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Research

Is Impaired Hypoglycemia Awareness Associated with Obstructive Sleep Apnea in Diabetic Patients?

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Abstract

Background: Hypoglycemia triggers a complex physiologic response designed to restore euglycemia. Repeated hypoglycemic events, as seen in patients using insulin, blunt the appropriate sympathetic response thus leading to impaired hypoglycemia awareness. Obstructive sleep apnea also triggers a similar sympathetic response; however, whether or not obstructive sleep apnea predisposes an individual to impaired hypoglycemia awareness remains unknown.

Objective: The purpose was to determine if there is an association between obstructive sleep apnea and impaired hypoglycemia awareness.

Methods: Patients with Type 2 diabetes undergoing sleep studies were invited to participate. All consented participants underwent nocturnal polysomnography and were administered questionnaires to assess symptoms of obstructive sleep apnea, frequency of hypoglycemic events, and ability to detect hypoglycemia. Ability to detect hypoglycemia classified the population into one of two groups: no impaired hypoglycemia awareness (normal awareness, NIHA) versus impaired hypoglycemia awareness (IHA).

Results: Thirty-one of the 78 participants were classified as having IHA. Patients with IHA were significantly younger than those with NIHA (55.5 ± 14.1 vs. 62.3 ± 9.6 yrs). There were no significant differences in body mass index or body weight in those with NIHA vs. IHA. No difference in obstructive sleep apnea severity was found for NIHA vs. IHA based on apnea-hypopnea index. There was a positive association between use of any long acting insulin and report of autonomic symptoms of hypoglycemia (adjusted OR 4.75, p = 0.036).

Conclusions: This cross-sectional study did not find an association between OSA and IHA. Further studies with better characterization of hypoglycemia awareness and sympathetic activation are warranted to better evaluate this potential relationship.

Key words: Diabetes complications; Diabetes mellitus type 2; Diabetic neuropathies

Introduction

As plasma glucose level falls, protective mechanisms are activated to defend against hypoglycemia. Those mechanisms include counterregulatory hormone responses such as lowering of insulin secretion, increased secretion of glucagon and an increase in the adrenomedullary hormone, epinephrine [1]. In addition, the body activates behavioral defenses that make the individual aware of the hypoglycemia prompting food intake to ensure a continuous supply of glucose to the brain [2].

Patients with absolute deficiency of endogenous insulin, such as those with established type 1 diabetes or advanced type 2 diabetes who depend on exogenous insulin, have compromised defenses against hypoglycemia including failure to decrease insulin levels, failure of glucagon stimulation, and attenuated epinephrine secretion [1, 3-4]. Hypoglycemia is a significant mortality risk for type I diabetic patients and type II diabetic patients treated with advanced disease who are also treated with exogenous insulin [5]. Hypoglycemia is responsible for 6-10% of deaths in type 1 diabetics [6].

The concept of hypoglycemia-associated autonomic failure (HAAF) refers to an attenuated sympathoadrenal response to hypoglycemia. This response normally includes release of epinephrine, increased neural sympathetic tone, and onset of neurogenic symptoms such as pallor (adrenergic vasoconstriction), diaphoresis (cholinergic stimulation of sweat glands), anxiety, and tachycardia (adrenergic). The lack of such symptoms known as impaired hypoglycemia awareness blunts the behavioral defenses and predisposes the individual to repeated hypoglycemic events establishing a vicious cycle [1]. The risk of recurrent severe hypoglycemia is increased by at least 6 fold by impaired hypoglycemia awareness, and severe hypoglycemic events have been associated with fatal arrhythmias in animals, and death in humans [1, 7-8]. A key finding that led to the concept of HAAF in diabetics is that an event of hypoglycemia (as may occur during sleep or exercise), impairs the sympathetic response to a subsequent hypoglycemic event in nondiabetics and diabetics [9]. Thus, frequent hypoglycemic events can contribute to HAAF. HAAF is a functional disorder different from diabetic autonomic neuropathy, which is a structural disorder; however, HAAF prevalence is greater in patients with diabetic autonomic neuropathy [10].

Obstructive sleep apnea (OSA) is especially common in obese patients with type 2 diabetes. In the Look Ahead study, 86% of type 2 diabetic patients had undiagnosed OSA and 22% had severe OSA [11]. A recent meta-analysis indicates the prevalence of OSA is also significantly higher in non-obese type 1 diabetic patients (52%, mean BMI 22.9-25.8 kg/m2) compared to the general population . These data are consistent

with a large clinical study that reported OSA in 46% of type 1 diabetic patients (mean BMI 24.4-26.4 kg/m2), suggesting the comorbidity of diabetes and OSA may not be due to obesity. Diabetic patients with severe OSA have higher prevalence rates of diabetic complications including diabetic peripheral neuropathy and diabetic retinopathy compared to diabetic patients with mild-moderate OSA [12]. Furthermore, the apnea hypopnea index was associated with PARP activation (a marker of oxidative stress), decreased intraepidermal nerve fiber density, and diabetic foot ulcers in patients with type 2 diabetes [13]. Importantly, controlled experiments in healthy human subjects have shown that key features of OSA including sleep restriction, sleep fragmentation, and intermittent hypoxia can lead to glucose dysregulation [14-18]. Further supporting comorbidity of OSA and type 2 diabetes, a recent meta-analysis by Reutrakul et al. reports OSA is independently associated with type 2 diabetes (unadjusted pooled relative risk: 1.62, 95% CI, 1.45-1.80) which is larger than the risk of type 2 diabetes by being physically inactive (adjusted relative risk: 1.2) [19]. In addition to the association between OSA and type 2 diabetes, OSA is associated with several other risk factors for atherosclerosis including endothelial dysfunction [20], vascular inflammation [21] hypertension [22], dyslipidemia [23], type 2 diabetes [11, 24], and the metabolic syndrome.

Intermittent hypoxia that occurs during obstructive sleep apnea (OSA) also triggers a response that involves the activation of the sympathetic system, including the activation of the carotid body chemoreceptor which results in increased ventilatory drive and minute ventilation to restore normoxia [25-27]. Thus, in a similar mechanism of repeated sympathetic stimulation, OSA could potentially contribute to autonomic dysfunction, predisposing patients with OSA and diabetes to impaired hypoglycemia awareness.

It is known that diabetic autonomic neuropathy is associated with impaired hypoglycemia awareness and that diabetic autonomic neuropathy can be associated with more severe obstructive sleep apnea [28]. Thus, it is plausible that other conditions associated with diabetic autonomic neuropathy, such as impaired hypoglycemia awareness and HAAF, may be affected by obstructive sleep apnea, particularly as they trigger similar pathophysiologic responses at the sympathetic level. Interestingly, adrenergic activation mediates the reduced sympathoadrenal response to subsequent hypoglycemia (following a preceding hypoglycemic episode), which is a key feature of HAAF and the use of adrenergic blockage prevents antecedent hypoglycemia from impairing adrenergic activation to subsequent hypoglycemia [29], thus beta-adrenergic antagonists may prevent the development of HAAF. Furthermore, patients with untreated OSA have increased sympathetic tone [30], perhaps providing a chronically activated sympathetic environment, thus predisposing the patient to the development of HAAF. It has been established that sleep and exercise can increase the sympathetic tone and also predispose to HAAF, but the relationship between OSA and HAAF has not been investigated in the current literature.

Objective

Our overall hypothesis is that OSA in part influences the severity of impaired hypoglycemia awareness. The purpose of the study is to evaluate whether or not OSA is associated with attenuation of the sympathoadrenal response to hypoglycemia (HAAF), presenting clinically as impaired hypoglycemia awareness.

Methods

Subjects

Type 2 diabetic patients undergoing overnight diagnostic polysomnography for the evaluation of sleep problems at the Sleep Center at Alton Memorial Hospital (Alton, IL) were invited to participate and sign an institutionally-approved consent form. Diabetic patients were considered eligible if they were using medication for diabetes, either insulin or noninsulin therapies. Exclusion criteria were: 1) unable to provide informed consent; 2) unable to read or understand hypoglycemia questions; 3) children or pregnant women; 4) alcohol intake in the last 24h; and 5) patients on stimulants (i.e. methylphenidate, mixed amphetamine salts).

Questionnaires

Upon reporting to the sleep center and following completion of informed consent, patients self-administered the Hypoglycemia Awareness Questionnaire [31] (Appendix 1). This survey has been previously validated for assessment of hypoglycemia awareness [31] and compared to other surveys, it is easier to administer. The Hypoglycemia Awareness Questionnaire validation study [31] meets requirements for a positive rating for the following quality criteria for measurement properties of health status questionnaires: content validity, criterion validity, construct validity, and reproducibility, as described in [32] and included in the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) checklist. Thus, we are confident the Hypoglycemia Awareness Questionnaire is an appropriate instrument to assess hypoglycemia awareness.

Specifically, the question "Do you recognize symptoms when you have a hypo?" was used to classify the respondents. The categories for answers were always, usually, occasionally, never, or don't know. All subjects who selected 'always or usually' were classified as having no impaired hypoglycemia awareness (NIHA). Subjects who selected 'occasionally or never' were classified as having impaired hypoglycemia awareness (IHA). However, subjects who selected 'never' and were not using insulin or oral antihyperglycemics associated with hypoglycemia were classified as NIHA, as the 'never' response indicates that they do not experience hypoglycemia versus IHA. In addition, the included patients completed a sleep history and medical history questionnaire, as part of usual care prior to undergoing polysomnography.

Polysomnography

Diagnostic polysomnography was performed using the Natus Sleepworks 7.1.1 (Pleasanton, CA). This methodology records brain activity, eye movements, heart rate, blood pressure, oxygen, carbon dioxide, air flow, chest movement, and oxygen saturation among other variables. The American Academy of Sleep Medicine (AASM) "recommended" guidelines were used for scoring apnea/hypopnea index [33]. Apnea hypopnea index was scored using positional data (body position: supine, lateral, or prone) for each patient. An apnea/hypopnea index greater than or equal to 5 events per hour is consistent with a diagnosis of OSA according to current AASM guidelines [34]. In the current study, severity of sleep apnea was classified according to the apnea/hypopnea index with 5-15 events per hour categorized as mild OSA, 16-30 events per hour categorized as moderate OSA, and > 30 events per hour categorized as severe OSA.

Statistical analysis

Clinical and demographic characteristics (Table 1), comorbid conditions (Table 2), medication use (Table 3), and apnea-related symptoms (Table 4) were categorized by NIHA or IHA status. Data were examined for normality using a histogram. Continuous data that were normally distributed were compared using a two-sided t-test with unequal variances. Non-normally distributed continuous data were analyzed usingthe Wilcoxon Rank Sum test. Categorical variables were analyzed using Pearson Chi-Square or Fisher's Exact Tests.

Self-reported hypoglycemia symptoms from the Hypoglycemia Awareness Questionnaire (Appendix 1) were stratified by mechanism (i.e., autonomic, neuroglycopenic, or nonspecific, Table 5). Univariate and multivariate logistic regression models were constructed to assess the relation of autonomic (Table 6), neuroglycopenic (Table 7), or nonspecific symptoms of hypoglycemia (Table 8) to the presence other disease states and medication use. All variables were included in the multivariate models at the same time. Explanatory variables were selected based on a theoretical or hypothesized relation to the outcomes being modeled. The baseline set of covariate values was for a person who was 59.98 years of age, male, obese, with no comorbid conditions or use of medications from the drug classes studied. Statistical significance was assumed when $p < .05$. All analyses were performed using Stata MP 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

For this study, we included all diabetic patients undergoing diagnostic sleep studies in our center in one calendar year. We calculated approximately 250-300 diabetic patients would have a diagnostic polysomnography, and assumed 30-40% of them would agree to participate in our study, aiming for approximately 90-100 patients.

	No impaired hypoglycemia awareness (n = 47, column %)	Impaired hypoglycemia awareness (n = 31, column%)	p-value
Mean age (median, SD, range)	62.3 (64, 9.6, 38-79)	55.5 (56, 14.1, 30-78)	0.024 (2- tailed t-test with un-equal variances)
Age by category			0.032 (Fisher's Exact Test)
18-34	0 (0.0)	3 (9.7)	
35-44	2 (4.3)	4 (12.9)	
45-54	8 (17.0)	7 (22.6)	
55-64	14 (29.8)	8 (25.8)	
65-74	20 (42.6)	5 (16.1)	
≥75	3 (6.4)	4 (12.9)	
Sex: Female	22 (46.8)	17 (54.8)	0.488 (Pearson chi squared)
Male	25 (53.2)	14 (45.2)	
Weight (lb, mean, median, SD, range)	249.3 (250, 53.2, 162-376)	256.1 (265, 140-350)	0.475 (Wilcoxon Rank-Sum)
Body Mass Index (kg/m2, mean, median, SD, range)	39.8 (38.9, 7.8, 28.1 – 59.3)	40.8 (38.7, 8.7, 25.6–64.1)	0.744 (Wilcoxon Rank-Sum)
Body Mass Index (kg/m2) by category			0.697 (Fisher's Exact Test)
Underweight (<18.5)	0 (0.0)	0 (0.0)	
Normal or healthy weight (18.5 – 24.9)	0 (0.0)	0 (0.0)	
Overweight (25.0 – 29.9)	5 (10.6)	2 (6.4)	
Obese (≥ 30)	42 (89.4)	29 (93.6)	

Table 1: Clinical and demographic characteristics (n = 78)

	No impaired hypoglycemia awareness (n = 47, column %)	Impaired hypoglycemia awareness (n = 31, column %)	p-value
Dementia: No	47 (100.0)	31(100.0)	NA
Yes	0 (0.0)	0(0.0)	
Hypertension: No	14 (29.8)	8 (25.8)	0.702 (Pearson chi squared)
Yes	33 (70.2)	23 (74.2)	
Insomnia: No	30 (63.8)	23 (74.2)	0.337 (Pearson chi squared)
Yes	17 (36.2)	8 (25.8)	
Diabetes: No	0 (0.0)	0 (0.0)	NA
Yes	47 (100.0)	31 (100.0)	
Stroke: No	35 (74.5)	27 (87.1)	0.176 (Pearson chi squared)
Yes	12 (25.5)	4 (12.9)	
Heart Attack: No	40 (85.1)	26 (83.9)	>0.999 (Fisher's Exact Test)
Yes	7 (14.9)	5 (16.1)	
Depression: No	28 (59.6)	18 (58.1)	0.894 (Pearson chi squared)
Yes	19 (40.4)	13 (41.9)	
Hypercholesterolemia: No	39 (83.0)	21 (67.7)	0.118 (Pearson chi squared)
Yes	8 (17.1)	10 (32.3)	
Heart failure: No	42 (89.4)	25 (80.7)	0.329 (Fisher's Exact Test)
Yes	5 (10.6)	6 (19.4)	
Atrial fibrillation: No	43 (91.5)	28 (90.3)	>0.999 (Fisher's Exact Test)
Yes	4 (8.5)	3 (9.7)	
Parkinson's Disease: No	46 (97.9)	31(100.0)	>0.999 (Fisher's Exact Test)
Yes	1 (2.1)	0 (0.0)	
Cardiac arrhythmia: No	41 (87.2)	29 (93.6)	0.467 (Fisher's Exact Test)
Yes	6 (12.8)	2 (6.5)	

Table 2 : Comorbid conditions (n = 78, %)

	No impaired hypoglycemia awareness (n = 47, column %)	Impaired hypoglycemia awareness (n = 31, column %)	p-value
Long-acting insulin: no	29 (61.7)	26 (83.9)	0.036 (Pearson chi squared)
Yes	18 (38.3)	5 (16.1)	
Short-acting insulin: No	37 (78.7)	28 (90.3)	0.179 (Pearson chi squared)
Yes	10 (21.3)	3 (9.7)	
Other insulin: No	40 (85.1)	29 (93.6)	0.304 (Fisher's Exact Test)
Yes	7 (14.9)	2 (6.4)	
Metformin: No	22 (45.8)	5 (15.6)	0.005 (Pearson chi squared)
Yes	26 (54.2)	27 (84.4)	

Table 3: Medication use (n = 78, %)

	No impaired hypoglycemia awareness (n = 47)	Impaired hypoglycemia awareness (n = 31)	p-value
Apnea-Hypopnea Index	35.8 (19.2, 33.0, 3.2 – 113.9)	41.6 (41.3, 32.1, 1.4 – 115.4)	0.312 (Wilcoxon Rank-Sum)
Snoring: No	7 (14.9)	5 (16.1)	>0.999 (Fisher's Exact Test)
Yes	40 (85.1)	26 (83.9)	
Restless sleep: No	14 (29.8)	10 (32.3)	0.817 (Pearson chi squared)
Yes	33 (70.2)	21 (67.7)	
Talk in sleep: No	33 (70.2)	26 (83.9)	0.169 (Pearson chi squared)
Yes	14 (29.8)	5 (16.1)	
Walk in sleep: No	44 (93.6)	30 (96.8)	>0.999 (Fisher's Exact Test)
Yes	3 (6.4)	1 (3.2)	
Creeping or crawling legs: No	36 (76.6)	22 (71.0)	0.577 (Pearson chi squared)
Yes	11 (23.4)	9 (29.0)	
Stop breathing: No	23 (48.9)	13 (41.9)	0.544 (Pearson chi squared)
Yes	24 (51.1)	18 (58.1)	
Morning headaches: No	33 (70.2)	19 (61.3)	0.413 (Pearson chi squared)
Yes	14 (29.8)	12 (38.7)	
Take medication for sleep: No	35 (74.5)	23 (74.2)	0.978 (Pearson chi squared)
Yes	12 (25.5)	8 (25.8)	
Have leg jerks: No	33 (70.2)	18 (58.1)	0.270 (Pearson chi squared)
Yes	14 (29.8)	13 (41.9)	
Feel like you have to move your legs: No	24 (51.1)	18 (58.1)	0.544 (Pearson chi squared)
Yes	23 (48.9)	13 (41.9)	
Wake up gasping: No	28 (59.6)	21 (67.7)	0.465 (Pearson chi squared)
Yes	19 (40.4)	10 (32.3)	
Episodes of confusion: No	38 (80.8)	25 (80.6)	0.982 (Pearson chi squared)
Yes	9 (19.2)	6 (19.4)	
Have vivid dreams: No	20 (42.6)	23 (74.2)	0.006 (Pearson chi squared)
Yes	27 (57.4)	8 (25.8)	
Nighttime wheezing: No	36 (76.6)	21 (67.7)	0.388 (Pearson chi squared)
Yes	11 (23.4)	10 (32.3)	
Epworth score (Mean, Median, SD, Range)	10.7 (11.0, 6.3, 0-24, n = 43)	10.9 (10.0, 6.0, 0-23, n = 27)	0.912 (2-sided t-test, with unequal variances)

Table 4: Apnea-related symptoms (n = 78, column %)

Autonomic	Neuroneuroglycopenic	Nonspecific
Palpitations	Cognitive impairment	Warmness
Tremor	Behavioral changes	Nausea
Anxiety	Syncope	Double vision
Sweating	Seizure	Tiredness
Hunger		
Paresthesias		

Table 5 : Categorization of common hypoglycemia symptoms

Dependent Variable = Autonomic Symptoms	Adjusted Odds Ratio	p-value	95% confidence interval
Age (centered at the mean = 59.6)	1.02	0.547	0.96 – 1.07
Sex = Male	1.43	0.563	0.43 – 4.82
BMI = Obese	1.06	0.961	0.01 – 11.64
Hypertension	1.29	0.724	0.31 – 5.34
Insomnia	0.99	0.983	0.26 – 3.66
Stroke	0.57	0.525	0.10 – 3.24
Heart Attack	0.19	0.070	0.03 – 1.15
Depression	6.58	0.005	1.79 – 24.17
Hypercholesterolemia	0.71	0.654	0.16 – 3.15
Heart Failure	1.47	0.729	0.17 – 12.86
Atrial fibrillation	0.84	0.872	0.11 – 6.50
Cardiac arrhythmia	2.40	0.447	0.25 – 23.09
Medication use			
Insulin: Any long acting insulin	4.75	0.036	1.11 – 20.38
Opioids	0.83	0.830	0.16 – 4.44
Metformin	2.17	0.261	0.56 – 8.42
Constant (y-intercept)	0.26	0.380	0.01 – 5.30

Table 6: Logistic regression of autonomic symptoms (n = 76)

Dependent Variable = Neuroneuroglycopenic Symptoms	Adjusted Odds Ratio	p-value	95% confidence interval
Age (centered at the mean = 9.6)	0.97	0.259	0.91 – 1.02
Sex = Male	5.16	0.026	1.21 – 22.02
BMI = Obese	1.61	0.686	0.16 – 16.18
Hypertension	0.63	0.512	0.16 – 2.48
Insomnia	1.36	0.642	0.37 – 5.04
Stroke	1.39	0.691	0.27 – 7.04
Heart Attack	2.85	0.224	0.53 – 15.43
Depression	4.34	0.039	1.08 – 17.49
Hypercholesterolemia	0.75	0.700	0.17 – 3.24
Heart failure	1.96	0.456	0.33 – 11.61
Cardiac arrhythmia	0.53	0.555	0.06 – 4.44
Medication use			
Insulin: Any long acting Insulin	2.24	0.215	0.63 – 8.05
Opioids	4.16	0.077	0.86 – 20.22
Metformin	0.57	0.413	0.15 – 2.20
Constant (y-intercept)	0.08	0.100	0.004 – 1.62

Table 7: Logistic regression of neuroneuroglycopenic symptoms (n = 76)

Dependent Variable = Nonspecific Symptoms	Adjusted Odds Ratio	P-value	95% confidence interval
Age (centered at the mean = 59.6)	0.94	0.068	0.89 – 1.00
Sex = Male	0.44	0.244	0.11 – 1.76
BMI = Obese	0.68	0.751	0.06 – 7.48
Hypertension	1.08	0.930	0.21 – 5.54
Insomnia	2.19	0.269	0.54 – 8.82
Stroke	2.07	0.463	0.30 – 14.52
Heart Attack	0.63	0.666	0.08 – 5.12
Depression	1.63	0.468	0.43 – 6.12
Hypercholesterolemia	1.77	0.483	0.36 – 8.69
Heart Failure	3.76	0.219	0.46 – 31.14
Cardiac arrhythmia	0.32	0.403	0.02 – 4.61
Medication use			
Insulin: Long acting insulin	1.14	0.866	0.25 – 5.24
Opioids	0.90	0.921	0.12 – 6.57
Metformin	1.08	0.921	0.24 – 4.74
Constant (y-intercept)	0.20	0.330	0.01 – 5.14

Table 8: Logistic regression of nonspecific symptoms (n = 76)

Results

Baseline Characteristics and Impaired Hypoglycemia Awareness A total of 78 diabetic patients undergoing diagnostic polysomnography were consented to participate in the study. The mean age of the included patient was 59.6 ± 11.4 years. Forty were women and 73 were obese. Forty-seven patients had NIHA and 31 patients had IHA. Although patients with IHA were significantly younger compared to patients with NIHA (55.5 ± 14.1 vs. 62.3 ± 9.6, p = 0.024), there were no other statistical differences in the demographic features of these two groups (Table 1) or in the prevalence of other comorbid conditions (Table 2).

Distribution of Medication Use in Patients with Impaired Hypoglycemia Awareness

A greater proportion of subjects reporting long-acting insulin use had IHA (83.9%) compared to those with retained hypoglycemia awareness (61.7%, p = .036). A similar relationship was identified for those reporting metformin use (84.4% vs. 54.2%, p = .005) in all patients (including those on insulin and those not on insulin). The proportion of patients with IHA was not significantly different for patients reporting short-acting insulin or other insulin (Table 3).

OSA was Not Associated with Prevalence of Impaired Hypoglycemia Awareness

There was no significant difference in apnea-hypopnea index (measure of OSA severity) for NIHA vs. IHA (Table 4). Interestingly, only the subject-reported symptom of "vivid dreams" differed between NIHA (57.4%) and IHA (25.8%, p = .006).

Predictors of Hypoglycemic Symptoms

Regression analysis was performed based on the presence or absence of hypoglycemia symptoms self-reported in the Impaired hypoglycemia awareness Questionnaire (Appendix 1) and stratified by mechanism (i.e., autonomic, neuroglycopenic, or nonspecific, Table 5). Those participants self-reporting a previous diagnosis of depression (adjusted OR 6.58; p = .005; 95% CI 1.79 – 24.17) and those using any long acting insulin (adjusted OR 4.75, p = .0.036; 95% CI 1.11-20.38) were more likely to experience autonomic hypoglycemia symptoms (Table 6). Males were more likely to experience neuroglycopenic symptoms of hypoglycemia (adjusted OR 5.16, p =.026, 95% CI 1.21-22.02) (Table 7).

An indicated history of atrial fibrillation perfectly predicted the lack of nonspecific hypoglycemic symptoms, thus was omitted from the model (Table 8).

Discussion

Previous reports indicate diabetic autonomic neuropathy is associated with OSA [28], but no investigations have assessed the relationship between OSA and HAAF . The current study tested the novel hypothesis that OSA is associated with impaired hypoglycemia awareness, a clinical representation of HAAF. In contrast with our hypothesis, the current study did not find an association between OSA (characterized by apnea-hypopnea index) and impaired hypoglycemia awareness.

Inherent to the cross-sectional design, the main limitation of the present study is the inability to establish causality, in other words, which factor is the independent variable (OSA or hypoglycemia). Our analysis is limited by the use of self-reported answers to identify patients with impaired hypoglycemia awareness, however, we used a validated questionnaire Hypoglycemia Awareness Questionnaire [31].

While the presence of OSA failed to predict the likelihood of impaired hypoglycemia awareness, other interesting associations were identified. Significantly more participants in the IHA group reported metformin use or long-acting insulin use compared to the NIHA group (Table 3). However, in patients using insulin (short-acting, long-acting, or any insulin) and metformin, there was no significant difference in the prevalence of IHA. Thus, the increased prevalence of IHA in patients on metformin cannot be attributed to concomitant insulin use. Metformin is not typically associated with hypoglycemia. However, little is known about metformin's potential impact on hypoglycemia awareness. As beta-adrenergic sensitivity may be restored in type 1 diabetes with strict avoidance of hypoglycemia, metformin may indirectly contribute to frequency of episodes and autonomic blunting [35]. While this finding may be an anomaly, considering the prevalence of metformin use, further study is certainly justified.

Beta-adrenergic antagonists are frequently used to treat atrial fibrillation, and self-reported atrial fibrillation perfectly predicted the absence of nonspecific symptoms of hypoglycemia. This relationship is not surprising since pharmacologic blockade of the adrenergic system prevents antecedent hypoglycemia from reducing the adrenergic response to subsequent hypoglycemia, [29], thus preventing symptoms of IHA.

Patients self-reporting depression were more likely to experience autonomic symptoms of hypoglycemia. Although the use of antidepressant medications was not reported here, we may presume that the majority of patients with a self-reported diagnosis of depression are taking an antidepressant medication. Interestingly, antidepressant medications have been associated with increased risk of hypoglycemia in patients with diabetes, but their potential for maintaining hypoglycemia aware-

ness has not been evaluated [36]. Antidepressants, especially selective serotonin and norepinephrine reuptake inhibitors (SNRIs), impact the function of the sympathetic nervous system [37, 38], potentially modulating the body's adaptive response to recurrent hypoglycemia, thereby reducing the risk of HAAF.In addition, patients taking any long acting insulin were more likely to experience autonomic symptoms of hypoglycemia, but not neuroglycopenic or nonspecific symptoms. Autonomic symptoms are typically present before the onset of neuroglycopenic symptoms [39]. Thus, patients who are taking long acting insulin appear to be more aware of symptoms of hypoglycemia in comparison to patients who are on other diabetic medications.

All patients in the study were overweight (BMI ≥ 25) or obese (BMI ≥ 30) and there was no statistically significant difference between the BMI of patients with NIHA vs. NIHA, although a greater proportion of patients with IHA (93.8%) were obese compared to the proportion of patients with NIHA (89.6%) who were obese. Overweight/obesity is well-documented as one of the most prominent risk factors for OSA [40] and type 2 diabetes, thus it is not surprising that the subset of patients with NIHA, a potential comorbidity of OSA and type 2 diabetes, includes a higher percentage of obese patients in the current study.

Although there were no statistically significant differences in the prevalence of other reported comorbid conditions between patients with NIHA vs. IHA, the percentage of patients reporting cardiovascular disease and associated risk factors including hypertension, stroke, heart attack, hypercholesterolemia, heart failure, and atrial fibrillation was greater in IHA compared to NIHA. OSA is associated with increased prevalence of cardiovascular disease and associated risk factors (reviewed in [41]). Additionally, experimental evidence indicates that OSA can increase blood pressure, subsequently increasing cardiovascular risk [42]. Despite the lack of positive data to support our hypothesis that OSA is associated with impaired hypoglycemia awareness, the greater proportion of patients with NIHA reporting cardiovascular disease and associated risk factors together with the evolving hypothesis that OSA may influence the pathogenesis of cardiovascular disease, suggests OSA may also be associated with impaired hypoglycemia awareness.

Conclusion

Despite the failure to identify a relationship between OSA and impaired hypoglycemia awareness, this study identified important relationships between specific medications and comorbid conditions associated neurodegeneration and dysfunction. Future studies with more stringent methods to stratify patients into NIHA vs. IHA, are warranted to determine a relationship between OSA and impaired hypoglycemia awareness. Hypoglycemia is a life-threatening complication in diabetic patients, thus there is urgent need to further understand and reduce the prevalence of impaired hypoglycemia awareness in effort to reduce hypoglycemia-induced mortality. This study lays the groundwork or future studies on the relationship between OSA and impaired hypoglycemia awareness in diabetic patients.

Abbreviations

HAAF: hypoglycemia-associated autonomic failure
IHA: impaired hypoglycemia awareness
NIHA: no impaired hypoglycemia awareness
OSA: obstructive sleep apnea
SNRIs: selective serotonin and norepinephrine reuptake inhibitors

Declarations

Ethics Approval and Consent to Participate
This study was approved by the Christian Hospital Institutional Review Board (no reference number assigned). All participants signed an informed consent before participating in this study.

Availability of Data and Material

The datasets used and/or analyzed during this study are not publicly available (due to no funding received for this study), but are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Data collection occurred during a diagnostic sleep study as part of usual care for patients seeking treatment for sleep disorders, thus no funding was required or obtained in support of this study.

Authors' Contributions

BLG assisted with study design, data interpretation, and was a major contributor in writing the manuscript. SAS performed statistical analysis. JAL was responsible for study design, data collection management, data interpretation, and assisted with manuscript writing. AR recruited patients, assisted with study design and methodology, and assisted with polysomnography data interpretation. CMH performed statistical analysis, data interpretation, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Appendix 1. Hypoglycemia Awareness Questionnaire

1. Do you recognize symptoms when you have a hypo?

a. Always
b. Usually
c. Occasionally
d. Never
e. Do not know

2. How low do you believe your blood sugar is when you recognize the first symptoms of hypo? (write down the glucose level at which you start having symptoms)

_____(maximum 10 mg/dl range example 60-70 or 80-90)

3. Which symptoms do you have when you have hypo (0 no problems 3 very intense)?

Sweating (0) (1) (2) (3)	Blurred vision (0) (1) (2) (3)
Difficulty speaking (0) (1) (2) (3)	Warmness (0) (1) (2) (3)
Feeling faint of weak (0) (1) (2) (3)	Irritability (0) (1) (2) (3)
Tingling lips of tongue (0) (1) (2) (3)	Dizziness (0) (1) (2)(3)
Nausea or vomiting (0) (1) (2) (3)	Hunger (0) (1) (2) (3)
Drowsiness (0) (1) (2) (3)	Shivering (0) (1) (2) (3)
Feeling confused (0) (1) (2) (3)	Pounding Heart (0) (1) (2) (3)
Double vision (0) (1) (2) (3)	Headache (0) (1) (2) (3)
Difficulty in sleeping (0) (1) (2) (3)	Tiredness (0) (1) (2) (3)
Stomach pain (0) (1) (2) (3)	Anxiety (0) (1) (2) (3)
Difficulty in concentrating (0) (1) (2) (3)	Trembling (0) (1) (2) (3)