

Role of DPP-4 inhibitors in the management of type 2 diabetes**Ramesh*, D. D. Gupta**

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ABSTRACT

Among various insulinotropic agents used in treatment of Type 2 DM, inclusion of DPP4 inhibitors are considered as major breakthrough as far as new drug development is concerned. In this review article we have discussed in detail about the pathogenesis of diabetes mellitus especially the role of incretin, DPP4 enzyme and implication of its inhibitors in treatment of DM. Also, various clinical studies regarding use of DPP4 inhibitors as monotherapy and as combination therapy with other antidiabetic agents were discussed. DPP-4 inhibitors control glucose in fasting as well as in postprandial state both in monotherapy and in combination with other oral antidiabetic agents. Significant reduction in HbA1c observed with DPP4 inhibitors as monotherapy. On combining DPP 4 inhibitor as add-on therapy to metformin, glitazone or sulphonylurea therapy in patients with type 2 diabetes not reaching therapeutic goals, DPP-4 inhibitors reduce HbA1c, fasting plasma glucose and 2-h postprandial plasma glucose up to the desired level. Various DPP-4 inhibitors have been proven to be as safe and tolerable both as monotherapy and combination with other antidiabetic agents. Inhibition of DPP-4 enzyme has been proven as a promising aspect in the treatment of type 2 diabetes and various drugs inhibiting DPP4 enzymes have been developed now. They are highly recommended in the treatment of Type 2 DM both as monotherapy as well as combination therapy.

Keywords: Diabetes mellitus, DPP4 inhibitors, Incretin

INTRODUCTION

Metabolic abnormalities seen in individuals with type 2 diabetes mellitus (T2DM) are usually abnormalities in insulin secretion both qualitative and quantitative, insulin resistance, obesity, increased endogenous glucose production and dysregulation of other islet hormones secretion such as amylin and glucagon.

During recent development on diabetes research, another important abnormality, which has been encountered, is the decreased incretin effect due to impairment in secretion and action of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). It has been recognized that glucose homeostasis is

governed by a complex interaction among various mediators, including insulin, glucagon, amylin, and incretin hormones. Deficits in any one of these components may contribute to the pathophysiology of T2DM (Table 1).¹

Large number of studies on drugs used in T2DM has been directed at increasing insulin secretion or sensitivity using various agents. A number of reviews on the effect of incretin-based therapies have been published.²

The present review examines the pathophysiology of T2DM, with a focus on understanding the incretin dysregulation and role of DPP-4 inhibitors in treatment of patients with Type 2 DM.

Table 1: Effects of various hormones on glucose regulation.

Secreted by	Hormone	Glucose-regulatory effects
Alfa cells	Glucagon	Increased glycogenolysis, Enhances gluconeogenesis and ketogenesis in liver.
Beta cells	Insulin	Increased glucose uptake by cells, decreases glucagon secretion, promotes protein and fat synthesis,
	Amylin	Decreases postprandial glucagon release, slows down gastric emptying, enhances satiety and decreases weight
Intestine	GLP-1 and GIP	Increases glucose dependent insulin secretion, decreases glucagon synthesis, gastric emptying and body weight. Decreases B cell apoptosis

The GI system and glucose homeostasis in the healthy state

In glucose homeostasis, gastrointestinal system plays an integral role. In healthy individuals, it has been observed that orally administered glucose provides a stronger stimulus for insulin secretion than does an intravenous glucose. Incretin effect may be responsible for 50% to 70% of the total insulin secretion following oral glucose administration. This incretin effect is thought to be produced by GLP-1 and GIP (GI peptide hormones) which exert major Glucose-regulatory actions.³ These peptide hormones act by binding to different receptors expressed on alpha, beta and delta cells present mainly on G.I system. Other sites for GLP-1 receptors are lung, heart, central nervous system (CNS) and peripheral nervous system whereas GIP receptors are expressed in adipose tissue and the CNS.³

Fasting glucose is controlled by tonic secretion of insulin/glucagon, however excursions of glucose after meal (postprandial glucose) is controlled by insulin along with the incretin effect of G.I peptide hormones. Additionally, preclinical studies demonstrated the effect of GLP-1 to induce the transcription of the insulin gene and insulin biosynthesis, thus justifying the role of peptide hormones in increasing beta-cell proliferation and decreasing beta-cell apoptosis.⁴ Extra intestinal actions of GLP-1 are CNS-mediated insulin secretion, delaying gastric emptying, increasing CNS-mediated satiety leading to decreased food intake, indirectly increasing insulin sensitivity and nutrient uptake in skeletal muscle and adipose tissue also have some neuroprotective effects.⁵

Role of the incretin pathway

Until recently, the pathophysiology of type 2 diabetes mellitus (T2DM) is based on the triad of progressive

decline in insulin-producing pancreatic beta cells, an increase in insulin resistance and increased hepatic glucose production.⁶ but it is well understood that other factors like defective actions of the gastrointestinal (GI) incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) also play significant role in pathogenesis of type 2 diabetes mellitus. A hypothesis based upon the observation that oral intake of glucose resulted in a greater insulin response when compared with intravenous glucose administration lead to the origin of a term 'incretin effect', which is the stimulation of insulin release by the oral intake of nutrients. Incretin hormones that attribute to this effect are glucose-dependent insulinotropic peptide (GIP), secreted mainly from duodenal K cells of the proximal small bowel, and glucagon-like peptide-1 (GLP-1), secreted from the enteroendocrine L cells of the distal gut.⁷

The physiological role of GLP-1 are multiple in normal individuals which includes glucose-dependent insulin secretion, inappropriate glucagon secretion from the pancreas, and slowing of gastric emptying.⁸ Despite their therapeutic potential, most notably GLP-1, in the management of patients with type 2 diabetes, these endogenous GLP-1 and GIP are rapidly degraded by the enzyme DPP-4.⁷

The incretin effect has been demonstrated to be impaired in people with type 2 diabetes, which may contribute to the inability of these patients to secrete an adequate amount of insulin to meet physiologic needs. The pathophysiology of this deficient incretin response has not been entirely understood. Up to 60% insulin release to a given glucose load has been identified as incretin effect.⁹

REVIEW OF LITERATURE***DPP 4 enzyme and its inactivation in type 2 DM***

Dipeptidyl peptidase (DPP)-4 is a complex enzyme that exists as a membrane-anchored cell surface peptidase that transmits intracellular signals via a short intracellular tail. Both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are endogenous physiological substrates for DPP-4, and chemical inhibition of DPP-4 activity, or genetic inactivation of DPP-4 in rodents, results in increased levels of intact bioactive GIP and GLP-1. Furthermore, mice and rats with genetic inactivation or inhibition of DPP-4 exhibit improved glucose tolerance, elevated levels of GLP-1 and GIP, and resistance to diet-induced obesity and hyperglycemia. The available preclinical data suggests that highly selective DPP-4 inhibition represents an effective and safe strategy for the therapy of type 2 diabetes. DPP-4 is a widely expressed cell surface peptidase that exhibits a complex biology encompassing cell membrane associated activation of intracellular signal transduction pathways, cell-cell interaction, and enzymatic activity exhibited by both the membrane-anchored and soluble forms of the enzyme.¹⁰

By blocking the enzymatic inactivation of the incretins, DPP-4 inhibitors make it possible for higher levels of active incretins to circulate and carry out their physiologic gluco-regulatory functions. Pharmacologically, selectivity for the DPP-4 inhibitors is important due to potential issues with safety and tolerability as enzyme has wide range of distribution. DPP 4 enzyme is found in highest concentration in the kidneys, intestines, and bone marrow, but it is also found in the liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells.¹¹

This review explores the growing understanding of the role of the incretins in normal insulin secretion, as well as in the pathogenesis of T2DM, and examines the pathophysiologic basis for the benefits and therapeutic application of incretin-based therapies in T2DM.

Chemical structure of DPP-4 inhibitor

The DPP 4 inhibitors are broadly divided into two groups. First group comprise of nitrile containing compounds such as sitagliptin (β -amino acid based) vildagliptin and saxagliptin they resemble the dipeptide structure of DPP-4 substrates, whereas alogliptin (modified pyrimidinedione) and linagliptin (xanthine-based) constitute the second group, which are non-peptidomimetic (Figure 1).¹²⁻¹⁶ All compounds are competitive-reversible inhibitors having high affinity for DPP4 enzyme. Various DPP 4 inhibitors interact differently at enzymatic sites as sitagliptin, alogliptin and linagliptin form non-covalent interactions with their residues.¹⁶ Whereas enzyme inhibition by vildagliptin and saxagliptin is a two-step process that involves the formation of a reversible covalent enzyme-inhibitor complex where binding as well as dissociation between enzyme and its inhibitor are a slow process, resulting in the enzyme slowly equilibrating between the active and inactive forms.¹⁷ This means that the catalytic activity will be inhibited even after the free drug has been cleared from the circulation, this explains why vildagliptin and saxagliptin inhibit DPP-4 activity for longer duration even after their shorter half-lives.

Pharmacological differences between DPP-4 inhibitors

DPP-4 inhibitors have marked structural heterogeneity (Figure 1). This may account for variations in the pharmacokinetic profile between DPP-4 inhibitors. Linagliptin, has a unique xanthine-based structure has long terminal half-life (up to 184 h), whereas the terminal half-life of sitagliptin is between 10 and 12 h.¹⁸ Saxagliptin (half-life 2.5 h) is metabolized by cytochrome P450 3A4/5 (CYP3A4/5) yields an active metabolite, which is about half as potent as the parent compound, with terminal half-lives of 3.1 h. However, the mean $t_{1/2}$ value for plasma DPP-4 inhibition is 26.9 h.¹⁹ In contrast; metabolites of linagliptin, vildagliptin and sitagliptin appear to be inactive. Therefore, linagliptin, sitagliptin and saxagliptin effectively control glycemia over 24 h, despite the

relatively short half-lives of the latter two agents. The structural heterogeneity of DPP-4 inhibitors probably accounts for variations in pharmacological potency of different compounds.

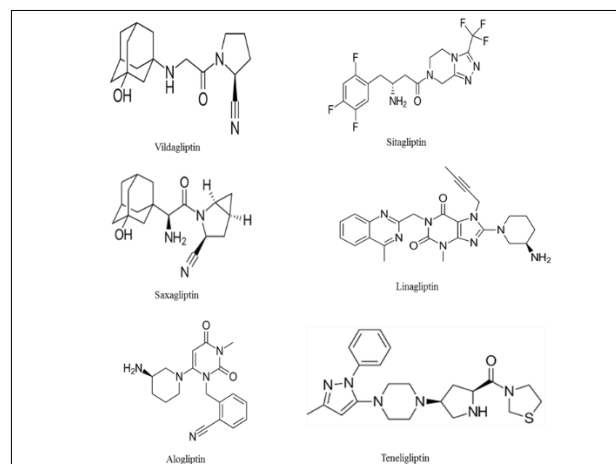


Figure 1: Chemical structure of DPP4 inhibitors.

In vitro, linagliptin inhibits DPP-4 (IC₅₀ approximately 1nM) more potently than sitagliptin (19nM), alogliptin (24nM), saxagliptin (50nM) and vildagliptin (62nM).²⁰ In rodent models, 24 h after linagliptin administration, the extent of DPP-4 inhibition and effects on glucose tolerance was greater than that produced by sitagliptin, alogliptin, saxagliptin and vildagliptin. In a study using Zucker diabetic fatty rats and mice with diabetes induced by a combination of high-fat diet and low-dose streptozotocin, linagliptin found to have better control on HbA1c and GLP-1 than vildagliptin.²¹ Since DPP-4 belongs to serine peptidases family, selective inhibition of DPP-4 would be advantageous in order to avoid unexpected adverse effects. Teneligliptin is a new gliptin, has advantage over others in terms of its high efficacy and long duration of action. It has a long half-life of 26.9 hours and a convenient once-daily administration.

Mode of action of DPP-4 inhibitors

The biological half-life of circulating GLP-1 and GIP is very short because of the high affinity and activity of DPP-4 towards these substrates. Therefore, native GLP-1 is not practical for therapeutic purposes, but DPP-4 inhibition offers a novel way to increase endogenous incretin concentrations as a treatment option.²²

DPP-4 inhibitors are the first orally administered agents that modulate the physiology of GLP-1 by inhibiting the enzyme DPP-4.²³ In contrast to other insulinotropic agents, for example the sulphonylureas, the insulinotropic effect of GLP-1 has more potential in managing optimum blood glucose concentration thus limiting the events of hypoglycaemias. It has the ability to restore the blunted first phase of insulin secretion in type 2 diabetes.²³ GLP-1 has other 'noninsulinotropic' physiological actions that may be advantageous in type 2 diabetes therapy: it

suppresses glucagon secretion from the alpha-cells and slows gastric emptying thus contributes to satiety and to a slower passage of carbohydrates. Additionally, GLP-1 contributes to satiety in the hypothalamus, where it is found as a neurotransmitter. Furthermore, it stimulates the process of beta-cell formation and also inhibits their apoptosis leading to an increase in beta-cell mass.²³

Both sitagliptin and vildagliptin do not cause hypoglycaemia because they stimulate insulin secretion only under hyperglycaemic conditions. Also, they are not involved in drug-drug interactions, especially with other anti hyperglycaemic oral agents.²⁴

DPP-4 has high affinity for GLP-1 than for other peptides including GIP. DPP-4 belongs to an enzyme of endopeptidase family; therefore DPP-4 inhibitors need to have a high selectivity to inhibit DPP-4 exclusively and no other DPPs.

Clinical studies with DPP-4 inhibitors

DPP-4 inhibitors control glucose in fasting as well as in postprandial state both in monotherapy and in combination with other oral antidiabetic agents. They improve beta-cell functions, which is evident by improvement in parameters of postprandial insulin, C-peptide responses, HOMA-B and proinsulin/insulin ratio in patients with type 2 diabetes.^{23,25} Treatment with DPP-4 inhibitors is weight neutral.²⁵ On combining DPP-4 inhibitor as add-on therapy to metformin, glitazone or sulphonylurea therapy in patients with type 2 diabetes not reaching therapeutic goals, DPP-4 inhibitors reduce HbA1c, fasting plasma glucose and 2-h postprandial plasma glucose up to the desired level.²⁶ In 52-week study Sitagliptin was compared to glipizide and it was found that HbA1c and fasting glucose decreased equally in both groups with less incidence of hypoglycaemic episodes in the sitagliptin group. When compared for body weight, glipizide treated patients showed an increase of 1.1kg, whereas the patients on sitagliptin experienced a weight loss of 1.5kg.²⁷ In active-controlled trials, a vildagliptin-metformin combination therapy has been shown to produce equivalent reductions in HbA1c to pioglitazone-metformin and glimepiride-metformin combinations, without significant risk of hypoglycaemia and weight gain. In a vast number of clinical studies, sitagliptin and vildagliptin were well tolerated in terms of the number of adverse events and the incidence of hypoglycaemia.²⁵

Glycaemic effects of DPP-4 inhibitors as monotherapy

A 12-week study examined vildagliptin as monotherapy in patients with a mean baseline HbA1c of 7.7%.²⁸ vildagliptin reduced HbA1c by 0.46% at 50mg and 0.4% at 100mg daily, compared to the non-significant 0.13% reduction by placebo. Another study examined vildagliptin as a single dose versus twice-daily divided doses for 24 weeks in drug-naïve patients with type 2 diabetes with a baseline HbA1c of 8.4%.²⁹ HbA1c was reduced by 0.7%

by vildagliptin at 50mg twice daily and 0.9% at 100mg once daily.

Sitagliptin (100mg daily) was initially evaluated as monotherapy in drug-naïve patients with type 2 diabetes using different doses for duration of 12 weeks. In one study (n/4 555; mean baseline HbA1c 7.7%), HbA1c was reduced by 0.56% by sitagliptin.³⁰

A second study (n/4 743) examined sitagliptin (50mg twice daily) in patients with a mean baseline HbA1c of 7.8%. It was found to have reduced HbA1c over 12 weeks by 0.8%. These research studies thus demonstrated clinically important and efficacious DPP-4 inhibitors in improving the glycaemia as monotherapy. Patients with higher baseline HbA1c have higher reduction and there have been no difference observed among younger and older subjects and no relation to the degree of obesity in terms of efficacy of drug.³¹

Comparison with other agents in monotherapy, A 24-week head-to-head study compared the effect of vildagliptin (50mg twice daily, n/4 519) with that of rosiglitazone (8mg once daily, n/4 267) in subjects with type 2 diabetes with a mean baseline HbA1c of 8.7%.³² HbA1c was reduced by 1.1% by vildagliptin versus 1.3% by rosiglitazone. Furthermore, a 52-week study examined the influence of vildagliptin (50mg twice daily; n/4 526) versus metformin (1g twice daily; n/4 254) in subjects with type 2 diabetes with a mean baseline HbA1c of 8.7%.³³ Vildagliptin reduced HbA1c by 1.0%, which was not non-inferior to metformin, which reduced HbA1c by 1.4%.

Glycaemic effects of DPP-4 inhibitors in combination therapy

Combination of DPP-4 inhibitors with different oral hypoglycaemic agents have been discussed as follows.

Combination with metformin

In a 12 week study (n/4 107) with combination of vildagliptin and metformin in patients with a mean baseline HbA1c of 7.8%, there was reduction of HbA1c levels by 0.7%, however an extended study of 40-week period (n/4 71), vildagliptin reduced HbA1c by 1.1% versus placebo. Another 24-week study observed similar reduction of HbA1c (by 1.1%) in patients (n/4 362) with a mean baseline HbA1c of 7.5% who were treated with combination of vildagliptin (100mg once daily) and metformin.³⁴ Sitagliptin at 100mg daily was added to ongoing metformin in subjects with a mean baseline HbA1c of 8.0% (n/4 701).³⁵ After 24 weeks, HbA1c was reduced by the use of this combination by 0.65% compared to treatment with metformin alone.

Comparison with other agents as add-on to metformin

A study compared the effect of vildagliptin (50mg twice daily; n/4 295) to that of pioglitazone (30mg once daily;

n/4 281) when combined with ongoing metformin therapy in subjects with baseline HbA1c of 8.4%. After 24 weeks, both vildagliptin (by 0.9%) and pioglitazone (by 1.0%) had reduced HbA1c with no significant difference between the groups. Another active-controlled study compared the effect of sitagliptin (100mg daily) plus metformin versus glipizide (up to 20mg daily) plus metformin in subjects (n/4 1172) with a mean baseline HbA1c of 7.5%. The HbA1c was reduced by 0.67% in both groups.³⁶

Hence, DPP-4 inhibition shows an efficient effect in improving glycaemic control as sulphonylureas and thiazolidinediones when added to metformin.

Combination with thiazolidinediones

A comparative study on 463 patients with baseline HbA1c of 8.7% was conducted with vildagliptin 50mg or 100mg versus placebo as add on therapy to pioglitazone at 45mg. It was observed that HbA1c was reduced by 0.8% with 50mg, by 1.1% with 100 mg vildagliptin versus 0.3% in the placebo group treated with pioglitazone alone.³⁷ 45% of the subjects reached target for control (<7%) at the end of the study compared to 23% of patients treated with pioglitazone alone.

Combination with sulphonylurea

A 24-week study in 515 patients with a mean baseline HbA1c of 8.5% was conducted where vildagliptin (50 mg once or twice daily) versus placebo were added to glimepiride (4mg daily).³⁸

The Placebo-adjusted group showed HbA1 reduction by 0.6% as compared to 0.76% reduction shown by vildagliptin 50mg once daily and 50mg twice daily. In another study, add-on of sitagliptin (100mg daily) to glimepiride alone versus glimepiride and metformin combination in patients (n ¼441) with a mean baseline HbA1c of 8.3%, demonstrated a reduction in HbA1c of 0.7% in patients given sitagliptin and glimepiride in comparison to 0.9% reduction in patients given triple therapy.³⁹

Combination with insulin

In 24 weeks study with patients having baseline mean HbA1c 8.9%, when vildagliptin was added to insulin, the mean HbA1c was reduced by 0.5% in vildagliptin group versus 0.2% in the group given insulin alone.⁴⁰ To summarize the effect of DPP-4 inhibitor, it reduces HbA1C by 0.6-1.15% over 24-52 weeks duration as monotherapy, however as add on therapy with metformin, sulphonylureas and thiazolidinediones the DPP-4 inhibitors reduce HbA1C by 0.6-1.1%. Further, various studies showed that DPP-4 inhibitors are similar in potency to sulphonylureas and thiazolidinediones when added to metformin also, DPP-4 inhibition improves glycaemic control when combined with insulin.

Safety profile

Various DPP-4 inhibitors have been proven to be as safe and tolerable both as monotherapy and combination with other OHA. The incidence of hypoglycaemic events seen with DPP4 inhibitors were considerably less as compared to seen with other existing drugs used in treatment of type 2 DM. In a comparative study, sitagliptin was compared with glipizide both of which were administered as add on therapy to conventional metformin, it was observed that hypoglycemia was reported in 5% cases in sitagliptin group versus 32% cases in glipizide group.⁴¹ In another study in which vildagliptin was added to insulin, the incidences of hypoglycemia were less (113) in vildagliptin group as compared to placebo group (185).⁴² Thus it is clearly observed that DPP-4 inhibitors are less known for occurrence of hypoglycemia as an adverse effect. DPP4 inhibitors are considered as weight neutral, it is in contrast to weight reduction effect shown by GLP1 analogues and weight gain effect shown by sulfonylureas. A study comparing effect of sitagliptin in combination with metformin with that of glipizide in combination with metformin showed a clear difference in body weight as reduced body weight in the group treated with sitagliptin (by 1.5kg) versus increased body weight in the group treated with glipizide (by 1.1kg).⁴¹

DISCUSSION

Possible long-term effects of DPP-4 inhibitors on beta-cell

In animal models, the number of insulin-positive beta-cells in islets and the beta to alpha cell ratio in different diabetic animals was normalized by DPP-4 inhibitors. Furthermore, glucose-stimulated insulin secretion in isolated islets was found to be improved in comparison to glipizide treated mice. According to these experimental results, DPP-4 inhibitors may have the potential to delay or prevent disease progression in type 2 diabetes and to improve beta-cell mass and function.²⁵

In mice deficient in DPP-4 (DPP-4 knockout mice) concentrations of circulating intact GLP-1 and GIP are elevated and these animals are resistant to streptozotocin (STZ)-induced beta-cell destruction.⁴³ Preclinical studies have demonstrated that both sitagliptin and vildagliptin increased beta-cell mass in rodent models by increasing the number of replicating islet cells and reducing the number of apoptotic islet cells as assessed in neonatal rats and high-fat diet STZ-induced diabetic mice as models for rapid beta-cell turnover and growth.

In drug naive patients, treatment with vildagliptin (in a high dose of 100mg twice daily) improved beta-cell function by increasing insulin secretion at any glucose level, whereas the slope of beta-cell dose response and the potentiation factor were not affected using a mathematical model. In a similar study over 1 year of vildagliptin as add-on therapy to metformin, an improvement was

demonstrated in beta-cell function, with enhanced postprandial insulin secretion and increased insulin sensitivity and disposition index. A 12-week treatment of drug naive type 2 diabetic patients with vildagliptin (50mg twice daily) restored the acute insulin response to glucose (AIRg) and the sensitivity index (Si) determined by a fast sampling intravenous glucose tolerance test. The disposition index (AIRg \times Si) increased greater than fourfold, and part of its effect remained after a 2-4-week washout, suggesting that vildagliptin may exert some disease-modifying effect.⁴⁴ In summary, more study data are needed to evaluate the effect of DPP-4 inhibitors on beta-cell function, disease progression and beta-cell mass.

CONCLUSION

Inhibition of DPP-4 enzyme has been proven as a promising aspect in the treatment of type 2 diabetes and various drugs inhibiting DPP4 enzymes have been developed now. They are highly recommended in the treatment of Type 2 DM both as monotherapy as well as combination therapy. Drugs like vildagliptin, sitagliptin and saxagliptin are highly effective in reducing raised blood sugar and thereafter maintaining its normal level in all type 2 DM patients. Major role of DPP4 inhibitors remain as add on therapy to metformin in patients with inadequate glycemic control with metformin alone, however patients not tolerating metformin or if it is contraindicated can be managed with DPP4 inhibitor as monotherapy. Furthermore, DPP-4 inhibitors also have significant role in replacing sulfonylurease or thiozolidindione and also as add on therapy to these drugs if glycemic control is poor with individual drugs. However, therapeutic potential of DPP-4 inhibitor in combination with insulin needs to be explored in future.

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