Severe Hypoglycemia and Smoking in a Long-Term Type 1 Diabetic Population

Wisconsin Epidemiologic Study of Diabetic Retinopathy

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OBJECTIVE — The purpose of this study was to evaluate the relationship of severe hypoglycemia and smoking in a population-based cohort of individuals with long-term type 1 diabetes.

RESEARCH DESIGN AND METHODS — This was a cross-sectional analysis of the population-based cohort of the Wisconsin Epidemiologic Study of Diabetic Retinopathy. The analyses in this report were limited to 537 type 1 diabetic individuals with complete data who participated in the last examination phase (2000–2001). Severe hypoglycemia was defined as having one or more episodes of loss of consciousness or overnight hospitalization attributable to hypoglycemia in a 1-year period before the examination.

RESULTS — The prevalence of severe hypoglycemia in this population was 14.3%. In univariate analysis, current smokers had a greater chance of having severe hypoglycemia compared with never smokers (odds ratio 2.40 [95% CI 1.30–4.40]). When we controlled for relevant confounders such as age, sex, A1C, waist-to-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 ~2.6 times greater odds of developing severe hypoglycemia.

CONCLUSIONS — Current smokers with type 1 diabetes have higher odds of severe hypoglycemia episodes.

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Over the last few decades, new therapeutic agents have been introduced to improve glycemic control and reduce complications of type 1 diabetes. The Diabetes Control and Complications Trial showed the benefits of tight glycemic control, but it also showed that individuals receiving intensive insulin treatment had an increased risk of developing severe hypoglycemia. Thus, this complication remains a major challenge in treatment of diabetic patients (1–5). Age, diabetes duration, history of previous episodes of hypoglycemia, intensive insulin treatment, and lower levels of A1C have been described previously 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 severe hypoglycemia in population-based studies. Smoking, through its effect on hormone regulation and insulin clearance, has been hypothesized to result in severe hypoglycemia (6–8). The purpose of this study was to evaluate the relationship of severe hypoglycemia and smoking in a population-based study of individuals with long-term type 1 diabetes.

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Abbreviations: WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

— This study was a cross-sectional analysis of the population seen in the last examination (2000–2001) of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). The WESDR is an ongoing prospective population-based cohort study initiated in 1980–1982 of individuals with type 1 and 2 diabetes 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, A1C, height, weight, and hip and waist circumference; 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 caused by hypoglycemia in a 1-year period before 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 <100 cigarettes in their lifetime, current smokers if they had smoked >100 cigarettes and continue to smoke, and past smokers if they had smoked >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 three or more insulin injections per day or use of a continuous insulin pump. The definition of past history of severe hypoglycemia 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 or diastolic blood pressure of at least 20 or 10 mmHg, 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 undergoing renal dialysis, had 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 nonproliferative, moderate to severe nonproliferative, and proliferative retinopathy.

Data analysis

Statistical analysis consisted of univariate analysis of continuous and categorical data using Student's *t* test and χ^2 test, respectively. Multivariate analysis using logistic regression was performed to adjust for several confounders: age, sex, A1C, alcohol consumption, waist-to-hip ratio, 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 because of possible correlations among them. Odds ratios (ORs) with 95% CIs were estimated, and $P < 0.05$ was considered significant. Analyses were performed in SAS (SAS Institute, Cary, NC)

The institutional review board approved the study, and all participants provided consent. This research was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

— A total of 537 individuals presenting complete data on insulin reaction were included in the current analysis. Compared with those who were excluded because of incomplete data ($n = 115$), this group had lower levels of A1C and lower waist-to-hip ratios and tested their blood glucose more frequently each day (data not shown). The mean ± SD age of this population was 45.3 ± 9.9 years, duration of diabetes was 31.3 ± 7.9 years, and A1C was 7.8 ± 1.4%. Regarding insulin treatment, 44.8% took insulin ≥3 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 a 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% were current smokers. Smoking status was similar in men and women; 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 severe hypoglycemia in a period of 1 year. Table 1 shows the characteristics of the WESDR cohort in the 2000–2001 follow-up according to severe hypoglycemia status.

In the univariate analysis, smoking was significantly associated with the development of severe hypoglycemia (Table 2). Current smokers were more likely to report a history of severe hypoglycemia compared with never smokers (OR 2.40 [95% CI 1.30–4.40]). In multivariable analysis (Table 3), smoking remained significantly associated with severe hypoglycemia while controlling for confounders in two models. ORs for comparisons of 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, sex, duration of diabetes, or intensive insulin treatment).

CONCLUSIONS

— The relationship of smoking and low blood glucose was described in the 1950s when Bohan and Berry (7) and Berry (6) published a series of cases in which individuals with type 1 diabetes had fewer hypoglycemic episodes after smoking cessation. In our study, current smokers were 2.6 times as likely to report at least one episode of severe hypoglycemia compared with nonsmokers after controlling for relevant confounders. One study in Denmark also showed that smoking was an independent factor associated with severe hypoglycemia, attributing this to differences in lifestyle, carbohydrate metabolism, and neuropathy (8). The relation of smoking to severe hypoglycemia may be due to an effect of smoking on insulin clearance, leading to hyperinsulinemia, increasing the risk of postprandial hypoglycemia, and worsening metabolic control; such an effect was found in individuals 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 nonsmokers 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 severe hypoglycemia in smokers.

Although the WESDR provided a unique opportunity to analyze data from a large population-based cohort of type 1 diabetic individuals, there are some limitations that should be considered. First, the definition of a history of severe hypoglycemia included only those who lost consciousness or were hospitalized, whereas other studies used a broader definition including all individuals who had episodes of hypoglycemia that required help from another individual (1,2,5,8). This difference might be reflected in the prevalence found in our study (14.5%), which approximates more the lower end of prevalence values found by others (4–40%) (2,5,8,18). Differences might also be due to higher frequencies of intensive insulin treatment in some specialty clinics than in the general population of individuals with type 1 diabetes. Second, the history of severe hypoglycemia was not validated by examination of medical records or measurement of glycemia during the episodes. Therefore, severe hypoglycemia might have been misclassified in some participants 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 was un-

Table 1—*Clinical characteristics of participants of the WESDR according to severe hypoglycemia status*

	All	Severe hypoglycemia	
		Yes	No
n	537	78	459
Women (%)	49.9	51.3	49.6
Age (years)	45.3 ± 9.9	44.1 ± 10.7	45.5 ± 9.7
BMI (kg/m^2)	27.5 ± 4.7	26.7 ± 4.9	27.7 ± 4.7
Waist-to-hip ratio	0.86 ± 0.09	0.84 ± 0.08*	0.86 ± 0.09*
A1C (%)	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 glucose 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
LDL cholesterol (mg/dl)	102.8 ± 30.9	106.2 ± 33.4	102.2 ± 30.4
HDL cholesterol(mg/dl)	56.8 ± 15.9	59.4 ± 15.9	56.3 ± 15.9
Orthostatic hypotension (%)	16.5	15.8	16.7
Alcohol consumption (ounces/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 to mild NPDR	42.4	51.1	41.2
Moderate to severe NPDR	18.8	15.6	19.2
Proliferative	38.8	33.3	39.6

Data are means ± SD or percent. *$P < 0.05$; †$P < 0.01$. NPDR, nonproliferative diabetic retinopathy.

Table 2—*ORs and 95% CI in univariate analysis of factors related to severe hypoglycemia*

	OR (95% CI)	*P* value
Sex, male vs. female	1.07 (0.67–1.72)	0.79
Age, 1 year increase	0.98 (0.96–1.01)	0.24
A1C, 1 SD increase	0.99 (0.79–1.25)	0.95
Waist-to-hip ratio, 1 SD increase	0.72 (0.54–0.96)	0.02
Orthostatic hypotension, present	0.94 (0.44–2.01)	0.86
Alcohol consumption, 1 SD 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 to severe NPDR vs. none to mild NPDR	0.65 (0.26–1.60)	0.59
Proliferative vs. none to mild NPDR	0.68 (0.33–1.36)	0.63

NPDR, nonproliferative diabetic retinopathy.

Table 3—*ORs and 95% CI in multivariate analysis of factors related to severe hypoglycemia*

	OR (95% CI)		
	Nephropathy	Neuropathy	Retinopathy
Sex, 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)
A1C, 1 SD increase	0.86 (0.62–1.20)	0.85 (0.61–1.19)	0.93 (0.64–1.33)
Waist-to-hip ratio, 1 SD 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, 1 SD 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 (0.36–2.39)
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 to severe NPDR vs. none to mild NPDR	—	—	0.70 (0.25–1.99)
Proliferative vs. none to mild NPDR	—	—	0.99 (0.44–2.25)

*$P < 0.05$. NPDR, nonproliferative diabetic retinopathy.

likely to affect the association because excessive insulin use has not been shown to be related to smoking. Fourth, although the 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 with 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 severe hypoglycemia were more likely to die and not participate than those without a history of severe hypoglycemia, leading to the lack of a finding with these complications. However, we believe the findings represent results from those with long-term type 1 diabetes and are still generalizable to such a group. Despite these limitations, our study showed that current smokers presented significantly higher odds for severe hypoglycemia episodes compared with never smokers in this cohort of type 1 diabetic individuals.

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