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MODERN APPROACHS IN THE TREATMENT OF DIABETES MELLITUS BY SITAGLIPTIN

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ABSTRACT

The burden of type 2 diabetes mellitus (T2DM) is increasing in India, leading to higher rates of death and illness. Managing type 2 diabetes mellitus (T2DM) in India is challenging due to unique clinical features and socioeconomic issues among patients. These factors impact blood sugar control and result in worse health outcomes. Consequently, there's a need for safer long-term treatment options that require minimal follow-up. Sitagliptin is a DPP-4 inhibitor that stops the action of DPP-4, an enzyme that breaks down GLP-1, a hormone that helps regulate blood sugar. Sitagliptin improves blood sugar control in people with T2DM, both as a standalone treatment and alongside other diabetes medications, and has a low risk of side effects. This review evaluates the effectiveness and safety of sitagliptin as an additional therapy with other diabetes drugs and insulin.Sitagliptin is an oral antihyperglycemic agent belonging to the class of dipeptidyl peptidase-4 inhibitors. It plays a significant role in the management of type 2 diabetes mellitus by enhancing incretin hormone activity. Incretins

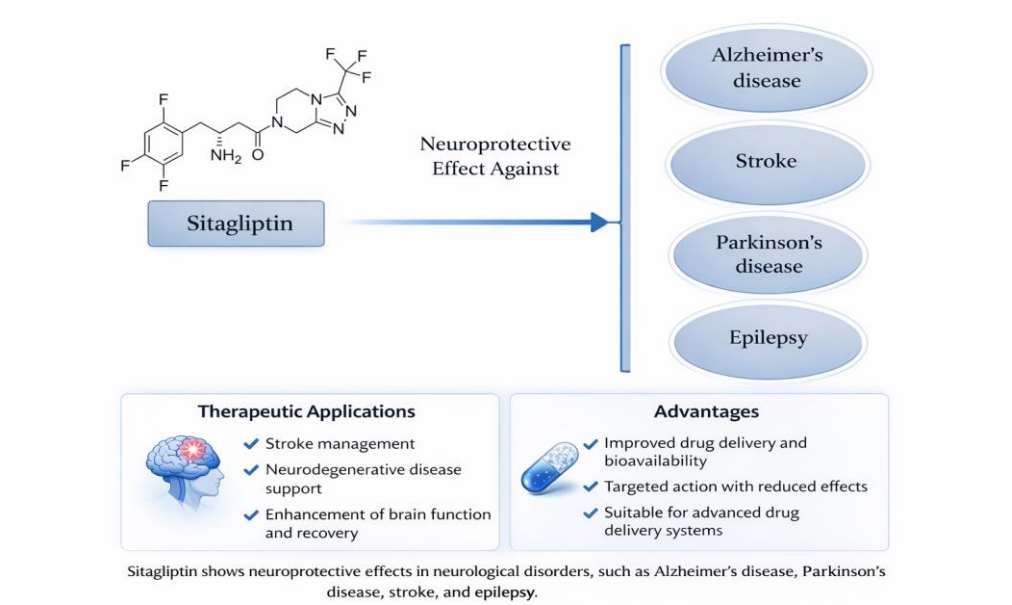
such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide regulate glucose homeostasis by increasing insulin secretion and decreasing glucagon release in a glucose-dependent manner. This mechanism ensures effective glycemic control without causing excessive hypoglycemia. The pharmacological profile of sitagliptin makes it particularly suitable for long-term therapy in patients who require stable glycemic management with minimal adverse effects.

KEYWORDS

Glycated hemoglobin (HbA1c), efficacy, glucagon-like peptide-1 receptor agonist (GLP-1RA), oral, semaglutide, subcutaneous, type 2 diabetes, incretins, diabetes therapy, DPP-4 inhibitors, sitagliptin

INTRODUCTION

Current estimates suggest that by 2030, the global prevalence of diabetes will reach 336 million. In the UK, 3 million people have diabetes, and these numbers are expected to grow. A study from the UK showed that diabetes prevalence rose from 2.8% in 1996 to 4.3% in 2005, mainly due to an increase in T2DM.[1]



Sitagliptin shows neuroprotective effects in neurological disorders, such as Alzheimer's disease, Parkinson's disease, stroke, and epilepsy.

In the US, roughly 18.8 million people have diabetes, with around 7.0 million remaining undiagnosed, accounting for 8.3% of the population. The goal in managing diabetes is to achieve good blood sugar control and reduce complications related to diabetes. Besides lifestyle changes and dietary adjustments, metformin is the first-line treatment for T2DM[2]. Other medications include sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, DPP-4

inhibitors, GLP-1 analogs, and insulin, chosen based on individual needs. These practices may shift if future studies show that early use of newer agents like DPP-4 inhibitors and GLP-1 analogs offer better metabolic benefits. Significant studies, such as the Diabetes Control and Complications Trial (DCCT), Epidemiology of Diabetes Interventions and Complications (EDIC) study, and the UK Prospective Diabetes Study (UKPDS), have shown the advantages of achieving lower HbA1c levels. Recently, trials like ADVANCE and ACCORD found that intensive blood sugar control reduced the risk of macroalbuminuria.[3] One major risk of intensive management is hypoglycemia, making it a challenge to maintain ideal control without causing low blood sugar. Complications like nephropathy further raise the risk of hypoglycemia and may require reducing or stopping certain medications. Recent studies indicate that DPP-4 inhibitors have a low risk of hypoglycemia when not used alongside sulfonylureas or insulin.[4] The appropriate dose reductions for sitagliptin and saxagliptin also allow their use in patients with chronic kidney disease (CKD) stages 1 to 5 and end-stage renal disease (ESRD) on hemodialysis. Additionally, improvements in β-cell function observed in previous studies are benefits of early sitagliptin use.[5,6]

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, provides effective and stable glycemic control by preventing incretin degradation without increased the risk of hypoglycemia or resulting in clinically significant weight gain [16]. Previous studies demonstrated that the addition of DPP-4 inhibitors to insulin therapy limited the insulin dose, decreased the frequency of hypoglycemia, improved glycemic control, and did not increase body weight [17]. These effects of DPP-4 inhibitors may contribute to the prevention of CVD. Five recent cardiovascular outcome trials showed that DPP-4 inhibitors were not inferior to placebo or to sulfonylureas, suggesting their cardiovascular neutrality. However, these trials did not demonstrate superior prevention of CVD in individuals with type 2 diabetes and either a history of CVD or a high risk of CVD. In four of these trials, approximately 10%–40% of participants were treated with insulin at baseline. However, the effect of DPP-4 inhibitors on CVD development in these participants remains unclear. Another post hoc pool analysis using data from four randomized clinical trials showed that the addition of linagliptin, a DPP-4 inhibitor, to insulin therapy had a neutral effect on cardiovascular outcomes. On the other hand, a retrospective cohort study using the population-based National Health Insurance Research Database of Taiwan, which included 3120 individuals with type 2 diabetes who received insulin therapy, demonstrated that the use of DPP-4 inhibitors was associated with a lower risk of mortality than their non-use. Thus, the effect of DPP-4 inhibitors as add-on

therapy to insulin remains inconclusive.[18] We previously conducted the Sitagliptin Preventive study of Intima media thickness Evaluation (SPIKE) trial and found that the addition of sitagliptin to insulin therapy slowed down the progression of carotid intima–media thickness in individuals with type 2 diabetes who had no apparent history of CVD .However, due to insufficient statistical power, it was difficult to detect differences in CVD outcomes between groups in the SPIKE trial. Thus, we investigated if the early initiation of DPP-4 inhibitors improved long-term CVD outcomes in this extension study of the SPIKE trial.[15]

METHODS

We reviewed several databases to find all relevant articles published until April 1, 2021. These included Web of Science, MEDLINE, Embase, Scopus, Cochrane Central Register of Controlled Trials, Cochrane Library, and Google Scholar. The research focused on clinical trials examining the effect of sitagliptin in obese or overweight adults with type 2 diabetes, without language restrictions.[7]

Sitagliptin shows neuroprotective effects against Alzheimer's disease, stroke, Parkinson's disease, and epilepsy.[8]

Methods	Requirements	Excipients	References
1. Literature search in multiple databases	1. Access to databases (Web of Science, MEDLINE, etc.)	1. Lactose monohydrate	[9]
2. Use of keywords related to sitagliptin & T2DM	2. Defined inclusion/exclusion criteria	2. Microcrystalline cellulose	[10]
3. Screening of titles and abstracts	3. Research protocol	3. Magnesium stearate	[11]
4. Selection of clinical trials only	4. Ethical considerations	4. Croscarmellose sodium	[12]
5. Data extraction from selected studies	5. Data extraction forms	5. Hydroxypropyl cellulose	[13]
6. No language restriction applied	6. Skilled reviewers	6. Titanium dioxide	[14]
7. Focus on obese/overweight T2DM patients	7. Study population criteria	7. Talc	[15]
8. Evaluation of neuroprotective effects	8. Outcome measures defined	8. Polyvinylpyrrolidone (PVP)	[16]
9. Analysis of diseases (Alzheimer's, stroke, etc.)	9. Statistical tools/software	9. Sodium starch glycolate	[17]
10. Compilation and interpretation of results	10. Peer review process	10. Film coating agents	[18]

The pharmacological profile of sitagliptin

Sitagliptin (MK-0431), chemically (2R)-4-Oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4] triazolo[4,3-a] pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, has very high selectivity for DPP-4, with an IC(50) of 18 nM. It shows no affinity for other DPP enzymes (DPP-8 and DPP-9). It has been approved for T2DM treatment in the USA and Europe under the name Januvia® (Merck Pharmaceuticals, Whitehouse Station, NJ, USA).[19] In studies with healthy volunteers and patients of diverse ethnic backgrounds, different doses given once or twice daily showed good tolerability. Key pharmacokinetic parameters measured in studies Tmax, Cmax, and t1/2—remained similar at the start and during longer administration. Steady-state plasma levels of sitagliptin are reached after three days. When given once daily, the accumulation rate is modest, with an AUC accumulation ratio ranging from 1.05 to 1.29. The elimination and excretion happen mainly through the kidneys, with 75% of an oral dose appearing in urine as unchanged drug; the rest is metabolized via CYP 3A4 and CYP 2C8. Clinical studies did not observe drug-drug interactions during sitagliptin therapy, especially with other diabetes medications[20]. The elimination half-life is 12 to 14 hours. Doses of 50 to 200 mg per day of sitagliptin, administered once daily, lead to more than 80% DPP-4 inhibition over 24 hours and plasma levels above 100 nM. This results in a 2- to 3-fold increase in biologically active, intact GLP-1 after meals. Safety data from all studies showed very few adverse events, with no significant differences in hypoglycemia rates compared to control groups. Whether used alone or in combination with metformin or thiazolidinediones, sitagliptin did not cause hypoglycemia.[21]

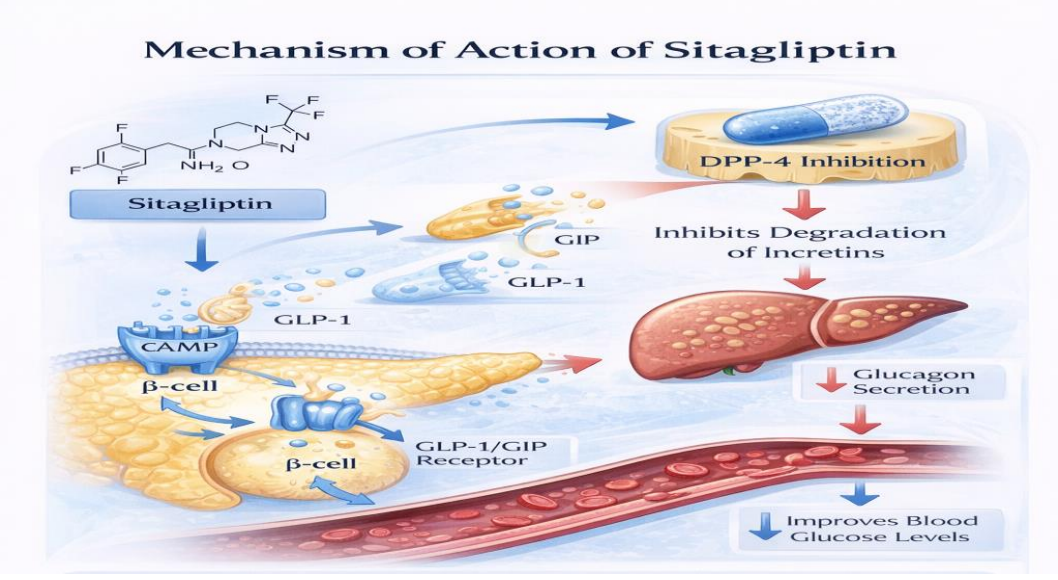


Fig. 2 Mechanism Action Of Sitagliptin.

Sitagliptin is an oral antidiabetic drug with a recommended dose of 100 mg once a day. Oral absorption is not affected by food. Sitagliptin displays 87% of bioavailability and a reversible fraction bound to plasma proteins of 38% [22]; its half-life is around 12.4 hours; hepatic metabolism of sitagliptin is minimal, mainly by cytochrome P450 3A4, while excretion occurs mainly (70–80%) by the kidney in its unchanged form, with a renal clearance of approximately 350 ml/min [23]. In general, the pharmacokinetic profile of sitagliptin is similar in both healthy volunteers and T2DM patients. The pharmacokinetic properties of the drug have also been evaluated in special patient populations with varying grades of hepatic and renal dysfunction. As a result of its metabolism and elimination route, dose adjustment is only required in patients with severe renal insufficiency, being effective and safe in patients with mild/moderate renal or hepatic impairment . No dosage adjustment is necessary related to age, gender and race, or body mass index. Sitagliptin also has a low propensity for pharmacokinetic drug interactions [24]

Sitagliptin is a potent and highly selective DPP-4 competitive inhibitor that does not affect the closely related enzymes DPP-8 or DPP-9 at therapeutic concentrations . Sitagliptin acts by inhibiting over 80% of the activity of DPP-4 enzyme (at 12 h postdose for 50 mg/day and at 24 h postdose for ≥100 mg/day), which is responsible for degrading GLP-1, preventing therefore its inactivation. This increases and prolongs plasma concentrations of the active form of GLP-1, allowing the consequent stimulation of insulin synthesis and secretion from pancreatic β-cells in a glucose-dependent manner.

As T2DM patients exhibit relative resistance to the actions of GIP [25], the main goals of DPP-4 inhibitors are to prolong the beneficial effects of endogenous GLP-1 in order to maintain its insulinotropic activity . Glycaemic levels are then further regulated by the resulting higher insulin levels and glucagon suppression from the direct action of GLP-1 on pancreatic α-cells Sitagliptin reduces blood glucose levels, in either the postprandial or the fasting state. It works differently from the previous drugs available for diabetes treatment and is orally active.

Clinical trials have demonstrated the efficacy of sitagliptin in terms of improving glycaemic control in T2DM patients, used as either monotherapy, initial combination therapy (usually with a fixed dose combination of sitagliptin/metformin) or add-on therapy to metformin or to other antihyperglycaemic drugs, with or without metformin. Sitagliptin showed efficacy in decreasing HbA1c, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG)

levels and also increasing the proportion of patients achieving target HbA1c levels (<7.0%), as shown in several clinical studies.[26]

CLINICAL TRIAL OF SITAGLIPTIN

As the first DPP-4 inhibitor available for treatment, sitagliptin has undergone extensive trials and has shown to be both effective and safe. The studies have included various population groups and clearly demonstrated a significant reduction in HbA1c with minimal side effects. Sitagliptin can be used as a first-line option for patients who are intolerant to metformin and need only a modest decrease in HbA1c to reach their target. Its benefits include a low risk of hypoglycemia, weight neutrality, and potential improvement in β-cell function.[27]

Sitagliptin clinical effects when used in triple therapy

Sitagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, is widely used as part of triple therapy in the management of type 2 diabetes mellitus when dual therapy fails to achieve adequate glycemic control. Typically, sitagliptin is combined with metformin and either a sulfonylurea, thiazolidinedione, or insulin. This combination approach targets multiple pathophysiological defects of diabetes, resulting in improved overall metabolic control. Clinically, the addition of sitagliptin to existing dual therapy significantly reduces glycated hemoglobin (HbA1c) levels, with reductions generally ranging from 0.6% to 1.0%, depending on baseline glycemic status. The glucose-lowering effect is primarily mediated through enhancement of incretin hormones, leading to glucose-dependent insulin secretion and suppression of glucagon release. As a result, both fasting plasma glucose and postprandial glucose excursions are effectively reduced. One of the key advantages of sitagliptin in triple therapy is its favorable safety profile. Unlike sulfonylureas, it carries a low risk of hypoglycemia due to its glucose-dependent mechanism of action. Additionally, sitagliptin is considered weight-neutral, which is beneficial compared to agents such as insulin or thiazolidinediones that may cause weight gain. This makes it particularly suitable for long-term diabetes management. Triple therapy including sitagliptin has been associated with improved β-cell function and durability of glycemic control. Emerging evidence also suggests potential pleiotropic benefits, including modest anti-inflammatory and cardioprotective effects, although these require further clinical validation. The inclusion of sitagliptin in triple therapy provides an effective, well-tolerated, and patient-friendly strategy for achieving glycemic targets in individuals with type 2 diabetes mellitus inadequately controlled on dual therapy.[28,29]

Combination Therapy of Sitagliptin

Sitagliptin is frequently used in combination therapy for the effective management of type 2 diabetes mellitus, particularly when monotherapy does not achieve adequate glycemic control. Its mechanism of inhibiting DPP-4 enhances incretin hormones, making it suitable for use with other antidiabetic agents that act through different pathways. The most common combination is with metformin, where sitagliptin improves insulin secretion while metformin reduces hepatic glucose production. This combination provides significant reductions in HbA1c with a low risk of hypoglycemia and is widely available as fixed-dose formulations.Sitagliptin is also combined with sulfonylureas, which increase insulin release. This combination enhances glycemic control but may increase the risk of hypoglycemia, requiring careful dose adjustment. When used with thiazolidinediones, such as pioglitazone, sitagliptin improves insulin sensitivity along with incretin activity, although weight gain may occur. In advanced cases, sitagliptin can be combined with insulin to improve glycemic control and reduce insulin requirements. Additionally, combination with SGLT-2 inhibitors offers added benefits such as weight reduction and cardiovascular protection.[30,31]

Combination	Mechanism / Action	Clinical Benefits	Limitations
Sitagliptin + Metformin	Increases insulin secretion (incretin effect) + decreases hepatic glucose production	Significant HbA1c reduction, low hypoglycemia risk, weight neutral	GI side effects (metformin)
Sitagliptin + Sulfonylureas	Dual stimulation of insulin release	Enhanced glucose lowering effect	Increased risk of hypoglycemia
Sitagliptin + Thiazolidinediones (Pioglitazone)	Improves insulin sensitivity + incretin enhancement	Effective in insulin-resistant patients	Weight gain, fluid retention
Sitagliptin + Insulin	Enhances insulin action and reduces glucagon	Better glycemic control, reduced insulin dose	Risk of hypoglycemia
Sitagliptin + SGLT-2 Inhibitors	Incretin effect + increased glucose excretion via urine	Weight loss, cardiovascular and renal benefits	Risk of dehydration, UTI
Triple Therapy (e.g., Sitagliptin + Metformin + Others)	Multi-target approach for glucose regulation	Superior glycemic control when dual therapy fails	Increased cost, complexity

Sitagliptin-based combination therapy provides synergistic effects, improved glycemic control, and good tolerability, making it an important component of modern diabetes

management. Another study looked at how sitagliptin (100 mg daily) affected patients combining metformin with rosiglitazone. This study involved 277 patients with a mean baseline HbA1c of 8.8%. The addition of sitagliptin reduced HbA1c by 0.9%, while those continuing only with metformin and rosiglitazone saw a reduction of 0.2%.[32,33]

CONCLUSIONS

In conclusion, Sitagliptin has emerged as a valuable therapeutic agent in the management of type 2 diabetes mellitus, owing to its unique mechanism of action, favorable safety profile, and versatility in combination therapy. By selectively inhibiting the DPP-4 enzyme, sitagliptin enhances endogenous incretin levels, thereby promoting glucose-dependent insulin secretion and suppressing glucagon release. This targeted approach ensures effective glycemic control with a minimal risk of hypoglycemia, making it particularly suitable for long-term use and for patients requiring safer treatment options. The clinical utility of sitagliptin is further strengthened when used in combination with other antidiabetic agents such as metformin, sulfonylureas, thiazolidinediones, insulin, and SGLT-2 inhibitors. These combination strategies provide synergistic effects, addressing multiple pathophysiological aspects of diabetes and resulting in improved glycemic outcomes. Additionally, sitagliptin demonstrates weight-neutral properties and good tolerability, which contribute to enhanced patient adherence and overall treatment success. Beyond glycemic control, emerging evidence suggests potential pleiotropic benefits of sitagliptin, including anti-inflammatory, cardioprotective, and neuroprotective effects. Although these additional benefits require further clinical validation, they highlight the broader therapeutic potential of this drug.

Overall, sitagliptin represents a promising and adaptable component of modern diabetes management. Future research should focus on long-term clinical outcomes, expanded therapeutic applications, and the development of advanced drug delivery systems to further optimize its efficacy and patient-centered benefits.

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