weight increase than pioglitazone and offered a compatible profile equivalent to constitutive monotherapy. Thence, such combination may offer a worthwhile connected beginning intervention choice for type 2 diabetes mellitus, especially in situations where metformin is contraindicated in patients with renal insufficiency.

SAFETY AND TOLERABILITY²

DPP-4 inhibitors have been all things considered especially endured in short-run thinks about. As a rule, accounted untoward issues join nasopharyngitis, UTI, pancreatitis, and cerebral torments. Real horribly vulnerable reactions have been accounted including anaphylactic reactions, angioedema, and exfoliative dermatological reactions. The DPP-4 inhibitors in like manner have all the earmarks of being less conceivable to be consociated with weight get. Since these things are respectably unexampled accessible, long run, honest to goodness feel with their usage is required to support substantiate their prosperity profile.

CONCLUSION

Intervention of diabetic patients with medications from the incretin category is one of the fundamental and focal intervention devices accessible to the practitioner today. It is impertinent to deliberate DPP-4 inhibitors in view of their restricted impact on bringing down blood glucose and impersonal impact on caloric ingestion and hence more positive impact on muscle and total body protein mass. They are all evidently well endured and ensue in clinically significant decreases in fasting and postprandial blood glucose levels. They are simpatico with first-line treatment and they afford inevitable additivity to other drugs, where they can be utilized without dosage modification. Merely, long-term conglomerated clinical go through will uncover whether compound-related qualities prompt any clinically important contrasts.

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