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SHORT REPORT

Trends of severe hypoglycemia in patients with type 2 diabetes in Korea: A longitudinal nationwide cohort study

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ABSTRACT

To estimate the trends in the prevalence of severe hypoglycemia (SH) in patients with type 2 diabetes in Korea, we investigated the total number of SH episodes among type 2 diabetes patients aged ≥30 years who visited the emergency department between 2002 and 2019, using the Korean National Health Insurance Service database. The prevalence of SH events increased from 2002 to 2012; however, it has decreased gradually since 2012. In 2019, the prevalence of SH was 0.6%, with an incidence rate of 4.43 per 1,000 person-years. Approximately 23,000 SH events occur every year in Korea. Although the incidence is steadily decreasing, there are a considerable number of SH events in type 2 diabetes patients. The decline in the incidence of SH seems to most likely be due to the increased prescription rate of hypoglycemic agents without hypoglycemia risk, less-strict treatment goals and the individualization of therapy.

INTRODUCTION

Severe hypoglycemia (SH) is an advanced and life-threatening form of hypoglycemia that can cause loss of consciousness and cardiovascular disease[1,2], and has a negative impact on health-related quality of life with increased costs[3,4]. The frequencies of SH in diabetes patients substantially vary across studies. A systematic review of 46 population-based studies estimated that the prevalence of SH was 6%, with an incidence rate (IR) of 0.80 per person-years (PYs) in type 2 diabetes patients[5]. According to a cohort study from OptumLabs Data Warehouse in the USA, there were 9.1 SH visits per 1,000 PYs[6]. Claims data from privately insured and Medicare Advantage patients with type 2 diabetes reported that the overall rate of SH remained constant (1.3 per 100 PYs) from 2006 to 2013 in the USA.[7]

Clinical practice for diabetes care, the introduction of new antihyperglycemic agents, and trends in prescription patterns changed remarkably around 2010 and over the past decades. In the present study, we aimed to investigate the trends in the prevalence and incidence of SH in Korean adults with type 2 diabetes between 2002 and 2019. The clinical characteristics of the patients with and without SH occurrence in 2002 and 2019 were also further compared.

MATERIALS AND METHODS

We used the Korean National Health Insurance Service claim database[8]. In this analysis, we included individuals with type 2 diabetes aged ≥30 years from 1 January 2002 to 31 December 2019. To estimate the trends in the prevalence and IR of SH in type 2 diabetes, we analyzed the total number of patients who visited the emergency department with SH episodes among type 2 diabetes patients. To investigate the temporal changes in SH development, we collected data on all episodes reporting SH as the primary outcome, which was defined as the diagnostic clinical codes for hypoglycemia (ICD-10 codes of E160-162, E1163, E1463)[2]. We further analyzed the information on the prescription patterns of antihyperglycemic agents and a prior history of SH within 3 years before the current SH events in 2002 and 2019. Data on antihyperglycemic agents (insulin, metformin, sulfonylurea, meglitinide, a-glucosidase inhibitors, thiazolidinedione, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium–glucose cotransporter 2 [SGLT-2] inhibitors) were included. Type 2 diabetes was defined based on the diagnostic ICD-10 codes (E11-E14) and/or the claims for prescriptions of

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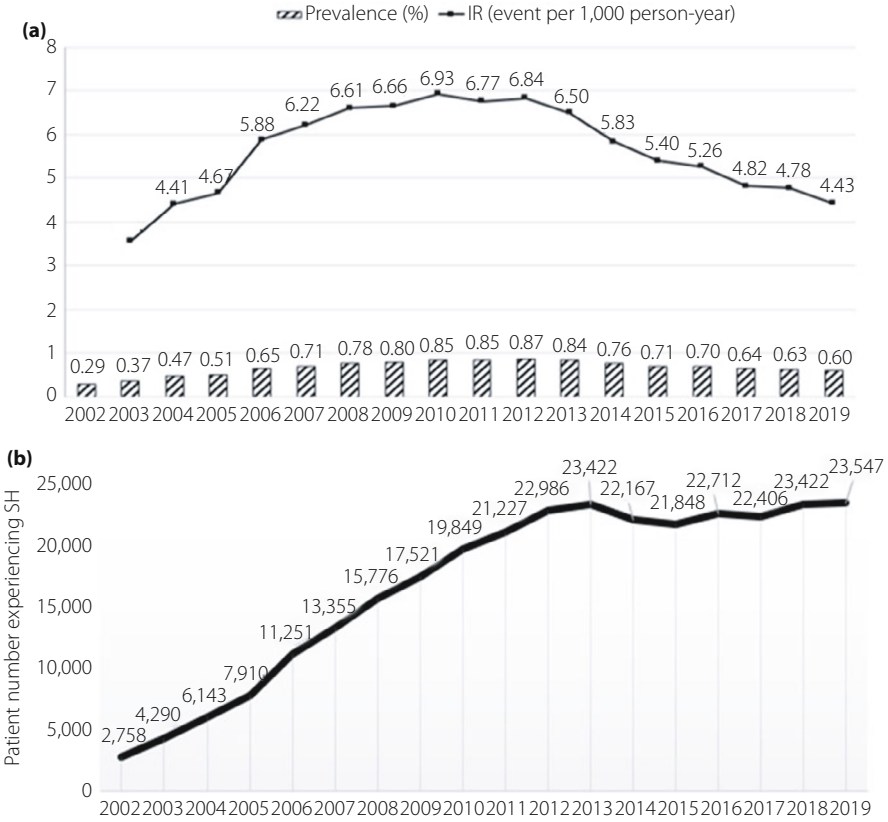

Figure 1 | The trends of (a) severe hypoglycemia (SH) prevalence and incidence, and (b) total number experiencing severe hypoglycemia in Korean adults with type 2 diabetes from 2002 to 2019. The annual incidence rate (IR) of severe hypoglycemia is presented as the number of events per 1,000 person-years.

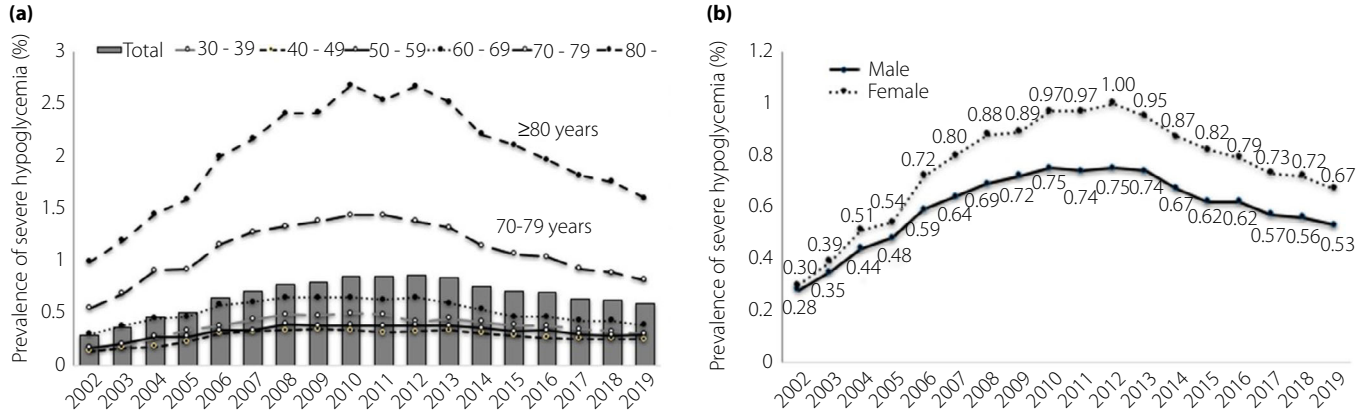

Figure 2 | The trends of severe hypoglycemia prevalence according to (a) age group and (b) sex in Korean adults with type 2 diabetes from 2002 to 2019.

antidiabetic medications. Hypertension was defined as diagnostic ICD-10 codes (I10-13 or I15) and at least one claim per year for antihypertensive medications. Dyslipidemia was defined as a diagnostic code (E78) and at least one claim per year for a lipid-lowering agent[2,9].

The baseline characteristics are presented as numbers and percentages for categorical variables, and means ± standard deviations for continuous variables. Analyses for the comparison of the baseline characteristics were carried out using independent *t*-tests for continuous variables, and χ^2-tests for categorical variables. We additionally carried out a multiple

Table 1 | Clinical characteristics of severe hypoglycemia in type 2 diabetes patients in 2002, 2009 and 2019

	2002			2009			2019			
	SH (–)	SH (+)	*P*-value	SH (–)	SH (+)	*P*-value	SH (–)	SH (+)	*P*-value	*P*-value†
n	940,198	2,758		2,162,667	17,521		3,926,874	23,547		
Age (years)										
30–39	48,052 (5.11)	82 (2.97)	<0.001	71,547 (3.31)	346 (1.97)	<0.001	102,596 (2.61)	312 (1.33)	<0.001	<0.001
40–49	160,286 (18.1)	219 (7.94)		293,100 (13.6)	1,017 (5.8)		373,420 (9.51)	953 (4.05)		
50–59	248,842 (26.5)	423 (15.3)		556,869 (25.8)	2,135 (12.2)		912,918 (23.3)	2,733 (11.6)		
60–69	311,606 (33.1)	952 (34.5)		630,425 (29.3)	4,139 (23.6)		1,162,173 (29.6)	4,534 (19.3)		
70–79	143,142 (15.2)	798 (28.9)		478,131 (22.1)	6,680 (38.1)		919,886 (23.4)	7,622 (32.4)		
≥80	28,270 (3.01)	284 (10.3)		128,962 (5.96)	3,204 (18.3)		455,881 (11.6)	7,393 (31.4)		
Sex (male)	476,051 (50.6)	1,347 (48.8)	0.060	1,144,232 (52.9)	8,342 (47.6)	<0.0001	2,188,623 (55.7)	11,747 (49.9)	<0.0001	0.0003
Hypertension (yes)	443,998 (47.2)	1,921 (69.7)	<0.001	1,405,957 (65.0)	14,260 (81.4)	<0.001	2,534,352 (64.5)	18,967 (80.6)	<0.001	0.0214
Dyslipidemia (yes)	153,321 (16.3)	530 (19.2)	<0.001	872,499 (40.3)	6,995 (39.9)	0.259	2,794,104 (71.2)	15,944 (67.7)	<0.001	<0.001
Insulin use	129,271 (13.8)	1,240 (45.0)	<0.001	251,481 (11.6)	5,666 (32.3)	<0.0001	361,526 (9.2)	7,981 (33.9)	<0.0001	<0.0001
Basal	88,093 (68.1)	876 (70.6)		197,152 (78.4)	4,494 (79.3)		228,418 (63.2)	4,957 (62.1)		<0.0001
Pre-meal	9,120 (7.05)	119 (9.60)		46,185 (18.4)	1,133 (20.0)		105,178 (29.1)	2,730 (34.2)		<0.0001
Pre-mixed	13,322 (10.3)	130 (10.5)		46,854 (18.6)	1,218 (21.5)		47,412 (13.1)	1,421 (17.8)		<0.0001
Oral hypoglycemic agents										
0‡	79,788 (8.49)	834 (30.2)	<0.001	123,816 (5.73)	3,174 (18.1)	<0.0001	117,852 (3.0)	3,198 (13.6)	<0.0001	<0.0001
1 class	500,255 (53.2)	1,095 (39.7)		834,629 (38.6)	5,083 (29.0)		1,094,483 (27.9)	4,733 (20.1)		
2 classes	304,295 (32.4)	700 (25.4)		943,531 (43.6)	6,585 (37.6)		1,657,180 (42.2)	8,486 (36.0)		
3 classes	55,860 (5.94)	129 (4.68)		260,691 (12.1)	2,679 (15.3)		1,057,359 (26.9)	7,130 (30.3)		
Sulfonylurea	763,954 (81.3)	1,654 (60.0)	<0.001	1,516,023 (70.1)	11,523 (65.8)	<0.0001	1,393,724 (35.5)	12,591 (53.5)	<0.0001	<0.0001
Metformin	334,143 (35.5)	648 (23.5)	<0.001	1,332,656 (61.6)	8,619 (49.2)	<0.0001	3,310,902 (84.3)	14,499 (61.6)	<0.0001	<0.0001
Meglitinides	2,992 (0.32)	14 (0.51)	0.078	73,710 (3.41)	868 (5.0)	<0.0001	9,879 (0.3)	204 (0.9)	<0.0001	<0.0001
a-Glucosidase inhibitor	141,977 (15.1)	459 (16.6)	0.024	368,900 (17.1)	4,005 (22.9)	<0.0001	50,353 (1.3)	753 (3.2)	<0.0001	<0.0001
Thiazolidinedione	34,257 (3.64)	108 (3.92)	0.446	185,573 (8.6)	1,238 (7.1)	<0.0001	339,460 (8.6)	2,308 (9.8)	<0.0001	<0.0001
DPP-4 inhibitor	–	–		33,762 (1.6)	113 (0.6)	<0.0001	2,225,267 (56.7)	12,393 (52.6)	<0.0001	<0.0001
SGLT-2 inhibitor	–	–		–	–		283,798 (7.2)	688 (2.9)	<0.0001	–
No insulin/no SU	76,563 (8.36)	117 (4.24)	<0.0001	456,717 (21.1)	1,581 (9.02)	<0.0001	2,934,986 (74.7)	13,794 (58.6)	<0.0001	<0.0001
Duration of DM medication (years)	–	–		4.0 ± 2.6	4.9 ± 2.4	<0.0001	8.1 ± 5.8	12.1 ± 5.4	<0.0001	<0.0001
SH in previous 3 years	–	–		23,677 (1.1)	2,639 (15.1)	<0.0001	41,936 (1.1)	4,090 (17.4)	<0.0001	<0.0001
SH event number in previous 3 years										
0	–	–		2,138,990 (98.9)	14,882 (84.9)	<0.0001	3,884,938 (98.9)	19,457 (82.6)	<0.0001	<0.0001
1	–	–		20,250 (0.9)	1,811 (10.3)		34,680 (0.9)	2,695 (11.5)		
2	–	–		2,647 (0.1)	472 (2.7)		5,381 (0.1)	774 (3.3)		
≥3	–	–		780 (0.04)	356 (2.0)		1,875 (0.05)	621 (2.6)		

Data are *n* (%) or mean ± standard deviation. DM, diabetes; DPP-4, dipeptidyl peptidase-4, SGLT-2, sodium–glucose cotransporter 2; SH, severe hypoglycemia; SU, sulfonylurea. †*P*-value for 2009 versus 2019. ‡0 means insulin monotherapy.

logistic regression analysis between the groups with and without SH. A two-sided *P*-value of <0.05 was considered significant. All statistical analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The trends of SH prevalence and incidence in Korean adults with type 2 diabetes are shown in Figure 1. The number of all adults diagnosed with type 2 diabetes was 942,956 in 2002 and 3,950,421 in 2019. The prevalence of SH was 0.29% in 2002 and 0.60% in 2019. It steadily increased from 2002 to 2012 (0.87%), and then gradually decreased until 2019 (Figure 1a). The IR increased between 2003 (3.56/1,000 PYs) and 2012 (6.84/1,000 PYs), and then, the trend has gradually declined since 2012. The IR for SH was 4.43/1,000 people in 2019 (Figure 1a). Although the prevalence and IRs showed decreasing tendencies, the absolute number of patients experiencing SH has been steadily increasing. This increase seems to result from an increase in the total population of people with type 2 diabetes and a growing portion of the aging population. Approximately 23,000 cases of SH occur every year among type 2 diabetes patients in Korea. (Figure 1b). The prevalence increased rapidly with age and was remarkably higher in adults aged ≥70 years. In 2019, the prevalence of SH in patients aged in their 30s, 40s, 50s, 60s and 70s, and those aged ≥80 years was 0.30%, 0.25%, 0.30%, 0.39%, 0.82%, and 1.60%, respectively (Figure 2a). A total of 63.8% of total SH cases occurred in people aged ≥70 years in 2019. Severe hypoglycemia was more prevalent in women than men throughout the study period (women vs men, 0.30% vs 0.28% in 2002, and 0.67% vs 0.53% in 2019, respectively; Figure 2b).

We analyzed the changes in the characteristics of people with type 2 diabetes who experienced SH over the past 10 years by comparing the data from 2002 and 2019. The trends in the utilization of antihyperglycemic agents have changed dramatically among type 2 diabetes patients in Korea. The proportion of people with SH receiving sulfonylurea was 65.8% in 2009 and 53.5% in 2019 ($P < 0.001$). However, the proportion of insulin users in the population with SH events was not significantly different between 2009 and 2019 (32.3% vs 33.9%, $P = 0.117$). The proportions of people with type 2 diabetes receiving meglitinide or α-glucosidase inhibitor decreased significantly; however, the proportions of patients receiving metformin, DPP-4 inhibitors and SGLT-2 inhibitors remarkably increased from

Table 2 | Multiple logistic regression analysis between the groups with and without severe hypoglycemia

	Odds ratio (all adjusted)					
	2002	*P*-value	2009	*P*-value	2019	*P*-value
Age (years)						
30–39	1 (ref.)	<0.0001	1 (ref.)	<0.0001	1 (ref.)	<0.0001
40–49	0.763 (0.591, 0.984)		0.711 (0.628, 0.805)		0.874 (0.768, 0.995)	
50–59	0.808 (0.636, 1.026)		0.699 (0.622, 0.784)		0.895 (0.794, 1.008)	
60–69	1.236 (0.983, 1.556)		1.007 (0.9, 1.127)		0.963 (0.856, 1.082)	
70–79	1.929 (1.527, 2.439)		1.763 (1.576, 1.972)		1.428 (1.270, 1.605)	
80	3.015 (2.337, 3.89)		2.614 (2.327, 2.936)		1.935 (1.719, 2.179)	
Sex (female)	0.965 (0.893, 1.043)	0.3695	0.993 (0.962, 1.025)	0.6839	1.051 (1.022, 1.080)	0.0004
Hypertension	1.524 (1.395, 1.665)	<0.0001	1.482 (1.423, 1.543)	<0.0001	1.295 (1.251, 1.340)	<0.0001
Dyslipidemia	0.967 (0.876, 1.068)	0.5074	0.947 (0.917, 0.978)	0.0009	0.908 (0.881, 0.935)	<0.0001
Insulin use	2.96 (2.629, 3.332)	<0.0001	2.641 (2.519, 2.768)	<0.0001	1.729 (1.668, 1.793)	<0.0001
Oral hypoglycemic agents						
0	1 (ref.)	0.004	1 (ref.)	<0.0001	1 (ref.)	<0.0001
1 class	2.491 (0.345, 17.994)		0.88 (0.691, 1.119)		0.617 (0.485, 0.785)	
2 classes	9.259 (0.179, 479.475)		1.376 (0.859, 2.204)		0.559 (0.347, 0.901)	
≥3 classes	–		2.103 (1.033, 4.281)		0.508 (0.246, 1.048)	
Sulfonylurea	0.339 (0.047, 2.44)	0.2825	1.201 (0.948, 1.521)	0.1293	1.940 (1.526, 2.467)	<0.0001
Metformin	0.272 (0.038, 1.957)	0.1957	0.769 (0.607, 0.974)	0.0296	0.687 (0.541, 0.874)	0.0022
Thiazolidinedione	0.417 (0.058, 2.983)	0.3835	0.955 (0.754, 1.209)	0.6998	1.578 (1.244, 2.003)	0.0002
DPP-4 inhibitors	–	–	0.663 (0.493, 0.89)	0.0062	1.155 (0.909, 1.468)	0.2385
α-Glucosidase inhibitors	0.388 (0.054, 2.797)	0.3475	1.002 (0.79, 1.27)	0.9875	1.965 (1.528, 2.526)	<0.0001
SGLT-2 inhibitors	–	–	–	–	0.783 (0.611, 1.004)	0.0543
Previous SH history	–	–	7.607 (7.262, 7.969)	<0.0001	8.470 (8.155, 8.798)	<0.0001

Adjusted for age, sex, presence of hypertension or dyslipidemia, insulin use, classes of hypoglycemic agents, use of sulfonylurea, metformin, thiazolidinedione, dipeptidyl peptidase-4 inhibitors (DPP-4), alpha-glucosidase inhibitors or sodium–glucose cotransporter 2 (SGLT-2) inhibitors, and presence or history of severe hypoglycemia (SH) within the past 3 years.

2009 to 2019 (P for all <0.001). Compared with patients without SH events, the patients with SH events showed higher use of insulin and meglitinide, longer durations of diabetes treatment, use of multiple oral hypoglycemic agents, and lower use of metformin, DPP-4 inhibitors and SGLT-2 inhibitors (P for all <0.001). In particular, 15–17% of patients with SH experienced at least one event of antecedent SH within the preceding 3 years (Table 1). Multiple logistic regression analysis showed that older age, insulin or SU use and previous SH history were significantly associated with SH (Table 2).

DISCUSSION

From the present study, we found that the prevalence and incidence of SH decreased gradually from 2012 in type 2 diabetes patients. However, the absolute frequency of SH remains largely unchanged and steadily increases despite several efforts to reduce SH, because the diabetes population has increased. As large-scale intensive glucose control studies have shown at least a two- to threefold increased risk of SH compared with standard treatment groups, many clinical practice guidelines have recommended active avoidance of hypoglycemia or SH[10–13]. DPP-4 inhibitors were introduced and began to be prescribed from 2008 to 2010 in Korea. Therefore, the reduction in the incidence of SH seems to most likely be due to the increased prescription rate of antihyperglycemic medications without hypoglycemia risk, such as DPP-4 inhibitors or SGLT-2 inhibitors, less strict treatment goals, the individualization of diabetes therapy according to clinical practice guidelines and active diabetes education for preventing hypoglycemia[14].

The strength of the present study was that it was a large-scale nationwide study with long-term follow up in type 2 diabetes patients. At the same time, our study lacked important variables for glycemic control status, medication dosages and detailed information about disease duration. Despite these limitations, it is very important to know the current situation of SH occurrence, because there are still a considerable number of patients suffering from SH, and it could induce very serious clinical outcomes, especially in patients who are very old, fragile, and have long-standing diabetes and multiple underlying advanced comorbidities[15–17]. In addition to comprehensive diabetes care, a more intensive, individualized and patient-centered detailed approach with education for the prevention of SH should be emphasized in this high-risk population of type 2 diabetes patients.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: Approved by both the Korean National Health Insurance Service and the Institutional Review Board of the Catholic University of Korea (XC19WIDI0105).
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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