Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1360-18
Intern Med 58: 1067-1072, 2019
http://internmed.jp

【 ORIGINAL ARTICLE 】

Seasonal Variation in Severe Glucose-lowering Drug-induced Hypoglycemia in Patients with Type 2 Diabetes

Mayu Minamoto-Higashioka[1,2], Ryoichi Kawamura[2], Hironobu Umakoshi[1], Maki Yokomoto-Umakoshi[1], Daisuke Utsunomiya[1], Haruhiko Osawa[2] and Shiori Kondo[1]

Abstract:

Objective Glucose-lowering drug-induced hypoglycemia is a serious complication and there have been a few reports of seasonal variations in hypoglycemia in patients with type 2 diabetes. The aim of the present study was to examine the association between severe drug-induced hypoglycemia and seasonal variations, and to elucidate the contributing factors.

Methods This retrospective, single center clinical study, analyzed the cases of 125 patients who required emergency hospitalization for severe drug-induced hypoglycemia between January 1, 2001 and December 31, 2014. The period from November to April was defined as the cold season.

Results Severe hypoglycemia occurred more often in the cold season than in the warm season. In the cold season, 62 of 9,981 (0.6%) emergency department visits involved patients who required hospitalization for drug-induced hypoglycemia. In contrast, in the warm season, 27 of 8,649 (0.3%) visits involved patients who required hospitalization for drug-induced hypoglycemia (p=0.002). The proportion of patients treated with sulfonylurea (SU) in the cold season was higher than that in the warm season. Even the use of low-dose SU caused hypoglycemia in the cold season. In the SU-treated group, the proportion of patients with white blood cell and/or C-reactive protein elevation was higher in the cold season than in the warm season (p=0.04).

Conclusion Severe glucose-lowering drug-induced hypoglycemia occured more frequently in the cold season than in the warm season, and was associated with an inflammatory state in patients treated with SU.

Key words: drug-induced hypoglycemia, type 2 diabetes, seasonal variation, sulfonylureas

(Intern Med 58: 1067-1072, 2019)
(DOI: 10.2169/internalmedicine.1360-18)

Introduction

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self- management, education, and support are critical for preventing acute complications and reducing the risk of long-term complications (1). It has been reported that hospital admission rates for hypoglycemia exceeded those for hyperglycemia among older adults in the United States (2). The number of elderly diabetic patients is increasing in step with the aging of the population in Japan (3). Results from several studies suggest that hypoglycemia increases the risk of acute cardiovascular events (4), falls (5) and fall-related fractures (6), the progression of dementia (7, 8), and all-cause mortality (8-12). Thus, drug-induced hypoglycemia is a very serious complication that should be avoided in aging societies.

Glycemic control shows clear seasonal variations: HbA1c levels decrease in the warm season and increase in the cold season in Japan (13-15). On the other hand, Tsujimoto et al. reported that incidence of severe hypoglycemia in winter tended to increase in comparison to that in summer in patients with type 2 diabetes (16). Hashimoto et al. reported that older patients required emergency admission for severe hypoglycemia more frequently during the cold season than the warm season in 67 patients with type 2 diabetes (17). Although these two studies reported a seasonal variation in

[1]Department of Medicine, Diabetes, Metabolism and Endocrinology, Matsuyama Red Cross Hospital, Japan and [2]Department of Diabetes and Molecular Genetics, Ehime University Graduate School of Medicine, Japan
Received: April 12, 2018; Accepted: October 1, 2018; Advance Publication by J-STAGE: January 10, 2019
Correspondence to Dr. Shiori Kondo, shiori@matsuyama.jrc.or.jp

drug-induced hypoglycemia in patients with type 2 diabetes, the factors that contribute to this seasonal variation remain unclear.

The aim of the present study was to examine the association between drug-induced hypoglycemia and seasonal variation and to elucidate the contributing factors.

Materials and Methods

Study design and subjects

We retrospectively reviewed the medical records of 125 patients who required emergency hospitalization for drug-induced hypoglycemia in the Matsuyama Red Cross Hospital Japan, between January 1, 2001 and December 31, 2014. Hypoglycemia was defined as a blood glucose level <70 mg/dL or the presence of any hypoglycemic symptoms both of which required medical assistance by other persons. Diabetes was confirmed when the patient had previously been diagnosed or was taking antidiabetic drugs. We excluded 12 patients with type 1 diabetes and 24 patients for whom data were missing. Patients who were hospitalized more than once were analyzed as separate cases. Finally, 89 patients with type 2 diabetes in whom drug-induced hypoglycemia was diagnosed were included in the present study.

This clinical study was approved by the Medical Ethics Committee of Matsuyama Red Cross Hospital.

Seasons and temperatures

The mean temperatures for each month between 2001 and 2014 in Matsuyama, Ehime, Japan, were as follows: January 5.8℃, February 7.0℃, March 9.8℃, April 14.8℃, May 19.4℃, June 23.1℃, July 27.3℃, August 28.2℃, September 24.9℃, October 19.3℃, November 13.4℃, and December 8.1℃, based on data from the Japan Meteorological Agency (18).

The period from May to October, which was the warmer 6 months of the year, was defined as the warm season. The period from November to April was defined as the cold season. The mean temperatures over the years from 2001 to 2014 were 23.7℃ in the warm season and 9.8℃ in the cold season. We categorized the subjects into two groups based on the season in which hypoglycemia occurred: the cold season group (n=62) and the warm season group (n=27).

Causes of hypoglycemia

We retrospectively reviewed the medical records and attempted to determine the cause of hypoglycemia in each patient. We categorized the causes as infectious disease, anorexia, alcohol intake, others and not known. We categorized anorexia with infectious disease as 'infectious disease'.

Measurements

Blood glucose levels were typically measured using venous blood at the central laboratory; arterial blood was used in some cases. Medisafe Fit (Terumo, Tokyo, Japan) was used in a few cases. Plasma/blood glucose was measured before the intravenous injection of glucose. HbA1c levels were measured at the nearest time within 3 months of the arrival of each patient, and most of the data reported here were collected during the period of hospitalization. The HbA1c levels of patients who arrived before March 31, 2012 were calculated using the following formula: National Glycohemoglobin Standardization Program (NGSP) (%) = 1.02×Japan Diabetes Society (JDS) (%) +0.25%. Serum creatinine levels were measured upon arrival. The estimated glomerular filtration rate (eGFR) was calculated using the following formula, as recommended by the Japanese Society of Nephrology: eGFR (mL/min/173 m^2)=194×$Cre^{-1.094}$×$Age^{-0.287}$ (×0.739, if the patient was female). White blood cell (WBC) and C-reactive protein (CRP) elevation were defined as values that exceeded the upper limit of the reference value in the hospital, which were 9,640/μL, and 0.18 mg/dL, respectively. The body mass index (BMI) was calculated using the following formula: BMI = weight (kg) / $height^2$ (m). Drug-induced hypoglycemia was comprehensively diagnosed when a patient with type 2 diabetes who had been prescribed a glucose-lowering drug developed hypoglycemia. The level of insulin or C peptide at the time of hypoglycemia was also considered. A high-dose sulfonylurea (SU) was defined as glimepiride >2 mg, gliclazide >40 mg, or glibenclamide >1.25 mg, based on the recommendations for the combined use of a dipeptidyl peptidase-4 (DPP-4) inhibitor or a sodium glucose transporter 2 (SGLT2) inhibitor from the Japan Association for diabetes education and care (JADEC) or the JDS (19, 20).

Statistical analysis

All analyses were performed using the SAS software program (version 9.4; SAS Institute, Cary, NC). The characteristics were summarized as the mean with the standard deviation or as frequencies. Continuous variables between groups were compared by an analysis of covariance and categorical variables were compared using the chi-squared test or Fisher's exact test. A logistic regression analysis was performed with adjustment for age, sex, and eGFR. P values of <0.05 were considered to indicate statistical significance in all analyses.

Results

A total of 18,630 patients were transported to the emergency department by ambulance during the study period. Severe hypoglycemia occurred more frequently in the cold season than in the warm season, with 62 of 9,981 (0.6%) patients who visited the emergency department in the cold season requiring hospitalization for drug-induced hypoglycemia and 27 of 8,649 (0.3%) patients requiring hospitalization during the warm season (p=0.002). Seasonal variations in the occurrence of severe hypoglycemia are also shown in Fig. 1. Severe hypoglycemia appeared to occur more frequently in the cold season than in the warm season.

The clinical characteristics of the patients with drug-

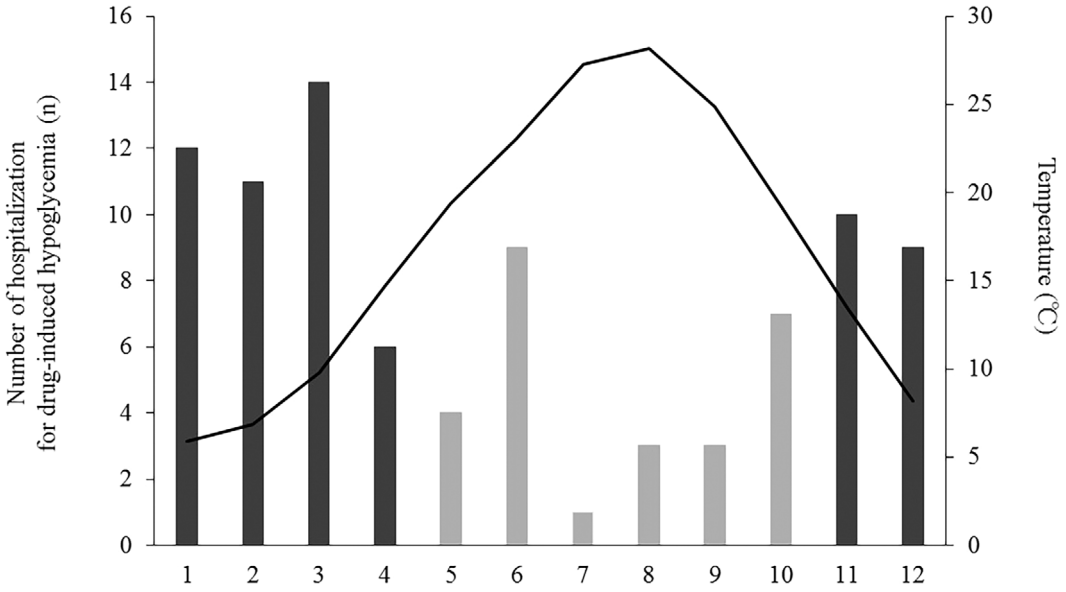

Figure 1. **The monthly average temperature in Matsuyama City and the number of hospitalizations for severe drug-induced hypoglycemia in Matsuyama Red Cross Hospital between 2001 and 2014. The 6-month period from May to October, was defined as the warm season; the 6-month period from November to April, was defined as the cold season.**

Table 1. **Characteristics of Patients with Severe Drug-induced Hypoglycemia in the Cold Season and the Warm Season.**

	Cold Season	Warm Season	p	Adjusted p
n (%)	62 (70)	27 (30)	<0.001	-
Age (years)	75±11	75±13	0.95	0.93
Men/women (n)	(25/37)	(15/12)	0.18	0.15
BMI	22±3	21±4	0.32	0.80
eGFR (mL/min/1.73m^2)	54±33	66±48	0.25	0.14
WBC (/μL)	8,829±3,280	8,560±3,517	0.73	0.95
CRP (mg/dL)	0.35 (0.13-2.13)	0.23 (0.10-1.26)	0.72	0.33
WBC and/or CRP elevation (%)	73 (45/62)	52 (14/27)	0.057	0.11
Plasma/blood glucose (mg/dL)	34±17	34±18	0.98	0.88
HbA1c (%)	6.6±1.2	6.9±1.5	0.20	0.24
SU all (%)	71 (44/62)	48 (13/27)	0.039	0.041
SU only (%)	27 (17/62)	11 (3/27)	0.09	0.27
SU or insulin (%)	94 (58/62)	85 (23/27)	0.20	0.17
SU and insulin (%)	10 (6/62)	0 (0/27)	0.09	0.95
Insulin (%)	32 (20/62)	37 (10/27)	0.66	0.93
Metformin (%)	11 (3/27)	19 (12/62)	0.34	0.22
Thiazolidine (%)	11 (7/6)	0 (0/27)	0.069	0.94
α-glucosidase inhibitor (%)	24 (15/62)	19 (5/27)	0.56	0.52
DPP-4 inhibitor (%)	3 (2/62)	15 (4/27)	0.045	0.14
Glinide (%)	46 (4/62)	4 (1/27)	0.60	0.60
High dosage of SU (%)	32 (20/62)	37 (10/27)	0.66	0.72

Data are presented as the mean±standard deviation, frequencies, or median (interquartile range). WBC or CRP elevation is defined as values greater than the reference ranges for the hospital: WBC>9,640 /μL, CRP>0.18 mg/dL, respectively. eGFR: estimated glomerular filtration rate, WBC: white blood cell count, CRP: C-reactive protein, SU: sulfonylurea, DPP-4 inhibitor: dipeptidyl peptidase-4 inhibitor

Adjusted p: adjusted for age, sex, and eGFR. In the multivariable analysis of age, sex, or eGFR, each variable was removed from the adjustment factor. BMI (n=56)

induced hypoglycemia in the cold and warm seasons are shown in Table 1. The C peptide and insulin levels of patients who had been prescribed SU or glinide or an incretin-related drug were not diminished (data not shown). The mean age of the patients was 75 years in both seasons. The proportion of the patients treated with SU in the cold season

Table 2. Characteristics of Patients with Severe Drug-induced Hypoglycemia Treated with Sulfonylurea in the Cold Season and the Warm Season.

	Cold season	Warm season	p	Adjusted p
n (%)	44 (77)	13 (23)	<0.001	-
Age (years)	78±9	83±7	0.0495	0.10
Men/women (n)	(25/19)	(4/9)	0.10	0.16
BMI	22±3	21±3	0.62	0.96
eGFR (mL/min/1.73m^2)	51±26	43±24	0.32	0.24
WBC (/μL)	8,710±3,569	9,015±2,772	0.78	0.74
CRP (mg/dL)	0.39 (0.16-2.33)	0.13 (0.10-2.03)	0.72	0.44
WBC and/or CRP elevation (%)	80 (35/44)	54 (7/13)	0.065	0.04
Plasma/blood glucose (mg/dL)	35±30	32±12	0.61	0.36
HbA1c (%)	6.4±1.1	6.4±1.1	0.94	0.79
SU only (%)	39 (17/44)	23 (3/13)	0.30	0.43
SU and insulin (%)	14 (6/44)	0 (0/13)	0.16	0.96
Metformin (%)	23 (10/44)	23 (3/13)	0.98	0.97
Thiazolidine (%)	11 (5/44)	0 (0/13)	0.20	0.95
α-glucosidase inhibitor (%)	27 (12/44)	23 (3/13)	0.76	0.99
DPP-4 inhibitor (%)	5 (2/44)	31 (4/13)	0.007	0.10
Glinide (%)	5 (2/44)	0 (0/13)	0.43	0.95
High dosage of SU (%)	45 (20/44)	77 (10/13)	0.046	0.040

Data are presented as the mean±standard deviation, frequencies, or median (interquartile range). WBC and/or CRP elevation is defined as values greater than the reference ranges for the hospital: WBC>9,640 /μL, CRP>0.18 mg/dL, respectively. eGFR: estimated glomerular filtration rate, WBC: white blood cell count, CRP: C-reactive protein, SU: sulfonylurea, DPP-4 inhibitor: dipeptidyl peptidase-4 inhibitor

Adjusted p: adjusted for age, sex, and eGFR. In the multivariable analysis of age, sex, or eGFR, each variable was removed from the adjustment factor. BMI (n=32)

was higher than that in the warm season (71%, and 48%, respectively, p=0.039). This association remained significant after adjustment for age, sex, and eGFR (p=0.041). The proportion of patients with WBC and/or CRP elevation in the cold season tended to be higher than that in the warm season. No significant differences between the two seasons were found in any of the other clinical characteristics, including height, weight, BMI, eGFR and the proportion of patients treated with insulin or oral hypoglycemic agents (with the exception of SU).

We then focused on patients who had been treated with SU. Their characteristics in the cold and warm seasons are shown in Table 2. Fewer patients were treated with high-dose SU (glimepiride >2 mg, gliclazide >40 mg, or glibenclamide >1.25 mg) in the cold season than in the warm season (45% and 77%, respectively, p=0.046). This association remained significant after adjustment for age, sex, and eGFR (p=0.040). The proportion of patients with WBC and/or CRP elevation in the cold season tended to be higher than that in the warm season (80% and 54%, respectively, p=0.06). This association was significant after adjustment for age, sex, and eGFR (p=0.040). In patients not treated with SU, there was no significant difference between the cold and warm seasons.

We further examined differences in the causes of hypoglycemia between the patients with and without WBC and/or CRP elevation in patients who had been treated with SU (Fig. 2). The subgroup of patients with WBC and/or CRP elevation included a larger proportion of patients with infectious disease in comparison to patients without WBC and/or CRP elevation (49% and 0%, respectively, p<0.001).

Discussion

The findings reported in the present study indicate that severe glucose-lowering drug-induced hypoglycemia occurred more frequently in the cold season than in the warm season. The proportion of patients treated with SU was higher in the cold season. Even the use of low-dose SU caused severe hypoglycemia in the cold season. In the SU-treated group, the proportion of patients with WBC and/or CRP elevation was higher in the cold season than in the warm season. The subgroup of patients with WBC and/or CRP elevation included a larger proportion of patients in whom infectious disease was the cause of hypoglycemia.

In the present study, severe glucose-lowering drug-induced hypoglycemia occurred more frequently in the cold season, and the use of SU was a risk factor for this seasonal variation. Seasonal variations in drug-induced hypoglycemia in patients with type 2 diabetes have been reported previously (16, 17, 21). Hashimoto et al. showed that the average number of admissions for hypoglycemia was higher in the cold season. They also presumed that anorexia related to infections in patients taking SU might have been responsible for this seasonal variation. In contrast, Tsujimoto et al. and Holstein et al. reported that the occurrence of severe hypo-

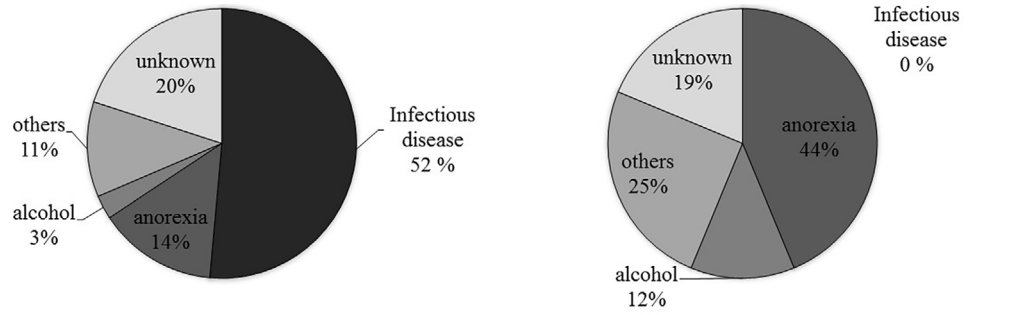

Figure 2. The causes of drug-induced hypoglycemia in SU-treated patients with and without WBC and/or CRP elevation. Patients with WBC and/or CRP elevation had a significantly larger proportion of infectious disease than patients without WBC and/or CRP elevation (p<0.001). WBC: white blood cell count, CRP: C-reactive protein, SU: sulfonylurea

glycemia did not differ among the seasons in patients with type 2 diabetes. The higher proportion of SU use in the present study could account for this difference. SU could induce hypoglycemia more frequently by interacting with antibiotics or antipyretics (22, 23). The difference in climate and the definition of a season among the studies might also affect the study results. The lower BMI of the patients in the present study could explain their higher sensitivity to SU.

In our study, WBC and/or CRP elevation was found to be a risk factor for severe hypoglycemia in patients treated with SU. The subgroup of patients with WBC and/or CRP elevation included a larger proportion of patients with infectious disease in comparison to patients without WBC and/or CRP elevation. In most cases the infectious disease that was likely associated with mild WBC and/or CRP elevation was a mild cold or enteritis (data not shown). Anorexia related to mild viral infections would have been responsible for the seasonal variation.

The rate of SU monotherapy is decreasing and the rate of combination therapy with SU and other drugs is increasing in Japan, which is expected to result in a decreased incidence of hypoglycemia induced by high-dose SU (24). In the present study, there was no significant decline in the annual number of hypoglycemia episodes induced by high-dose SU (p for trend=0.50) (data not shown). The use of high dosage of SU was more frequently associated with severe hypoglycemia in the warm season. The patients treated with SU in the warm season were older than those treated without SU (p=0.002), and tended to have a lower eGFR and HbA1c level (data not shown). Elderly patients with a low eGFR and HbA1c might have been prescribed SU inappropriately during the warm season.

In the present study, the mean HbA1c levels in the cold season appeared to be lower than those in the warm season; however, the association was not significant. In contrast, it has been reported that HbA1c levels are lower in the warm season and higher in the cold season in Japan (13, 15, 25-27). The glycemic control in the patients analyzed by the present study might have been too strict. The 2018 American Diabetes Association (ADA) Clinical Practice Recommendations state that patients who are expected to live sufficiently long to reap the benefits of long-term intensive diabetes management may be treated using therapeutic interventions and goals similar to those used for younger adults with diabetes (HbA1c levels of 7.5%). For patients with advanced diabetic complications, life-limiting comorbidities, or substantial cognitive or functional impairment, it would be reasonable to set less stringent glycemic goals (HbA1c levels of 8.0-8.5%) (28). The Japanese guidelines also recommend mild glycemic control in elderly patients (29).

The present study was associated with several limitations. First, this was a retrospective study and subjects with missing data were excluded. This study design and missing data might have influenced the results and the statistical analyses. Second, this study was performed at a single institution in the Matsuyama region. Not all of the patients who suffered from hypoglycemia in Matsuyama City were hospitalized at this hospital; thus, there might have been a selective bias in the present study. Third, the number of subjects was insufficient to permit an analysis of the relationship between the use of oral hypoglycemic agents other than SU and the season.

In conclusion, severe glucose-lowering drug-induced hypoglycemia was found to occur more frequently in the cold season than in the warm season. In the SU-treated group, hypoglycemia was associated with inflammatory states. How the seasonal variation occurs, and whether this phenomenon is specific to Japanese during this period remain unclear. Further studies are required to clarify these points.

Human rights statement: All procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent is not necessarily required for observational studies using existing data.

The authors state that they have no Conflict of Interest (COI).

References

1. American Diabetes Association. Introduction: Standards of medical care in diabetes-2018. Diabetes Care **41**: S1-S2, 2018.
2. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med **174**: 1116-1124, 2014.
3. Charvat H, Goto A, Goto M, et al. Impact of population aging on trends in diabetes prevalence: A meta-regression analysis of 160,000 Japanese adults. J Diabetes Investig **6**: 533-542, 2015.
4. Johnston SS, Conner C, Aagren M, et al. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. Diabetes Care **34**: 1164-1170, 2011.
5. Schwartz AV, Vittinghoff E, Sellmeyer DE, et al. Diabetes-related complications, glycemic control, and falls in older adults. Diabetes Care **31**: 391-396, 2008.
6. Johnston SS, Conner C, Aagren M, et al. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab **14**: 634-643, 2012.
7. Whitmer RA, Karter AJ, Yaffe K, et al. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA **301**: 1565-1572, 2009.
8. Yaffe K, Falvey CM, Hamilton N, et al. Health ABC Study. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Intern Med **173**: 1300-1306, 2013.
9. Zoungas S, Patel A, Chalmers J, et al. ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med **363**: 1410-1418, 2010.
10. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ **340**: b4909, 2010.
11. Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes mellitus: a nationwide population-based study. Diabetes Care **36**: 894-900, 2013.
12. McCoy RG, Van Houten HK, Ziegenfuss JY, et al. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care **35**: 1897-1901, 2012.
13. Ishii H, Suzuki H, Baba T, et al. Seasonal variation of glycemic control in type 2 diabetic patients. Diabetes Care **24**: 1503, 2001.
14. Sohmiya M, Kanazawa I, Kato Y. Seasonal changes in body composition and blood HbA1c levels without weight change in male patients with type 2 diabetes treated with insulin. Diabetes Care **27**: 1238-1239, 2004.
15. Iwao T, Sakai K, Ando E. Seasonal fluctuations of glycated hemoglobin levels in Japanese diabetic patients: effect of diet and physical activity. Diabetol Int **4**: 173-178, 2013.
16. Tsujimoto T, Yamamoto-Honda R, Kajio H, et al. Seasonal variations of severe hypoglycemia in patients with type 1 diabetes mellitus, type 2 diabetes mellitus, and non-diabetes mellitus: clinical analysis of 578 hypoglycemia cases. Medicine **93**: e148, 2014.
17. Hashimoto T, Morita A, Hashimoto Y, et al. Seasonal variation of severe hypoglycemia in hospitalized patients 60 years of age or older presenting to an emergency center hospital between 2004 and 2010. Intern Med **52**: 2721-2726, 2013.
18. Temperature and precipitation of Matsuyama, Ehime. [Internet]. [cited 2018 Sep. 24]. Available from: http://weather.time-j.net/Stations/JP/matsuyama (in Japanese).
19. Kimura T, Shiosakai K, Takeda Y, et al. Quantitative evaluation of compliance with recommendation for sulfonylurea dose co-administered with DPP-4 inhibitors in Japan. Pharmaceutics **4**: 479-493, 2012.
20. Committee for appropriate use of SGLT2 inhibitor. Recommendation for appropriate use of SGLT2 inhibitor. [Internet]. [cited 2018 Sep. 24]. Available from: http://www.fa.kyorin.co.jp/jds/uploads/recommendation_SGLT2.pdf (in Japanese).
21. Holstein A, Wohland T, Patzer OM, et al. Accumulation of severe hypoglycemia at weekends and in warm seasons in patients with type 1 diabetes but not with type 2 diabetes. J Diabetes Complications **30**: 1308-1314, 2016.
22. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med **354**: 1352-1361, 2006.
23. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycemia in Type 2 diabetes. Diabetic Med **25**: 245-254, 2008.
24. Oishi M, Yamazaki K, Okuguchi F. Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). J Diabetes Investig **5**: 581-587, 2014.
25. Sakura H, Tanaka Y, Iwamoto Y. Seasonal fluctuations of glycated hemoglobin levels in Japanese diabetic patients. Diabetes Res Clin Pract **88**: 65-70, 2010.
26. Iwata K, Iwasa M, Nakatani T, et al. Seasonal variation in visceral fat and blood HbA1c in people with type 2 diabetes. Diabetes Res Clin Pract **96**: e53-e54, 2012.
27. Maguire GA, Edwards OM. Seasonal variation in glycated haemoglobin in diabetics. Ann Clin Biochem **38**: 59-60, 2001.
28. American Diabetes Association. 11. Older adults: standards of medical care in diabetes-2018. Diabetes Care **41** (Suppl. 1): S119-S125, 2018.
29. Practice Guideline for the Treatment for Diabetes in Japan 2016. The Japan Diabetes Society, Ed. Goals and Strategies for Diabetes Management. Nankodo, Tokyo, 2016: 23-35 (in Japanese).