Severe Hypoglycemia and Smoking in a Long-Term Type 1 Diabetic Population: Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Abstract
Objective
To evaluate the relationship of severe hypoglycemia (SH) and smoking in a population-based cohort of persons with long-term type 1 diabetes.
Research Design and Methods
Cross-sectional analysis of the population-based cohort of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). The analyses in this report were limited to 537 type 1 diabetes individuals with complete data who participated in the last examination phase (2000-2001). SH was defined as having one or more episodes of loss of consciousness or overnight hospitalization due to hypoglycemia in a one year period prior to the examination.
Results
The prevalence of SH in this population was 14.3%. In univariate analysis, current smokers had a greater chance of having SH compared to never smokers: OR and 95% CI 2.40 (1.30-4.40). When controlling for relevant confounders such as age, gender, glycosylated hemoglobin, waist-hip ratio, orthostatic hypotension, alcohol consumption, intensive insulin treatment, past history of severe hypoglycemia, and late complications of diabetes (nephropathy, neuropathy, and retinopathy), the association remained statistically significant with current smoking presenting approximately 2.6 times greater odds of developing SH.
Conclusions
Current smokers with type 1 diabetes have higher odds of SH episodes.

Over the last decades, new therapeutic agents have been introduced to improve glycemic control and reduce complications of type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) showed the benefits of tight glycemic control but it also showed that individuals under intensive insulin treatment had increased risk of developing severe hypoglycemia (SH). Thus, this complication remains a major challenge when treating diabetic patients (1-5). Age, diabetes duration, history of previous episodes of hypoglycemia, intensive insulin treatment, and lower levels of glycosylated hemoglobin (HbA1c) have been previously described as factors associated with this complication (1-5). Smoking has been reported to be associated with hypoglycemia in previous clinical studies (6-8), and it has been studied but not related to SH in population-based studies. Smoking through its effect on hormone regulation and insulin clearance has been hypothesized to result in SH (6-8). The purpose of this study was to evaluate the relationship of SH and smoking in a population-based study of persons with long-term type 1 diabetes.

Research Design and Methods

Study Population

This study is a cross-sectional analysis of the population seen in the last examination (2000-01) of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). The WESDR is an ongoing prospective population-based cohort study initiated in 1980-82 of persons with type 1 and 2 diabetes mellitus living in 11 counties of Wisconsin(9). Participants were examined at baseline (n=996) and every 4-6 years. The last examination phase (2000-2001) was restricted to individuals (n=652) with type 1 diabetes. Detailed protocols used in this period were published elsewhere (10,11). Briefly, relevant evaluations included history of hypoglycemic reactions, neuropathy, nephropathy, cigarette smoking and alcohol consumption; measurements of blood pressure in supine and standing positions, glycosylated hemoglobin, height, weight, hip and waist; and fundus photography graded for diabetic retinopathy.

Definitions

Severe hypoglycemia was defined as having one or more episodes of loss of consciousness or overnight hospitalization due to hypoglycemia in a one year period prior to the examination. Therefore, two groups (with and without severe hypoglycemia) were defined and compared for the purpose of this study. Participants were considered to be never smokers if they had smoked less than 100 cigarettes in their lifetime; current smokers if they had smoked more than 100 cigarettes and continue to smoke; and past smokers if they had smoked more than 100 cigarettes but had stopped. All individuals classified as past smokers had stopped smoking for at least 12 months in this study. Intensive insulin treatment was defined as the use of 3 or more insulin injections/day or continuous insulin pump. The definition of past history of SH only included positive history of hospitalization due to hypoglycemia in previous WESDR examinations because information about loss of consciousness due to hypoglycemia was only obtained in this last examination phase. Orthostatic hypotension was defined as a decrease in systolic blood pressure (SBP) or diastolic blood pressure (DBP) of at least 20 mmHg or 10mmHg, respectively, after changing from supine to standing positions. Neuropathy was defined by positive history of tingling or numbness in

the hands, loss of tactile sensation, or loss of temperature sensitivity. Nephropathy was diagnosed if the participant had been under renal dialysis, submitted to renal transplantation, or had gross proteinuria. Diabetic retinopathy was assessed by fundus photographs and classified according to a modified Early Treatment Diabetic Retinopathy Study protocol (12). It was categorized into three groups: none to mild non-proliferative, moderate to severe non-proliferative and proliferative retinopathy.

Data analysis

Statistical analysis consisted of univariate analysis of continuous and categorical data using Student's t-test and χ^2, respectively. Multivariate analysis using logistic regression was performed to adjust for several confounders: age, gender, HbA1c, alcohol consumption, waist-hip ratio (WHR), orthostatic hypotension, intensive insulin treatment, and history of severe hypoglycemia. Three different regression models were built. Each model contained the same confounders; the only difference among them was the presence of one of the variables related to long term complications of diabetes (nephropathy, neuropathy, and retinopathy). These variables were analyzed separately due to possible correlations among them. Odds ratios (OR) with 95% confidence intervals (CI) were estimated and p values less than .05 were considered significant. Analyses were performed in SAS (SAS Institute, Cary, NC, USA)

The Institutional Review Board approved the study and all participants were consented. This research was conducted in accordance to the principles of the Declaration of Helsinki.

Results

A total of 537 individuals presenting complete data regarding insulin reaction were included in the current analysis. Compared to those who were excluded due to incomplete data (n=115), this group had lower levels of HbA1c and waist-hip ratio and tested the blood sugar more frequently each day (data not shown). The mean ± SD age of this population was 45.3 ± 9.9 years, duration of diabetes 31.3 ± 7.9 years, and glycosylated hemoglobin (HbA1c) 7.8 ± 1.4%. Regarding insulin treatment, 44.8% took insulin 3 or more times/day, 90.1% tested their glucose levels using blood from a fingerstick specimen (mean (±SD) 3.6 ± 2.1 tests/day), and 88.8% adjusted insulin as a result of these glucose tests. The use of continuous insulin pump was observed in 20.5% of this population. Most of the participants were never smokers (57.7%), 27.0% were past smokers, and 15.3% current smokers. Smoking status was similar in men and women; ~~a~~ pack-year history was 1.4 times higher in men than women, although not statistically significant (p=0.11). Seventy-eight individuals (14.5%) reported one or more episodes of SH in a period of 1 year. Table 1 shows the characteristics of the WESDR cohort in the 2000-2001 follow-up according to SH status.

In the univariate analysis, smoking was significantly associated with the development of SH (Table 2). Current smokers were more likely to report a history of SH compared to never smokers: OR and 95% CI 2.40 (1.30-4.40). In multivariable analysis (Table 3), smoking remained significantly associated with SH while controlling for confounders in two models. The odds ratios and 95% CIs comparing current to never smokers were 2.65 (1.20-5.82), 2.68 (1.21-5.92), and 2.10 (0.90-5.01) for the models including nephropathy, neuropathy, and retinopathy, respectively. No interactions were

observed (with age, gender, duration of diabetes, and intensive insulin treatment).

Conclusions

The relationship of smoking and low blood sugar was described in the 1950's when Bohan and Berry (7) and Berry (6) published a series of cases in which persons with type 1 diabetes had fewer hypoglycemic episodes after smoking cessation. In our study, current smokers were ~~3~~ 2.6 times as likely to report at least one episode of severe hypoglycemia when compared to non-smokers after controlling for relevant confounders. One study in Denmark also showed that smoking was an independent factor associated with SH, attributing this to differences in lifestyle, carbohydrate metabolism, and neuropathy (8). The relation of smoking to SH may be due to an effect of smoking on insulin clearance leading to hyperinsulinemia, increasing the risk of post-prandial hypoglycemia, and worsening metabolic control; such an effect was found in persons with type 2 diabetes (13). In addition, smoking has been shown to increase the secretion of hormones (i.e. growth hormone, arginine vasopressin, and cortisol) that counteract insulin action leading to an increased insulin requirement (14). Smokers have been found to require more insulin than non-smokers to achieve the same level of glycemic control in some but not all studies (15-17). This increased insulin requirement may also account for the higher susceptibility to SH in smokers.

Although the WESDR provided a unique opportunity to analyze data from a large population-based cohort of type 1 diabetes individuals, there are some limitations that should be considered. First, the definition of a history of SH included only those who lost consciousness or were hospitalized while other studies used a broader definition including all persons who had episodes of hypoglycemia that required help from another person (1,2,5,8). This might be reflected in the prevalence found in our study (14.5%) which approximates more the lower end of prevalence values found by others (4 to 40%)(2,5,8,18). Differences might also be due to higher frequencies of intensive insulin treatment in some specialty clinics then in the general population of persons with type 1 diabetes. Second, history of SH were not validated by examination of medical records or measurement of glycemia during the episodes. Therefore, SH might have been misclassified in some cases in our study. In addition, our assessment of smoking was based on cigarette smoking only. There were no questions regarding the use of smokeless tobacco or other sources of nicotine or exposure to passive smoking in our questionnaire. Third, it is possible that excessive exogenous insulin use may have resulted in residual confounding. However, we feel it is unlikely to affect the association because excessive insulin use has not been shown to be related to smoking. Fourth, although WESDR is a prospective study, we performed a cross-sectional analysis because new information regarding insulin reactions and blood pressure measurements in standing positions were only obtained in this last phase (2000-2001). As a consequence, this type of analysis limits us from determining antecedent-consequent relationships. Finally, the exclusion of some participants in the analysis resulted in a population with different characteristics compared to the baseline cohort that might have compromised the generalizability of our findings. In a long term perspective, death was the most common cause for exclusion. If smokers had a higher risk of

death, we might have underestimated the strength of the association reported. In addition, it is possible that individuals with complications such as neuropathy and nephropathy who had a history of SH were more likely to die and not participate than those without a history of SH leading to the lack of a finding with these complications. However, we believe the findings represent results from those with long-term type 1 DM and are still generalizable to such a group.

Despite these limitations, our study showed that current smokers presented significantly higher odds for SH episodes when compared to never smokers in this cohort of type 1 diabetic persons.

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Table 1. Clinical characteristics of participants of the WESDR according to severe hypoglycemia (SH) status. Data are means ± SD or %.

	All (n=537)	Yes SH (n=78)	No SH (n=459)
Women (%)	49.9	51.3	49.6
Age (years)	45.3 ± 9.9	44.1 ± 10.7	45.5 ± 9.7
Body mass index (kg/m^2)	27.5 ± 4.7	26.7 ± 4.9	27.7 ± 4.7
Waist-hip ratio	0.86 ± 0.09	0.84 ± 0.08†	0.86 ± 0.09†
Glycosylated hemoglobin (%)	7.8 ± 1.4	7.8 ± 1.6	7.8 ± 1.4
Diabetes duration (years)	31.3 ± 7.9	31.4 ± 9.5	31.2 ± 7.7
Intensive insulin treatment (%)	65.3	68.4	64.7
Number of times/day taking insulin	2.8 ± 0.9	2.8 ± 0.8	2.8 ± 1.0
Test blood sugar by fingerstick (%)	90.1	97.4†	88.9†
Number of tests/day	3.6 ± 2.1	4.0 ± 2.2	3.6 ± 2.1
Use of continuous pump (%)	20.5	23.7	19.9
Triglycerides (mg/dl)	99.5 ± 68.8	100.04 ± 68.7	99.45 ± 68.9
Cholesterol (mg/dl)	179.2 ± 35.2	185.6 ± 35.5	178.1 ± 35.0
Low density lipoprotein (LDL-mg/dl)	102.8 ± 30.9	106.2 ± 33.4	102.2 ± 30.4
High density lipoprotein (HDL-mg/dl)	56.8 ± 15.9	59.4 ± 15.9	56.3 ± 15.9
Orthostatic hypotension (%)	16.5	15.8	16.7
Alcohol consumption (oz/day)	0.17 ± 0.4	0.17±0.5	0.17±0.3
Smoking (%)			
Never	57.7	47.4	59.4
Past	27.0	26.9	27.1
Current	15.3	25.7§	13.5§

Past severe hypoglycemia (%)	4.6	7.9	4.1
Nephropathy (%)	25.1	28.2	24.6
Neuropathy (%)	47.2	52.6	46.3
Retinopathy* (%)			
None-Mild NPDR	42.4	51.1	41.2
Moderate-Severe NPDR	18.8	15.6	19.2
Proliferative	38.8	33.3	39.6

*NPDR: non-proliferative diabetic retinopathy
† p-value < 0.05
§ p-value < 0.01

Table 2. Odds ratios (OR) and 95% confidence interval (CI) in univariate analysis of factors related to severe hypoglycemia.

	OR (95%CI)	P value
Gender, male vs. female	1.07 (0.67-1.72)	0.79
Age, 1 year increase	0.98 (0.96-1.01)	0.24
Glycosylated hemoglobin, 1 SD increase	0.99 (0.79-1.25)	0.95
Waist-hip ratio, 1 SD increase	0.72 (0.54-0.96)	<0.05
Orthostatic hypotension, present	0.94 (0.44-2.01)	0.86
Alcohol consumption, 1SD increase	0.99 (0.78-1.27)	0.96
Smoking		
Past vs. Never Smoker	1.25 (0.70-2.22)	0.45
Current vs. Never Smoker	2.40 (1.30-4.40)	0.01
Intensive insulin treatment, current	1.18 (0.70-1.99)	0.53
Past severe hypoglycemia, present	2.00 (0.76-5.21)	0.15
Neuropathy, present	1.28 (0.79-2.08)	0.30
Nephropathy, present	1.20 (0.70-2.05)	0.49
Diabetic Retinopathy*		
Moderate-Severe NPDR vs. None-Mild NPDR	0.65 (0.26-1.60)	0.59
Proliferative vs. None-Mild NPDR	0.68 (0.33-1.36)	0.63

*NPDR: non-proliferative diabetic retinopathy

Table 3. Odds ratios (OR) and 95% confidence interval (CI) in multivariate analysis of factors related to severe hypoglycemia.

	Nephropathy	Neuropathy	Retinopathy
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Gender, male vs. female	1.64 (0.75-3.58)	1.74 (0.79-3.85)	1.47 (0.59-3.67)
Age, 1 year increase	1.01 (0.97-1.04)	1.01 (0.97-1.04)	0.98 (0.95-1.03)
Glycosylated hemoglobin, 1SD increase	0.86 (0.62-1.20)	0.85 (0.61-1.19)	0.93 (0.64-1.33)
Waist-hip ratio, 1SD increase	0.60 (0.40-0.90)†	0.59 (0.39-0.89)†	0.69 (0.44-1.10)
Orthostatic hypotension, present	0.80 (0.32-1.99)	0.82 (0.33-2.05)	1.05 (0.39-2.83)
Alcohol consumption, 1SD increase	0.99 (0.71-1.41)	1.08 (0.76-1.53)	1.05 (0.72-1.53)
Smoking			
Past vs. Never Smoker	1.02 (0.50-2.41)	0.98 (0.44-2.15)	0.93 (0.363-2.39)
Current vs. Never Smoker	2.65 (1.20-5.82)†	2.68 (1.21-5.92)†	2.10 (0.90-5.01)
Intensive insulin treatment, present	1.21 (0.60-2.43)	1.24 (0.62-2.48)	1.59 (0.72-3.54)
Past severe hypoglycemia, present	2.76 (0.87-8.74)	2.59 (0.81-8.28)	2.60 (0.71-9.52)
Nephropathy, present	1.86 (0.91-3.79)	-	-
Neuropathy, present	-	1.88 (0.98-3.60)	-
Retinopathy*			
Moderate-Severe NPDR vs. None-Mild NPDR	-	-	0.70 (0.25-1.99)
Proliferative vs. None-Mild NPDR	-	-	0.99 (0.44-2.25)

*NPDR: non-proliferative diabetic retinopathy

†p-value < 0.05