Review Article Open Access

Iranian Journal of Diabetes and Obesity (IJDO)

Dipeptidyl peptidase-4 Inhibitors in Type 2 Diabetes Mellitus: Mechanisms and Efficacy in Clinical Practice

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Abstract

Type 2 diabetes mellitus (T2DM) is a long-term metabolic condition marked by reduced insulin release, decreased sensitivity to insulin, and hyperglucagonemia. In recent years, dipeptidyl peptidase-4 (DPP-4) inhibitors have become increasingly significant within the newer classes of antidiabetic medications, thanks to their distinct mechanism of action, advantageous safety profile, and the convenience of oral administration. In contrast to sulfonylureas, which have a significant risk of causing hypoglycemia, DPP-4 inhibitors offer insulin stimulation that depends on glucose levels, making them a safer choice for many patients. The aim of this study is to investigate the mechanisms and efficacy of DPP-4 inhibitors in clinical practice. The incretin effects of DPP-4 inhibitors are mediated by the hormone glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP stimulates insulin secretion. Furthermore, DPP-4 inhibitors hinder apoptosis in cells. For example, suppressing apoptosis in cardiac, renal, and pancreatic beta cells may be advantageous for enhancing insulin secretion and minimizing complications related to diabetes. DPP-4 inhibitors reduce inflammatory cytokines and chemokines by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). In addition, they mitigate inflammation through modulation of immune cell activity and upregulation of anti-inflammatory chemokines and adipokines. Also, DPP-4 inhibitors have antioxidant roles, such as improving antioxidant factors and downregulating oxidant agents. Considering that T2DM is characterized as an inflammatory disease, DPP-4 inhibitors elevate insulin secretion and sensitivity, improve glycemic indices, and mitigate diabetic complications through incretin, anti-inflammatory, and antioxidant effects.

Keywords: T2DM, DPP-4, GLP-1, GIP, Insulin, NF-κB, Glycemic

QR Code:

Citation: Nosrati Andevari A. Dipeptidyl peptidase-4 Inhibitors in Type 2 Diabetes Mellitus: Mechanisms and Efficacy in Clinical Practice. IJDO 2026; 18 (1) :68-76

URL: http://ijdo.ssu.ac.ir/article-1-1019-en.html

10.18502/ijdo.v18i1.21063

Article info:

Received: 9 October 2025
Accepted: 10 December 2025
Published in February 2026

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[DOI: 10.18502/ijdo.v18i1.21063]

Introduction

Type 2 diabetes mellitus (T2DM) is a long-term metabolic condition marked by reduced insulin release, decreased sensitivity to insulin, and hyperglucagonemia. Diabetes cases worldwide are increasing, underlining the need for reliable and safe treatments. T2DM constitutes 90-95% of all cases, primarily influenced by obesity, lack of physical activity, and poor dietary habits (1-3). In recent years, dipeptidyl peptidase-4 (DPP-4) inhibitors have become enhancely notable within the newer classes of antidiabetic medications, thanks to their distinct mechanism of action, advantageous safety profile, and the convenience of oral administration (4). DPP-4 inhibitors function by extending the effects of incretin hormones, mainly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are essential for maintaining glucose homeostasis (5). In contrast to sulfonylureas, which have a significant risk of causing hypoglycemia (6), DPP-4 inhibitors offer insulin stimulation that depends on glucose levels, making them a safer choice for many patients (7). DPP-4 inhibitors approved by the Food and Drug Administration (FDA) include sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin, gemigliptin, teneligliptin, anagliptin, trelagliptin, and omarigliptin (8).The aim of this study is to investigate the mechanisms and efficacy of DPP-4 inhibitors in clinical practice.

Mechanism of action

The incretin effect of DPP-4 inhibitors

The incretin effect is a phenomenon in which the consumption of glucose through the mouth triggers a significantly higher insulin response than the administration of glucose via intravenous means, even if blood glucose levels remain comparable. This heightened response is attributed to the release of incretin hormones from the intestines in reaction to food consumption (9).This phenomenon is mediated primarily by two gut-derived hormones:

Glucagon-like peptide-1 (GLP-1)

GLP-1 is a significant incretin hormone that is crucial for managing blood sugar levels, appetite, and digestion. It is a hormone originating from the gut, primarily produced in the small intestine's L-cells, in response to the ingestion of food. GLP-1 is part of the incretin system, which raises insulin secretion after meals (10).

GLP-1 has several important effects on metabolism:

Stimulating insulin secretion: GLP-1 enhances insulin release from pancreatic beta (β) cells, occurring in a glucose-dependent manner (only when blood sugar levels are elevated (10).

Suppresses glucagon secretion: GLP-1 hinders glucagon secretion (a hormone that raises blood sugar) from pancreatic alpha cells (11).

Slows gastric emptying: It delays stomach emptying, leading to prolonged satiety and mitigated post-meal blood sugar spikes (12).

Promotes satiety: It acts on the brain (hypothalamus) to lower appetite and food intake (13).

Enhances beta cell growth: GLP-1 helps to maintain and even restore insulin-producing beta cells in the pancreas (14).

Glucose-dependent insulinotropic polypeptide (GIP)

GIP, an essential incretin hormone, substantially contributes to glucose metabolism and the regulation of energy balance. It is released by K-cells located in the duodenum and jejunum when food is consumed, especially in response to glucose and fat (15). GIP collaborates with GLP-1 to enhance insulin secretion after meals (16). Additionally, GIP promotes the proliferation and survival of β-cells, while decreasing apoptosis (17). In a study published by Abd-Eldayem et al., the administration of

[DOI: 10.18502/ijdo.v18i1.21063]

saxagliptin at a dose of 10 mg/kg/day for 14 days notably downregulated the apoptotic factor Bax in rats with renal injury. This effect of saxagliptin may be attributed to the stimulation of GIP (18). Suppressing apoptosis in cardiac, renal, and pancreatic beta cells may be advantageous for enhancing insulin secretion and minimizing complications related to diabetes (19-21).

Both GLP-1 and GIP are swiftly broken down by the DPP-4 enzyme, which cuts their N-terminal dipeptides, causing them to become inactive within a few minutes. DPP-4 inhibitors prevent this breakdown, resulting in elevated levels of active incretins and amplifying their physiological effects (22). In a randomized controlled trial (RCT) published by Mashayekhi et al., sitagliptin (100 mg/day for 14 weeks) elevated the values of endogenous GLP-1 and GIP in subjects with obesity and prediabetes (23).

Anti-inflammatory Effects of DPP-4 Inhibitors

DPP-4 inhibitors exhibit considerable anti-inflammatory properties in both preclinical and clinical research. These properties are facilitated through various mechanisms, such as modulating immune responses, decreasing pro-inflammatory cytokines, and engaging with chemokine pathways. Inflammation plays a crucial role in reducing insulin sensitivity (24). A key pathway involved in the production of inflammatory mediators is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and toll-like receptor 4 (TLR4) pathway (25,26). Meng et al. showed, the content of NF-κB and TLR4 was attenuated by saxagliptin (10 and 30 mg/kg/day) in rats (27).

Reduction of pro-inflammatory cytokines

It was shown, DPP-4 inhibitors downregulate pro-inflammatory cytokines C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). In a meta-analysis published by Xie et al., the therapy with DPP-4 inhibitors in T2DM patients showed a notable connection with decreased levels of CRP, TNF-α, and IL-1β (28). Mechanisms related to TNF-α and IL-1β agitate the development of T2DM (25). Li et al. showed, administering saxagliptin at a dosage of 5 mg once daily for a duration of 24 weeks considerably lowered the content of CRP and glycosylated hemoglobin (HbA1c) in overweight patients with type 2 diabetes mellitus (29).

Modulation of immune cell activity

DPP-4 inhibitors mitigate T-cell activation and proliferation by disrupting the binding of adenosine deaminase (ADA), which typically promotes T-cell responses (24). Kitagawa et al. showed, that the proliferation of CD4 and CD8 T cells was inhibited by the addition of DPP4 inhibitors in a dosage-dependent manner (30). Furthermore, these medications decrease the infiltration of macrophages and the formation of foam cells, both of which are significant agents in atherosclerosis and vascular inflammation. Wang et al. stated that the presence of linagliptin (50 nM and 100 nM for 24 hours) notably decreased the production of IL-1β and reactive oxygen species (ROS) induced by oxidized low-density lipoprotein cholesterol (ox-LDL). Linagliptin improved lipid accumulation and impaired cholesterol efflux caused by ox-LDL in macrophages. Furthermore, this study demonstrated that linagliptin attenuates the ox-LDL-induced expression of the scavenger receptor CD36 (31).

Also, DPP-4 inhibitors hinder NALP3 inflammasome activation. Contributing to lowered insulin sensitivity and the stimulation of diabetic complications by activating IL-1β (32). Birnbaum et al. demonstrated that linagliptin (3 mg/kg) mitigated the elevation of NALP3, IL-1β, and TNF-α levels in db/db mice (33). NALP3 serves as a crucial mediator of neuroinflammation in conditions such as Parkinson's and Alzheimer's diseases (34).

[DOI: 10.18502/ijdo.v18i1.21063]

Chemokine regulation

DPP-4 can cleave stromal cell-derived factor-1 (SDF-1) a chemokine that promotes the recruitment of endothelial progenitor cells, facilitating vascular repair and diminishing chronic inflammation in ischemic injuries. In models of fibrosis, SDF-1 can alter macrophage polarization towards an anti-inflammatory M2 phenotype, encouraging resolution instead of ongoing inflammation. SDF-1 engages with its receptor CXCR4 within the central nervous system (CNS), contributing to the maintenance of microglial inactivity and inhibiting excessive neuroinflammation. In neurodegenerative disorders such as Alzheimer's and Parkinson's, SDF-1/CXCR4 signaling diminishes microglial activation, thereby lowering the release of pro-inflammatory cytokines and oxidative stress (35). In a study published by Liu et al., DPP4 inhibitors enhanced the biological activities of human endothelial progenitor cells (EPCs) by upregulating SDF-1 (36). Wiciński et al. declared that administration of linagliptin prior to a stroke enhanced neuronal survival and promoted the proliferation of neuronal stem cells. This effect appears to be linked to the SDF-1α/CXCR4 signaling pathway (37).

DPP4 inhibitors also affect inflammatory chemokines. In research published by Meng et al., trelagliptin downregulated monocyte chemoattractant protein 1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) in human aortic endothelial cells (HAECs) (38).

Anti-inflammatory effects on adipose tissue

Oxidative stress plays a crucial role in reducing insulin sensitivity. DPP4 inhibitors have shown anti-inflammatory effects by reducing inflammatory factors like TNF-α and IL-1β, which are also synthesized in adipose tissue and decreasing the infiltration of macrophages in this tissue. Another element presents in adipose tissue, which has an anti-inflammatory function, is soluble frizzled-related protein 5 (sFRP5). sFRP5 is a specific antagonist of Wnt5a, a glycopeptide produced by macrophages in adipose tissue that plays a pro-inflammatory role in various diseases. Brandes et al. declared, the treatment with DPP4 inhibitors is associated with elevated levels of the anti-inflammatory adipokine sFRP5 in individuals with T2DM (39).

Antioxidant effects of DPP-4 inhibitors

DPP-4 inhibitors contribute to the reduction of diabetic complications by enhancing antioxidant factors and decreasing oxidative stress factors. Ramos et al. demonstrated that sitagliptin (10 mg/ml twice per day for two weeks) shielded the diabetic retina from oxidative stress caused by diabetes by decreasing levels of superoxide (O_2^-), thioredoxin interacting protein (TXNIP), and protein kinase C (PKC) in diabetic db/db mice. It also prevented the downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant enzymes, including glutathione peroxidase (GPx), superoxide dismutase (SOD), and glutathione reductase (GR) (40). Nrf2 plays a crucial role as a transcription factor in protecting cells from oxidative stress. This factor agitates the production of antioxidant proteins and detoxifying enzymes, thus protecting cells from damage caused by various stressors (41). TXNIP directly interacts with thioredoxin (Trx), a protein that plays a key role in maintaining the cellular redox balance. By associating with Trx, TXNIP can inhibit its antioxidant functions, resulting in heightened oxidative stress within cells, which frequently serves as a precursor to inflammation. Furthermore, TXNIP participates in the activation of the NALP3 (42). PKC participates in oxidative stress through stimulation of NADPH oxidase (43). Malonaldehyde (MDA) is another factor that participates in inducing oxidative stress. In a study conducted by Meng et al., saxagliptin at a dosage of 10 mg/kg per day notably attenuated the concentrations of MDA in rats (27). Abd-Eldayem et al., declared the consumption of saxagliptin at a dose of 10 mg

[DOI: 10.18502/ijdo.v18i1.21063]

per day for 14 days upregulated antioxidant agents such as catalase, superoxide dismutase (SOD), and reduced glutathione (44), and downregulated renal oxidative agents MDA, and myeloperoxidase (MPO) (18). Endothelial nitric oxide synthase (eNOS) acts as an antioxidant and anti-inflammatory agent, playing a vital role in the prevention of vascular diseases. In a study published by Fontes and colleagues, intake of vildagliptin 120 mg/kg during four weeks to heart failure (HF) rats resulted in mitigated NADPH oxidase expression, enhanced eNOS expression, and increased protein kinase A (PKA) activity, which is upstream of eNOS (45).

Glycemic control as clinical efficacy of DPP-4 inhibitors

Monotherapy and Combination Therapy

Based on the mechanisms outlined above, DPP-4 inhibitors may contribute to the improvement of sugar indicators.

Zamani et al. reported, the administration of linagliptin (5 mg/day) substantially lowered serum levels of fasting blood sugar (FBS), 2 hours postprandial (2hpp), HbA1c, and CRP in T2DM patients after 12 weeks when compared to pioglitazone. Pioglitazone is prescribed to regulate blood sugar in T2DM patients (46). Mashayekhi et al. showed, sitagliptin consumption for 14 weeks in obese and pre - diabetic people attenuated postprandial glucose and glucagon values (23). Nagao et al. indicated that sitagliptin attenuated fasting plasma glucose (FPG) by 27.2 mg/dl, HbA1c by 0.61%, and glycated albumin (GA) by 2.39% in patients with T2DM (47). Mohamed et al. stated that in newly diagnosed patients T2DM, administering 50 mg of vidagliptin orally twice daily for six months resulted in a notable reduction in FBG and HbA1c (48).

When DPP-4 Inhibitors combine with other blood glucose-reducing drugs such as metformin, sulfonylureas, and insulin, they will further mitigate glycemic indicators. DeFronzo et al. reported, that adding empagliflozin/linagliptin to metformin results in a greater reduction in HbA1c than using empagliflozin or linagliptin alone as an addition to metformin (49). Sahay et al. declared, that after 16 weeks of treatment, the decrease in HbA1c from baseline was substantially larger with the combination of dapagliflozin (DAPA) + sitagliptin (SITA) + metformin (MET) extended release (ER) compared to the combination of SITA + sustained release (SR) MET and DAPA + MET ER (50).

Conclusion

DPP-4 inhibitors are drugs that are used either as monotherapy or as combination therapy to improve glycemic indicators. Considering that T2DM is characterized as an inflammatory disease studies conducted in vitro, on rats and mice, and humans, suggest that DPP-4 inhibitors have the potential to increase insulin secretion and sensitivity, improve glycemic indices, and mitigate diabetic complications through incretin, anti-inflammatory, and antioxidant effects. The doses and duration of treatment in rats, mice, and humans that contribute to the reduction of diabetic complications range 5-120 mg/day and 2-24 weeks, respectively. However, further studies in the preclinical and clinical phases are needed to examine the effects of these drugs in preventing diabetic complications in more detail.

Acknowledgments

No potential conflicts of interest were disclosed.

Funding

No financial support was received from any specific organization for the design or writing of this article.

Conflict of Interest

There is no conflict of interest.

[DOI: 10.18502/ijdo.v18i1.21063]

Authors' contributions

A.N: Researched the manuscript, conceived and designed the study, and wrote the manuscript. A.N agreed to be fully accountable for the integrity and accuracy of the study.

[DOI: 10.18502/ijdo.v18i1.21063]

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[DOI: 10.18502/ijdo.v18i1.21063]