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

The Edinburgh Type 2 Diabetes Study

Berit Inkster, mbchb[1]
Renata L. Riha, md[2]
Liesbeth Van Look, mbchb[3]
Rachel Williamson, md[3]
Stela McLachlan, phd[4]
Brian M. Frier, md[1]
Mark W.J. Strachan, md[3]
Jackie F. Price, md[4]
Rebecca M. Reynolds, phd[5]

OBJECTIVE—Sleep-disordered breathing and sleepiness cause metabolic, cognitive, and behavioral disturbance. Sleep-disordered breathing is common in type 2 diabetes, a condition that 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.

Diabetes Care 36:4157–4159, 2013

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/m^2) (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/m^2). 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

From the [1]Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh, U.K.; the [2]Department of Sleep Medicine, Royal Infirmary of Edinburgh, Edinburgh, U.K.; the [3]Metabolic Unit, Western General Hospital, Edinburgh, U.K.; the [4]Centre for Population Health Sciences, University of Edinburgh, Edinburgh, U.K.; and the [5]Endocrinology Unit, Centre for Cardiovascular Sciences, Queen's Medical Research Institute, Edinburgh, U.K.
Corresponding author: Rebecca M. Reynolds, r.reynolds@ed.ac.uk.
Received 12 April 2013 and accepted 29 June 2013.
DOI: 10.2337/dc13-0863

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).

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. [a]Measure of whether b-coefficient is significantly different from zero. [b]Significance of Wald statistic; if $P < 0.05$, then predictor is making a significant contribution. [c]Proportionate change in odds resulting from change in the predictor (if <1, severe hypoglycemia more likely with increase in variable and vice versa).

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 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.

Acknowledgments—This study was supported by funding from the Medical Research Council and the Chief Scientist Office, Scotland. The support of the Wellcome Trust Clinical Research Facility is gratefully acknowledged.

This study was also supported by Pfizer. No other potential conflicts of interest relevant to this article were reported.

B.I. designed and carried out the analysis and wrote the manuscript. R.L.R. designed the analysis and participated in writing the manuscript. L.V.L., R.W., and S.M. collated and analyzed data and approved the manuscript. B.M.F., M.W.J.S., J.F.P., and R.M.R. are principal investigators of the Edinburgh Type 2 Diabetes Study and participated in the study design, collection and analysis of data, and writing the manuscript. R.M.R. 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 the accuracy of the data analysis.

References

1. Graveling AJ, Frier BM. Hypoglycaemia: an overview. Prim Care Diabetes 2009;3:131–139
2. Davis TME, Brown SGA, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. J Clin Endocrinol Metab 2010;95:2240–2247

3. Inkster B, Zammitt NN, Frier BM. Drug-induced hypoglycaemia in type 2 diabetes. Expert Opin Drug Saf 2012;11:597–614
4. Schopman JE, Geddes J, Frier BM. Prevalence of impaired awareness of hypoglycaemia and frequency of hypoglycaemia in insulin-treated type 2 diabetes. Diabetes Res Clin Pract 2010;87:64–68
5. Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. Chest 2008;133:496–506
6. Czeisler CA. Impact of sleepiness and sleep deficiency on public health—utility of biomarkers. J Clin Sleep Med 2011;7(Suppl.):S6–S8
7. Price JF, Reynolds RM, Mitchell RJ, et al. The Edinburgh Type 2 Diabetes Study: study protocol. BMC Endocr Disord 2008;8:18
8. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–545
9. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 1999;131:485–491
10. Jauch-Chara K, Schultes B. Sleep and the response to hypoglycaemia. Best Pract Res Clin Endocrinol Metab 2010;24:801–815
11. Chico A, Vidal-Ríos P, Subirà M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;26:1153–1157
12. Allen KV, Frier BM. Nocturnal hypoglycemia: clinical manifestations and therapeutic strategies toward prevention. Endocr Pract 2003;9:530–543
13. Bendtson I, Gade J, Thomsen CE, Rosenfalck A, Wildschiødtz G. Sleep disturbances in IDDM patients with nocturnal hypoglycemia. Sleep 1992;15:74–81
14. Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: reduced awakening from sleep during hypoglycemia. Diabetes 2003;52:1195–1203
15. Czeisler CA. The Gordon Wilson Lecture: work hours, sleep and patient safety in residency training. Trans Am Clin Climatol Assoc 2006;117:159–188