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Risk of non-hypoglycemic agents for hypoglycemia-related hospitalization in patients with type 2 diabetes: a large-scale medical receipt database analysis

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ABSTRACT

Introduction Hypoglycemia is listed as an adverse effect in the package inserts of not only hypoglycemic agents but also many other drugs. We aimed to clarify real-world factors related to an increased risk of hypoglycemia-related hospitalization (HRH) in Japanese patients with type 2 diabetes (T2D) on non-hypoglycemic agents that have been associated with hypoglycemia.

Research design and methods This cross-sectional study was performed using data from the Medical Data Vision administrative claims database. We identified patients with T2D who were enrolled in the database between April 2014 and October 2019. Logistic regression analyses were performed to identify clinical factors associated with HRH due to non-hypoglycemic agents.

Results Among 703 745 patients with T2D, 10 376 patients (1.47%) experienced HRH. The use of 332 non-hypoglycemic agents was associated with hypoglycemia. Multivariate analysis was performed to calculate OR for HRH. Seventy-five drugs had an OR greater than 1, and the values were significant. The OR was the highest for diazoxide (OR 15.5, 95% CI 4.87 to 49.3). The OR was higher than 2.0 for methylphenidate (OR 5.15, 95% CI 1.53 to 17.3), disulfiram (OR 4.21, 95% CI 2.05 to 8.62) and hydrocortisone (OR 2.89, 95% CI 1.11 to 7.51).

Conclusion This large retrospective analysis revealed that the risk of HRH from some non-hypoglycemic agents in patients with T2D may be increased. The results of this study are expected to support treatment planning by physicians and healthcare professionals involved in diabetes care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The mechanisms of action of hypoglycemic agents differ, depending on the drug group, and each group has characteristic side effects. Nevertheless, the most notable side effect common to all hypoglycemic agents is hypoglycemia.

⇒ Hypoglycemia is listed as an adverse effect in the package inserts of not only hypoglycemic agents but also many other drugs.

WHAT THIS STUDY ADDS

⇒ In this real-world retrospective analysis, we were able to clarify factors related to an increased risk of hypoglycemia-related hospitalization (HRH) in Japanese patients with type 2 diabetes on non-hypoglycemic agents that have been associated with hypoglycemia.

⇒ In this study, we elucidated the OR of HRH was particularly elevated with diazoxide, disulfiram and hydrocortisone use.

⇒ We were able to clarify other factors that were associated with a higher risk of hypoglycemia, such as a body mass index of <25 kg/m^2.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By considering the comorbidities and various concomitant drugs of individual patients and clarifying the risk of HRH under various conditions, the risk of hypoglycemia may be minimized.

INTRODUCTION

In Japan, the goal of type 2 diabetes (T2D) treatment is to achieve good glycemic control. To do this, clinicians are free to use two injectable hypoglycemic drugs and seven oral hypoglycemic drugs. The mechanisms of action of hypoglycemic agents differ, depending on the drug group, and each group has characteristic side effects. Nevertheless, the most notable side effect common to all hypoglycemic agents is hypoglycemia.[1] Therefore, utmost attention should be paid to it since it is associated with decreased quality of life,[2] decreased work efficiency,[3] and increased risk of falls and car accidents.[4] Furthermore, hypoglycemia due to T2D drug therapies has been reported to increase the risk of cardiovascular events,[5 6] dementia,[7 8] and death.[9 10] Hypoglycemia is listed as an adverse effect in the package inserts of not only hypoglycemic agents but also many other drugs. It is speculated that hypoglycemia caused by non-hypoglycemic agents is more likely to be severe in patients with T2D taking hypoglycemic agents than in those not taking hypoglycemic agents. It is considered that patients taking hypoglycemic medications

pay attention to severe hypoglycemia caused by hypoglycemic medications but do not pay enough attention to hypoglycemia caused by non-hypoglycemic medications. By investigating the relationship between concomitantly used drugs other than hypoglycemic agents and hypoglycemia in detail, hypoglycemia severe enough to require hospitalization could be prevented in patients with T2D. Therefore, in this study, we aimed to clarify real-world factors related to an increased risk of hypoglycemia-related hospitalization (HRH) in Japanese patients with T2D on non-hypoglycemic agents that have been reported to be associated with hypoglycemia.

METHODS

This real-world, cross-sectional study was performed using data from the Medical Data Vision (MDV) administrative claims database (MDV Co., Tokyo, Japan). The aforementioned database is a nationwide hospital-based claims database covering almost 31 million cumulative patients since April 2008, who, as of October 2019, had been treated as inpatients or outpatients at approximately 360 hospitals in Japan (21% of the total number of hospitals) that participated in the diagnosis procedure combination/per-diem payment system. Approximately 3 million (~10%) of these patients were diagnosed with diabetes mellitus (DM). The MDV database contains anonymized information about patient characteristics, diagnoses, medical expenses, medical procedures, and drug prescriptions. All patient data were encrypted before entry into the database. Data on administrative claims made from April 1, 2014, to October 31, 2019, were extracted. Patients with T2D who did not develop HRH were observed until the end of the study period, and if a patient developed hypoglycemia at a particular time point during the study period, observation was terminated at that time point for the said patient.

Study population

Information was obtained for 3 129 105 patients registered in the MDV database from April 1, 2008, to October 31, 2019. In addition, data for patients diagnosed with DM (International Classification of Diseases, 10th Edition (ICD-10) code: E10-E14) were extracted. The following patients were excluded (figure 1): (1) patients not using hypoglycemic agents (n=1 460 086); (2) patients without BMI data (n=860 035); (3) patients under the age of 20 years (n=1838); and (4) patients diagnosed with type 1 diabetes (T1D, ICD-10 code: E10), both T1D and T2D and with other types of DM, except T1D and T2D (n=103 810). As a result, 703 745 patients with T2D were eligible for inclusion.

Identification of HRH

HRH events were identified based on previous definitions.[11 12] Hospitalizations for hypoglycemia in the MDV database were identified using the following ICD-9 codes: 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), and 251.2 (hypoglycemia, unspecified).

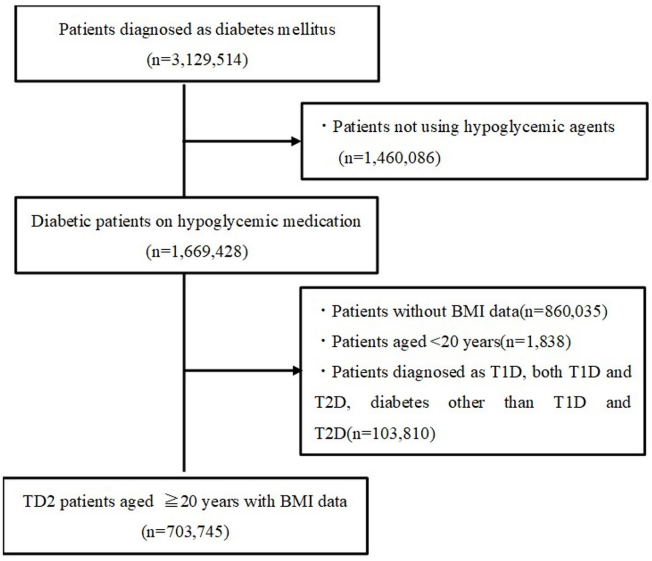

Figure 1 Characteristics of the patients. BMI, body mass index; T1D, type 1 diabetes; T2D, type 2 diabetes.

Additionally, the following ICD-10 codes were used: E08.641, E11.641, E11.649, E13.64, E13.641, E13.649, E16.0, E16.1, E15, and E16.2. Patients who did not receive a 50% glucose injection on the day of admission were excluded. HRH was defined as hospitalization due to hypoglycemia that met the aforementioned conditions.

Patient characteristics

Age, sex, and body mass index (BMI) were included as baseline characteristics and identified using the data originally provided in the billing record during the period covered. Obesity was defined as a BMI of 25 kg/m^2 or higher according to Japanese guidelines.[13]

Non-hypoglycemic agents that have been reported to be associated with hypoglycemia

Details of the non-hypoglycemic agents that have been reported to be associated with hypoglycemia are shown in online supplemental table 1. In Japan, drug manufacturers and pharmaceutical personnel are required by law to report cases suspected to be due to side effects when they become aware of them. The reported cases are published by the Pharmaceuticals and Medical Devices Agency (PMDA) in the line list and CSV file formats. Drugs reported to be associated with the onset of hypoglycemia were extracted from the data published by the PMDA and used as the target drugs.

Statistical analysis

Patient data following a normal distribution (age, BMI, hemoglobin A1C (HbA1c), and estimated glomerular filtration rate (eGFR)) are expressed as mean±SD values. Continuous variables were analyzed using a one-tailed, unpaired t-test. Categorical variables were analyzed using the χ^2 test and are expressed as absolute numbers and/or percentages. ORs for the risk of HRH were analyzed using univariate analysis. The explanatory variables used

Table 1 Baseline clinical characteristics of patients with T2D

	Total (N=703 745)	HRH (+) (N=10 376)	HRH (–) (N=693 369)	P value
Sex				
Male	434 569 (61.8)	6274 (60.5)	428 295 (61.8)	0.007
Female	269 176 (38.2)	4102 (39.5)	265 074 (38.2)	
Age (years)	70.4±12.3	71.8±11.5	70.4±12.2	<0.001
20–64	190 603 (27.1)	2350 (22.6)	188 253 (27.2)	<0.001
65–74	227 115 (32.3)	3280 (31.6)	223 835 (32.3)	
≥75	286 027 (40.6)	4746 (45.7)	281 281 (40.6)	
BMI (kg/m^2)	24.1±4.3	22.7±4.3	24.1±4.3	<0.001
≥25	256 330 (36.4)	2516 (24.2)	253 814 (36,6)	<0.001
<25	447 415 (63.6)	7860 (75.8)	439 555 (63.4)	
Hypoglycemic agents				
Biguanides	203 923 (29.0)	2616 (25.2)	201 307 (29.0)	<0.001
DPP-4 inhibitors	469 393 (66.7)	7173 (69.1)	462 220 (66.7)	<0.001
Glinides	81 736 (11.6)	2039 (19.7)	79 697 (11.5)	<0.001
GLP-1 RA	32 171 (4.6)	831 (8.0)	31 340 (4.5)	<0.001
Insulin	445 129 (63.3)	8910 (85.9)	436 219 (62.9)	<0.001
SGLT2 inhibitors	72 315 (10.3)	726 (7.0)	71 589 (10.3)	<0.001
Sulfonylureas	192 847 (27.4)	4207 (40.5)	188 640 (27.2)	<0.001
Thiazolidines	65 737 (9.3)	1384 (13.3)	64 353 (9.3)	<0.001
α-GI	158 055 (22.5)	3738 (36.0)	154 317 (22.3)	<0.001

P values were calculated for differences between patients with and without hypoglycemic events.
BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HRH (+), patients with HRH events; HRH, hypoglycemia-related hospitalization; HRH (–), patients without HRH events; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes; α-GI, alpha-glucosidase inhibitor.

in the univariate analysis were administration of antidiabetic agents (yes/no), non-hypoglycemic agents that have been reported to be associated with hypoglycemia (yes/no), sex, age (20–64, 65–74, and ≥75 years), and BMI (cut-off value: 25 kg/m^2). Multivariate analysis was performed using the explanatory variables for which the p value was <0.2 in the univariate analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows V.25.0 (IBM Corp., Armonk, NY).

RESULTS

During the study period, 703 745 patients with T2D were included. Table 1 shows the characteristics of the patients with T2D in this study. The mean patient age and BMI were 70.4±12.3 years and 24.1±4.3 kg/m^2, respectively. HRH developed in 10 376 patients (1.47%). Compared with the patients without HRH, those with T2D having HRH included more men, were older, and had lower BMIs.

Online supplemental table 1 shows the use of 331 of non-hypoglycemic agents reportedly associated with HRH. The frequency of use of 43 drugs was significantly different between patients with T2D who experienced HRH and those who did not experience HRH (online supplemental table 2).

Next, the risk of HRH was examined by calculating OR using patient background, hypoglycemic agents, and non-hypoglycemic agents, which have been reported to

Table 2 Logistic regression analysis for predictors of hypoglycemia-related hospitalization in T2D

	OR	95% CI	P value
Sex			
Male	Reference	–	0.012
Female	1.05	1.01 to 1.10	
Age (years)			
20–64	Reference	–	
65–74	1.03	0.97 to 1.08	0.331
≥75	1.10	1.04 to 1.16	<0.001
BMI (kg/m^2)			
≥25	Reference	–	<0.001
<25	1.61	1.54 to 1.69	

BMI, body mass index; T2D, type 2 diabetes.

be associated with hypoglycemia as an explanatory variable (table 2). Compared with an age of <65 years, an age of ≥75 years was associated with an increased OR for HRH (OR 1.1, 95% CI 1.04 to 1.16). The value was significant for BMI of <25 kg/m^2 (OR 1.61, 95% CI 1.54 to 1.69) with BMI of ≥25 kg/m^2 serving as the reference. Online supplemental table 3 shows the ORs for the individual components of the hypoglycemic agents. The ORs for insulin and Sulfonilureas (SU) agents were high, whereas the ORs for all SGLT2 inhibitors were less than 1.

Online supplemental table 4 shows the results of the multivariate analysis of non-hypoglycemic agents that have been reported to be associated with hypoglycemia. Seventy-five drugs had an OR greater than 1 and the values were significant. The OR was the highest for diazoxide (OR 15.5, 95% CI 4.87 to 49.3). The OR was higher than 2.0 for methylphenidate (OR 5.15, 95% CI 1.53 to 17.3), disulfiram (OR 4.21, 95% CI 2.05 to 8.62), and hydrocortisone (OR 2.89, 95% CI 1.11 to 7.51).

DISCUSSION

Patients with T2D develop multimorbidity because of persistent hyperglycemia, and thus, they are prescribed more drugs compared with those prescribed to patients with other disorders.[14] In this study, we analyzed non-hypoglycemic agents that have been reported to be associated with hypoglycemia. The strength of this study is that we were able to clarify the risk of developing HRH in settings that better reflect actual settings in which drug therapy is used for the management of T2D compared with those in previous studies. In our study, approximately 1.5% of patients with T2D showed HRH. Although the definitions of hypoglycemia severity are not identical, the incidence of HRH in this study was slightly higher than that reported in multiple intervention studies.[15–17] The reason for this is that the observation period was longer than in these studies, and the age of the patients with T2D in this study was approximately 70 years. In our study, a higher proportion of elderly people and an insulin usage rate as high as approximately 70% seem to affect the incidence of HRH. Patients associated with an increased risk of developing HRH in this study were women aged ≥75 years or with a BMI of <25 kg/m^2. The most frequently reported association with the risk of developing hypoglycemia was in the elderly.[18–20] Elderly patients with T2D have many comorbidities and are at an increased risk of polypharmacy. In the ACCORD trials,[8] the lower the BMI, the higher the risk of developing severe hypoglycemia, and a survey report on severe hypoglycemia conducted in Japan[21] showed similar results. Patients with a low BMI are presumed to have endogenously impaired insulin secretion or to be elderly patients with frailty or sarcopenia-related weight loss. In a cohort study of the risk of developing severe hypoglycemia among patients with T2D in Japan, there was no difference in the risk of developing severe hypoglycemia between men and women.[22] In this study, the risk slightly increased to 1.05 for female patients, with male patients serving as the reference. Ikeda *et al* reported that the OR for severe hypoglycemia increased among women in a study limited to elderly patients with T2D,[23] and it is necessary to investigate the details in the future.

We also examined the non-hypoglycemic agents that have been reported to be associated with hypoglycemia. The ORs for the onset of HRH were significant in the cases of 75 types of drugs, with ORs being higher than 2.0 for diazoxide, methylphenidate, disulfiram, and hydrocortisone. The OR for diazoxide was the highest (23.13). Diazoxide is used to treat low blood sugar levels due to several specific causes.[24] In other words, it is considered to have the highest OR because it is actively administered to patients with HRH. The next highest OR was that for methylphenidate. Loss of appetite is a well-known side effect of methylphenidate.[25 26] Skipping food or reducing food intake is a major risk factor for the development of severe hypoglycemia.[27] Since the patients with T2D targeted in this study were on at least one hypoglycemic agent, it is thought that the OR was high because the appetite-suppressing effect of methylphenidate caused HRH. Disulfiram is an irreversible aldehyde dehydrogenase inhibitor approved for the treatment of chronic alcoholism.[28] It has been confirmed to have a strong anti-obesity effect in in vivo studies[29] and a hypoglycemic effect[30 31] by inhibiting fructose 1,6-bisphosphatase activity. In addition, it is speculated that patients with T2D on disulfiram may develop hepatic dysfunction due to habitual alcohol intake. Owing to a combination of these factors, disulfiram is thought to have increased the OR for the onset of HRH. Hydrocortisone is used to treat adrenocortical insufficiency. Since hypoglycemia is one of the typical symptoms of adrenocortical insufficiency, it is considered that the OR for HRH increased in this study. Other frequently reported drug-induced hypoglycemia include β-blockers, ACE inhibitors/angiotensin II receptor blockers (ARBs), and fluoroquinolone antibiotics.[32] In this study, ACE inhibitors (imidapril and enalapril) and ARBs (valsartan, irbesartan, telmisartan, olmesartan, losartan, and candesartan) were associated with an increased risk of developing HRH. ACE inhibitors and ARBs have been reported to improve insulin resistance by antagonizing the AT_1 receptor and activating the peroxisome proliferator-activated receptor-γ).[33 34] These actions improve insulin resistance and increase the risk of hypoglycemia. On the other hand, in T2D, the benefits of administering ACE inhibitors/ARBs, such as prevention of diabetic nephropathy progression, are very large. Since the increase in OR is not large, the risks and benefits should be considered while administering these agents. Among β-blockers, carteolol was associated with an increased risk of developing hypoglycemia (OR 1.61, 95% CI 1.37 to 1.88). Since insulin secretion from pancreatic β-cells is associated with autonomic nerves, β-blockers have been reported to increase the risk of developing hypoglycemia.[35] Furthermore, among β-blockers, β-1 selective blockers have been reported to increase the risk

of developing severe hypoglycemia[36]; therefore, selection of drugs that specifically target particular receptors is considered important. Fluoroquinolone antibiotics are thought to promote insulin secretion and induce hypoglycemia.[37] Gatifloxacin was withdrawn from the market due to concerns regarding severe glucose disturbances. Aspinall *et al*[38] reported that levofloxacin increased the risk of severe hypoglycemia. In addition to levofloxacin, prulifloxacin and moxifloxacin were associated with significant OR values for HRH in this study. Regarding the three fluoroquinolone antibiotics that showed significant values in this study, it is recommended that their package inserts specify HRH as a serious side effect and caution should be exercised while using these drugs. When these drugs are administered to patients with T2D having risk factors for developing HRH, fluctuations in blood glucose levels should be carefully monitored.

Limitations

This study has some limitations. The MDV database consists only of data from patients treated in hospitals where acute care is administered in Japan. Therefore, it is important to recognize that it does not represent data for all patients with T2D. However, the percentage of patients with T2D (11%) in the overall MDV database were fairly close to those used in the 2017 Japan Health and Nutrition Examination Survey (14%).[39] This suggests that the T2D data in the MDV dataset may closely represent the T2D scenario in Japan as a whole. In addition, information about specific confounders of hypoglycemia (eg, HbA1c and eGFR) was available only for a limited number of patients in the MDV database. For example, cinacalcet and furosemide are frequently used drugs for patients with considerably reduced renal function. Although the ORs for these drugs were not very high in this study, they were significant, suggesting that the reduced renal function may influence risk of HRH. In addition, there may also be unknown factors that increase the risk of HRH. This was particularly influential in the analysis of drugs that have been reported to cause hypoglycemia. For drugs with a high OR, such as disulfiram, it is necessary to focus on individual drugs and to eliminate the effects of comorbidities. It is also possible that confounding factors that could not be investigated in this study may have influenced factors that showed a slight increase in OR, such as gender. One of the features of the MDV Receipt Database is that a disease title may be assigned for the purpose of T2D testing. In this study, we were unable to determine whether T2D was diagnosed and not treated with hypoglycemic drugs or whether the disease was assigned a disease title for the purpose of testing. Therefore, we had to exclude patients with T2D who were not using hypoglycemic drugs from the study. In this study, the ORs for diazoxide and hydrocortisone were high. These drugs may be used to treat hypoglycemia for a variety of reasons, including insulinoma. As this study involved patients with T2D who were receiving hypoglycemic medications, it is unlikely that patients with insulinoma were included. On the contrary, we cannot rule out the possibility that patients with underlying blood glucose-lowering diseases, such as insulinoma, were not completely excluded, which may have influenced the results. The patients with T2D who were hospitalized for hypoglycemia may have been patients with conditions that make them susceptible to the hypoglycemic effects of non-hypoglycemic agents, such as having various comorbidities. As we were not able to collect detailed laboratory values or information on complications in this study, further details should be considered. Finally, this study did not consider the time between drug administration and the onset of HRH. To develop a plan for the prevention of HRH, it is important to understand the period from the administration of the drug to the onset of HRH. In this study, we focused on drugs that are strongly associated with the development of HRH, and we would like to perform further investigations using an analysis method that includes the passage of time.

CONCLUSION

This large retrospective analysis revealed that the risk of HRH from some non-hypoglycemic agents in patients with T2D may be increased. Early identification of risk and consideration of a personalized treatment plan are essential to minimize the development of HRH. The results of this study highlight the need for continued intervention strategies by physicians and healthcare professionals involved in diabetes treatment and support treatment planning.

Contributors TH and MO conceptualized the study, performed the literature search and statistical analysis, and analyzed the data. TH, MO and TY analyzed the results. TH wrote the manuscript and is responsible for the overall content as the guarantor.

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Competing interests TH received lecture fees from Kowa KK.

Patient consent for publication Not applicable.

Ethics approval The ethics board of Kitasato University admitted that the research protocol for this study does not require ethics approval because all available data are completely anonymous with no personal information, which is characteristic ofDiagnosis Procedure Combination(DPC)-based clinical databases (control number B19-285, dated January 31, 2020). All patient data were anonymized and contained no personal data; thus, informed consent was not required. This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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