Drug Saf (2013) 36:981–987
DOI 10.1007/s40264-013-0077-z

SHORT COMMUNICATION

Risk Factors for Adverse Symptoms During Dipeptidyl Peptidase-IV Inhibitor Therapy: A Questionnaire-Based Study Carried Out by the Japan Pharmaceutical Association Drug Event Monitoring Project in Kumamoto Prefecture

Ayami Kajiwara · Junji Saruwatari · Misaki Sakata · Kazunori Morita · Ayana Kita · Kentaro Oniki · Masato Yamamura · Motoji Murase · Haruo Koda · Seisuke Hirota · Tadao Ishizuka · Kazuko Nakagawa

Published online: 7 June 2013

Abstract

Background Meta-analyses of randomized clinical trials have reported that dipeptidyl peptidase IV (DPP-4) inhibitors are well tolerated and that the incidence of hypoglycemia with the use of DPP-4 inhibitors is similar to that observed with placebos. However, in general, provider-oriented methods using medical record reviews offer lower rates of non-serious, symptomatic adverse drug reactions (ADRs) than patient-oriented methods. Moreover, severe hypoglycemia occurred in three clinical trials using sitagliptin, but in two of these trials this phenomenon has been previously described only in the drug application data in the US.

Objective The aim of this study was to assess the profile of patient-reported symptomatic ADRs under DPP-4 inhibitor therapy and to detect risk factors for hypoglycemic and non-hypoglycemic adverse symptoms in daily clinical practice.

Methods We analyzed a subpopulation of participants in the Drug Event Monitoring (DEM) project of the Japan Pharmaceutical Association. An anonymous survey was conducted in February 2012 to assess the self-perception of adverse symptoms during a median 28 (4–88) days after the last prescription of DPP-4 inhibitors by means of interviews of pharmacists using structured questionnaires.

Results A total of 864 males and 686 females were included. The prescribed DPP-4 inhibitors included sitagliptin (75.4 %), alogliptin (15.5 %), vildagliptin (8.8 %) and linagliptin (0.3 %). Mild hypoglycemic symptoms were reported by 34 individuals (2.2 %) receiving monotherapy of sitagliptin (10/402) or alogliptin (3/65), or combination therapy of sitagliptin (15/767) or alogliptin (6/176) with other hypoglycemic agents. In the multiple regression model, hypoglycemic symptoms were found to be significantly associated with liver disease, female sex and alcohol consumption more than three times per week. Non-hypoglycemic symptoms were reported by 57 individuals (3.7 %), the most common symptoms of which were gastrointestinal symptoms (2.1 %). Combination therapy was only found to be associated with nonhypoglycemic symptoms.

Conclusions The present study suggested that hypoglycemic symptoms under therapy with sitagliptin or alogliptin may be associated with liver disease, female sex and alcohol consumption, all of which are potentially capable of leading to poor gluconeogenesis because they decrease the counter-regulatory hormonal responses to hypoglycemia.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-013-0077-z) contains supplementary material, which is available to authorized users.

A. Kajiwara · J. Saruwatari · M. Sakata · K. Morita · A. Kita · K. Oniki · K. Nakagawa (✉)
Division of Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-honmachi, Kumamoto 862-0973, Japan
e-mail: kazukon@gpo.kumamoto-u.ac.jp

M. Yamamura · M. Murase · H. Koda · S. Hirota
Kumamoto Pharmaceutical Association, Kumamoto, Japan

T. Ishizuka
Division of Pharmaceutical Molecular Design, Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan

T. Ishizuka · K. Nakagawa
Center for Clinical Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan

1 Background

The anti-diabetic actions of dipeptidyl peptidase IV (DPP-4) inhibitors are based on the effects of two incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are rapidly inactivated by DPP-4. These incretins potentiate glucose-induced insulin release. In addition, GLP-1 also suppresses glucagon release and slows down gastric emptying during the postprandial period [1, 2]. Meta-analyses of randomized clinical trials have reported that DPP-4 inhibitors significantly improve the HbA1c levels in comparison with placebos, with an incidence of hypoglycemia similar to that observed with placebos [2–4]. These results are consistent with the glucose-dependent actions of incretins. However, severe hypoglycemia occurred in five patients treated with sitagliptin, either with monotherapy or in combination with metformin, in three different clinical trials [5–7]. Notably, although two of these trials did not report the events in the literature, information regarding severe hypoglycemia was described in the data for the drug application in the US, which can be retrieved from the FDA website. [2, 3, 5, 6]. In daily clinical practice, hypoglycemia-related emergency department and outpatient visits due to DPP-4 inhibitor monotherapy have been reported [8], and the number of patient-reported hypoglycemic episodes is two times higher with the use of sitagliptin than placebos [4].

Patient self-reports are more sensitive to underlying changes in functional status than health care providers' reports and appear to be more suitable for assessing symptomatic adverse drug events (ADEs) [9, 10]. Non-serious symptomatic ADEs, which affect the real benefit-risk ratios of drugs, are often missed by health care providers. Recently, Hakobyan et al. [10] reported that health care provider-oriented assessment methods using medical record reviews offered considerably lower rates for gastrointestinal adverse drug reactions (ADRs) of oral glucose-lowering drugs than a patient questionnaire method. In 2003, the Japan Pharmaceutical Association (JPA) initiated a Drug Event Monitoring (DEM) project involving nationwide surveillance for ADEs using a patient questionnaire method in cooperation with JPA member pharmacies conducted in the fourth week of February every year [11]. The DEM project includes selected drugs or drug classes that have an impact on daily practice because of their targeted or adverse effects. DPP-4 inhibitors were the focus of investigation in 2012. The affiliated pharmacists put up a poster advertising the projects and noted the patients who were receiving the focused drug prior to the surveillance. Then during the 7-day surveillance period in the 4th week of February, every visitor who had been identified as a potential subject was asked to participate in the project. The aim of this study was to assess the profile of patient-reported symptomatic ADRs under DPP-4 inhibitor therapy and to detect risk factors for hypoglycemic and non-hypoglycemic adverse symptoms in daily clinical practice.

2 Methods

2.1 Study Design

Every patient who was receiving a DPP-4 inhibitor (sitagliptin, alogliptin, vildagliptin or linagliptin) from pharmacies affiliated with a cross-sectional nationwide survey of the JPA DEM project and visited there with a prescription of any drug(s) during the surveillance from 20 through 26 February 2012 were asked to participate in the project. The participants were interviewed by pharmacists using structured questionnaires to assess the self-perception of adverse symptoms after the last prescription of a DPP-4 inhibitor. The median duration from the last prescription to the interview was 28 (4–88) days. The questionnaires included open questions regarding demographic information and adverse symptoms, and a check list of symptoms that can be caused by DPP-4 inhibitors (Supplemental Table 1). The pharmacists asked participants further regarding their symptoms as needed and filled in the check list. A total of 649 (89.1 %) pharmacies in Kumamoto prefecture, Japan, responded to the survey, and the survey results of 2,002 participants were collected via a Web-based system linked to a reporting portal in the KUMAYAKU Network for Community Pharmacies in Kumamoto. This protocol was approved by the institutional ethics committees of the Faculty of Life Sciences, Kumamoto University.

2.2 Data Analysis

Patients with dementia or missing data of adverse symptoms, diseases under pharmacotherapy, alcohol consumption and/or smoking habits were excluded from the present study. Consequently, 1,550 patients were included in the statistical analyses. The patient characteristics, i.e. the demographic characteristics listed in Table 1, were not significantly different between the included and excluded patients (Supplemental Table 2). We defined hypoglycemic symptoms, on a theoretical basis, according to the review by Barnett et al. [12].

We identified independent risk factors associated with hypoglycemic or nonhypoglycemic symptoms during DPP-4 inhibitor use, employing univariate and multiple logistic regression analyses with calculation of the odds ratios (ORs) and 95 % confidence intervals (95 % CIs). In the multiple regression model, the ORs were adjusted for potentially confounding factors, including patient characteristics (e.g. age, sex) and factors that showed a statistical

Table 1 Characteristics of the study population

	Total[a] $N = 1,550$	Monotherapy[a] $N = 532$	Combination therapy[a] $N = 1,018$
Female (%)	44.3	44.2	44.3
Age (years)	68.0 ± 11.8	70.2 ± 11.7	66.8 ± 11.7
BMI[b] (kg/m^2)	24.8 ± 4.3	24.0 ± 3.5	25.2 ± 4.6
HbA1c[b] (%)	6.8 ± 1.0	6.4 ± 0.7	7.0 ± 1.1
Alcohol consumption (%)			
Non-drinking	52.1	54.5	50.8
Less than 1 time/week	18.9	17.3	19.7
1–3 times/week	8.8	8.5	8.9
More than 3 times/week	20.3	19.7	20.5
Smoking (%)			
Never	60.8	62.6	59.8
Past	23.4	22.9	23.7
Current	15.8	14.5	16.5
Liver disease (%)	4.1	3.8	4.3
Renal disease (%)	3.4	3.9	3.0
The ratio of daily dose to maximum dose[c]	0.59 ± 0.24	0.55 ± 0.23	0.61 ± 0.24
Prescribed DPP-4 inhibitor (%)			
Sitagliptin	75.4	75.6	75.3
Alogliptin	15.5	12.2	17.3
Vildagliptin	8.8	11.5	7.4
Linagliptin	0.3	0.8	0.0

BMI Body mass index, *DM* diabetes mellitus

[a] The values are presented as the percentage of subjects or the mean ± standard deviation

[b] Some data were missing

[c] To assess the daily doses of the four DPP-4 inhibitors in the same scale, we divided the prescribed daily dose by the approved maximum dose for each subject

tendency ($P < 0.1$) in the univariate model. To assess the goodness of fit of our logistic regression models, we performed the Hosmer–Lemeshow test and calculated Nagelkerke's R squared. In addition, we investigated the association between the daily dose and diseases or sex and assessed the effects on adverse symptoms. To assess the daily doses of four different DPP-4 inhibitors in the same way, we divided the prescribed daily dose for each subject by the defined maximum dose. The maximum daily doses approved for the treatment of diabetes mellitus (DM) in Japan were used as the defined maximum doses, i.e. 100 mg for sitagliptin and vildagliptin, 25 mg for alogliptin and 5 mg for linagliptin. The presence of renal or liver disease was defined as the use of pharmacotherapy for these diseases.

Categorical and continuous variables were also compared using Fisher's exact test and Student's *t* test, respectively. A *P* value of <0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS software package for Windows (Version 17.0, IBM Japan Ltd., Tokyo, Japan).

3 Results

The mean age of the subjects was 68.0 ± 11.8 years (19–98 years), including 864 males and 686 females (Table 1). The prescribed DPP-4 inhibitors included sitagliptin in 1,169 subjects, alogliptin in 241 subjects, vildagliptin in 136 subjects and linagliptin in 4 subjects (Table 1). Hypoglycemic symptoms occurring after previous prescriptions during a median interval of 28 days were reported by 34 (2.2 %) of 1,550 subjects: 13/532 (2.4 %) under monotherapy consisting of sitagliptin (10/402) or alogliptin (3/65) and 21/1,018 (2.1 %) under combination therapy consisting of sitagliptin (15/767) or alogliptin (6/176) and other hypoglycemic agents; however, no patients were treated with either vildagliptin or linagliptin (Supplemental Table 3). The most common symptoms were dizziness and hunger (0.9 and 0.4 %, respectively) as shown in the symptom profiles (Table 2).

In the univariate regression model, liver disease was found to be a risk factor for hypoglycemic symptoms ($P = 0.032$) (Supplemental Table 4). The type of DPP-4 inhibitor was not found to be associated with hypoglycemic or nonhypoglycemic symptoms (data not shown).

In the multiple regression model, hypoglycemic symptoms were found to be associated with liver disease (OR 3.17, 95 % CI 1.07–9.43), female sex (OR 3.26, 95 % CI 1.39–7.62) and alcohol consumption more than three times per week (OR 3.68, 95 % CI 1.30–10.43) (Table 3). When stratified according to the use of DPP-4 inhibitors as monotherapy or combination therapy, liver disease was

Table 2 Reported symptoms

Hypoglycemic symptoms	*n*	Non-hypoglycemic symptoms	*n*
Dizziness	14	Constipation	16
Hunger	6	Abdominal discomfort	8
Fatigue	5	Abdominal distension	7
Blurred vision	4	Myalgia, muscle stiffness or cramp	7
Palpitation	3	Cough	6
Drowsiness	3	Diarrhea	4
Shaking	2	Edema	4
Sweating	1	Nasopharyngitis	4
		Rash	4
		Gastritis	3
		Abdominal pain	2
		Nausea	2
		Headache	2
		Stomatitis	2
		Periodontitis	1
		Vertigo	1
		Arrhythmia	1
		Numbness in fingers	1
		Blood pressure increased	1
		Erythema	1

Symptoms known to be side effects of DPP-4 inhibitors are shown
More than one symptom was reported in some cases

identified as the sole independent risk factor (OR 5.11, 95 % CI 1.04–25.24) in patients receiving monotherapy, whereas female sex (OR 7.94, 95 % CI 2.42–26.10) and alcohol consumption of 1–3 times per week (OR 5.53, 95 % CI 1.31–23.40) or more than three times per week (OR 9.71, 95 % CI 2.55–36.90) were identified as risk factors in patients receiving combination therapy (Table 4).

Nonhypoglycemic symptoms were reported by 57 (3.7 %) individuals receiving monotherapy with sitagliptin (11/402) or vildagliptin (1/61) and combination therapy with sitagliptin (28/767), alogliptin (13/176) and vildagliptin (4/75) (Supplemental Table 3). Gastrointestinal symptoms (2.1 %) were the most common nonhypoglycemic symptom (Table 2). In the logistic regression analysis, combination therapy was identified as the sole risk factor for non-hypoglycemic symptoms (OR 1.97, 95 % CI 1.03–3.78) (Supplemental Table 5). The adjusted regression models were statistically fitted for hypoglycemic symptoms among all subjects, among individuals receiving monotherapy and among those receiving combination therapy, as well as for non-hypoglycemic symptoms among all subjects ($P = 0.262$, 0.412, 0.674 and 0.419, respectively, Hosmer–Lemeshow test). The other hand, the percentages explained by the variances (i.e. Nagelkerke's R squared) were 4.5, 4.2, 9.4 and 2.0 %, respectively, for these regression models.

The daily dose did not differ between females and males; however the females took significantly higher doses per weight than the males (sitagliptin; 0.93 ± 0.32 vs. 0.77 ± 0.27 mg/kg/day, $P < 0.001$; alogliptin; 0.37 ± 0.15 vs. 0.30 ± 0.13 mg/kg/day, $P = 0.002$). The associations between adverse symptoms and the higher daily doses of sitagliptin (the most common DPP-4 inhibitor used in this study) were not observed among all subjects, male or female subjects, or subjects with liver disease (Supplemental Table 6).

4 Discussion

In this study, mild hypoglycemic symptoms were reported in 34 (2.2 %) of the total subjects under sitagliptin or alogliptin therapy, among the four DPP-4 inhibitor therapy groups. The risk factors associated with hypoglycemic symptoms include liver disease, female sex and alcohol consumption more than three times per week. Interestingly, all of these factors have been identified as physiological or pathological predisposing factors for hypoglycemia [8, 12–16]. No hypoglycemic symptoms were reported under vildagliptin or linagliptin therapy, which might be due to the small number of patients who were prescribed these drugs in this study. The lower prescription rates (linagliptin: 0.3 %, vildagliptin: 8.8 %) compared with sitagliptin (75.4 %) might result from the differences in the dates when these drugs were marketed in Japan, i.e. September 2011 for linagliptin, April 2010 for vildagliptin and December 2009 for sitagliptin.

DM and nonalcoholic fatty liver disease (NAFLD) appear to have common origins related to obesity and insulin resistance, and DM is also common among patients with alcoholic and viral chronic liver disease (CLD). Abnormalities of glucagon secretion are often observed in patients with DM or CLD and may actually reflect an impairment of α-cell glucose sensing [17–19]. Glucagon secretion plays an essential role in the regulation of hepatic glucose production and in the counter-regulatory response to hypoglycemia [17, 18]. Consequently, patients with both DM and NAFLD or CLD are at high risk for hypoglycemia regardless of the severity of liver disease [8, 15, 16]. Sulfonylurea and insulin dose adjustment is required in patients with DM and CLD, whereas DPP-4 inhibitor dose adjustment is not [1, 15]. Evidence exists to suggest that DPP-4 is an important player in the pathogenesis of NAFLD, and DPP-4 inhibitors therefore have considerable therapeutic potential for CLD [19, 20]. However, our results suggest that patients with DM and NAFLD or CLD being treated with DPP-4 inhibitor therapy must be

Table 3 Crude and adjusted odds ratios for the symptoms of hypoglycemia

	With symptoms[a] $N = 34$	Without symptoms[a] $N = 1{,}516$	Crude ORs [95 % CI]	Adjusted ORs[b] [95 % CI]
Liver disease	11.8	4.0	3.24 [1.11–9.48]	3.17 [1.07–9.43]
Female	58.8	43.9	1.82 [0.91–3.64]	3.26 [1.39–7.62]
Alcohol consumption[c]				
Less than 1 time/week	20.6	18.9	1.39 [0.55–3.47]	1.91 [0.74–4.93]
1–3 times/week	11.8	8.7	1.72 [0.56–5.29]	3.05 [0.91–10.20]
More than 3 times/week	26.5	20.1	1.67 [0.72–3.90]	3.68 [1.30–10.43]
Age	68.2 ± 10.7	68.0 ± 11.8	1.00 [0.97–1.03]	1.01 [0.98–1.04]

OR Odds ratio, *CI* confidence interval, *DM* diabetes mellitus

[a] The values are presented as the percentage of subjects or the mean ± standard deviation

[b] Adjusted for other factors listed in this table

[c] Compared with non-drinker

Table 4 Crude and adjusted odds ratios for the symptoms of hypoglycemia among individuals receiving monotherapy or combination therapy with other DM medications

	Monotherapy			Combination therapy		
	With symptoms[a] $N = 13$	Without symptoms[a] $N = 519$	Adjusted ORs[b] [95 % CI]	With symptoms[a] $N = 21$	Without symptoms[a] $N = 997$	Adjusted ORs[b] [95 % CI]
Liver disease	15.4	3.5	5.11 [1.04–25.24]	9.5	4.2	2.32 [0.50–10.70]
Female	46.2	44.1	1.33 [0.38–4.70]	66.7	43.8	7.94 [2.42–26.10]
Alcohol consumption[c]						
Less than 1 time/week	30.8	17.0	2.29 [0.57–9.19]	14.3	19.9	1.49 [0.38–5.81]
1–3 times/week	7.7	8.5	1.25 [0.13–11.82]	14.3	8.8	5.53 [1.31–23.40]
More than 3 times/week	15.4	19.8	1.06 [0.18–6.24]	33.3	20.3	9.71 [2.55–36.90]
Age	69.2 ± 11.1	70.2 ± 11.8	1.00 [0.95–1.04]	67.7 ± 10.7	66.8 ± 11.7	1.01 [0.97–1.06]

OR Odds ratio, *CI* confidence interval, *DM* diabetes mellitus

[a] The values are presented as the percentage of subjects or the mean ± standard deviation

[b] Adjusted for other factors listed in this table

[c] Compared with non-drinker

counseled carefully regarding recognition and management of hypoglycemia in order to maximize efficacy.

This is the first report to suggest that females are more susceptible to DPP-4-induced hypoglycemia. Elucidation of sex differences in the physiology and pathophysiology of glucose homeostasis is a key issue for gender-specific care of DM [21]. In the past 30 years, the all-cause mortality and cardiovascular mortality rates for females with DM have not declined, in contrast to the decreased rates observed in males [21]. Females have an increased risk of experiencing hypoglycemic events requiring medical intervention in the emergency department or outpatient setting [8]. Reduced counter-regulatory hormonal responses to hypoglycemia in females have been postulated to be a risk factor [8, 22]. Physiologically, females have lower fasting plasma glucose levels [21, 23]. Lower rates of gluconeogenesis in females in the exercising and/or fasting state may be the result of lower increments in glucagon secretion in females than in males [22]. On the other hand, we speculated that no associations between hypoglycemic symptoms and the dose of the therapeutic agents were found due to the specific mechanism of DPP-4 inhibitors, i.e., that DPP-4 inhibitors may improve the ability of both α- and β-cells to sense and respond appropriately to hypoglycemia [24]. Nevertheless, further investigations are needed to confirm whether the dose being used for the treatment is associated with hypoglycemia.

Alcohol intake is known to be a risk factor for hypoglycemia, particularly in patients who take oral glucose-lowering agents [12, 13, 25]. Ethanol delays recovery from hypoglycemia by impeding counter-regulatory hormonal responses and enhances glucose-lowering effects by decreasing hepatic gluconeogenesis [16, 25]. The effects of chronic ethanol consumption may be pronounced in

females [14]. In the present study, however, neither alcohol intake nor female sex was related to hypoglycemic symptoms among the patients receiving monotherapy. These results suggest that the effects of alcohol intake and female sex become apparent only in subjects taking other glucose-lowering agents.

In this study, nonhypoglycemic symptoms were found to be associated with combination therapy. Age was not found to be a risk factor for DPP-4-related hypoglycemic and nonhypoglycemic symptoms, even though most of the subjects were over 65 years of age (mean age: 68.0 ± 11.8 years, range 19–98 years) and did not receive dose adjustments. The risk of hypoglycemia in older subjects is higher because of the physiology of aging and cognitive decline [12, 26]. The risk might be at least partly masked in this study because self-reports can be affected by lower perceptions of hypoglycemia among the elderly. Meanwhile, there is much clinical evidence supporting the efficacy and safety of DDP-4 inhibitor therapy in older patients [26].

This investigation has some obvious limitations. First, a cross-sectional design does not allow causality between the drugs and the ADRs to be established. The ADRs were reported largely on the basis of the patient's memory; therefore, they may have been overestimated. It is important to consider the "nocebo" effect, that is, a patient's negative expectations of experiencing adverse effects [27]. Second, we did not have adequate information regarding complications, laboratory evidence or medication history. The prevalence of chronic liver disease (4.1 %) in this study was obviously lower than that reported in DM patients [15]. This is because the presence of liver disease was judged according to the prescription of antiviral agents and/or hepatoprotective agents, such as ursodeoxycholic acid. These findings are therefore biased based on the proxy assessment with high specificity and low sensitivity. Third, in this study, we defined 'hypoglycemic symptoms' on a theoretical basis, according to a previous study [12]. Moreover, we defined a single symptom as a 'hypoglycemic symptom' in most cases since few participants had more than one hypoglycemic symptom. Therefore, we could not exclude the possibility that there were misclassifications of symptoms in some participants. In addition, we excluded 452 patients because of a lack of data; therefore, a selection bias in the study population may exist, although the patient characteristics were not significantly different between the included and excluded patients. Lastly, the follow-up period for investigating ADRs was short (i.e., the median interval was 28 days), which might have contributed to the low incidence of ADRs observed in this study. In this study, the adjusted regression models explained only a small part of the variance of these risks (Nagelkerke's R squared: 2.0–9.4 %), because all potential risk factors could not be included and the incidence of ADRs was relatively small. Therefore, the results of this study should be verified by clinical studies of longer duration, more parameters and with a larger sample size.

5 Conclusion

This study suggests that mild hypoglycemic symptoms, as reported by 2.2 % of the total subjects treated with sitagliptin or alogliptin therapy, are associated with liver disease in patients receiving monotherapy, and female sex and alcohol consumption in patients receiving combination therapy. All of these factors are potentially capable of causing poor gluconeogenesis as a result of decreased counter-regulatory hormonal responses to hypoglycemia. Health care providers should thus monitor hypoglycemic symptoms carefully in patients with these potential risk factors, and clinical studies of higher quality and with a larger sample size should be undertaken to confirm the present findings.

Acknowledgments We would like to thank the Japan Pharmaceutical Association and the Kumamoto Pharmaceutical Association.

This work was supported by Dr. Saruwatari—"Grants-in-aid from Japan Research Foundation for Clinical Pharmacology and the Yokoyama Foundation for Clinical Pharmacology," Dr. Ishizuka—"A grant-in-aid for scientific research (KAKENHI no. 21590013) from the Ministry of Education, Culture, Sports, Science and Technology, Japan," Dr. Nakagawa—"A grant-in-aid for scientific research (KAKENHI no. 23510348) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a grant-in-aid from the Smoking Research Foundation." Ayami Kajiwara, Junji Saruwatari, Misaki Sakata, Kazunori Morita, Ayana Kita, Kentaro Oniki, Masato Yamamura, Motoji Murase, Haruo Koda, Seisuke Hirota, Tadao Ishizuka and Kazuko Nakagawa have no conflicts of interest that are directly relevant to the content of this article.

References

1. Mikhail N. Safety of dipeptidyl peptidase 4 inhibitors for treatment of type 2 diabetes. Curr Drug Saf. 2011;6(5):304–9.
2. Richard KR, Shelburne JS, Kirk JK. Tolerability of dipeptidyl peptidase-4 inhibitors: a review. Clin Ther. 2011;33(11):1609–29.
3. Monami M, Iacomelli I, Marchionni N, et al. Dipeptydil peptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2010;20(4):224–35.
4. Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology. 2010;86(1):44–57.
5. Hanefeld M, Herman GA, Wu M, et al. Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. Curr Med Res Opin. 2007;23(6):1329–39.
6. Scott R, Wu M, Sanchez M, et al. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over

12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007;61(1):171–80.
7. Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007;9(2):194–205.
8. Simeone JC, Quilliam BJ. Predictors of emergency department and outpatient visits for hypoglycemia in type 2 diabetes: an analysis of a large US administrative claims database. Ann Pharmacother. 2012;46(2):157–68.
9. Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med. 2010;362(10):865–9.
10. Hakobyan L, Haaijer-Ruskamp FM, de Zeeuw D, et al. Comparing adverse event rates of oral blood glucose-lowering drugs reported by patients and healthcare providers: a post-hoc analysis of observational studies published between 1999 and 2011. Drug Saf. 2011;34(12):1191–202.
11. Japan Pharmaceutical Association. Annual Report of JPA 2010-2011 [online]. http://www.nichiyaku.or.jp/e/data/annual_report2010e.pdf. Accessed 14 March 2013.
12. Barnett AH, Cradock S, Fisher M, et al. Key considerations around the risks and consequences of hypoglycaemia in people with type 2 diabetes. Int J Clin Pract. 2010;64(8):1121–9.
13. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94(3):709–28.
14. Sumida KD, Hill JM, Matveyenko AV. Sex differences in hepatic gluconeogenic capacity after chronic alcohol consumption. Clin Med Res. 2007;5(3):193–202.
15. Khan R, Foster GR, Chowdhury TA. Managing diabetes in patients with chronic liver disease. Postgrad Med. 2012;124(4):130–7.
16. Arky RA. Hypoglycemia associated with liver disease and ethanol. Endocrinol Metab Clin N Am. 1989;18(1):75–90.
17. Taborsky GJ Jr, Mundinger TO. Minireview: the role of the autonomic nervous system in mediating the glucagon response to hypoglycemia. Endocrinology. 2012;153(3):1055–62.
18. Holst JJ, Christensen M, Lund A, et al. Regulation of glucagon secretion by incretins. Diabetes Obes Metab. 2011;13(Suppl 1):89–94.
19. Charbonneau A, Unson CG, Lavoie JM. High-fat diet-induced hepatic steatosis reduces glucagon receptor content in rat hepatocytes: potential interaction with acute exercise. J Physiol (Lond). 2007;579(Pt 1):255–67.
20. Iwasaki T, Tomeno W, Yoneda M, et al. Non-alcoholic fatty liver disease adversely affects the glycemic control afforded by sitagliptin. Hepatogastroenterology. 2012;59(117):1522–5.
21. Szalat A, Raz I. Gender-specific care of diabetes mellitus: particular considerations in the management of diabetic women. Diabetes Obes Metab. 2008;10(12):1135–56.
22. Horton TJ, Grunwald GK, Lavely J, et al. Glucose kinetics differ between women and men, during and after exercise. J Appl Physiol. 2006;100(6):1883–94.
23. Færch K, Borch-Johnsen K, Vaag A, et al. Sex differences in glucose levels: a consequence of physiology or methodological convenience? The Inter99 study. Diabetologia. 2010;53(5):858–65.
24. Ahren B, Schweizer A, Dejager S, et al. Vildagliptin enhances islet responsiveness to both hyper- and hypoglycemia in patients with type 2 diabetes. J Clinl Endocrinol Metab. 2009;94(4):1236–43.
25. Pietraszek A, Gregersen S, Hermansen K. Alcohol and type 2 diabetes. A review. Nutr Metab Cardiovasc Dis. 2010;20(5):366–75.
26. Paolisso G, Monami M, Marfella R, et al. Dipeptidyl peptidase-4 inhibitors in the elderly: more benefits or risks? Adv Ther. 2012;29(3):218–33.
27. Isacson D, Johansson L, Bingefors K, et al. Nationwide survey of subjectively reported adverse drug reactions in Sweden. Ann Pharmacother. 2008;42(3):347–53.