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Efficacy of Saxagliptin versus Mitiglinid in patients with type 2 diabetes and end-stage renal disease

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Abstract

Background: There are very few oral antidiabetic drugs recommended for patients on dialysis. Saxagliptin is known for its potent effect and long duration of action. In this study, we compared the efficacy of Saxagliptin with Mitiglinid for diabetes control and renal anemia in hemodialysis patients with type 2 diabetes mellitus.

Methods: We performed a 6-month prospective, open-label, parallel group study of 41 patients with type 2 diabetes mellitus undergoing hemodialysis who took alpha-glucosidase inhibitors or meglitinides and did not use insulin. Saxagliptin and Mitiglinid were administered at 2.5 and 5 mg/day, respectively. The primary outcomes were changes in hemoglobin A1c (HbA1c) and glycated albumin (GA). Other efficacy assessments included changes in Hb, darbepoetin alpha (DA) dose, and erythropoietin responsiveness index (ERI).

Results: No patient required an increase in Saxagliptin or Mitiglinid dose, and there were no cases of hypoglycemia with symptoms. HbA1c and GA values were not significantly different between both groups. For HbA1c, the gradient of the regression line of the Saxagliptin and Mitiglinid groups were $Y = -7.144e\text{-}005*X + 6.023$ and $Y = -0.02604*X + 6.292$, respectively, and no significant difference was found ($p = 0.3281$). However, for GA, the regression line of the Saxagliptin group significantly decreased ($Y = -0.5036*X + 19.34$ and $Y = -0.2346*X + 18.79$, $p = 0.0371$). Both groups did not have a significant change in the DA dose through the observation period. However, the DA dose of the Saxagliptin group significantly decreased when we compared the regression lines ($Y = -0.8304*X + 21.06$ and $Y = 0.6286*X + 16.12$, $p = 0.0019$) of both groups. Furthermore, ERI did not change significantly but showed a significant difference when regression lines were compared ($Y = -0.2030*X + 6.654$ and $Y = 0.1116*X + 5.288$, $p = 0.0082$).

Conclusions: The present study showed that Saxagliptin was not inferior to Mitiglinid in the glycemic control of ESRD patients with type 2 diabetes mellitus, and it is well tolerated and safe. Saxagliptin may also improve bioavailability of iron compared to Mitiglinid, but long-term follow-up in a large scale study with more precise ferrokinetic marker measurements are necessary to confirm these results.

Keywords: End-stage renal disease, Diabetes mellitus, Hemodialysis, DPP-4 inhibitor, Saxagliptin, Glycated albumin

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Background

Type 2 diabetes mellitus is on a rapid increase globally, especially in Asia [1, 2]. In Japan, the number of hemodialysis patients where diabetic nephropathy is a primary disease is increasing. Currently, diabetic nephropathy is the primary disease for approximately 40% of all patients on dialysis [3].

The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines recommend standard hemoglobin A1c (HbA1c) targets for patients with type 2 diabetes mellitus and end-stage renal disease (ESRD) to potentially reduce the risk of other microvascular complications (neuropathy and retinopathy) [4, 5]. However, treatment options available for these patients are limited due to safety and tolerability issues [6]. Oral medications recommended in the Japanese guidelines include only alpha-glucosidase inhibitors, meglitinides, and dipeptidyl peptidase-4 (DPP-4) inhibitors [7]. These three drug types in combination and insulin preparation are used in treatment. However, there is no evidence indicating which drug is ideal.

The DPP-4 inhibitor has few hypoglycemic side effects [8]. Also, it is hard to cause the weight gain too [9]. It has been reported to exert a kidney protection effect and is expected as the new drug of choice in diabetes treatment where there is decreased renal function [10–16]. Recently, DPP-4 inhibits hemopoietic factors such as granulocyte-colony stimulating factor (G-CSF) or erythropoietin, and it is reported that the antagonism is inhibited by DPP-4 inhibitors [17–19]. However, the clinical effect on renal anemia treatment is unknown. Meglitinides are a class of oral hypoglycaemic agents that increase insulin secretion in the pancreas. Their effect is to produce a rapid, short-lived insulin output [20].

Saxagliptin is a selective DPP-4 inhibitor specifically designed for extended inhibition of the DPP-4 enzyme that is primarily metabolized by cytochrome P450 (CYP) 3A4/5 to form an active metabolite, 5-hydroxy Saxagliptin, which is cleared by the kidney [21, 22]. Saxagliptin is eliminated by both renal and hepatic routes [23, 24]. Recent studies have shown that Saxagliptin is a well-tolerated treatment option for patients with type 2 diabetes mellitus and renal impairment [13, 25–27].

To further characterize the use of Saxagliptin in patients with kidney disease, the present study compared the efficacy of Saxagliptin with that of Mitiglinid monotherapy for diabetes control and renal anemia administered over 6 months in patients with type 2 diabetes mellitus and ESRD requiring hemodialysis.

Methods

Patients

The inclusion criteria was intended for patients who took alpha-glucosidase inhibitors or meglitinides, among patients who were on hemodialysis in an outpatient setting for chronic renal failure due to type 2 diabetes mellitus and who were not on insulin.

Patients were on hemodialysis therapy for at least 6 months and were 20 years or older at the screening visit. Exclusion criteria were as follows: (1) age <20 years; (2) a history of severe heart failure, angina, myocardial infarction, or stroke within the past 6 months; (3) the presence of infectious disease, liver dysfunction, thyroid disease, malignant tumors, or treatment with steroids or immunosuppressants; and (4) treatment with any DPP-4 inhibitor within the past 6 months.

Hemodialysis

All patients underwent dialysis for 4 or 5 h. Blood flow rate was 200 mL/min and a dialysate flow rate was 500 mL/min. All centers used the high-flux membrane, and the size of the dialyzer was decided according to the physique of the patient. The ultrafiltration-rate was decided according to the dry weight. The glucose concentration of the dialysate was 125 mg/dL. Heparin was administered at a dose of 2500–6000 U per dialysis session for anticoagulation.

Study design

This was a 6-month, prospective, open-label, parallel-group, bi-center study and was conducted between May 2014 and April 2015. Before randomization, patients stopped alpha-glucosidase inhibitors or meglitinides intake and entered a 1-month drug washout.

The patients were subsequently randomly assigned to the Saxagliptin or Mitiglinid group (open-label random assignment). For the randomization method, we performed simple randomization with alternate assignment. In the Saxagliptin group, patients received 2.5 mg of Saxagliptin once a day. In the mitiglinide group, patients received 5 mg of mitiglinide three times a day.

Downtitration, including interruption of treatment, could occur if a patient had unexplained hypoglycemia or at the clinical judgment of the investigator, to reduce the risk of hypoglycemia. Treatment adherence was assessed by patient query at prespecified visits throughout the study.

Blood samples were obtained before the first hemodialysis session of the week. Postprandial plasma glucose, complete blood cell counts, and other biochemical measurements were performed every month. All patients received Darbepoetin alpha (DA) and DA dose was adjusted according to the severity of anemia. The erythropoietin responsiveness index (ERI) was defined as the mean weekly erythropoiesis stimulating agents (ESA) dose divided by the clinical dry weight and mean blood hemoglobin [i.e., ERI = weekly ESA dose (units)/dry

weight (kg)/hemoglobin (g/dL), DA (μg): ESA (units) = 1: 200] [28].

Efficacy endpoints

The primary efficacy endpoint was changes in HbA1c and GA values and comparison between the two groups. Other efficacy assessments included changes in Hb, DA dose, and ERI. Patients could be withdrawn from the study in the event of drug intolerance, if either the serum transaminase concentration or creatine kinase concentration increased to more than two times the upper limit of the normal range or other adverse events, based on the investigator's judgment.

Statistical analyses

Measurement values are shown as mean +/− standard deviation (mean +/− SD). Continuous variables were compared using the Student's *t* test, and one-way ANOVA was performed on the longitudinal data to address its multiplicity. Tukey's multiple comparison test was used as the post-hoc test. *P* values less than 0.05 were regarded as statistically significant. Regression lines were separately determined for the data collected during the 6-month period and compared. All analyses were performed using Prism software version 6 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Patient characteristics

A total of 94 patients were initially screened, and 41 patients were randomly assigned to the Saxagliptin ($n = 21$) or Mitiglinid ($n = 20$) group. Colorectal cancer was detected during an observation period, and one case in the Saxagliptin group was excluded. There was a final of 20 subjects in each group. For the premedication in both groups, there were 6 acarbose, 6 voglibose, and 8 mitiglinide in the Saxagliptin group and 8 acarbose, 5 voglibose, and 6 mitiglinide in the mitiglinide group. There was also one Glimepiride recipient in the mitiglinide group. The patient profiles are shown in Table 1. There were no significant differences in the baseline age, anthropometric variables, and laboratory data between the two groups except for serum Ca concentration.

Table 1 Patients' baseline profiles ($N = 40$)

	Saxagliptin	Mitiglinide	*P* value
Number	20	20	
Female (*n*)	2	5	0.4075
Age	68.6 ± 10.1	63.0 ± 13.1	0.1288
BMI	22.5 ± 2.7	24.2 ± 3.5	0.0973
HD dulation (months)	42.8 ± 36.3	70.4 ± 58.2	0.0745
DM dulation (years)	14.5 ± 6.2	15.7 ± 7.4	0.5853
Acarbose (mg/day)	225.0 ± 82.2	187.5 ± 69.4	0.3728
Voglibose (mg/day)	0.75 ± 0.16	0.66 ± 0.13	0.3527
Mitiglinide (mg/day)	16.9 ± 5.3	15.0 ± 0.0	0.4082
Glimepiride (mg/day)	–	0.50 ± 0.0	–
HbA1c (%)	6.0 ± 0.9	6.3 ± 1.4	0.5219
GA (%)	19.2 ± 3.2	18.9 ± 4.4	0.8372
BUN (mg/dL)	59.7 ± 11.9	64.4 ± 14.6	0.2724
Cr (mg/dL)	9.36 ± 2.63	10.81 ± 3.47	0.1396
UA (mg/dL)	5.8 ± 1.4	6.5 ± 1.5	0.1427
Na (mEq/L)	133.9 ± 2.2	138.4 ± 2.7	0.384
K (mEq/L)	5.0 ± 0.7	4.7 ± 0.7	0.1736
Cl (mEq/L)	107.3 ± 3.3	95.0 ± 3.2	0.0898
Ca (mg/dL)	8.2 ± 0.4	8.6 ± 0.7	0.0285
P (mg/dL)	5.1 ± 1.0	5.4 ± 1.1	0.246
TP (g/dL)	6.8 ± 0.5	6.7 ± 0.4	0.5831
Glu (mg/dL)	163.0 ± 59.8	158.2 ± 55.9	0.7934
AST (U/L)	13.9 ± 6.1	11.5 ± 5.2	0.2023
ALT (U/L)	10.3 ± 5.4	9.8 ± 4.6	0.7818
LDH (U/L)	208.4 ± 45.8	179.7 ± 44.3	0.0515
ALP (U/L)	238.5 ± 68.2	256.3 ± 146.5	0.6199
GTP (U/L)	34.5 ± 78.2	23.3 ± 14.1	0.5437
iPTH (pg/mL)	191.0 ± 101.3	204.2 ± 151.0	0.7457

BMI body mass index, *HD* hemodialysis, *DM* diabetes mellitus, *HbA1c* hemoglobin A1c, *GA* glycated albumin, *BUN* blood urea nitrogen, *Cr* creatinine, *UA* uric acid, *TP* total protein, *Glu* glucose, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GTP* γ-glutamyl transpeptidase, *iPTH* intact parathyroid hormone

Glycemic control

No parameter showed any significant changes during the period of examination. There were no changes in the doses of Saxagliptin and Mitiglinid.

No significant change was found in postprandial plasma glucose values over the study duration. Mean postprandial plasma glucose value 6 months after Saxagliptin administration was 152.4 +/− 74.71 mg/dL (ANOVA; $p = 0.0938$), and the regression line gradient was $Y = -0.5571^*X + 150.6$ (Fig. 1), while mean postprandial plasma glucose value 6 months after Mitiglinid administration was 138.1 +/− 71.77 mg/dL (ANOVA; $p = 0.9357$), and the regression line gradient was $Y = -2.404^*X + 149.3$. No significant difference was found when the regression line gradient of Saxagliptin and Mitiglinid was compared ($p = 0.5252$).

No significant change was found in HbA1c values over the study duration. Mean HbA1c value 6 months after Saxagliptin administration was 5.905 +/− 0.9770% (ANOVA; $p = 0.9099$), and the gradient of the regression line was $Y = -7.144\text{e-}005^*X + 6.023$ (Fig. 2), while mean HbA1c value of the Mitiglinid group was 6.145 +/− 1.1540 (ANOVA; $p = 0.9994$), and the gradient of the regression line was $Y = -0.02604^*X + 6.292$. No significant

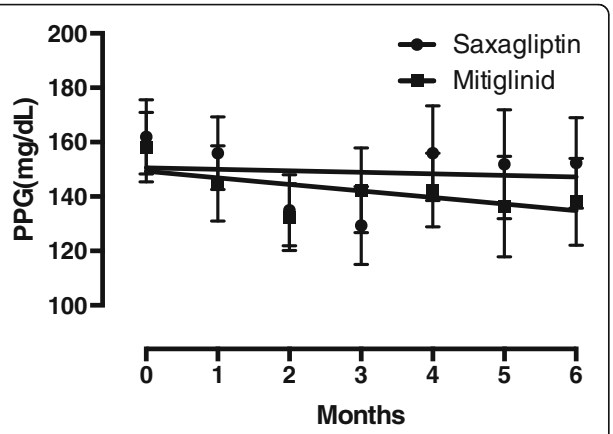

Fig. 1 Comparison of regression line gradients of postprandial plasma glucose between Saxagliptin and Mitiglinid groups. Saxagliptin group $Y = -0.5571*X + 150.6$, Mitiglinid group $Y = -2.404*X + 149.3$. *PPG* postprandial plasma glucose

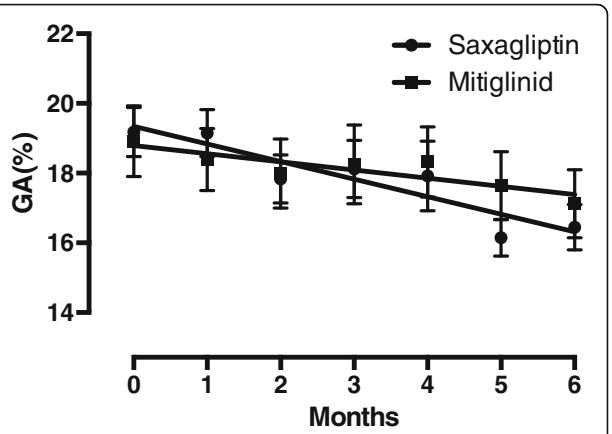

Fig. 3 Comparison of regression line gradients of GA between Saxagliptin and Mitiglinid groups. Saxagliptin group:$Y = -0.5036*X + 19.34$, Mitiglinid group $Y = -0.2346*X + 18.79$, $p = 0.0371$

difference was found when the slope of regression lines of Saxagliptin and Mitiglinid was compared ($p = 0.3281$).

Mean GA value 6 months after Saxagliptin administration was 16.45 +/− 2.981% (ANOVA; $p = 0.0883$), and the gradient of the regression line was $Y = -0.5036*X + 19.34$, while mean GA value of the Mitiglinid group was 17.12 +/− 4.383% (ANOVA; $p = 0.9552$), and the gradient of the regression line was $Y = -0.2346*X + 18.79$. There was a significant difference in the slope of regression lines between the two groups ($p = 0.0371$) (Fig. 3).

ESA dose and laboratory variables

Renal anemia was well controlled in both groups. After 6 months, in Saxagliptin group mean DA dose was 16.75 +/− 22.08 μg/w, and in Mitiglinid group was 19.50 +/− 11.46 μg/w. Both groups did not have a significant change through the observation period (Saxagliptin group, ANOVA $p = 0.4333$; Mitiglinid group, ANOVA, $p = 0.3768$). However, the slope of the regression lines of both groups had a significant difference (Saxagliptin group, $Y = -0.8304*X + 21.06$; Mitiglinid group, $Y = 0.6286*X + 16.12$, $p = 0.0019$) (Fig. 4).

Both groups also did not have a significant change in ERI over the study duration (Saxagliptin group, from 6.891 +/− 6.958 to 5.561 +/− 8.330, ANOVA $p = 0.5856$; Mitiglinid group, from 4.982 +/− 4.107 to 5.842 +/− 3.766, ANOVA $p = 0.9910$), but a significant difference was observed when the slope of regression lines were compared between the two groups (Saxagliptin group, $Y = -0.2030*X + 6.654$; Mitiglinid group, $Y = 0.1116*X + 5.288$, $p = 0.0082$) (Fig. 5).

Baseline parameters were not different between the two groups (Table 1), but subjects administered Saxagliptin showed a significant increase in transferrin saturation (TSAT) ($p = 0.0148$) and serum Fe level ($p =$

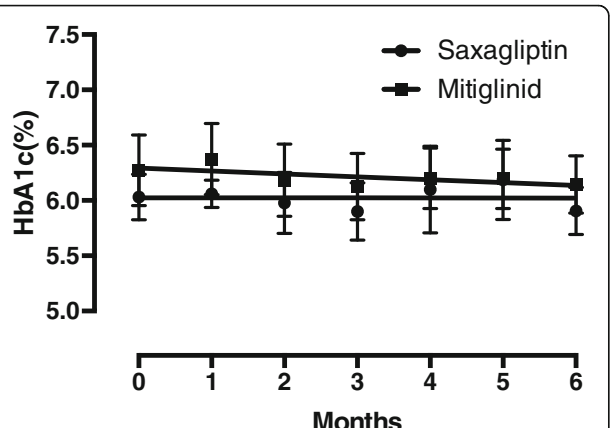

Fig. 2 Comparison of regression line gradients of HbA1c between Saxagliptin and Mitiglinid groups. Saxagliptin group $Y = -7.144e\text{-}005*X + 6.023$, Mitiglinid group $Y = -0.02604*X + 6.292$, $p = 0.3281$

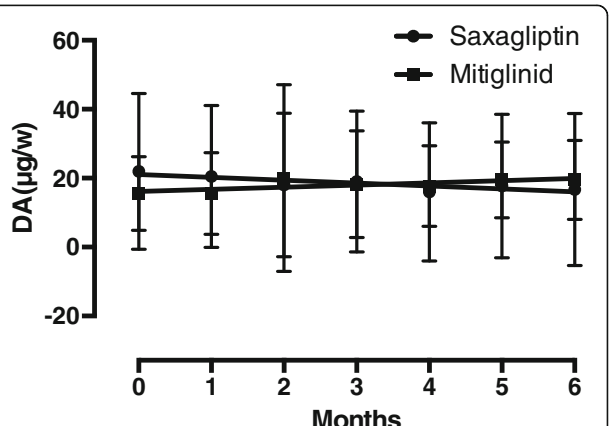

Fig. 4 Comparison of regression line gradients of DA dose between Saxagliptin and Mitiglinid groups. Saxagliptin group $Y = -0.8304*X + 21.06$, Mitiglinid group $Y = 0.6286*X + 16.12$, $p = 0.0019$

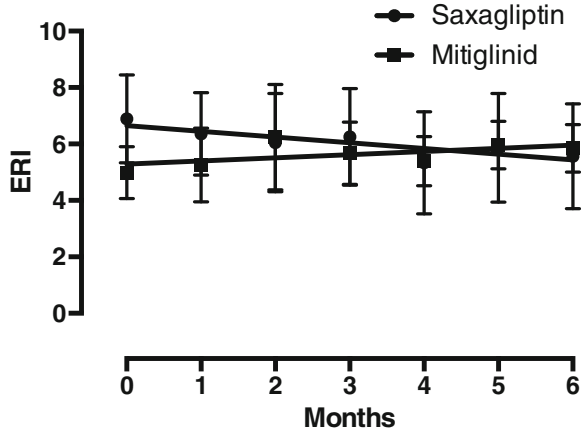

Fig. 5 Comparison of regression line gradients of ERI between Saxagliptin and Mitiglinid groups. Saxagliptin group: $Y = -0.2030*X + 6.654$, Mitiglinid group $Y = 0.1116*X + 5.288$, $p = 0.0082$

0.0085) when these were compared during the observation period. Ferritin showed a tendency to decrease. These trends observed in subjects in the Saxagliptin group were reversed in the Mitiglinid group, but significant changes in parameters such as the serum Fe level were not found (Table 2).

Also, during the observation period, the Mitiglinid group received saccharated ferric oxide more than the Saxagliptin group (188.6 +/− 117.1 mg versus 131.4 +/− 79.04 mg), but there was no significant difference ($p = 0.3056$) (Fig. 5).

No significant changes were found between both groups for the nutrition index-related marker and inflammatory reaction marker (e.g., CRP) (Table 2).

Adverse event

In this study, no patients experienced liver dysfunction. No cases required an increase in Saxagliptin or Mitiglinid dose over the study duration. There were also no recognized cases of hypoglycemia with symptoms or abnormal liver function. There were no patients who stopped medicine. During the study period, neoplasm was reported for one patient in the Saxagliptin group and none in the Mitiglinid group. However, as it was a colorectal cancer detected during the early phase of this study, the relationship with the drug is thought to be low.

Discussion

Patients with type 2 diabetes mellitus and ESRD have limited therapeutic options to manage hyperglycemia [7, 29]. Furthermore, few randomized controlled trials have compared antihyperglycemic agents in these patients [30].

In this study, we demonstrate that Saxagliptin can be used safely in diabetic patients undergoing hemodialysis, but cannot significantly reduce HbA1c and GA levels during a 6-month treatment period. Analysis of this study's results demonstrated that Saxagliptin was not inferior to Mitiglinid in the glycemic control of ESRD patients with type 2 diabetes mellitus.

The usefulness of Mitiglinid in dialysis patients is usually reported as a meglitinide preparation with

Table 2 Effect on renal anemia during study period and changes in nutritional status and CRP

	Saxagliptin			Mitiglinide		
	Pre	Post	*P* value	Pre	Post	*P* value
Hb (g/dL)	10.5 ± 0.8	10.9 ± 0.8	0.1523	10.7 ± 0.9	10.7 ± 0.7	0.9855
DA (μg/w)	22.0 ± 22.6	16.8 ± 22.1	0.2238	15.5 ± 10.7	19.5 ± 11.5	0.1343
Fe (mg/dL)	58.1 ± 21.0	73.9 ± 25.0	0.0085	70.8 ± 34.2	68.5 ± 25.9	0.733
TIBC (mg/dL)	295.8 ± 58.5	296.6 ± 62.1	0.921	285.4 ± 34.7	286.7 ± 50.5	0.8657
TSAT (%)	20.2 ± 7.7	25.9 ± 10.5	0.0148	25.3 ± 12.8	24.5 ± 9.5	0.7349
Ferritin (ng/mL)	58.8 ± 145.0	40.3 ± 37.7	0.5738	33.5 ± 29.7	54.1 ± 99.2	0.3343
DW (kg)	62.4 ± 9.6	62.1 ± 9.9	0.3695	67.7 ± 18.4	68.0 ± 18.6	0.7227
ERI	6.9 ± 7.0	5.6 ± 8.3	0.3769	5.0 ± 4.1	5.8 ± 3.8	0.3522
Alb (g/dL)	3.7 ± 0.3	3.8 ± 0.3	0.2698	3.7 ± 0.3	3.7 ± 0.2	0.5929
TC (mg/dL)	148.9 ± 38.2	148.2 ± 39.7	0.852	148.4 ± 41.2	147.4 ± 41.9	0.8656
HDL-C (mg/dL)	43.4 ± 10.9	46.0 ± 11.2	0.1802	38.8 ± 12.0	39.3 ± 12.7	0.6884
LDL-C (mg/dL)	83.6 ± 26.7	83.1 ± 27.8	0.8805	76.9 ± 24.4	81.8 ± 33.3	0.276
TG (mg/dL)	126.0 ± 85.0	126.6 ± 89.6	0.9351	187.6 ± 178.4	163.2 ± 123.1	0.2044
CRP (mg/dL)	0.16 ± 0.17	0.17 ± 0.18	0.6847	0.20 ± 0.26	0.33 ± 0.31	0.1201

Hb hemoglobin, *DA* darbepoetin alfa, *TIBC* total iron binding capacity, *TSAT* transferrin saturation, *DW* dry weight, *ERI* erythropoietin responsiveness index, *Alb* albumin, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *CRP* C-reactive protein

accommodation to a patient on dialysis, and it has become the drug of choice in glycemic control for patients on dialysis who have few treatment options [31–33]. Saxagliptin, in contrast, has been reported for use in patients with moderate CKD with type 2 diabetes mellitus and ESRD [13, 27, 30]. In particular, the SAVOR-TIMI53 study, which included large-scale clinical trials that followed approximately 16,000 patients for an average of 2.1 years, reported that the safety of Saxagliptin is not significantly different from placebo in chronic kidney disease (CKD) patients not on dialysis [34].

No changes in HbA1c in comparison with GA were found in this study. This may be due to our target population where patients having difficulty in glycemic control and using insulin were excluded from this study, and only patients who could control blood glucose with oral medication only were included. Therefore, the baseline GA and HbA1c values were low, and it seems that there was no difference in value at the end of the study. Based on a report using a different DPP-4 inhibitor, the rate of HbA1c decline may depend on the baseline value [9, 35]. GA is recognized as a more reliable marker than HbA1c for monitoring glycemic control in ESRD patients with diabetes [36, 37]. In this study, there was a significant difference in the regression line gradient in GA but not HbA1c in the Saxagliptin group. Our data also suggest that GA is a better marker for glycemic control in diabetic patients with ESRD compared to HbA1c.

Meglitinides and DPP-4 inhibitors are both medicines classified as insulin secretagogue, but their duration of action is different [29, 38]. Meglitinide is a drug aimed at primarily correcting postprandial hyperglycemia to avoid a delay in insulin secretion and the concomitant protraction of the hyperglycemic state and therefore has a relatively short duration of action [33, 39]. However, DPP-4 inhibitors exert a hypoglycemic effect through incretin effects that lasts for 24 h [23]. This difference in duration of action may explain the difference in glycemic control profile, and the likelihood that GA is decreased more in the Saxagliptin group has been considered.

In this study, increase in serum iron concentrations and transferrin saturation (TSAT) were significant in the Saxagliptin but not the Mitiglinid group. The ferritin was not significantly altered in both group, but a decrease trend was found in the Saxagliptin group, adversely an upward trend was found in the Mitiglinid group. For Hb, no significant alteration was found in both groups, but a decrease in the DA dose and improvement of the ERI was found in the Saxagliptin group. Though there was less consumption of saccharated ferric oxide in the Saxagliptin group, thus, bioavailability of the iron might be improved in the Saxagliptin group. However, it is necessary to measure a more precise ferrokinetic marker such as hepciden 25 or ferroportin [40–44].

DPP-4 inhibits hemopoietic factors such as G-CSF or erythropoietin, and it has been reported that the antagonism is inhibited by a DPP-4 inhibitor [16–18]. Several reports suggest that DPP-4 inhibitors have antiinflammatory effects and can improve bone marrow function [45, 46]. The possibility of scission protection by DPP-4 with anti-inflammatory agents such as BNP/ANP (brain natriuretic peptide/atrial natriuretic peptide) or NPY (neuropeptide), which are substrates of DPP-4, is suggested, and an intracorporeal inflammation condition is therefore thought to be ameliorated by DPP-4 inhibitor [47–50]. This may explain the improved iron bioavailability.

No significant alteration was found in the marker used to indicate inflammatory status in this study during the study period. We used C-reactive protein (CRP), a common laboratory examination item, as the inflammatory associated marker. A difference between both groups might be detected if a high-precision inflammatory marker, such as high-sensitivity CRP or interleukin-6 (IL-6), was used instead. These possibilities need to be addressed in future studies.

Limitations

There are some limitations to this study. First, it was conducted at just two centers; therefore, subject numbers were limited. This trial also did not have a double-blind design, and results might have been biased. While this study was too small to allow robust statistical analysis, it demonstrated obvious contrasts between the two groups in renal anemia and Fe movement parameters at each evaluation.

Conclusions

The present study showed that Saxagliptin was not inferior to Mitiglinid in the glycemic control of ESRD patients with type 2 diabetes mellitus, and it is well tolerated and safe. Furthermore, Saxagliptin may improve iron bioavailability compared to Mitiglinid. However, long-term follow-up in a larger scale study with more precise ferrokinetic markers is necessary to confirm its efficacy and safety.

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Availability of data and materials

Please contact author for data requests.

Authors' contributions

Y Sakai designed and performed the study, analyzed the data, and wrote the paper. SS, KM, AK, Y Sumi, YO, and TO performed the study and acquired the laboratory data with Y Sakai. ST supervised the study. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable

Ethics approval and consent to participate
All patients provided informed consent to participate in the study after the study protocol, and associated risks were explained to each patient individually. The present study protocol was approved by the Ethical Committee of Nippon Medical School Musashikosugi Hospital (246-25-14) and was designed in accordance with the Declaration of Helsinki.

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