Association Between Hypoglycemia and Fall-Related Events in Type 2 Diabetes Mellitus: Analysis of a U.S. Commercial Database

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ABSTRACT

BACKGROUND: Hypoglycemia is a major barrier to achieving optimal glycemic control and managing diabetes successfully in patients with diabetes. Falls are the most significant consequences caused by hypoglycemia episodes. Both hypoglycemia and falls lead to substantial economic burden on the health care system in the United States.

OBJECTIVE: To examine the association of hypoglycemia with fall-related outcomes in elderly patients with type 2 diabetes mellitus (T2DM).

METHODS: Records were obtained for T2DM patients (N = 1,147,937) from January 1, 2008, to December 31, 2011. The nonhypoglycemia patients were randomly matched 1:1 by age and gender to the hypoglycemia patients. Fall-related events (composite of fall-related outcomes) were defined using ICD-9-CM codes. Conditional logistic regression models were used to compare the fall-related events within 30 days, 90 days, 180 days, and 365 days between the 2 cohorts.

RESULTS: A total of 21,613 hypoglycemia patients were matched with 21,613 nonhypoglycemic patients. Patients with hypoglycemia had higher fall-related events within 30 days, 90 days, 180 days, and 365 days ($P < 0.001$ for all frequency differences). Conditional logistic regression analyses showed an elevated risk for fall-related events over 365 days (aOR = 1.95, 95% CI = 1.70-2.24). Subgroup analysis showed elevated risk for patients aged < 75 years and ≥ 75 years. Elevated risks were also seen for individual fall-related outcomes of fractures, head injuries, long-term care placement, and hospital admissions.

CONCLUSIONS: The risk of fall-related events over 365 days increased 2-fold among elderly patients with diabetes who experienced hypoglycemia.

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What is already known about this subject

- Hypoglycemia is a major barrier to achieving optimal glycemic control and managing diabetes successfully in patients with diabetes.
- Falls are the most significant consequences caused by hypoglycemia episodes.
- Hypoglycemia and falls lead to substantial economic burden on the health care system in the United States.
- Currently, there exists limited evidence reporting the association between hypoglycemia and fall-related events among elderly diabetes patients in the United States.

What this study adds

- This study reported the association between hypoglycemia and fall-related events among elderly diabetes patients and highlighted an increased risk of fall-related events among elderly patients with diabetes who experienced hypoglycemia.
- The analyses reported the association overall for all fall-related events as well as for the specific fall-related outcomes, which included fractures, head injury, long-term care placement, and hospitalizations.
- This study provides a real-world picture of elderly diabetic patients who experience hypoglycemia.

Type 2 diabetes mellitus (T2DM) is a progressive disorder with more than 347 million people worldwide suffering from this disease.[1] It results in at least a 2-fold increase in the risk of death and, hence, has become a major global concern.[1] As per 2012 U.S. estimates, about 22.3 million people (~7% of the U.S. population) have been diagnosed with diabetes, leading to an estimated economic burden of $245 billion ($176 billion in direct medical costs and $69 billion in indirect costs).[2] Diabetes leads to an increase in the risk of macrovascular and microvascular complications, thereby predisposing these patients to hospitalization.[3-5] Oral antidiabetes medications are used to control the glycemic levels in patients with diabetes; however, some of these medications have been linked to an increased risk of hypoglycemia (abnormally low blood sugar levels < 70 milligrams per deciliter).[1,4,5] Consequently, hypoglycemia has remained 1 of the critical limiting factors that has troubled health care providers in achieving optimal glycemic control and managing diabetes successfully in these patients.

Hypoglycemia leads to a substantial economic burden on the health care system, as highlighted by studies from across the globe. The direct medical costs spent on treating hypoglycemia range from approximately $188 to $2,100 per episode, depending on disease severity and the extent of medical care needed, while the indirect costs are approximately $3,169 per patient per year due to lost productivity.[6] A population-based Scottish study reported that the annual direct cost of treating severe hypoglycemia in the United Kingdom could exceed £13 million (~$21 million).[7] A Spanish study has reported the cost of hypoglycemia as approximately €3,500 (~$4,700) per episode of severe hypoglycemia.[8] A Korean study reported costs ranging from $135.50 to $1,391.00 per episode of severe hypoglycemia.[9] Swedish studies report the direct costs of hypoglycemia per patient being $12.90 for a 1-month period, while the indirect costs are $14.10 for a 1-month period, with the total cost (in base case) of hypoglycemia in Sweden being approximately €4,250,000 (~$5.74 million) per year.[10,11] In addition to an increase in health care utilization and costs, hypoglycemia also leads to decline in the quality of life of the patients.[6,12,13]

In the United States, falls remain a critical issue of concern, since they are a major cause of morbidity and mortality in the elderly population, with current literature suggesting that the economic burden of falls may reach $54.9 billion in 2020.[14,15] The most common nonfatal outcome of falls is fractures, which constitutes approximately 61% of all fall-related costs, with other outcomes being injuries to internal organs, traumatic brain injuries including subdural hematomas, injuries resulting in surgical interventions, and even death.[15,16] A study at 3 midwestern hospitals reported that the operational costs for fallers with serious injury (fracture, subdural hematoma, any injury resulting in surgical intervention, or death) were $13,316 higher than inpatient controls who do not experience a fall, with an additional 6.3 days of hospital stay needed for the average faller in the general population.[16] The study also indicated that the fallers were significantly more likely to have diabetes with preexisting organ damage.

A recent study of Medicare-covered patients with T2DM by Johnston et al. (2012) reported 70% higher adjusted odds of fall-related fractures among patients with hypoglycemic events as compared with patients without hypoglycemic events.[15] Signorovitch et al. (2013) reported that in patients with T2DM who received antidiabetes drugs without insulin, hypoglycemia was associated with a significantly higher risk of accidents that resulted in hospital visits (hazard ratio [HR] = 1.39, 95% confidence interval [CI] = 1.21-1.59), accidental falls (HR = 1.36, 95% CI = 1.13-1.65), and motor vehicle accidents (HR = 1.82, 95% CI = 1.18-2.80).[17] Currently, a dearth of literature exists on studies evaluating the association between hypoglycemia and various key fall-related outcomes. The objective of this study was to examine the association between hypoglycemia and fall-related events (a composite of all fall-related outcomes) among elderly diabetes patients. This examination included the association overall for all fall-related events, as well as for the specific fall-related outcomes, which included fractures, head injury, long-term care placement, and hospitalizations.

Methods

A retrospective cohort study was conducted in patients with T2DM. Records were obtained from Truven Health MarketScan Medicare Supplemental Database for patients with at least 2 records of T2DM diagnosis from January 1, 2008, to December 31, 2011. Patients were required to be aged ≥ 65 years at index date (first T2DM date in the study period). The first date of a recorded hypoglycemia diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 250.8, 251.0, 251.1, and 251.2) was defined as the cohort entry date for patients in the hypoglycemia group (HG).[18] A 6-month baseline and 1-year follow-up period from cohort entry date was required. Patients in the nonhypoglycemia group (NHG) were 1:1 randomly matched by age and gender. For the NHG patients, their cohort entry dates were kept the same as their respective matched patients from the HG.

Fall-related events were defined as ICD-9-CM codes 800.x-995.x, with a fall being the external cause defined as ICD-9-CM E-codes E880-E888, which were recorded within ± 2 days of each other in any order.[15,19] In administrative claims data, the ICD-9-CM diagnosis coding for fracture sites does not possess a level of specificity that allows identification of whether a fall specifically caused a fracture. To determine whether a fall caused a fracture, ICD-9-CM Index to External Cause of Injury codes (E codes) is still employed, even though E codes may be flawed. The approach is the best we can do at this time, and the limitation of using E codes to define fall-related events is recognized by the Centers for Disease Control and Prevention.[20] ICD-9-CM codes were also used to capture the 2 individual outcomes: hospitalizations (inpatients) and long-term care placements. In addition to ICD-9-CM codes, provider type codes, place of service codes, discharge status codes, and procedure codes were used to identify long-term care placement patients. ICD-9-CM codes for fractures included 800.x-839.x, with a fall being the external cause defined as ICD-9-CM E-codes E880-E888. Head injuries were defined as ICD-9-CM codes 800.x-804.x, 850.x-854.x, 905.0, 907.0, and 873, with a fall being the external cause defined as ICD-9-CM E-codes between E880-E888. The ICD-9-CM codes for fractures and head injuries were verified and finalized from the ICD-9-CM coding book. If 2 claims were observed within 30 days of each other, they were assessed as the result of the same fall event.

Statistical Analysis

Two study cohorts were formed. The first cohort (HG) included those patients who had at least 1 claim for hypoglycemia. The data of the first such claim during the study period was considered the patient's cohort entry date. The 6-month period immediately prior to this cohort entry date was considered the baseline period. The 12-month period following this cohort entry date was the follow-up period. The NHG cohort was randomly formed, by assigning a cohort entry date to those patients who did not have a hypoglycemia claim such that the mean days between the index date of the patient and this cohort entry date was the same as in the HG cohort. The NHG cohort was 1:1 randomly matched by age and gender to patients in the HG cohort.

TABLE 1 Demographic Characteristics, Comorbidities, and Medication Use in the Baseline Period

Demographic Characteristics	Hypoglycemia Patients N = 21,613		Nonhypoglycemia Patients N = 21,613		McNemar's Test Statistic	*P* Value
	N	%	N	%		
Age group						
65-69	8,678	40	8,678	40.15	NS	NS
70-74	4,849	22	4,849	22.44	NS	NS
75-79	4,511	21	4,511	20.87	NS	NS
80-84	2,595	12	2,595	12.01	NS	NS
85-89	840	4	840	3.89	NS	NS
90-94	128	1	128	0.59	NS	NS
95-100	11	0	11	0.05	NS	NS
≥ 100	1	0	1	0.00	NS	NS
Gender						
Male	10,494	48.55	10,494	48.55	NS	NS
Female	11,119	51.45	11,119	51.45	NS	NS
U.S. census region						
North East	4,068	18.82	3,865	17.88	6.42	0.0116
North Central	7,395	34.22	6,639	30.72	60.59	< 0.0001
South	6,069	28.08	6,321	29.25	7.32	0.0070
West	3,562	16.48	3,858	17.85	14.36	0.0002
Unknown	519	2.40	930	4.30	-	-
Plan type						
Comprehensive	8,749	40.48	7,511	34.75	154.00	< 0.0001
EPO	102	0.47	36	0.17	31.56	< 0.0001
HMO	3,250	15.04	3,045	14.09	7.94	0.0051
POS	401	1.86	504	2.33	11.85	0.0006
PPO	8,135	37.64	9,625	44.53	216.21	< 0.0001
POS with capitation	15	0.07	33	0.15	6.75	0.0133
CDHP	81	0.37	159	0.74	25.78	< 0.0001
HDHP	11	0.05	12	0.06	0.04	1.0000
Missing	869	4.02	688	3.18	-	-
Falls in the baseline period[a]						
Yes	637	2.95	238	1.10	184.90	< 0.0001
No	20,976	97.05	21,375	98.90	184.90	< 0.0001
Medication						
Metformin	4,883	22.6	5,302	24.5	22.70	< 0.0001
Sulfonylurea	8,651	40.0	4,594	21.3	1,728.37	< 0.0001
Thiazolidinediones	2,794	12.9	2,081	9.6	119.64	< 0.0001
Insulin[b]	4,531	21.0	1,474	6.8	1,739.94	< 0.0001
Comorbidities[c]						
Cardiovascular events	945	4.4	289	1.3	364.07	< 0.0001
Stroke	1,798	8.3	681	3.2	526.23	< 0.0001
Obesity	851	3.9	472	2.2	113.19	< 0.0001
Dyslipidemia	8,519	39.4	7,151	33.1	188.04	< 0.0001
Atherosclerosis	1,990	9.2	1,030	4.8	327.04	< 0.0001
Hypertension	14,431	66.8	11,214	51.9	984.41	< 0.0001
Nephropathy	273	1.3	87	0.4	96.64	< 0.0001
Diabetic foot problem	7	0.0	3	0.0	1.60	0.3438
Diabetes with neurological manifestations	11	0.1	3	0.0	4.57	0.0574
Dental disease	30	0.1	24	0.1	0.67	0.4966
Osteoporosis	1,035	4.8	789	3.7	35.35	< 0.0001
Chronic kidney disease	4,224	19.5	1,626	7.5	1,313.15	< 0.0001
Hyperparathyroidism	592	2.7	201	0.9	195.25	< 0.0001
Impaired vitamin D deficiency	591	2.7	345	1.6	67.24	< 0.0001
Depression	1,547	7.2	742	3.4	300.43	< 0.0001
Arthritis	4,570	21.1	3,300	15.3	249.29	< 0.0001

TABLE 1 Demographic Characteristics, Comorbidities, and Medication Use in the Baseline Period *(continued)*

Demographic Characteristics	Hypoglycemia Patients N = 21,613		Nonhypoglycemia Patients N = 21,613		McNemar's Test Statistic	*P* Value
	N	%	N	%		
Leg and foot amputation	43	0.2	8	0.0	24.02	< 0.0001
Impaired vision	1,430	6.6	637	2.9	317.44	< 0.0001
Lack of urine control	649	3.0	414	1.9	53.15	< 0.0001
Dizziness	1,964	9.1	924	4.3	397.35	< 0.0001
Low blood pressure	1,269	5.9	417	1.9	444.79	< 0.0001
Fainting	1,847	8.5	621	2.9	638.52	< 0.0001
Any mental health-related disorder[d]	5,084	23.5	2,319	10.7	1,234.10	< 0.0001

Note: The patient counts in this table are not mutually exclusive, since a patient might have multiple medications in the baseline.
[a]*Fall events during 6 months immediately prior to the baseline period.*
[b]*HCPCS codes as well as NDCs were used to identify patients with insulin.*
[c]*Comorbidities were identified in the 6-month period prior to the baseline period.*
[d]*ICD-9-CM codes from 290-319 were used to search for patients with any mental health-related disorders.*
CDHP = consumer-driven health plan; EPO = exclusive provider organization; HCPCS = Healthcare Common Procedure Coding System; HDHP = high-deductible health plan; HMO = health maintenance organization; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NDC = National Drug Code; POS = point of service; PPO = preferred provider organization; NS = not significant.

Comparison of the baseline categorical variables was reported as percentages and baseline continuous variables as means ± standard deviation (SD) for both of these cohorts. McNemar's test statistic was used to test the comparison of baseline characteristics between cohorts. Due to the matched study design, conditional logistic regression models were used to compare fall-related events within 30 days, 90 days, 180 days, and 365 days between the 2 cohorts in the follow-up period. Adjusted odds ratios (aOR) and corresponding 95% CIs, controlling for baseline characteristics and comorbidities, were estimated from logistic regression models. Understanding that matching on age and gender do not sufficiently control for all potential confounders, the regression models were adjusted for Charlson Comorbidity Index (CCI) scores. Subgroup analyses for age (aged < 75 years and ≥ 75 years) were also conducted. The association between hypoglycemia and fall-related events among elderly diabetes patients with recurrent hypoglycemia was also evaluated. All analyses were done using SAS 9.2 (SAS Institute, Inc., Carey, NC). Statistical significance was defined as a $P < 0.05$ (two-tailed).

Results

A total of 1,147,937 patients with at least 2 records of T2DM diagnosis from January 1, 2008, to December 31, 2011, were available for the analyses. A total of 21,613 hypoglycemia patients were matched with 21,613 patients with no hypoglycemia. Table 1 provides the baseline demographics and comorbidities data. In the hypoglycemia cohort, most of the patients were aged 65-69 years (40%), female (51.4%), from the North Central region (34.2%), and had comprehensive insurance (40.5%). The most common comorbidities in the HG included hypertension (66.8%) followed by dyslipidemia (39.4%), any mental health-related disorder (23.5%), arthriitis (21.1%), and chronic kidney disease (19.5%). A significantly higher proportion of patients with hypoglycemia had comorbidities compared with patients with no hypoglycemia, and this was true for all comorbidities (Table 1; $P \leq 0.001$ for all comorbidities, except diabetic foot problem [$P = 0.344$], diabetes with neurological manifestations [$P = 0.057$], and dental disease [$P = 0.497$]). The mean CCI score was 1.99 (± 2.31) for hypoglycemia patients, compared with 0.95 (± 1.55) for nonhypoglycemia patients ($P < 0.001$). Forty percent of the patients in the HG had been prescribed sulfonylureas.

Patients with hypoglycemia consistently had higher fall-related events: 235 events (1.09%) among the HG patients and 37 events (0.17%) among the NHG patients within 30 days; 373 events (1.73%) and 118 events (0.55%) within 90 days; 520 events (2.41%) and 204 events (0.94%) within 180 days; and 720 events (3.33%) and 351 events (1.62%) within 1 year. All frequency differences between HG patients and NHG patients were statistically significant ($P < 0.001$; Table 2). Conditional logistic regression analyses showed an elevated risk of fall-related events over 365 days (aOR = 1.95, 95% CI = 1.70-2.24). The subgroup analyses by age for the 365-day analysis showed elevated risk for both age groups: aged < 75 years (aOR = 2.20, 95% CI = 1.77-2.73) and aged ≥ 75 years (aOR = 1.77, 95% CI = 1.48-2.12). Elevated risks were seen for other time points as well, which included within 30 days, within 90 days, and within 180 days. These analyses highlight the greatest risk of fall-related events within the first 30 days (aOR = 5.86, 95% CI = 4.08-8.43), with the risk gradually decreasing over time. Table 2 shows the results for all fall-related events by groups. The analyses shown in Table 2 were replicated using relative risk (RR) as a different summary measure (see Appendix A).

TABLE 2 Fall-Related Events by Group (Including 30-Day to 1-Year Definition Sensitivity Analysis)

Fall Events[a,b]	Total	Hypoglycemia Group N = 21,613 N	Hypoglycemia Group %	Nonhypoglycemia Group N = 21,613 N	Nonhypoglycemia Group %	Conditional Logistic Regression[d] Adjusted Odds Ratio[c]	95% Confidence Limits Lower	95% Confidence Limits Upper
Within 30 days	272	235	1.09	37	0.17	5.86	4.08	8.43
Aged < 75 years	117	107	0.50	10	0.05	10.34	4.94	21.62
Aged ≥ 75 years	155	128	0.59	27	0.12	4.52	2.94	6.94
Within 90 days	491	373	1.73	118	0.55	2.91	2.34	3.62
Aged < 75 years	211	165	0.76	46	0.21	3.07	2.17	4.36
Aged ≥ 75 years	280	208	0.96	72	0.33	2.77	2.09	3.67
Within 180 days	724	520	2.41	204	0.94	2.40	2.02	2.85
Aged < 75 years	319	238	1.10	81	0.37	2.56	1.95	3.35
Aged ≥ 75 years	405	282	1.30	123	0.57	2.27	1.81	2.85
Within 365 days	1,071	720	3.33	351	1.62	1.95	1.70	2.24
Aged < 75 years	470	335	1.55	135	0.62	2.20	1.77	2.73
Aged ≥ 75 years	601	385	1.78	216	1.00	1.77	1.48	2.12

[a]*Includes patients with baseline fall events.*
[b]*Composite fall events identified by ICD-9-CM codes 800.x-995.x and E codes E880-E888 occurring within 2 days.*
[c]*By baseline characteristics, Charlson Comorbidity Index, and comorbidities.*
[d]*Matched on age and gender.*
E code = ICD-9-CM Index to External Cause of Injury code; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

The interpretation of the results remained the same, regardless of the summary measure used. The analyses shown in Appendix A were also done excluding any patient in a matched pair who used insulin at baseline (see Appendix B). Compared with Appendix A, the risk of falls in the HG were even higher when insulin users were excluded (particularly notable at 30-day and 90-day estimates).

For the analyses on individual fall-related outcomes (Table 3), conditional logistic regression analyses showed an elevated risk of fracture events for the 365-day analysis (aOR = 2.16, 95% CI = 1.74-2.67). All analyses presented in this paragraph are for the 365-day time period. The subgroup analyses by age showed elevated risk for both age groups: aged < 75 years (aOR = 2.30, 95% CI = 1.63-3.24) and aged ≥ 75 years (aOR = 2.07, 95% CI = 1.58-2.72). Elevated risks were also seen for head injury-related events (aOR = 1.63, 95% CI = 1.22-2.19). The subgroup analyses by age showed elevated risk for both age groups: aged < 75 years (aOR = 1.77, 95% CI = 1.08-2.89) and aged ≥ 75 years (aOR = 1.56, 95% CI = 1.08-2.24). For the analyses of all fall-related hospital admissions, conditional logistic regression analyses showed an elevated risk (aOR = 2.20, 95% CI = 1.57-3.08). The subgroup analyses by age showed elevated risk for both age groups: < 75 years (aOR = 2.24, 95% CI = 1.22-4.13) and ≥ 75 years (aOR = 2.20, 95% CI = 1.45-3.34). Elevated risks were also seen for patients with long-term care placement days (aOR = 2.59, 95% CI = 1.93-3.46). The subgroup analyses by age showed elevated risk for both age groups: < 75 years (aOR = 3.75, 95% CI = 2.10-6.69) and ≥ 75 years group (aOR = 2.20, 95% CI = 1.57-3.10). The analyses shown in Table 2 were also replicated using RR as a different summary measure (see Appendix C). Again, the interpretation of the results remained the same, regardless of the summary measure used.

For all the individual fall-related outcomes, elevated risks were also seen for other time points as well, which included within 30 days, within 90 days, and within 180 days (data not shown). For individual fall-related outcomes as well, the analyses highlighted the greatest risk within the first 30 days, with the risk gradually decreasing over time (data not shown).

Additional analyses on all composite fall-related events in patients with recurring hypoglycemia (Table 4) also showed an elevated risk over 365 days (aOR = 2.43, 95% CI = 1.95-3.02). The subgroup analyses by age for the 365-day analysis showed elevated risk for both age groups: < 75 years (aOR = 2.32, 95% CI = 1.64-3.27) and ≥ 75 years (aOR = 2.47, 95% CI = 1.85-3.28). Elevated risks were seen for other time points as well, which included within 30 days, within 90 days, and within 180 days. The greatest risk of fall-related events was within the first 30 days (aOR = 12.41, 95% CI = 6.24-24.67), with the risk gradually decreasing over time.

We also ran the regression analysis for all fall outcomes adjusting for CCI and falls at baseline. The change in the aORs was very minimal (less than a 10% difference in aORs was found) when we included falls in the baseline period as a covariate in addition to the CCI score in the regression model. For example, aOR = 1.95, 95% CI = 1.70-2.24 for all fall-related events within 365 days instead of 2.16 as previously noted. Hence, we have presented the results for the model adjusted for the CCI score only.

TABLE 3 Specific Fall-Related Outcomes (Within 365 Days Only) by Age Subgroup

Fall Events[a,b]	Total	Hypoglycemia Group N = 21,613		Nonhypoglycemia Group N = 21,613		Conditional Logistic Regression[d]		
		N	%	N	%	Adjusted Odds Ratio[c]	95% Confidence Limits Lower	95% Confidence Limits Upper
All fracture-related events	445	308	1.43	137	0.63	2.16	1.74	2.67
Aged < 75 years	182	129	0.60	53	0.25	2.30	1.63	3.24
Aged ≥ 75 years	263	179	0.83	84	0.39	2.07	1.58	2.72
All head injury-related events	222	145	0.67	77	0.36	1.63	1.22	2.19
Aged < 75 years	85	58	0.27	27	0.12	1.77	1.08	2.89
Aged ≥ 75 years	137	87	0.40	50	0.23	1.56	1.08	2.24
All fall-related hospital admissions	184	128	0.59	56	0.26	2.20	1.57	3.08
Aged < 75 years	62	46	0.21	16	0.07	2.24	1.22	4.13
Aged ≥ 75 years	122	82	0.38	40	0.19	2.20	1.45	3.34
All composite fall-related outcomes for patients with long-term care placement	260	186	2.20	74	0.87	2.59	1.93	3.46
Aged < 75 years	88	69	0.81	19	0.22	3.751	2.10	6.69
Aged ≥ 75 years	172	117	1.38	55	0.65	2.204	1.57	3.10

[a]*Includes patients with baseline falls events.*
[b]*Composite fall events identified by ICD-9-CM codes 800.x-995.x and E codes E880-E888 occurring within 2 days.*
[c]*Adjusted odds ratio by baseline characteristics, Charlson Comorbidity Index, and comorbidities.*
[d]*Matched on age and gender.*
E code = ICD-9-CM Index to External Cause of Injury code; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Discussion

This study highlights an increased risk of fall-related events among elderly patients with diabetes who experienced hypoglycemia. In our conditional logistic regression analysis, we observed a 2-fold risk of fall-related events over a 365-day period among elderly diabetic patients who experienced hypoglycemia compared with patients without hypoglycemic events. Higher risks were also observed for individual fall-related outcomes. Signorovitch et al. reported that hypoglycemia was associated with a significantly higher risk of accidental falls resulting in hospital visits.[17] Johnston et al. have also reported 70% higher regression-adjusted odds of fall-related fractures among patients with hypoglycemic events as compared with patients without hypoglycemic events after 1 year of follow-up.[15] However, Johnston et al. only looked at the fracture outcome. Our study looked at fall-related events overall, as well as examined other key fall-related outcomes that included fractures, head injury, long-term care placement, and hospitalizations. Fractures, along with head injuries, may lead to serious complications. Some of the possible fall-inducing symptoms that may be connected with a symptomatic presentation of hypoglycemia have been reported previously in the literature.[15] A more detailed study is needed to find if a causal link exists between the 2 or if the falls are a result of the neurologic, vascular, and ophthalmic complications associated with diabetes. A more focused approach is also needed to understand our observations in patients with recurring hypoglycemia. The larger ORs that were observed in patients with recurrent hypoglycemia suggest higher risks in those patients. These patients may require a more careful and monitored approach in the management of diabetes.

For all of the analyses, we observed the greatest risk of fall-related events (as well as for individual fall-related outcomes) within the first 30 days. Education is the key to minimizing the occurrence of falls. Patients, as well as their caregivers, should be better educated about the high risk of falls, especially within the first 30 days of a hypoglycemic episode, and counseling should be provided so appropriate steps can be taken to minimize the occurrence of falls. In addition to educating patients and caregivers on hypoglycemia-related topics such as definition, symptoms, and risk factors, they should be also trained to recognize and treat these episodes. Our findings also highlight the need for a better patient-monitoring strategy immediately after a hypoglycemic event in diabetic patients.

Previously published literature has evaluated the association between fractures and medications used by diabetic patients. A few studies have evaluated the risk for bone fractures associated with exposure to insulin or other oral hypoglycemic agents.[21-23] These studies show that a patient's functional level and risk factors for falls should be considered during the drug selection decision-making process, since some of the medications may increase fracture risk and thereby worsen fall-related outcomes. In addition, these studies also show that falls are most likely to occur during hypoglycemic episodes. Some studies, however, contradict these findings.[15,21,22] Consequently, focused research evaluation of the impact of diabetes medications on risk of falls is needed. The recently published American Diabetes Association and European Association

TABLE 4 All Composite Fall-Related Outcomes for Patients with Recurring Hypoglycemia (Including 30-Day to 1-Year Definition Sensitivity Analysis), Adjusted for CCI Score

Fall Events[a,b]	Total	Recurrent Hypoglycemia Group N=8,472[c]		Nonhypoglycemia Group N=8,472		Conditional Logistic Regression[e]		
						Adjusted Odds Ratio[d]	95% Confidence Limits	
		N	%	N	%		Lower	Upper
Within 30 days	137	128	1.51	9	0.11	12.41	6.24	24.67
Within 90 days	241	193	2.28	48	0.57	3.65	2.61	5.09
Within 180 days	345	261	3.08	84	0.99	3.06	2.34	4.00
Within 365 days	491	349	4.12	142	1.68	2.43	1.95	3.02

[a]*Composite fall events identified by ICD-9-CM codes 800.x-995.x and E codes E880-E888 occurring within 2 days.*

[b]*Baseline fall event is allowed; 1:1 match was used.*

[c]*Out of 21,613 hypoglycemia patients, only 8,472 patients had recurrent hypoglycemia (defined as at least 2 diagnosis of hypoglycemia on 2 different dates). For these 8,472 patients in the hypoglycemic group, the corresponding 8,472 nonhypoglycemic patients were identified.*

[d]*Adjusted odds ratio by baseline characteristics, CCI, and comorbidities.*

[e]*Matched on age and gender.*

CCI = Charlson Comorbidity Index; E code = ICD-9-CM Index to External Cause of Injury code; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

for the Study of Diabetes position statement has also raised concerns about hypoglycemia and sulfonylurea use among the elderly, since they are at highest risk for hypoglycemia.[4,5] This position statement highlights the fact that sulfonylureas are associated with risk of hypoglycemia and recommend that medications predisposing patients to hypoglycemia should be avoided, since it may worsen myocardial ischemia and may cause dysrhythmias. Existing literature on the association between sulfonylurea use and risk of falls and fall-related fractures is sparse and includes studies that have reported conflicting findings.[24] Future studies are needed to understand this association given that falls induced by hypoglycemia are the hypothesized mechanism for fractures related to sulfonylurea use. Continuous and intermittent sulfonylurea availability has also been reported as a predictor for hypoglycemia-related hospitalization.[25] A detailed understanding of sulfonylureas is a critical need, given that an estimated 50%-66% T2DM patients use sulfonylureas alone or in combination with other diabetes medications.[26]

Physicians treating elderly diabetes patients need to make treatment decisions that minimize the risk of hypoglycemia thereby avoiding the ensuing complications of falls. Falls lead to an increase in the direct and indirect health care utilization and cost burden, so it is critical to take preventive steps to minimize hypoglycemia in elderly diabetic patients.[15] Minimizing the hypoglycemic events in these patients may also lead to improvement in their quality of life.[15] In addition, patients with hypoglycemia may need additional education and other preventive measures to reduce the risk and clinical impact of falls. Research on the merits of diabetes education in T2DM patients has highlighted that the more knowledge and awareness patients have regarding the disease, the more efficient their glycemic control is.[27] Health care professionals should guide patients in identifying the proper educational resources, as well as educate them on key topics such as influence of nutrition and lifestyle, self-monitoring of blood glucose, knowledge regarding hemoglobin A1c, as well as the need for proper glucose, lipid, and blood pressure control to minimize the development of macrovascular complications.

Hypoglycemia is not often recognized as a risk that could lead to potential health-related consequences in T2DM patients.[28] In 2011, it was reported that patients with diabetes are aware of the importance of controlling blood sugar, but they may not know the risks associated with extremely low blood sugar.[29] A recent publication has revealed that there could be underreporting of this issue because of patient discomfort in disclosing hypoglycemia with treating physicians due to fear of losing driving licenses or jobs, especially with regard to serious or frequent events.[30] A recent survey also revealed that almost one-third of patients surveyed (32%) said they do not regularly discuss hypoglycemia with their physicians, in part because of patients' limited understanding of hypoglycemia and lack of time, highlighting a need for improving patient and physician communication.[31] Hypoglycemia unawareness further complicates the situation, which leads to more underreporting of hypoglycemic incidences.[32]

In addition to underreporting, the longer-term impact of hypoglycemia is also not well characterized. If one looks only at emergency room visits and hospitalizations, the true impact of hypoglycemia will be underestimated. A recent survey conducted in Germany, France, and the United Kingdom has shown the potential scale in a real-world setting of what the authors refer to as "hidden costs" associated with hypoglycemia, including absenteeism from work and disturbance of daily life due to fear of hypoglycemia.[33]

Finally, frequently occurring hypoglycemia is associated with increased morbidity and mortality. Mild episodes can cause unpleasant symptoms and disrupt daily activities, while severe hypoglycemia can result in disorientation and unusual behavior and may be life threatening. Severe hypoglycemia was a predictor of cardiovascular mortality in the Action to Control Cardiovascular Risk in Diabetes trial, with a previous occurrence of severe hypoglycemia being an important predictor of a primary cardiovascular event.[34] Also, in the Veterans Affairs Diabetes Trial, hypoglycemia was an important predictor of cardiovascular death.[34] Although a causal relationship was not definitely established, these trials highlight that hypoglycemia might precipitate other morbidities, such as dementia, as well.[31] A recent study has reported a bidirectional association between hypoglycemia and dementia in elderly diabetic patients.[35] Dementia could be associated with a decreased ability to manage medications. This is an important finding, since existing literature suggests an increased prevalence of hip fractures in elderly patients with dementia.[36]

Limitations

The key strength of this study is that it provides a real-world picture of elderly diabetic patients who experience hypoglycemia. Some of the limitations of this study include the use of ICD-9-CM codes for extracting relevant information. As such, there is potential for misclassification, since it is possible that some of these codes may be incorrectly entered in the database or on the claim form or might not have been entered at all. Potential for residual confounding also exists. The administrative databases may also lack information of some critical covariates. Also, this study may have missed patients who may have had severe hypoglycemia that resulted in death before hospital admission. This study may also have missed episodes of mild hypoglycemia that did not result in a doctor's visit or medical claim. The exclusion of events (e.g., fall or death) prior to the index date for the HG may introduce selection bias of lower risk than the general population. We also excluded death in the comparison group (bias of lower risk). There may be other limitations with regard to the generalizability of the study population, since the data do not include uninsured patients and are weighted towards patients who are able to afford supplemental Medicare health insurance, which may not represent the general U.S. population. In the database, we do not have information on whether these patients were previously employed or whether they had supplement health insurance from a previous employer. Due to nature of this study, estimating attributable risks for hypoglycemia was beyond the study's scope. Also, our study design only used a simple matching mechanism. We used conditional logistic regression to analyze the matched pairs on age and sex, for the comparison of hypoglycemia groups, and these groups ended up having different frequencies in baseline characteristics. A more extensive matching or propensity score matching will be used in a future study to strengthen the argument and verify the associations found in this study.

Conclusions

This study shows an increased risk of fall-related events among elderly diabetic patients who experience hypoglycemia. This highlights the need to take preventive measures to reduce the incidence of hypoglycemia in elderly diabetic patients, which may thereby lead to a reduction of fall-related events. Well-designed and conducted prospective studies are needed to further evaluate our findings.

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Fonseca, Kachroo, Shi, Mukherjee, and Iloeje conceptualized the study design. Shi and Kawabata coordinated data analyses. Colilla conducted data analysis and consulted in the analysis plan. Shi and Kachroo led the development of the manuscript. All authors participated in interpreting the results and commenting on the manuscript.

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APPENDIX A All Fall-Related Events by Group

Fall Events[a,b]	Total	Hypoglycemia Group N = 21,613		Nonhypoglycemia Group N = 21,613		Conditional Logistic Regression[c]		
						Relative Risk	95% Confidence Limits	
		N	%	N	%		Lower	Upper
Within 30 days	272	235	1.09	37	0.17	5.6621	3.9817	8.0518
Aged < 75 years	117	107	0.50	10	0.05	9.5423	4.9815	18.2789
Aged ≥ 75 years	155	128	0.59	27	0.12	4.2285	2.7634	6.4703
Within 90 days	491	373	1.73	118	0.55	2.8259	2.2841	3.4962
Aged < 75 years	211	165	0.76	46	0.21	3.2003	2.2907	4.4709
Aged ≥ 75 years	280	208	0.96	72	0.33	2.5870	1.9619	3.4113
Within 180 days	724	520	2.41	204	0.94	2.3149	1.9625	2.7307
Aged < 75 years	319	238	1.10	81	0.37	2.6740	2.0675	3.4583
Aged ≥ 75 years	405	282	1.30	123	0.57	2.0818	1.6774	2.5838
Within 365 days	1,071	720	3.33	351	1.62	1.8874	1.6573	2.1494
Aged < 75 years	470	335	1.55	135	0.62	2.2469	1.8327	2.7548
Aged ≥ 75 years	601	385	1.78	216	1.00	1.6640	1.4043	1.9718

[a]*Includes patients with baseline falls events.*
[b]*Composite fall events identified by ICD-9-CM codes 800.x-995.x and E codes E880-E888 occurring within 2 days.*
[c]*Matched on age and gender, and relative risk estimate adjusted for Charlson Comorbidity Index.*
E code = ICD-9-CM Index to External Cause of Injury code; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B All Fall-Related Events by Group (Sensitivity Analyses: Excluding Insulin Users)

Fall Events[a,b]	Total	Hypoglycemia Group N = 15,925		Nonhypoglycemia Group N = 15,925		Conditional Logistic Regression[c]		
						Relative Risk	95% Confidence Limits	
		N	%	N	%		Lower	Upper
Within 30 days	209	186	1.17	23	0.14	7.1266	4.6003	11.0401
Aged < 75 years	86	81	0.51	5	0.03	14.3684	5.8114	35.5251
Aged ≥ 75 years	123	105	0.66	18	0.11	5.1225	3.0845	8.5072
Within 90 days	380	293	1.84	87	0.55	2.9691	2.3206	3.7987
Aged < 75 years	156	124	0.78	32	0.20	3.3897	2.2701	5.0615
Aged ≥ 75 years	224	169	1.06	55	0.35	2.7262	1.9938	3.7276
Within 180 days	564	407	2.56	157	0.99	2.3435	1.9437	2.8256
Aged < 75 years	235	178	1.12	57	0.36	2.8214	2.0809	3.8254
Aged ≥ 75 years	329	229	1.44	100	0.63	2.0744	1.6355	2.6311
Within 365 days	834	561	3.52	273	1.71	1.8934	1.6354	2.1921
Aged < 75 years	343	249	1.56	94	0.59	2.4182	1.9016	3.0750
Aged ≥ 75 years	491	312	1.96	179	1.12	1.6193	1.3442	1.9507

[a]*Includes patients with baseline falls events.*
[b]*Composite fall events identified by ICD-9-CM codes 800.x-995.x and E codes E880-E888 occurring within 2 days.*
[c]*Matched on age and gender, and relative risk estimate adjusted for Charlson Comorbidity Index.*
E code = ICD-9-CM Index to External Cause of Injury code; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX C Specific Fall-Related Outcomes (Within 365 Days Only) by Age Subgroups

Fall Events[a,b]	Total	Hypoglycemia Group N = 21,613		Nonhypoglycemia Group N = 21,613		Conditional Logistic Regression[c]		
						Relative Risk	95% Confidence Limits	
		N	%	N	%		Lower	Upper
All fracture-related events	445	308	1.43	137	0.63	2.1061	1.7140	2.5878
Aged < 75 years	182	129	0.60	53	0.25	2.2662	1.6339	3.1433
Aged ≥ 75 years	263	179	0.83	84	0.39	2.0048	1.5376	2.6139
All head injury-related events	222	145	0.67	77	0.36	1.7696	1.3279	2.3582
Aged < 75 years	85	58	0.27	27	0.12	2.0061	1.2513	3.2162
Aged ≥ 75 years	137	87	0.40	50	0.23	1.6413	1.1422	2.3585
All fall-related hospital admissions	184	128	0.59	56	0.26	2.1541	1.5596	2.9753
Aged < 75 years	62	46	0.21	16	0.07	2.4424	1.3283	4.4910
Aged ≥ 75 years	122	82	0.38	40	0.19	2.0532	1.4042	3.0022
All composite fall-related outcomes for patients with long-term care placement	260	186	2.20	74	0.87	2.3623	1.7954	3.1084
Aged < 75 years	88	69	0.81	19	0.22	3.3522	2.0132	5.5817
Aged ≥ 75 years	172	117	1.38	55	0.65	2.0200	1.4537	2.8071

[a]*Includes patients with baseline falls events.*
[b]*Composite fall events identified by ICD-9-CM codes 800.x-995.x and E codes E880-E888 occurring within 2 days.*
[c]*Matched on age and gender, and relative risk estimate adjusted for Charlson Comorbidity Index.*