Journal of Clinical & Translational Endocrinology 15 (2019) 62–64

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Relationship between depression, sleep quality, and hypoglycemia among persons with type 2 diabetes

Alana Biggers[a,*], Lisa K. Sharp[b], Hataikarn Nimitphong[c], Sunee Saetung[c], Nantaporn Siwasaranond[c], Areesa Manodpitipong[c], Stephanie J. Crowley[d], Megan M. Hood[d], Ben S. Gerber[a], Sirimon Reutrakul[c,e]

[a] Division of Academic Internal Medicine and Geriatrics, University of Illinois at Chicago, United States
[b] Department of Pharmacy Systems, Outcomes, & Policy, University of Illinois at Chicago, United States
[c] Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand
[d] Department of Behavioral Sciences, Rush University Medical Center, United States
[e] Division of Endocrinology and Metabolism, University of Illinois at Chicago, United States

ARTICLE INFO

Keywords:
Diabetes mellitus
Type 2
Hypoglycemia
Depression
Sleep

ABSTRACT

Objective: We analyzed two cohorts of people with type 2 diabetes to evaluate the relationships between depression, sleep quality, and history of hypoglycemia.
Research design and methods: Two adult cohorts from Chicago (n = 193) and Bangkok, Thailand (n = 282) with type 2 diabetes completed questionnaires to assess sleep quality, depressive symptoms, and hypoglycemia frequency. Proportional odds logistic regression models for each cohort adjusted for duration of therapy, insulin and sulfonylurea management, and other factors.
Results: Those with hypoglycemia in both cohorts had a longer duration of diabetes, greater use of insulin, and worse sleep quality. The Chicago cohort used less sulfonylureas but had higher depressive symptom scores. The Thailand cohort had greater sulfonylurea use. In the final Thailand regression model, depressive symptoms were independently associated with hypoglycemia frequency. In both final Chicago and Thailand models, sleep quality was not associated with hypoglycemia frequency.
Conclusions: In the Thailand cohort, depressive symptoms were associated with hypoglycemia frequency.

Introduction

Hypoglycemia is a major complication of people with type 2 diabetes taking insulin or other hypoglycemic medication. Risk for hypoglycemia varies with factors such as duration of diabetes, insulin and sulfonylurea use, reduced renal function, older age, and other comorbidities [1]. Poor sleep quality, excessive daytime sleepiness, and depressive symptoms may also be related to hypoglycemia, a relationship that may be complex, bidirectional, and reflect poor self-care, nonadherence to diet or glucose self-monitoring [2–4]. We hypothesized that these factors are associated with an increased frequency of hypoglycemia in people with type 2 diabetes.

Material and methods

This secondary data analysis included participants with a clinical diagnosis of type 2 diabetes recruited from urban academic medical centers in Chicago, IL (n = 193; February to May 2012) and Bangkok, Thailand (n = 282; January 2014 to June 2016). During routine clinic visits, patients were asked if they would be interested in participating in studies exploring the sleep characteristics of patients with type 2 diabetes [5]. The studies were approved by the Institutional Review Boards of Rush University Medical Center and the Faculty of Medicine Ramathibodi Hospital. Consenting participants were interviewed during clinic or research study visits by trained study staff. The following questionnaires were completed: the Pittsburg Sleep Quality Index (PSQI; poor sleep ≥ 5) [6,7], the Epworth Sleepiness Scale (ESS; excessive daytime sleepiness ≥ 11) [8,9], and the Center for Epidemiologic Studies Depression Scale (CES-D) [10,11]. The CESD consists of 20 items that measure symptoms of depression (e.g., crying spells, feeling fearful, lonely or sad). Individual scores [from none of the time (0) to all the time (3)] are summed to calculate a total score, which ranges from 0 to 60, with higher scores reflecting greater depressive symptoms.

Participants were provided with a definition of hypoglycemia as

* Corresponding author at: Institute for Health Research and Policy (M/C 275), 1747 W. Roosevelt Rd., Chicago, IL 60608, United States.
E-mail address: abigger2@uic.edu (A. Biggers).

https://doi.org/10.1016/j.jcte.2018.12.007
Received 1 September 2018; Received in revised form 20 December 2018; Accepted 28 December 2018
2214-6237/ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

follows: “As you probably know, patients with diabetes can sometimes have episodes of low blood sugar. These are called hypoglycemic events. Symptoms of low blood sugar can be mild, such as sweating, trembling, or difficulty concentrating. Symptoms can also be severe, such as needing the help of someone else to bring you food or drink to manage the event, losing consciousness or needing to be hospitalized.” Self-reported history of hypoglycemia was then assessed by asking: “Have you had any episodes of hypoglycemia?” and “Have you had any episodes of hypoglycemia in the past six months? If so, then how often?”

Additional variables included body mass index, hemoglobin A1c (HbA1c, within past 3 months in medical record), medication use (abstracted from medical records) and history of obstructive sleep apnea (OSA) or OSA risk measured by the Berlin questionnaire [12,13].

Statistical analysis

In each cohort, we compared these measures for patients with and without self-reported hypoglycemia. We conducted a proportional odds logistic regression [14,15] analyses to evaluate relevant ($p < 0.1$) demographic factors and diabetes history/management (diabetes duration, insulin use, sulfonylurea use), PSQI, ESS, CES-D in relationship with hypoglycemia frequency. We evaluated the parallel regression assumption as well as collinearity. A stepwise logistic regression approach using backward elimination identified the best predictors of hypoglycemia. McFadden pseudo R^2 values were calculated for model fitness [16]. Data was analyzed using R v3.4.3 [17].

Results

In the Chicago cohort, those with a history of hypoglycemia were older (59.4 vs. 55.1 yrs, $p = .047$), had a longer duration of diabetes (15.5 vs. 8.0 yrs., $p < .01$), had greater use of insulin (65.7 vs. 30.2%, $p < .01$) and less sulfonylurea (27.1 vs. 43.4%, $p = .046$), and higher CES-D score (14.8 vs. 10.3, $p < .01$) and PSQI score (7.2 vs. 5.8, $p = .019$; Table 1). In the Thailand cohort, those with a history of hypoglycemia had a longer duration of diabetes (13.9 vs. 6.2 yrs, $p < .01$), greater use of insulin (48.8 vs. 19.6%, $p < .01$) and sulfonylurea (52.7 vs. 38.4%, $p = .026$), and higher PSQI score (8.4 vs. 7.4, $p = .021$). There were no statistically significant differences in gender, BMI, HbA1c, antidepressant/anxiolytic use, ESS, or OSA status by hypoglycemia history in either cohort. PSQI and CES-D scores were positively correlated with each other (Spearman $r = 0.41$ for Thailand cohort, $r = 0.59$ for Chicago cohort).

In the Chicago and Thailand cohorts, hypoglycemia frequency occurred never (45% and 62%), once or twice (25% and 21%), once a month (14% and 8%), twice a month (7% and 5%), once a week (7% and 4%), and daily (3% and 1%) in the past 6 months respectively. In the proportional odds logistic regression models, insulin users in both the Chicago and Thailand cohorts had a greater frequency of hypoglycemia (Table 2). In the Thailand cohort, sulfonylurea users and those with longer diabetes duration also had higher hypoglycemia frequency. Backwards regression yielded a final model that included insulin use and diabetes duration in the Chicago cohort (pseudo $R^2 = 0.046$), and insulin use, sulfonylurea use, diabetes duration, and CES-D score in the Thailand cohort (pseudo $R^2 = 0.092$).

Table 2
Proportional Odds Ratios in Frequency of Hypoglycemia in Chicago and Thailand Cohorts.

Variable	Chicago		Thailand	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age (years)	1.01	0.99–1.04	0.98	0.96–1.01
Gender (1 = male, 2 = female)	1.43	0.78–2.67	1.10	0.65–1.85
BMI (kg/m^2)	0.98	0.95–1.02	1.01	0.96–1.06
Insulin Use	2.58	1.28–5.27	4.67	2.52–8.80
Sulfonylurea Use	0.83	0.43–1.61	2.17	1.24–3.89
Diabetes Duration (years)	1.02	0.99–1.05	1.04	1.00–1.08
CESD Score	1.01	0.97–1.05	1.04	0.99–1.09
PSQI Score	1.02	0.93–1.11	1.03	0.96–1.12

McFadden Pseudo R^2: 0.100 (Thailand) and 0.055 (Chicago).

Discussion

In these samples of adults with type 2 diabetes from Chicago and Thailand, those with a history of hypoglycemia compared to those without were more likely to have poor sleep quality and higher depressive symptoms in bivariate analysis. In the cohort from Thailand, more depressive symptoms were associated with more frequent hypoglycemia, adjusting for insulin and sulfonylurea use as well as duration of diabetes. However, the model R^2 level was low, suggesting relatively weak prediction. This may reflect the need to include additional key clinical factors that influence hypoglycemia and the sporadic nature of hypoglycemic events [2].

A few studies have shown a relationship between depression and hypoglycemia (minor and severe) [4,5]. Similarly, we were unable to address any causal pathways with this cross-sectional sample between depression and hypoglycemia. This relationship may reflect lifestyle

Table 1
Demographics, sleep characteristics, depressive symptoms in Chicago and Thailand Cohorts.

Variable	Chicago (N = 193)			Thailand (N = 282)		
	Hypoglycemia (N = 140)	No Hypoglycemia (N = 53)	p-value	Hypoglycemia (N = 170)	No Hypoglycemia (N = 112)	p-value
Age, mean years (SD)	59.4 (12.4)	55.1 (13.8)	.047	56.4 (11.8)	54.6 (11.1)	.19
Female, N (%)	99 (70.7)	35 (66.0)	.65	98 (57.6)	64 (57.1)	1
BMI, mean kg/m^2 (SD)	35.5 (8.2)	36.0 (8.6)	.71	28.4 (4.7)	29.0 (5.6)	.42
Diabetes Duration, mean years (SD)	15.5 (10.8)	8.0 (7.9)	< .01	13.9 (9.4)	6.2 (6.4)	< .01
Hemoglobin A1c, Mean (SD) (%)	7.8 (1.5)	8.0 (2.1)	.69	7.8 (1.6)	7.7 (1.5)	.38
Insulin Use, N(%)	92 (65.7)	16 (30.2)	< .01	83 (48.8)	22 (19.6)	< .01
Sulfonylurea Use, N (%)	38 (27.1)	23 (43.4)	.046	89 (52.7)	43 (38.4)	.026
CES-D Score, Mean (SD)	14.8 (9.6)	10.3 (6.2)	< .01	12.6 (6.5)	11.1 (6.2)	.055
Antidepressant/antianxiolytic Use, N (%)	29 (20.7)	11 (20.8)	1	13 (7.7)	5 (4.5)	.33
OSA Risk (High) or Diagnosed, N (%)	83 (59.3)	36 (67.9)	.35	63 (37.3)	42 (38.2)	.98
Excessive daytime sleepiness N (%)	43 (30.7)	15 (28.3)	.88	42 (24.7)	30 (26.8)	.8
PSQI Score, Mean (SD)	7.2 (4.4)	5.8 (3.2)	.019	8.4 (3.5)	7.4 (3.6)	.021

Missing Data: Diabetes duration (Chicago 1), Sulfonylurea use (Thailand 1), Antidepressant use (Thailand 2), OSA Risk/Diagnosis (Thailand 3), PSQI Score (Thailand 1), Hypoglycemia frequency (Chicago 1, Thailand 1).

behaviors (eating habits and physical inactivity), metabolic changes, lack of self-monitoring, and poor medication adherence [4]. People with diabetes complications and potentially related dementia more likely experience depression [18]. Conversely, depression may cause dysregulation of the hypothalamic–pituitaryadrenal axis, autonomic dysfunction and inflammation leading to variation in glucose levels [18–20]. Given these complex, bidirectional interactions between depression and hypoglycemia, it is feasible that people with more depressive symptoms more likely have hypoglycemia (and *vice versa*). Future studies will need to explore causal pathways and temporal relationship between depression and hypoglycemia. Additionally, very few Thailand participants (5–8%) indicated antidepressant medication therapy use, which could contribute to the observed association between hypoglycemia and untreated depression. Limited antidepressant use may also reflect social stigma associated with depression and underdiagnosis in Eastern populations [3].

While we observed poorer sleep quality among those with a history of hypoglycemia, it was not selected in our final regression model. Additionally, there was no difference in the ESS daytime sleepiness measure. In contrast, a large cohort of elderly people in the United Kingdom with type 2 diabetes demonstrated an association between sleepiness and severe hypoglycemia [2]. As opposed to mild or minor hypoglycemia, severe episodes can result in sleep disruption, and sleepiness can cause less awareness or recognition of hypoglycemia [21]. Possibly, the majority of the self-reported hypoglycemia episodes in this study were mild.

One strength of our study is the use of two relatively large, diverse patient samples. Additionally, we considered multiple, inter-related potential risk factors for any history of hypoglycemia, including depression and sleep quality. However, there were limitations. This observational study relied on self-report data which is subject to recall bias and inaccuracy. This is of particular importance in self-reported hypoglycemia, where a diary would have been helpful in capturing episodes [22]. We also did not assess hypoglycemia unawareness specifically. Additionally, we cannot generalize to other populations, where variation exists in societal and cultural self-management behaviors. For instance, diabetes self-management education in Thailand is not standardized, unlike the United States [23].

Conclusions

In both cohorts studied, individuals with a history of hypoglycemia experienced a significant and greater burden of depressive symptoms and poorer sleep compared to those without a history of hypoglycemia. As poor sleep and depression may result in greater glycemic variation, clinical screening for these problems should be considered broadly in populations with type 2 diabetes, especially among those with hypoglycemia. To understand these complex relationships further, research could include remote monitoring of glucose levels, sleep (actigraphy), and ecological momentary assessment.

Acknowledgements

This project was supported by a research supplement to promote diversity in health-related research grant from the National Institute of Diabetes and Digestive and Kidney Disease (R01DK108141S). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funding source had no role in study design, conduct, analysis, or decision to submit findings for publication. The research was supported by a departmental grant, Rush University Medical Center; a grant from Mahidol University and a grant from the Endocrine Society of Thailand.

Conflict of interest statement

There are no conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2018.12.007.

References

[1] Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005;28:2948–61.
[2] Inkster B, et al. Association between excessive daytime sleepiness and severe hypoglycemia in people with type 2 diabetes the edinburgh type 2 diabetes study. Diabetes Care 2013;36:4157–9.
[3] Zhang Y, et al. Depression in Chinese patients with type 2 diabetes: associations with hyperglycemia, hypoglycemia, and poor treatment adherence. J Diabetes 2015;7:800–8.
[4] Asuzu C, Walker R, Williams J, Egede L. Pathways for the relationship between diabetes distress, depression, fatalism and glycemic control in adults with type 2 diabetes. J Diabetes Complications 2017;31:169–74.
[5] Saetung S, et al. Eveningness is associated with greater depressive symptoms in type 2 diabetes patients: a study in two different ethnic cohorts. Behav Sleep Med 2017. https://doi.org/10.1080/15402002.2017.1342169.
[6] Buysse D, Reynolds C, Monk T, Berman S, Kupfer D. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
[7] Sitasuwan T, Bussaratid S, Ruttanaumpawan P, Chotinaiwattarakul W. Reliability and validity of the thai version of the pittsburgh sleep quality index. J Med Assoc Thail Chotmaihet Thangphaet 2014;97(Suppl 3):S57–67.
[8] Johns M. A new method for measuring daytime sleepiness: the epworth sleepiness scale. Sleep 1990;14:540–5.
[9] Banhiran W, Assanasen P, Nopmaneejumruslers C, Metheetrairut C. Epworth sleepiness scale in obstructive sleep disordered breathing: the reliability and validity of the Thai version. Sleep Breath 2011;15:571–7.
[10] Radloff L. The CES-D scale. Appl Psychol Meas 1977;1:385–401.
[11] Trangkasombat U, Larpboonsarp V, Havanond P. CES-D as a screen for depression in adolescents. J Psychiatric Assoc Thailand 1997;42(1):2–13.
[12] 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.
[13] Suksakorn S, Rattanaumpawan P, Banhiran W, Cherakul N, Chotinaiwattarakul W. Reliability and validity of a Thai version of the Berlin questionnaire in patients with sleep disordered breathing. J Med Assoc Thail Chotmaihet Thangphaet 2014;97(Suppl 3):S46–56.
[14] Agresti A. Categorical Data Analysis. (John Wiley & Sons, Inc.).
[15] Long JS. Regression Models for Categorical and Limited Dependent Variables. Advanced Quantitative Techniques in the Social Sciences Number 7. (Sage Publications).
[16] McFadden D. Conditional logit analysis of qualitative choice. behavior 1973.
[17] Team, R. C. R: A language and environment for statistical computing. (2017).
[18] Musselman D, Betan E, Larsen H, Phillips L. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiat 2003;54:317–29.
[19] Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci 2011;13:7–23.
[20] Gilsanz P, Karter AJ, Beeri MS, Quesenberry CP, Whitmer RA. The bidirectional association between depression and severe hypoglycemic and hyperglycemic events in type 1 diabetes. Diabetes Care 2018;41:446–52.
[21] Banarer S, Cryer P. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes. Diabetes 2003;52:1195–203.
[22] Khunti, et al. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. DiabetesObes Metabol 2016;18:907–15.
[23] Reutrakul S, Deerochanawong C. Diabetes in Thailand: status and policy. Curr DiabRep 2016;16:28.