

Association Between Excessive Daytime Sleepiness and Severe Hypoglycemia in People With Type 2 Diabetes

The Edinburgh Type 2 Diabetes Study

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OBJECTIVE—Sleep-disordered breathing and sleepiness cause metabolic, cognitive, and behavioral disturbance. Sleep-disordered breathing is common in type 2 diabetes, a condition which requires adherence to complex dietary, behavioral, and drug treatment regimens. Hypoglycemia is an important side effect of treatment, causing physical and psychological harm and limiting ability to achieve optimal glycemic control. We hypothesized that sleep disorder might increase the risk of hypoglycemia through effects on self-management and glucose regulation.

RESEARCH DESIGN AND METHODS—People with type 2 diabetes ($n = 898$) completed questionnaires to assess sleep-disordered breathing, daytime sleepiness, and occurrence of severe hypoglycemia.

RESULTS—Subjects who scored highly on the Epworth Sleepiness Scale were significantly more likely to have suffered from severe hypoglycemia. This was a significant predictor of severe hypoglycemia in regression analysis including the variables age, sex, duration of diabetes, HbA_{1c}, BMI, and treatment type.

CONCLUSIONS—Daytime sleepiness may be a novel risk factor for hypoglycemia.

Hypoglycemia is an adverse side effect of insulin and sulfonylurea treatment for type 2 diabetes. Factors influencing risk of severe hypoglycemia (requiring external assistance) include duration of diabetes (1), duration of insulin treatment (2), renal impairment (2), age (1), comorbidities (3), and impaired awareness of hypoglycemia (4). Sleep-disordered breathing with associated daytime somnolence is reported in up to 75% of people with type 2 diabetes (5) and is linked to a range of cardiovascular and metabolic morbidities (6). We hypothesized that sleep disorder and

increased daytime sleepiness would be associated with increased frequency of severe hypoglycemia in people with diabetes.

RESEARCH DESIGN AND METHODS—Participants ($n = 898$) from the Edinburgh Type 2 Diabetes Study (7) completed the Epworth Sleepiness Scale (ESS) (8) and Berlin questionnaires (9) assessing daytime sleepiness and risk of sleep apnoea, respectively. History of severe hypoglycemia was obtained from the question, “Have you ever had an episode of low blood glucose when you have needed someone else to

treat you?” All subjects were recruited in 2006–2007 and were aged 60–75 years and domiciled in the Lothian region of Scotland.

High-risk Berlin score was defined as two of three categories positive (categories were snoring, sleepiness, and either self-reported hypertension or BMI >30 kg/m²) (9). The ESS was considered high if the score was ≥ 11 (8). Prevalence of severe hypoglycemia was compared in those with high- and low-risk Berlin and ESS scores using Pearson χ^2 test. Logistic regression (forced-entry method) was used to assess the impact of ESS, Berlin score, age, sex, duration of diabetes, HbA_{1c}, BMI, and treatment type on probability of severe hypoglycemia. Stepwise logistic regression using the backward elimination (likelihood ratio) method was performed to explore the best predictors of severe hypoglycemia. Data were analyzed using IBM SPSS Statistics (version 19; SPSS, Chicago, IL).

RESULTS—Subjects were representative of the original Edinburgh Type 2 Diabetes Study cohort in terms of age (67.9 years), sex (51.6 vs. 51.3% male), and BMI (31.1 vs. 31.4 kg/m²). The subjects in the current study had a longer duration of diabetes (9.0 vs. 8.1 years) and a lower HbA_{1c} (7.2 vs. 7.4% [55 vs. 58 mmol/mol]) than the original cohort. Median alcohol intake was 1.31 units/week (interquartile range 0.00–10.1), and use of sedatives/hypnotics (British National Formulary codes 4.1.1–4.1.3) was listed for 24 subjects.

People with diabetes who scored highly on the ESS were more likely to have suffered from severe hypoglycemia than those with low scores (15.6 vs. 9%, $P = 0.016$). A positive score in the sleepiness category of the Berlin questionnaire was also associated with a history of previous severe hypoglycemia compared with a negative sleepiness category score (13 vs. 8% $P = 0.024$). The overall Berlin score and the snoring category of the Berlin questionnaire were not related to

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previous severe hypoglycemia. High-risk Berlin scores and Epworth scales were positively associated with each other ($P < 0.001$).

Regression analysis confirmed the ESS as a significant independent predictor of severe hypoglycemia (Table 1). When the regression analysis was performed using Berlin sleepiness category, the Wald statistic was not significant ($P = 0.129$). Stepwise regression of these variables (including Berlin sleepiness category) confirmed ESS, sex, diabetes duration, and treatment type as independent predictors of severe hypoglycemia. Berlin sleepiness category, age, BMI, and then HbA_{1c} were removed from the model sequentially (Nagelkerke R^2 for model = 0.117).

CONCLUSIONS—In this large cohort of elderly people with type 2 diabetes, those with increased daytime sleepiness, as measured by two different scoring systems, were more likely to have experienced severe hypoglycemia. This was not observed for other measures of sleep-disordered breathing assessed by the Berlin scale. Sleepiness is a nonspecific symptom caused by a range of underlying causes and should be differentiated from sleep-disordered breathing and sleep deficiency. The data presented here suggest that sleepiness as a symptom, rather than sleep-disordered breathing per se, may be a risk factor for hypoglycemia.

Severe hypoglycemia is more likely to occur during sleep (mainly at night), and hypoglycemia is often prolonged and unrecognized at this time (10–12). These episodes are likely to cause sleep disruption (13) with resulting daytime somnolence, which may be the mechanism of the association. Conversely, daytime sleepiness may reduce awareness and recognition of hypoglycemia (14), therefore increasing risk of severe hypoglycemia because of failure to self-treat at an early stage. Sleepiness may also influence hypoglycemia risk through its effects on behavior and cognition. Sleepiness causes cognitive slowing, reduced attention, increased automatic behavior, and increased errors (for example, medical errors made by interns and motor vehicle crashes) (6,15). This may lead to poorer self-management and increased medication errors in patients.

Sleepiness may alternatively act as a marker of an underlying causative factor such as comorbidity or general frailty. The HbA_{1c} in the people with high ESS scores who had experienced severe hypoglycemia tended to be higher than the rest

Table 1—Regression analysis for predictors of severe hypoglycemia

Variable	Wald statistic ^a	Significance ^b	Exp b ^c
Epworth category	4.939	0.026	0.537
Age (years)	0.731	0.393	1.025
Sex (1 = male, 2 = female)	6.537	0.011	0.539
Duration of diabetes (years)	10.354	0.001	0.947
HbA _{1c} (%)	12.894	0.169	0.860
BMI (kg/m ²)	1.264	0.261	1.025
Oral antidiabetes agent	5.805	0.016	1.860
Insulin use	5.951	0.015	0.487

Nagelkerke $R^2 = 0.126$ for regression model. ^aMeasure of whether b-coefficient is significantly different from zero. ^bSignificance of Wald statistic; if $P < 0.05$, then predictor is making a significant contribution. ^cProportionate change in odds resulting from change in the predictor (if <1 , severe hypoglycemia more likely with increase in variable and vice versa).

of the cohort (7.6 vs. 7.2% [60 vs. 55 mmol/mol], $P = 0.09$). This could represent suboptimal self-management, which may increase the risk of hypoglycemia. Alternatively, glycemic targets in these individuals may have been relaxed to try to prevent further severe hypoglycemia.

The main limitation of the current study is the cross-sectional design that does not allow an examination of the temporal nature of the association. Information was not available about potential confounders such as social class, work and sleep habits, comorbidities, and stress. Alcohol and sedative drug use were not included in the regression model, as use of these substances was very low. The R^2 values for the regression models were small, indicating that the variables included were relatively weak predictors of severe hypoglycemia. This may relate to the absence of important predictors in the model; however, it also reflects the infrequent and sporadic occurrence of severe hypoglycemia.

The subjective method of capturing severe hypoglycemia may have led to inaccuracies owing to poor recall of previous events, misinterpretation of the question to include episodes where third-party help was provided but not necessarily required, and events that may not have been due to hypoglycemia, as no evidence of low blood glucose was required. Although information about the number of previous episodes was collected, numbers were too small to allow satisfactory assessment of a dose-response relationship, which would strengthen the plausibility of such an association.

This observation in a large, representative cohort is novel and needs to be replicated. Future research should collect prospective data on hypoglycemia, as well as important confounding factors. If further

evidence of sleepiness contributing to risk of severe hypoglycemia were available, sleepiness would be another factor to consider in the clinical assessment of hypoglycemia risk. This is an important consideration for treatment decisions and determining an individual's HbA_{1c} target. Inclusion of a quick and simple questionnaire to assess sleepiness could be incorporated into routine diabetes management to identify those at risk for hypoglycemia.

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