

## Diabetes therapies in hemodialysis patients: Dipeptidase-4 inhibitors

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### Abstract

Although several previous studies have been published on the effects of dipeptidase-4 (DPP-4) inhibitors in diabetic hemodialysis (HD) patients, the findings have yet to be reviewed comprehensively. Eyesight failure caused by diabetic retinopathy and aging-related dementia make multiple daily insulin injections difficult for HD patients. Therefore, we reviewed the effects of DPP-4 inhibitors with a focus on oral antidiabetic drugs as a new treatment strategy in HD patients with diabetes. The following 7 DPP-4 inhibitors are available worldwide: sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, and saxagliptin. All of these are administered once daily with dose adjustments in HD patients. Four types of oral antidiabetic drugs can be administered for combination oral therapy with DPP-4 inhibitors, including sulfonylureas, meglitinide, thiazolidinediones, and alpha-glucosidase inhibitor. Nine studies examined the antidiabetic effects in HD patients. Treatments decreased hemoglobin A1c and glycated albumin levels by 0.3% to 1.3% and 1.7% to 4.9%, respectively. The efficacy of DPP-4 inhibitor treatment is high among HD patients, and no patients exhibited significant severe adverse effects such as hypoglycemia and liver dysfunction. DPP-4 inhibitors are key drugs in new treatment strategies for HD patients with diabetes and with limited choices for diabetes treatment.

**Key words:** Dipeptidase-4 inhibitors; Hemodialysis; Diabetes mellitus; Blood glucose-related factors; Anti-inflammatory effects

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**Core tip:** Until now, the effectiveness of dipeptidase-4 (DPP-4) inhibitors on diabetic hemodialysis (HD) patients has not been reviewed. All 7 DPP-4 inhibitors are available for HD patients; administration is once daily with dose adjustments. The effectiveness of DPP-4 inhibitor treatment in HD patients is high, and adverse events do not increase as a result. DPP-4 inhibitors may prevent inflammation and atherosclerosis, which are principal prognostic factors for HD patients. In summary, DPP-4 inhibitors are key drugs in new treatment strategies for HD patients with diabetes and limited choices for its treatment.

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## INTRODUCTION

Diabetes is the biggest cause of renal failure worldwide<sup>[1,2]</sup>. Diabetes treatment is an very important factor in the overall survival of hemodialysis (HD) patients<sup>[3,4]</sup>. While insulin therapy is the primary treatment for HD patients, impaired eyesight caused by diabetic retinopathy and aging-related dementia make multiple daily insulin injections difficult for many patients<sup>[5]</sup>. Moreover, in HD patients, many diabetes oral medicines cause serious side effects such as hypoglycemia and lactic acidosis. Hence, the development of new diabetes oral medicines with little or no side effects is needed for these patients.

Dipeptidase-4 (DPP-4) inhibitors are the most highly used diabetic drugs and show both a lower incidence of hypoglycemia and good safety<sup>[6]</sup>. In addition, they induce an ingestion control effect and may also prevent atherosclerosis and reduce cardiovascular events<sup>[7,8]</sup>. Therefore, these medications are strongly expected to improve the quality of life and prognosis of diabetic HD patients.

As a new class of diabetic medications, sodium-glucose co-transporter 2 (SGLT2) inhibitors both inhibit glucose reabsorption in renal tubules and increase glucose excretion, but cannot be administered to dialysis patients. G-protein-coupled receptor 40 (GPR40) agonist, GPR119 receptor agonist, and glucokinase activators are new antidiabetic medications currently in clinical trials and thus are not yet available. Therefore, DPP-4 inhibitors have been the mainstay drugs during the past several years for HD patients with diabetes. Accordingly, a comprehensive research of the pharmacokinetics and pharmacodynamics of DPP-4 inhibitors in HD patients is important. Some reports have investigated the effectiveness of DPP-4 inhibitors in HD patients<sup>[9-18]</sup>. However, there has

been no review of new treatment strategies for HD patients who have diabetes and limited choices for its treatment. Therefore, this review evaluated the effects of DPP-4 inhibitors as a new therapeutic strategy for diabetic patients.

## SEARCH STRATEGY

A MEDLINE search (1966 to July 2014) for published clinical studies and pertinent review articles published in English was conducted with the following keywords: "DPP-4 inhibitor", "hemodialysis", "end stage renal disease", "sitagliptin", "vildagliptin", "alogliptin", "linagliptin", "teneligliptin", "anagliptin", "saxagliptin", "glucagon-like peptide-1 (GLP-1)", "insulin", "glucagon", and "insulin resistance". References of identified articles were searched for additional relevant sources. Articles relevant to the efficacy, safety, and pharmacology of DPP-4 inhibitors in HD patients were also identified from the references cited in works obtained from the MEDLINE search results.

## SEVEN DPP-4 INHIBITORS

At present, 7 DPP-4 inhibitors are available worldwide: sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, and saxagliptin. All DPP-4 inhibitors are available to HD patients, and administration is once daily. However, the dose adjustments are different for each DPP-4 inhibitor. Five DPP-4 inhibitors are excreted renally (*i.e.*, sitagliptin, vildagliptin, alogliptin, anagliptin, and saxagliptin). Meanwhile, both linagliptin and teneligliptin are excreted through bile; therefore, a reduction of the dose is unnecessary for HD patients. In particular, the renal excretion rate of linagliptin is 5%, which is the lowest among the DPP-4 inhibitors<sup>[19]</sup>. Therefore, linagliptin is easy to use in patients with renal failure including HD patients. DPP-4 inhibitors interact with dipeptidase-4 in 2 different ways<sup>[20]</sup>. The inhibition of DPP-4 by vildagliptin and saxagliptin is a 2-step process entailing the formation of a reversible covalent enzyme-inhibitor complex; this is characterized by slow rates of inhibitor binding and inhibitor dissociation, and results in the enzyme equilibrating slowly between its active and inactive forms<sup>[21,22]</sup>. In contrast, the other DPP-4 inhibitors form noncovalent bonds (*i.e.*, hydrogen bonds) with residues present in the catalytic site<sup>[23-25]</sup>. Some metabolites of DPP-4 inhibitors have drug activities. For example, 5-hydroxysaxagliptin is a metabolite of saxagliptin and has a half of the activity of the original drug<sup>[26]</sup>. Therefore, unchanged substances are not representative of the effects of all drugs (Table 1).

### Sitagliptin

The molecular weight of sitagliptin is 523.32 Da, and the administration therapeutic dosage is 25 mg once daily in HD patients. The bioavailability of this medicine is 87%<sup>[27]</sup>, and the protein-binding rate is 38%<sup>[28]</sup>. Hepatic metabolism by CYP3A4 and CYP2C8 is low,

**Table 1** Seven dipeptidase-4 inhibitors

Dose and pharmacokinetics	Sitagliptin	Vildagliptin	Alogliptin	Linagliptin	Teneligliptin	Anagliptin	Saxagliptin
Daily dose (mg)	25	50	6.25	5	20	100	2.5
Molecular weight (Da)	523.32	303.4	461.51	472.54	628.86	383.45	333.43
Bioavailability	87%	85%	100%	30%	Unknown	73.2%	Unknown
Protein binding	38.0%	9.3%	28.2%-38.4%	> 80%	77.6%-82.2%	37.1%-48.2%	Negligible
Cmax ( <i>vs</i> healthy volunteer)	1.4 fold	1.4 fold	3.2 fold	1.5 fold	1.0 fold	1.4 fold	Unknown
AUC ( <i>vs</i> healthy volunteer)	4.5 fold	2.0 fold	3.8 fold	1.5 fold	1.5 fold	3.2 fold	2.1 fold
t <sub>1/2</sub> (h) ( <i>vs</i> healthy volunteer)	2.2	2	Unknown	Unknown	1.0 fold	0.9 fold	Unknown
Dialyzability	13.50%	3.00%	7.20%	Unknown	15.60%	Unknown	4.00%

Cmax, AUC and t<sub>1/2</sub> were measured under different dose conditions. AUC: Area under the curve.

and active metabolites are not produced. Therefore, most sitagliptin is excreted unchanged in the urine (87%) and feces (13%)<sup>[29]</sup>. After the administration of sitagliptin 50 mg, compared to cohorts with normal renal function, HD patients had 1.4-fold higher observed plasma maximum concentration (Cmax) levels, 4.5-fold higher area under the curve (AUC), and a 2.2-fold higher half-life (t<sub>1/2</sub>)<sup>[28,30]</sup>. Furthermore, 13.5% of this drug is excreted by 4 h of HD<sup>[31]</sup>.

#### Vildagliptin

Vildagliptin has a molecular weight of 303.40 Da and is administered therapeutically at a dosage of 50 mg once daily in HD patients. The bioavailability and protein binding rate are 85%<sup>[32,33]</sup> and 9.3%<sup>[33,34]</sup>, respectively. The mean elimination t<sub>1/2</sub> after intravenous administration is short (about 2 h), and the amount of renal excretion of unchanged vildagliptin is 23% of the oral administration dose<sup>[34,35]</sup>. Relative to cohorts with normal renal function, HD patients who received an administration of vildagliptin 50 mg had 1.4-fold and 2.0-fold higher Cmax levels and AUC, respectively. Following the administration of vildagliptin 100 mg, HD patients had 2.0-fold higher t<sub>1/2</sub> as compared to those with normal renal function. Additionally, 3% of this drug is removed by 4 h of HD<sup>[34]</sup>.

#### Alogliptin

At a molecular weight of 339.39 Da, alogliptin is administered at a therapeutic dosage of 6.25 mg once daily in HD patients. Its bioavailability is 100%, and the protein-binding rate is 28.2%-38.4%<sup>[36]</sup>. In comparison to cohorts with normal renal function, HD patients had 3.2-fold and 3.8-fold higher Cmax levels and AUC, respectively, following administration of alogliptin 50 mg. The t<sub>1/2</sub> is unknown in HD patients. Furthermore, 7.2% of this drug is removed by 4 h of HD<sup>[36,37]</sup>.

#### Linagliptin

Linagliptin has a molecular weight of 472.54 Da, and the therapeutic dosage is 5 mg once daily in HD patients. Its bioavailability and protein binding rate are 30%<sup>[38,39]</sup> and > 80%<sup>[19]</sup>, respectively. Relative to cohorts with normal renal function, the HD patients

showed 1.5-fold higher Cmax levels and 1.5-fold higher AUC after the administration of linagliptin 5 mg. The t<sub>1/2</sub> and dialyzability are unknown in HD patients<sup>[40,41]</sup>.

#### Teneligliptin

The molecular weight of teneligliptin is 628.86 Da, and the therapeutic dosage is 20 mg once daily in HD patients. Its bioavailability is unknown, and the protein-binding rate is 77.6%-82.2%<sup>[42]</sup>. Compared to cohorts with normal renal function, HD patients had 4.5-fold higher AUC after teneligliptin 20 mg administration. The Cmax levels and t<sub>1/2</sub> in HD patients are the same as those in subjects with normal renal function after teneligliptin 20 mg administration. Furthermore, 15.6% of this drug is removed by 4 h of HD<sup>[42]</sup>.

#### Anagliptin

Anagliptin has a molecular weight of 383.45 Da, and is administered at a therapeutic dose of 100 mg once daily in HD patients. Its bioavailability and protein-binding rate are 73.2% and 37.1%-48.2%, respectively<sup>[43]</sup>. Relative to cohorts with normal renal function, HD patients had 1.4-fold higher Cmax levels, 3.2-fold higher AUC, and 0.9-fold higher t<sub>1/2</sub> after anagliptin 400 mg administration<sup>[43]</sup>. The dialyzability of this drug in HD patients is unknown.

#### Saxagliptin

At a molecular weight of 333.43 Da, saxagliptin is administered at a therapeutic dosage of 2.5 mg once daily in HD patients. Its protein-binding rate is negligible<sup>[44]</sup>. Compared to cohorts with normal renal function, HD patients had a 2.1-fold higher AUC after saxagliptin 10 mg administration<sup>[45]</sup>. The Cmax levels and t<sub>1/2</sub> are unknown in HD patients. Furthermore, 4.0% of this drug is removed by 4 h of HD<sup>[45]</sup>.

## COMBINATION THERAPIES OF ORAL ANTIDIABETIC DRUGS WITH DPP-4 INHIBITORS IN HD PATIENTS

At present, 7 types of oral antidiabetic drugs are

**Table 2** Combinations of oral antidiabetic drugs with dipeptidase-4 inhibitors

Class	Action mechanism	Glucose target	Drug	Daily dose (mg)
Sulfonylurea	Increases insulin secretion	Fasting and postprandial	Glipizide	2.5-10
			Gliclazide	40-240
			Gliquidone	45-60
Meglitinide	Increases insulin secretion	Postprandial	Repaglinide	0.5-12
			Mitiglinide	7.5-15
Thiazolidinediones	Insulin sensitizer	Fasting and postprandial	Rosiglitazone	4-8
			Pioglitazone	15-45
Alpha-glucosidase inhibitor	Delays carbohydrate absorption	Postprandial	Voglibose	0.6-0.9
			Acarbose	75-300
			Miglitol	150-225

available worldwide: sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, SGLT2 inhibitors, and DPP-4 inhibitors. Beyond agreement on DPP-4 inhibitors, the guidelines differ with respect to the oral diabetes therapeutic drugs that can be administered to HD patients, and countries vary as to recommendations on oral antidiabetic medicines<sup>[46]</sup>. According to the Kidney Disease Outcomes Quality Initiative (KDOQI), glipizide (sulfonylurea), gliclazide (sulfonylurea), repaglinide (meglitinide), and thiazolidinediones can be administered to HD patients. In the guideline of the Japanese Society for Dialysis Therapy, HD patients can take repaglinide (meglitinide), mitiglinide calcium hydrate (meglitinide), and alpha-glucosidase inhibitor. Some reports state that gliquidone can be administered to HD patients<sup>[47]</sup>. Many oral diabetes therapeutic drugs induce serious side effects in HD patients. In particular, sulfonylureas, biguanides, and thiazolidinediones can induce hypoglycemia, lactic acidosis, and fluid retention, respectively. Only a few oral antidiabetic drugs can be administered to HD patients before the use of DPP-4 inhibitors. Therefore, the side effects of drugs administered concomitant with DPP-4 inhibitors must be examined in detail (Table 2).

### Sulfonylureas

With progressive decreases in kidney function, the clearance of sulfonylureas and their active metabolites decrease, and the  $t_{1/2}$  is prolonged<sup>[48-51]</sup>. First-generation sulfonylureas should generally be avoided in HD patients because they depend on the kidney to eliminate both the original drug and active metabolites. Accordingly, the  $t_{1/2}$  and risk of hypoglycemia increase. According to the KDOQI, glipizide and gliclazide are among the usable second-generation sulfonylureas because they do not produce active metabolites or increase the risk of hypoglycemia in patients with decreased renal function. Glipizide and gliclazide are administered at a dose of 2.5-10 mg/d<sup>[47]</sup> and 40-240 mg/d<sup>[47,52]</sup>, respectively. There are also reports of the administration of gliquidone in HD patients at a more than twice daily dose of 45-60 mg<sup>[47]</sup>.

### Meglitinides

According to the KDOQI and guideline of the Japanese

Society for Dialysis Therapy, repaglinide and mitiglinide calcium hydrate (mitiglinide) can be administered to HD patients. In those with an estimated glomerular filtration rate (eGFR) of < 30 mL/min, repaglinide results in a 4-fold increase in the  $t_{1/2}$  after 1 wk following its administration, as well as increase in AUC, in comparison to subjects with no renal failure. However, no changes are seen in the maximal plasma concentration, suggesting chronic kidney disease (CKD) influences both the metabolism and hepatic clearance of this medicine rather than bioavailability<sup>[47,53]</sup>. Furthermore, active metabolite concentrations do not increase with repaglinide<sup>[1]</sup>. Therefore, there is no relationship between renal failure and risk of hypoglycemia for this medicine in treated patients<sup>[54]</sup>. Repaglinide is usually taken preprandially at each meal at a dose of 0.5-12 mg/d<sup>[47,55]</sup>. Mitiglinide acts on liver metabolism<sup>[56]</sup>; hence, the metabolites of mitiglinide calcium hydrate have no antidiabetic effects. Therefore, the risk of hypoglycemia from this drug is low in HD patients. Accordingly, HD patients can take this drug preprandially at each meal at a dose of 7.5-15 mg/d.

### Thiazolidinediones

As rosiglitazone is metabolized in the liver, it is not necessary to reduce its dose in patients with renal failure<sup>[57]</sup>, since it does not increase the risk of hypoglycemia in CKD patients. Meanwhile, pioglitazone shows similar pharmacokinetic properties between patients with or without CKD because of its high molecular weight, protein-binding competency, and hepatic metabolism, and there is no effect in HD patients<sup>[58,59]</sup>. Therefore, it is not necessary to adjust the dose in CKD patients. Pioglitazone is administered once daily at a dose of 15-45 mg. There are no specific data regarding fluid retention in CKD patients. Nevertheless, there is the potential risk of congestive heart failure by fluid overload, particularly in those patients with both renal and cardiac failure.

### Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors increase glucagon-like peptide-1 levels and reduce gastric inhibitory polypeptide responses after eating. Therefore, combination therapies



**Table 3** Efficacies of dipeptidase-4 inhibitor monotherapies

Ref.	Study duration (mo)	n	DPP-4 inhibitor	Treatment dose (mg)	Parameter (%)	Pre-treatment	Post-treatment	Efficacy
Arjona Ferreira <i>et al</i> <sup>[9]</sup>	12	64	Sitagliptin	25	HbA1c	7.9	7.2	-0.7
					GA	Unknown	Unknown	Unknown
Ito <i>et al</i> <sup>[10]</sup>	6	5	Vildagliptin	50	HbA1c	6.0	5.5	-0.5
					GA	21.8	19.7	-2.1
Kume <i>et al</i> <sup>[11]</sup>	6	26	Vildagliptin	50	HbA1c	Unknown	Unknown	Unknown
					GA	23.8	21.2	-2.6
Ito <i>et al</i> <sup>[12]</sup>	6	9	Vildagliptin	50 or 100	HbA1c	6.7	6.0	-0.7
					GA	24.7	20.1	-4.6
Nakamura <i>et al</i> <sup>[13]</sup>	24	16	Alogliptin	6.25	HbA1c	7.1	5.8	-1.3
					GA	22.5	19.6	-2.9
Nakamura <i>et al</i> <sup>[14]</sup>	6	21	Linagliptin	5	HbA1c	Unknown	Unknown	Unknown
					GA	21.3	18.0	-2.3
Otsuki <i>et al</i> <sup>[15]</sup>	6 7	14	Teneligliptin	20	HbA1c	6.4	Unknown	-0.3 to -0.8
					GA	21.1	Unknown	-1.7 to -2.3

HbA1c: Hemoglobin A1c; GA: Glycated albumin.

with DPP-4 inhibitors may be more effective<sup>[60]</sup>.

The guideline of the Japanese Society for Dialysis Therapy states that all 3 types of alpha-glucosidase inhibitors can be administered in HD patients. Voglibose is not absorbed in the blood and is orally administered before each meal at 0.6-0.9 mg/d<sup>[61]</sup>. The plasma levels of acarbose and its metabolites increase several fold in patients with renal failure. The peak plasma concentration and exposure of this drug in patients with severe renal impairment (eGFR < 25 mL/min) are 5- and 6-fold higher than in patients with normal renal function, respectively<sup>[46,48]</sup>. However, only a small amount of acarbose is absorbed, since its bioavailability is very low<sup>[62]</sup>. Additionally, its metabolites have very small antidiabetic effects. Acarbose is orally administered before each meal at 75-300 mg/d. Miglitol accumulates with a decrease in renal function. Those patients with an eGFR of < 25 mL/min and taking 75 mg miglitol (25 mg three times a day) have double the plasma exposure as subjects with an eGFR of > 60 mL/min<sup>[46]</sup>. However, miglitol has no antidiabetic effects. The molecular weight of miglitol (383.45 Da) is low, and its protein binding rate is < 3.9%. Therefore, miglitol is eliminated by HD treatment. Miglitol is orally administered at 150-300 mg/d, usually before each meal<sup>[47,63]</sup>.

## EFFICACIES OF DPP-4 INHIBITORS IN HD PATIENTS

The effectiveness of DPP-4 inhibitors is summarized in Table 3. DPP-4 inhibitor treatment decreases hemoglobin A1c (HbA1c) and glycated albumin (GA) levels by 0.3%-1.3% and 1.7%-4.9%, respectively. It is difficult to compare the effects of DPP-4 inhibitors, because the strength and selectivity of DPP-4 inhibition are related to their respective therapeutic effects. Moreover, the curative effects of these drugs might be related to ethnicity. For example, some studies report

greater effectiveness of DPP-4 inhibitor treatment in Japanese patients with diabetes based on the evaluation of GA levels<sup>[64-66]</sup>.

### Monotherapy

Eight studies have investigated the diabetes therapeutic effects of DPP-4 inhibitors only in HD patients and not CKD patients. Of these, seven studied the antidiabetic effectiveness of only DPP-4 inhibitor monotherapy (*i.e.*, sitagliptin, vildagliptin, alogliptin, linagliptin, and teneligliptin) (Table 3). However, there have been no studies of anagliptin or saxagliptin monotherapy.

Arjona Ferreira *et al*<sup>[9]</sup> investigated the efficacies of sitagliptin monotherapy in 64 diabetic HD patients. All patients were administered sitagliptin 25 mg once daily for the monotherapy research. Forty patients newly started sitagliptin therapy, and 24 switched from other medications. Mean HbA1c and fasting plasma glucose levels decreased from 7.95% to 7.2% and from 159 to 133 mg/dL, respectively, 12 mo after treatment initiation.

Three studies have evaluated vildagliptin monotherapy in HD patients. Of these, 2 studied only vildagliptin monotherapy, while the other was a sub-analysis study in which the patients were categorized into either vildagliptin monotherapy or combination therapy groups. Ito *et al*<sup>[10]</sup> investigated the efficacies of vildagliptin monotherapy in 5 diabetic HD patients who were following diet and exercise regimens. All patients were administered vildagliptin 50 mg once daily for the monotherapy research. At 6 mo after treatment, HbA1c and GA levels had decreased from 6.0% ± 0.3% and 21.8% ± 2.6% to 5.5% ± 0.6% and 19.7% ± 3.3%, respectively. Kume *et al*<sup>[11]</sup> investigated the efficacies of vildagliptin monotherapy in 26 diabetic HD patients. Sixteen patients newly started sitagliptin therapy, and 7 patients switched from other oral antidiabetic drugs (3 patients were

**Table 4** Efficacies of both monotherapies and combination therapies with dipeptidase-4 inhibitors

Ref.	Study duration (mo)	n	DPP-4 inhibitor	Treatment dose (mg)	Combination therapy	Parameter (%)	Pre-treatment	Post-treatment	Efficacy
Ito <i>et al</i> <sup>[12]</sup>	6	30	Vildagliptin	50 or 100	Mitiglinide and/or voglibose	HbA1c	6.7	6.1	-0.6
						GA	24.5	20.5	-4.0
Fujii <i>et al</i> <sup>[16]</sup>	12	30	Alogliptin	6.25	Mitiglinide and/or voglibose	HbA1c	7.2	6.3	-0.9
						GA	25.6	20.7	-4.9
Nowicki <i>et al</i> <sup>[17]</sup>	12	19	Saxagliptin	2.5	Unknown	HbA1c	8.7	7.5	-1.2
						GA	Unknown	Unknown	Unknown

HbA1c: Hemoglobin A1c; GA: Glycated albumin.

unknown). All patients were administered vildagliptin 50 mg once daily for the monotherapy research. Mean GA and postprandial plasma glucose (PPG) levels had decreased from 23.8% to 21.2% and 204 to 157 mg/dL respectively, 6 mo after treatment initiation. In the subanalysis study, all 9 patients were administered an initial dose of vildagliptin 50 mg once daily. Thereafter, if 8 wk of continuous vildagliptin administration did not result in the target HbA1c value (< 7.0%) or GA value (< 21.0%) being achieved, the vildagliptin dose was increased to 100 mg daily from week 8. The HbA1c, GA, and PPG levels showed mean changes of -0.7%, -4.6%, and -54 mg/dL in the monotherapy group<sup>[12]</sup>.

Nakamura *et al*<sup>[13]</sup> investigated the diabetes therapeutic effects of alogliptin and linagliptin monotherapy in HD patients in 2 studies. In the study of alogliptin monotherapy, 16 diabetic HD patients were eligible based on diet and exercise regimens. All patients were administered alogliptin 6.25 mg once daily. At 2 years after treatment initiation, the HbA1c and GA levels had decreased from 7.1% ± 0.2% to 5.8% ± 1.6% and from 22.5% ± 0.7% to 19.6% ± 0.6%<sup>[13]</sup>. In the study of linagliptin monotherapy, 21 diabetic HD patients were eligible based on diet and exercise regimens. All patients were administered linagliptin 5 mg once daily. GA levels decreased from 21.3% ± 0.6% to 18.0% ± 0.6% 6 mo after treatment initiation<sup>[14]</sup>.

Otsuki *et al*<sup>[15]</sup> investigated the efficacies of teneligliptin monotherapy in 14 diabetic HD patients. All patients were administered teneligliptin 20 mg once daily. Seven patients newly started teneligliptin therapy, and 7 patients switched from other medications. The mean changes in HbA1c and GA were -0.3% to -0.8% and -1.7% to -2.3% after treatment<sup>[15]</sup>.

### Monotherapy and combination therapies

Two studies have evaluated the combined efficacies of both monotherapy and combination oral diabetic therapy with DPP-4 inhibitors in HD patients. In the evaluation of combination therapy with vildagliptin, 30 HD patients with diabetes were eligible to participate. All patients were administered vildagliptin 50 mg once daily as an initial dose. Nine patients newly started vildagliptin therapy, and 21 patients switched from other medications. Thereafter, if 8 wk of continuous

vildagliptin administration did not result in the target HbA1c value (< 7.0%) or GA value (< 21.0%) being achieved, the vildagliptin dose was increased to 100 mg daily from week 8; this was done in 19 patients. Another 11 patients were administered 50 mg daily. Mean HbA1c, GA, and PPG decreased from 6.7% to 6.1%, 24.5% to 20.5%, and 186 to 140 mg/dL, respectively, 6 mo after treatment initiation<sup>[12]</sup>.

In the study of combination therapy with alogliptin, 30 HD patients with diabetes were eligible. All patients were administered alogliptin 6.25 mg once daily. Fifteen patients newly started sitagliptin therapy, and 15 patients switched from other medications. Mean HbA1c, GA, and PPG decreased from 7.1% to 6.3%, 25.6% to 20.7%, and 212 to 156 mg/dL, respectively, 12 mo after treatment initiation. When patients were divided into the alogliptin monotherapy and combination (alogliptin plus mitiglinide and/or voglibose) therapy groups (*n* = 15 each), the mean changes in GA and PPG were greater in the monotherapy group (the specific decreases are unclear)<sup>[16]</sup>.

There is one subanalysis study of DPP-4 inhibitors that included only HD patients from among those with CKD. A total of 19 HD patients with diabetes were eligible. All patients were administered saxagliptin 2.5 mg once daily. The diabetes treatments before saxagliptin therapy were unknown. Mean HbA1c and PPG decreased from 8.75% to 7.5% and 177 to 138 mg/dL, respectively, 12 mo after treatment initiation (the details of monotherapy and combination therapies are unclear)<sup>[17,18]</sup> (Table 4).

### Glycemic control parameters

Blood glucose is a principal parameter for assessing the effects of diabetes therapy. Blood is collected at 3 time points: PPG, fasting plasma glucose, and the start of HD treatment. Therefore, it is difficult to compare blood glucose levels among studies. GA may more accurately reflect glycemic control, because HbA1c, the more general available parameter, is falsely low in HD patients<sup>[67-69]</sup>. This probably results from the shortened survival time of erythrocytes in CKD patients, as well as the reduced time for the glucose-hemoglobin chemical reaction to occur<sup>[70]</sup>. Another reason underlying the falsely low HbA1c levels in HD patients is related to the erythropoietin injections and

resultant increase in younger erythrocytes<sup>[71]</sup>. GA is a predictor of death, hospitalization, and cardiovascular events in HD patients with diabetes<sup>[72,73]</sup>.

## IMPACTS OF DPP-4 INHIBITORS ON BLOOD GLUCOSE-RELATED FACTORS IN HD PATIENTS

Some studies have investigated the impacts of DPP-4 inhibitors on blood glucose-related factors (*i.e.*, insulin, glucagon, and insulin resistance) in HD patients. In the study of sitagliptin, HOMA-IR increased 12 mo after sitagliptin treatment, while fasting insulin, proinsulin, proinsulin/insulin ratio, and HOMA-IR showed no changes from baseline<sup>[9]</sup>. Meanwhile, the study of vildagliptin investigated insulin and C-peptide but observed no significant differences for these parameters from baseline after 6 mo<sup>[11]</sup>. The study of alogliptin investigated insulin, C-peptide, and glucagon monthly for 3 mo. However, they were not significantly different before and after alogliptin treatment<sup>[13]</sup>. In the study of teneligliptin, C-peptide level at baseline was 4.94 ng/mL and increased significantly to 5.96 ng/mL after 5 mo of treatment<sup>[15]</sup>. Three studies assessed active GLP-1 levels before and after DPP-4 inhibitor treatment in HD patients. Samples were taken before the start of HD treatment, and active GLP-1 levels increased 2-3 fold after DPP-4 inhibitor therapy<sup>[11,13,14]</sup>.

## ANTI-INFLAMMATORY EFFECTIVENESS OF DPP-4 INHIBITORS IN HD PATIENTS

Inflammation is an important prognostic factor in HD patients<sup>[74]</sup>. Therefore, if DPP-4 inhibitors prevent inflammation and atherosclerosis, they may improve the prognosis of HD patients. However, almost no research has investigated the anti-inflammatory or anti-atherosclerosis efficacies of DPP-4 inhibitors in HD patients. Only 2 reports have assessed the anti-inflammatory efficacies of DPP-4 inhibitors in HD patients. In the study of vildagliptin, interleukin-6 levels decreased after 6 mo, although not significantly<sup>[11]</sup>. In the study of linagliptin, PGE2 and interleukin-6 levels decreased significantly<sup>[14]</sup>. Four mechanisms have been proposed to underlie the anti-inflammation properties of linagliptin: increased GLP-1<sup>[75,76]</sup>, DPP-4 (CD26) suppression<sup>[77,78]</sup>, xanthine-related skeletal structure, and a diabetic therapy effect<sup>[79,80]</sup>. Increased GLP-1, DPP-4 suppression, and an antidiabetic effect are the effects that are common among all DPP-4 inhibitors. However, among the 7 DPP-4 inhibitors, linagliptin is the only one with xanthine-related skeletal structure effects. The pharmacological anti-inflammatory mechanisms of xanthine-related skeletal structure are unknown. The meta-analysis of the cardiovascular events with DPP-4 inhibitors examined 73678 patients in a total of 82 randomized controlled

trials including the SAVOR-TIMI 53 and EXAMINE trials<sup>[81-83]</sup>. Only linagliptin reduced major adverse cardiovascular events compared to placebo/alternative diabetes therapy. This suggests the anti-inflammatory effectiveness of linagliptin may be involved in its anti-atherosclerotic effects.

## SAFETY/TOLERABILITY

Hypoglycemia is the most serious general side effect of diabetes treatment. In clinical trial data, the incidence of hypoglycemic events due to DPP-4 inhibitors ranges from < 0.1%-5%. Meta-analysis of data from clinical trials indicated few hypoglycemic events due to vildagliptin and sitagliptin<sup>[6]</sup>. Adverse events other than hypoglycemia due to DPP-4 inhibitors include rash, hives, abdominal fullness, pancreatitis, constipation, headache, giddiness, nasopharyngitis, headache, and upper respiratory tract infection. However, the occurrence of these side reactions is low<sup>[84]</sup>.

One study reports higher incidences of cellulitis and headache (6.3%) with sitagliptin compared to glipizide<sup>[9]</sup>. One patient experienced a drug-related rash<sup>[13]</sup>, and another experienced constipation<sup>[15]</sup>. However, in 8 studies that evaluated the diabetes therapeutic effects of DPP-4 inhibitors in HD patients, no patients showed severe side effects (*e.g.*, hypoglycemia and liver dysfunction). Therefore, adverse events resulting from DPP-4 inhibitor treatments do not occur at a higher incidence than in HD patients.

## CONCLUSION

Treating HD patients with DPP-4 inhibitors does not result in an increased incidence of adverse events. Furthermore, DPP-4 inhibitors are strongly anticipated to be effective in HD patients with diabetes. Moreover, drugs with anti-inflammatory and anti-atherosclerotic effects are attractive options for HD patients, whose prognosis is associated with inflammation and atherosclerosis. DPP-4 inhibitors are key drugs that are part of new treatment strategies for HD patients with diabetes, whose choices for diabetes treatment are limited. A once-weekly oral DPP-4 inhibitor, SYR-472<sup>[85]</sup>, which could reduce the number of required administrations, might be approved in the future. Therefore, the number of treatment options for HD for diabetic patients is anticipated to increase.

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