

# Pleiotropic Benefits of DPP-4 Inhibitors Beyond Glycemic Control

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**ABSTRACT:** Dipeptidyl peptidase (DPP)-4 inhibitors are oral anti-diabetic medications that block the activity of the ubiquitous enzyme DPP-4. Inhibition of this enzyme increases the level of circulating active glucagon-like peptide (GLP)-1 secreted from L-cells in the small intestine. GLP-1 increases the glucose level, dependent on insulin secretion from pancreatic  $\beta$ -cells; it also decreases the abnormally increased level of glucagon, eventually decreasing the blood glucose level in patients with type 2 diabetes. DPP-4 is involved in many physiological processes other than the degradation of GLP-1. Therefore, the inhibition of DPP-4 may have numerous effects beyond glucose control. In this article, we review the pleiotropic effects of DPP-4 inhibitors beyond glucose control, including their strong beneficial effects on the stress induced accelerated senescence of vascular cells, and the possible clinical implications of these effects.

**KEYWORDS:** DPP-4 inhibitors, pleiotropic effects, senescence, vascular cell

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## Introduction

The incidence of type 2 diabetes mellitus (T2DM) is increasing worldwide because of obesity, a sedentary lifestyle, and widespread senescence.<sup>1</sup> T2DM is associated with various chronic complications (eg, neuropathy, nephropathy, and retinopathy), and macrovascular complications (eg, cardiovascular heart disease, stroke, and peripheral artery disease), all of which increase mortality.<sup>2</sup>

Various classes of antidiabetic drugs have been developed to treat T2DM. Most of the researches thus far have been focused on the development of incretin-based therapies, which have become widely used treatment options in clinical practice. The 2 types of incretin-based therapies are glucagon-like peptide (GLP)-1 receptor agonists, and inhibitors of the incretin-degrading enzyme dipeptidyl peptidase-4 (DPP-4).<sup>3</sup>

Since the first DPP-4 inhibitor was approved to treat T2DM in 2006, 10 types of DPP4 inhibitors have become available worldwide.<sup>4</sup> DPP-4 inhibitors lower blood glucose levels by blocking the degradation of active GLP-1 secreted from intestinal L cells and enhancing meal-stimulated insulin secretion from pancreatic  $\beta$ -cells.<sup>5,6</sup> DPP-4 inhibitors also have various non-glycemic actions because of their ubiquitous distribution and numerous substrates/ligands.<sup>7,8</sup> In particular, recent studies have revealed the protective effect of DPP-4 inhibitors against vascular senescence.<sup>9–11</sup> In this article, we review the non-glycemic systemic actions of DPP-4 inhibitors beyond glycemic homeostasis, including and anti-aging effect on vascular endothelial cells, and discuss future clinical implications of these actions.

## Dipeptidyl Peptidase-4

DPP-4, also known as T-cell activation antigen cluster of differentiation (CD)-26, or as the adenosine deaminase (ADA)-binding protein was first discovered in 1966.<sup>12–15</sup> This unique

aminopeptidase is a member of the serine peptidase/prolyl oligopeptidase gene family subclassified by structure and function into membrane-bound peptidase, fibroblast activation protein/seprase (DPP-8 and DPP-9), nonenzymatic members (DPP-6 and DPP-10), and prolyl endopeptidase.<sup>16</sup> DPP-4 is a 100-kDa transmembrane peptidase that cleaves the N-terminus of peptides containing proline or alanine at the penultimate position with high selectivity.<sup>17</sup> DPP-4 is present soluble form in plasma, seminal fluid, cerebrospinal fluid, bile, and synovial fluid; it is present in membrane-bound form in the kidneys, intestinal mucosa, hepatocytes, and vascular endothelial cells.<sup>18</sup> DPP-4 is expressed on T-cells, B-cells, natural killer cells, subsets of macrophages, and hematopoietic progenitor cells; it also acts as a modulator of T-cell proliferation.<sup>19</sup>

## DPP-4 Inhibitors and GLP-1 Degradation

The rapid degradation of native GLP-1 by DPP-4 is inhibited when a DPP-4 inhibitor is administered, thereby increasing the plasma level of active GLP-1. Active GLP-1 is secreted from L-cells in the distal portion of the intestine and circulates as GLP-1(7-37) and GLP-1(7-36)NH<sub>2</sub>; these peptides are cleaved by DPP-4 within minutes to generate GLP-1(9-37) and GLP-1(9-36)NH<sub>2</sub>, respectively.<sup>20</sup> GLP-1(9-36)NH<sub>2</sub> is the predominate circulating form of DPP-4-cleaved GLP-1 and does not perform typical actions of intact GLP-1, such as enhancing glucose-stimulated insulin secretion and suppressing glucagon secretion, appetite, and gastric emptying.<sup>21,22</sup> Rather, GLP-1 (9-36) and GLP-1 (28-36) are cleaved from GLP-1 by DPP-4; they exert beneficial cardiovascular functions, such as improving left ventricular function, vasodilation, and improving intrahepatic lipid metabolism.<sup>23–25</sup> Thus, the inhibition of DPP-4 cancels the positive effects of the GLP-1 degradation products, and the actual effect of inhibiting DPP-4



on the beneficial effects of GLP-1 degradation products on the cardiovascular system is unknown.

The plasma level of intact GLP-1 increases in DPP4<sup>-/-</sup> mice. In contrast to control group, genetic inactivation of DPP-4 leads to reduced N-terminal degradation of GLP-1 and increased plasma level of intact GLP-1, increased levels of insulin, and improved glucose tolerance in DPP4<sup>-/-</sup> mice group in vivo study.<sup>26</sup> Furthermore, circulating plasma DPP-4 levels in patients with T2DM are significantly higher (approximately 33%) than in controls, and the inhibition of circulating DPP-4 leads to increases in the concentration of active GLP-1 and decreases glycated hemoglobin in patients with T2DM.<sup>27,28</sup> These gliptins are orally available; neutral or minimally active with respect to body weight, blood pressure, and lipid profile; and are well tolerated with a low risk of hypoglycemia.<sup>29,30</sup>

### The Pleiotropism of DPP-4 Inhibitors

Numerous endocrine peptides, chemokines, and neuropeptides contain an alanine or proline at the N-terminus start site and can be DPP-4 substrates. Therefore, many biological actions of DPP-4 are not related to the control of glucose homeostasis because of variety of substrates and widespread expression of DPP-4.<sup>31</sup> This article focuses on the pleiotropic actions of DPP-4 inhibitors, including their strong beneficial effects against stress induced accelerated senescence (SIAS) of vascular endothelial cells, and the possible clinical implications.

#### *DPP-4 inhibition and stromal cell-derived factor (SDF)-1 $\alpha$ , brain natriuresis protein (BNP), Neuropeptide Y (NPY), and peptide YY (PYY)*

SDF-1 $\alpha$ , which is alternately derived from SDF-1 $\beta$  by a single SDF-1 gene, is widely expressed in numerous cell types and tissue<sup>32,33</sup>; its expression and secretion are often induced by cellular damage.<sup>34</sup> SDF-1 $\alpha$  is cleaved by soluble or transmembrane DPP-4 into SDF-1 $\alpha$  (3-67), thus inactivating its antiviral and chemotactic properties.<sup>35,36</sup> Because the main role of SDF-1 $\alpha$  and its receptor CXCR4 is to enhance migration of hematopoietic stem cells, bone marrow-derived endothelial progenitor cells are mobilized from the bone marrow into the blood stream in response to SDF-1 $\alpha$ , which is released from damaged tissue.<sup>37,38</sup> Therefore, the inhibition of DPP-4 activity reduces degradation of SDF-1 $\alpha$  and potentiates the SDF-1 $\alpha$ /CXCR4 signaling pathway, resulting in greater hematopoietic progenitor cell mobilization to the ischemic injury site.<sup>37</sup> In addition, administration of granulocyte colony-stimulating factor (G-CSF) increases enzymatic cleavage of SDF-1 $\alpha$  by DPP-4 in the bone marrow and generates a circulation/bone marrow SDF-1 $\alpha$  gradient, which mobilizes stem cells into circulation.<sup>39,40</sup> The combined strategy of G-CSF and a DPP-4 inhibitor ameliorates vascular remodeling and wound healing after myocardial infarction via direct antiapoptotic effects on ischemic myocardium and indirect effects on enhancement of mobilizing stem cells

from bone marrow which circulate to the damaged heart, where they homing via SDF-1 $\alpha$ /CXCR4 signaling pathway.<sup>37,41,42</sup> Moreover, the DPP-4 inhibitor vildagliptin enhanced the wound closure rate over 12 weeks in patients with T2DM and complicated peripheral artery disease, compared with controls.<sup>43</sup> In another retrospective analysis, DPP-4 inhibitor users exhibited a lower risk of peripheral arterial disease and lower extremity amputation, compared with nonusers.<sup>44</sup> Furthermore, the SDF-1 $\alpha$ /CXCR4 signaling pathway plays an important role in protecting kidney function by decreasing oxidative stress, ischemia, and fibrotic processes.<sup>45-47</sup> Recently, Zhu et al<sup>48</sup> revealed that DPP-4 inhibition by DPP-4 inhibitor anagliptin enhances bone marrow-derived hematopoietic stem cell activation and inflammatory cell production via an Adr $\beta$ 3 ( $\beta$ 3-adrenergic receptor)/CXCL12 (C-X-C motif chemokine 12) signal dependent mechanism in mice under chronic restrain stress.

Secretion of BNP increases in patients with heart failure, thus promoting natriuresis. BNP is synthesized as a 134-amino acid precursor protein (preproBNP) that is subsequently processed into proBNP, active BNP (1-32), and NT-proBNP (1-76).<sup>49</sup> All of these forms have a proline in the second N-terminal position; therefore, they can be DPP-4 substrates. Low levels of BNP are observed in patients with obesity, insulin resistance, and diabetes, which may contribute to the increased cardiovascular risk in these populations.<sup>50</sup> However, no significant changes in BNP or NT-proBNP levels are observed after treatment with linagliptin or sitagliptin in patients with T2DM or healthy subjects, respectively.<sup>51,52</sup> Further studies are needed to evaluate the effects of inhibiting DPP-4 and lowering BNP on subsequent cardiovascular protection.

NPY and PYY are a members of the pancreatic polypeptide family that exert opposing actions on the control of food intake.<sup>53</sup> Inhibition of DPP-4 activity results in changes in receptor affinities of DPP-4-cleaved NPY (3-36) and PYY (3-36) from the Y<sub>1</sub> receptor to the Y<sub>2</sub> and Y<sub>5</sub> receptors.<sup>54,55</sup> Although the effects of inhibiting DPP-4 on NPY and PYY have been extensively studied in experimental models, integrated *in vivo* responses to these peptides after DPP-4 inhibitor therapy are not fully evaluated and further studies are needed.

#### *DPP-4 inhibition and immune system*

DPP-4 has been associated with the control of lymphocytes and immune function, cell migration, viral entry, cancer metastasis, and inflammatory reactions.<sup>56</sup> Two mechanisms used by DPP-4/CD26 to exert its effects on the immune system: one is the enzymatic activity of DPP-4, which degrades a targeted substrate into inactive and active fragments with subsequent actions on the immune system; the other is DPP-4/CD26, which acts as a potent co-stimulatory factor of T-cell proliferation and signal transduction.<sup>57</sup>

DPP-4 degrades and regulates the activities of many cytokines, such as fibroblast growth factor 2, interleukin-3, GM-CSF, G-CSF, and erythropoietin. These cytokines are truncated by DPP-4, which reduces their activity and function.<sup>58-60</sup> Inhibition of DPP-4 activity is associated with changes in tumor growth, enhanced metastasis, and invasive behavior.<sup>61,62</sup> The interaction between DPP-4 and adenosine deaminase (ADA) is regulated in a more complex manner by factors/immune cells, rather than direct degradation. The ADA/DPP-4 interaction is a co-stimulatory signal during T-cell receptor signaling, which results in enhanced secretion of interferon- $\gamma$  and tumor necrosis factor- $\alpha$ . However, the functional importance of the ADA/DPP-4 interaction remains incompletely understood.

#### *DPP-4 inhibition and stroke*

DPP-4 inhibitors reduce brain damage and improve functional parameters after stroke in various animal models via several mechanisms including reduction of inflammation, endothelial leakage and excitotoxicity, oxidative stress, and apoptosis and neuronal damage, independent of their control of glucose homeostasis.<sup>63-66</sup> Although the effects of DPP-4 inhibitors on the development of cardiovascular disease (including stroke) and death are neutral,<sup>67</sup> the efficacies of DPP-4 inhibitors on functional outcomes after stroke have not been fully studied.<sup>68</sup> The DPP-4 substrate, SDF-1 $\alpha$ , is an important factor during neovascular remodeling after stroke in the brain.<sup>69-72</sup> Chiazza et al<sup>73</sup> showed that administrating the DPP-4 inhibitor linagliptin specifically increases active SDF-1 $\alpha$  (but not GIP or GLP-1) in the brain, and linagliptin improves functional outcomes of stroke in a manner dependent on the SDF-1 $\alpha$ /CXCL4 signaling pathway. Further studies are needed determine the mode of action of DPP-4 inhibitors in the brain and the effects of DPP-4 on functional recovery after stroke.

#### *Results of cardiovascular outcome trials (CVOT) and other clinical trials*

DPP-4 inhibitors truncate numerous substrates, which are cardioprotective and immunoprotective. Thus, DPP-4 inhibitor treatment may have a favorable effect preventing and recovering cardiovascular damage after ischemic insult through glyce-mic control and direct regulation of the cardiovascular system. However, large CVOTs of the DPP-4 inhibitors saxagliptin, alogliptin, sitagliptin, and linagliptin have failed to show an association between DPP-4 inhibitor use and reduced risk of major adverse cardiovascular events (MACEs).

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) study recruited 16,492 patients with T2DM who had a history of or were at risk for cardiovascular events. The study was designed to detect the superiority of saxagliptin over placebo for mean interval of

2.1 years.<sup>74</sup> Although the rate of the composite primary end-point was not different (73% and 72% of patients taking saxagliptin and placebo, respectively), saxagliptin was associated with a significant increase in the hospitalization rate for heart failure.

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial included 5,380 patients with T2DM who had experienced recent acute coronary syndrome requiring hospitalization within 15 to 90 days; it compared the effect of alogliptin with placebo.<sup>75</sup> During a median 18-month follow-up period, alogliptin did not increase the MACE rate, suggesting safety and non-inferiority over placebo.

The Trial Evaluation Cardiovascular Outcomes with Sitagliptin (TECOS) study was designed to investigate the superiority of sitagliptin, compared with placebo; it included 14,671 patients with T2DM who had cardiovascular disease.<sup>76</sup> Sitagliptin did not appear to increase the risk of MACE or hospitalization for heart failure during a median follow-up interval of 3.0 years. However, the study only demonstrated the noninferiority of sitagliptin.

No significant difference in the risk of cardiovascular events between a DPP-4 inhibitor and placebo or comparator groups—was observed in a large meta-analysis of 69 trials.<sup>77</sup> Another meta-analysis showed a similar safety profile of DPP-4 inhibitors, compared with placebo, except for weak evidence indicating an increased risk of heart failure.<sup>78</sup>

The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) trial was a randomized, double-blind, placebo-controlled study that compared linagliptin with placebo in patients with T2DM who had high cardiovascular risk or existing chronic kidney disease.<sup>79</sup> This study was the only CVOT designed to demonstrate cardioprotection focused on patients with diabetes who had increased CV risk; however, linagliptin proved only to be non-inferior to placebo.

The Cardiovascular Outcome Study of Linagliptin Versus Glimperide in Patients with Type 2 Diabetes (CAROLINA) study was designed to evaluate the cardiovascular superiority of the DPP-4 inhibitor linagliptin compared with the sulfonylurea glimepiride.<sup>80-82</sup> Although, sulfonylurea was associated with an increased risk for hypoglycemia, no significant difference in cardiovascular outcomes was observed during this head-to-head active comparative study.

No CVOT has been performed for vildagliptin, but the Vildagliptin in Ventricular Dysfunction Diabetes (VIVID) trial was designed to determine the effect of vildagliptin on left ventricular ejection fraction in patients with T2DM who had heart failure.<sup>83</sup> No significant change in left ventricular ejection fraction was observed during 1 year of treatment.

Although the results of pooled analyses and meta-analyses of previous, smaller trials using DPP-4 inhibitors have suggested a reduction in the risk of MACEs with DPP-4 inhibitor

treatment, the results of major CVOTs did not reveal increased cardiovascular safety. This discrepancy may be related to differences in study design (CV outcome vs CV safety trials) and patient characteristics (selected for high CV risk, typically older with longer duration of diabetes, greater impairment of renal function, higher comorbidity).<sup>84</sup> In addition, longer duration of CV safety trial increases the risk for missing data and loss of beneficial effect of DPP4 inhibitors.<sup>85-87</sup>

#### *Protective effects of DPP-4 inhibitors against vascular disease in SIAS*

Cellular senescence is classically characterized as irreversible cell cycle arrest. Cells alter gene expression, resulting in the production of proinflammatory, and matrix-degrading molecules known as the senescent-associated secretory phenotype (SASP).<sup>88,89</sup> Cells can exhibit SIAS because of DNA damage, oxidative stress, oncogenic insults, and chemotherapeutic-induced toxicity.<sup>90</sup> The potential involvement of cellular senescence in aging and age-related disorders has been supported, such as in cardiovascular diseases.<sup>91,92</sup> Senescent vascular endothelial cells accelerate the formation and progression of plaque, and vascular disease development through chronic inflammation and tissue remodeling.<sup>93,94</sup> Thus, senolytics (ie, bioactive compounds that selectively target and eliminate senescent cells) are emerging as a new treatment modality for cardiovascular disease.<sup>95,96</sup>

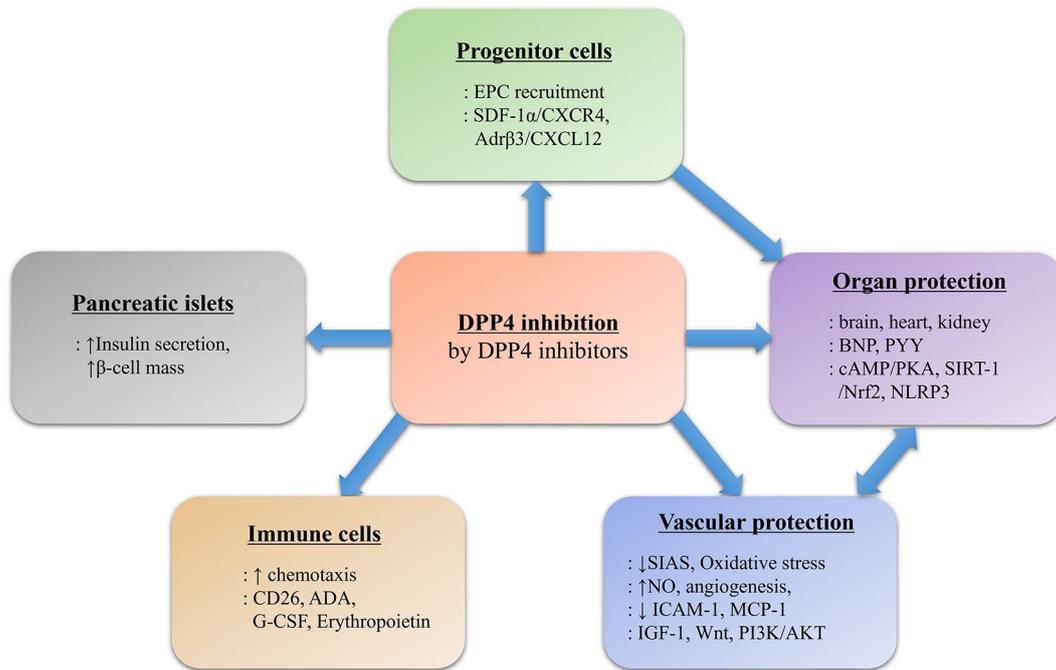
DPP-4 inhibitors have direct cardiovascular effects, such as the capacity to attenuate vascular inflammation, improve lipid metabolism and endothelial function, and reduce of oxidative stress.<sup>8,97-99</sup> We found that inhibition of DPP-4 by anagliptin reduces the SIAS of human vascular endothelial cells (HUVECs) under oxidative or glucolipotoxic stress by reducing endoplasmic reticulum stress, reactive oxygen species generation, and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome signal transduction.<sup>100</sup> Treatment of Zucker diabetic fatty rats with vildagliptin reduces reactive oxygen species-induced senescence and DNA damage through the cAMP/protein kinase A (PKA) signaling pathway.<sup>101</sup> In other studies, inhibition of DPP-4 has been shown to prevent vascular aging in mice under chronic psychological stress by modulating oxidative stress and inflammation.<sup>102</sup> Chen et al<sup>10</sup> revealed that the inhibition of DPP-4 improves endothelial senescence by activating the AMP-activated protein kinase/NDA-dependent deacetylase sirtuin-1 (SIRT-1)/nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathway. A study in apo E-deficient mice under chronic stress condition, DPP-4 inhibition attenuated vascular aging mediated by increased GLP-1 and adiponectin.<sup>103</sup> In immobilized mice, DPP-4 inhibition improved FeCl<sub>3</sub>-induced thrombosis of carotid artery via the improvement of ADAMTS13 and oxidative stress.<sup>104</sup> DPP-4 inhibitor gemigliptin attenuates the proliferation and migration of vascular

smooth muscle cells VSMCs via p62–Keap1–Nrf2 pathway in mouse carotid arteries which enhanced neointimal hyperplasia induced by ligation injury.<sup>105</sup> In a study of adenosine-induced chronic kidney disease model mice, DPP-4 inhibitor gemigliptin attenuated vascular calcification and osteogenic trans-differentiation in vascular smooth muscle cells through various mechanisms including downregulation of PiT-1 expression and suppression of reactive oxygen species generation, phospho-PI3K/AKT, and the Wnt signaling pathway.<sup>106</sup> Novel DPP-4 inhibitor, evogliptin attenuates vascular calcification by preventing the insulin-like growth factor-1 (IGF-1) inactivation and potentiating IGF-1 receptor-dependent signaling pathway.<sup>107</sup> In a study of calcific aortic valve disease (CAVD) animal model, evogliptin attenuated valvular calcification and CAVD progression via inhibiting inflammatory cytokine expression, fibrosis, and calcification.<sup>108</sup> Taken together, the findings thus far indicate that DPP-4 inhibitors can be used novel therapeutic target or treatment strategies for stress-related vascular disorders, although further studies are needed for clinical application.

#### **DPP-4 Inhibitors and COVID-19**

It is known that underlying diabetes, especially T2DM is recognized as a risk factor for developing the more severe form of coronavirus disease 2019 (COVID-19) and worse disease outcomes, including high mortality.<sup>109-111</sup> Recently, it raised the possibility that the DPP-4 is recognized as coronavirus receptor protein to intracellular entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although angiotensin-converting enzyme 2 (ACE2) is recognized as the main receptor.<sup>111-113</sup> In a study using human bronchial epithelial cells, there was no blocking effect on the entry of coronavirus into cells with DPP-4 inhibitors sitagliptin, vildagliptin, or saxagliptin.<sup>114</sup>

As mentioned above, DPP-4 has not only an important role in glucose homeostasis, but also central role in the immune system as a marker of activated T lymphocytes and regulator of numerous chemokines. Furthermore, DPP-4 inhibitors have anti-inflammatory properties and vascular protective effects through various mechanisms such as reducing oxidative stress and endoplasmic reticulum stress. These finding indicates a possibility of DPP-4 as a potential treatment strategy of SARS-CoV-2 infection.<sup>115</sup> However, there have been no clear-cut conclusions about the role of DPP-4 inhibitors on the clinical outcomes associated with SARS-CoV-2 infection.<sup>116</sup> In a multicenter, retrospective, case-control study in Northern Italy hospitals including 338 patients with COVID-19 underlying T2DM, sitagliptin treatment during hospitalization was associated with reduced mortality and improved clinical outcomes.<sup>117</sup> In another single center, case series involving COVID-19 patients revealed the association between DPP-4 inhibitor and lower risk of mortality.<sup>118</sup> On the other hand, DPP-4 inhibitor treatment was associated with worse outcome in 27 patients with T2DM treated with DPP-4 inhibitors than



**Figure 1.** Schematic illustration of endocrine pathways and possible molecular mechanism altered during DPP4 inhibition. Selective inhibition of DPP-4 protease activity by DPP-4 inhibitors produce various biological actions in peripheral tissues and target organs.

Abbreviations: ADA, adenosine deaminase; ADRβ3, β3-adrenergic receptor; BNP, brain natriuretic peptide; cAMP, cyclic adenosine monophosphate; CXCL, C-X-C motif ligand; EPC, endothelial progenitor cell; G-CSF, granulocyte colony-stimulating factor; GLP-1, glucagon-like peptide-1; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; MCP-1, monocyte chemoattractant protein-1; NLRP, nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing proteins; NO, nitric oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; SDF-1α, stromal cell-derived factor 1α, SIRT1, NAD-dependent deacetylase sirtuin-1.

in 49 treated with other anti-diabetic agents.<sup>119</sup> Thus, prospective randomized clinical trials (RCTs) are necessary, and currently at least 3 parallel-group RCTs investigating the potential survival benefits of DPP-4 inhibitors diverse populations with T2DM and COVID-19.

### Conclusions and Future Perspectives

We schematically summarized the endocrine pathways that change during DPP4 inhibition in response to selective DPP4 inhibitors in Figure 1. DPP-4 inhibitors have been widely used to treat T2DM because they have good safety and tolerability profiles with low incidences of adverse events, such as hypoglycemia. However, evidence from recent CVOTs has produced a paradigm shift in the guidelines and recommendations. The published ADA/EASD 2019 Consensus Report Update<sup>98</sup> emphasized the importance of treating patients with T2DM and high risk of atherosclerosis with a GLP-1 receptor agonist or a sodium-glucose cotransporter 2 inhibitor. Nevertheless, DPP-4 inhibitors remain important in diabetes treatment because of their safety and pleiotropic effects unrelated to glycemic control. We wish to further elucidate the mechanisms of the pleiotropic effects of DPP-4 inhibitors and demonstrate whether the actions confirmed in preclinical studies can be reproduced in clinical practice. In particular, additional research is needed regarding the development and utilization of DPP-4 inhibitors as therapeutic target or modality against SIAS.

### Author Contributions

SM Kang and JH Park wrote and edit this review.

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### Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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