A Population-Based Study of All-Cause Mortality and Cardiovascular Disease in Association With Prior History of Hypoglycemia Among Patients With Type 1 Diabetes

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OBJECTIVE

This study investigated the effects of severe hypoglycemia on risks of all-cause mortality and cardiovascular disease (CVD) incidence in patients with type 1 diabetes mellitus (T1DM).

RESEARCH DESIGN AND METHODS

Two nested case-control studies with age- and sex-matched control subjects and using the time-density sampling method were performed separately within a cohort of 10,411 patients with T1DM in Taiwan. The study enrolled 564 nonsurvivors and 1,615 control subjects as well as 743 CVD case subjects and 1,439 control subjects between 1997 and 2011. History of severe hypoglycemia was identified during 1 year, 1–3 years, and 3–5 years before the occurrence of the study outcomes. Conditional logistic regression analyses were performed to estimate the odds ratio (OR) and 95% CI of the study outcomes.

RESULTS

Prior severe hypoglycemic events within 1 year were associated with higher risks of all-cause mortality and CVD (adjusted OR 2.74 [95% CI 1.96–3.85] and 2.02 [1.35–3.01], respectively). Events occurring within 1–3 years and 3–5 years before death were also associated with adjusted ORs of 1.94 (95% CI 1.39–2.71) and 1.68 (1.15–2.44), respectively. Significant dose–gradient effects of severe hypoglycemia frequency on mortality and CVD were observed within 5 years.

CONCLUSIONS

Although the CVD incidence may be associated with severe hypoglycemic events occurring in the previous year, the risk of all-cause mortality was associated with severe hypoglycemic events occurring in the preceding 5 years. Exposure to repeated severe hypoglycemic events can lead to higher risks of mortality and CVD.

Cardiovascular disease (CVD) is the major cause of death for patients with type 1 diabetes mellitus (T1DM) (1). Although intensive glycemic control reportedly has long-term beneficial effects on CVD onset in T1DM (2), hypoglycemic events often accompany such strategy and must be addressed simultaneously.

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Severe hypoglycemia was reported to be associated with increased risk of CVD incidence and death among patients with type 2 diabetes mellitus (T2DM) (3–7). Although patients with T1DM may suffer more frequently from hypoglycemia than those with T2DM (8), very few studies have investigated whether hypoglycemia may also increase the risk of CVD (6,9,10) or death (1,6,7) in patients with T1DM; moreover, the results of these studies have been inconclusive (6,9,10) because of the dissimilarities in their methodological aspects, including their enrollment of populations with T1DM with different levels of glycemic control, application of different data collection methods, and adoption of different lengths of observational periods.

Only a few population-based studies have examined the potential cumulative effect of repeated severe hypoglycemia on all-cause mortality or CVD incidence in T1DM (9). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study of T2DM found a weakly inverse association between the annualized number of hypoglycemic episodes and the risk of death (11,12). By contrast, some studies find that repeated hypoglycemia may be an aggravating factor to atherosclerosis in T1DM (13,14). Studies on the compromised sympathetic-adrenal reaction in patients with repeated hypoglycemia have been inconclusive regarding whether such a reaction may further damage intravascular coagulation and thrombosis (15) or decrease the vulnerability of these patients to adverse health outcomes (12).

Apart from the lack of information on the potential dose–gradient effect associated with severe hypoglycemic events in T1DM from population-based studies, the risks of all-cause mortality/CVD incidence associated with severe hypoglycemia occurring at different periods before all-cause mortality/CVD incidence have never been examined. In this study, we used the population-based medical claims of a cohort of patients with T1DM to examine whether the risks of all-cause mortality/CVD incidence are associated with previous episodes of severe hypoglycemia in different periods and whether severe hypoglycemia may pose a dose–gradient effect on the risks of all-cause mortality/CVD incidence.

RESEARCH DESIGN AND METHODS

The study proposal was approved by the Chi Mei Medical Center Institutional Review Board (No. 10202-E01). The access to the National Health Insurance (NHI) research database was approved by the National Health Research Institutes Review Committee (NHIRD-102-021).

Data Source

Data were retrieved from Taiwan's NHI research database, a medical claim database that stores the medical records of beneficiaries that are uploaded by medical institutions to obtain reimbursement from NHI. Taiwan's NHI program is run and supervised by the Administration of NHI, Ministry of Health and Welfare. This program universally covers medical insurance for nearly all (>97%) Taiwanese citizens (prisoners and military personnel were exempted in our study period) (16). The Bureau of NHI performs quarterly expert reviews on a random sample of inpatient and outpatient claims to ensure their accuracy (17). In this study, we retrieved several parts of the NHI claim data sets, including the inpatient and outpatient medical claims, the Catastrophic Illness Database (CID), and the sociodemographic characteristics of the beneficiaries.

T1DM is among the listed catastrophic illnesses in the CID. Individuals who are registered in the CID for T1DM must provide to the NHI Administration review board a physician's diagnosis certificate and relevant medical records, including examination results, fasting or glucagon-stimulated C-peptide level, anti-GAD antibody level, and history of diabetic ketoacidosis. Disease diagnosis was validated through an expert review process. When the applications are approved, the patients are exempted from disease-related copayments for medical services. T1DM diagnosis in the CID has been used to report the incidence of T1DM in Taiwan (18,19), with a positive predictive rate of 98.3% (19).

To investigate the underlying cause of death (UCOD) in patients with T1DM, we linked the claim data of NHIRD to those of the Taiwan Death Registry.

Study Design and End Points

A cohort of 10,411 patients with T1DM registered in the CID (ICD-9CM: 250.x1 or 250.x3) was identified from 2003 to 2011. Given that the registration for T1DM in CID was initiated in 2003, those registered in 2003 included prevalent and also incident cases of T1DM. For prevalent cases, the earliest date of clinical visit for T1DM can be traced back to as early as 1 January 1997. Ten patients without birth date information and 87 patients with a history of CVD events before the first diagnosis (or first clinical visit) for T1DM between 1997 and 2011 were excluded. Among the remaining 10,314 patients with T1DM, 830 had experienced their first CVD attack, and 615 patients died of any cause during the study period (1997 to 2011). By taking all-cause mortality and CVD incidence as two separate outcomes, we conducted two nested case-control studies within the study cohort.

For all-cause mortality, those patients who died of any cause were selected as case subjects (nonsurvivors). For each nonsurvival case subject, other patients with T1DM who survived on the date of the case subject's death were treated as candidates for control subjects (survivors). By using the time-density sampling method, 564 of the 615 nonsurvivors (91.7%) were successfully matched to 1 to 3 control subjects for sex, age at death, and birthday (±90 days). For CVD incidence, those patients who developed their first major CV events from the first diagnosis (for incident case) or clinical visit (for prevalent case) to the end of the follow-up period were selected as "CVD case" subjects. The incidence of major CV events was defined as the first occurrence of coronary artery disease (CAD) (ICD-9CM: 410, 411, 413, and 428; A-code: A291, A292, A293, and A299) or cerebral vascular attack (ICD-9CM: 430–436; A-code: A291, A292, A293, and A299) in outpatient (i.e., at least three visits for the same diagnosis within 1 year) or inpatient (with one or more admissions during the study period) medical records. Other patients with T1DM with no history of CVD on the date of CVD incidence were treated as candidates for inclusion in the "CVD control" group. Among 830 patients with CVD incidence, 743 (89.5%) were successfully matched to 1 to 2 control subjects by sex, age at CVD incidence, and birthday (±60 days).

History of Severe Hypoglycemia

The American Diabetes Association (20) defines severe hypoglycemia as an event that requires the assistance of

another person. We therefore identified such events in the medical claims of the emergency or inpatient department. By modifying the coding algorithm proposed by Ginde et al. (21), we included the following ICD-9CM codes as hypoglycemia: 250.8, 251.0, 251.1, 251.2, 270.3, and 962.3.

Histories of severe hypoglycemia occurring after the first diagnosis or clinical visit of T1DM were categorized in three time windows (i.e., 1 year, 1–3 years, and 3–5 years before each study end point) to find a critical period that was most relevant to the occurrence of all-cause mortality/CVD incidence (Supplementary Fig. 1).

Covariates

Sociodemographic characteristics were abstracted, including age, sex, urbanization level of residence, and monthly income–based insurance premium. Age was determined by the date of first diagnosis (incident case) or earliest clinical visit (prevalent case) for T1DM during the study period. Diabetic complications, including retinopathy, nephropathy, neuropathy, and cerebrovascular, cardiovascular, peripheral vascular, and metabolic disorders, were identified to calculate the total score of the adapted Diabetes Complication Severity Index (aDCSI) (22,23), which reportedly has a favorable correlation with diabetes duration. Each predefined diabetic complication was identified according to the relevant ICD-9CM codes presented in three or more outpatient medical records within 1 year or at least one inpatient record between 1 January 1997 (or entry of NHI) and the initiation of each exposure time window (Supplementary Fig. 1). Similar rules were also applied in identifying histories of hypertension (ICD-9CM: 401, 402, and 405; A-code: A269) and hyperlipidemia (ICD-9CM: 272.0, 272.1, 272.2, 272.3, and 272.4; A-code: A189).

Statistical Methods and Sensitivity Analysis

The distributions of covariates were compared between case and control subjects. The comparisons were performed by using the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. To examine the correlation between the risks of all-cause mortality/CVD incidence and history of severe hypoglycemia, their crude odds ratio (OR), covariate-adjusted OR (aOR), and 95% CIs were estimated from conditional logistic regression analyses. Two separate regression models were created to investigate the effects of having a history of severe hypoglycemia and the cumulative frequency of severe hypoglycemia during the exposure time windows on the risks of all-cause mortality/CVD incidence. The aOR associated with severe hypoglycemia occurring in each specific exposure time window was calculated from multivariate logistic regression models with adjustment for covariates. The occurrences of severe hypoglycemia in the two other exposure time windows were simultaneously adjusted in the model. We examined the dose–gradient relationships between the study outcomes and the cumulative frequency of severe hypoglycemia during a longer period of 5 years before all-cause mortality/CVD incidence (Fig. 1).

To preclude the potential confounding by frailty, which is simultaneously related to a propensity to develop severe hypoglycemia and a higher risk of all-cause mortality or CVD incidence, we conducted a sensitivity analysis of the aforementioned dose–gradient relationship by including only those patients who did not develop any diabetic complications and had a baseline aDCSI of 0 (sample sizes [*n*] were 164 for nonsurvival case subjects, 744 for survival control subjects, 406 for CVD case subjects, and 890 for non-CVD control subjects).

To explore the distributions of major UCOD in T1DM, the overall and age-specific (<45, 45–64, and ≥65 years) distributions of leading UCODs were presented as proportions. The data were analyzed using SAS 9.3 software (SAS Institute, Inc., Cary, NC).

RESULTS

The case and control subjects were very comparable in the two case-control series (Table 1). Table 2 reports the socioeconomic factors, diabetic complications, aDCSI, and comorbidities of case and control subjects from 1 January 1997 (or entry of NHI) to the first day of the 5-year exposure time window before study outcomes. The nonsurvivors had higher aDCSI and prevalence rates of retinopathy, nephropathy, neuropathy, CAD, peripheral vascular disease, metabolic diseases, and hypertension. Nonsurvivors were also more likely to live in less urbanized areas and have a lower monthly income–based insurance premium. Similarly, compared with non-CVD control subjects, the CVD case subjects had higher aDCSI and prevalence of most components of aDCSI and selected comorbidities except CAD. CVD case and non-CVD control subjects both had similar distributions of urbanization level of residence, but CVD case subjects had significantly lower monthly income–based insurance premiums than non-CVD control subjects. The distributions of covariates for the case and control subjects were identified from different exposure time windows (i.e., 1, 1–3, and 3–5 years). The prior study outcomes were very similar to those reported in Table 2.

Table 3 reports the associations of severe hypoglycemia that are ascertained in three selected exposure time windows with the risks of all-cause mortality/CVD incidence. Compared with control subjects, nonsurvivors and CVD case subjects were more likely to experience severe hypoglycemia and tended to experience a higher frequency of severe hypoglycemic events. After adjusting for covariates, we found that those patients with a history of severe hypoglycemia

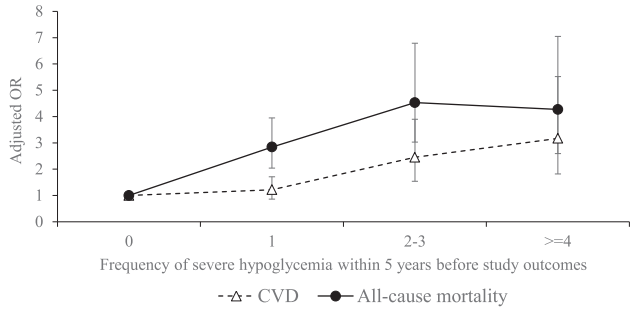

Figure 1—Dose–gradient effect of cumulative frequency of severe hypoglycemia in 5 years before all-cause mortality and CVD incidence.

Table 1—Clinical and demographic characteristics of case and control subjects

	All-cause mortality		CVD incidence	
Characteristics	Survivors (*n* = 1,615)	Nonsurvivors (*n* = 564)	Control subjects (*n* = 1,439)	CVD case subjects (*n* = 743)
Sex				
Female	679 (42.04)	238 (42.20)	725 (50.38)	374 (50.34)
Male	936 (57.96)	326 (57.80)	714 (49.62)	369 (49.66)
Year of birth				
Before 1950	224 (13.87)	100 (17.73)	188 (13.06)	117 (15.75)
1950–1959	277 (17.15)	91 (16.13)	277 (19.25)	138 (18.57)
1960–1969	365 (22.60)	122 (21.63)	357 (24.81)	178 (23.96)
1970–1979	426 (26.38)	143 (25.35)	367 (25.50)	185 (24.90)
1980–1989	250 (15.48)	84 (14.89)	218 (15.15)	109 (14.67)
After 1990	73 (4.52)	24 (4.26)	32 (2.22)	16 (2.15)
Age at death or CVD incidence, years				
<20	101 (6.25)	33 (5.85)	81 (5.63)	40 (5.38)
20–29	309 (19.13)	104 (18.44)	329 (22.86)	164 (22.07)
30–39	416 (25.76)	138 (24.47)	365 (25.36)	183 (24.63)
40–49	386 (23.90)	127 (22.52)	364 (25.30)	183 (24.63)
≥50	403 (24.95)	162 (28.72)	300 (20.85)	173 (23.28)
Mean ± SD	41.02 ± 15.24	42.56 ± 16.51	39.16 ± 13.56	39.95 ± 14.12
Median (Q1–Q3)	39.63 (29.93–50.00)	40.42 (30.23–51.95)	38.57 (28.78–48.40)	39.36 (28.99–49.21)
Age at diagnosis or first clinical visit for T1DM, years				
<20	343 (21.24)	120 (21.28)	278 (19.32)	151 (20.32)
20–29	428 (26.5)	134 (23.76)	370 (25.71)	183 (24.63)
30–39	380 (23.53)	130 (23.05)	370 (25.71)	179 (24.09)
40–49	258 (15.98)	90 (15.96)	265 (18.42)	129 (17.36)
≥50	206 (12.76)	90 (15.96)	156 (10.84)	101 (13.59)
Mean ± SD	32.69 ± 14.88	33.83 ± 16.05	32.67 ± 13.76	33.28 ± 14.54
Median (Q1–Q3)	31.00 (21.45–41.27)	32.01 (21.41–42.96)	31.53 (21.99–41.79)	32.04 (22.23–42.62)

Data are presented as *n* (%) or as indicated. Q1, first quartile; Q3, third quartile.

within 1 year were 2.74 times more likely to die and 2.02 times more likely to develop CVD. Despite attenuating the strength of such association, all-cause mortality was still significantly and positively associated with severe hypoglycemia occurring in 1–3 years (aOR 1.94; 95% CI 1.39–2.71) and 3–5 years (aOR 1.68; 95% CI 1.15–2.44) before death. However, severe hypoglycemia occurring in 1–3 years and 3–5 years before CVD incidence did not significantly increase the risk of CVD incidence.

By examining the dose–gradient relationship further, we found that a greater frequency of severe hypoglycemia occurring 1 year before death was significantly associated with a higher OR of all-cause mortality (1 vs. 0: 2.45 [95% CI 1.65–3.63]; ≥2 vs. 0: 3.49 [2.01–6.08], $P < 0.001$ for trend). Although the strength of the association was attenuated, a significant dose–gradient effect still existed for severe hypoglycemia occurring in 1–3 years ($P < 0.001$ for trend) and 3–5 years ($P < 0.015$ for trend) before death. By contrast, the dose–gradient effect of frequency of severe hypoglycemia and CVD incidence was only observed for the 1-year exposure time window ($P < 0.002$ for trend).

The dose–gradient relationship was further examined by considering all episodes of severe hypoglycemia within 5 years before all-cause mortality or CVD incidence (Fig. 1). All-cause mortality and CVD incidence were both significantly increased along with the increasing cumulative frequency of severe hypoglycemia ($P < 0.001$ for trend). A similar relationship was observed in a subset of patients who had no history of any diabetic complication ($P < 0.001$ for trend for all-cause mortality, $P = 0.009$ for CVD incidence).

The three leading UCODs for the 564 subjects with T1DM who died were diabetes (44.8%), malignant neoplasm (16.4%), and circulatory disease (12.4%). The age-specific analysis further revealed that diabetes was the major UCOD for those deceased patients with T1DM at age <45 years (54.5%) or 45–64 years (35.1%). The second and third major UCODs for those who died at 45–64 years were malignant neoplasm (26.3%) and circulatory disease (19.3%). The younger patients with T1DM (<45 years) had equal chances of dying of malignant neoplasm and circulatory disease, each accounting for 9.1% of the deaths. The three most prevalent UCODs for the patients with T1DM who died at ≥65 years were malignant neoplasm (30.3%), diabetes (18.3%), and circulatory disease (13.8%).

CONCLUSIONS

Main Findings

The increased risks of all-cause mortality/CVD incidence were mostly associated with a history of severe hypoglycemia that occurred in the year before death or CVD incidence. The strength of such a significant association was reduced for severe hypoglycemic events 1–3 years and 3–5 years before death, and the hypoglycemic events occurring in 1–3 years and 3–5 years before CVD incidence were no longer significantly associated with risk of CVD incidence. Dose–gradient relationships were observed between all-cause mortality/CVD incidence and cumulative frequency of severe hypoglycemia occurring in the

Table 2—Basic characteristics, history, and frequency of severe hypoglycemia among case and control subjects before the first day of the 5-year exposure time window for all-cause mortality or CVD incidence

	All-cause mortality			CVD incidence		
Basic characteristics	Survivors	Nonsurvivors	*P* value	Control subjects	CVD case subjects	*P* value
Severe hypoglycemia	112 (6.93)	93 (16.49)	<0.001	81 (5.63)	67 (9.02)	0.003
Frequency of severe hypoglycemia						
0	1,503 (93.07)	471 (83.51)	<0.001	1,358 (94.37)	676 (90.98)	0.002
1	72 (4.46)	54 (9.57)		61 (4.24)	41 (5.52)	
≥2	40 (2.48)	39 (6.91)		20 (1.39)	26 (3.50)	
Baseline DCSI						
Mean ± SD	1.37 ± 1.73	2.41 ± 2.36	<0.001	0.84 ± 1.31	1.26 ± 1.74	0.002
Median (Q1–Q3)	1 (0–2)	2 (0–4)		0 (0–2)	0 (0–2)	
Retinopathy	305 (18.89)	158 (28.01)	<0.001	181 (12.58)	142 (19.11)	<0.001
Nephropathy	230 (14.24)	137 (24.29)	<0.001	122 (8.48)	106 (14.27)	<0.001
Neuropathy	329 (20.37)	201 (35.64)	<0.001	194 (13.48)	135 (18.17)	0.004
CVA	26 (1.61)	33 (5.85)	<0.001	0 (0)	0 (0)	
CAD	110 (6.81)	72 (12.77)	<0.001	31 (2.15)	22 (2.96)	0.246
PVD	385 (23.84)	200 (35.46)	<0.001	225 (15.64)	149 (20.05)	0.010
Metabolic disease	195 (12.07)	126 (22.34)	<0.001	122 (8.48)	101 (13.59)	<0.001
Hypertension	209 (12.94)	131 (23.23)	<0.001	28 (1.95)	53 (7.13)	<0.001
Hyperlipidemia	296 (18.33)	120 (21.28)	0.125	51 (3.54)	54 (7.27)	<0.001
Urbanization level of residence						
High	1,075 (70.35)	339 (63.48)	<0.001	972 (70.69)	472 (68.41)	0.523
Median	354 (23.17)	128 (23.97)		307 (22.33)	163 (23.62)	
Low	99 (6.48)	67 (12.55)		96 (6.98)	55 (7.97)	
Monthly income–based insurance premium (NTD)						
<15,840	641 (39.69)	346 (61.35)	<0.001	528 (36.69)	395 (53.16)	<0.001
15,840–24,000	466 (28.85)	168 (29.79)		456 (31.69)	216 (29.07)	
>24,000	508 (31.46)	50 (8.87)		455 (31.62)	132 (17.77)	

Data are presented as *n* (%) or as indicated. CVA, cerebrovascular attack; NTD, New Taiwan dollar (1 USD ≅ 32 NTD); PVD, peripheral vascular disease; Q1, first quartile; Q3, third quartile.

5-year period before all-cause mortality/CVD incidence.

Comparison With Previous Studies

Very few studies have examined the associations of severe hypoglycemia with all-cause mortality/CVD incidence in T1DM, and their findings seemed inconsistent. Such inconsistencies might be attributed to their use of various methods to determine the history of hypoglycemic events and use of different observational periods to ascertain all-cause mortality/CVD incidence. The EURODIAB project (9) failed to associate baseline hypoglycemic events with CV events after more than 7 years of follow-up. A study from the U.K. counted any severe hypoglycemic event occurring during the 5-year follow-up period and showed significant associations between severe hypoglycemia and increased risks of CVD incidence (hazard ratio 1.92; 95% CI 1.32–2.79) and all-cause mortality (hazard ratio 2.05; 95% CI 1.69–2.49) in patients with T1DM without CVD history (6). A U.S. study found that self-reported severe hypoglycemia at baseline was associated with death in 5 years of follow-up (aOR 3.38, 95% CI 1.55–7.39) (7). In sum, severe hypoglycemia was associated with all-cause mortality within 5 years but was only associated with risk of CVD incidence within a 1-year period.

The results from the nested case-control study of the EURODIAB project were not consistent with our findings. Specifically, the case-control study of the EURODIAB project showed the beneficial effects of severe hypoglycemia in the past year of CVD incidence, with an aOR of 0.47 (95% CI 0.23–0.93) without adjustment for HbA_{1c}, and an aOR of 0.61 (95% CI 0.28–1.30) with adjustment for HbA_{1c}. The EURODIAB project was limited by its potential underestimation of hypoglycemic events because it depended on self-reported hypoglycemic data. Moreover, the lack of information on cause of death might have biased the estimation of cardiovascular events (24). The EURODIAB project also counted the episodes of severe and nonsevere hypoglycemia separately and estimated their respective effects by adjusting each other. Simultaneous inclusion of both nonsevere and severe hypoglycemia in a model could be problematic because it is not appropriate clinically to treat repeated nonsevere hypoglycemia and severe hypoglycemia as distinct variables. The patients who repeatedly experienced nonsevere hypoglycemia tended to lack an awareness of lower plasma glucose or even hypoglycemia, which leads to a higher risk of later severe hypoglycemia in these patients (25,26).

Our findings were in accord with those of Khunti et al. (6), who used administrative health data to investigate episodes of severe hypoglycemia that occurred any time during the 5-year follow-up period. They reported twice-greater risks of all-cause mortality/CVD incidence associated with severe hypoglycemia in patients with T1DM without a

Table 3—aORs of history and frequency of severe hypoglycemia on risks of all-cause mortality/CVD incidence

Exposure time windows for severe hypoglycemia	History/frequency of severe hypoglycemia	All-cause mortality				CVD incidence			
		Survivors (*n*)	Nonsurvivors (*n*)	aOR* (95% CI)	*P* value	Control subjects (*n*)	CVD case subjects (*n*)	aOR* (95% CI)	*P* value
<1 year	Without	1,490	417	Ref.		1,364	650	Ref.	
	With	125	147	2.74 (1.96–3.85)	<0.001	75	93	2.02 (1.35–3.01)	0.001
1–3 years before	Without	1,464	421	Ref.		1,330	648	Ref.	
	With	151	143	1.94 (1.39–2.71)	<0.001	109	95	1.33 (0.91–1.94)	0.143
3–5 years before	Without	1,503	471	Ref.		1,358	676	Ref.	
	With	112	93	1.68 (1.15–2.44)	0.007	81	67	1.21 (0.80–1.84)	0.364
<1 year	0	1,490	417	Ref.	<0.001†	1,364	648	Ref.	0.002†
	1	88	94	2.45 (1.65–3.63)	<0.001	51	63	2.04 (1.28–3.25)	0.003
	≥2	37	53	3.49 (2.01–6.08)	<0.001	24	30	1.95 (0.96–3.97)	0.094
1–3 years before	0	1,464	421	Ref.	<0.001†	1,330	648	Ref.	0.098†
	1	93	75	1.85 (1.24–2.77)	0.003	69	54	1.19 (0.75–1.88)	0.462
	≥2	58	68	2.10 (1.28–3.43)	0.003	40	41	1.57 (0.91–2.69)	0.105
3–5 years before	0	1,503	471	Ref.	0.015†	1,358	676	Ref.	0.083†
	1	72	54	1.69 (1.07–2.65)	0.023	61	41	1.13 (0.70–1.83)	0.615
	≥2	40	39	1.67 (0.92–3.01)	0.091	20	26	1.44 (0.72–2.88)	0.309

Ref., reference group. *aORs were adjusted for with or without history of severe hypoglycemia during the other exposure time windows, age at death, or CVD incidence, age at diagnosis of or first clinical visit for T1DM, urbanization level of residence, monthly income–based insurance premium, aDCSI, history of hypertension, and history of hyperlipidemia. †*P* for trend.

history of CVD. We obtained similar findings from our analyses based on the similar exposure time window. We also found dose–gradient relationships between frequency of severe hypoglycemia and risks of all-cause mortality/CVD incidence. By contrast, the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study reported a higher incidence of severe hypoglycemia (27) but a lower risk of CV outcomes in the arm that received intensive glycemic control (2,28). Nevertheless, the findings from the DCCT/EDIC study should not be considered as evidence against the potential adverse effects of severe hypoglycemia. The DCCT/EDIC study did not directly examine the effect of severe hypoglycemia on CV outcomes or all-cause mortality. A report from the DCCT/EDIC even showed that severe hypoglycemia was associated with the progression of atherosclerosis in those patients with HbA_{1c} <7.5% (14). Hyperglycemia and hypoglycemia may both contribute to the progression of CVD pathology. The current evidence suggests that the tight control of blood glucose may significantly reduce the risk of CV outcomes but may also increase the possibility of developing severe hypoglycemia and incur risks of all-cause mortality/CVD incidence. Although the CVD risk that is associated with tight glycemic control may not be overwhelmed, this risk counteracts, at least to a certain extent, the considerable benefits of intensive glycemic control.

The inconsistent findings in the literature may also be attributed to the relatively young age of their subjects. The mean baseline age of these subjects was similar to that of the subjects in the EURODIAB study (33 years) (9), the DCCT/EDIC study (27 years) (2), and our study (33 years), but was much younger than that of subjects (60 years) in the study by Khunti et al. (6). Such dissimilarity challenges the comparison of findings from these studies because death and CV events are more likely to occur in older patients than in younger patients. In addition, the distribution of UCODs among the deceased may vary across studies that enroll patients with different ages.

We also observed a dose–gradient effect of severe hypoglycemia occurring in the 5-year period before all-cause mortality/CVD incidence. Our findings

are supported by two previous studies that investigated atherosclerosis risk in T1DM (13,14). The DCCT/EDIC project reported that the prevalence of coronary artery calcification, an established atherosclerosis marker, was linearly correlated with the incidence rate of hypoglycemia on the DCCT stage (14). Giménez et al. (13) also demonstrated that repeated episodes of hypoglycemia were an aggravating factor for preclinical atherosclerosis in T1DM.

Interpretation

The mechanism of hypoglycemia that predisposes to all-cause mortality/CVD incidence remains unclear. This mechanism may be explained by sympathetic-adrenal activations (15), prolonged cardiac repolarization and increased cardiac arrhythmia risk (15), hypoglycemically induced coagulation abnormalities (29), inflammatory reactions (30), and endothelial dysfunctions (29). Sympathetic-adrenal activations can also provoke hemodynamic changes and increase the workload of the heart (15,31). Inflammatory reactions and endothelial dysfunctions may lead to intravascular coagulation and thrombosis, thereby encouraging the development of tissue ischemia (15). Nonetheless, these possible explanations are mostly based on short-term observations (32,33). Alternatively, severe hypoglycemia may not be a direct causal factor for death or CVD incidence but may only be a marker of vulnerability to these events, thereby indicating a greater disease burden, such as old age, having multiple clinical conditions, or longer duration of diabetes (4,34).

Methodological Concerns and Conclusion

This study has several strengths. First, this population-based study uses a case-control design that is nested within a cohort with T1DM, thereby largely reducing the potential for selection bias. Second, a potential confounding by severity of T1DM can be largely reduced by adjusting aDCSI in the regression models. As a specific index for the severity of diabetic complications and a valid predictor of hospitalization and mortality in patients with diabetes, aDCSI is considered a favorable surrogate of duration of diabetes (23).

The limitations of this study must also be mentioned. First, the severe hypoglycemic events were merely defined by diagnosis codes, thereby introducing certain degrees of disease misclassification. Nevertheless, given that we used the same algorithm on both case and control subjects, the potential of miscoded severe hypoglycemia is likely to be nondifferential and can only bias the observed association toward the null.

Second, although previous studies found that the effects of hypoglycemia on mortality and progression of atherosclerosis in diabetes can be modified by the HbA_{1c} level (11,14,35), we were unable to examine the potential effect modification by HbA_{1c} on the relationship between severe hypoglycemia and all-cause mortality/CVD incidence because the medical claims of Taiwan's NHI program do not include laboratory data such as HbA_{1c}.

Third, despite adjusting for several risk factors for all-cause mortality/CVD, we were unable to measure the physical conditions of the subjects from the claim data. Therefore, the associations between severe hypoglycemia and the risks of all-cause mortality/CVD incidence should not be considered as a cause-and-effect relationship. Hypoglycemia may also be the consequence and not the cause of frailty that leads to death. Our findings might also suffer from confounding by various lifestyle and behavior factors, such as smoking, poor adherence to glycemic control, lack of physical activity, and higher BMI, which were unavailable from Taiwan's NHI claims.

Fourth, our study might also be subject to Berkson bias (36) because the patients with T1DM who suffer from severe hypoglycemia and CVD events had a greater risk of being admitted. However, this bias, if present, would only produce a weak effect because patients with severe hypoglycemia were identified from the claims of both emergency and inpatient departments, which captured nearly all severe hypoglycemic events regardless of their CVD status and because patients with CVD would seek clinical care whether they were suffering from severe hypoglycemia or not.

The risk of CVD incidence was significantly associated with severe hypoglycemic events that occurred within the 1-year period before CVD incidence, whereas the risk of all-cause mortality was significantly associated with the occurrence of severe hypoglycemia in the 5-year period before death. In addition, exposure to repeated severe hypoglycemic events could lead to greater risk of all-cause mortality/CVD incidence. Patients and clinical practitioners should appropriately manage T1DM to prevent the occurrence of severe hypoglycemia and must be alerted by the possible risks of all-cause mortality/CVD incidence in the following year after the patient experiences severe hypoglycemic events.

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