Risk Factors Associated With Severe Hypoglycemia in Older Adults With Type 1 Diabetes

Diabetes Care 2016;39:603–610 | DOI: 10.2337/dc15-1426

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OBJECTIVE

Severe hypoglycemia is common in older adults with long-standing type 1 diabetes, but little is known about factors associated with its occurrence.

RESEARCH DESIGN AND METHODS

A case-control study was conducted at 18 diabetes centers in the T1D Exchange Clinic Network. Participants were ≥60 years old with type 1 diabetes for ≥20 years. Case subjects (*n* = 101) had at least one severe hypoglycemic event in the prior 12 months. Control subjects (*n* = 100), frequency-matched to case subjects by age, had no severe hypoglycemia in the prior 3 years. Data were analyzed for cognitive and functional abilities, social support, depression, hypoglycemia unawareness, various aspects of diabetes management, C-peptide level, glycated hemoglobin level, and blinded continuous glucose monitoring (CGM) metrics.

RESULTS

Glycated hemoglobin (mean 7.8% vs. 7.7%) and CGM-measured mean glucose (175 vs. 175 mg/dL) were similar between case and control subjects. More case than control subjects had hypoglycemia unawareness: only 11% of case subjects compared with 43% of control subjects reported always having symptoms associated with low blood glucose levels ($P < 0.001$). Case subjects had greater glucose variability than control subjects ($P = 0.008$) and experienced CGM glucose levels <60 mg/dL for ≥20 min on 46% of days compared with 33% of days in control subjects ($P = 0.10$). On certain cognitive tests, case subjects scored worse than control subjects.

CONCLUSIONS

In older adults with long-standing type 1 diabetes, greater hypoglycemia unawareness and glucose variability are associated with an increased risk of severe hypoglycemia. A study to assess interventions to prevent severe hypoglycemia in high-risk individuals is needed.

Older adults with type 1 diabetes (T1D) are a growing but underevaluated population (1–4). Of particular concern in this age group is severe hypoglycemia, which, in addition to producing altered mental status and sometimes seizures or loss of consciousness, can be associated with cardiac arrhythmias, falls leading to fractures, and in some cases, death (5–7). In Medicare beneficiaries with diabetes, hospitalizations related to hypoglycemia are now more frequent than those for hyperglycemia and are associated with high 1-year mortality (6). Emergency department visits due to hypoglycemia also are common (5). These reports likely underestimate

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Received 1 July 2015 and accepted 11 October 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-1426/-/DC1.

A slide set summarizing this article is available online.

*A list of the T1D Exchange Clinic Network sites with participating principal investigators, coinvestigators, and coordinators is available in the Supplementary Data.

the problem of hypoglycemia in older adults with T1D because they include individuals with type 2 diabetes in whom severe hypoglycemic events are considerably less frequent. In addition, glucose levels at the time of falls (hip fractures) and the onset of cardiac events are frequently unavailable (8). The T1D Exchange clinic registry reported a remarkably high frequency of severe hypoglycemia resulting in seizure or loss of consciousness in older adults with long-standing T1D (9). One or more such events during the prior year was reported by 1 in 5 of 211 participants ≥65 years of age with ≥40 years' duration of diabetes (9).

Unlike treatment guidelines in younger individuals with T1D, which focus on optimizing glycated hemoglobin (HbA_{1c}) levels, treatment approaches for older adults with T1D often focus on minimizing hypoglycemia rather than attempting to achieve low HbA_{1c} levels (10,11). Despite this approach, data from the T1D Exchange (9) indicate that severe hypoglycemia in adults with T1D is as common with higher (>8.0%) HbA_{1c} levels as it is with lower (<7.0%) levels (9).

Despite the high frequency of severe hypoglycemia in older adults with long-standing T1D, little information is available about the factors associated with its occurrence. We conducted a case-control study in adults ≥60 years of age with T1D of ≥20 years' duration to assess potential contributory factors for the occurrence of severe hypoglycemia, including cognitive and functional measurements, social support, depression, hypoglycemia unawareness, various aspects of diabetes management, residual insulin secretion (as measured by C-peptide levels), frequency of biochemical hypoglycemia, and glycemic control and variability.

RESEARCH DESIGN AND METHODS

The study was conducted at 18 diabetes centers participating in the T1D Exchange Clinic Network (12). The centers are listed in the Supplementary Data. The study adhered to the tenets of the Declaration of Helsinki and was approved by the respective multiple institutional review boards. Study participants provided written informed consent before study participation.

Case subjects were required to have had at least one severe hypoglycemic event in the prior 12 months, defined as an event requiring assistance of another person as a result of altered consciousness or confusion, to administer carbohydrate or glucagon or other resuscitative actions. Control subjects were required to have not had a severe hypoglycemic event in the past 3 years. Case and control subjects were frequency matched on clinic and age in 5-year bins. Major eligibility criteria for case and control subjects included clinical diagnosis of autoimmune T1D being treated with insulin, age ≥60 years, and diabetes duration of ≥20 years. Exclusion criteria included current use of a

Table 1—Participant characteristics

	Case subjects *n* = 101	Control subjects *n* = 100	*P* value
Sex: women∫	51 (50)	44 (44)	0.36
Ageμ (years)	68.6 ± 6.4	68.0 ± 5.9	0.52
60 to <65	32 (32)	36 (36)	
65 to <70	33 (33)	31 (31)	
70 to <75	19 (19)	20 (20)	
≥75	17 (17)	13 (13)	
Race/ethnicity: non-Hispanic white∫	94 (93)	91 (91)	0.59
T1D durationμ (years)	40.5 ± 11.6	39.6 ± 11.9	0.58
20 to <30	22 (22)	29 (29)	
30 to <40	28 (28)	22 (22)	
40 to <50	26 (26)	23 (23)	
≥50	25 (25)	26 (26)	
Education*∫			0.62
Less than high school or high school diploma/GED	14 (14)	11 (11)	
Some college/associate or bachelor degree	59 (59)	65 (65)	
Master/professional or doctorate degree	27 (27)	23 (23)	
Insurance*∫ϑ			0.35
Government and commercial	35 (35)	37 (37)	
Only commercial	26 (26)	34 (34)	
Only government	38 (38)	27 (27)	
None	1 (1)	2 (2)	
Income (annual)*∫			0.41
<$35,000	24 (26)	22 (26)	
$35,000 to <$50,000	12 (13)	9 (11)	
$50,000 to <$100,000	30 (33)	33 (39)	
≥$100,000	26 (28)	20 (24)	
BMI (kg/m^2)*€μ	26.9 ± 5.0	27.0 ± 4.4	0.94
Underweight	3 (3)	—	
Normal weight	37 (37)	37 (38)	
Overweight	34 (34)	36 (37)	
Obese	25 (25)	25 (26)	
Exercise*‡μ (days/week)	6 (4, 7)	5 (4, 7)	0.52
Alcohol use*μ (days/month)	3.5 (0, 25)	2.5 (0, 20)	0.64
At least 1 day per month of binge drinking¥∫	6 (6)	3 (3)	0.50
Live alone∫	25 (25)	22 (22)	0.64

Categorical variables are shown as *n* (%) and continuous variables as mean ± SD or median (25th, 75th percentile). ∫*P* value obtained from χ^2 test or Fisher exact test when appropriate. μ*P* value obtained from *t* test or Wilcoxon test when appropriate. *Education data missing for 1 case and 1 control subject; health insurance data missing for 1 case subject; income data missing for 9 case and 16 control subjects; BMI data missing for 2 case and 2 control subjects; exercise data missing for 2 case subjects; alcohol data missing for 1 case subject. ϑThe government and commercial insurance group includes those with government insurance (Medicare, Medigap, Medicaid, TRICARE, Indian Health Service Plan, State Children's Health Insurance Program, etc.) and commercial insurance (commercial, fee-for-service, health maintenance organization, preferred provider organization, point-of-service) or a single-service plan (e.g., dental, vision, prescriptions). The only commercial insurance group includes those with commercial insurance only, and the only government insurance group includes those with government insurance only. ‡Exercise defined as at least 20 min of physical activity. ¥Binge drinking defined as ≥5 drinks in a row, within a couple of hours. €BMI is weight in kilograms divided by height in meters^2; underweight defined as BMI <18.5 kg/m^2, normal weight defined as BMI 18.5 to <25.0 kg/m^2, overweight defined as BMI 25.0 to <30.0 kg/m^2, and obese defined as BMI ≥30.0 kg/m^2.

Table 2—Diabetes management and clinical factors

	Case subjects *n* = 101	Control subjects *n* = 100	*P* value
Pump useχ	59 (58)	59 (59)	0.99
Total daily insulinχ*† (units/kg)	0.5 (0.4, 0.7)	0.5 (0.4, 0.6)	0.28
<0.40	20 (23)	27 (29)	
0.40 to <0.60	41 (47)	39 (42)	
≥0.60	27 (31)	27 (29)	
Home blood glucose monitoringχ† (times/day)	6 ± 3	5 ± 2	0.02
0	1 (<1)	0 (0)	
1–3	5 (5)	18 (18)	
4	21 (21)	24 (24)	
5–6	41 (41)	31 (31)	
7–9	20 (20)	22 (22)	
≥10	13 (13)	5 (5)	
HbA_{1c}*†Π, % (mmol/mol)	7.8 ± 1.3 (62.1 ± 13.9)	7.7 ± 1.1 (60.4 ± 12.0)	0.06
<7.0 (<53)	26 (26)	28 (28)	
7.0 to <8.0 (53 to <64)	31 (31)	36 (36)	
8.0 to <9.0 (64 to <75)	25 (25)	24 (24)	
≥9.0 (≥75)	18 (18)	12 (12)	
Detectable C-peptide*$\beta\Phi$	19 (19)	26 (26)	0.25
Glucose*†$\Pi\beta$ (mg/dL)	161 (106, 221)	176 (122, 237)	0.35
Abnormal creatinine*Þ	19 (19)	8 (8)	0.03
Diabetic ketoacidosis requiring hospitalization in past yearχ*			
≥1 event	7 (7)	2 (2)	0.17
β-Blocker useϑ	40 (40)	21 (21)	0.006

Variables are shown as *n* (%), mean ± SD, or median (25th, 75th percentile). χ*P* value adjusted for age and random site effect. *Total daily insulin data missing for 13 case and 7 control subjects; HbA_{1c} data for 1 case subject was excluded due to a falsely low reading as a result of anemia; creatinine level missing for 2 case subjects; C-peptide missing for 2 case subjects; glucose data missing for 2 case subjects; diabetic ketoacidosis hospitalization data missing for 1 case subject. †*P* value obtained using continuous variable. Π*P* value adjusted for age, self-monitoring of blood glucose, and random site effect. βObtained from a random blood draw at time of C-peptide measurement. ΦDetectable C-peptide defined as ≥0.017 nmol/L; *P* value adjusted for T1D duration and diagnosis age. ÞAbnormal creatinine defined as >1.1 mg/dL for females and >1.2 mg/dL for males; *P* value adjusted for age and T1D duration. ϑIncludes oral and ophthalmologic β-blockers; *P* value adjusted for age and T1D duration.

continuous glucose monitor (CGM), chronic kidney disease stage 4 or 5 (glomerular filtration rate <30 mL/min/1.73 m^2 [if known]), diagnosis of moderate or advanced dementia, serious illness with life expectancy of <1 year, and history of pancreatic transplant.

Testing Procedures

In addition to a standard history including information about prior severe hypoglycemia and diabetes management and a physical examination, a battery of tests were completed at two visits ~2 weeks apart. The cognitive test battery included measures of general mental status (Montreal Cognitive Assessment [13]), psychomotor processing speed (Symbol Digit Modalities Test [14]), executive functioning (Trail Making Test–Trail A and B [15,16]), and verbal memory (Hopkins Verbal Learning Test–Revised [17]). Before the cognitive testing, the blood glucose was checked, and the testing was deferred to another day if <70 mg/dL (3.9 mmol/L). Raw scores were used because there were no significant differences in demographic factors between groups.

Fine motor dexterity and speed (Grooved Pegboard Test [18]), depression symptoms (Geriatric Depression Scale Short Form [19]), instrumental activities of daily living (Functional Activities Questionnaire [20]), social support (Duke Social Support Index [21]), diabetes numeracy (Diabetes Numeracy Test–15 question [22]), visual acuity (Colenbrander Reading Card [English Continuous Text Near Vision Card] [23]), and physical frailty (timed 10-foot walk [24]) were also assessed.

Diabetes-related questionnaires included hypoglycemia unawareness (Clarke Hypoglycemia Unawareness Questionnaire [25]), hypoglycemia fear (Hypoglycemia Fear Survey [26]), and hyperglycemia fear (Preferring Hypoglycemia Scale; W.H. Polonsky, personal communication).

All questionnaires and functional testing were scored using recommended approaches, except for the Clarke Questionnaire (Supplementary Table 1). Because this survey includes questions regarding recent hypoglycemic events, an overall score would be invalid; therefore, scores for pertinent items were tabulated individually. Measurements of HbA_{1c}, random C-peptide, glucose, and creatinine levels were performed at a central laboratory.

A SEVEN PLUS CGM (Dexcom, Inc., San Diego, CA) in blinded mode (participant unable to see the glucose values) was worn for 14 days (two 7-day sensors) with daily calibration according to the label. Excluding the data from one case subject who used acetaminophen frequently despite instructions to the contrary (acetaminophen can affect the accuracy of the Dexcom sensor) and one control subject with no available CGM glucose data, the median (interquartile range) amount of CGM data was 277 h (235–309) for case subjects and 294 h (255–315) for control subjects. CGM metrics were computed overall and separately for daytime (6 A.M. to midnight) and nighttime (midnight to 6 A.M.). The calculation of proportion of days with at least one CGM hypoglycemic event (defined as at least 20 min with CGM glucose values <60 mg/dL) was limited to participants with at least 7 days of data.

Statistical Analysis

Characteristics between the case and control subjects were compared with the χ^2 test, Fisher exact test, *t* test, and Wilcoxon test (dependent on variable distribution). Adjusted regression models were run to assess the relationship between case-control status and various clinical factors, diabetes management factors, CGM data, and assessments. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). All *P* values are two-sided. A priori, in view of the multiple comparisons, only *P* values <0.01 were considered statistically significant.

Table 3—Blinded CGM data£

	Case subjects n = 101	Control subjects n = 100	P value*
Overall			
Mean glucose (mg/dL)	174.9 ± 31.6	175.4 ± 33.8	0.57
Percentage of time <70 mg/dL (%)	6.9 (3.4, 12)	5.3 (2.4, 9.3)	0.09
Min/day <70 mg/dL	99 (49, 173)	76 (34, 134)	
Percentage of time <60 mg/dL (%)	4.5 (1.7, 8.2)	3.0 (1.2, 5.7)	0.04
Min/day <60 mg/dL	65 (24, 117)	43 (18, 83)	
Percentage of time <50 mg/dL (%)	2.7 (0.7, 5.0)	1.6 (0.6, 3.7)	0.05
Min/day <50 mg/dL	39 (11, 73)	23 (8, 54)	
Percentage of time >180 mg/dL (%)	41.6 (28.2, 53.1)	40.3 (26.9, 58.1)	0.67
Min/day >180 mg/dL	600 (406, 765)	581 (387, 836)	
Percentage of time in target range (70–180 mg/dL) (%)	50.9 (40.6, 62.8)	51.7 (39.1, 61.7)	0.26
Min/day in target range	733 (585, 905)	745 (563, 888)	
Glucose variability≠ (%CV)	46.4 (38.8, 50.2)	41.9 (37.0, 45.7)	0.008
Percentage of days with ≥1 hypoglycemic event¥ (%)	46.2 (26.7, 61.5)	33.3 (20.0, 53.3)	0.10
Daytime (6 A.M. to 12 midnight)			
Mean glucose (mg/dL)	177.4 ± 32.3	178.8 ± 33.8	0.66
Percentage of time <70 mg/dL (%)	7.0 (3.7, 10.6)	4.7 (2.4, 8.0)	0.01
Percentage of time <60 mg/dL (%)	4.6 (1.8, 7.4)	2.6 (1.2, 4.8)	0.01
Percentage of time <50 mg/dL (%)	2.4 (0.8, 4.2)	1.3 (0.4, 2.7)	0.02
Percentage of time >180 mg/dL (%)	44.3 (30.3, 54.0)	42.0 (30.1, 55.5)	0.82
Percentage of time in range (70–180 mg/dL) (%)	49.2 (39.6, 60.0)	51.0 (39.7, 62.2)	0.30
Glucose variability≠ (%CV)	44.9 (38.9, 48.8)	41.2 (36.8, 45.4)	0.004
NighttimeΩ (12 midnight to 6 A.M.)			
Mean glucose (mg/dL)	164.9 ± 37.8	164.2 ± 42.6	0.50
Percentage of time <70 mg/dL (%)	7.7 (1.6, 15.2)	6.3 (0.9, 14.6)	0.51
Percentage of time <60 mg/dL (%)	4.1 (0.7, 11.5)	2.5 (0.0, 9.4)	0.32
Percentage of time <50 mg/dL (%)	2.2 (0.3, 7.0)	1.2 (0.0, 5.9)	0.19
Percentage of time >180 mg/dL (%)	34.4 (20.6, 49.3)	33.8 (19.3, 50.5)	0.80
Percentage of time in range (70–180 mg/dL) (%)	54.6 (42.6, 65.6)	55.6 (40.9, 65.0)	0.78
Glucose variability≠ (%CV)	42.2 (35.6, 51.8)	39.9 (33.2, 46.1)	0.03

Values are shown as mean ± SD or median (25th, 75th percentile). £CGM data missing for 1 control subject and excluded for 1 case subject due to continual acetaminophen use throughout wear, which affects CGM accuracy; blinded CGM data from subsets of day and night presented in Supplementary Table 3. *P value adjusted for age and SMBG; rank scores used to obtain P value. ≠Coefficient of variation (CV) of glucose variability [(SD/mean of glucose) × 100]. ¥Event defined as at least 20 min <60 mg/dL; additional CGM data missing for 3 case subjects due to not having the minimum requirement of at least 7 days of data (at least 6 full h/day). ΩAdditional CGM data missing for 4 case and 2 control subjects due to less than 24 h of nighttime CGM readings available.

RESULTS

The study included 201 participants (101 case subjects and 100 control subjects) enrolled between August 2013 and April 2014. Among the case subjects, 33% reported having 1 severe hypoglycemic event that required assistance in the past year, 25% reported 2 events, 25% reported 3–9 events, and 18% reported ≥10 events, with 33% reporting that the most recent hypoglycemic episode resulted in seizure or loss of consciousness. Among the control subjects, 33% reported never having had a severe hypoglycemic event that required assistance, 22% had an event 3 to <5 years ago, 16% had an event 5 to <10 years ago, and the remaining 29% had an event >10 years ago. Fifty-two percent of case subjects compared with 9% of control subjects reported having ≥20 severe hypoglycemic events in the past (P < 0.001) (Supplementary Table 2).

Demographic, Clinical, and Diabetes Management Characteristics

Demographics for case and control subjects were similar for most factors, including sex, age, race, diabetes duration, education, income, and BMI (Table 1). Similar proportions of case and control subjects were using an insulin pump (58% vs. 59%, P = 0.99) to manage insulin. Among participants using an insulin pump, 93% of case and control subjects had been using a pump for ≥3 years. Among participants currently using injection therapy, 5% of case and control subjects reported using a pump at some point during the past year. Rapid-acting insulin analogs were being used by 98% of those participants who used insulin pump therapy and by 96% of those who used injection therapy. This did not differ by case and control subjects. Total daily insulin amounts were similar (median 0.5 units/kg/day in case and control subjects, P = 0.28). Among case subjects, 51% reported using an insulin-to-carbohydrate ratio to decide how much mealtime insulin to take, compared with 41% of control subjects who used this method.

There was a trend toward more frequent self-reported home blood glucose meter testing in case subjects compared with control subjects (mean 6 vs. 5 times/day, respectively; P = 0.02) (Table 2). For nonglycemic management, β-blockers were used in 40% of case subjects and in 21% of control subjects (P = 0.006). Among those on β-blockers, there were no differences in selective versus nonselective β-blocker usage between case and control subjects (73% of case subjects vs. 86% of control subjects were on a selective β-blocker, P = 0.20). There also were no differences in β-blocker use between those aware and those with hypoglycemia unawareness (31% vs. 30%, respectively; P = 0.80). C-peptide levels were detectable in 19% of case subjects versus 26% of control subjects (P = 0.25).

Glycemic Measures

Mean HbA_{1c} was 7.8% in case subjects versus 7.7% in control subjects (P = 0.06) (Table 2). Mean CGM glucose levels were similar in case and control subjects (175 mg/dL [9.7 mmol/L], P = 0.57). The percentage of time in the range of 70 to 180 mg/dL (51% vs. 52%, respectively; P = 0.26), and >180 mg/dL (42% vs. 40%, respectively; P = 0.67) was also similar in both groups. However, there was a trend toward more time with CGM glucose level <60 mg/dL in case subjects compared with control subjects: 4.5% (65 min/day) vs. 3.0% (43 min/day), respectively (P = 0.04) (Table 3). This trend was observed during daytime (P = 0.01) but not nighttime (P = 0.32). There also was a trend toward case subjects more frequently experiencing

Table 4—Assessments§

	Case subjects *n* = 101	Control subjects *n* = 100	*P* value€
Montreal Cognitive Assessment*χ	25.2 ± 3.1	26.1 ± 2.8	0.04
<22	16 (16)	7 (7)	
22–25	32 (32)	32 (32)	
≥26	52 (52)	61 (61)	
Hopkins Verbal Learning Test–Total Recall*	22.4 ± 5.7	23.2 ± 5.0	0.49
<19	27 (27)	17 (17)	
19 to <23	22 (22)	27 (27)	
23 to <27	25 (25)	27 (27)	
≥27	27 (27)	28 (28)	
Hopkins Verbal Learning Test–Delayed Recall*χ	8.0 (6.0, 10.0)	8.5 (7.0, 10.0)	0.35
<6	23 (23)	17 (17)	
6 to <8	19 (19)	17 (17)	
8 to <10	28 (28)	31 (32)	
≥10	31 (31)	33 (34)	
Symbol Digit Modalities Test–Written*χ	36.5 ± 10.5	41.8 ± 10.4	0.001
<32	29 (30)	12 (13)	
32 to <38	30 (31)	24 (25)	
38 to <47	19 (20)	26 (27)	
≥47	19 (20)	34 (35)	
Symbol Digit Modalities Test–Oral*χ	42.3 ± 11.7	46.8 ± 11.0	0.01
<36	27 (28)	15 (16)	
36 to <44	30 (31)	21 (22)	
44 to <52	20 (21)	30 (32)	
≥52	20 (21)	29 (31)	
Trail Making Test–Trail Aχ†	39 (30, 47)	34 (26, 44)	0.06
<27 s	18 (18)	29 (29)	
27–35 s	23 (23)	25 (25)	
36–45 s	31 (31)	26 (26)	
>45 s	29 (29)	20 (20)	
Trail Making Test–Trail B*χ	103 (79, 140)	86 (66, 111)	0.002
<71 s	18 (18)	29 (30)	
71–95 s	21 (21)	30 (31)	
96–120 s	28 (28)	21 (22)	
>120 s	32 (32)	16 (17)	
Grooved Pegboard Test (Dominant Hand)*χ†	99 (80, 121)	87 (77, 107)	0.02
<80 s	20 (20)	28 (28)	
80 to <100 s	30 (30)	40 (40)	
≥100 s	50 (50)	31 (31)	
Geriatric Depression Scale*χ	1 (0, 2)	1 (0, 3)	0.83
0–5	90 (89)	86 (87)	
6–9	7 (7)	10 (10)	
≥10	4 (4)	3 (3)	
Diabetes Numeracy Test*χα	86.7 (66.7, 93.3)	80.0 (66.7, 93.3)	0.58
<70% correct	27 (28)	25 (26)	
70 to <90% correct	34 (35)	33 (34)	
≥90% correct	37 (38)	40 (41)	
Functional Activities Questionnaireχ	0 (0, 2)	0 (0, 0)	0.85
0	68 (67)	77 (77)	
1–8	28 (28)	19 (19)	
≥9	5 (5)	4 (4)	
Hypoglycemia Fear Survey*χ	38.5 ± 12.8	31.6 ± 11.8	<0.001
<25	17 (17)	34 (34)	
25 to <35	25 (25)	28 (28)	
35 to <45	22 (22)	21 (21)	
≥45	35 (35)	16 (16)	
Preferring Hypoglycemia Scale (hyperglycemic fear)*	12 (12)	16 (16)	0.42

Continued on p. 608

periods of hypoglycemia with CGM glucose levels <60 mg/dL for ≥20 min (46% vs. 33% of days with at least one hypoglycemic event, respectively; $P = 0.10$). The only CGM metric that differed significantly between case and control subjects was glucose variability, as measured by the coefficient of variation ($P = 0.008$), with the difference being predominantly during the day compared with the night. When defining high glucose variability as a coefficient of variation greater than the study cohort's 75th percentile (0.481), 38% of case and 12% of control subjects had high glucose variability ($P < 0.001$).

Cognitive and Functional Testing

Case subjects performed worse than control subjects on the written version of the Symbol Digit Modalities Test (mean 36.5 vs. 41.8, $P = 0.001$) and worse on the Trail Making Test–Test B (median 103 vs. 86 s to complete, $P = 0.002$) (Table 4). There was a trend for slightly lower scores in case than in control subjects on the Montreal Cognitive Assessment (mean score 25.2 vs. 26.1, $P = 0.04$), with over twice as many case subjects scoring in the impaired range on this measure (i.e., <22). There also was a trend toward less dexterity among case subjects ($P = 0.02$). No large differences were found between case and control subjects for other cognitive tests, functional testing, or diabetes numeracy (Table 4).

Psychosocial Factors

Case and control subjects had similar depression scores, but there was a trend for slightly lower scores on the Duke Social Support Scale in case versus control subjects (mean score 27.5 vs. 28.4, $P = 0.04$). Case subjects scored higher on the Hypoglycemia Fear Survey than control subjects (mean score 38.5 vs. 31.6, $P < 0.001$) (Table 4).

Hypoglycemia Unawareness

Case subjects were substantially more likely than control subjects to have significant hypoglycemia unawareness (Fig. 1*A* and *B* and Supplementary Table 1). Only 11% of case subjects compared with 43% of control subjects indicated that they always had symptoms when blood glucose was low ($P < 0.001$), and 17% vs. 6%, respectively, indicated that they never or rarely had symptoms ($P = 0.04$). Twenty percent of case subjects reported not

Table 4—Continued

	Case subjects n = 101	Control subjects n = 100	P value€
Duke Social Support Scale*χ	27.5 ± 3.6	28.4 ± 3.1	0.04
11–25	23 (23)	15 (15)	
26–30	56 (56)	60 (60)	
31–33	21 (21)	25 (25)	
Frailty 10-Foot Walk*χϑ	3.3 (3.0, 4.0)	3.0 (3.0, 3.5)	0.01
<3 s	18 (18)	21 (21)	
3–4 s	66 (66)	73 (74)	
>4 s	16 (16)	5 (5)	
Colenbrander Reading Card—Lowest LineΦ			
<20/40	13 (13)	11 (11)	0.28

Values are shown as n (%), mean ± SD, or median (25th, 75th percentile). §Scoring details: Montreal Cognitive Assessment, Hopkins Verbal Learning Test, and Symbol Digit Modalities Test cognitive tests—lower scores indicate reduced capacity; Trail Making and Grooved Pegboard cognitive tests—higher scores indicate reduced capacity; Geriatric Depression Scale—higher scores indicate increased depression; Diabetes Numeracy Test—lower scores represent diminished mathematical skills; Functional Activities Questionnaire—higher scores indicate less functional independence; Hypoglycemia Fear Survey—higher scores indicate more hypoglycemia fear; Duke Social Support—lower scores indicate reduced support; Frailty Walk—higher scores indicate increased physical frailty. Additional scoring details are listed in the Supplementary Data. €P value adjusted for age and random site effect. *Montreal Cognitive Assessment data missing for 1 case subject; Hopkins Verbal Learning Test–Total Recall data missing for 1 control subject and –Delayed Recall data missing for 2 control subjects; Symbol Digit Modalities Test–Written data missing for 4 case and 4 control subjects and –Oral data missing for 4 case and 5 control subjects; Trail Making Test–Trail B data missing for 2 case and 4 control subjects; Grooved Pegboard data missing for 1 case and 1 control subject; Geriatric Depression Scale data missing for 1 control subject; Diabetes Numeracy Test data missing for 3 case and 2 control subjects; Hypoglycemia Fear Survey data missing for 2 case subjects and 1 control subject; Preferring Hypoglycemia Scale (hyperglycemic fear) data missing for 2 case subjects; Duke Social Support Index data missing for 1 case subject; Frailty Walk data missing for 1 case and 1 control subject. χP value obtained using continuous variable. †Due to extreme outliers, rank scores used to obtain P value. αP value adjusted for insulin method (pump vs. injections), in addition to age and site. ϑP value adjusted for use of assistive devices during the test, in addition to age and site. ΦEnglish Continuous Text Near Vision Card; P value obtained from treating reading vision as an ordinal variable and adjusting for visual aids used during the test (such as a magnifying glass), in addition to age and site.

feeling symptoms of hypoglycemia until blood glucose was <40 mg/dL vs. 3% of control subjects (P = 0.009).

When defining hypoglycemia unawareness as never, rarely, or sometimes having symptoms when blood glucose is low (as opposed to often or always having symptoms), 58% of case subjects and 25% of control subjects had hypoglycemia unawareness ($P < 0.001$). Case subjects were more likely to have a combination of hypoglycemia unawareness and high glucose variability (as defined above) compared with control subjects (24% vs. 5%, respectively; P = 0.003).

CONCLUSIONS

This case-control study of older adults with long-standing T1D found that the occurrence of recent severe hypoglycemia was associated with greater hypoglycemia unawareness and higher glucose variability but not with lower HbA_{1c} or mean glucose levels. The latter finding indicates that the risk of severe hypoglycemia in this age group was not due to tighter glycemic control. The greater risk also was not due to less fear of hypoglycemia, and in fact, those with recent severe hypoglycemia, not surprisingly, had greater fear of hypoglycemia. The slightly higher daily frequency of blood glucose monitoring in case subjects compared with control subjects might be related to their higher fear of hypoglycemia. Hypoglycemia unawareness, which is associated with altered counterregulation, is more common in older adults with long-duration T1D than in younger individuals or those with type 2 diabetes (27). Individuals with reduced hypoglycemia awareness are more prone to severe hypoglycemia and high morbidity and mortality, particularly in the elderly (5–7,28). Current insulin therapies are unable to eliminate this risk. Routine screening for hypoglycemia unawareness in this population is recommended and can be accomplished using a brief questionnaire (25). Whether the glucose counterregulatory failure that characterizes hypoglycemia unawareness may explain the greater glucose variability reported here requires further study, and future work should explore strategies to correct defective glucose counterregulation in T1D.

The finding of greater glucose variability in case subjects than in control subjects is a concern, particularly when combined with a lack of awareness of hypoglycemia. Earlier studies examining limited glucose data from self-monitoring of blood glucose in younger patients suggested that blood glucose variance was related to hypoglycemia (29,30). A more recent study in long-standing T1D complicated by reduced awareness of hypoglycemia showed that glucose variability as determined by 72-h CGM was related to the severity of clinically problematic hypoglycemia (31).

Although the percentages of participants with measurable C-peptide levels were not different between the two groups, single C-peptide measurements are not as sensitive as provocative testing. Further research is required to determine if endogenous insulin secretion can assist in explaining our findings.

β-Blockers, which are commonly used in older patients with diabetes for a variety of indications, were more commonly used by case subjects than by control subjects. In younger age groups with shorter durations of diabetes than in our report, the adverse effect of selective and nonselective β-blockers on hypoglycemia unawareness has been studied (32,33), although we did not find an association between hypoglycemia unawareness and β-blocker use. We also note that there are no data about hypoglycemia risks in elderly patients with T1D, although one report of 13,559 subjects with type 2 diabetes did not find that β-blockers significantly increased the risk of severe hypoglycemia (34). Use of β-blockers in that report included oral and eye drop preparations, and the indications for use were not recorded. Further research is needed to better understand the possible influence of nonselective β-blocker use on hypoglycemia in this population.

The study found some differences in executive function and psychomotor processing speed between case and control subjects. These could be contributory

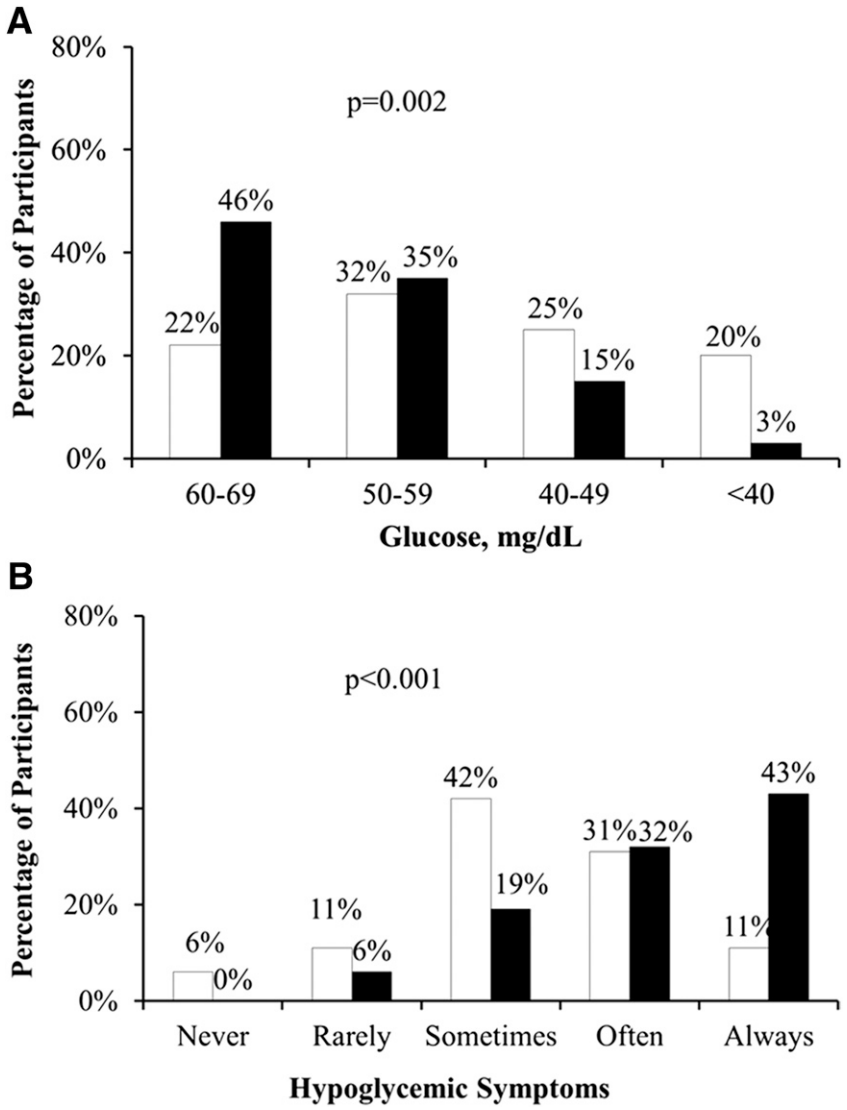

Figure 1—*A*: How low does your blood glucose need to go before you feel symptoms? *B*: To what extent can you tell by your symptoms that your blood glucose is low? Case subjects, □; control subjects, ■. Hypoglycemia Unawareness Questionnaire response missing for two case subjects and one control subject.

factors for severe hypoglycemia, could result from recurrent hypoglycemia, or could be part of a vicious cycle involving both. Those with cognitive impairment may be less able to determine and self-administer the correct insulin doses (for meals and correction of hyperglycemia) and amounts of carbohydrate for falling glucose levels. They may fail to anticipate the consequences of exercise or missed meals. This may be particularly problematic in those who lack physiological symptoms to alert them of hypoglycemia. Conversely, hypoglycemia could be related to the development of these cognitive impairments. No differences between case and control subjects were seen in functional activities score, numeracy, vision testing, depression, or social support.

A potential limitation of the study is that participants were from specialized diabetes centers; however, because case and control subjects were matched within centers, this was not likely a source of bias. Nevertheless, it is possible that results could differ in patients meeting study eligibility criteria receiving care in other settings. There is also the possibility of survivor bias. Individuals with a history of more severe hypoglycemia could have had earlier mortality. The study excluded users of CGM at home because frequency of use in this age group is low and it would be inappropriate to pool data from CGM and non-CGM users. The number of participants (n = 201) is also a limitation, and the quantity and quality of diabetes education they received over their many years of diabetes is unknown.

Because hypoglycemia is a major problem in older adults with longstanding T1D, current guidelines suggest higher HbA_{1c} goals for this population based on the assumption that this will lead to less hypoglycemia (9). Our results suggest that raising HbA_{1c} goals in many patients will be insufficient to reduce severe hypoglycemia in this population due to the presence of hypoglycemia unawareness and increased glucose variability. Therefore, until an artificial pancreas or β-cell replacement therapy becomes available, frequent home glucose measurements may be an important strategy for these patients. Other methods to reduce hypoglycemic exposure (35) and minimize β-blocker use should be considered. The use of current technologies, such as CGM and threshold suspend pumps, in this population requires further study.

Funding. Funding was provided by the Leona M. and Harry B. Helmsley Charitable Trust. The nonprofit employer of R.M.B. has received grant funding from the National Institutes of Health and the Leona M. and Harry B. Helmsley Charitable Trust. The nonprofit employer of N.S.C. has received grant funding from the National Institutes of Health.

Duality of Interest. R.S.W.'s nonprofit employer is the site for multicenter clinical trials sponsored by Eli Lilly, Medtronic Inc., AstraZeneca, GlaxoSmithKline, and Johnson & Johnson. R.M.B.'s nonprofit employer has received consultancy payments from Abbott Diabetes Care, Amylin, Bayer, Boehringer Ingelheim, Calibra, Eli Lilly, Halozyme, Hygieia, Johnson & Johnson, Medtronic, Novo Nordisk, ResMed, Roche, Sanofi, Takeda, and Valeritas, and grants from Abbott Diabetes Care, Amylin, Bayer, Becton Dickinson, Boehringer Ingelheim, Calibra, Daiichi Sankyo Inc., Dexcom, Eli Lilly, Halozyme, Hygieia, Intarcia, Intuity Medical, Johnson & Johnson, MannKind, Medtronic, Merck, Novo Nordisk, ResMed, Roche, Sanofi, and Takeda, with no personal compensation to R.M.B. R.M.B. receives royalties from the *Betty Crocker Diabetes Cookbook* and holds stock in Merck. M.N.M.'s nonprofit employer has received grant funding from Sanofi. R.W.B.'s nonprofit employer has received consultant payments on his behalf from Sanofi and Animas and a research grant from Novo Nordisk, with no personal compensation to R.W.B. G.A. has received lecture fees from BRIOmed. J.B.B. has received consultancy payments and stock from PhaseBio. J.B.B.'s nonprofit employer has received consultancy payments from Eli Lilly, Roche,

Bristol-Myers Squibb, LipoScience, GI Dynamics, Amylin, Orexigen, Elcelyx, Merck, Novo Nordisk, Metavention, TransTech Pharma, AstraZeneca, Dance Biopharm, Takeda, and Quest, and grants from Amylin, Novo Nordisk, Medtronic MiniMed, Eli Lilly, Tolerex, Osiris, Halozyme, Pfizer, Roche, Merck, Sanofi, Johnson & Johnson, Bristol-Myers Squibb, Andromeda, Boehringer Ingelheim, Orexigen, GlaxoSmithKline, Takeda, GI Dynamics, Astellas, AstraZeneca, MacroGenics, Intarcia Therapeutics, and Lexicon. H.R. has received payments as a board member for Eli Lilly, Merck, Novartis, and Sanofi and consultancy payments from Roche Diagnostics. H.R.'s nonprofit employer has received grants from Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Lexicon, Novartis, and Novo Nordisk, with no personal compensation to H.R. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.S.W., R.W.B., and I.B.H. researched data and wrote and edited the manuscript. S.N.D. researched data, wrote and edited the manuscript, and performed statistical analyses. R.M.B., N.S.C., C.P., B.A.O., M.N.M., A.J.S.P., K.M.M., D.R.L., G.A., J.B.B., D.K., A.B., R.S.G., R.C.E., R.E.P., A.L.P., H.R., A.J.A., J.-P.L., S.K.G., and M.R.R. researched data and reviewed and edited the manuscript. R.W.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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