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Mechanism of Action of Vildagliptin and its Role in Type 2 Diabetes Management

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Background: Insulin resistance and lower production of insulin define a metabolic disorder called type 2 diabetes mellitus (T2DM). Appropriate management of blood glucose levels helps to reduce the risk of diabetes-related complications. Vildagliptin reduces dipeptidyl peptidase-4 (DPP-4) and is a viable new therapeutic choice. DPP-4 inhibitors help to sustain a constant blood sugar level by modulating the incretin system, which oversees either boosting or lowering glucagon levels depending on glucose synthesis. Unlike more traditional therapies li ke sulfonylureas, vildagliptin lowers blood sugar levels while also lessening the possibility of hypoglycemia and extra weight gain.
Aim: This study intends to understand how vildagliptin works and what that implies for clinical practice so that type 2 diabetes might be better managed. This study investigates if vildagliptin is better than other antidiabetic drugs, how it affects glycemic indices, and how it increases incretin hormone action.
Conclusion: Type 2 diabetes mellitus (T2DM) is a major health concern around the world due to its high treatment costs and rising incidence. Reducing related effects, especially microvascular disorders and cardiovascular ones, requires good glycemic management. An increasingly important class of antidiabetic medications, dipeptidyl peptidase-4 (DPP-4) inhibitors like vildagliptin are among the several treatment alternatives. Vildagliptin offers a variety of therapeutic benefits without a high risk of hypoglycemia or weight gain, depending on the incretin-enhancing method it employs—glucose-dependent insulin secretion, reduced glucagon release, or postprandial glucose management. In combination therapy with other antidiabetic medications, it provides a good balance and is well-tolerated, making it appropriate for a wide range of patients, including those with moderate to severe renal impairment. Vildagliptin treats multiple facets of diabetes thanks to its synergistic effects with insulin, sulfonylureas, metformin, and other medications. Vildagliptin's efficacy in protecting pancreatic beta-cell activity, improving overall medication adherence, and meeting glycemic objectives. Incorporating DPP-4 inhibitors into diabetes treatment improves clinical results and patient quality of life, as research highlights their wider therapeutic implications.
Keywords: Vildagliptin, DPP-4 Inhibitor, Type 2 Diabetes Mellitus (T2DM), Incretin Hormones.

Introduction

Type 2 Diabetes Mellitus (T2DM)

Nearly 415 million individuals worldwide, ranging in age from 20 to 79, suffer with diabetes mellitus (DM), a metabolic disorder characterized by persistently high blood sugar levels. The disease is expected to become a major concern for public health worldwide when the estimated number of cases reaches 200 million by 2040. Chronic hyperglycemia, like other metabolic illnesses, can cause organ failure or death in the long run. Cardiovascular diseases are two to four times more likely to occur in patients with microvascular and macrovascular problems,

respectively. The purpose of this review is to provide a comprehensive overview of the disorder, covering its causes, symptoms, diagnostic criteria, and potential treatments.1

Pathophysiology of T2DM

Diabetes mellitus (DM) can be broadly categorized into three main forms: type 1, type 2, and gestational diabetes. The immune system attacks and destroys the insulin-producing pancreatic beta cells in type 1 diabetes mellitus (T1DM), resulting in an insulin deficiency. Although it can manifest in anyone's life, it is more common among the younger generations. Of all people with diabetes, about 90% have type 2 diabetes mellitus. Insulin resistance decreases in people with type 2 diabetes. Although it primarily affects those over the age of 45, factors like obesity, lack of exercise, and calorie-heavy meals are making it more prevalent among younger generations. Hyperglycemia, also known as gestational diabetes mellitus (GDM), affects about 7% of pregnant women.[2]

Obesity, advanced maternal age, rapid weight gain during pregnancy, a history of congenital malformations in prior pregnancies, stillbirth, and a family history of diabetes are all risk factors for gestational diabetes mellitus (GDM). One to five percent of all instances of diabetes, known as monogenic diabetes, are caused by a single mutation in an autosomal dominant gene. Typically, this hereditary condition manifests in persons younger than 25 years old. Hormonal abnormalities, specific medications (such corticosteroids), or consequences from pancreatic illness might lead to secondary diabetes.[3]

Gestational diabetes, type 2 diabetes, and type 1 diabetes mellitus (DM) are the three main forms of the disease. The immune system attacks and destroys the insulin-producing pancreatic beta cells, leading to the onset of type 1 diabetes mellitus (T1DM) and the complete cessation of insulin production. Although it can manifest at any age, it usually strikes younger people first. Out of all the instances of diabetes, type 2 diabetes mellitus concerns over 90%. Reduced insulin resistance is a hallmark of type 2 diabetes. Causes like as obesity, inactivity, and calorie-dense diets are making it more common in younger generations, even though it is mainly found in persons over the age of 45.[4]

The condition known as gestational diabetes mellitus (GDM) is characterized by hyperglycemia that is detected during pregnancy and affects 7% of pregnancies. The risk factors for gestational diabetes mellitus (GDM) include being overweight or obese during pregnancy, being an older mother, gaining a lot of weight during pregnancy, having a history of congenital abnormalities, having a stillbirth, or having diabetes in the family. One in five cases of diabetes is monogenic, meaning it is caused by a single mutation in a dominant gene that is passed down through generations. Symptoms of this hereditary condition tend to manifest in people less than 25 years old. Some medications, hormonal imbalances, or pancreatic illnesses might cause type 2 diabetes mellitus to develop.[5]

Problems in managing blood sugar levels

A Review of Drug-Protein Interferon-4

Gliptins, an oral diabetic medicine that inhibits dipeptidyl peptidase-4, has been approved for the treatment of type 2 diabetes mellitus by the Food and Drug Administration. The Food and Drug Administration has authorized four drugs that inhibit dipeptidyl peptidase-4: alogliptin, linagliptin, sitagliptin, and saxagliptin. Although the FDA has not yet approved vildagliptin, it has been granted the go light by the EMA. Increasing hormones are involved in maintaining steady blood sugar levels following oral meals, and these medications block them. Beyond their principal role of lowering blood sugar levels, these medications have numerous other benefits. Without involving the incretin pathway, they can also alter immunological responses in the heart, kidneys,

and blood vessels; reduce inflammation, prevent cell death, and reduce blood pressure. This family of medications has also shown some promise in treating NODAT, or new-onset diabetes after transplantation, in persons who have undergone a liver or kidney transplant. The benefits of these drugs are the reason behind this. They work well when used alone or in conjunction with other drugs. Additional therapies may involve insulin, thiazolidinediones, sulfonylureas, or Metformin.[6]

Role of the DPP-4 enzyme

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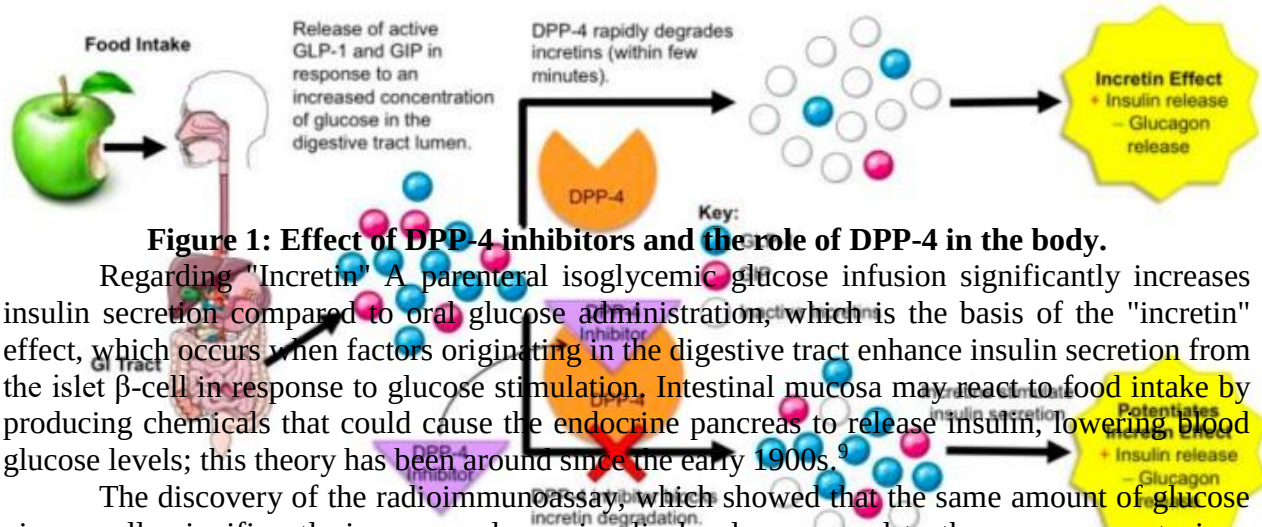

Figure 1: Effect of DPP-4 inhibitors and the role of DPP-4 in the body.

Regarding "Incretin" A parenteral isoglycemic glucose infusion significantly increases insulin secretion compared to oral glucose administration, which is the basis of the "incretin" effect, which occurs when factors originating in the digestive tract enhance insulin secretion from the islet β-cell in response to glucose stimulation. Intestinal mucosa may react to food intake by producing chemicals that could cause the endocrine pancreas to release insulin, lowering blood glucose levels; this theory has been around since the early 1900s.[9]

The discovery of the radioimmunoassay, which showed that the same amount of glucose given orally significantly increases plasma insulin levels compared to the same amount given intravenously, proved the connection between the intestine and the endocrine pancreas. Half to three quarters of the insulin secreted in response to oral glucose delivery in healthy individuals is thought to be accounted for by the incretin effect. The ability to control gastric acid output in dogs led to the first naming of the first incretin hormone as gastric inhibitory polypeptide (GIP). Its

production began with crude pig small intestine extracts. We renamed GIP to "glucose-dependent insulinotropic polypeptide" since at normal doses it increases insulin production in humans and animals alike.[10]

The acronym is the same. The small intestine K-cells secrete the 42-amino acid peptide hormone GIP in reaction to the consumption of fat (and less so glucose). In reaction to glucose, GIP triggers the release of insulin via a designated receptor known as the GIP receptor (GIPR). The majority of intestinal K cells are located at the duodenum's proximal end. The idea of a link between α-cells within an islet and β-cells has been advanced due to the discovery of bioactive GIP in pancreatic α-cells.[11]

Nearly ten years passed following the identification of proglucagon and related mammalian genes before the second incretin hormone, glucagon-like peptide-1 (GLP-1), was identified. The proglucagon gene encodes GLP-1, a posttranslational proteolytic product that is unique to certain tissues. Intestinal L-cells secrete GLP-1 after a meal, which increases insulin production in response to glucose stimulation.[12]

The intestinal endocrine cells create two main molecular forms of glucagon-like peptide-1, GLP-1(7-36) amide and GLP-1(7-37), which are collectively referred to as intact bioactive GLP-1. The majority of GLP-1 in the bloodstream is the amide form, while trace levels of the bioactive GLP-1(7-37) form are also detectable. In the interprandial state and during fasting, the colon continuously releases small amounts of GLP-1 into the bloodstream. After eating, the concentration in the bloodstream increases by a factor of two or three. After nutrients have been consumed, it maintains metabolic equilibrium in multiple ways. The physiologic roles of GLP-1 include reducing food intake, increasing insulin synthesis and glucose-dependent insulin secretion, decreasing stomach emptying, and glucagon release. One of GLP-1's many actions in the gut and brain is to make you feel fuller for longer by delaying the emptying of your stomach.[13]

The peptides GLP-1 and GIP work together to increase insulin production in response to glucose stimulation, which is the main mechanism by which incretin acts in humans. The precise nature of the incretin axis deficiencies is unknown, although they are likely associated with type 2 diabetes, hyperglycemia, and other metabolic repercussions of the condition. Initial research suggests that type 2 diabetics experience a reduced incretin impact. Weak GIP activity and decreased GLP-1 secretion are thought to be responsible for the diminished incretin impact. The idea that type 2 diabetics often have inadequate GLP-1 secretory reactions to meals has been challenged by current research. Because factors including age, length of diabetes, concurrent medication therapy, and individual variances in GLP-1 secretion are likely to play a role, it would be unreasonable to claim with certainty that diabetes invariably causes reduced GLP-1 secretion. Most research suggests that diabetes and an acquired lack of GLP-1 secretion and GIP action are the root causes of glucose intolerance, rather than a preexisting abnormality in GLP-1 secretion.[14]

After 20 to 120 minutes, even with larger doses of GIP injected, diabetic subjects exhibit a totally reduced insulin response to GIP, even though the first phase of insulin secretion in response to GIP is unaltered. Research involving human volunteers found this impact, regardless of the cause of type 2 diabetes. The secretory response to insulin is maintained by GLP-1. Diabetic patients may benefit from a strategy that enhances GLP-1 signaling since GLP-1 reduces blood glucose levels and there is evidence that GLP-1 can restore β-cell sensitivity to exogenous secretagogues.[15]

One of its functions is to bind to the GLP-1 receptor (GLP-1R), which is present in several organs. Tissues that fall into this category include the hypothalamus, epidermis, kidneys, lungs, skin, pancreatic beta cells, gastric ducts, and immune cells. The secretion of insulin in response to

glucose is one of the primary roles of GLP-1. Because it is quickly cleaved into GLP-1(9-36), which has its own biological activity (but no longer insulin production), impaired GLP-1 has a circulation half-life of one to two minutes, even if its major biological actions are mediated by a single GLP-1 receptor. The natural conversion of GLP-1(7-36) amide to GLP-1(9-36) amide can be completely or greatly reduced by using inhibitors of dipeptidyl peptidase-4 (DPP-4).[16]

More often than the full-length bioactive peptide, GLP-1(9-36) amide has sparked hypothesis that it may serve as an endogenous GLP-1R antagonist, a weak agonist, or maybe a novel agonist with insulin-independent glucose-lowering characteristics. Following GIP cleavage by DPP-4, inactive GIP(3-42) is another result. Insulin secretion and glucose clearance were not impacted by GLP-1(9-36) amide in human trials.[17]

The DPP-4 Enzyme

The dipeptidyl peptidase-4 (DPP-4) transmembrane glycoprotein exopeptidase, which is 110 kDa in size, was first identified as a surface protein on lymphocytes (CD-26, the T-cell activation antigen cluster of differentiation). It serves several purposes in living organisms. The enzyme may be found in a soluble form in the bloodstream (sDPP-4) after being released from cell membranes through a process known as "shedding"—which involves specialized metalloproteases for each type of cell.[18]

Both membrane-bound and soluble DPP-4 are capable of catalyzing the cleavage of proteins that contain alanine or proline at position 2. There may be a requirement for stereochemistry because DPP-4 cleaves alternate penultimate residues besides proline at position 2, including hydroxyproline, dehydroproline, alanine, glycine, threonine, valine, and leucine. Diverse biological activities are regulated by DPP-4, which inactivates peptides and/or generates new bioactive peptides by cleaving at postproline peptide links. As complicated biochemical messengers, incretin hormones, cytokines, growth factors, neuropeptides, and other bioactive DPP-4 substrates are utilized by numerous organs, including neuroendocrine and immunological systems. Since endothelial cells in various artery beds express DPP-4, enzymes that breakdown peptide substrates are easily accessible to the intestines, lungs, kidneys, and liver.[19]

There are pharmacological and physiological substrates that can activate dipeptidyl peptidase-4. Physiological substrates for dipeptidyl peptidase-4 include GIP, GLP-1, GLP-2, Peptide tyrosine tyrosine [PYY], Stromal cell-derived factor-1 [SDF], and GLP, among others. These types of substrates show very different levels of intact vs cleaved peptide in animals and humans that have genetically rendered DPP-4 inactive or that have been given DPP-4 inhibitors. Alternatively, DPP-4 can cleave pharmaceutical substrates even when no living things are present.[20]

Endogenous peptides such aprotinin, BNP, β-casomorphin, chorionic gonadotrophin, endomorphin-1, endomorphin-2, enterostatin, eotaxin, erythropoietin, GCSF, and countless more have not been validated through in vivo cleavage studies. Some DPP-4 substrates that are now believed to be pharmacological may actually be cleaved by DPP-4 in vivo, considering the low quantities of these substrates in blood and tissues and the difficulties in differentiating intact from cleaved peptides.[21]

Retaining the diminished function of the incretin hormones (GLP-1 and GIP) by blocking DPP-4 can alleviate diabetes glycemia because these hormones are necessary for glucose regulation. The neuronal membrane-resident prolyl endopeptidase (DPP6) and its close relatives, the serine peptidase/prolyl oligo-peptidase (DPP) genes DPP8 and DPP9, are all part of the same family of genes. DPP-4 belongs to this category. Scientists in the field of biology are taking an interest in the dipeptidyl peptidase-4 (DPP-4) enzyme because of the creation and approval of very

selective DPP-4 inhibitors for the management of type 2 diabetes. These medications boost the incretin action at the same time that they selectively deactivate DPP-4.[22]

Inhibitors of dipeptidyl peptidase-4 (1.3)

Currently, there are five different selective dipeptidyl peptidase-4 inhibitors on the market: vildagliptin (exclusive to Europe), alogliptin (available in the US and Europe), linagliptin, and sitagliptin. Teneligliptin, anagliptin, omarigliptin, and trelagliptin are the only four gliptins available in the Korean and Japanese markets. Although all gliptins work by the same mechanism, variations in pharmacodynamic and pharmacokinetic properties may impact patient care. They seem to have comparable effects as antidiabetic drugs and in decreasing plasma DPP-4 activity. There are a number of important distinctions between them, including dose adjustment for renal and liver insufficiency, elimination half-life, binding to plasma proteins, metabolic pathways, potency, target selectivity, oral bioavailability, and possible drug-drug interactions.[23]

Clinical Benefits of Vildagliptin

Vildagliptin is an excellent and well-tolerated option for the treatment of type 2 diabetes mellitus (T2DM) due to its many beneficial therapeutic effects. Significant reductions in hemoglobin A1c levels (often ranging from 0.5 to1.0%) and better control of postprandial glucose spikes are two of its primary advantages. An advantage over other antidiabetic drugs, such as sulfonylureas, is that it minimizes the risk of hypoglycemia by increasing insulin production and decreasing glucagon release only in response to elevated blood glucose levels. Additionally, vildagliptin is ideal for overweight or obese patients with type 2 diabetes because it is weight neutral.[24]

Vildagliptin has the potential to slow the progression of type 2 diabetes because of its ability to preserve pancreatic beta-cell activity. It has an excellent safety profile because the medicine is not very likely to cause adverse events, such as hypoglycemia or gut problems. It is considered safe for patients with cardiovascular disease, even though it lacks the cardioprotective effects of several other newer antidiabetic medications. Vildagliptin and metformin are common combination therapy medications because they both work well together and provide additional ways to improve glycemic control.[25]

Because it does not necessitate a significant change in dosage for patients with mild to moderate renal impairment, vildagliptin is an excellent option for a wider range of individuals. Its little risk of side effects and once-daily dosage schedule make it easier for patients to follow their treatment plans and improve their quality of life overall. For individuals seeking effective and trouble-free glycemic control, vildagliptin is a great alternative for therapy in the management of type 2 diabetes.[26]

Role in Combination Therapy

Vildagliptin is an important component of combination therapy for the treatment of type 2 diabetic mellitus (T2DM). It is an excellent supplement to other antidiabetic drugs due to its distinctive action as a DPP-4 inhibitor; this is particularly true when monotherapy fails to produce the desired glycemic control. Insulin secretion is enhanced, and glucagon release is reduced in a glucose-dependent manner by vildagliptin, an incretin hormone enhancer. The advantages of this compound are amplified when taken alongside medications that influence several facets of glucose regulation.[27]

It is usual practice to combine vildagliptin and metformin in order to address insulin resistance and pancreatic dysfunction simultaneously. Metformin lowers glucose synthesis in the liver, but vildagliptin enhances beta-cell responsiveness and postprandial glucose control. This is a very efficient combination. This combination is used by many patients because clinical trials

have shown significant reductions in HbA1c levels with minimal risk of hypoglycemia and weight neutrality. When used with insulin, sulfonylureas, or thiazolidinediones, vildagliptin can help control blood sugar levels even more effectively. Hypoglycemia is less likely to occur when used with sulfonylureas than when taken alone. Like insulin, vildagliptin lowers insulin requirements, which means less glucose spikes and hypoglycemia. Patients whose insulin treatment is just beginning or who are already taking insulin will find this especially useful.[28]

Patients can obtain personalized treatment plans that match their unique needs because vildagliptin is versatile in combination therapy. Its glucose-dependent action, positive safety profile, and effectiveness in numerous combinations make it an essential component in the treatment of type 2 diabetes.[29]

Conclusion

The increasing prevalence and exorbitant expense of treating type 2 diabetes mellitus (T2DM) make this condition a global health emergency. Maintaining a healthy blood sugar level is essential for lowering the risk of complications, particularly microvascular and cardiovascular diseases. Vildagliptin and other dipeptidyl peptidase-4 (DPP-4) inhibitors are part of a growing category of antidiabetic drugs. Based on the incretin-enhancing mechanism it uses—glucose-dependent insulin secretion, reduced glucagon release, or postprandial glucose management—vildagliptin provides several therapeutic benefits without a large risk of hypoglycemia or weight gain.

It is suitable for a broad spectrum of patients, including those with moderate to severe renal impairment, because it is well-tolerated and provides a good balance when used in combination therapy with other antidiabetic drugs. By enhancing the effects of insulin, sulfonylureas, metformin, and other diabetic drugs, vildagliptin is able to treat several aspects of the disease. Vildagliptin's ability to safeguard pancreatic beta-cell function, enhance medication adherence generally, and achieve glycemic goals. Research has shown that DPP-4 inhibitors have broader therapeutic implications, and their incorporation into diabetes management improves clinical outcomes and patient quality of life.

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