Association Between Severe Hypoglycemia, Adverse Macrovascular Events, and Inflammation in the Edinburgh Type 2 Diabetes Study

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OBJECTIVE

To determine whether a history of severe hypoglycemia was associated with an increased risk of subsequent macrovascular events in people with type 2 diabetes and to explore possible mediation of this association by inflammation.

RESEARCH DESIGN AND METHODS

A cohort of 1,066 adults aged 60–75 years with type 2 diabetes was evaluated prospectively. Baseline history of severe hypoglycemia and plasma levels of the inflammatory markers C-reactive protein, fibrinogen, interleukin-6, and tumor necrosis factor-α were recorded. Their association with incident macrovascular events after 4 years was explored.

RESULTS

At baseline, 87 participants (8.2%) reported one or more episodes of severe hypoglycemia within the preceding year, and at follow-up 99 participants (9.3%) had suffered a new macrovascular event. Hypoglycemia was associated with increased odds of macrovascular events (odds ratio [OR] 2.11 [95% CI 1.06, 4.21], *P* = 0.035), including coronary heart events (OR 2.44 [95% CI 1.13, 5.26], *P* = 0.023), largely due to increased myocardial infarction (OR 4.02 [95% CI 1.54, 10.48], *P* = 0.004). Hypoglycemia was also associated with increased levels of inflammatory markers, including a general inflammation factor derived using principal-components analysis (*P* = 0.030, after adjustment for cardiometabolic risk factors). However, the significant association between hypoglycemia and macrovascular events persisted after adjustment for inflammatory markers.

CONCLUSIONS

The odds of suffering a macrovascular event were higher in patients with type 2 diabetes who had a history of severe hypoglycemia. There was no evidence that a proinflammatory state had a major role in mediating this association.

Macrovascular disease is the major cause of mortality in people with type 2 diabetes (1). Hypoglycemia is a potentially serious side effect of insulin and sulfonylureas when used to treat diabetes (2). It is associated with significant morbidity and mortality and can provoke acute cardiovascular and cerebrovascular events (2–4). Hypoglycemia may also have a role in aggravating other chronic complications (4)

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such as the possible development of dementia through acceleration of cognitive impairment (5–8).

Because of the high prevalence of vascular disease in people with diabetes, considerable research effort has been directed toward determining whether intensive therapy and strict glycemic control will lower the risk of vascular disease. Several randomized controlled trials have been undertaken to determine the effect of intensive versus conventional glycemic control on microvascular and macrovascular outcomes. These trials, along with other studies, have demonstrated significant benefits of strict glycemic control on limiting the frequency and severity of microvascular and macrovascular disease, but at the cost of a higher risk of severe hypoglycemia (9–15). In some of the large end point studies in people with type 2 diabetes, an excess mortality was observed in the intensively treated groups (10,11,13).

The relationship between glycemic control and macrovascular disease and how they are influenced by intensive therapy is complex, but appears to be J shaped, with increased risk associated with both high and low HbA_{1c} concentrations. This association has been studied within randomized controlled trials, in observational studies, and using retrospectively collected data. Data from prospective observational studies are sparse.

Chronic inflammation has been shown to be associated with macrovascular disease as well as insulin resistance and diabetes (16,17). In healthy participants, hypoglycemia was found to be associated with an acute increase in interleukin-6 (IL-6) (18), and two studies (19,20) in participants with type 1 diabetes both found increments in proinflammatory mechanisms after the induction of hypoglycemia, compared with euglycemia. To our knowledge, no prospective cohort study has evaluated the relationship between hypoglycemia and markers of chronic inflammation, and whether altered levels of inflammatory markers might mediate the association between hypoglycemia and macrovascular events in type 2 diabetes.

The aim of the current study was to determine whether a prospective association exists between severe hypoglycemia and macrovascular outcomes in people with type 2 diabetes, and to explore possible mediation of this association by an inflammatory mechanism.

RESEARCH DESIGN AND METHODS

Study Population

The Edinburgh Type 2 Diabetes Study (ET2DS) was established to investigate the role of risk factors underlying the progression of complications in a prospective cohort of people with type 2 diabetes (21). The cohort was recruited in 2006 and comprises 1,066 men and women between the ages of 60 and 75 years with established type 2 diabetes, living in the Lothian region of Scotland. Participants were selected by sex and 5-year age bands from a randomized list produced from the Lothian Diabetes Register, which contains electronic medical records on >20,000 patients with diagnosed type 2 diabetes. The cohort has been shown previously to be largely representative of patients with type 2 diabetes aged 60–75 years in terms of demographic and metabolic characteristics. Ethical permission was granted by the Lothian Medical Research Ethics Committee, and all participants gave written informed consent.

In subjects selected from the Lothian Diabetes Register, the diagnosis of diabetes was confirmed according to World Health Organization (WHO) criteria, and classification of type 2 diabetes was performed by medical staff. A diagnosis of diabetes was accepted if participants were receiving treatment with insulin and/or antidiabetes agents, or were on diet alone but had an HbA_{1c} level of >6.5% (>48 mmol/mol). Further assessment was made of participants in whom diagnostic classification was in doubt (21).

Data Collection

Participants attended a dedicated research clinic at baseline to undergo physical examination, and the measurement of BMI, HbA_{1c}, total cholesterol, HDL cholesterol, and estimated glomerular filtration rate (eGFR), as well as plasma inflammatory markers C-reactive protein (CRP), fibrinogen, IL-6, and tumor necrosis factor-α (TNF-α). Systolic and diastolic blood pressures were measured, and urine was obtained to determine the albumin-to-creatinine ratio, and whether microalbuminuria was present. A self-administered questionnaire was used to collect data on age, sex, smoking, diabetes duration, and current treatment.

Participant history of hypoglycemia was collected at the baseline clinic by a self-administered questionnaire, along with information about previous myocardial infarction (MI), angina, stroke, and transient ischemic attack (TIA). A standard 12-lead electrocardiogram (ECG) was performed, and linkage was made to previous medical and surgical discharge records from Scottish hospitals via the Scottish Morbidity Record-1 scheme administered by the Information and Services Division (ISD) of National Health Service Scotland (22). The presence of macrovascular disease (a composite of MI, angina, stroke, and TIA) at baseline was accepted if subjects met predefined criteria based on the results of the questionnaire, a positive WHO history of chest pain, an abnormal ECG result, and hospital discharge data linkage from ISD (23).

At follow-up, macrovascular disease was identified using a similar method, including a repeat self-report questionnaire (or via a general practitioner questionnaire if participants did not attend the follow-up clinic), WHO chest pain questionnaire, ECG, and data from ISD linkage to hospital discharge and death certificate data. Complete information on study design, participant selection, and data collection have been described previously (21,23–25).

Hypoglycemia

Severe hypoglycemia was defined as any episode of hypoglycemia that required external assistance for recovery. While data were collected on any event of hypoglycemia in the history of a participant's diabetes, only hypoglycemic events occurring within the year preceding the baseline assessment were used for this analysis. The question used to determine hypoglycemic events was: "Have you ever had an episode of low blood glucose (hypoglycemia) when you have needed someone else to treat you e.g. give sugary drink or glucagon?" If subjects responded "yes," then they were asked how many times this had ever happened (answer options: "1-2," "3-4," or "5 or over") and also how many times this had happened over the past year (answer options: "1-2," "3-4," and "5 or over"). Self-reporting of severe hypoglycemic events has been shown to be a relatively robust measure, particularly for events that have occurred

within the preceding year (26,27). This is not true for mild hypoglycemia, which was therefore not assessed.

Macrovascular Outcomes

The primary outcomes for the analyses were MI (fatal or nonfatal), angina, TIA, or stroke (fatal or nonfatal). The composite macrovascular disease outcome was defined as one or more episodes of MI, angina, TIA, or stroke. Coronary heart disease was defined by the occurrence of MI or angina, and cerebrovascular disease was defined by the occurrence of stroke or TIA. (As few events of stroke and TIA were recorded, these counts were combined.)

Statistical Analysis

Baseline means and proportions were compared between participants who reported severe hypoglycemic events at baseline and participants who did not, using an independent Student *t* test for continuous data and Pearson χ^2 or Fisher exact test for categorical variables.

Prospective analyses were conducted using binary logistic regression, evaluating the relationship between severe hypoglycemia at baseline and macrovascular events at follow-up. The macrovascular event categories at follow-up included composite macrovascular events, coronary heart disease, cerebrovascular disease, and the individual "hard" outcomes of MI and stroke. Univariate and multivariate-adjusted models were performed for each individual outcome, adjusting for the continuous baseline variables age, sex, blood pressure, HbA_{1c}, total cholesterol, HDL cholesterol, BMI, eGFR, and duration of diabetes; and for the categorical baseline variables smoking (ever or never), diabetes treatment method (diet alone, antidiabetes medications, or insulin with or without antidiabetes agents), use of lipid-lowering and blood pressure–lowering medications (both yes or no), or microalbuminuria (yes or no) with the addition of the relevant baseline macrovascular disease variable. The microalbuminuria variable was determined using albumin-to-creatinine ratio (>2.5 mg/mmol in men and >3.5 mg/mmol in women).

The association between severe hypoglycemia and the inflammatory markers CRP, fibrinogen, IL-6, and TNF-α was evaluated using a multivariate linear model, controlling for the covariates used in the binary logistic model. A general inflammation factor was derived from the four inflammatory markers using an unrotated principal components analysis. All four markers loaded quite strongly onto the first principal component (0.439–0.805), which accounted for 49.7% of the total variance. Inflammatory markers and the general inflammation factor were then added to the binary logistic models to explore the effect on the association between hypoglycemia and macrovascular events.

Interaction terms were calculated between the severe hypoglycemia variable and all other variables controlled for. Model evaluation and diagnostics were performed using Cook's distance and DfBeta plots to detect outliers and other data points that could have strong influence on the model, as well as for overall goodness-of-fit.

All reported *P* values are two-sided and a *P* value <0.05 was considered to be the threshold for statistical significance. Data are presented as odds ratios (ORs) or β-values with 95% CIs. Statistical analyses were conducted using SPSS software, version 20.0, and were re-evaluated by a separate author using R software version 3.0.2.

RESULTS

Severe Hypoglycemic Events

At baseline, 87 participants (8.2%) reported having experienced one or more events of severe hypoglycemia within the preceding year; 55 (5.2%) reported one to two events, 16 (1.5%) reported having three to four events, and 16 (1.5%) reported five or more events.

Baseline Characteristics

Baseline characteristics are shown in Table 1. On average, participants who experienced hypoglycemia compared with those who did not were more likely to be female and to have evidence of microalbuminuria, a higher HbA_{1c} level, lower systolic and diastolic blood pressures, a lower eGFR, and a longer duration of diabetes. With respect to treatment of diabetes, participants who experienced hypoglycemia were more likely to be receiving treatment with insulin than antidiabetes medications or diet alone.

At baseline, 374 participants (35.1%) reported having had one or more macrovascular events; 330 (31.0%) reported a coronary heart event, 93 (8.7%) reported a cerebrovascular event, 150 (14.1%) reported a previous MI, and 62 (5.8%) had sustained a previous stroke.

Association Between Severe Hypoglycemia and Incident Macrovascular Events

After 4 years of follow-up, 99 participants (9.3%) reported the occurrence of one or more macrovascular events since baseline. Coronary heart events were reported in 64 participants (6.0%), of whom 36 (3.6%) had sustained an MI. Cerebrovascular events occurred in 42 participants (3.9%), of whom 32 (3.0%) reported having a stroke.

Logistic regression analysis was performed in incremental steps that included *1*) unadjusted; *2*) age/sex adjusted; *3*) age/sex, plus cardiovascular risk factors (smoking, blood pressure, HbA_{1c} level, total cholesterol, HDL, BMI, eGFR, microalbuminuria, use of lipid-lowering or blood pressure–lowering medications, and baseline macrovascular events); and *4*) fully adjusted (addition of diabetes duration and treatment) (Table 2). Adjusting for a wide range of possible confounders, statistically significant increased odds were observed for the composite macrovascular event outcome (OR 2.11 [95% CI 1.06, 4.21], *P* = 0.035), coronary heart events (OR 2.44 [95% CI 1.13, 5.26], *P* = 0.023), and MI (OR 4.02 [95% CI 1.54, 10.48], *P* = 0.004). No significant association was found between severe hypoglycemia and cerebrovascular events or stroke. All statistical analyses were also conducted using "history of severe hypoglycemia at any time before baseline," with ORs similar for the two severe hypoglycemia variables, although *P* values varied slightly (data not shown).

Inflammation Mediators

In a multivariate linear model, severe hypoglycemia was associated with statistically significant higher levels of all five inflammatory variables. After controlling for possible cardiometabolic confounders, a statistically significant association was observed for TNF-α (β 1.27 [95% CI 1.07, 1.52], *P* = 0.007) and the general inflammation factor (β 0.24 [95% CI 0.02, 0.46], *P* = 0.030) (Table 3).

When individual inflammatory markers (CRP, fibrinogen, IL-6, and TNF-α) were added, as covariates to the binary logistic

Table 1—Characteristics of participants at baseline

Characteristic	*n**	All		At least one episode of severe hypoglycemia at baseline		
		Mean (SD) or *n* (%)	Median (IQR)	Yes (*n* = 87)	No (*n* = 979)	*P* value
Age, years	1,066	67.9 (4.2)	67.9 (64.4–71.5)	68.0 (4.5)	67.9 (4.2)	0.881
Male sex	1,066	547 (51.3%)		32 (36.8%)	515 (52.6%)	0.005
HbA_{1c}	1,028					
%		7.4 (1.1)	7.2 (6.7–7.9)	7.7 (1.4)	7.4 (1.1)	0.031
mmol/mol		57 (12)	55 (50–63)	61 (15.3)	57 (12)	
BP, mmHg						
Systolic	1,064	133.3 (16.4)	132.0 (122.0–142.0)	129.8 (18.0)	133.6 (16.3)	0.036
Diastolic	1,064	69.1 (9.0)	68.0 (62.0–76.0)	65.6 (9.7)	69.4 (8.9)	<0.001
Cholesterol, mmol/L	1,057	4.3 (0.9)	4.2 (3.7–4.8)	4.2 (0.8)	4.3 (0.9)	0.192
HDL, mmol/L	1,057	1.3 (0.4)	1.3 (1.1–1.5)	1.3 (0.4)	1.3 (0.4)	0.762
BMI, kg/m^2	1,066	31.4 (5.8)	30.7 (27.4–34.5)	32.4 (6.0)	31.3 (5.8)	0.094
eGFR, mL/min/1.73 m^2	1,060	78.1 (23.5)	78.6 (63.4–92.5)	68.4 (30.5)	78.9 (22.5)	<0.001
Microalbuminuria	1,056	176 (16.5%)		27 (31.4%)	149 (15.4%)	<0.001
Duration of diabetes, years	1,053	8.1 (6.5)	6.0 (3.0–11.0)	8.9 (3.8)	6.0 (2.2)	<0.001
Taking lipid-lowering medications	1,064	912 (85.6%)		79 (90.8%)	833 (85.3%)	0.157
Taking BP-lowering medications	1,059	873 (81.9%)		77 (88.5%)	796 (81.9%)	0.120
Smoker (ever)	1,066	652 (61.2%)		50 (57.5%)	602 (61.5%)	0.461
Treatment	1,036					<0.001
Diet alone		198 (18.6%)	5 (6.0%)	193 (20.3%)		
Tablets		652 (61.2%)	41 (49.4%)	611 (64.1%)		
Insulin		186 (17.4%)	37 (44.6%)	149 (15.6%)		
Macrovascular event	1,066	374 (35.1%)		45 (51.7%)	329 (33.6%)	0.001
Coronary heart event	1,066	330 (31.0%)		40 (46.0%)	290 (29.6%)	0.002
Cerebrovascular event	1,066	93 (8.7%)		13 (14.9%)	80 (8.2%)	0.032
MIs	1,066	150 (14.1%)		17 (19.5%)	133 (13.6%)	0.126
Stroke	1,066	62 (5.8%)		8 (9.2%)	54 (5.5%)	0.160

Values are mean (SD), *n* (%), or median (IQR), unless otherwise indicated. BP, blood pressure; IQR, interquartile range. *Complete data were available for age, BMI, sex, smoking, and macrovascular events. Less than 3% of data (from the total ET2DS population) were missing for systolic and diastolic blood pressure, cholesterol level, HDL level, eGFR, microalbuminuria, duration of diabetes, lipid-lowering medications, blood pressure–lowering medications, and diabetes treatment. For HbA_{1c} level, ~3.6% of data were missing. Data on "any hypoglycemia" were missing for five participants (~0.5%). Although this is not completely accurate for data on "1-year prior hypoglycemia," it is the best approximation as it was not possible to determine missing data for the "1-year prior" variable by the way the data were coded.

regression model evaluating hypoglycemia and macrovascular events, little change was observed in the model outcomes, and hypoglycemia remained significantly associated with macrovascular events (Table 4). Similar findings were apparent when the general inflammation factor was used to replace the four individual inflammatory markers (data not shown).

Model Evaluation

Testing interaction terms provided no evidence of interaction effect beyond what was controlled for in the model. The Cook's and DfBeta plots demonstrated some evidence of influence by several data points. When the model was reanalyzed with these data points removed, this did not significantly affect the outcome. The original models were therefore used for analysis.

CONCLUSIONS

In this cohort of people with type 2 diabetes, a prospective association was observed between a history of severe hypoglycemia and an increased odds of experiencing subsequent events associated with macrovascular disease and coronary heart disease, primarily as a consequence of the increased odds of sustaining an MI. Compared with those with no history of severe hypoglycemia at baseline, participants who reported at least one episode of hypoglycemia were ~1.1 times more likely to experience a macrovascular event, 1.4 times more likely to experience a coronary heart event, and 3 times more likely to experience an MI at follow-up. Increased levels of plasma inflammatory markers were observed in participants who experienced a hypoglycemic event, and TNF-α and the general inflammatory factor remained significantly associated with severe hypoglycemia after controlling for potential confounders. However, there was no evidence that a proinflammatory state had a major role in mediating the increased odds of macrovascular events in participants who experienced hypoglycemia.

Study Strengths and Limitations

Few high-quality studies have directly analyzed the relationship between severe hypoglycemia and macrovascular events in a truly observational, prospective manner. Most evidence has been derived from randomized controlled trials, hospital-based studies, and retrospectively collected data from clinical data sources. The current study benefits from use of a large, well-characterized cohort that is representative of most

Table 2—Effects of history of severe hypoglycemia at baseline on macrovascular events at 4-year follow-up

	Unadjusted		Age/sex adjusted		CV risk factor adjusted*		Adjusted†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Macrovascular disease events	2.43 (1.35, 4.38)	0.003	2.63 (1.45, 4.78)	0.001	2.26 (1.17, 4.36)	0.015	2.11 (1.06, 4.21)	0.035
Coronary heart disease event	3.20 (1.66, 6.14)	<0.001	3.27 (1.69, 6.33)	<0.001	2.59 (1.24, 5.41)	0.011	2.44 (1.13, 5.26)	0.023
Cerebrovascular disease event	1.19 (0.42, 3.43)	0.742	1.39 (0.48, 4.03)	0.550	1.16 (0.36, 3.78)	0.804	1.01 (0.29, 3.61)	0.983
MI	4.76 (2.21, 10.23)	<0.001	4.98 (2.29, 10.84)	<0.001	3.67 (1.48, 9.07)	0.005	4.02 (1.54, 10.48)	0.004
Stroke	1.17 (0.35, 3.92)	0.799	1.37 (0.40, 4.64)	0.616	1.02 (0.27, 3.84)	0.978	0.86 (0.21, 3.56)	0.836

Sample size: unadjusted n = 1,066; adjusted n = 978. CV, cardiovascular. *Logistic regression adjusted for baseline age, sex, smoking, blood pressure, HbA_{1c} level, cholesterol level, HDL level, BMI, eGFR, microalbuminuria, use of lipid-lowering and blood pressure–lowering medications; and prevalent (baseline) composite macrovascular events, cardiovascular disease events, cerebrovascular disease events, MI, and stroke. †Logistic regression model adjusted for same variables as cardiovascular risk factor–adjusted model, with the addition of baseline diabetes treatment and duration.

patients with type 2 diabetes, including those treated in primary and secondary care, and using a full range of treatment modalities from diet to insulin therapy. Loss to follow-up was limited by study design; completeness of outcome data was achieved by using data linkage from hospital admissions and death certificates, and was not dependent on participant attendance at the follow-up clinic. The frequency of reported hypoglycemic events was sufficient to draw relatively precise conclusions from the data. Of the participants in the ET2DS, 8.2% had a history of at least one episode of severe hypoglycemia within 1 year preceding the baseline assessment, whereas in the ADVANCE study, only 2.1% of participants reported an episode throughout the entire trial (28). In the current study, the macrovascular outcomes that were collected had strict criteria and verification procedures, increasing the validity of the variables.

Weaknesses of the current study include the relatively short period of follow-up, which limited the number of macrovascular outcomes that were observed. Because of this limitation, we avoided subgroup analyses, which would have further reduced power. One exploratory post hoc analysis, which was undertaken to exclude participants with a history of macrovascular disease, confirmed this to be the case: after excluding such participants, the data set had a total of only 42 hypoglycemia events, and, although the subsequently calculated point estimate still demonstrated increased odds of macrovascular disease for participants with hypoglycemia at baseline (OR 1.77), the wide 95% CI (0.59, 5.30) confirmed the imprecision of this estimate due to limited power. It should be noted that by controlling for prevalent macrovascular disease within the original model using the full data set, we had already reduced confounding by this variable. Another concern in the study is that self-reporting of severe hypoglycemia may be unreliable and prone to recall bias. Any potential bias in reporting was limited by the definition and the time frame of hypoglycemic episodes that were collected in the ET2DS. In the current study, five participants who were using dietary methods to control their diabetes reported experiencing an episode of severe hypoglycemia. This is unusual but not unknown, yet could be the result of either recall bias or misclassification bias and could indicate similar bias within the larger group of participants who reported hypoglycemia but were in the antidiabetes agents or insulin treatment groups. It should be noted that all analyses were made with those five participants included and excluded, with similar results being obtained (in the reported analyses, these five participants have been included). It is possible that hypoglycemia was under-reported, which would reduce the strength of an association, although the clinical syndrome of impaired hypoglycemia awareness that is associated with severe hypoglycemia is relatively uncommon in people with insulin-treated type 2 diabetes (29).

Table 3—Association between severe hypoglycemia and inflammation mediators

	Unadjusted		Adjusted*	
Inflammation marker	Severe hypoglycemia	*P* value	Severe hypoglycemia	*P* value
CRP (mg/L)	1.35 (1.04, 1.76)	0.024	1.17 (0.90, 1.53)	0.236
Fibrinogen (g/L)	0.31 (0.15, 0.48)	<0.001	0.12 (−0.05, 0.29)	0.156
IL-6 (pg/mL)	1.24 (1.07, 1.44)	0.005	1.10 (0.94, 1.28)	0.242
TNF-α (pg/mL)	1.47 (1.24, 1.74)	<0.001	1.27 (1.07, 1.52)	0.007
Inflammation factor†	0.50 (0.28, 0.72)	<0.001	0.24 (0.02, 0.46)	0.030

Values are β (95% CI), unless otherwise indicated. Sample size: n = 953. *Multivariate linear model adjusted for age, sex, smoking, blood pressure, HbA_{1c} level, cholesterol level, HDL level, BMI, eGFR, microalbuminuria, use of lipid-lowering and blood pressure–lowering medications, and baseline diabetes treatment and duration. †The general inflammation factor has a mean of 0 and an SD of 1.

While a novel aspect, and therefore a major strength, of the current study was the ability to evaluate the effects of chronic inflammation mediators on the association between hypoglycemia and macrovascular events in people with type 2 diabetes, caution is required in interpretation in view of the fact that

Table 4—Effects of inflammation mediators on the association between severe hypoglycemia and macrovascular events

	OR (95% CI)	*P* value
Macrovascular disease events	2.30 (1.13, 4.64)	0.021
Coronary heart disease event	2.45 (1.11, 5.36)	0.026
Cerebrovascular disease event	1.27 (0.35, 4.66)	0.716
MI	3.97 (1.49, 10.60)	0.006
Stroke	1.11 (0.25, 4.86)	0.893

Sample size: $n = 973$. Logistic regression adjusted for baseline age, sex, smoking, blood pressure, HbA_{1c} level, cholesterol level, HDL level, BMI, eGFR, microalbuminuria, use of lipid-lowering and blood pressure–lowering medications; and prevalent (baseline) composite macrovascular events, cardiovascular disease events, cerebrovascular disease events, MI, and stroke; baseline diabetes treatment and duration; and CRP, fibrinogen, IL-6, and TNF-α levels at baseline.

inflammation mediators were evaluated at only a single time point and not during, or soon after, a hypoglycemic episode. It is therefore unlikely that inflammation markers represented a subject's inflammatory status during a single such event. However, it should be noted that only severe hypoglycemia was reported for this data set, and is likely that more frequent, mild (self-treated) hypoglycemic events also occurred. Thus, it can be postulated that an accumulation of hypoglycemic episodes could lead to (or at least be associated with) a chronic proinflammatory state and thus with increased macrovascular disease. Another unresolved issue in the current study is whether a baseline history of severe hypoglycemia was merely a predictor of incident hypoglycemic events (during the 4-year follow-up), suggesting a role for incident hypoglycemic events in the association with macrovascular events and in the production of any potentially mediating proinflammatory state. Although 39% of participants with a history of severe hypoglycemia at baseline had an incident severe hypoglycemic event, the absolute number of incident events in people who also had experienced a macrovascular event was too small for meaningful analysis (30).

Comparison of Findings With Previous Studies

The findings of the present analysis are consistent with those of previous studies (28,31–33). However, the definitions of hypoglycemia, the major study outcomes, and their analyses differed considerably among these previous studies, so direct comparisons should be made with caution. The study by Zoungas et al. (28), which was a secondary analysis of data from the ADVANCE trial, demonstrated a strong association between severe hypoglycemia and macrovascular events with a hazard ratio (HR) of 2.88 (95% CI 2.01, 4.12). The ADVANCE trial was a prospective multicenter trial examining the effects of intensive glycemic control on cardiovascular events in 11,140 people with type 2 diabetes, with an average age of 65.6 years and an average of 4.9 years of follow-up. The retrospective study by Zhao et al. (31), which used medical and pharmacy records to create a cohort of 44,261 veterans with type 2 diabetes with a mean age of 62.6 years and 3.9 years of follow-up, estimated that participants who had experienced a hypoglycemic event had an increased risk of a cardiovascular event (HR 2.00 [95% CI 1.63, 2.44]). Hsu et al. (32) studied retrospective data from a Taiwanese insurance database in a cohort of 77,611 people with type 2 diabetes, with a mean age of 63.3 years but an unknown follow-up time, and determined an HR of 2.09 (95% CI 1.63, 2.67) for the relationship between all forms of hypoglycemia and cardiovascular disease. The ORIGIN trial (33) was a prospective randomized control trial, with a mean follow-up time of 6.2 years, examining the effects of intensive glycemic control on cardiovascular events in people >50 years of age with previously diagnosed type 2 diabetes, newly diagnosed type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose level. This study reported that in the 12,537 participants with dysglycemia, the risk of composite cardiovascular death, nonfatal MI or stroke was increased when people had experienced severe hypoglycemia (HR 1.58 [95% CI 1.24, 2.02]).

The present findings are not consistent with those of a study by Mellbin et al. (34), which did not find an increased risk of future morbidity in people who experienced hypoglycemia. This study was an analysis of the DIGAMI 2 trial, a randomized controlled trial of the effect of strict glycemic control following MI in which hypoglycemic episodes were recorded only during the initial, hospital phase of the trial. During this phase, intensive therapy was used in two of the three study arms and nonsymptomatic hypoglycemic events were included. The average age of the 1,253 men and women was 68 years, with 2.1 years of follow-up.

A meta-analysis (35), which has evaluated the relationship between hypoglycemia and cardiovascular disease, found an increased relative risk for cardiovascular events of 2.05 (95% CI 1.74, 2.42) for participants who had experienced hypoglycemia, which is consistent with the observations of the current study. Of the six studies in the review, two were randomized controlled trials and four were retrospective in nature, most of which have been discussed above. Retrospective studies are generally inferior to prospective, observational studies, such as the present evaluation, in their assessment of hypoglycemia and macrovascular disease. Further, the data for hypoglycemia for the four retrospective cohorts were collected by the use of diagnostic codes, resulting in lower rates of hypoglycemic events and possibly a different profile of severity.

One interpretation of the putative relationship between severe hypoglycemia and macrovascular outcomes is that hypoglycemia is not the direct cause of adverse vascular events but is a marker of vulnerability to such events (28). This premise was suggested previously by Bonds et al. (36) in their analysis of the ACCORD study, when they calculated that the excess mortality observed in the intensively treated group with strict glycemic control could not be fully accounted for by the higher number of hypoglycemic events in that study arm. It has also been argued that the increased morbidity and mortality associated with hypoglycemia may result from greater blood glucose fluctuations and is not specific to hypoglycemia per se (37,38). In a recent meta-analysis

(35), bias analysis was used to determine whether coexisting comorbid illnesses, and not hypoglycemia alone, could account for the increased risk of cardiovascular morbidity. The strength of the relationship between comorbidities and cardiovascular events was not sufficiently strong to account for the heightened risk associated with hypoglycemia, indicating that hypoglycemia may not simply be an index of ill health and susceptibility to adverse events. The current study cannot address this possibility, but, regardless of whether hypoglycemia is a cause or a marker of macrovascular disease, it is apparent from this and previous studies that a relationship between the two exists. This is worthy of further assessment to determine whether it can be modified to reduce the risk of sustaining macrovascular events.

Study Implications

The findings from the present analysis indicate that in people with type 2 diabetes, a history of severe hypoglycemia is strongly associated with subsequent macrovascular morbidity, principally related to MI. In such people, careful consideration should be given to what targets are appropriate, particularly in those people with a long duration of diabetes and in older people, who are at a greater risk of hypoglycemia (38). In addition, the study illustrates the need for careful management and frequent monitoring of all people with type 2 diabetes to minimize the risk of hypoglycemia.

No single mechanism can explain why hypoglycemia in people with type 2 diabetes precedes the development of adverse cardiovascular events. Acute vascular events may be provoked by subsequent hypoglycemia through the profound hemodynamic and electrophysiological changes that occur with sympatho-adrenal activation (3,38). Hypoglycemia also induces hemorrheological changes, white cell activation, vasoconstriction, and the release of inflammatory mediators and cytokines (3,4,39). While anecdotal evidence supports the induction of cardiac arrhythmias and ischemia by hypoglycemia, in the current study the temporal relationship between incident hypoglycemia and macrovascular events was not examined prospectively. Analysis undertaken in the current study did not provide evidence of a role for inflammatory mediators in a mechanistic pathway, but with only four markers evaluated, and only a single measurement of each, further research is required in this area.

In a representative cohort of people with type 2 diabetes, a significant association was observed between a history of preceding severe hypoglycemia and a higher frequency of subsequent macrovascular events, raising concerns about the advisability of strict glycemic control in people with type 2 diabetes who already have a degree of underlying macrovascular disease. The association between hypoglycemia and macrovascular events did not appear to be mediated by inflammation to any large extent, and further investigation into underlying mechanisms is required.

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