Efficacy and safety of saxagliptin, a dipeptidyl peptidase-4 （DPP-4) inhibitor, in hemodialysis patients with type 2 diabetes

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Background

The potent and selective dipeptidyl peptidase 4 (DPP-4) inhibitor improves glycemic control in patients with type 2 diabetes through incretin-mediated increases in both, α- and β-cell responsiveness to glucose. Some studies have suggested that the HbA1c level is not the optimal index for assessing glycemic control in diabetic dialysis patients receiving erythropoiesis-stimulating agents (ESA). Instead, glycated albumin (GA) has been suggested to be a more reliable indicator of glycemic control. Therefore, the Japanese Society for Dialysis Therapy recommends GA levels < 20% as a target for glycemic control in patients with diabetes.

The aim of this study was to verify the efficacy and safety of saxagliptin in hemodialysis (HD) patients with type 2 diabetes.

Methods

In this prospective, open-label, randomized, parallel, controlled, multi-center trial, we screened 386 patients, of which, 84 HD patients were randomly assigned to either the saxagliptin (n = 42) or the control group (n = 42). Patients in the saxagliptin group received the drug at a dose of 2.5 mg daily and those in the control group received the usual care without DPP-4 inhibitor therapy. Patients were monitored for 24 weeks.

All patients had poor glycemic control, which was defined as a GA level exceeding 20.0% after 8 consecutive weeks of daily administration of conventional therapy (dietary therapy alone, oral antidiabetic agents, and/or insulin). The erythropoietin responsiveness index (ERI) was defined as the average weekly ESA dose divided by the clinical dry weight and average blood hemoglobin (weekly ESA dose [units]/dry weight [kg]/hemoglobin [g/dL]), to normalize the amount of required ESA to the severity of anemia.

Results

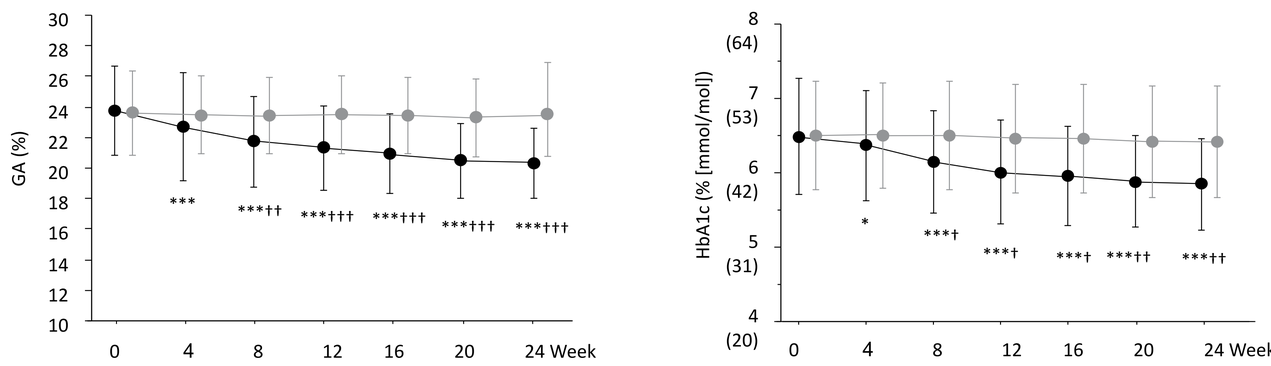
Overall, two patients did not complete the trial, including one in the either group. The remaining 41 patients from each group were included in the final analysis. There were no significant differences in the baseline demographic, hemodynamic, or anthropometric variables between the groups. The dialysis mode, types of vascular access, cardiovascular comorbidity, or medications were also not different between the groups.

Table 1. Patient characteristics at baseline.

Variable	Saxagliptin group	Control group	P value
N	41	41	
Males	27 (65.9)	28 (68.3)	0.816
Age (years)	66.9 ± 9.4	66.3 ± 9.4	0.282
Hemodialysis duration (m)	50.9 ± 33.7	50.2 ± 33.0	0.929
Duration of diabetes mellitus (y)			
Body mass index (kg/m^2)	22.8 ± 3.7	22.9 ± 3.7	0.837
Postprandial plasma glucose (mg/dL)	186 ± 35	185 ± 47	0.832
Glycated albumin (%)	23.7 ± 2.9	23.6 ± 2.7	0.597
Glycated hemoglobin (%)	6.5 ± 0.8	6.5 ± 0.7	0.929
Cardiovascular comorbidities			
Ischemic heart disease	7 (17.1)	6 (14.6)	0.765
Cerebral vascular events	2 (4.9)	1 (2.4)	0.562
Peripheral artery disease	3 (7.3)	2 (4.9)	0.649
Dialysis mode			0.697
Hemodialysis	38 (92.7)	37 (90.2)	
Hemodiafiltration	3 (7.3)	4 (9.8)	
Type of vascular access			0.727
Arteriovenous fistula	36 (87.8)	35 (85.4)	
Arteriovenous graft	5 (12.2)	6 (14.6)	
Catheter	0	0	
Antidiabetic therapy			
Oral antidiabetic agents	20 (48.8)	21 (51.2)	0.827
Insulin therapy	5 (12.2)	6 (14.6)	0.749
Oral antidiabetic agents + insulin	4 (9.7)	3 (7.4)	0.697
Diet alone	12 (29.3)	11 (26.8)	0.808
Use of RAS inhibitors	34 (82.9)	33 (80.5)	0.778
Use of statins	18 (43.9)	19 (46.3)	0.827

Values are shown as the *n* (%) or mean ± standard deviation.

Figure 1. GA, HbA1c, and PPG at each visit.



Results are presented as the mean (95% confidence interval).
Black circles, saxagliptin group; grey circles, control group.
*P <0.01 and ***P <0.0001 vs. Week 0.
†P <0.01, ††P <0.001, and †††P <0.0001 vs. the control group.
GA, glycated albumin; HbA1c, hemoglobin A1c; PPG, postprandial glucose.

Figure 2. Changes from baseline to the end of treatment in GA, HbA1c, and PPG in saxagliptin-treated patients according to baseline GA (A), HbA1c (B), and PPG (C).

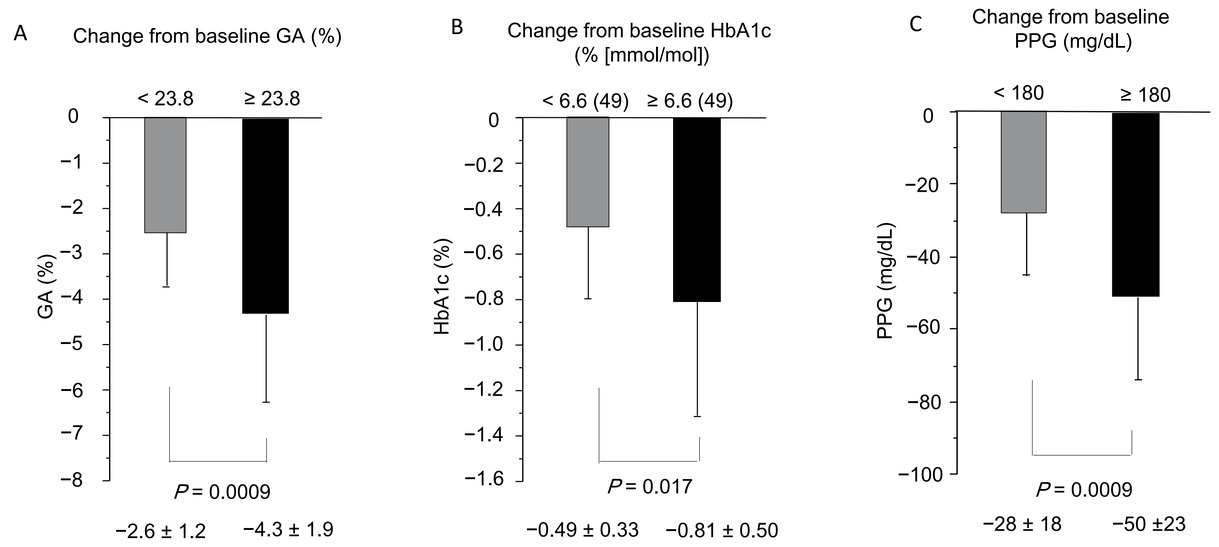


Table 2. Changes in vital signs and laboratory variables.

Variables	Saxagliptin group			Control group			Between-group P values	
	Baseline	Endpoint	P value[a]	Baseline	Endpoint	P value[a]	Baseline	Endpoint
Systolic BP (mmHg)	147 ± 12	146 ± 12	0.073	147 ± 12	148 ± 14	0.101	0.936	0.506
Diastolic BP (mmHg)	76 ± 9	76 ± 10	0.057	77 ± 13	77 ± 13	0.351	0.829	0.583
Heart rate (bpm)	77 ± 10	77 ± 10	0.937	77 ± 8	77 ± 8	0.509	0.971	0.925
Hemoglobin (g/dL)	11.0 ± 0.6	11.0 ± 0.7	0.392	11.0 ± 0.7	10.9 ± 0.7	0.381	0.923	0.332
ESA dose (U/week)	5902 ± 2421	4768 ± 2466	< 0.0001	5926 ± 2639	5963 ± 2665	0.33	0.965	0.038
ERI	9.49 ± 4.42	7.77 ± 4.63	0.0008	9.73 ± 5.67	10.02 ± 5.15	0.847	0.829	0.041
Serum albumin (g/dL)	3.6 ± 0.2	3.7 ± 0.3	0.141	3.7 ± 0.6	3.6 ± 0.3	0.157	0.477	0.184
Total cholesterol (mg/dL)	154 ± 32	151 ± 29	0.173	149 ± 22	148 ± 20	0.877	0.292	0.638
HDL-cholesterol (mg/dL)	44.7 ± 12.7	45.0 ± 12.7	0.781	42.4 ± 12.1	42.1 ± 12.0	0.755	0.39	0.286
Triglyceride (mg/dL)	98 (57–140)	86 (56–124)	0.0015	118 (77–144)	112 (84–167)	0.64	0.491	0.041
Body mass index (kg/m^2)	22.7 ± 3.7	22.7 ± 3.6	0.813	22.9 ± 3.7	22.9 ± 3.8	0.969	0.837	0.848
CTR (%)	49.0 ± 2.7	49.0 ± 2.6	0.222	49.9 ± 2.8	49.6 ± 3.0	0.761	0.136	0.355
Intradialytic weight gain (kg)	2.91 ± 0.99	2.77 ± 0.93	0.0015	2.93 ± 0.99	2.96 ± 1.05	0.145	0.904	0.573

BP, blood pressure; CTR, cardiothoracic ratio; ESA, erythropoietin stimulating agent; ERI, erythropoietin responsiveness index; HDL, high-density lipoprotein;.
[a]Within-group comparisons. Values are shown as the mean ± standard deviation or median (interquartile range).

Conclusions

After 24 weeks, saxagliptin decreased the average GA levels from 23.7 ± 2.9% at baseline to 20.3 ± 2.3%; average HbA1c levels from 6.5 ± 0.8% at baseline to 5.9 ± 0.6% and average PPG levels from 186 ± 34 mg/dL at baseline to 148±30 mg/dL (all p < 0.0001). Twenty-two (53.7%) patients reached the target GA (<20%) level. In the control group, no such changes were observed. Saxagliptin efficacy did not differ according to the age or body mass index. However, the GA reduction was significantly greater in the anti-diabetic agents-naïve group. Furthermore, the triglyceride levels and ERI were significantly decreased in the saxagliptin group. No serious adverse effects such as hypoglycemia or liver impairment were observed in any patient.

Saxagliptin as monotherapy or in combination with other antidiabetic agents improved glycemic control and was generally well tolerated in patients with HD over a 24-week period.

We declare no conflict of interest.

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