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Clinical factors associated with the occurrence of nausea and vomiting in type 2 diabetes patients treated with glucagon-like peptide-1 receptor agonists

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ABSTRACT

Aims/Introduction: Research has proved a correlation between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and gastrointestinal adverse events. Predominantly, nausea and vomiting are frequent gastrointestinal adverse events that lead to the discontinuation of GLP-1 RAs treatment. The present study aims to investigate clinical factors related to nausea and vomiting, considering diabetic complications and agents affecting the gastrointestinal tract, such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), in patients with type 2 diabetes treated with GLP-1 RAs.

Materials and Methods: This retrospective study included Japanese patients with type 2 diabetes who started receiving GLP-1 RAs therapy. We assessed nausea and vomiting up to 48 weeks after treatment with GLP-1 RAs and used Fine–Gray's proportional hazards model to investigate clinical factors related to nausea and vomiting.

Results: A total of 130 patients were included in this study. Patients with PPIs or H2RAs showed a higher incidence of nausea and vomiting at 48 weeks than those without PPIs or H2RAs. The multivariate analysis revealed that female sex, retinopathy and treatment with PPIs or H2RAs were statistically significant risk factors for nausea and vomiting. Analysis of patients without PPIs or H2RAs showed that female sex and retinopathy were also statistically significant risk factors.

Conclusions: The present study showed a significant correlation of PPIs or H2RAs, female sex, and diabetic retinopathy with nausea and vomiting in patients with type 2 diabetes treated with GLP-1 RAs. Hence, the occurrence of nausea and vomiting in patients with these factors warrants attention.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve glycemic control because of their ability to promote insulin secretion in a glucose concentration-dependent manner and inhibit glucagon secretion without the risk of hypoglycemia[1,2]. In addition, they show diverse physiological effects, including weight loss by a decrease in appetite and suppression of cardiovascular events[2–7]. Research has established the safety and efficacy of GLP-1 RAs, and they are widely used for the treatment of type 2 diabetes in the clinical practice[8].

The major adverse events (AEs) of GLP-1 RAs are gastrointestinal (GI) disorders, including nausea, vomiting and diarrhea, which are perhaps caused by the delay of gastric emptying because of GI motility suppression or centrally mediated effects[1,9,10]. GI AEs caused by GLP-1 RAs occur in a dose-dependent manner; however, they are alleviated by treatment with lower doses of GLP-1 RAs and gradually increasing the doses[11–13]. Furthermore, other studies have reported that GI AEs depend on short- or long-acting characteristics of GLP-1 RAs[13–15], implying that GI AEs are associated with delayed gastric emptying in the short-acting GLP-1 RAs[1]. However, some patients experience GI AEs despite a gradual increase in the

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dose and being administered the long-acting GLP-1 RAs. As factors focused on patients' clinical background, GI AEs are known to be positively associated with age, renal function and background of glucose-lowering medication[13,16–19]. Although the studies discussed above have shown the importance of identifying the risk factors for GI AEs, agents affecting GI tracts, including proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), have not been considered. In addition, whether diabetic complications, which are characteristic of diabetes, could predict the risk factor for GI AEs remains unclear. Among GI AEs, nausea and vomiting (nausea/vomiting) have been recognized as frequent AEs that lead to the discontinuation of GLP-1 RAs treatment[20,21]. Hence, exploring factors that can predict the occurrence of nausea/vomiting is imperative. The present study aims to determine the risk factors for nausea/vomiting, considering diabetic complications and agents affecting the GI tract in patients with type 2 diabetes treated with GLP-1 RAs.

METHODS

Study design and participants

The present retrospective study included Japanese patients with type 2 diabetes who started receiving GLP-1 RAs therapy (e.g., liraglutide or lixisenatide) at Kitasato University Medical Center (Kitamoto, Japan) between November 2010 and July 2017. First, liraglutide was administered at a dose of 0.3 mg once daily for 1 week or longer, followed by an increment in the dose to 0.6 mg once daily for 1 week or longer and, finally, to 0.9 mg once daily depending on patients' conditions, which is the maximum dose approved in Japan. Then, lixisenatide was administered at a dose of 10 μg once daily for 1 week or longer, followed by the dose increment to 15 μg once daily for 1 week or longer and, finally, 20 μg once daily depending on patients' conditions. Oral hypoglycemic agents, except dipeptidyl peptidase-4 inhibitors, and insulin therapy were continued after administering GLP-1 RAs. Patients who discontinued GLP-1 RAs therapy for reasons other than nausea/vomiting without increasing the dose, as it is proved to be GI AEs of GLP-1 RAs that occurs in a dose-independent manner[11–13], were excluded from the study. Other exclusion criteria of the study were as follows: (i) administration of other GLP-1 RAs before starting liraglutide or lixisenatide; (ii) use of anti-emetics; (iii) showing poor drug compliance based on regular prescribing from their medical records; and (iv) the presence of malignancy. The investigation lasted up to 48 weeks after GLP-1 RAs treatment. This study was approved by the ethics committee of Kitasato University Medical Center, and was carried out in accordance with the principles of the Declaration of Helsinki.

Parameters evaluated

We collected the patients' baseline characteristics using medical records, including sex, age, duration of diabetes, body mass index, glycated hemoglobin, systolic and diastolic blood pressure, aspartate aminotransferase, alanine aminotransferase, estimated glomerular filtration rate (eGFR), creatinine clearance, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, diabetes complications (such as retinopathy and nephropathy), and the use of oral hypoglycemic agents, insulin and agents affecting the GI tract. The development of nausea/vomiting was extracted from the medical records, which were confirmed on examination. In addition, the glycated hemoglobin values were recorded as National Glycohemoglobin Standardization Program values; if recorded as the Japan Diabetes Society values, they were converted into National Glycohemoglobin Standardization Program values[22]. While eGFR was calculated using the Japan Nephrology Society equation[23], creatinine clearance was estimated using the Cockcroft–Gault equation[24]. We defined diabetic retinopathy as simple retinopathy or more, and the presence and severity of diabetic retinopathy were determined by a qualified ophthalmologist. Diabetic nephropathy was defined as the urine albumin : creatinine ratio ≥30 mg/g creatinine and/or eGFR <30 mL/min/1.73 m^2[25].

Statistical analysis

In the present study, data are expressed as the mean ± standard deviation, median and interquartile range (IQR) or numbers and percentages. We compared the difference between the two groups using the Student's *t*-test or the Mann–Whitney *U*-test for continuous variables. Categorical variables were compared using the Fisher's exact test. The cumulative incidence of nausea/vomiting was estimated using the Fine–Gray method[26], and compared using the Gray's test. In addition, any discontinuation of GLP-1 RAs was considered a competing risk in the analysis. Univariate analysis was carried out using the Fine–Gray's proportional hazards model to determine the predictor of nausea/vomiting. Using univariate analysis, we determined factors with $P < 0.10$ to be potential risk factors for nausea/vomiting and further investigated these factors using multivariate analysis. If the factors determined by univariate analysis were continuous variables, multivariate analysis was carried out after obtaining the cut-off values using the receiver operating characteristic curve analysis to evaluate the performance of the prognostic parameters predicting nausea/vomiting. Pearson's correlation coefficient was used to measure collinearity. Statistical analyses were carried out using the R software (version 3.4.1; The R Foundation for Statistical Computing, Vienna, Austria)[27]. We considered $P < 0.05$ to be statistically significant.

RESULTS

During the study period, liraglutide and lixisenatide therapy was given to 181 patients. We excluded nine patients who discontinued GLP-1 RAs for reasons other than nausea/vomiting without increasing its dose, 13 patients who were administered GLP-1 RAs other than liraglutide or lixisenatide in the beginning, one patient who used an anti-emetic, six patients who

showed poor drug compliance and one patient with malignancy. In addition, 21 patients were excluded because of incomplete data. In total, 130 patients, who were administered liraglutide and lixisenatide, were included in the present study. The median follow-up period was 48 weeks (IQR 20–48 weeks). Table 1 presents the demographic and clinical characteristics of 130 patients at the baseline. The mean age of the study population was 56.8 ± 13.3 years, and the mean duration of diabetes was 12.2 ± 9.6 years. Diabetic retinopathy and nephropathy were 37.7 and 41.5%, respectively. During the previous antidiabetic treatment, metformin was the most frequently used drug (41.5%), and its median dose was 875 mg (IQR 750–1,500 mg). In the present study, 14.6% of all the patients were treated with PPIs or H2RAs as agents affecting the GI tract. The therapeutic targets with PPIs or H2RAs in this study were gastroesophageal reflux disease (GERD), nonsteroidal anti-inflammatory drugs (NSAIDs)-induced gastropathy and gastric ulcer (GU). Before receiving GLP-1 RAs treatment, symptoms of nausea/vomiting were controlled by PPIs or H2RAs. The median doses of liraglutide and lixisenatide at the occurrence of nausea/vomiting were 0.6 mg (IQR 0.3–0.6 mg) and 10 μg (IQR 10–15 μg), respectively. At the last follow up, the median doses of liraglutide and lixisenatide were 0.9 mg (IQR 0.75–0.9 mg) and 15 μg (IQR 15–20 μg), respectively. Table 1 also shows the demographic and clinical characteristics of patients in their respective groups (with and without nausea/vomiting). Furthermore, 34.6% of all patients experienced nausea/vomiting during the follow-up period. Patients with nausea/vomiting comprised a significantly high number of women ($P = 0.026$) and had a higher occurrence of diabetic retinopathy ($P = 0.013$) than those without nausea/vomiting.

Figure 1 shows the results of the cumulative incidence of nausea/vomiting in the present study using the Fine–Gray method[26], accounting for the competing risk of any discontinuation of GLP-1 RAs. During the 48-week follow-up period, the

Table 1 | Baseline demographic and clinical characteristics of the patients

	Total	Nausea and vomiting (–)	Nausea and vomiting (+)	*P*-value
n (Liraglutide/lixisenatide)	130 (83 / 47)	85 (59 / 26)	45 (24 / 21)	
Sex (% male)	45.4	52.9	31.1	0.026
Age (years)	56.8 ± 13.3	56.3 ± 13.7	57.8 ± 12.6	0.529
Duration of diabetes (years)	12.2 ± 9.6	11.5 ± 9.3	13.4 ± 10.1	0.309
BMI (kg/m^2)	27.5 (24.6–32.2)	27.8 (25.4–32.3)	25.9 (24.1–31.1)	0.292
HbA1c (%)	9.0 ± 1.7	9.0 ± 1.7	8.9 ± 1.8	0.673
SBP (mmHg)	133.9 ± 18.8	133.8 ± 17.4	134.2 ± 21.2	0.899
DBP (mmHg)	75.4 ± 13.5	75.2 ± 13.5	75.8 ± 13.6	0.796
AST (U/L)	22 (17–31)	21 (17–29)	23 (17–32)	0.448
ALT (U/L)	24 (17–39)	24 (17–39)	24 (20–37)	0.609
eGFR (mL/min/1.73 m^2)	75.1 ± 20.5	77.0 ± 19.5	71.5 ± 22	0.146
CrCl (mL/min)	110.7 ± 54.0	116.2 ± 55.6	100.3 ± 49.8	0.140
HDL cholesterol (mmol/L)	50.8 ± 11.1	50.1 ± 10.8	52.1 ± 11.7	0.350
LDL cholesterol (mmol/L)	115.2 ± 31.6	118.4 ± 31.5	109.1 ± 31.1	0.111
TG (mmol/L)	145 (99–227)	146 (99–228)	144 (102–214)	0.619
Diabetes complications (%)				
Retinopathy	37.7	29.4	53.3	0.013
Nephropathy	41.5	37.6	48.9	0.160
Previous antidiabetic treatment (%)				
Diet only	14.6	17.6	8.9	0.204
Sulfonylureas	39.2	40.0	37.8	0.852
Metformin	41.5	41.2	42.2	1
Glinides	6.2	5.9	6.7	1
α-Glycosidase inhibitors	15.4	14.1	17.8	0.615
Pioglitazone	8.5	10.6	4.4	0.328
DPP-4 inhibitors	27.7	24.7	33.3	0.310
Insulin	29.2	30.6	26.7	0.690
Treatment with PPIs or H2RAs (%)	14.6	10.6	22.2	0.115

Data are expressed as the mean ± standard deviation, median and interquartile range or numbers and percentages. The statistical significance was estimated using Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, and Fisher's exact test for categorical variables. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CrCl, creatinine clearance; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; H2RAs, histamine-2 receptor antagonists; LDL, low-density lipoprotein; PPIs, proton pump inhibitors; SBP, systolic blood pressure; TG, triglyceride.

total cumulative incidence was 35.8%. More than 90% of patients developed nausea/vomiting by 8 weeks after the initiation of GLP-1 RAs (Figure 1a). Analysis of with or without treatment with PPIs or H2RAs showed a higher incidence rate of nausea/vomiting among patients with PPIs or H2RAs than in those without PPIs or H2RAs, the cumulative incidence rate of nausea/vomiting of 52.6% at 48 weeks in patients with PPIs or H2RAs, and 32.9% in patients without PPIs or H2RAs (Gray's test, $P = 0.06$; Figure 1b). Table 2 shows the results of univariate analysis using the Fine–Gray models. Nausea/vomiting was associated with sex (women hazard ratio [HR] 1.95, 95% confidence interval [CI] 1.10–3.45; $P = 0.023$), retinopathy (HR 1.99, 95% CI: 1.18–3.35; $P = 0.009$) and treatment with PPIs or H2RAs (HR 1.78, 95% CI: 0.99–3.21; $P = 0.053$). In multivariate analysis, the risks of nausea/vomiting included sex (women HR, 2.08, 95% CI: 1.18–3.65; $P = 0.011$), retinopathy (HR 1.89, 95% CI: 1.13–3.15; $P = 0.016$) and treatment with PPIs or H2RAs (HR 2.05, 95% CI: 1.12–3.74; $P = 0.020$). We observed no significant differences in the incidence of nausea/vomiting in the previous antidiabetic treatment. In addition, no significant differences were noted in antidiabetic treatment 8 weeks after the initiation of GLP-1 RAs. We carried out the subgroup analysis to assess the incidence of nausea/vomiting using the Fine–Gray models by assigning patients to either of the two groups: patients treated with liraglutide and lixisenatide. In patients treated with liraglutide, sex, diabetic nephropathy and retinopathy were the determining factors ($P < 0.10$; Table S1). The treatment with PPIs or H2RAs was more likely to increase the risk of nausea/vomiting (without nausea/vomiting 11.9%, with nausea/vomiting 20.8%; HR 1.56, 95% CI:

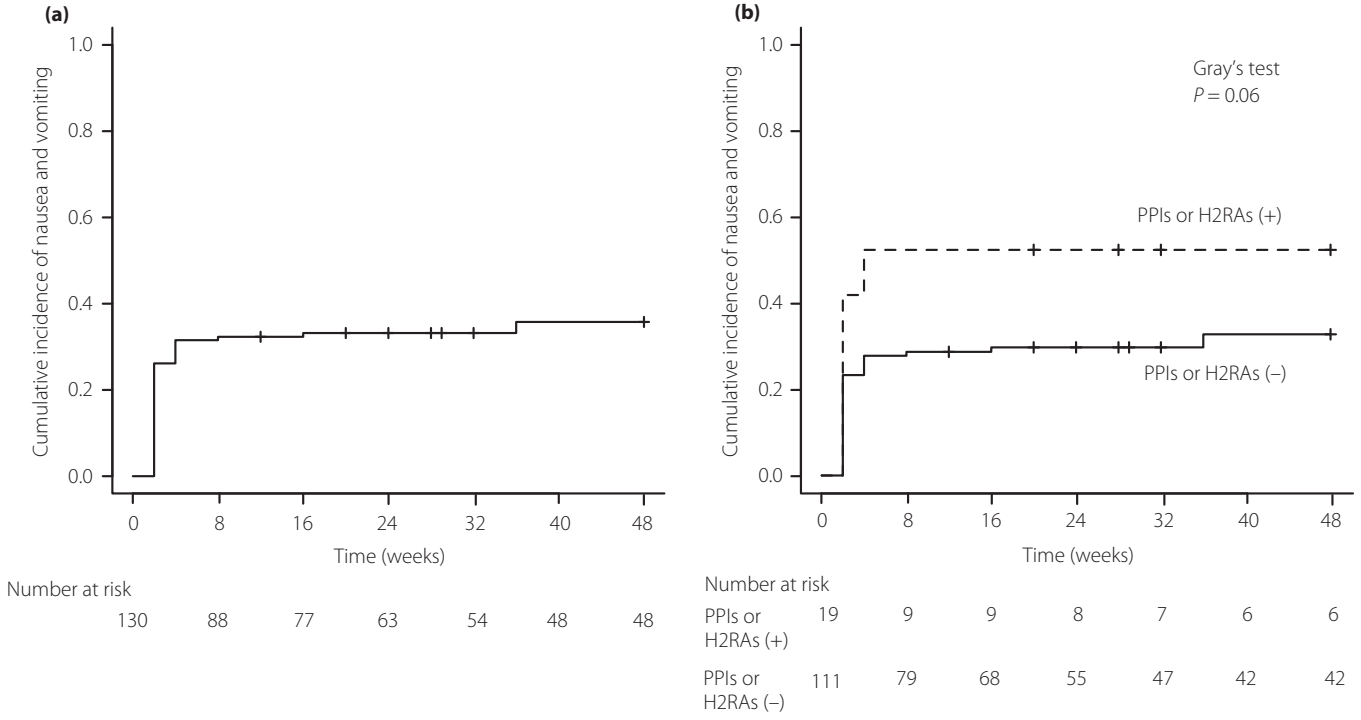

Figure 1 | Cumulative incidence of nausea/vomiting caused by glucagon-like peptide-1 receptor agonists in type 2 diabetes patients. (a) Total (b) with or without treatment with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs), PPIs or H2RAs (+), PPIs or H2RAs (–). Cumulative incidence of nausea/vomiting was determined using the Fine–Gray method. The *P*-value was determined using Gray's test.

Table 2 | Risk factors for nausea and vomiting as assessed by Fine–Gray's proportional hazards model

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Sex (female)	1.95	1.10–3.45	0.023	2.08	1.18–3.65	0.011
Diabetic retinopathy	1.99	1.18–3.35	0.009	1.89	1.13–3.15	0.016
Treatment with PPIs or H2RAs	1.78	0.99–3.21	0.053	2.05	1.12–3.74	0.020

CI, confidence interval; HR, hazard ratio; H2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

0.68–3.57), although it was not a potential risk factor ($P < 0.10$). In patients treated with lixisenatide, the treatment with PPIs or H2RAs was the determining factor ($P < 0.10$; Table S2). Sex and diabetic retinopathy were more likely to increase the risk of nausea/vomiting (women without nausea/vomiting 50%; women with nausea/vomiting 61.9%, HR 1.31, 95% CI: 0.60–2.88; retinopathy without nausea/vomiting 42.3%, retinopathy with nausea/vomiting 61.9%, HR 1.71, 95% CI: 0.77–3.80), although these were not potential risk factors ($P < 0.10$). Of note, we did not carry out the multivariate analysis because of the limited number of participants in the present study[28].

Table 3 shows the results of univariate analysis using the Fine–Gray models for patients without treatment with PPIs or H2RAs. Nausea/vomiting was associated with sex (women HR 2.63, 95% CI: 1.26–5.51; $P = 0.01$), eGFR (HR 0.98, 95% CI: 0.97–0.99; $P = 0.005$) and retinopathy (HR 2.13, 95% CI: 1.17–3.89; $P = 0.014$). In multivariate analysis, the risks of nausea/vomiting included sex (women HR 2.49, 95% CI: 1.20–5.18; $P = 0.015$) and retinopathy (HR 2.00, 95% CI: 1.11–3.63; $P = 0.022$; Table 3). In the subgroup analysis, systolic blood pressure, high-density lipoprotein cholesterol, sex and diabetic retinopathy were the determining factors ($P < 0.10$) in patients treated with liraglutide (Table S3). In patients treated with lixisenatide, eGFR was a determining factor ($P < 0.10$; Table S4). Both sex and diabetic retinopathy were more likely to increase the risk for nausea/vomiting (women without nausea/vomiting 48.0%, women with nausea/vomiting 73.3%, HR 2.12, 95% CI: 0.72–6.23; retinopathy without nausea/vomiting 40.0%, retinopathy with nausea/vomiting 66.7%, HR 2.31; 95% CI: 0.83–6.39), although these were not potential risk factors ($P < 0.10$). The multivariate analysis was not carried out because of the limited number of participants in the present study[28]. Figure 2 shows the cumulative incidence of nausea/vomiting in sex and retinopathy (women and retinopathy 61.0%, women and no retinopathy 32.9%, men and retinopathy 25.0%) using the Fine–Gray method[26], accounting for the competing risk of any discontinuation of GLP-1 RAs. We observed a significantly higher incidence of nausea/vomiting among patients with female sex and retinopathy than those with other factors (Gray's test, $P = 0.004$).

DISCUSSION

The present study suggests that treatment with PPIs or H2RAs, female sex and diabetic retinopathy are risk factors for nausea/vomiting in patients with type 2 diabetes treated with GLP-1 RAs. In addition, female sex and diabetic retinopathy are recognized as risk factors in patients not treated with PPIs or H2RAs. To the best of our knowledge, this is the first study to investigate the risk factors for nausea/vomiting considering

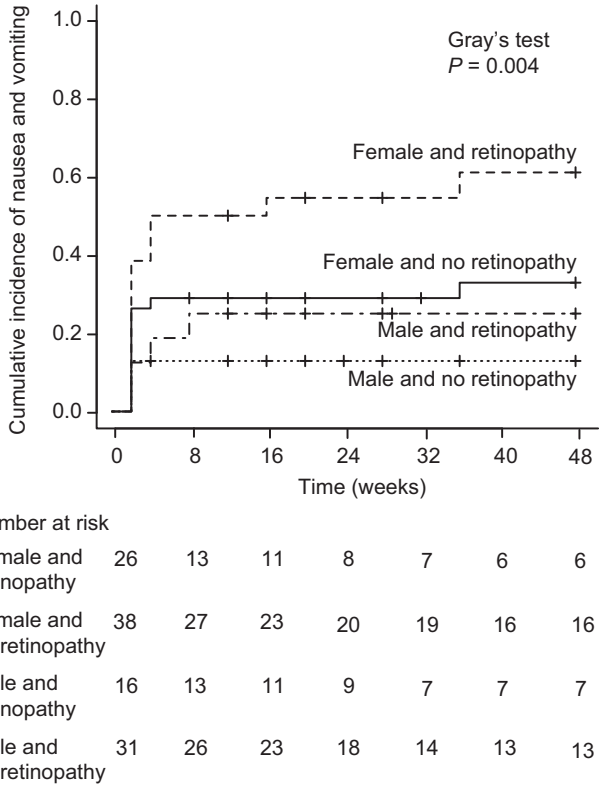

Figure 2 | Cumulative incidence of nausea/vomiting caused by glucagon-like peptide-1 receptor agonists by sex and retinopathy in type 2 diabetes patients without proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) treatment. The cumulative incidence of nausea/vomiting was determined using the Fine–Gray method. The *P*-value was determined using Gray's test.

Table 3 | Receiver operating characteristic curve analysis and risk factors for nausea and vomiting in patients without treatment with proton pump inhibitors or histamine-2 receptor antagonists as assessed by Fine–Gray's proportional hazards model

	Univariate			ROC			Multivariate		
	HR	95% CI	*P*-value	Cut-off value	AUC	95% CI	HR	95% CI	*P*-value
Sex (female)	2.63	1.26–5.51	0.010				2.49	1.20–5.18	0.015
eGFR (mL/min/1.73 m^2)	0.98	0.97–0.99	0.005	75.3	0.614	0.50–0.72	0.77	0.42–1.44	0.420
Diabetic retinopathy	2.13	1.17–3.89	0.014				2.00	1.11–3.63	0.022

AUC, area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; H2RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors; ROC, receiver operating characteristic.

diabetic complications and agents affecting the GI tract in patients with type 2 diabetes treated with GLP-1 RAs.

Nausea/vomiting are major symptoms of GERD, NSAIDs-induced gastropathy and GU, which were the therapeutic targets of PPIs or H2RAs in the present study. GERD is attributed to various conditions, including lower esophageal pressure caused by lower esophageal sphincter relaxation, increased intragastric pressure and increased gastric acid production[29], and is also one of the AEs of GLP-1 RAs. As GLP-1 RAs primarily inhibit gastric peristalsis through the vagal reflex[30], it is hypothesized that the gastric peristalsis-suppressing effect caused elevated intragastric pressure, potentiating GERD symptoms. Because NSAIDs and GU cause delayed gastric emptying action[31–34], the gastric emptying rate of patients treated with NSAIDs and those with GU might be delayed by GLP-1 RAs. Regarding the correlation between PPIs and GLP-1, some studies have reported that the elevation of serum gastrin levels by PPIs stimulates the GLP-1 secretion[35,36]. However, whether indirect GLP-1 secretion by PPIs affects the development of nausea/vomiting remains unclear. Therefore, symptoms and actions of GERD, NSAIDs and GU, which are therapeutic targets of PPIs or H2RAs, could have been exacerbated by the treatment of GLP-1 RAs. In the present study, although few patients were endoscopically examined before initiating GLP-1 RAs, we could not confirm the relationship between GI AEs after initiating GLP-1 RAs and GERD or GU severity. Further studies are thus required for clarifying these relationships.

Metformin causes GI AEs. Nausea, vomiting and diarrhea caused by GLP-1 RAs have been observed in background treatment with metformin[13]. However, no other study has reported any association between metformin and GI AEs[37]. Thong *et al.*[16] have highlighted that non-metformin use is associated with more significant GI AEs, leading to the discontinuation of liraglutide treatment. In the present study, metformin used before and after the initiation of GLP-1 RAs was not a risk factor for nausea/vomiting caused by GLP-1 RAs. Metformin has been reported to result in GI AEs in a dose-dependent manner[38], but previous studies did not provide details about the dose. However, as patients in the present study used a small dose of metformin, its association with nausea/vomiting was not apparent. In our study, although two patients added metformin after the initiation of GLP-1 RAs, we did not consider the duration of all metformin use. Furthermore, as it was used only for patients who could tolerate metformin, it might not have been associated with the development of nausea/vomiting.

A previous study has suggested that GI AEs are positively associated with age[16]. That study reported that eGFR was highly collinear with age, and that it did not achieve significance in multivariate models. However, other studies have reported that GI AEs are positively associated with renal function[18,19,39]. Idorn *et al.*[18] showed that nausea/vomiting occurred in the liraglutide-treated group with end-stage renal disease. Hanefeld *et al.*[19] reported that in patients receiving lixisenatide, those with mild renal impairment (eGFR = 60–89 mL/min) were at an increased risk of experiencing any GI AEs compared with patients with normal renal function (eGFR ≥90 mL/min). In addition, Davidson *et al.*[39] observed an increasing trend of nausea among patients with moderate or severe renal impairment (creatinine clearance <60 mL/min) receiving liraglutide. In the present study, we did not confirm collinearity in eGFR and age, and approximately 80% patients showed normal renal function or mild renal impairment. Hence, age and renal function were not related to nausea/vomiting. However, eGFR was significantly associated with nausea/vomiting in univariate analysis. As GLP-1 RAs show different eliminations depending on their type, the influence of renal impairment also varies. Liraglutide is catabolized in a manner similar to that of large proteins, without a specific organ as the primary route of elimination. Conversely, lixisenatide is eliminated through glomerular filtration with subsequent proteolytic degradation, resulting in smaller peptides and amino acids reintroduced into protein metabolism. In patients receiving liraglutide, it has been reported that renal impairment has not been found to increase the exposure of liraglutide[40]. However, another study has reported that the plasma liraglutide concentration increased in patients with type 2 diabetes and end-stage renal disease[18]. In patients receiving lixisenatide, a significant increase has been reported in the area under the plasma concentration–time curve of lixisenatide in type 2 diabetes patients with severe renal impairment[17]. Although a causal relationship between GI AEs and GLP-1 RAs has not been shown, advanced renal dysfunction might be associated with the occurrence of GI AEs because of the elevated blood concentration, necessitating further investigation by considering the type of GLP-1 RAs.

The present study shows that female sex was a risk factor for nausea/vomiting in patients with type 2 diabetes treated with GLP-1 RAs. A post-hoc analysis of GLP-1 RAs showed that upper GI AEs were more frequent in women than in men[37]. Regarding GI disorders, a study has reported a higher prevalence of GI symptoms among women than men, regardless of diabetes[41]. In addition, female patients with non-insulin-dependent diabetes have been reported to show a higher prevalence of GI symptoms, especially nausea, than men[42]. Furthermore, studies have recognized female sex as a risk factor for postoperative and chemotherapy-induced nausea/vomiting in fields other than diabetes[43–47]. Although the underlying reason for female sex being a risk factor for nausea/vomiting is unclear, female sex might be a risk factor for nausea/vomiting caused by GLP-1 RAs, and it is considered to be necessary when starting therapy with GLP-1 RAs.

Furthermore, the present study highlighted diabetic retinopathy as a risk factor. Reportedly, nausea and vomiting, diabetic GI motility disorders, are caused by autonomic neuropathy[48], and autonomic neuropathy has been associated with delayed gastric emptying in diabetic patients[49–53]. Diabetic neuropathy is associated with diabetic retinopathy and nephropathy[54–56]. In retinopathy, it is reported that the prevalence of neuropathy increases with the severity of retinopathy[57], and that patients

with neuropathy with impaired glucose tolerance and impaired fasting glycemia are twofold more likely to have albuminuria, and fourfold more likely to have retinopathy[58]. A recent study has shown that diabetic retinopathy is a risk factor for constipation, which is a diabetic GI disorder in patients with diabetes[59]. Hence, diabetes patients with retinopathy also have neuropathy; both neuropathy and GLP-1RAs could enhance delayed gastric emptying and might have been related to the development of nausea/vomiting. However, the relationship between diabetic retinopathy and nausea/vomiting remains unclear. In the present study, diabetes patients with retinopathy were at significantly higher risk for nausea/vomiting caused by GLP-1 RAs. Based on these findings and previous studies, diabetes patients with retinopathy might be at a higher risk of nausea/vomiting caused by GLP-1 RAs through diabetic neuropathy.

The incidence of nausea/vomiting in the present study was consistent with some previous studies of Japanese patients treated with lixisenatide[60–62]. However, in patients treated with liraglutide, the present study showed a high incidence of nausea/vomiting compared with previous studies in which the occurrence of GI AEs was reported to be 44–60%, of which nausea occurred in 5–14%[63–66]. In addition, symptoms of nausea/vomiting were confirmed by an individual physician's method. Therefore, patients might have complained about upper gastrointestinal AEs, including heartburn, dyspepsia and stomach discomfort as nausea.

Regrettably, our subgroup analysis could not determine risk factors in patients treated with liraglutide and lixisenatide; however, it showed a tendency for female sex and diabetic retinopathy to be risk factors in patients treated with liraglutide, and treatment with PPIs or H2RAs is a risk factor, as well as GLP-1RAs, in patients treated with lixisenatide. Perhaps, by increasing the sample size, the risk factors for liraglutide and lixisenatide could be determined.

The present study had several limitations. First, we did not evaluate diabetic polyneuropathy, especially autonomic neuropathy by the heart rate variability. There are no symptoms or tests specific to diabetic polyneuropathy, and no diagnostic criteria have been established for obtaining international consensus. Definitions of minimal criteria for typical diabetic polyneuropathy proposed by the Toronto Diabetic Neuropathy Expert Group have high relevance and can be used in daily clinical practice[67]; however, in the present study, only the presence of symptoms or signs of diabetic polyneuropathy, only ankle reflexes, only nerve conduction or their combination existed. Hence, we could not confirm diabetic polyneuropathy. However, considering the result of the present study, the application of the assessment according to certain criteria of diabetic polyneuropathy would be beneficial to ensure risk factors for nausea/vomiting in patients with type 2 diabetes treated with GLP-1 RAs. Second, the present study was retrospective. Accordingly, nausea and vomiting were confirmed by individual physicians' methods at the time of examination without specific criteria for appropriate assessment. Perhaps this limitation might have introduced some bias, and thus a prospective study with predefined criteria of nausea/vomiting is warranted. Finally, the present study comprised a limited sample size. Accordingly, an extensive prospective study with a larger sample size is required to confirm the present results.

In conclusion, the present study highlights that agents affecting the GI tract, such as PPIs or H2RAs, are risk factors for nausea/vomiting in patients with type 2 diabetes treated with GLP-1 RAs. Furthermore, we determined that female sex and diabetic retinopathy are risk factors for nausea/vomiting in patients with type 2 diabetes treated with GLP-1 RAs regardless of treatment with PPIs or H2RAs. Nevertheless, further extensive research is required; it is necessary to pay attention to the occurrence of nausea/vomiting when receiving GLP-1 RAs for patients with these factors. The results of the present study are expected to be helpful to clinicians administering GLP-1 RAs.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Risk factors for nausea and vomiting in patients treated with liraglutide as assessed by the Fine–Gray's proportional hazards model.
Table S2 | Risk factors for nausea and vomiting in patients treated with lixisenatide as assessed by the Fine–Gray's proportional hazards model.
Table S3 | Risk factors for nausea and vomiting in patients treated with liraglutide and without treatment with proton pump inhibitors or histamine-2 receptor antagonists as assessed by the Fine–Gray's proportional hazards model.
Table S4 | Risk factors for nausea and vomiting in patients treated with lixisenatide and without treatment with proton pump inhibitors or histamine-2 receptor antagonists as assessed by the Fine–Gray's proportional hazards model.