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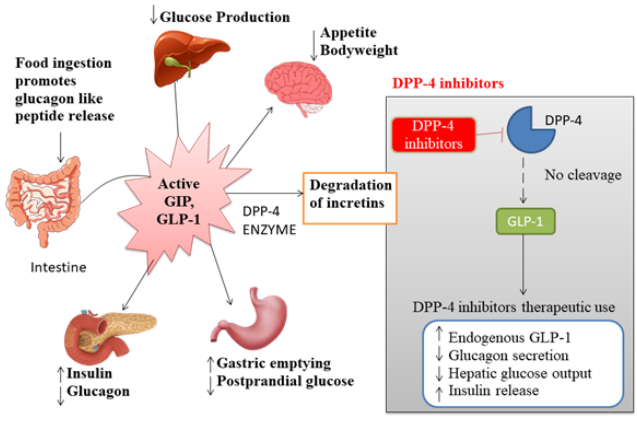
REVIEW ARTICLE

DPP-4 Inhibitors in the Management of Diabetes: Exploring Molecular Insights and Clinical Significance

Leesha Varshney, Payal Kesharwani*, Anupam, Pallavi Manish Lavhalle

ABSTRACT

Diabetes is a metabolic illness that affect millions of people worldwide. The current therapy used in the treatment of diabetes leads to various adverse effect such as improper dosing schedule, low potency, ineffective targeting, reduced metabolism and weight gain. Therefore, there is the great need of antidiabetic drugs which helps to reduce the suffering of patients. Dipeptidyl peptidase 4 (DPP-4) has emerged as highly a powerful therapeutic treatment option for the management of type-2 diabetes mellitus (T2DM). The DPP-4 inhibitors works at a molecular level by blocking the enzymatic activity of DPP-4 that increases the half-life of endogenous incretin hormones that includes glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). This leads to enhanced glucose-dependent insulin secretion, suppression of glucagon secretion, delayed gastric emptying and ultimately improved glycemic control. In clinical trials, DPP-4 inhibitors have demonstrated efficacy as monotherapy or in combination with other anti-diabetic drugs, like metformin, sulfonylureas etc. Various clinical trials have highlighted their ability to reduce hemoglobinA1c (HbA1c) level, fasting plasma glucose and post-prandial hyperglycaemic excursions, they also give benefits on weight neutrality and low risk of hypoglyceamia. This review provides a comprehensive overview of the molecular mechanisms and clinical implications of DPP-4 inhibitors in diabetes management. In addition, DPP-4 inhibitors represent a valuable therapeutic option for the management of T2DM.



DPP-4 Inhibitors and GLP-1 in the treatment of diabetes

GRAPHICAL ABSTRACT

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INTRODUCTION

Diabetes is a metabolic illness defined as a hyperglycemic state that impairs insulin production and raises blood sugar levels[1]. It is the most prevalent endocrine condition that affects more than 422 million people globally[2] with the majority residing in low- and middle-income nations. The disease is directly responsible for 1.5 million fatalities annually. Over the past few decades, because of the lifestyle of people, the number of cases has been rising tremendously (WHO). Hyperglycemia is related to carbohydrates, fats, and protein metabolic dysfunction, which may affect the vital organs of the body, disrupting its normal functioning. This disruption may result in structural and functional changes in normal vital organs, leading to organ damage and failure, including the eye, kidney and heart[3].

Many countries confront countless obstacles in managing diabetes, such as the disease's increasing incidence in both urban and rural regions, lack of adequate health care facilities, high cost of diagnosis, low public awareness of the condition, inadequate glycemia control, and an increase in the frequency of diabetic complications[4]. Some of these challenges are reactive oxygen species that are produced with increased levels of blood glucose, which aggravate diabetes. As a result, lowering elevated blood glucose levels is essential for preventing complications from diabetes[5]. The conventional medicine used for treating hyperglycemia are biguanides (which decrease hepatic glucose synthesis), sulfonylureas (which increase pancreatic islet insulin release), and PPARγ agonists (which increase the action of insulin), α-glucosidase inhibitors (hinders the gut's ability to absorb glucose)[4]. But these therapies result in adverse effects such as weight gain, reduced therapeutic efficiency because of

an improper or ineffective dosing schedule, low potency, gastrointestinal disorders, reduced drug metabolism, and reduced targeting effectivity due to lack of specificity, solubility, and permeability of drug[6]

There is a great need for anti-diabetic drugs due to the rising number of people suffering with diabetes caused by sedentary lifestyle patterns and an increased prevalence of obesity[7]. Many national and international guidelines for treatment. DPP-4 inhibitors are a family of oral antidiabetic medications that are becoming increasingly well-established.[8] In 2006, sitagliptin was the first medication to be introduced; followed by other drugs alogliptin, vildagliptin, saxagliptin, linagliptin, teneligliptin, gemigliptin, etc. The physiological function of DPP-4 in controlling the incretin hormones GLP-1 and GIP is known.[9] Animals with DPP-4 genetic deficiencies or those treated pharmacologically with DPP-4 inhibitors showed enhanced glucose tolerance, higher GIP, and improved active GLP-1.19, 20, 22, and 23.[10] Moreover, DPP-4-deficient mice, rats, and humans treated pharmacologically with inhibitors showed increased insulin and decreased glucagon levels, which is consistent with the function of this enzyme in incretin regulation and metabolic control.

To treat T2D, DPP-4 inhibitors are used either as the first line of treatment or as a component of a combination therapy. The medications in this class appear to be comparable in terms of safety and efficacy, although linagliptin is the only DPP-4 inhibitor that does not require dosage modification in cases of renal impairment. Drug interactions based on drug transport or the CYP450 system are unaffected by alogliptin.

The review discusses DPP-4 inhibitors in diabetes management: From molecular insights to clinical impact". This study provides a comprehensive overview of DPP-4 inhibitors, a class of oral hypoglycemic agents, in the context of diabetes management. This study investigated the molecular mechanisms underlying DPP-4 inhibition and the clinical implications of using these agents to treat diabetes.

Diabetes in India

Based on current projections, 285 million individuals globally (6.6%) within the 20–79 age were diagnosed with diabetes in 2010, and by 2030, 438 million adults (7.8% of the total adult population) are predicted to have the disease. India holds the dubious title for being the "diabetes capital of the world" because it has the highest percentage of diabetic patients worldwide. The Diabetes Atlas 2006, released by the International Diabetes Federation, projects that 69.9 million Indians would have diabetes by 2025 if immediate preventive measures are not taken (Soni, 2013). Currently, there are approximately 40.9 million diabetics in India. An estimated 77 million people above the age of 18 years suffer from T2DM, and nearly 25 million are pre-diabetics (at a higher risk of developing diabetes in near future).[11]

Types of Diabetes

It is essential to understand that the term diabetes mellitus applies to a broad category of illnesses that cause chronic hyperglycemia. The basis for classifying the various forms of diabetes is the variation in the mechanisms that contribute to its development (Figure 1).

Type 1 Diabetes Mellitus

This type of diabetes used to be known as juvenile-onset or ketosis-prone polygenic illness. It is sometimes referred to as response diabetes. The patient may also present with several autoimmune diseases, such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease [12]. Insulin-dependent diabetes mellitus (IDDM), commonly known as type I diabetes, is primarily seen in children and young people. Its onset is typically sudden and fatal. Type 1 diabetes mellitus is occasionally distinguished by the presence of hormone, islet cell, or anti-glutamic acid decarboxylase antibodies, which identify the chemical reactions that lead to beta-cell death, which typically results in an absence of hormones[13].The rate at which β-cells break down varies among people; it occurs in a fast manner in some people and slow in others, where the duct gland's ß-islets cells are destroyed, resulting in a severe shortage or absence of hormone production. Hormone injections are necessary for its treatment [14]

Type 2 Diabetes Mellitus

Diabetes mellitus resistant to ketosis is another term for type 2 diabetes. Secretary dysfunction of the progressive hypoglycemic agent in the circumstances of insulin resistance[15].People who have this kind of polygenic disease often have resistance to the effects of hypoglycemic drugs[16].The primary causes of morbidity and death associated with polygenic disease include semi-permanent problems in the kidneys, eyes, nerves, and blood arteries, which have been reported. causes are many, but among the risk factors include genetic predisposition, aging (which impacts middle-aged and older persons), obesity, and inactivity. Individuals who have these disorders are more susceptible to macrovascular and small-tube problems[17.]

Gestational diabetes mellitus

The term "physiological state diabetes mellitus" describes aldohexose intolerance that appears during pregnancy[18]. The World Health Organization states that Type 1 diabetes mellitus can develop in pregnant women at any

Table 1: List of nations with the greatest predicted diabetes cases between 2000 and 2030 Taken from Wild S[11]

2000			*2030*		
Ranking	*Countries*	*People with diabetes mellitus*	*Ranking*	*Countries*	*People with diabetes mellitus*
1	India	31.7	1	India	79.4
2	China	20.8	2	China	42.3
3	U.S.	17.7	3	U.S.	30.3
4	Indonesia	8.4	4	Indonesia	21.3
5	Japan	6.8	5	Japan	13.9
6	Pakistan	5.2	6	Pakistan	11.3

point in their pregnancy. Women who are diagnosed with diabetes during pregnancy but do not show any symptoms are classified as having physiological state diabetes mellitus (GDM). Physiological state diabetes, or GDM, is a kind of diabetes that is not readily over diagnosed in pregnant women[19].During pregnancy, diabetes mellitus may appear at any time and gradually go away after the delivery. Because prenatal exposure to hyperglycemia is connected to obesity and type 2 diabetes, children born to mothers with gestational diabetes mellitus have an increased risk of developing these conditions in the near future[18]

Pathogenesis of diabetes mellitus

DM development may be triggered by two different pathophysiological pathways. The first and most significant is a lack of secreted insulin [15]. The second is decrease in the action of insulin (insulin resistance), which ordinarily prompts an increase in insulin production as a countermeasure (hyperinsulinemia)[16]. Environmental conditions, genetic defects, or a mix of the two can lead to insulin resistance. T2DM is a polygenic disease in which a person acquires a set of genes that increases their risk of developing the disease. Interactions between environmental conditions and genetic background are necessary for developing T2DM (Figure 2)[17]. Diet and physical exercise are environmental variables that promote the clinical condition. Obesity and insulin resistance are caused by excessive consumption of calories, a high-fat diet, and insufficient physical exercise[18]. Hyperglycemia and T2DM are caused by insulin resistance in individuals with insufficient β-cell insulin secretory response. Rather than lower body or generalized fat, insulin resistance develops with upper body (central or visceral) obesity. Visceral adipose tissue differs from subcutaneous adipose tissue in numerous ways, which accounts for its distinct influence on insulin action. The regulation of various adipose tissue depots is genetically regulated[19]. The very tiny quantities (2 to 3 kg) that accumulate. (Figure 2 depicts the pathogenesis of diabetes mellites)

Pathophysiology of diabetes

Peripheral insulin resistance and insufficient insulin production by pancreatic β-cells are two characteristics of T2DM. Insulin resistance reduces glucose transport into muscle cells, increases hepatic glucose synthesis, and accelerates fat breakdown. It has been linked to increased levels of free fatty acids and proinflammatory cytokines in plasma.[20]

It is important to recognize that too much glucagon plays a role in T2DM, which is an islet paracrinopathy in which the β-cells that secrete insulin and the α-cells that secrete glucagon cease to reciprocate, resulting in hyperglycemia and hyperglucagonemia[21]. T2DM development requires both insulin resistance and inadequate insulin production.. For instance, insulin resistance is a condition that affects everyone who is overweight, but diabetes only strikes those who are unable to secrete enough insulin to compensate for their insulin resistance. Their insulin levels could be modest for the degree of glycemia, but they could still be excessive.[22] Figure 3 shows a simplified approach to the pathophysiology of impaired glucose metabolism in patients with T2DM.

Existing diabetes mellitus treatment.

Current approaches for the management of diabetes encompass a range of interventions aimed at glycemic

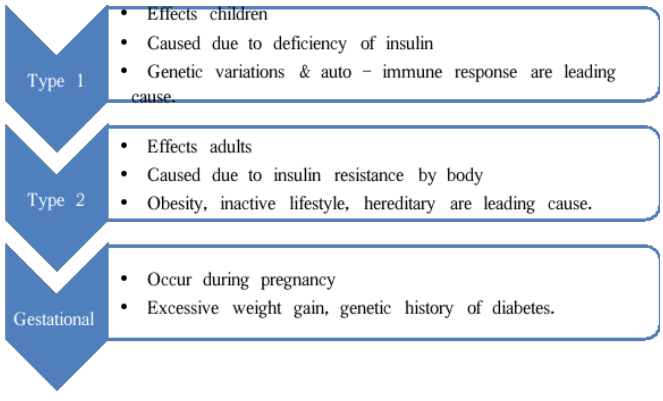


Figure 1: Diabetes categorization: An illustrative overview of its types

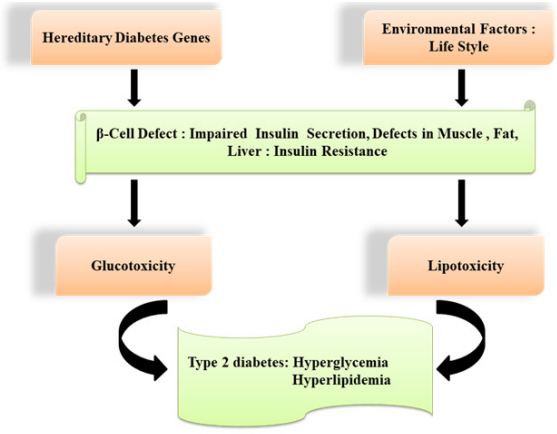


Figure 2: Unraveling the pathogenesis of diabetes mellitus: insights into the underlying mechanisms and disease progression

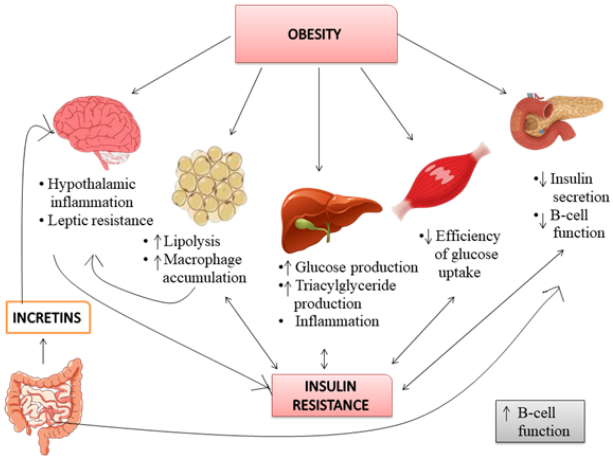


Figure 3: Simplified approach for the pathophysiology of impaired glucose metabolism in type 2 diabetes

control, prevention of complications, and improvement of patient quality of life. These approaches include lifestyle modifications, pharmacological therapies, and advanced treatment modalities. Drugs and lifestyle changes can help to manage the severity and symptoms of type 2 diabetes, even though there is no cure for the condition. Some of the most commonly used pharmacological agents management of diabetes of T2DM include drugs from different classes such as biguanides (metformin), sulfonylureas (glyburide and glipizide), meglitinides (repaglinide and nateglinides) and thiazolidinediones (pioglitazone). Drugs belonging to these classes are administered as the first line of defense to prevent the deterioration of the diabetic state [23].

DPP 4 Inhibitors and their role in diabetes management

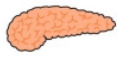
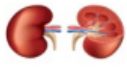
DPP-4 is a transmembrane glycoprotein that was first identified as the T-cell surface marker cluster of differentiation 26 (CD26). Its molecular mass ranges between 220-240 kDa [25]. The three main parts of human DPP-4/CD26 are an extracellular domain with DPP activity that only cleaves off the N-terminal dipeptides from peptides containing proline, alanine, or, to a lesser extent, serine at the penultimate position. The intracellular domain is short and includes six amino acids. The transmembrane region forms the third domain. [26]

In addition to being widely expressed in the gastrointestinal tract, kidney, liver, bone marrow, and on the surface of diverse cell types like stromal, stem, epithelial, endothelial, and immune cells, DPP-4/CD26 is also soluble and can be found in bodily fluids in the form of DPP-4/CD26, which is made up of extracellular amino acids and exhibits significant DPP-4 activity[27].

The maintenance of glucose homeostasis is known to depend on the gut-derived incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 and GIP are rapidly degraded by DPP-4. For more than 10 years, gliptins, also known as DPP-4 inhibitors, have been used as effective oral antidiabetic medications (OADs) to treat T2DM by prolonging the half-life of native incretins. Many gliptins are produced following the FDA's 2006 approval of sitagliptin, the first DPP-4i, for elders with T2DM. These include saxagliptin, alogliptin, vildagliptin, linagliptin, teneligliptin, trelagliptin, and omarigliptin [9]

To maintain stable hypoglycemia, insulin secretion must be regulated. Hyperglycemia develops in T2DM as cells because of peripheral insulin resistance and a decrease in insulin production. During a fast, a small amount of insulin is constantly released by the body to help the peripheral tissues absorb glucose[28]. After a meal, there is an immediate and substantial increase in insulin secretion to maintain blood sugar levels within a specific physiological range. Along with the rise in postprandial glucose concentrations, the gastrointestinal hormones GIP and GLP-1 also play a role in the postprandial stimulation of glucose[29].Approximately 70% of the insulin released after a meal is attributed to these two hormones, which also promote insulin secretion when blood sugar levels are high. Because of their significant physiological role in promoting postprandial insulin production, these hormones are called incretin hormones[30]. The phenomenon whereby oral glucose administration results in a significantly larger insulin response than intravenous glucose administration is known as the incretin effect. The incretin effect is reduced and postprandial insulin secretion is declining in individuals with T2DM. In patients with T2DM, insulin secretion can be restored by pharmaceutical increase of GLP-1[31]. There is relatively little intrinsic risk of hypoglycemia because the GLP-1-dependent increase in insulin secretion only occurs under

Table 2: Summary of possible future therapies showing main sites and modes of action in comparison to present therapies. 11βHSD1, 11β-hydroxysteroid dehydrogenase-1; AMPK, adenosine monophosphate-activated protein kinase; DPP-4; FGF21, fibroblast growth factor-21; GLP-1, glucagon-like peptide-1; PYY, peptide YY; SGLT, sodium–glucose cotransporter; SPPARM, selective peroximeproliferatorr-activated receptor modulator[24]

Present therapies	*Targeted therapy*	*Possible future approaches*
------	Diet	Prebiotic and probiotic food supplements alter the gut microbiome
a-glucosidase inhibitors slow carbohydrate digestion Colesevelam* bile sequestrant Pramlintide* amylin analogue		SGLT1 and SGLT1/2 inhibitors delay glucose absorption
Bromocriptine* dopamine D2 agonist		Satiety-inducing agents, reduce adiposity, eganalogues of GLP-1, PYY, and oxyntomodulin Incretin mimetics and small molecule receptor agonists enhance the incretin effect e.g. oral GLP-1 receptor agonists and hybrid and chimeric peptides
GLP-1 receptor agonists enhance the incretin effect DPP4 inhibitors enhance the incretin effect Sulfonylureas stimulate insulin secretion Meglitinides stimulate insulin secretion		Insulinotropic agents that enhance insulin secretion, e.g. B-cell mitochondrial stimulants, fatty acid receptor agonists, and glucokinase activators. Glucagon secretion inhibitorseg GLP-1 receptor agonists
Metformin counters insulin resistance and reduces glucose production Insulin Increases glucose uptake. decreases glucose output and lipolysis		Direct inhibitors of hepatic glucose production and stimulants of muscle glucose uptake and metabolism, e.g. AMPK activators
Thiazolidinediones Increase insulin sensitivity		Adipokine analogs/agonists/inhibitors, FGF21 analogs, SPPARMS, 11BHSD1 inhibitors, and various anti-insulin resistance
SGLT2 inhibitors glucosuric effect		Novel SGLT2 Inhibitors ,glucosuric effect

hyperglycemic conditions. Another advantageous impact of GLP-1 in T2DM is its ability to sustain glycemia because the disease causes excessive stimulation of glucagon secretion, which in turn increases the synthesis of glucose in the liver. In hyperglycemic situations, GLP-1 reduces glucagon release, which lowers blood sugar levels. The plasma half-life of GLP-1, a peptide hormone, is only a few minutes [32]. The rapid enzymatic breakdown of GLP-1 (and GIP) by the enzyme DPP-4 causes the short biological half-life. DPP-4 inhibitors are tiny, active compounds that can be taken orally that inhibit DPP-4. The endogenous GLP-1 concentration is increased two to three times when DPP-4 inhibitors are administered[33] . High affinity substrate GLP-1 has for DPP-4, often known as the "direct target." DPP-4 has substrates other than GLP-1 as well, and its inhibition can raise these substrates, which is known as a "indirect target" or "off-target," and help normalize glycemic levels in people with T2DM [34].The mechanism of action of DPP-4 inhibitors and the physiology of incretin hormones following a meal are depicted in Figure 4.

History of DPP-4 Inhibitor:

In 1966, a novel aminopeptidase with distinct substrate properties was identified as DPP-4. Later research revealed that it was identical to the mouse thymocyte-activating factor, rat liver membrane glycoprotein gp110, and T-cell activation antigen cluster of differentiation (CD26). The 70 kb human gene found in 1992 is situated on the long arm of chromosome-2. (2q24.3), which consists of 26 exons encoding a 766-amino acid protein, the traditional catalytic location of serine proteases is encoded by exons 21 and 22, respectively. In mouse, DPP-4 is located on the chromosome-2 and interestingly,

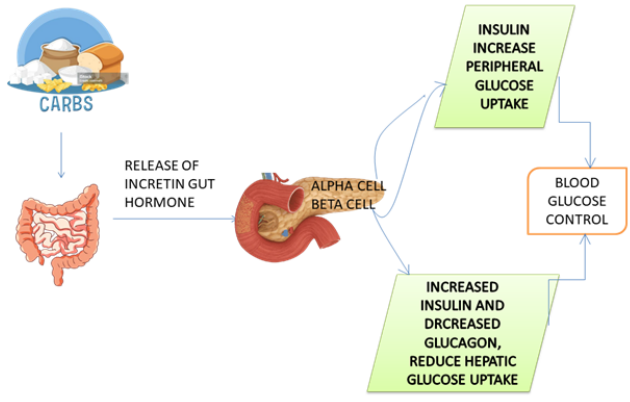


Figure 4: Physiological Effect on the Incretin System and Its Role in Glycemic Control

exon 21 and 22 are present as a single 156 bp exon.[35]. DPP-4 is frequently seen in many organs, including endothelial cells in many vascular beds, making the enzyme extremely obtainable to peptide substrates moving via the liver, intestines, renal, and lungs.[36] Two main mRNA transcripts are encoded by the human gene. Its availability is broad, together with a 2.8-kb transcript limited to the liver, lung, kidney, and placenta[37]. Additionally, there are several small splice variations in the DPP-4 gene have been discussed; yet, the practical importance, if any, of the distinct mRNA transcripts, each of which could have a unique 3-untranslated sequence. The traditional bioactive DPP-4 protein is still translated ambiguous. Serine peptidase/prolyl oligopeptidase gene family, which includes DPP-4; membrane-bound peptidases, fibroblast activation protein (FAP) / seprase; resident cytoplasmic enzymes, DPP8 and DPP9; and non-enzymatic members, DPP6 and DPP10, found in neuronal membranes, and prolyl endopeptidase, is frequently sub-classified in part based on structure and function. Despite other notable sequence changes, the location and identity of the residues necessary for catalytic activity within the C-terminal region of these related enzymes are substantially conserved in prokaryotes and eukaryotes. The functionally related DASH (DPP activity and/or structure homologs) enzymes, which mimic DPP-4's enzymatic activity despite structural and localization differences, contribute to further enzymatic complexity and explain DPP-4-like activity that endures following genetic deletion or pharmacology [38].

Mechanism of Action of the DPP-4 Inhibitor

The physiological function of DPP-4 in controlling the incretin hormones GLP-1 and GIP are well established. Animals treated pharmacologically with DPP-4 inhibitors showed improved glucose tolerance, higher GIP, and improved active GLP-1 levels[39] [40]. Moreover, rats, mice and humans also treated pharmacologically with inhibitors showed increased insulin and decreased glucagon levels, which is consistent with the function of this enzyme in incretin regulation and metabolic control. When GLP-1 and GIP receptors are absent in mice, DPP-4 inhibitors do not increase glucose tolerance, suggesting that these incretins alone are responsible for the increased glucose tolerance observed in these animals.[30] All of these findings clearly show that these incretins are endogenous substrates for DPP-4. Along with GLP-1 and GIP, this enzyme has also been connected to the regulation of other peptides, such as pituitary adenylate cyclase-activating polypeptide (PACAP), gastrin-releasing peptide (GRP), glucagon-like peptide 2 (GLP-2), growth hormone-releasing hormone (GHRH), and PACAP.[41,42] Additionally, this enzyme's in vitro substrates include neuropeptides and chemokines. Although many of these peptides cleave effectively *in-vitro*, it is challenging to determine if DPP-4 regulates these peptides *in-vivo*, partly because of the absence of suitable assays for measuring the endogenous levels of the suspected substrates and products. This enzyme has also been connected to the control of other peptides, including GLP-1 and GIP, gastrin -releasing peptide (GRP), glucagon-like peptide 2 (GLP-2), growth hormone-releasing hormone (GHRH), and pituitary adenylate cyclase-activating polypeptide (PACAP) [8]. Furthermore, neuropeptides and chemokines are among the in vitro substrates of this enzyme. It is hard to figure out whether DPP-4 regulates these peptides *in-vivo*, although many of them cleave efficiently *in-vitro*. This is partly due to the absence of suitable assays for determining the endogenous levels of the suspected substrates and products. Figure 5 depicts the mechanism of action of the DPP-4 inhibitor[43].

Classification of DPP-4 Inhibitors

DPP-4 inhibitors, a group of prescription medications, are utilized alongside diet and exercise to manage elevated blood sugar levels in adults diagnosed with T2DM. Sitagliptin, saxagliptin, ligandliptin, and Alogliptin are examples of medications within this class, available either as standalone products or in combination with additional anti-diabetic medication metformin. These drugs function by assisting the body in increasing insulin levels following meals. Insulin facilitates the transfer of sugar from the bloodstream into tissues, enabling the body to use sugar for energy production and maintaining stable blood sugar levels (FDA) (Figure 6).

Sitagliptins

To be utilized as a solo therapeutic approach or in conjunction with metformin or thiazolidinediones to enhance glycemic control in individual with T2DM in addition to diet and exercise, the US Food and

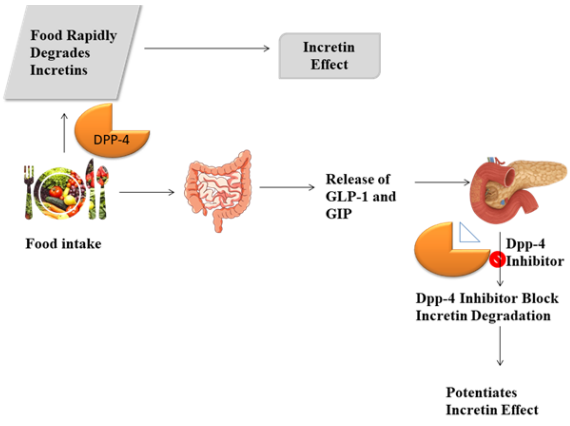


Figure 5: Mechanism of DPP-4 Inhibitor: DPP-4 inhibitor inhibits the degradation of the incretins, GLP-1 and GIP which potentiate incretin effect

Drug Administration (US-FDA) authorized Sitagliptin phosphate* in October 2006. Sitagliptin was introduced as an oral therapy alternative as the first drug in the world in a new family of drugs known as DPP-4 inhibitors. Reviewing the pharmacology, pharmacokinetics, pharmacodynamics, clinical effectiveness, side effects, and cost of sitagliptin phosphate treatment in elders patients with T2DM [34 44]

Chemistry

Sitagliptin phosphate is 7-[(3R)- 3 amino4-(2,4,5-trifluorophenyl) butyl-1-oxo-4-[6, 7, and 8-tetrahydro-Trifluoromethyl or 3--1,2,4-triazolo[4,3-a] monohydrate of pyrazine phosphate (1:1). The compound's chemical formula is C16H15F6N5O·H3PO4·H2O, and its molecular weight is 523.32 Da [45].

Pharmacokinetics

Pharmacokinetic profile of sitagliptin is often similar across T2DM patients and healthy people[46]. In healthy adult volunteers, oral sitagliptin was quickly absorbed following a single 100 mg dosage, with peak plasma concentrations reached 1-4 hours after the administration[47]. In healthy individuals, single doses of Sitagliptin ranging from 25 to 400 mg resulted in an increase in the area under the plasma concentration-time curve (AUC) from time zero to infinity in a dose-proportional manner. Sitagliptin's oral absorption is unaffected by food and has an absolute bioavailability of 87%; therefore, it can be taken without consideration for meal. At steady state, Sitagliptin's mean volume of distribution was 198 L following a single intravenous administration of 100 mg drug(Scott, 2017). Sitagliptin is mostly (80%) removed as unmodified medication in the urine, with metabolism having little effect on this process. For Sitagliptin, the obvious terminal elimination half-life is 12.4 hours, and the renal excretion is 350 mL.[48]

Saxagliptin

A very effective, competitive, reversible DPP-4 inhibitor called saxagliptin (Onglyza®) is prescribed to patients with T2DM. Saxagliptin is either used alone or in combination with more anti-hyperglycemic drugs, improves glycemic control, and is usually well tolerated by patients with T2DM for at least two years of therapy, according to several carefully planned clinical trials and their expansions [49].

Clinical pharmacology

Saxagliptin is a monocarboxylic acid amide that is produced by formally condensing the amino group of (1S,3S,5S)-2-azabicyclo [3.1. 0]hexane-3-carbonitrile with the carboxy group of (2S)-amino(3-hydroxyadamantan-1-yl)acetic acid, which is used to treat T2D when in monohydrate form (PubChem).

Pharmacokinetics

Orally, Saxagliptin is quickly absorbed, with bioavailability of approximately 67%. It is widely dispersed throughout the extravascular tissue, with kidney and intestine tissue samples containing the largest quantities. Because CYP3A4/5 hydrolyzes it mostly to main metabolite M2 and various minor metabolites, individuals using concomitant strong CYP3A4 inhibitors should lower their dose [50]. Expulsion of Saxagliptin occurs via the liver and renal systems. Saxagliptin is excreted in urine in 75% of cases and in feces in 22% of cases. Saxagliptin may be excreted in part by the kidneys because renal clearance (mean »230 mL/min) was greater than the estimated glomerular filtration rate (mean »120 ml/min)[51].Given that renal elimination is the principal pathway for both the parent medication and the active metabolite M2, a dose decrease is necessary for patients with moderate to severe renal impairment (Cr clearance <50 mL/min). Saxagliptin has first-order kinetics in the dosage range of 2.5 to 400 mg, and after taking it once daily, there was no discernible buildup[52]

Alogliptins

In T2DM patients, alogliptin was weight neutral, posed no risk of hypoglycemia, and was usually well tolerated. Alogliptin was not linked to an increased risk of severe cardiovascular happenings in a person with T2DM and recent acute coronary syndrome, according to the results of this sizable and carefully planned study. In summary, alogliptin is a helpful choice about the treatment of T2DM in patients.[53]

Chemistry

(2-[[6-[(3R)-3-amino-1-piperidinyl) or Alogliptin Phase 3 clinical studies are presently assessing -3,4-dihydro-3-

methyl-2,4-dioxo-1(2H)-pyrimidinyl]methyl]benzonitrile monobenzoate) as a powerful (IC50<10 nM) and selective inhibitor (selectivity >10,000 over DPP-8 and -9)[54]

Pharmacokinetic properties

The complete bioavailability of alogliptin is 100%. After single oral dosages of 25–800 mg given to healthy volunteers, Alogliptin was rapidly absorbed, with the maximum plasma concentration (Cmax) being achieved in a median of 1-2 hours [55].Alogliptin at a dose of 25 mg once daily for 14 days resulted in a mean Cmax of 153 ng/mL in a median of 1.1 hours in T2D individuals(Covington et al., 2008).Alogliptin did not undergo significant metabolism between 60 and 70 percent of the dosage and was eliminated in the urine as unaltered medication. After Alogliptin was administered with a radiolabeled label, The N-demethylated alogliptin (M-I) and N-acetylated alogliptin (M-II) minor metabolites were discovered.; M-I and M-II made up ~1% and \6% of the parent molecule. M-I, the active metabolite, exhibited a high degree of selectivity in its inhibition of DPP-4, whereas M-II exhibited inhibitory action. Analogliptin metabolism is aided by the cytochrome P450 (CYP450) enzymes CYP2D6 and CYP3A4 [54]

Linagliptins

Linagliptin is an oral diabetes medication that was recently licensed. It works by preventing the action of the enzyme that is DPP-4. More individuals receiving Linagliptin have shown notable improvement and met objectives for glycosylated hemoglobin. Linagliptin was also linked to substantial changes in fasting plasma glucose, postprandial glucose, and glycosylated hemoglobin. Bearing a low rate of hypoglycemia episodes and an adverse event profile similar to that of a placebo, Linagliptin was well tolerated. When considering therapies for patients with T2DM, Linagliptin is a valuable option because of its convenient oral dosing without requiring dosage modifications in those with hepatic or renal impairment. Linagliptin is safe and effective in patients with T2DM [56]

Chemistry

Linagliptin, 8-[aminopiperidin-1-yl (3R)-3]7–(but-2–yn–1–yl)3-[(4-methylquinazolin2-yl)methyl]-3-±A DPP-4 inhibitor produced from xanthine is -3,7-dihydro-1H-purine-2,6-dione.7 Compared with DPP-8 and DPP-9, linagliptin is more selective for DPP-4 by 40,000 and 10,000 times, respectively[57]

Pharmacokinetics

As for the medication's insert, linagliptin has half-life of 131 hours and reaches steady-state concentrations following three doses of 5 mg/d [58]. Because of its high affinity binding to the DPP-4 enzyme and broad binding to plasma proteins, linagliptin has a nonlinear pharmacokinetic profile, which contributes to its lengthy half-life [59] .Linigliptin has a 30% oral bioavailability .Owing to the prolonged half-life of Linagliptin, the DPP-4 enzyme is consistently inhibited, which permits the present, authorized oral dosage of one dose per day. Lignagliptin is mostly removed via the liver (85%), with the kidney eliminating the remaining 5%. Although Linagliptin is mostly eliminated by the liver, its primary metabolite (CD1790) is pharmacologically inert, and the prescription advice presently recommends no changes for individuals with hepatic impairment[60].

Vidagliptin

Vildagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor that is strong, selective, and active. It has been reported to be safe and effective in treating patients with type 2 diabetes mellitus (T2DM), either when used alone or in conjunction with other anti-diabetic medications. Vildagliptin has a minimal potential for medication interaction and lesser variability due to a number of advantageous pharmacokinetic characteristics.

Chemistry

Vildagliptin (1-[[(3-hydroxy-1-adamantyl)amino]acetyl]-2- cyano-(S)-pyrrolidine) is a free base with a molecular weight of 303 g.[61]

Pharmacokinetics

Vildagliptin had a mean terminal elimination half-life ranging from 1.32 to 2.43 hours and was readily absorbed (median time to reach maximal concentration: 1 hour). There was an approximate dose-proportional increase in both the peak concentration and total exposure. Vildagliptin had a dose-dependent effect on the duration of inhibition and inhibited DPP-4 (>90%) at

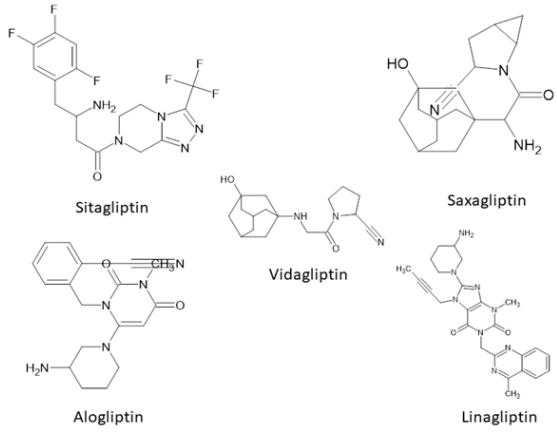


Figure 6: Schematic Structure of DPP IV inhibitors: (a) siagliptin (b) saxagliptin (c) alogliptin (d) linagliptin. The DPP-4 inhibitors bind to the dpp-4-GLP-1 interacting site

Table 3: A Comparative Analysis of Available DPP-4 Inhibitors

Drug	*Dosage Forms*	*Dosage Change in Renal Dysfunction*	*Dosage Change in Hepatic Dysfunction*	*Excretion*	*DPP-4 Inhibition*	*Half Life (Hours)*	*Metabolism*	*Available in Fixed-Dose Combination*	*Refrence*
Sitagliptin	25 mg 50 mg 100 mg	Yes	No	Renal (_80% unchanged as parent)	Max _97%; >80% 24 h post-dose	8–24	Not appreciably metabolized	With metformin, With simvastatin	44
Saxagliptin	2.5 mg	Yes	No	Renal (12–29% as parent, 21–52% as metabolite)	Max _80%; _70% 24 h post-dose	2–4 (parent) 3–7 (metabolite)	Hepatically metabolized to active metabolite (via P450 3A4/5)	With metformin, With dapagliflozin	65
Alogliptin	6.25 mg 12.5 mg 25 mg	Yes	No	Renal (>70% unchanged as parent)	Max _90%; _75% 24 h post-dose	12–21	Not appreciably metabolized	With metformin, With pioglitazone	66
Linagliptin	5 mg	No	No	Biliary (>70% unchanged as parent); <6% via kidney	Max _80%; _70% 24 h post-dose	10-40	Not appreciably metabolized	With metformin, With empagliflozin	60
Vildagliptin	50 mg Dose: 50mg bid; 50 mg qD in eGFR <45 ml/min	Yes	Not recommended in severe dysfunction. Liver testing before administration	Renal (22% as parent, 55% as primary metabolite)	Max _95%; >80% 12 h post-dose	1½–4½	Hydrolyzed to inactive metabolite (P450 enzyme independent)	With metformin	

Table 4: Clinical Efficacy of DPP-4 Inhibitors (clinicaltrial.gov)

Title	*Phase*	*Participants*	*No.of Participants*	*Intervention*	*Control group*	*Primary outcome*	*Status*
A Randomized blind Study of the Effect of the DPP-4 Inhibitor on HbA1c and Safety in Patients With Type 2 Diabetes	Phase 2	adult patients 18-75 years of age; type 2 diabetes diagnosed >=1 month before screening; no previous treatment, or previous treatment with no more than 2 oral medications	100-500 individuals.	DPP-4 Inhibitor	Placebo	HbA1c reduction	Unknown status
The Microvascular Function of GLP-1 and Its Analogues in Humans, in Vivo: the Role of DPP-4 Inhibition	Not applicable	Lean BMI ≤ 25.0 kg/m2 Obese BMI ≥30.0kg/m2 Non diabetic subjects and subjects with Type 2 diabetes on stable medication for at least 3 months	63 individuals	GLP-1	Placebo	Type 2 Diabetes Obesity	Completed
A Randomized, Double-blind Study of the Effect of the DPP-4 Inhibitor on HbA1c and Safety in Patients With Type 2 Diabetes Treated With a Stable Dose of Metformin	Phase 2	adult patients 18-75 years of age; type 2 diabetes; stable metformin therapy for >=3 months before screening.	100-500 individuals.	DPP-4 Inhibitor	Metformin Placebo	Diabetes Mellitus Type 2	Completed
Effect of DPP-4 Inhibitors on Occurence of Cancers and the Mechanism Using AGE and RAGE in Patients With Type 2 Diabetes	Not applicable	Type 2 diabetes mellitus patients with or without cancer Patients who have no treatment with DPP-4 inhibitors.	500	Sitagliptin Alogliptin Vildagliptin	DPP-IV inhibitors on frequency of cancers	AGE (RAGE)	Unknown status
What is the Effects of Prokinetic Drug on the Blood Glucose in Type 2 Diabetes Patients: Mosapride Comparing Placebo	Phase 4	Male or female, age between 30-65 years old Type 2 diabetes Duration of diabetes less than 5 years and pancreatic function be in compensated stage. 7%≤HbA1C≤9% Patients are able to control diet and exercise by themselves in intervention period.	200	Mosapride	Placebo	Type 2 Diabetes	Unknown status
Phase 3, Double Blinded, Placebo Controlled Study of the Effects of 12 Weeks DPP-4 Inhibitor Treatment on Secretion and Action of the Incretin Hormones in Patients With Type 2 Diabetes	Phase 3	Type 2 diabetes diagnosed according to and in accordance with the WHO criteria Metformin treatment of ≥ 1 gram 7,5 % ≤ HbA1c ≤ 10% Age > 18 BMI ≥ 25 kg/m2 Informed consent Contraception, if appropriate	49	Januvia	Placebo	Type 2 Diabetes	Completed
Randomized, Open Label, Two Parallel Arms, Intervention Trial Comparing the Effect of DPP-4 Inhibitor Vildagliptin vs. Glibenclamide on Circulating Endothelial Progenitor Cell Number in Patients With Type 2 Diabetes in Metformin Failure	Phase 3	Age equal or above 35 years; Diagnosis of type 2 diabetes mellitus as defined by the American Diabetes Association, with at least one year of disease duration at the time of the screening visit;	64	Vildagliptin Glibenclamide Metformin	DPP-IV inhibitor	Type 2 Diabetes	Completed

all dosages. When glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) plasma concentration-time curves were compared to a placebo, the areas under the curves increased and postprandial glucagon was significantly reduced at the 25 mg (p = 0.006) and 100 mg (p = 0.005) doses, respectively. The mean plasma glucose concentrations were lower with the 25 mg and 100 mg doses of vildagliptin, respectively, compared to the placebo treatment.[62]

Adverse Effects of DPP-4 Inhibitors

Upper respiratory tract infection, nasopharyngitis, headache with Sitagliptin, urinary tract infection, upper respiratory tract infection, and headache with Saxagliptin were the most frequent adverse effects that occurred in 5% of individuals or more who got DPP-4 inhibitors[1] .It has been observed that using insulin or Saxagliptin with a sulfonylurea increases the incidence of hypoglycemia, whereas using Saxagliptin with a sulfonylurea increases the risk[63].The co-administration of insulin with Saxagliptin has not been researched; however, it is likely to enhance a possibility of hypoglycemia. Dosage modifications are also required in individuals with renal impairment to lower the possibility of hypoglycemia[46].

Other adverse effects that have been found from Sitagliptin post-marketing reports include significant allergic responses, including anaphylaxis, angioedema, and Stevens–Johnson syndrome. Sitagliptin should not be administered to anyone who are allergic to any of the formulation's ingredients. Individuals with a prior pancreatitis history should use Sitagliptin with care. Acute pancreatitis associated with sitagliptin usage has been reported; this includes hemorrhagic and non-fatal necrotizing pancreatitis. While on sitagliptin, patients with a history of pancreatitis have not been assessed.. It is wise to keep an eye out for pancreatitis symptoms in patients and to stop using sitagliptin if the condition is detected[64]

Inactivation of Incretin Hormones and DPP-4

Some studies involving individuals with T2DM and chronic hyperglycemia have shown higher circulating levels of DPP-4 activity[67 68]. However, it is unknown whether circulating DPP-4 activity interacts with the levels of active plasma GLP-1 in particular human subjects.The observation that DPP-4 might break the incretin peptides GIP and GLP-1 in human serum in vitro and the proof that DPP-4 chemical inhibitors prevented GIP and GLP-1 from breaking down solidified DPP-4's significance as a crucial factor in incretin inactivation. Further studies showed decreased cleavage of intact GLP-1(7-36)amide and GIP(1-42) in serum from DPP-4-deficient rats cultured in vitro or when the peptides were infused into DPP-4-deficient rats in vivo, promoting the notion that DPP-4 plays a crucial role in the regulation of incretin inactivation[69] . Furthermore, DPP-4 inhibitors stopped GLP-1(7-36)amide from converting to GLP-1(9-36)amide in vitro, and both GLP-1(7-36)amide and the NH2-terminal DPP-4-generated metabolite GLP-1(9-36) amide were found in plasma from both fed and fasted humans. Similarly, the most common type of circulating immunoreactive GIP in human plasma is the NH2-terminally cleaved GIP(3–42) peptide, which accounts for 58% of total GIP after meals and 70% of total plasma GIP immunoreactivity when fasting.[69].Additionally, it was found that exogenous injection of GIP or GLP-1 by the subcutaneous or intravenous methods caused both peptides to rapidly degrade into the DPP-4 metabolites GIP (3-42) and GLP-1(9-36) amide, respectively, in a matter of minutes. Therefore, DPP-4 primarily determines the circulation t1/2 of intact bioactive GIP and GLP-1[70]

Clinical Trials

Clinical trials involving DPP-4 inhibitors aim to assess the safety, effectiveness, and adequacy of these medications in the management of T2DM. These trials typically involve randomized controlled studies conducted in individuals with T2DM over varying durations

CONCLUSION

The investigation of DPP-4 inhibitors in the treatment of diabetes, from molecular understanding to clinical application, has shown their promise as potent medicinal agents. The creation of specific medicines has been made easier by the molecular understanding of the mechanism of action, particularly in modifying incretin hormones. Clinical research has shown how effective they are in enhancing glycemic control while maintaining a favorable safety profile. In addition, the use of DPP-4 inhibitors into diabetic treatment regimens provides further advantages like weight neutrality and cardiovascular protection. The changing face of diabetes care emphasizes the value of tailored strategies, and DPP-4 inhibitors offer a useful choice, particularly for those with particular needs. The path from molecular understanding to clinical application emphasizes the potential utility of DPP-4 inhibitors in the treatment of diabetes.

Credit Authorship contribution Statement:

PK: Conceptualization & project administration; **LV**: Data curation & Writing-original draft; **A:** Critical analysis; **PL**: Supervision

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CONFLICT OF INTEREST

The authors declare no conflict of interest

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available within the article

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