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Poor Sleep Quality is Associated with Nocturnal Glycemic Variability and Fear of Hypoglycemia in Adults with Type 1 Diabetes

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Abstract

Aims: To examine sleep quality and its associations with glycemic control, glycemic variability and fear of hypoglycemia in adults with type 1 diabetes.

Background: Poor sleep quality has negative health consequences and is a frequent complaint among adults with type 1 diabetes. Sleep quality in adults with type 1 diabetes is likely affected by glucose levels as well as stressors associated with managing a chronic condition.

Design: A retrospective secondary analysis of pooled data from two previous cross-sectional studies was conducted.

Methods: We examined subjective sleep quality, fear of hypoglycemia; objective measures of glycemic control (HbA1c); and glycemic variability (three-day continuous glucose monitoring) in

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48 men and women aged 18-45 years with type 1 diabetes. The data were collected over 3 years in 2013-2016.

Results/Findings: Poor sleep quality was reported by 46% of subjects. Those with poor sleep quality had significantly greater nocturnal glycemic variability and fear of hypoglycemia. Nocturnal glycemic variability and fear of hypoglycemia were significantly associated with poor sleep quality. The interaction effect of glycemic variability and fear of hypoglycemia was significant.

Conclusion: These findings suggest that glycemic control and fear of hypoglycemia are targets for intervention to improve sleep quality in those with type 1 diabetes.

Keywords

sleep; glycemic control; glycemic variability; fear of hypoglycemia; type 1 diabetes; nursing

INTRODUCTION

Poor sleep quality is associated with many negative health conditions in the general population. These include sympathetic nervous system arousal (Knutson & Van Cauter, 2008), insulin resistance (Klingenberg et al., 2013), metabolic dysregulation (Y. Zhu et al., 2015) and a higher prevalence of cardiovascular disease (CVD) (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011). Poor sleep quality is a frequent complaint among those with type 1 diabetes (T1DM) (Brod, Christensen, & Bushnell, 2012), who are challenged by additional factors related to management of a chronic condition. Sleep quality in those with T1DM may be influenced by diabetes-related symptoms, physiological changes, psychological stressors and self-management demands (e.g., blood glucose testing during the night) (Barnard et al., 2014; van Dijk et al., 2011).

Background

Evidence suggests that sleep quality and glucose are related, yet explicit determinants of sleep quality and links with glucose levels in T1DM have not been well established. Most studies that have examined the associations of glucose and sleep have used HbA1c, the average blood glucose over a 2- to 3-month period, as a marker of glycemic control. In a systematic review and meta-analysis in patients with T1DM, those with self-reported good sleep quality (using validated questionnaires) had significantly lower HbA1c levels than those who reported poor sleep quality (Reutrakul et al., 2016). Mechanisms of action were not addressed in the analysis; however, in other T1DM sleep studies, higher HbA1c levels have been associated with more nighttime awakenings, shorter sleep duration and lighter less restorative sleep stages (Borel et al., 2013; Feupe, Frias, Mednick, McDevitt, & Heintzman, 2013; Jauch-Chara, 2008; Perfect et al., 2012). Using polysomnography, those with higher HbA1c levels spent more time in lighter stage 2 sleep and less time in deeper stage 3 sleep compared with healthy control subjects (Perfect et al., 2012).

In addition to glycemic control, glycemic variability (GV; minute-to-minute fluctuations in glucose) has been associated with sleep disturbances (Barone et al., 2015; Pillar, 2003). Using polysomnography to measure sleep and continuous glucose monitoring to measure

glucose fluctuations during sleep, Pillar (2003) observed that glucose fluctuations of 25-50 mg/dL led to sleep arousal. Glucose levels can fluctuate widely within 24 hours and these fluctuations may be missed if looking only at HbA1c (Hirsch, 2015). GV has important clinical relevance because greater GV has been associated with endothelial dysfunction (a marker of early cardiovascular disease), diabetes complications, cardiovascular events and mortality (Ceriello et al., 2012; Quagliaro et al., 2003; Soupal et al., 2014; Yoon et al., 2016).

In addition to glucose influencing sleep, sleep may influence glucose regulation. Donga et al. (Donga et al., 2010) reported that one night of shortened sleep was associated with decreased insulin sensitivity in T1DM adults. Reduced insulin sensitivity impairs glucose regulation by requiring more insulin to maintain the same blood glucose (Kaul, Apostolopoulou, & Roden, 2015). Thus, a cycle may be established, where glucose negatively influences sleep and the resulting poor sleep impairs glucose regulation.

Psychological states are also closely linked with sleep (Akerstedt, Kecklund, & Axelsson, 2007). Fear of hypoglycemia (FOH) places a major psychological burden on individuals with T1DM (Gjerlow, Bjorgaas, Nielsen, Olsen, & Asvold, 2014), which can affect sleep quality. FOH tends to be worse at night (Martyn-Nemeth, Schwarz Farabi, Mihailescu, Nemeth, & Quinn, 2016) and contributes to diabetes-related distress (Sturt, Dennick, Due-Christensen, & McCarthy, 2015). Those with greater FOH have reported more frequent nocturnal hypoglycemia (Anderbro et al., 2014) and greater sleep disruption due to waking to monitor blood glucose levels (Tanenbaum & Gonzalez, 2012). FOH has also been found to be associated with greater GV in a time-dependent relationship, with FOH preceding heightened GV (Martyn-Nemeth et al., 2017).

Despite knowledge of the detrimental effects of sleep impairment in the general population (Cappuccio et al., 2011; Y. Zhu et al., 2015) and extensive research on sleep impairment in type 2 diabetes (B. Zhu, Hershberger, Kapella, & Fritschi, 2017), the determinants of sleep quality in T1DM have not been well established. The purpose of this study was to examine the associations of sleep quality, glycemic control, glycemic variability and FOH in adults with T1DM. We hypothesized that glycemic control (HbA1c) and nocturnal glycemic variability would be negatively associated with sleep quality and that FOH would influence these relationships.

THE STUDY METHODS

Design

This was a secondary analysis of pooled data from two studies examining self-management behaviors in adults with T1DM ($n = 48$ unique participants).

Participants

In the parent study, individuals were eligible if they were 18 to 45 years of age and had T1DM for a minimum of one year. Study exclusions included pregnancy, shift-work, a history of cardiovascular disease, stroke, liver disease, cancer and chronic renal or

pulmonary diseases. Subjects were recruited from endocrinology clinics, as well as throughout the community in the metropolitan area of a large Midwestern U.S. city.

Data Collection

Those who met study criteria were scheduled for a study visit at which height, weight and HbA1c (A1C Now®, Polymer Technology Systems, Inc., Indianapolis, IN) were measured and surveys for diabetes self-management and FOH were completed. A CGM was placed and CGM recordings were obtained over three consecutive days. Data were collected over 3 years in 2013-2016.

Measures

Sleep Assessment.—Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a 19-item Likert-style scale that assesses sleep duration, efficiency, habitual sleep latency, disturbances, use of sleep medication and daytime functioning. *Sleep duration* was obtained from the question on the PSQI scale, “During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed).” *Sleep efficiency* was calculated from the total number of hours asleep divided by the total number of hours in bed. *Sleep latency* is the time it takes to fall asleep each night. *Sleep disturbances* are determined from a list of ten possible situations that disrupt sleep (e.g. waking up to use the bathroom, having pain, bad dreams). A summary sleep quality score is computed, ranging 0-21. Scores > 5 indicate poor sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The internal consistency and criterion validity have been established for healthy and clinical populations (Buysse et al., 1989). Cronbach’s alpha was 0.79 for this sample.

Glycemic Control and Glycemic Variability.—Glycemic control was measured with a single fingerstick for HbA1c (A1C Now®, Polymer Technology Systems Diagnostics Inc., Indianapolis, IN). To obtain GV, the CGM IPro2® continuous glucose recorder was used (Medtronic, Northridge, CA). The CGM IPro2® provides an average of interstitial glucose at five-minute intervals. Recorded interstitial glucose levels were downloaded using CGM Medtronic software and examined for nocturnal glycemic trends and excursions and then to calculate nocturnal GV.

To examine glycemic trends, mean glucose and time spent in hypo- and hyperglycemia during sleep (minutes and percent) were calculated from the CGM recordings. This was done by identifying the segments where interstitial glucose levels were less than 70 mg/dL and greater than 180 mg/dL (representing hypo- and hyperglycemia, respectively) during each subject’s self-reported sleep time. The standard deviation of the overnight glucose levels was computed for each participant and used to determine nocturnal GV. This procedure is recommended by experts on the standardization of glucose reporting (Bergenstal et al., 2013; Rodbard, 2009).

Fear of Hypoglycemia.—FOH was measured with the worry subscale of the Hypoglycemia Fear Survey-II, an 18-item, 4-point Likert-style scale that measures stressful aspects of hypoglycemia. It provides one overall FOH-worry score, ranging from 0-72;

higher scores indicate greater FOH. The psychometric characteristics of the subscale have been studied in the U.S. and internationally in over 700 subjects and has demonstrated strong reliability and validity (Gonder-Frederick et al., 2011) and the Cronbach's alpha was 0.93 for this sample.

Ethical Considerations

Institutional review board approval from the University of Illinois at Chicago and written informed consent were obtained prior to conducting the study. For this analysis, de-identified data from 48, non-shift-working men and women with complete glucose monitoring data were included.

Statistical Analysis

Demographic and diabetes characteristics, sleep quality, glycemic control, GV and FOH were summarized using descriptive statistics (SPSS 24). Findings were evaluated for normality and expressed as means (SDs) for all normally distributed continuous variables or as medians (interquartile range [IQR]) for non-normal distributions. Categorical variables were expressed by count and percent. Nocturnal mean glucose levels, time spent in hypo- and hyperglycemic ranges and GV were calculated using standard formulas described above.

Participants were classified according to the PSQI score (≤ 5 for good sleep quality and > 5 for poor sleep quality). Using an independent samples *t* test, the mean differences in glycemic measures and FOH were computed to identify variables to be included in a logistic regression analyses. Variables with levels of significance of 0.1 or less were selected as potential predictors for multivariate analysis.

Multivariate logistic regression was used to determine the predictors of poor sleep quality and to test the hypotheses that FOH would influence the associations between (a) sleep quality and glycemic control and (b) sleep quality and glycemic variability, respectively.

RESULTS

Sixty-three percent of the sample were women, 88% were White and 8% were Hispanic. The mean age was 27 (SD 5.8) years and median diabetes duration was 14 (IQR 9-20) years. Nearly two-thirds of the sample (60%) worked full time, 79% had earned a college degree or higher and 40% were married or living with a partner. All used basal/bolus insulin dosing regimens, with 96% using an insulin pump (Table 1).

Sleep Characteristics

Sleep duration ranged from 5 to 9 hours per night (Mean (SD) = 7.1 (1.1) hours). The sleep quality scores indicated that 46% had poor sleep quality (PSQI > 5). Sleep disturbances three or more times per week were reported by 52% of the sample. The most common disturbances were waking up in the middle of the night (38%) and getting up to urinate (27%).

Glycemic Control and Glycemic Variability

The mean HbA1c level was 7.2% (range 4.5%–9.4%). Continuous glucose monitoring recordings from the 48 subjects yielded 125 subject-nights with > 4 hours per night. The mean (SD) glucose level during sleep time was 150 (38) mg/dL. Examination of glucose trends revealed that 60% experienced episodes of hypoglycemia lasting 20 minutes or longer (median = 29 minutes), while 83% experienced periods of hyperglycemia for 20 minutes or longer (mean = 126 minutes). Nocturnal GV ranged from 9 to 71 mg/dL (Table 1).

Fear of Hypoglycemia

The mean (SD) FOH worry scale score was 25.1 (12.1). The greatest worries were not recognizing low blood glucose and losing control.

Comparisons by Sleep Group

Comparisons between sleep quality groups revealed that those with poor sleep quality ($n = 22$) had greater nocturnal glycemic variability ([M (SD), 39.3 (15.1) vs. 29.5 (13.1)], $p = .020$) and FOH [29.1 (9.9) vs. 21.7 (12.9) $p = .034$] than those with good sleep ($n = 26$). HbA1c did not vary between sleep quality groups (Table 2).

Multivariate Analysis

Potential predictor variables identified from the comparisons by sleep group, along with those hypothesized to be related to sleep, were entered into a multiple logistic regression: glycemic control, GV, FOH and the GV-FOH interaction. The regression model was adjusted for the potential confounders of age, gender, diabetes duration and BMI. The analysis revealed that GV and FOH were significantly associated with sleep quality (OR = 1.38; 95% CI: 1.07-1.77, $p = .012$ and OR = 1.51; 95% CI=1.08-2.11, $p = .017$ respectively). The interaction effect of GV and FOH was significant (OR = 0.991; 95% CI = .984-.999, $p = .025$; Table 3).

DISCUSSION

The purpose of this study was to examine sleep quality with glycemic control, glycemic variability and FOH among adults with T1DM. The major findings indicated that (1) those with poor sleep quality had greater nocturnal glycemic variability and FOH than those who reported good sleep quality and (2) the effect of glycemic variability on sleep quality was influenced by FOH.

Poor sleep quality is a persistent problem in those with T1DM. Our findings were consistent with previous studies indicating that individuals with T1DM suffer from poor sleep quality (Nefs et al., 2015). In a meta-analysis, persons with T1DM had poorer sleep quality compared with healthy control subjects (Reutrakul et al., 2016).

Glycemic control was not associated with subjective sleep quality. Glycemic control has been inconsistently related to subjective sleep in prior studies. Nefs et al. (2015); Perfect et al. (2012); and Van Dyk et al. (2011) found no association with glycemic control, whereas a recent meta-analysis reported a 19% lower mean HbA1c in those with good vs. poor sleep

quality (Reutrakul et al., 2016). The differences may be due to the larger pooled sample in the meta-analysis or the different sleep quality measurement scales used.

Many subjects in our study exhibited increased nocturnal GV (Bergenstal, 2015). Although HbA1c provides a biomarker for average blood glucose over a 2- to 3-month period, it does not capture daily blood glucose fluctuations. As previous research shows, individuals may have an optimal HbA1c yet high GV, with glucose levels ranging from 40 mg to 400 mg in a 24-hour period (Martyn-Nemeth et al., 2017). It is important to reduce GV because emerging evidence has linked GV with cardiovascular events and mortality (Yoon et al., 2016).

The finding that nocturnal GV was associated with poor sleep quality is consistent with two previous studies that examined CGM-derived GV during sleep using polysomnography in a sleep laboratory. Pillar et al. (2003) reported that glucose fluctuations of 25-50 mg/dL per hour were associated with sleep arousals in children with T1DM. These arousals occurred even when the glucose levels remained in euglycemic ranges and suggested that GV preceded arousals. In adults, Barone et al. (2015) reported that longer sleep latency was associated with greater GV and those with the greatest GV had significantly more disruptions in sleep. Both longer sleep latency and greater sleep disruptions indicate poor sleep quality. Although the methods for measuring sleep differed among studies, evidence supports that GV is associated with poor sleep and may be a target for sleep interventions.

FOH was significantly associated with poor sleep quality and FOH modified the association of GV with sleep. FOH continues to be a major concern at night (Gjerlow et al., 2014). Our data suggest that FOH may stimulate individuals to keep blood glucose levels consistently higher at night. It is plausible that the resulting hyperglycemia may lead to sleep disruption due to glycosuria (Richmond, 1996). FOH may also lead to more vigilant blood glucose monitoring, which adds to sleep disturbance if individuals feel compelled to wake during the night to monitor blood glucose (Hanna, Weaver, Stump, Fortenberry, & DiMeglio, 2014).

Normal fear is adaptive and some FOH is necessary to avoid hypoglycemia. Heightened fear, however, leads to increased anxiety (Green, Feher, & Catalan, 2000), which can impair sleep. Over the past three decades, newer technologies have been designed to help patients with diabetes manage their treatment regimens. While many of these technologies have improved glucose control, they have not consistently translated into reduced FOH (Barnard, Parkin, Young, & Ashraf, 2012; Barnard & Skinner, 2008; Davey, Stevens, Jones, & Fournier, 2012; Hermanides et al., 2011; Nicolucci et al., 2008; Rubin & Peyrot, 2012). Thus, research is needed to test interventions to reduce FOH in individuals with T1DM.

Limitations

Sleep quality was measured subjectively; although this is a valid measure of sleep perception, additional objective measures of sleep that quantify sleep duration, efficiency and disruption in real time would be an important next step. The PSQI includes questions that address symptoms of sleep apnea; although the number of subjects who answered these questions in the affirmative was low (four subjects), we cannot rule out sleep apnea as a cause of poor sleep quality. This was a secondary data analysis and was not fully powered to

address the aims of the current study. Despite this and our small sample, a post hoc analysis revealed an observed power of .80 for associations of FOH and GV with sleep quality. Additionally, our study used a cross-sectional design; therefore, causation cannot be inferred.

CONCLUSIONS

In summary, many adults with T1DM in this sample reported poor sleep quality. Those with poor sleep quality had greater nocturnal GV and FOH than those who reported good sleep quality. The association of GV with sleep quality was influenced by FOH. These findings identify potentially important subject-level factors associated with sleep quality. Further study is needed with a larger sample to determine the causal relationships among GV, FOH and sleep to develop targeted interventions to improve sleep quality.

These findings have important nursing implications. Nurses in clinical practice should assess their patients with type 1 diabetes for sleep quality, diabetes symptoms, fear of hypoglycemia and self-management practices that may be contributing to sleep impairment as outlined in the American Diabetes Association Standards of Medical Care (American Diabetes Association, 2018). Many patients routinely awaken during the night to monitor blood glucose levels while others may maintain blood glucose levels at a higher level to avoid hypoglycemia; both practices lead to sleep disruption and poor sleep quality. This underscores the need to consider how sleep may be influenced by diabetes-related physical and psychological factors as well as self-management behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY STATEMENT**Why is this research or review needed?**

- Poor sleep quality is a persistent problem among persons with type 1 diabetes, yet the determinants of sleep quality in this population have not been well-studied.
- Evidence suggests that glucose fluctuations (glycemic variability) and fear of hypoglycemia may be associated with sleep disturbances.
- Glucose levels can fluctuate widely and fear of hypoglycemia can be profound in persons with type 1 diabetes.
- The use of continuous glucose monitoring provided a means to address the knowledge gap of the associations between glycemic variability, fear of hypoglycemia and sleep.

What are the key findings?

- Adults with type 1 diabetes suffer from poor sleep quality.
- Nocturnal glycemic variability and fear of hypoglycemia are associated with poor sleep quality and are potential targets for sleep interventions.

How should the findings be used to influence policy/practice/research/education?

- Further study is needed to determine the causal relationships among glycemic variability, fear of hypoglycemia and sleep in adults with type 1 diabetes.
- Nurses in clinical practice should assess their patients with type 1 diabetes for sleep quality and self-management practices that may be contributing to sleep impairment.
- Nurse educators should underscore the need to consider how sleep may be influenced by diabetes-related physical and psychological factors as well as self-management behaviors.

Table 1*Participant Characteristics (N = 48)*

Characteristic	Results				IQ	
	N	%	Mean	SD	Median	range
Demographic Data						
Age (years)			27.0	5.8		
Gender						
Females	30	63%				
Race						
White	42	88%				
Black	3	6%				
Mixed	3	6%				
Ethnicity						
Hispanic or Latino	4	8%				
BMI (kg/m ²)			27.1	4.6		
Diabetes and Glycemic Data						
Diabetes duration (years)					14	9-20
HbA1c (%)			7.2	1.0		
Insulin pump use	46	96%				
GV (nocturnal Gluc SD)			34	14.8		
Glucose Mean (mg/dL/night)			150	38		
Hypoglycemia (min/night)					29	2-81
Hyperglycemia (min/night)			126	108		
Sleep and Psychological Data						
Poor Sleep Quality (PSQI > 5)	22	46%				
Sleep duration (hrs)			7.1	1.1		
FOH (Worry)			25.1	12.1		

Note. BMI = body mass index; GV = glucose variability; FOH = fear of hypoglycemia.

Table 2Comparisons of Subject Characteristics According to Sleep Quality Group^{*}

Characteristic	Sleep Quality Good (PSQI 5)	SD	Sleep Quality Poor (PSQI > 5)	SD	P-Value
Age (yrs)	28.0	7.0	27.0	4.0	0.540
Gender					0.178
Male (%)	67		33		
Female (%)	54		53		
BMI (kg/m ²)	26.5	3.7	27.8	5.4	0.342
Diabetes duration (yrs)	16.5	10.4	13.0	7.2	0.186
Glycemic Control (HbA1c [%])	7.2	1.2	7.2	0.8	0.832
Hypoglycemia (%)	57	65	42	49	0.470
Hyperglycemia (%)	114	108	144	102	0.137
GV (Glucose SD)	29.5	13.1	39.3	15.1	0.020
FOH (HFS Worry Scale)	21.7	12.9	29.1	9.9	0.034

^{*} Independent samples t-test

Table 3

Results of Multivariate Logistic Regression Analysis of Poor Sleep Quality

Parameter	B	Std. Error	OR [95% CI]	P-Value
Age (yrs)	.098	0.092	1.10 [0.92, 1.32]	.290
Gender (male)	−1.46	0.859	0.23 [0.04, 1.25]	.089
BMI (kg/m ²)	.206	0.110	1.23 [0.99, 1.53]	.061
Diabetes Duration (yrs)	−.085	0.066	0.92 [0.81, 1.05]	.200
Glycemic Control (HbA1c)	−.598	0.436	0.55 [0.23, 1.29]	.171
GV (GlucSD)	.321	0.128	1.38 [1.07, 1.77]	.012
FOH (HFS worry score)	.409	0.171	1.51 [1.08, 2.11]	.017
GV * FOH	−.009	0.004	0.991 [0.984, 0.999]	.025

Note. Outcome variable: Poor sleep quality.