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Efficacy of different dipeptidyl peptidase-4 (DPP-4) inhibitors on metabolic parameters in patients with type 2 diabetes undergoing dialysis

Se Hee Park, MD[a,b], Joo Young Nam, MD[c], Eugene Han, MD[a,b], Yong-ho Lee, MD, PhD[a], Byung-Wan Lee, MD, PhD[a], Beom Seok Kim, MD, PhD[d], Bong-Soo Cha, MD, PhD[a], Chul Sik Kim, MD, PhD[e], Eun Seok Kang, MD, PhD[a,*]

Abstract

Hyperglycemia is associated with increased mortality and morbidity in patients with type 2 diabetes mellitus (T2DM) who are undergoing dialysis. Although dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely used in end-stage renal disease (ESRD) patients with T2DM, there are few studies on their efficacy in this population. We studied the effect of 3 different DPP-4 inhibitors on metabolic parameters in ESRD patients with T2DM.

Two hundred ESRD patients with T2DM who were treated with DPP-4 inhibitors (sitagliptin, vildagliptin, or linagliptin) were enrolled and analyzed retrospectively. The changes in glycated hemoglobin (HbA1c), fasting plasma glucose, and lipid profiles were assessed before and after 3 months of treatment with DPP-4 inhibitors. Subgroup analysis was done for each hemodialysis (HD) and peritoneal dialysis (PD) group.

There was no significant difference in the decrease in the HbA1c level among sitagliptin, vildagliptin, and linagliptin treatment groups (-0.74 ± 1.57, -0.39 ± 1.45, and -0.08 ± 1.40, respectively, $P = 0.076$). The changes in fasting blood glucose and lipid profiles were also not significantly different. In HD patients (n = 115), there was no difference in the HbA1c level among the 3 groups. In contrast, in PD patients (n = 85), HbA1c was reduced more after 3 months of treatment with sitagliptin compared with vildagliptin and linagliptin (-1.58 ± 0.95, -0.46 ± 0.98, -0.04 ± 1.22, respectively, $P = 0.001$).

There was no significant difference in the glucose-lowering effect between the different DPP-4 inhibitors tested in ESRD patients. In PD patients, sitagliptin tends to lower the HbA1c level more than the other inhibitors. The glucose-lowering efficacy of the 3 DPP-4 inhibitors was comparable.

Abbreviations: CAOD = coronary artery occlusive disease, CKD = chronic kidney disease, DPP-4 = dipeptidyl peptidase-4, ESRD = end-stage renal disease, FPG = fasting plasma glucose, GA = glycated albumin, HbA1c = glycated hemoglobin, HD = hemodialysis, HDL-C = high-density lipoprotein cholesterol, KDOQI = Kidney Disease Outcomes Quality Initiative, LDL-C = low-density lipoprotein cholesterol, PAOD = peripheral artery occlusive disease, PD = peritoneal dialysis, T2DM = type 2 diabetes mellitus, TG = triglyceride.

Keywords: chronic kidney disease, dialysis, dipeptidyl peptidase-4, type 2 diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) has become the leading cause of end-stage renal disease (ESRD) worldwide. Hyperglycemia is associated with increased mortality and morbidity in patients with T2DM who are undergoing dialysis. Although the progression of nephropathy cannot be prevented with appropriate glucose control alone, glucose control can be helpful for

Editor: Yanqing Zhang.

Authorship—Study concept and design: SHP, CSK, and ESK. Analysis and interpretation of data: SHP, JYN, EH, YL, and ESK. Drafting of the manuscript: SHP, JYN, and EH. Critical revision of the manuscript for important intellectual content: YL, BWL, BSK, BSC, CSK, and ESK. Statistical analysis: SHP, JYN. Administrative, technical, or material support: YL, BWL, BSK, BSC, CSK, and ESK.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Division of Endocrinology and Metabolism, Department of Internal Medicine, [b] Department of Medicine, The Graduate School, Yonsei University College of Medicine, Seoul, [c] Division of Endocrinology and Metabolism, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Gyeonggi, [d] Division of Nephrology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, [e] Division of Endocrinology and Metabolism, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea.

[*] Correspondence: Eun Seok Kang, Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Korea (e-mail: edgo@yuhs.ac).

Medicine (2016) 95:32(e4543)

Received: 4 April 2015 / Received in final form: 30 June 2016 / Accepted: 14 July 2016

http://dx.doi.org/10.1097/MD.0000000000004543

prevention of other microvascular and macrovascular complications of diabetes in patients receiving dialysis.[1,2] In addition, optimal management of hyperglycemia in these patients is associated with improved survival.[3,4]

According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, glycated hemoglobin (HbA1c) targets of T2DM patients suffering from chronic kidney disease (CKD) are not different from those of diabetic patients without CKD.[5] Nonetheless, it is more challenging to achieve glycemic control goal for CKD patients. There are limitations when choosing diabetic medications for ESRD patients. Metformin, α-glucosidase inhibitors, and sodium-glucose cotransporter 2 inhibitors are contraindicated in patients receiving dialysis.[6] Various types of medications, such as sulfonylureas, meglitinides, and thiazolidinediones are available, but have significant side effects. Furthermore, drugs that are mainly excreted by the kidney have altered action time and limited effectiveness or toxic effects in T2DM patients with CKD.[7] Insulin is used widely, but can lead to hypoglycemia and the need for dose adjustments, especially in patients undergoing intermittent hemodialysis.[8] The inconvenience of injection and weight gain also indicate the need for other effective and safe oral hypoglycemic agents.

Dipeptidyl peptidase-4 (DPP-4) inhibitors provide a simple, effective therapeutic option without the drawback of inducing hypoglycemia. These drugs do not confound the comorbidities and have few significant side effects. Sitagliptin is the first DPP-4 inhibitor commercially approved in 2006. Dose reduction from 100 mg daily in patients with normal kidney function to 25 mg daily in patients on dialysis is recommended because ~80% of ingested drug metabolite is excreted by the kidney.[9] Vildagliptin, another DPP-4 inhibitor proven to be an option for effective glycemic control in ESRD patients, has an adjusted dose of 50 mg/day in ESRD patients compared with the 100 mg/day full dose for those with normal renal function.[10] The DPP-4 inhibitor linagliptin has a very low renal elimination profile, so dose adjustment is not required for patients whose kidney function is impaired, and many physicians prescribe it widely.[11] In patients with normal kidney function, the effects of DPP-4 inhibitors on the plasma glucose level and glycemic indices generally seem to be similar.[12] Despite widespread use of these inhibitors, few data about the effectiveness of these drugs for T2DM patients undergoing dialysis are available. Therefore, the object of this study was to evaluate the efficacy of 3 DPP-4 inhibitors on metabolic parameters in ESRD patients with T2DM.

2. Methods

2.1. Study patients

This retrospective study reviewed type 2 diabetic subjects who received renal replacement therapy, hemodialysis, or peritoneal dialysis (PD) from January 2008 through August 2015, at Severance Hospital, National Health Insurance Service Ilsan Hospital and Hallym University Sacred Heart Hospital in Korea. Subjects who took sitagliptin, vildagliptin, or linagliptin (which were available DPP-4 inhibitors at the study period) for >3 months were included in the study. Of 1137 ESRD patients who received these medications, 937 were excluded due to their concomitant medical condition, lack of medication period or absence of adequate laboratory data about glucose control. Subjects who underwent renal transplantation while taking these medications or those who did not have information about when the medication started were excluded. We also excluded patients who had advanced hepatic dysfunction, uncontrolled endocrine dysfunction, prolonged severe infection, or recent significant abdominal surgery. In total, we evaluated 200 ESRD patients undergoing dialysis. The patients were grouped according to the drug they were taking into the sitagliptin group, the vildagliptin group, or the linagliptin group. We also conducted a subgroup analysis according to the dialysis method the patients were receiving. Clinical characteristic data were collected at the start of medication and after 12 weeks of treatment. We reviewed the comorbidities of the subjects, such as hypertension, coronary artery occlusive disease (CAOD), peripheral artery occlusive disease (PAOD), and stroke. Statin administration status was checked using the patients' medical records. This study was approved by the Yonsei University College of Medicine Institutional Review Board (4-2014-0655).

2.2. Metabolic parameters

The levels of fasting plasma glucose (FPG) and HbA1c were measured at baseline and after 12 weeks of treatment and used as the glycemic control parameters. The FPG levels were measured with the standard glucose oxidase method using a 747 automatic analyzer (Hitachi, Tokyo, Japan). The HbA1c levels were estimated using high-performance liquid chromatography. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels were also evaluated at the same time. Postprandial glucose levels, glycated albumin levels, C-peptide levels, or related parameters could not be included because of lack of data.

2.3. Statistical analyses

Continuous variables were expressed as the mean ± standard deviation. The paired *t*-test was used to compare the levels of parameters before and after 12 weeks of treatment. These variables of each medication group were compared and analyzed using 1-way analysis of variance (ANOVA). To compare nominal variables, the chi-square tests were performed. A P value of <0.05 was considered to indicate statistical significance. Data were analyzed using the SPSS Software Package for Windows (version 20; IBM Corp., Armonk, NY).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 200 subjects are described in Table 1. Forty-four subjects were taking sitagliptin, 72 patients were taking vildagliptin, and 84 were taking linagliptin. The 33 patients administered an unadjusted dose of sitagliptin (50 mg or 100 mg) and 12 patients receiving vildagliptin (50 mg twice daily) were included. The population included 115 patients being treated with hemodialysis and 85 patients who underwent PD. The mean age was 62.8 ± 12.2 years in the sitagliptin group, 64.2 ± 11.0 years in the vildagliptin group, and 63.3 ± 11.8 years in the linagliptin group ($P=0.79$). The sex distribution between the medication groups was not significantly different. No significant difference was observed in the prevalence of comorbidities, such as CAOD, PAOD, or stroke. The mean duration of T2DM was 17.4 years. Because most of the cases of end-stage renal failure in this study were caused by diabetes mellitus, the average duration of diabetes was long. There were no differences between inhibitor groups in the baseline metabolic characteristics of FPG, HbA1c, and lipid profiles. The proportion of subjects taking statins was

Table 1

Baseline characteristics of study subjects.

	Sitagliptin (n = 44)	Vildagliptin (n = 72)	Linagliptin (n = 84)	P
Age, y	62.8 ± 12.2	64.2 ± 11.0	63.3 ± 11.8	0.790
Sex (male:female), n	27:17	46:26	49:35	0.776
Dialysis (HD:PD), n	31:13	37:35	47:37	0.122
Dose adjustment (HD:PD), n	6:5	31:29	–	–
SBP, mm Hg	137.6 ± 18.6	136.7 ± 20.3	138.2 ± 18.3	0.886
DBP, mm Hg	75.6 ± 12.2	73.9 ± 10.4	74.7 ± 10.3	0.696
Height, cm	162.6 ± 7.5	162.9 ± 9.6	162.1 ± 7.9	0.872
Weight, kg	63.5 ± 11.5	62.9 ± 10.3	62.8 ± 10.1	0.940
BMI, kg/m^2	23.9 ± 3.5	23.6 ± 3.1	23.9 ± 3.0	0.776
HTN (%)	44 (100)	71 (98.6)	82 (97.6)	0.572
CAOD (%)	16 (36.4)	30 (41.7)	37 (44.0)	0.703
PAOD (%)	7 (15.9)	10 (13.69)	9 (10.7)	0.681
Stroke (%)	10 (22.7)	18 (25)	15 (17.9)	0.543
Liver disease (%)	2 (4.5)	3 (4.2)	6 (7.1)	0.740
Statin use (%)	26 (59.1)	35 (48.6)	46 (54.8)	0.522
T2DM duration, y	17.7 ± 8.9	16.5 ± 7.5	18.0 ± 9.5	0.565
FPG, mg/dL	173.9 ± 68.5	174.8 ± 78.0	152.2 ± 63.4	0.096
HbA1c,%	7.69 ± 1.55	7.21 ± 1.66	7.08 ± 1.39	0.175
Cholesterol, mg/dL	149.0 ± 30.1	149.8 ± 52.6	156.7 ± 57.4	0.710
Triglyceride, mg/dL	176.8 ± 166.0	138.9 ± 76.8	141.3 ± 85.7	0.502
HDL-C, mg/dL	33.4 ± 9.8	38.7 ± 12.1	34.5 ± 9.5	0.064
LDL-C, mg/dL	81.5 ± 27.9	83.2 ± 33.7	80.1 ± 38.9	0.997
Hemoglobin, g/dL	9.9 ± 1.2	10.1 ± 1.5	10.1 ± 1.6	0.690

Data are presented as mean ± standard deviation or number (%). One-way ANOVA was performed.

BMI = body mass index, CAOD = coronary artery occlusive disease, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HD = hemodialysis, HDL-C = high-density lipoprotein cholesterol, HTN = hypertension, LDL-C = low-density lipoprotein cholesterol, PAOD = peripheral artery occlusive disease, PD = peritoneal dialysis, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus.

not significantly different (Table 1). The percentages of patients who received insulin or other oral hypoglycemic agents with each DPP-4 inhibitor were also comparable (Supplementary Table 1, http://links.lww.com/MD/B181) except that thiazolidinediones were administered more in lingaliptin groups. Most of these medications were not changed within study period.

3.2. Change in the metabolic parameters after 12 weeks of treatment

The glucose parameters FPG and HbA1c for each group were decreased after 12 weeks of DPP-4 inhibitor treatment (Table 2). FPG levels in the sitagliptin and linagliptin groups were reduced significantly compared to premedication levels, but not in the vildagliptin group. In contrast, HbA1c levels were reduced significantly in the sitagliptin and vildagliptin groups. Although the changes of FPG and HbA1c among the 3 groups did not exhibit significant differences, sitagliptin displayed a trend to lower glucose levels.

Total cholesterol, LDL-C, and TG levels of the 3 groups also showed decreasing trends, but the changes were not statistically significant. The HDL-C levels were elevated in patients treated with sitagliptin (6.5 ± 12.6, $P = 0.027$) and linagliptin (4.8 ± 9.7, $P = 0.002$), but not in the vildagliptin group. There was no

Table 2

Change in the metabolic parameters after 12 weeks of treatment.

	Sitagliptin (n = 44)			Vildagliptin (n = 72)			Linagliptin (n = 84)		
Parameter	Baseline	12 weeks	P	Baseline	12 weeks	P	Baseline	12 weeks	P
FPG,mg/dL	173.9 ± 68.5	144.2 ± 55.4	0.008	174.8 ± 78.0	156.3 ± 67.1	0.062	152.2 ± 63.4	139.7 ± 57.4	0.011
Δ FPG	-29.7 ± 69.4			−18.5 ± 81.5			−12.4 ± 43.4		0.332
HbA1c, %	7.69 ± 1.55	6.95 ± 1.21	0.006	7.21 ± 1.66	6.82 ± 1.34	0.034	7.08 ± 1.39	7.00 ± 1.31	0.605
Δ HbA1c	−0.74 ± 1.57			−0.39 ± 1.45			−0.08 ± 1.40		0.076
TC, mg/dL	149.0 ± 30.1	147.3 ± 41.0	0.787	149.8 ± 52.6	145.0 ± 42.5	0.440	156.7 ± 57.4	150.8 ± 40.2	0.251
Δ TC	−1.7 ± 38.9			−4.8 ± 51.9			−5.9 ± 46.3		0.897
HDL-C, mg/dL	33.6 ± 9.8	40.1 ± 19.2	0.027	38.7 ± 12.05	39.0 ± 11.2	0.818	34.5 ± 9.5	39.3 ± 14.5	0.002
Δ HDL-C	6.5 ± 12.6			0.3 ± 8.6			4.8 ± 9.7		0.087
LDL-C, mg/dL	81.5 ± 27.9	79.7 ± 32.3	0.792	83.2 ± 33.7	77.8 ± 34.8	0.255	80.1 ± 38.9	79.9 ± 28.4	0.968
Δ LDL-C	−1.8 ± 30.1			−5.5 ± 31.0			−0.2 ± 32.0		0.731
TG, mg/dL	176.8 ± 166.0	155.1 ± 116.2	0.378	138.9 ± 76.8	128.8 ± 75.1	0.389	141.3 ± 85.7	135.7 ± 79.0	0.570
Δ TG	−21.7 ± 113.0			−10.0 ± 78.4			−5.6 ± 68.0		0.749

Data are presented as mean ± standard deviation. Paired *t*-test (white box) and 1-way ANOVA (gray shades) were performed.

Δ, change between the level of baseline and the level of 12 weeks for the given parameter, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

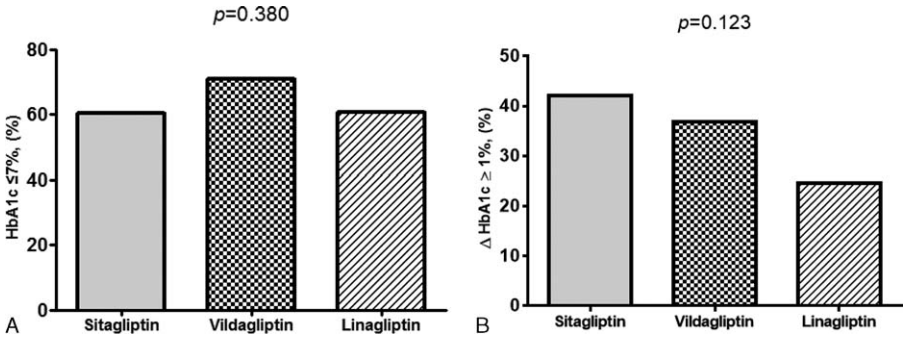

Figure 1. Proportion of patients who reached the target glycemic control. (A) The proportion of patients who reached the HbA1c level of <7% after 12-week treatment. (B) The proportion of patients who decreased HbA1c levels >1% after 12-week treatment. HbA1c, glycated hemoglobin; ΔHbA1c ≥1%, >1% decrease in the HbA1c level from baseline.

significant difference in HDL-C change among 3 groups. We also analyzed the change of glycemic parameters and lipid parameters in statin user and statin nonuser group. Three medications had comparable efficacy on lipid parameters in this subgroup analysis (Supplementary Tables 2 and 3, http://links.lww.com/MD/B181).

3.3. Proportion of patients who achieved the target glucose control range

The percentage of patients reaching the target HbA1c level of <7% were 61% (23 patients) of the sitagliptin group, 71% (46 patients) of the vildagliptin group, and 61% (45 patients) of the linagliptin group. These results were not significantly different between the 3 groups ($P=.38$) (Fig. 1A). A reduction in the HbA1c level of >1% from baseline was achieved in 42% of patients treated with sitagliptin, 37% of patients treated with vildagliptin, and 25% of patients treated with linagliptin (Fig. 1B). Overall, the 3 inhibitor drugs exhibited no significant differences in terms of glucose-lowering efficacy.

3.4. Drug effects on metabolic parameters in the subgroups according to dialysis methods

The effect of each medication on FPG, HbA1c, and total cholesterol levels of patients treated with hemodialysis (HD) are shown in Table 3. Sitagliptin administration significantly reduced FPG levels. FPG was also decreased in both the vildagliptin and linagliptin groups, but the decrease did not reach statistical significance. The decreases in HbA1c and total cholesterol levels also did not reach statistical significance.

Among subjects treated with PD, 12 patients were administered sitagliptin, 34 patients were administered vildagliptin, and 36 patients received linagliptin (Table 4). Vildagliptin was the most effective in reducing FPG, but the largest decrement of HbA1c levels was exhibited in the sitagliptin group. Sitagliptin reduced HbA1c levels significantly compared with vildagliptin ($P=0.012$) or linagliptin ($P < 0.001$) (Fig. 2). Comparing the effect of drugs on HbA1c after subgrouping the subjects according to their baseline HbA1c level, there is a tendency for sitagliptin to lower HbA1c levels more than the other inhibitors (Fig. 2).

4. Discussion

The current study evaluated the efficacy of 3 DPP-4 inhibitors on glycemic control and lipid profiles in T2DM patients who were undergoing dialysis. A 12-week treatment regimen of sitagliptin, vildagliptin, or linagliptin resulted in significant improvement in hyperglycemia. DPP-4 inhibitors are known to have overall comparable efficacy on glycemic control in patients with preserved kidney function.[13] In addition, many studies have demonstrated consistent results of similar mean HbA1c reduction with these drugs in people with renal impairment,[14] even if there is a lack of direct head-to-head trials. In our study, the mean HbA1c levels of a relatively small numbers of subjects undergoing PD in the sitagliptin group were higher than those of patients in the other medication groups. Confirmation of this observation would require prospective studies with more patients.

In our study, the mean HbA1c reductions were 0.74%, 0.39%, and 0.08% with sitagliptin, vildagliptin, and linagliptin treatments, respectively. A 54-week randomized trial showed that the mean change from baseline in the HbA1c level was –0.72% with sitagliptin in patients with ESRD who were undergoing dialysis,[15] which is consistent with the results of our study. A

Table 3

Drug effects on metabolic parameters in patients undergoing hemodialysis.

	Sitagliptin (n=31)			Vildagliptin (n=37)			Linagliptin (n=47)		
Parameter	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***
FPG, mg/dL	175.6±75.1	143.2±59.8	0.021	169.3±77.4	158.2±78.5	0.464	143.7±61.6	136.3±50.7	0.304
Δ FPG	−32.4±72.7			−11.1±90.3			−7.4±48.2		0.261
HbA1c, %	7.38±1.50	6.98±1.31	0.220	7.36±1.84	7.04±1.42	0.340	6.99±1.40	6.87±1.25	0.621
Δ HbA1c	−0.40±1.65			−0.31±1.82			−0.12±1.54		0.773
TC, mg/dL	146.5±30.6	140.6±36.4	0.411	161.4±62.8	144.9±32.8	0.105	145.2±51.4	145.3±38.9	0.987
Δ TC	−5.9±38.0			−16.4±59.3			0.1±43.7		0.300

Data are presented as mean±standard deviation. Paired *t*-test (white box) and 1-way ANOVA (gray shades) were performed.

Δ=change between the level of baseline and the level of 12 weeks for the given parameter, FPG=fasting plasma glucose, HbA1c=glycated hemoglobin, TC=total cholesterol.

Table 4

Drug effects on metabolic parameters in patients undergoing peritoneal dialysis.

	Sitagliptin (n = 13)			Vildagliptin (n = 35)			Linagliptin (n = 37)		
Parameter	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***	**Baseline**	**12 weeks**	***P***
FPG, mg/dL	169.6 ± 51.0	146.8 ± 44.8	0.235	180.6 ± 79.3	154.3 ± 53. 7	0.040	163.0 ± 65.0	144.1 ± 65.4	0.003
Δ FPG	−22.8 ± 62.7			−26.3 ± 71.5			−18.9 ± 35.9		0.861
HbA1c, %	8.47 ± 1.46	6.89 ± 0.99	<0.001	7.07 ± 1.48	6.61 ± 1.25	0.011	7.20 ± 1.38	7.16 ± 1.39	0.852
Δ HbA1c	−1.58 ± 0.95			−0.46 ± 0.98			−0.04 ± 1.22		0.001
TC, mg/dL	155.6 ± 28.9	165.0 ± 48.6	0.459	137.6 ± 36.3	145.1 ± 51.3	0.280	171.7 ± 62.1	158.0 ± 41.3	0.103
Δ TC	9.5 ± 40.7			7.5 ± 39.8			−13.7 ± 49.1		0.097

Data are presented as mean ± standard deviation. Paired *t* test (white box) and 1-way ANOVA (gray shades) were performed.

Δ = change between the level of baseline and the level of 12 weeks for the given parameter, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, TC = total cholesterol.

Japanese group reported that after 24 weeks of treatment with vildagliptin, the mean change of HbA1c levels was from 6.7% at baseline to 6.1%, average glycated albumin (GA) levels from 24.5% to 20.5%, and postprandial plasma glucose levels from 186 mg/dL at baseline to 140 mg/dL.[16] After 12 weeks of treatment, at the middle of the study, the HbA1c change was ~0.4%.[16] Another study also reported similar results.[17] The therapeutic effect of linagliptin monotherapy was investigated in HD patients with favorable outcomes: 6 months of treatment resulted in decreased GA levels from 21.3 ± 0.6% to 18.0 ± 0.6%.[18] The efficacy of sitagliptin and vildagliptin on blood glucose in our study was consistent with results previous reports, but linagliptin showed a smaller reduction than expected. This discrepancy may be related to the fact that the average FPG and HbA1c levels at baseline were relatively low in the linagliptin group.

There are some difficulties involved in the estimation of glycemic control in patients on dialysis. We measured FPG and HbA1c levels; however, HbA1c is a less reliable index of glycemia in renal impairment due to the effects of anemia from the reduced survival time of erythrocytes and the erythropoietin injections. As a consequence, HbA1c levels may lead to an underestimation of blood glucose status.[19] Several studies demonstrated that GA provides a better measurement for estimation of glycemic control in patients on HD,[20] but GA levels of the patients were not available in this retrospective study. GA levels have also been reported to be a predictor of death, hospitalization, and cardiovascular events in these patients.[21] In this study, hemoglobin levels of most of subjects remained stable during the observation period, and the levels were not different according to the medication groups. However, data combined with GA and postprandial glucose levels would be more helpful to estimate glycemic control for ESRD patients.

Linagliptin is a relatively widely used antidiabetes medication for patients with ESRD because dose adjustment is not necessary for these patients. Linagliptin is not significantly accumulated in patients with ESRD because it is mainly excreted in the feces in contrast with sitagliptin, which is predominantly excreted in the urine.[22] Previous studies of sitagliptin treatment in subjects without diabetes but with reduced renal excretion due to impaired renal function resulted in accumulation of sitagliptin and consequent increases in maximum plasma concentration and area under the plasma concentration–time curve (AUC).[23] The fraction of dose eliminated by HD was small so dose adjustment to 25 mg daily was recommended. Increases in sitagliptin AUC were 4.5-fold higher for patients with ESRD. However, in this study, some patients received 50 or 100 mg daily dose of sitagliptin, especially in the early period when DPP-4 inhibitors were just beginning to be used. But, a previous study reported that a daily dose of 600 mg of sitagliptin for 10 days did not lead to any adverse effects in healthy male volunteers.[24] Another study demonstrated that after sitagliptin administration at 200 mg/day for 6 months, there was no clear excess of adverse events. Similarly, in this study, no specific side effect of high-dose

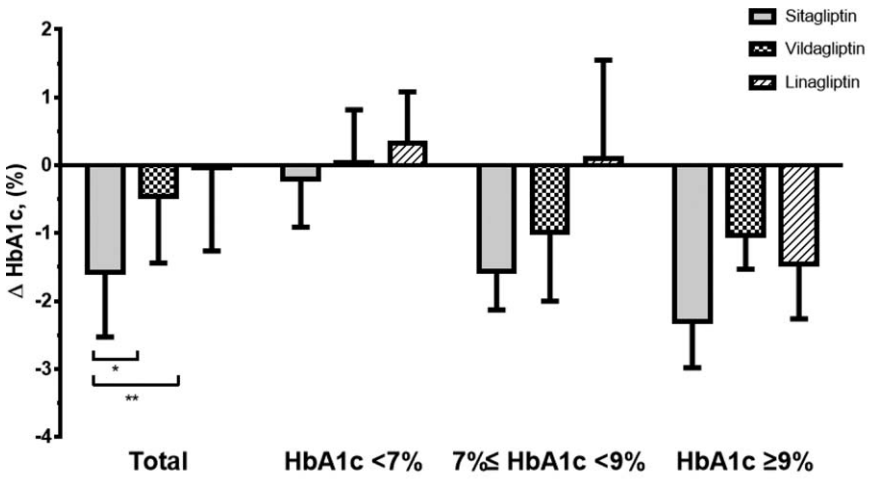

Figure 2. Change of HbA1c after 12-week treatment in PD patients. In the PD group, HbA1c levels were decreased more with sitagliptin. Subgroup analysis according to baseline HbA1c levels showed similar results (*$P = 0.012$, **$P < 0.001$). HbA1c, glycated hemoglobin. PD = peritoneal dialysis.

sitagliptin was found. In the case of vildagliptin, the renal elimination was about 20% to 25%.[25] In patients with severe degrees of renal impairment (creatinine clearance <30 mL/min), the AUC is about doubled.[26] Even though 400 or 600 mg daily was associated with some adverse effects, such as peripheral edema, paresthesia, and elevated serum concentrations of aspartate aminotransferase, there were no related side effects of high dose of vildagliptin in 2 previous reports (200 mg daily)[10,16] and in this study (50 mg bid).

In this study, all 3 DPP-4 inhibitors exhibited beneficial effects on serum lipid profiles. They seemed to have minimal effects on total cholesterol, LDL-C, triglyceride levels without statistical significance. HDL-C levels were elevated after 12 weeks of treatment, especially with sitagliptin and linagliptin. Many studies investigated the possible beneficial effects of DPP-4 inhibitors, but the results are inconclusive and diverse.[27] Several researchers demonstrated the positive effect of DPP-4 inhibitors on serum lipid profiles, particularly for sitagliptin on HDL-C[28,29] and for vildagliptin on total cholesterol.[30] Here we demonstrated that in ESRD patients, DPP-4 inhibitors exert possible beneficial effects on lipids, similar to previous studies with patients with normal renal function.

This study has some limitations. As it was a retrospective study, not a prospective randomized clinical trial, there might be biochemical, clinical differences among the groups at baseline. DPP-4 inhibitors may be prescribed not only given as a monotherapy, but also as a combination therapy. Thus, few patients started them alone or without any changes in other oral hypoglycemic medications, limiting the sample size. Other limitations were that the number of enrolled patients was relatively small and the period of study was short. For these reasons, we could not detect toxicity for any of the drugs or evaluate cardiovascular outcomes. As mentioned previously, because HbA1c is less reliable in ESRD patients, additional glycemic indices like GA, post-prandial glucose levels, or homeostatic model assessment of insulin resistance, will be helpful.

In conclusion, there is no significant difference in glucose-lowering efficacy among 3 different DPP-4 inhibitors in ESRD patients who are undergoing dialysis. Sitagliptin tends to lower HbA1c levels more than other inhibitors in PD patients. However, further prospective randomized clinical trials and long-term follow-up studies are warranted to confirm these conclusions.

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