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ORIGINAL RESEARCH

Relationship of Eating Patterns and Metabolic Parameters, and Teneligliptin Treatment: Interim Results from Post-marketing Surveillance in Japanese Type 2 Diabetes Patients

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ABSTRACT

Introduction: Healthy eating is a critical aspect of the prevention and management of type 2 diabetes (T2DM). Disrupted eating patterns can result in poor glucose control and increase the likelihood of diabetic complications.

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Teneligliptin inhibits dipeptidyl peptidase-4 activity for 24 h and suppresses postprandial hyperglycemia after all three daily meals. This interim analysis of data from the large-scale post-marketing surveillance of teneligliptin (RUBY) in Japan examined eating patterns and their relationship with metabolic parameters and diabetic complications. We also examined whether eating patterns affected safety and efficacy of teneligliptin.

Methods: We analyzed baseline data from survey forms collected in RUBY between May 2013 and June 2017, including patient characteristics, metabolic parameters, and eating patterns (eating three meals per day or not; timing of evening meal) before teneligliptin treatment was initiated. Safety and efficacy of 12 months' teneligliptin (20–40 mg/day) treatment was assessed.

Results: Data from 10,532 patients were available for analysis. Most patients who did not eat three meals per day (n =757) or who ate their evening meal after 10 PM (n =206) were 64 years old or younger. At baseline, glycated hemoglobin (HbA1c), fasting blood glucose, triglycerides, total and low-density lipoprotein cholesterol, body mass index, alanine aminotransferase, and aspartate aminotransferase levels were higher in those patients who did not eat three meals per day ($p < 0.05$) or who ate their evening meal late ($p < 0.05$). Diabetic complications were more common in patients who did not eat three meals per day. Treatment with teneligliptin reduced

HbA1c over 6 or 12 months across all eating patterns, with a low incidence of adverse drug reactions.

Conclusions: Eating patterns may be associated with altered metabolic parameters and diabetic complications among Japanese patients with T2DM. Teneligliptin may be well tolerated and improve hyperglycemia in patients with T2DM irrespective of eating patterns.

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Keywords: Dipeptidyl peptidase-4 inhibitor; Eating pattern; HbA1c; Post-marketing surveillance; Teneligliptin; Type 2 diabetes

INTRODUCTION

Chronic hyperglycemia with type 2 diabetes mellitus (T2DM) is associated with an increased risk of microvascular and macrovascular complications, including myocardial infarction, heart failure, or stroke [1]. The prevalence of diabetes, and in particular T2DM, is predicted to increase substantially in coming decades, in line with aging populations [2, 3], increased urbanization [2, 3], reduced physical activity [2], and a change in dietary constituents [2]. A report from the National Health and Nutrition survey in Japan in 2016 estimated that there were 10 million people in whom T2DM was strongly suspected based on reporting a glycated hemoglobin (HbA1c) level of $\geq$ 6.5% or being treated for diabetes [4].

Self-care plays an important role in the management of diabetes and its associated complications. In common with various metabolic-related diseases, including obesity [5–7] and non-alcoholic fatty liver disease [8–10], international and national guidance advocates lifestyle management (including healthy eating and physical activity) for the prevention and/or treatment of T2DM [11–13].

Disrupted eating patterns such as fluctuations in the timing of meals (e.g., breakfast skipping, overeating in the evening, or eating the evening meal late) can negatively influence outcomes in patients with diabetes, resulting in

poorer glucose control and a greater likelihood of diabetic complications [14–18]. It is known that β-cell dysfunction greatly contributes to the Japanese T2DM than the Caucasian [19]. There are few reports on large-scale studies on the relationship between eating pattern and glycaemic control in Japanese T2DM patients. In addition, few studies have examined the safety and efficacy of DPP-4 inhibitors due to differences in eating pattern.

Teneligliptin is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor that has been prescribed in Japan for the treatment of T2DM since 2012, and in South Korea since 2015. The safety and efficacy of teneligliptin, both as monotherapy and in combination with other antidiabetic agents, has been demonstrated in Japanese patients with T2DM in several clinical studies for up to 52 weeks [20–26]. Teneligliptin was also reported to provide 24-h DPP-4 inhibition and suppression of postprandial hyperglycemia after each of three meals in a day [20]. RUBY [exploRing the long-term efficacy and safety-included cardiovascUlar events in patients with type 2 diaBetes treated bY teneligliptin in the real-world (JapicCTI-153047)] is an ongoing post-marketing surveillance program that aims to verify the long-term safety and efficacy of teneligliptin in > 10,000 Japanese patients with T2DM [27]. In this surveillance, eating patterns were also recorded to evaluate the impact of teneligliptin on glycemic control in patients according to eating pattern.

The current interim analysis of data from patients registered for the RUBY post-marketing surveillance program examined the relationship between eating patterns and baseline metabolic parameters or diabetic complications. We also examined the safety and efficacy of teneligliptin in patients with T2DM with different eating patterns.

METHODS

RUBY Design: Patients and Procedure

Japanese patients with T2DM, who were initiating treatment with teneligliptin for the first time—prescribed at the discretion of the

treating physician—and who could be observed over the long term, were eligible for participation in the RUBY post-marketing surveillance program [27]. Patients were enrolled between May 2013 and February 2015, and each patient was observed for up to 3 years. Patients were enrolled via a central registration system. An online electronic data capture system was used to gather data from registration and survey forms. This paper reports the results of an interim analysis of survey forms collected between May 2013 and June 2017. The protocol of RUBY surveillance was approved by the Ministry of Health, Labour and Welfare of the Japan Government. The program is ongoing and is carried out by the Mitsubishi Tanabe Pharma Corporation, in accordance with the Japanese Ministry directive on Good Post-marketing Study Practice Guidelines; in compliance with Japanese regulations for post-marketing surveillance, it was not necessary to obtain informed consent from patients. All analyses in the present surveillance were performed on a fully anonymized dataset.

Prescribing physicians recorded the patients' demographics and baseline characteristics, including gender, age, duration of diabetes, medical history, and diabetic and other complications (such as renal disease, hepatic disease, and heart disease), before treatment with teneligliptin was initiated. Moreover, the physicians recorded information regarding the patients' eating patterns and lifestyle interventions at baseline. The questions posed to the patients included: "Do you eat three meals per day?" (answer: yes, no, or unknown; answer "no" if the patient skips meals or frequently snacks between meals) and "What is your normal time for dinner?" (answer: before 6 PM, 6–8 PM, 8–10 PM, after 10 PM, or unknown).

Patients were administered teneligliptin in-line with prescribing information, which indicates a usual adult dosage of 20 mg administered orally once daily [28]. If efficacy was considered insufficient, the dose of teneligliptin could be increased up to 40 mg once daily, while closely monitoring the clinical course [28]. Concurrent medications were administered at the discretion of the physician according to relevant treatment guidelines. Physicians completed survey forms at regular intervals following initiation of treatment with teneligliptin for up to 3 years for all enrolled patients. Information including concurrent medications, HbA1c, fasting blood glucose, triglycerides, low-density lipoprotein cholesterol (LDL-cholesterol), high-density lipoprotein cholesterol (HDL-cholesterol), total cholesterol, body mass index (BMI), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) was recorded. The frequency and severity of adverse drug reactions (ADRs; Medical Dictionary for Regulatory Activities/J v.20.0) were recorded. An ADR was defined as an adverse event with a possible causal relationship to teneligliptin, or an unknown relationship. ADRs considered to be of special interest included: hypoglycemia-related ADR (severe hypoglycemia was defined as blood glucose ≤ 50 mg/dL or as judged by the physician), skin and subcutaneous tissue disorders, gastrointestinal disorders (including pancreatitis and intestinal obstruction), hepatic impairment, and renal impairment.

Interim Analysis

An interim analysis of survey forms collected between May 2013 and June 2017 examined the relationship between eating patterns (whether the patient ate three meals per day and timing of evening meal) and baseline metabolic parameters or the prevalence of diabetic complications (diabetic retinopathy, nephropathy, and neuropathy). The impact of eating patterns on the incidence of ADRs and changes in HbA1c following administration of teneligliptin for 12 months was also studied. Analyses for the relationship between eating patterns and safety of teneligliptin were performed on the safety analysis set (all enrolled patients who had at least one safety assessment after receiving at least one dose of teneligliptin), and analysis for the efficacy of teneligliptin was performed on the efficacy analysis set (all enrolled patients who had at least one efficacy assessment after receiving at least one dose of teneligliptin) [27].

Statistical Analysis

Statistical analyses were performed using SAS v.9.1.3 (SAS Institute, Cary, NC, USA). Continuous data were summarized using descriptive statistics. Discrete data were summarized based on the number and percentage values for each category. The relationship between eating pattern (three meals per day and timing of evening meal) and metabolic parameters was analyzed using a two-sample t test for "three meals per day" and one-way analysis of variance (ANOVA) using contrast ($- 1, - 1/3, 1/3, 1$) of each category for "timing of evening meal", respectively. Analysis of covariance was also performed to adjust for patient gender and age. The relationship between eating pattern and diabetic complications (diabetic retinopathy, nephropathy, and neuropathy) was analyzed using Chi square tests. Given that data regarding eating patterns were only recorded prior to initiation of teneligliptin, and acknowledging that eating patterns may have changed during 3 years of surveillance, assessments of teneligliptin treatment were made up to the first 12 months only in the current analysis. A one-sample t test was performed between HbA1c levels at baseline and after 6 months or 12 months of teneligliptin treatment for each eating pattern. A significance level of 5% and two-sided 95% confidence intervals were defined.

RESULTS

Patient Demographics and Baseline Characteristics

From a total of 11,677 Japanese patients with diabetes enrolled in the RUBY surveillance program, the survey forms for 10,532 patients in the safety analysis set were available for this interim analysis. Patient demographics and baseline characteristics are presented in Table 1. The mean age [standard deviation (SD)] of patients included in the analysis was 65.4 (12.4) years and 60.2% of the population was male. Mean (SD) baseline HbA1c was 7.8 (1.5)% and baseline BMI was 25.3 (4.4) kg/m^2. The mean

Table 1 Patient demographics and baseline characteristics

All patients	(n = 10,532)	
Male sex, n (%)		6338 (60.2)
Age (years)	(n = 10,532)	65.4 (12.4)
Body weight (kg)	(n = 7661)	65.50 (14.34)
BMI (kg/m^2)	(n = 7009)	25.26 (4.40)
HbA1c (%)	(n = 9663)	7.76 (1.52)
Fasting blood glucose (mg/dL)	(n = 3659)	151.9 (52.5)
Fasting insulin (μU/mL)	(n = 590)	9.90 (9.77)
ALT (IU/L)	(n = 7942)	28.8 (23.4)
AST (IU/L)	(n = 7902)	26.6 (16.8)
Duration of T2DM (years)	(n = 7230)	7.38 (7.86)
Diabetic complications, n (%)		
Any		2745 (26.1)
Neuropathy		1041 (9.9)
Nephropathy		1970 (18.7)
Retinopathy		1050 (10.0)
Other complications, n (%)		
Hypertension		6595 (62.6)
Hyperlipidemia		6904 (65.6)
Alcohol intake, n (%)		
None		5099 (48.4)
Current		3199 (30.4)
Past		486 (4.6)
Unknown		1748 (16.6)
Dietary therapy, n (%)		8018 (76.1)
Exercise therapy, n (%)		6201 (58.9)
Teneligliptin starting dose (mg)	(n = 10,525)	20.2 (2.0)
Concurrent T2DM medication at initiation of teneligliptin, n (%)		
Any		5001 (47.5)

Table 1 continued

All patients	(*n* = 10,532)
Sulfonylurea	2320 (22.0)
Thiazolidine	774 (7.3)
Biguanide	1719 (16.3)
α-Glucosidase inhibitor	1056 (10.0)
Glinide	373 (3.5)
Insulin	710 (6.7)
SGLT2 inhibitor	27 (0.3)
Antidyslipidemic agents at initiation of teneligliptin, *n* (%)	3704 (35.2)

Data are mean (SD) unless otherwise stated

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *HbA1c* glycated hemoglobin, *n* number of patients, *SD* standard deviation, *SGLT2* sodium–glucose co-transporter-2, *T2DM* type 2 diabetes mellitus

duration of diabetes was 7.4 (7.9) years and approximately one-quarter of patients (26.1%) reported some form of diabetic complication, of which diabetic nephropathy was the most common (18.7%). Of other complications reported, hypertension and dyslipidemia occurred in 62.6% and 65.6% of patients, respectively. The proportions of patients on dietary therapy and exercise therapy were 76.1% and 58.9%, respectively.

At baseline, teneligliptin was initiated as monotherapy in 52.5% of patients, while 47.5% patients started teneligliptin therapy in combination with other diabetes drugs. The most commonly prescribed antidiabetic drugs were sulfonylurea (22.0%) or biguanide (16.3%) (Table 1). At baseline, 35.2% of patients were taking antidyslipidemic agents.

Eating Patterns

Of the 10,532 patients, 77.3% consumed three meals per day and 7.2% did not consume three meals per day (Fig. 1a). Of the overall patient population, 43.0% were ≤ 64 years of age, 31.5% were 65–74 years of age, and 25.5% were ≥ 75 years of age. Of the 8136 patients consuming three meals per day, 40.2% were ≤ 64 years of age, 32.4% were 65–74 years of age, and 27.4% were ≥ 75 years of age (Fig. 1b). Patients ≤ 64 years of age accounted for 62.4% of patients who did not eat three meals per day.

The most common time for eating the evening meal was between 6 and 8 PM (Fig. 1c). Patients ≤ 64 years of age accounted for 72.1% and 81.1% of patients who ate their evening meal at 8–10 PM and after 10 PM, respectively, compared with 12.6% and 36.1% of those eating before 6 PM and between 6 and 8 PM, respectively (Fig. 1d).

Eating Patterns and Metabolic Parameters at Baseline

Figure 2 and Fig. S1 show the relationship between eating patterns and various metabolic parameters at baseline. HbA1c levels were higher in those patients who did not eat three meals per day ($p < 0.001$); mean (SD) HbA1c was 8.41 (1.86)% compared with 7.68 (1.47)% in those patients who ate three meals per day. Mean (SD) fasting blood glucose, triglycerides, LDL-cholesterol, total cholesterol, and BMI were also significantly higher in patients who did not eat three meals per day than those who ate three meals per day [172.4 (69.7) vs. 148.6 (49.4) mg/dL, 186.8 (159.6) vs. 162.2 (124.4) mg/dL, 121.0 (35.8) vs. 113.8 (32.3) mg/dL, 202.2 (45.0) vs. 194.2 (40.0) mg/dL, and 26.38 (5.38) vs. 25.13 (4.25) kg/m^2, respectively; all $p < 0.001$]. Moreover, mean (SD) ALT and AST levels were significantly higher in patients who did not eat three meals per day compared with those who ate three meals per day [33.8 (29.0) vs. 28.1 (21.9) IU/L; $p < 0.001$, and 28.2 (18.3) vs. 26.3 (16.0) IU/L; $p = 0.019$, respectively].

Additionally, HbA1c, fasting blood glucose, triglycerides, LDL-cholesterol, total cholesterol, BMI, ALT, and AST all increased with lateness of eating dinner (all $p < 0.05$; Fig. 2 and Fig. S1).
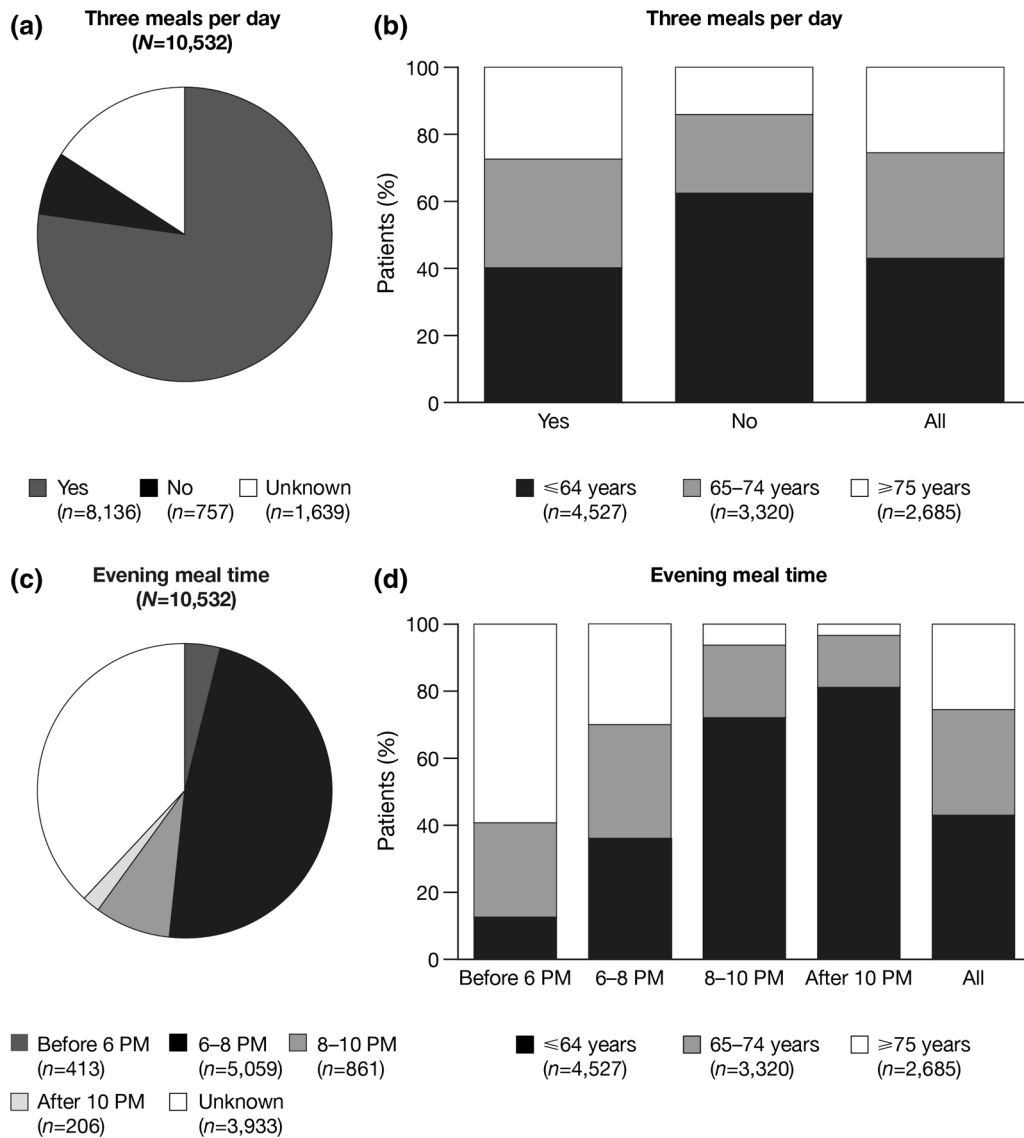
(a) Three meals per day
(N=10,532)

(b) Three meals per day

(c) Evening meal time
(N=10,532)

(d) Evening meal time

■ Yes   ■ No   □ Unknown
(n=8,136) (n=757) (n=1,639)

■ ≤64 years   ■ 65–74 years   □ ≥75 years
(n=4,527)   (n=3,320)   (n=2,685)

■ Before 6 PM   ■ 6–8 PM   ■ 8–10 PM
(n=413)   (n=5,059)   (n=861)

□ After 10 PM   □ Unknown
(n=206)   (n=3,933)

■ ≤64 years   ■ 65–74 years   □ ≥75 years
(n=4,527)   (n=3,320)   (n=2,685)

Fig. 1 Eating patterns: **a** proportion of patients eating three meals per day or not (a "no" response means not eating three meals per day); **b** proportion of patients in each age group eating three meals per day or not; **c** proportion of patients by timing of evening meal; and **d** proportion of patients in each age group by timing of evening meal

Patients who ate dinner before 6 PM and those who ate dinner after 10 PM had a mean (SD) HbA1c of 7.33 (1.23)% and 8.19 (1.59)%, respectively. For patients who ate dinner 6 PM or after 10 PM, mean (SD) values, respectively, were as follows: fasting blood glucose, 139.6 (45.5) and 159.7 (56.7) mg/dL; triglycerides, 141.4 (84.0) and 178.7 (140.1) mg/dL; LDL-c-holesterol, 109.3 (34.0) and 119.1 (33.8) mg/dL; total cholesterol, 185.8 (38.5) and 201.1 (41.2) mg/dL; and BMI, 24.22 (4.03) and 26.83 (4.92) kg/m^2. Mean (SD) ALT and AST levels in patients who ate dinner before after 6 PM and in those who ate dinner after after 10 PM were 21.7 (15.9) and 36.7 (26.7) IU/L, and 24.6 (14.8) and 27.8 (15.4) IU/L, respectively. No discernible

relationship was observed between eating patterns and HDL-cholesterol (Fig. S1).

Analysis of eating patterns adjusted for the sex and age of the patient showed a tendency towards higher HbA1c, fasting glucose, triglycerides, LDL-cholesterol, total cholesterol, BMI, and ALT levels in patients not eating three meals per day compared with those eating three meals per day (Table S1). In the sex- and age-adjusted analyses for evening meal time, HbA1c, fasting glucose, triglycerides, BMI, and ALT levels increased or tended to increase with lateness of eating dinner, although statistical power was limited due to the smaller sample size of patients $\geq$ 65 years of age who ate dinner late (Table S1).

Eating Patterns and Diabetic Complications at Baseline

Diabetic neuropathy and retinopathy were more prevalent in patients who did not eat three meals per day (13.1% and 12.9%, respectively) compared with those eating three meals per day (9.9% and 9.3%, respectively; p = 0.007 and p = 0.002 for neuropathy and retinopathy, respectively; Fig. 3). No significant difference in the prevalence of nephropathy was observed. There was no clear relationship between the prevalence of diabetic complications and the time at which the evening meal was consumed.

Eating Patterns and Safety of Teneligliptin

The incidence of ADRs following 12 months of treatment with teneligliptin is shown in Table 2. The overall incidence of ADRs in each eating pattern (three meals per day and timing of evening meal) was 1.94–3.43%. Eating patterns had no discernible influence on the incidence and nature of ADRs following the administration of teneligliptin. Although the incidence of ADRs related to hepatic impairment was higher in the patients not eating three meals per day than in patients eating three meals per day [0.79 (6 patients) vs. 0.23% (19 patients)], the relationship to teneligliptin in three of these six patients was unknown.
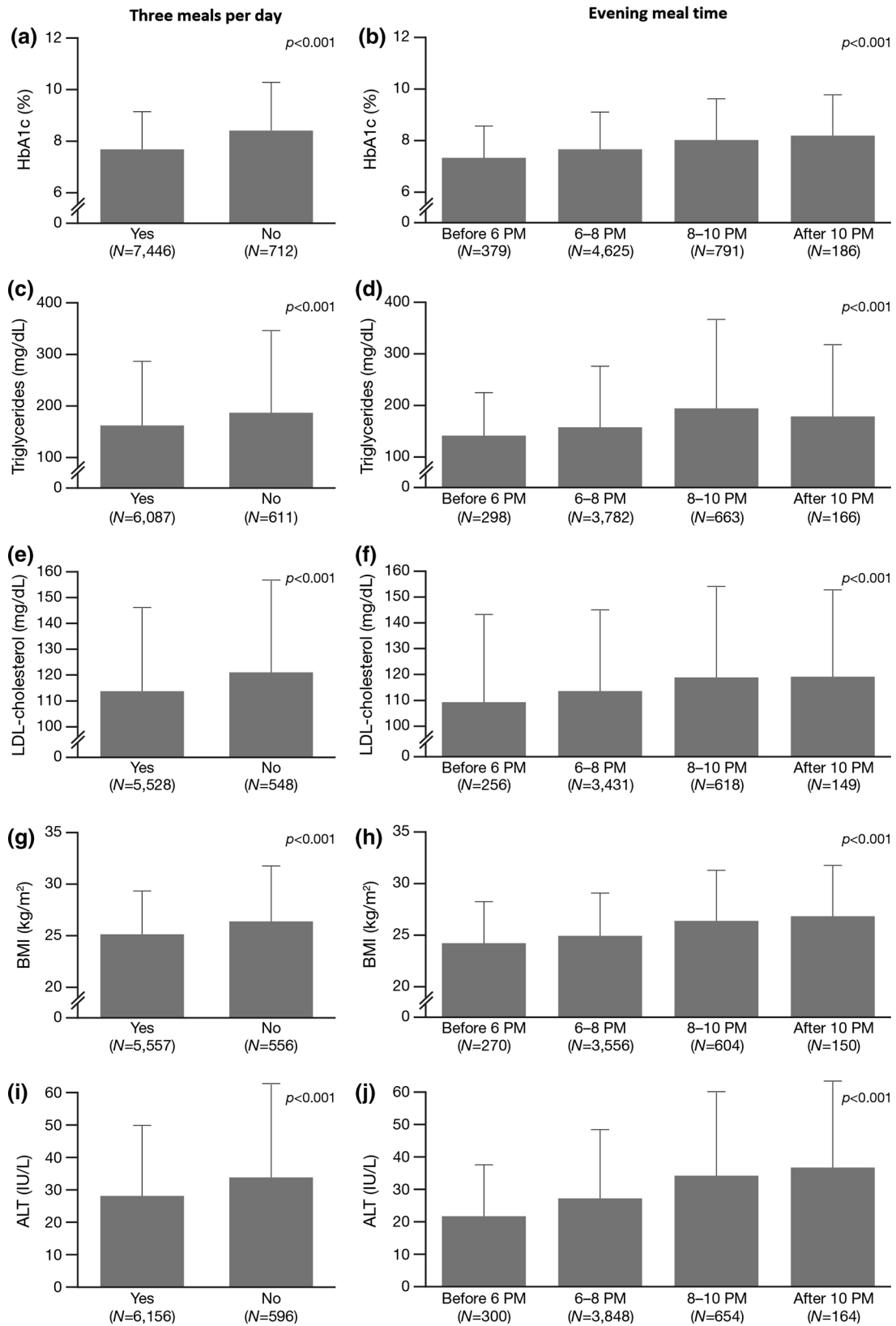
Eating Patterns and Efficacy of Teneligliptin

HbA1c-lowering effects of teneligliptin over a period of 6 or 12 months of treatment was observed for each eating pattern. Among patients who consumed three meals per day, mean (SD) HbA1c showed a significant reduction from baseline [7.68 (1.46)%] to 6 months [6.94 (1.01)%; $p < 0.001$] and 12 months [6.95 (1.00)%; $p < 0.001$] (Fig. 4). For patients who did not eat three meals per day, HbA1c decreased significantly from baseline [8.38 (1.84)%] at both 6 months [7.27 (1.31)%; $p < 0.001$] and 12 months [7.25 (1.22)%; $p < 0.001$]. Of patients with baseline HbA1c $\geq$7.0%, 47.0% of patients who ate three meals per day and 40.6% of those who did not eat three meals per day achieved HbA1c < 7.0% after 12 months of treatment with teneligliptin.

Similarly, the HbA1c-lowering effects of treatment with teneligliptin were observed at 6 and 12 months in each timing of the evening meal ($p < 0.001$ for all; Fig. 4). The mean (SD) HbA1c levels at baseline, and after 6 and 12 months of treatment in patients eating before 6 PM were 7.32 (1.23)%, 6.79 (0.90)%, and 6.70 (0.90)%, respectively. In patients eating after 10 PM, the mean HbA1c levels were 8.20 (1.60)%, 7.34 (1.37)%, and 7.58 (1.57)%, respectively. Of patients with baseline HbA1c $\geq$7.0%, the percentage who achieved HbA1c < 7% after 12 months of treatment with teneligliptin declined with the lateness of eating their evening meal (54.4, 47.9, 42.9, and 33.0% of those who ate their evening meal before 6 PM, 6–8 PM, 8–10 PM, after 10 PM, respectively).

DISCUSSION

This large-scale analysis of eating patterns in a real-world sample shows that the number of meals consumed and the timing of the evening meal may be associated with differences not only in glycemic control but also in blood lipids, obesity, and liver function in Japanese patients with T2DM. Moreover, the number of meals consumed may be associated with

Three meals per day

(a) HbA1c (%) — Yes (N=7,446), No (N=712); p<0.001

(c) Triglycerides (mg/dL) — Yes (N=6,087), No (N=611); p<0.001

(e) LDL-cholesterol (mg/dL) — Yes (N=5,528), No (N=548); p<0.001

(g) BMI (kg/m²) — Yes (N=5,557), No (N=556); p<0.001

(i) ALT (IU/L) — Yes (N=6,156), No (N=596); p<0.001

Evening meal time

(b) HbA1c (%) — Before 6 PM (N=379), 6–8 PM (N=4,625), 8–10 PM (N=791), After 10 PM (N=186); p<0.001

(d) Triglycerides (mg/dL) — Before 6 PM (N=298), 6–8 PM (N=3,782), 8–10 PM (N=663), After 10 PM (N=166); p<0.001

(f) LDL-cholesterol (mg/dL) — Before 6 PM (N=256), 6–8 PM (N=3,431), 8–10 PM (N=618), After 10 PM (N=149); p<0.001

(h) BMI (kg/m²) — Before 6 PM (N=270), 6–8 PM (N=3,556), 8–10 PM (N=604), After 10 PM (N=150); p<0.001

(j) ALT (IU/L) — Before 6 PM (N=300), 6–8 PM (N=3,848), 8–10 PM (N=654), After 10 PM (N=164); p<0.001

◀ **Fig. 2** Relationship between eating patterns and baseline: **a**, **b** HbA1c; **c**, **d** triglycerides; **e**, **f** LDL-cholesterol; **g**, **h** BMI; and **i**, **j** ALT. Data are presented as mean and standard deviation. The relationship between eating pattern and metabolic parameters was analyzed using two-sample *t*-test (three meals per day) and one-way ANOVA (evening meal time). *ALT* alanine aminotransferase; *ANOVA* analysis of variance; *BMI* body mass index; *HbA1c* glycated hemoglobin; *LDL* low-density lipoprotein

diabetic complications. HbA1c-lowering effects with a low incidence of ADRs were observed with the DPP-4 inhibitor, teneligliptin, over a period of 6 or 12 months in patients both with, and without, appropriate eating patterns.

International and national guidance advocates lifestyle management (including healthy eating and physical activity) for the prevention and/or management of T2DM [11–13]. Such guidance is vindicated by data from the Look AHEAD study, which examined the long-term effects of intensive lifestyle intervention in > 5000 patients with T2DM, and observed improved glycemic control, lower risk of cardiovascular disease, and reduced healthcare utilization among patients adopting the strategy [29–31].

In the current analysis, most of the sample population consumed three meals per day, and ate their evening meal between 6 and 8 PM. However, people ≤ 64 years of age were most likely not to manage a three-meals-per-day eating schedule and were more likely to consume their evening meal later in the evening. One of the reasons for irregular eating patterns among non-elderly patients in the current analysis may be their lifestyle characteristics, such as nocturnal living, longer working hours, or single-person households.

Among people with and without T2DM, breakfast skipping and/or snacking can lead to poor glucose control [14–17, 32, 33]. Skipping breakfast has been associated with significantly more pronounced hyperglycemic response and impaired insulin response after subsequent lunch and dinner [16]. It has been reported that night-eating behaviors may predispose patients to diabetic complications [15]. Moreover, late evening meals have been shown to increase the

risk of developing T2DM [18, 34]. For example, eating dinner within 2 h before bedtime has been linked to the development of hyperglycemia in a cross-sectional sample of > 61,000 apparently healthy Japanese adults [34]. Our findings support these observations that eating patterns may be associated with alterations in metabolic parameters and diabetic complications among Japanese patients with T2DM. Many patients with diabetes have complications such as dyslipidemia, obesity, or non-alcoholic fatty liver disease [9, 35–37]. In common with diabetes, dietary intervention is heavily recommended in the management of these disorders [5–10, 38, 39]. Unhealthy eating pattern in young people caused by characteristic lifestyles may be associated with future much advanced metabolic disorders. Our results may be helpful in the clinical management of metabolic disorders other than diabetes.

The timing of meals is believed to link to circadian rhythms in metabolic organs. The circadian clock has been reported to regulate metabolism and energy homeostasis in the peripheral tissues [40, 41]. This includes many of the metabolic pathways, such as insulin secretion from β-cells, insulin sensitivity, glucose metabolism, and lipid metabolism [40, 41]. For example, the heterodimeric transcription factor complex of circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein (BMAL)–1 have demonstrated their role in controlling insulin secretion from pancreatic β-cells and in regulating muscle insulin sensitivity through sirtuin 1 [42, 43]. Therefore, the management of eating patterns is important to prevent the development and progression of diabetes and its associated complications.

Teneligliptin has been reported to inhibit DPP-4 activity for 24 h and suppression of postprandial hyperglycemia after all three daily meals [20]. Treatment with teneligliptin for up to 12 months was well tolerated and reduced HbA1c levels in each eating pattern in the current analysis. However, after 6 and 12 months of treatment, mean HbA1c levels of < 7.0% were only achieved in patients eating three meals per day and not in those without this eating pattern. Such a distinction was also
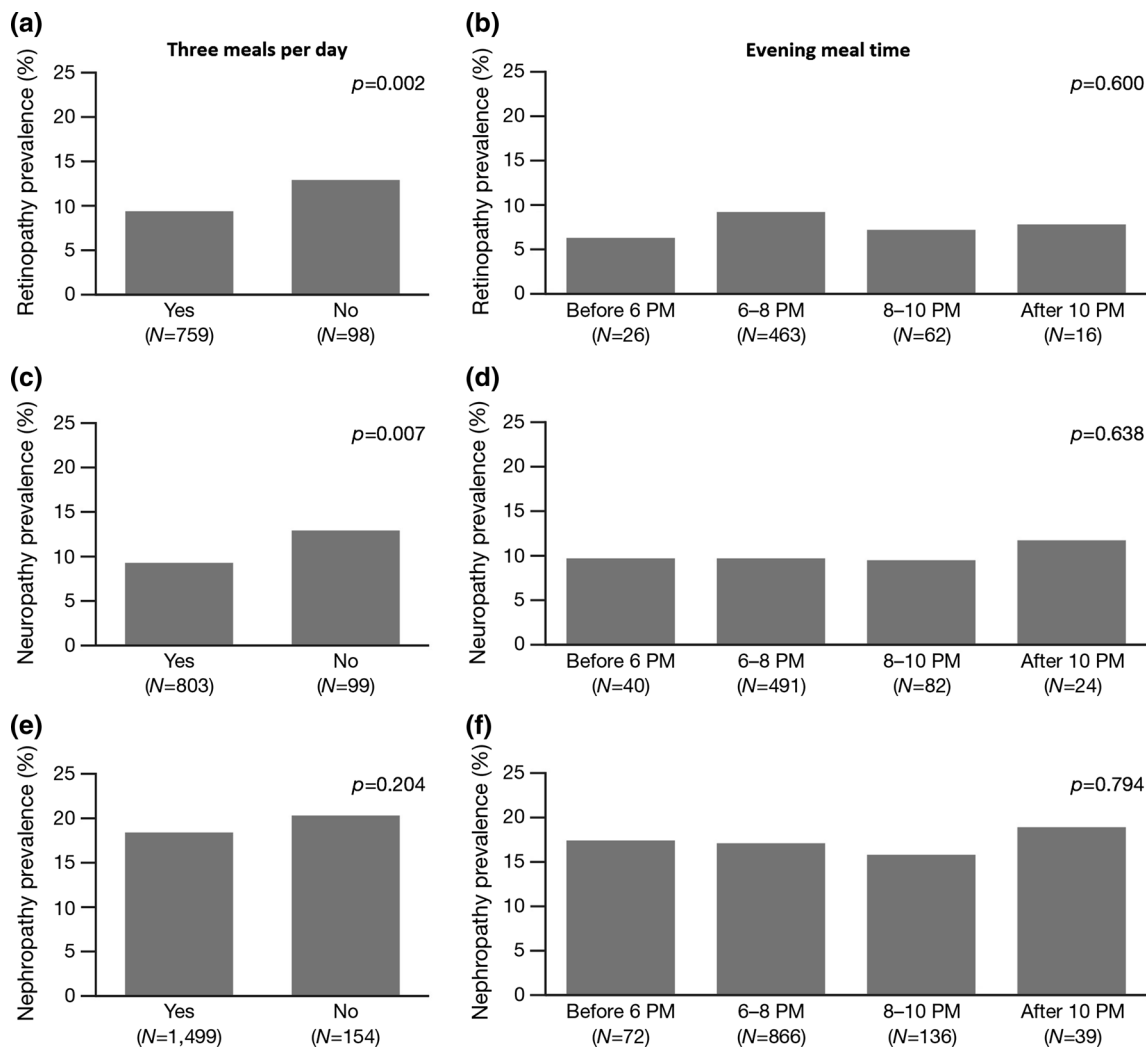
Fig. 3 Relationship between eating patterns and prevalence of: **a**, **b** retinopathy; **c**, **d** neuropathy; and **e**, **f** nephropathy. The relationship between eating pattern and diabetic complications was analyzed using Chi square test. *n* values indicate the number of patients with the complication

observed between patients eating their evening meal early (before 8 PM) and late (after 8 PM) following active treatment, with early eaters achieving a reduction of mean HbA1c levels to < 7.0%. These results suggest that in order to achieve HbA1c < 7.0%, it is important to manage dietary patterns, in addition to optimizing pharmacotherapeutic management. These finding may be helpful in information in pharmacotherapy with appropriate dietary therapy for patients with T2DM.

This analysis has several notable limitations. Questions regarding eating patterns (i.e.,

whether the patient eats three meals per day) were structured to allow for only "yes" or "no" responses, and so we are unable to further delineate whether a "no" answer to this question meant fewer or more than three meals per day. More detailed questioning regarding the frequency of skipping meals or between-meal snacking, and the size/quality/composition of meals and snacking would also have been informative. Although there was no clear relationship between eating three meals per day or not and the incidence of hypoglycaemia in this surveillance, consuming supplemental

Table 2 Incidence of adverse drug reactions (up to 12 months of treatment with teneligliptin; safety population)

	Three meals per day		Evening meal time			
	Yes ($n = 8136$)	No ($n = 757$)	Before 6 PM ($n = 413$)	6–8 PM ($n = 5059$)	8–10 PM ($n = 861$)	After 10 PM ($n = 206$)
Any ADR	195 (2.40)	26 (3.43)	11 (2.66)	111 (2.19)	24 (2.79)	4 (1.94)
Serious ADR	33 (0.41)	5 (0.66)	1 (0.24)	16 (0.32)	2 (0.23)	1 (0.49)
Breakdown of main ADR						
Hypoglycemia	21 (0.26)	2 (0.26)	0 (0.00)	10 (0.20)	3 (0.35)	1 (0.49)
SST disorders	23 (0.28)	3 (0.40)	1 (0.24)	12 (0.24)	5 (0.58)	0 (0.00)
GI disorders	40 (0.49)	5 (0.66)	5 (1.21)	20 (0.40)	5 (0.58)	1 (0.49)
Hepatic impairment	19 (0.23)	6 (0.79)	2 (0.48)	10 (0.20)	3 (0.35)	2 (0.97)
Renal impairment	13 (0.16)	2 (0.26)	0 (0.00)	8 (0.16)	4 (0.46)	0 (0.00)

Data are number of patients (%)

ADR adverse drug reaction, *GI* gastrointestinal, *SST* skin and subcutaneous tissue
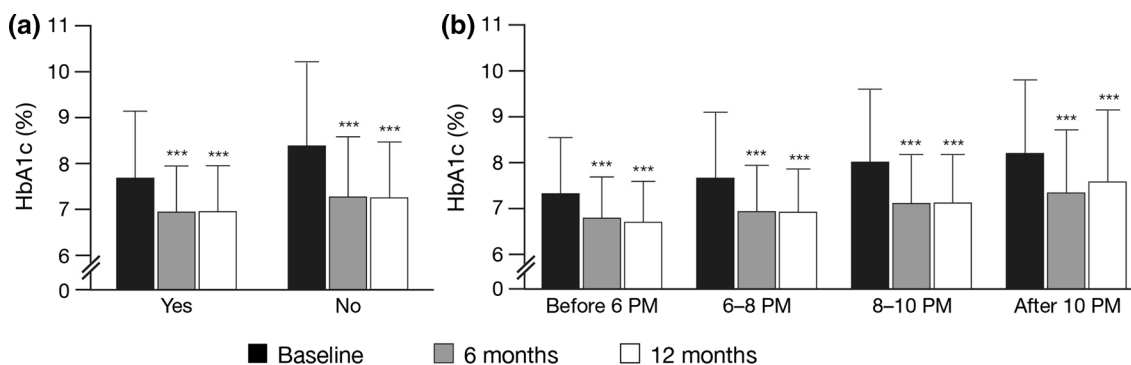
Fig. 4 Glycemic control after administration of teneligliptin for 6 and 12 months in patients: **a** with three meals per day or not; and **b** by evening meal time. Data are presented as mean and standard deviation. ***$p < 0.001$ vs. baseline (one-sample t test). *HbA1c* glycated hemoglobin

carbohydrates were reported to prevent hypoglycaemia [13]. Additionally, adherence to medical treatment, physical activity, and other lifestyle factors were not assessed. Eating patterns were recorded only at the beginning of the observation and, consequently, do not take into account any changes in eating patterns that occurred while treatment was ongoing. The analysis did not take into account any changes in concurrent antidiabetic treatments or lifestyle modifications over the course of treatment with teneligliptin. There are some of the typical limitations of a post-marketing surveillance design, which include having incomplete data, possible reporting biases, no matched control group, and limitations in the generalizability of the findings. These limitations should be taken into account when interpreting these data.

CONCLUSIONS

In conclusion, this interim analysis shows that the eating patterns of Japanese adults with T2DM vary according to age, with poor management of eating behaviors in non-elderly patients. We also demonstrate that eating patterns may be related not only to glycemic control—which, in turn, may eventually be related to the risk of developing diabetic complications—but also to blood lipid levels, obesity, and liver function. These findings support the importance of eating patterns on the management of diabetes and its associated complications. Teneligliptin may be well tolerated and improve hyperglycemia in patients with T2DM with and without appropriate eating patterns. Treatment with teneligliptin in addition to management of dietary patterns may further improve glycemic control.

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Compliance with Ethics Guidelines. The protocol of RUBY surveillance was approved by the Ministry of Health, Labour and Welfare of the Japan Government. The post-marketing surveillance program is ongoing and is carried out by the Mitsubishi Tanabe Pharma Corporation, in accordance with the Japanese Ministry directive on Good Post-marketing Study Practice Guidelines; in compliance with Japanese regulations for post-marketing surveillance, it was not necessary to obtain informed consent from patients. All analyses in the present surveillance were performed on a fully anonymized dataset.

Data Availability. The datasets analyzed during the current study are not publicly available due to protection of individual patient confidentiality, but are available from the corresponding author on reasonable request.

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