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RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNEA AND THE PRESENCE AND SEVERITY OF DIABETIC RETINOPATHY

AIMEE C. CHANG, BS[*], **TIMOTHY P. FOX, MD**[†], **SHUTAO WANG, PhD**[*], **ALBERT Y. WU, MD, PhD, FACS**[†]

[*]Icahn School of Medicine at Mount Sinai, New York, New York;

[†]Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, New York.

Abstract

Purpose: To evaluate the relationship between obstructive sleep apnea (OSA) and the presence and severity of diabetic retinopathy (DR).

Methods: Three hundred seventeen patients with *International Classification of Diseases* diagnoses of both DR and OSA were evaluated retrospectively. Diabetic retinopathy severity and diabetic macular edema status were determined by diagnostic coding and medical records. Obstructive sleep apnea severity and additional sleep measures were obtained from overnight polysomnography. Analysis was performed using multivariable logistic regression.

Results: After adjustment, an association was seen between DR and severe OSA (odds ratio [OR]: 2.18, 95% confidence interval [CI]: 1.14–4.18, $P = 0.019$). Proliferative DR was associated with severe OSA versus no DR (OR: 2.40, 95% CI: 1.12–5.14, $P = 0.024$) and mild nonproliferative DR (OR: 2.87, 95% CI: 1.26–6.55, $P = 0.012$). Comparing all nonproliferative DR with proliferative DR, proliferative DR and severe OSA were associated (OR: 2.20, 95% CI: 1.03–4.70, $P = 0.043$), as well as diabetic macular edema and severe OSA (OR: 2.89, 95% CI: 1.58–5.27, $P = 0.001$). No association was seen between DR/diabetic macular edema and secondary sleep measures.

Conclusion: The findings suggest an increased risk of DR, proliferative DR, and diabetic macular edema in patients with severe OSA. Ophthalmologists following these patients should be aware of this association to better manage ocular sequelae of diabetes.

Keywords

diabetes; diabetic macular edema; diabetic retinopathy; obstructive sleep apnea; ocular manifestations; systemic disease

Diabetic retinopathy (DR) is a serious microvascular complication of diabetes mellitus (DM) that is the leading cause of visual loss in adults aged 20 to 74.[1] Recent studies (Table 1) suggest an association between DR and obstructive sleep apnea (OSA), a sleep disorder

Reprint requests: Albert Y. Wu, MD, PhD, FACS, Department of Ophthalmology, Stanford University School of Medicine, 2370 Watson Court, Suite 200, Palo Alto, CA 94303; awu1@stanford.edu.

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characterized by episodes of shallow or paused breathing during sleep leading to hypoxemia, arousal, and sleep fragmentation.[18] Symptoms of OSA include snoring and daytime somnolence.[18] Obstructive sleep apnea is linked to central obesity and is caused by obstruction of the upper airway, which occurs during sleep because of decreased muscle tone and collapse of the soft tissue in the airway.[19,20] Obstructive sleep apnea is a common condition estimated to affect up to 9% of adult women and 24% of adult men, and the prevalence continues to rise along with the prevalence of obesity.[21,22]

Obstructive sleep apnea affects a large proportion of patients with DM—between 58% and 86%—and has been linked to increased insulin resistance and subsequent poor glucose control.[23–25] As a result, DM patients with OSA may be more likely to develop microvascular complications such as DR. In addition, it has been theorized that elevated levels of inflammatory markers secondary to transient hypoxemia during apneas may accelerate damage to retinal vasculature and contribute to the development of DR.[26] Intermittent nocturnal and sustained diurnal rises in blood pressure occurring with OSA have been hypothesized to further increase retinal vascular damage.[21] As DR is often asymptomatic until it has progressed to an advanced stage, identifying potentially associated medical conditions such as OSA may be valuable in recognizing at-risk patients.[1] If DR and OSA are associated, patients with DR may benefit from evaluation and treatment of OSA not only to prevent the progression of DR but also to avoid the serious cardiovascular sequelae of undiagnosed or untreated OSA which include hypertension, coronary artery disease, myocardial infarction, and stroke.[20]

Some studies have linked OSA to DR, although the relationship is still unclear and there is little research on how OSA may relate to diabetic macular edema (DME). In this study, we aim to clarify the relationship between OSA and DR severity by considering apnea–hypopnea index (AHI) and other polysomnography parameters. We also explore the possible association between OSA and DME. Our study stratifies patients with DR by severity and examines additional sleep measures from polysomnography to better characterize how OSA and DR may be associated.

Methods

Approval from the institutional review board of the Icahn School of Medicine at Mount Sinai was obtained for this study. The research was conducted in accordance with HIPAA regulations and the tenets of the Declaration of Helsinki.

Data Collection and Exclusion Criteria

We conducted a retrospective chart review that identified patients based on *International Classification of Diseases* (*ICD*) codes. The Mount Sinai Data Warehouse, a patient database of the Mount Sinai Health System, was searched using a cohort query tool to identify patients. In a search of 3 million patients from January 1, 2008, to October 7, 2016, 901 patients older than 18 years with *ICD* diagnoses of both OSA and DR were identified. Within these patients, *ICD* diagnosis of DME was recorded. The cohort query tool was also used to obtain data on demographics and comorbidities including age, sex, ethnicity, body mass index (BMI), hypertension, hyperlipidemia, carotid stenosis, smoking, DM duration,

and hemoglobin A1c percentage (HbA1c). Patient electronic medical records were reviewed to obtain polysomnography results and to confirm the presence of proliferative DR (PDR) or DME using documentation of an eye examination, injection, or surgery. Patients without these data were excluded. Data collected from polysomnography reports included AHI, minimum SpO2, oxygen desaturation index (ODI), sleep efficiency, arousal index, mean event time, and Epworth Sleepiness Scale scores. Three hundred seventeen patients were included in the final cohort.

Outcome Measurement

The primary outcome of interest was DR severity. Secondary outcomes included presence of DME. Diabetic retinopathy severity was classified as mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, PDR, and unspecified NPDR according to *ICD* codes. Electronic medical records of patients with unspecified DR were accessed to determine DR severity; some were determined to have no DR and some remained unspecified. Diabetic macular edema was classified using *ICD* as present or absent and was confirmed by review of ophthalmology notes.

Obstructive sleep apnea severity was determined using AHI from overnight polysomnography testing. The AHI is a measure of the number of apneas (breathing cessation >10 seconds with ≥90% airway flow decrease) and hypopneas (breathing cessation >10 seconds, with ≥30% airway flow decrease and associated ≥3% arterial oxygen desaturation or arousal) per hour of sleep. Apnea–hypopnea index 0 to 5 indicated no OSA, 6 to 15 mild, 16 to 30 moderate, and >30 severe.[27]

Statistical Analysis

Data were analyzed using multivariable logistic regression. For the main outcome of whether DR severity and OSA are associated, analysis was performed grouping DR severity as none, mild NPDR, moderate NPDR, severe NPDR, and PDR. Further analysis was performed comparing all NPDR to PDR, as well as no DR to all DR. This grouping was also used for the secondary outcome of whether DR severity and other sleep measures are associated. Analysis was adjusted for potential confounders including age, sex, ethnicity, BMI, DM duration, HbA1c, smoking history, presence of hypertension, dyslipidemia, and carotid stenosis. Summary statistics for the first DR severity grouping were calculated using analysis of variance and the linear-by-linear chi-square test. The independent samples *t*-test and Pearson chi-square test were used for the second and third DR severity groupings. The level of significance was $P < 0.05$. All analysis was performed using IBM SPSS Statistics (Armonk, NY).

Results

Demographics

Of the 317 patients included in the analysis, 97 (30.6%) had no DR, 72 (22.7%) had mild NPDR, 14 (4.4%) had moderate NPDR, 11 (3.5%) had severe NPDR, 79 (24.9%) had PDR, and 45 (13.9%) had unspecified DR (Table 2). Ninety-three (29.3%) patients had DME and 224 (70.7%) patients did not have DME. Based on electronic medical records, 70 (88.6%)

patients with PDR had undergone panretinal photocoagulation and 12 (15.2%) had received intravitreal bevacizumab. Thirty-four (36.6%) patients with DME had undergone focal photocoagulation and 17 (18.3%) had received intravitreal bevacizumab, aflibercept, or triamcinolone acetonide. Eleven (3.5%) patients had Type I DM, and 306 (96.5%) had Type II DM. Of the 11 patients with Type I DM, 1 (9.1%) had no DR, 8 (72.7%) had PDR, and 1 (9.1%) had unspecified DR. Two hundred one (63.4%) were insulin dependent, and 97 (30.6%) were insulin independent. The average age of diagnosis of DM was 54.2 ± 11.0 years, and the average duration of DM 9.60 ± 4.53 years. Within the cohort of 317 patients, 21 (6.6%) had no OSA, 53 (16.7%) had mild OSA, 71 (22.4%) had moderate OSA, and 172 (54.3%) had severe OSA.

Diabetic Retinopathy Severity and Obstructive Sleep Apnea

On univariate analysis, DR severity was found to be associated with OSA severity and AHI. With OSA categorized as mild-to-moderate and severe, there were 20 mild-to-moderate and 54 severe among patients with PDR, 34 mild-to-moderate and 34 severe among mild patients with NPDR, and 45 mild-to-moderate and 47 severe among patients without DR. Severe OSA was significantly more prevalent in patients with PDR, in comparison with mild patients with NPDR ($P = 0.007$) and patients without DR ($P = 0.005$). Higher AHI was seen in severe NPDR (59.3 ± 10.6) versus no DR (38.4 ± 3.06, $P = 0.036$) and mild NPDR (38.6 ± 3.94, $P = 0.044$). No relationship was seen between DR severity and the presence of OSA. Multinomial regression with adjustment found HbA1c to be significantly higher in mild NPDR (odds ratio [OR]: 1.36, 95% confidence interval [CI]: 1.09–1.69, $P = 0.006$), moderate NPDR (OR: 1.52, 95% CI: 1.02–2.26, $P = 0.038$), and PDR (OR: 1.30, 95% CI: 1.06–1.60, $P = 0.013$) compared with no DR. Patient age, sex, ethnicity, BMI, hypertension, hyperlipidemia, carotid stenosis, smoking, and DM duration were not associated with DR severity. After adjustment, PDR remained independently associated with severe OSA in comparison with no DR (OR: 2.40, 95% CI: 1.12–5.14, $P = 0.024$) and mild NPDR (OR: 2.87, 95% CI: 1.26–6.55, $P = 0.012$). Higher AHI was independently associated with severe NPDR versus mild NPDR (OR: 1.02, 95% CI: 1.00–1.05, $P = 0.048$).

Comparing all patients with NPDR to patients with PDR, univariate analysis showed an association between severe OSA and PDR ($P = 0.011$) that remained significant after adjustment (OR: 2.20, 95% CI: 1.03–4.70, $P = 0.043$). Within the patients with NPDR, 44 had mild-to-moderate OSA and 54 had severe OSA; within the patients with PDR, 20 had mild-to-moderate OSA and 54 had severe OSA. When comparing DR with no DR, severe OSA was significantly more prevalent in patients with DR on univariate analysis ($P = 0.035$). Among patients with DR, 58 had mild-to-moderate OSA and 111 had severe OSA, and among patients with no DR, 43 had mild-to-moderate OSA and 47 had severe OSA. Multinomial regression with adjustment found a significantly higher HbA1c level in patients with DR (OR: 1.23, 95% CI: 1.04–1.46, $P = 0.017$). After adjustment, DR remained associated with severe OSA (OR: 2.18, 95% CI: 1.14–4.18, $P = 0.019$). No association was seen with AHI or presence of OSA, and no comorbidities or other potential confounding factors were found to be independently associated.

Diabetic Retinopathy Severity and Secondary Sleep Parameters

Secondary sleep measures obtained from polysomnography include sleep efficiency, mean event time, arousal index, periodic limb movement index, minimum SpO2, and Epworth Sleepiness Scale scores (Table 3). Mean event time is defined as the average duration in seconds of apneic and hypopneic events during sleep, arousal index is the number of electroencephalogram-recorded arousals per hour of sleep (normal <10–25 based on age), and the periodic limb movement index is the number of periodic limb movements—brief muscle activations occurring at consistent intervals—per hour of sleep (normal <15 in adults).[29,30] The ODI, which is the number of oxygen desaturations by ≥ 4% during sleep per hour, was higher in patients with PDR (32.7 ± 26.4) compared with patients without DR (19.0 ± 17.6, $P = 0.017$) but was not significantly higher after adjustment (OR: 0.991, 95% CI: 0.975–1.01, $P = 0.254$).[29] Oxygen desaturation index was also higher in patients with PDR compared with mild patients with NPDR (18.0 ± 21.2, $P = 0.020$), but similarly, this association was not significant after adjustment (OR: 0.978, 95% CI: 0.953–1.004, $P = 0.097$). Sleep efficiency, defined as the ratio of total sleep time to time in bed (multiplied by 100 to yield a percentage) with values > 85% considered normal, was lower in moderate patients with NPDR (68.9 ± 19.6) versus patients without DR (74.2 ± 13.7, $P = 0.008$).[31] This association was not significant after adjustment (OR: 1.03, 95% CI: 0.993–1.08, $P = 0.106$). Compared with NPDR, no relationship between PDR and secondary sleep parameters was found.

Diabetic Macular Edema and Obstructive Sleep Apnea

On univariate analysis, severe OSA was significantly more prevalent in patients with DME compared with patients without DME: among patients with DME, 28 had mild-to-moderate OSA and 61 had severe OSA; among patients without DME, 116 had mild-to-moderate OSA and 97 had severe OSA ($P = 0.000$). No association was seen between DME and AHI or presence of OSA. After binomial regression with adjustment, severe OSA and DME remained associated (OR: 2.89, 95% CI: 1.58–5.27, $P = 0.001$). No comorbidities or potential confounding factors were independently associated with DME.

Diabetic Macular Edema and Secondary Sleep Parameters

No association was seen between DME and any secondary sleep parameter.

Discussion

Our study is the first to stratify DR severity as none, mild NPDR, moderate NPDR, severe NPDR, and PDR and OSA as mild-to-moderate and severe based on AHI. We found an association between severe OSA and the presence and severity of DR. Six studies (5 cross-sectional, one cohort) examined the relationship between OSA and DR severity (Table 1). Three of these studies compared NPDR with PDR: Baba et al[11] conducted a prevalence study on 60 patients and found an increased prevalence of NPDR and PDR in patients with OSA, compared with patients with non-OSA. Zhang et al[17] found no association, although the study focused on solely on inpatients and the results may not be generalizable. Shiba et al[6] found a significant association between PDR and OSA after adjustment (OR: 1.09, 95% CI: 1.01–1.06), as did our study which shows a two-to-threefold increase in likelihood of

PDR in patients with severe OSA (OR: 2.20, 95% CI: 1.03–4.70, $P = 0.043$). This suggests that OSA may have an impact on DR severity when comparing PDR with NPDR. In two U.K.-based studies, DR severity was measured using the National Screening Programme retinopathy grading system, which—like *ICD* codes—is based on the Early Treatment Diabetic Retinopathy classification scheme but has been modified to optimize sensitivity and specificity.[32] These studies found a significant association between OSA and advanced DR after adjustment. Similarly, our study found a significant association between DR severity and severe OSA. A cohort study lasting 4.4 years found that OSA was independently linked to progression to advanced DR (OR: 6.6, 95% CI: 1.2–35.1, $P = 0.03$).[33] Additional studies, especially with long-term follow-up and adjustment for potential confounding variables, should be conducted to clarify the effect of OSA on DR severity and progression.

Based on the association found between DR and OSA severity—which is determined by AHI—an association between DR and AHI was expected. Yet, in our study, higher AHI was found only to be associated with severe NPDR versus mild NPDR (OR: 1.02, 95% CI: 1.00–1.05, $P = 0.048$), and the OR was close to 1. This discrepancy between OSA severity and AHI may reflect a tipping point or threshold in the increasing degree of OSA after which it is linked to DR. The existence of this threshold may be reflected by the categorization of OSA as mild-to-moderate and severe and be obscured when using AHI as a continuous variable. Supporting the idea of a threshold is the lack of association seen between DR and the presence of OSA, with patients of mild, moderate, and severe OSA grouped together—in this situation, the threshold would be obscured as well. Two previous studies, Mehta et al[14] and Storgaard et al,[16] examined both OSA presence and AHI in relation to DR and had negative findings, which reinforces our findings. They did not concurrently examine OSA severity in categories, although no comparison is available for our study.

Findings from previous studies investigating AHI have been inconsistent. In 12 cross-sectional studies, 5 found a significant association between OSA/AHI and the presence of DR.[2,3,7,10,11] These findings, however, did not control for patient factors including HbA1c, medical comorbidities, or demographic variables. By contrast, our study controlled for age, sex, BMI, hypertension, hyperlipidemia, carotid stenosis, smoking, DM duration, HbA1c, and ethnicity—categorizing ethnicity as Hispanic and non-Hispanic as findings from population-based studies indicate that Hispanic ethnicity may be an independent risk factor for the development and progression of DR.[1] Of the 12 studies, 3 controlled for potential confounders and found no association between AHI and the presence of DR.[14,15,17] These findings may support our hypothesis explaining the relationship between DR and severe OSA, although these studies did not consider OSA severity. The potential association between AHI and DR requires further analysis, preferably with concurrent analysis of OSA severity.

Few studies have looked at the relationship between OSA and DME, and this study is the largest of its kind to date. Our findings show an almost threefold increase in risk of DME presence in patients with severe OSA (OR: 2.89, 95% CI: 1.58–5.27, $P = 0.001$). As with DR, the relationship between DME and severe OSA may reflect a threshold in increasing OSA severity after which DME is associated, as no relationship was found between DME and AHI or presence of OSA. No previous studies of DME have looked at both AHI and

OSA severity, so no comparison is available. Six studies have explored the potential association between DME and OSA. Of the cross-sectional studies that controlled for potential confounding variables, West et al[5] had positive findings while Banerjee et al[15] and Rudrappa et al[8] had negative findings. However, as West et al[5] and Rudrappa et al[8] exclusively studied male patients, their findings may not apply to the general population. One cohort study found a significant association between OSA and DME (OR: 4.5, 95% CI: 1.8–11.4, $P = 0.002$), although OSA was not linked to the progression of maculopathy at 4.4-year follow-up.[33] Although there is evidence that DME and OSA may be associated, the relationship remains unclear and further studies with long-term follow-up should be performed.

We considered several polysomnography parameters that had not been explored in previous studies and analyzed how they might relate to DR and DME (Table 3). Our study is the first to look at measures including mean event time, arousal index, sleep efficiency, and periodic limb movement index. The findings suggest that secondary sleep measures do not play a role in the relationship between DR/DME and OSA. Some previous studies have found an association between DR and markers of hypoxemia during sleep including ODI and minimum SpO2, supporting the theory that the potential relationship between OSA and DR/DME is driven by transient hypoxemia during apneas leading to ischemic damage and retinal neovascularization.[6,9,17,34] We found a higher ODI in patients with PDR (32.7 ± 26.4) compared with mild patients with NPDR (18.0 ± 21.2, $P = 0.020$) and patients without DR (19.0 ± 17.6, $P = 0.017$), although ODI was not significantly higher after adjustment. West et al[5] similarly found ODI to be associated with retinopathy scores on univariate analysis ($r = 0.3$, $P < 0.0001$), although the association was not significant after adjustment, and Zhang et al[17] had negative findings. Shiba et al,[34] however, reported a significant association between PDR and ODI ($r = 0.43$, $P = 0.03$) on multivariate analysis. The conflicting findings warrant further study of ODI and its relationship to DR/DME. As for studies looking at minimum SpO2, Zhang et al[17] reported an association between minimum SpO2 and PDR on univariate analysis that did not remain significant after adjustment. Shiba et al[6] found an association between minimum SpO2 and PDR on multivariate analysis, although the OR of 0.93 is close to 1, whereas Nishimura et al[9] found minimum SpO2 to be significantly lower in patients with DR, although no OR was reported. In our study, no relationship between DR/DME and minimum SpO2 was seen. Other physiologic effects of OSA may be at play in the development and progression of diabetic eye complications.

Although our study provides a comprehensive analysis of how DR severity may relate to OSA, our study has limitations. Our data from the Mount Sinai Data Warehouse spans from 2008 to 2016, an 8-year period during which DM treatment has continued to be transformed with the introduction of new oral hypoglycemic agents. As tight glycemic control is key to DR prevention and new oral hypoglycemic agents have been shown to help lower HbA1c levels, it is possible that our data contain inconsistencies because of changes in DM management over time.[1] A systematic review of 52 randomized, controlled trials and 13 observational studies published in February 2017 finds, however, that there is insufficient evidence showing comparative benefits of oral hypoglycemic agents in retinopathy.[35] Another limitation of our study is that while conducting a retrospective chart review using a database tool to identify patients based on diagnostic coding allows for a large sample size,

the data obtained is subject to intrinsic biases and limitations: these include misdiagnosis, inaccurate coding, inability to track disease change over time, and variability between providers. Data on continuous positive airway pressure therapy following diagnostic polysomnography were not accessible. Although the Mount Sinai Health System provides care for a diverse socioeconomic group, results may be limited by geographic bias. In addition, although all groups of OSA severity were included in our study, the Mount Sinai Sleep Center specializes in diagnosing and managing severe OSA. Despite these limitations, this study is the first to stratify DR severity into five levels, is the largest-to-date study on the relationship between OSA and DME, and is the first to explore additional polysomnography parameters including mean event time and arousal index.

In summary, our study found an association between DR/DME and OSA severity. Key findings include a two-to-threefold increased risk of DR, PDR, and DME presence in patients with severe OSA, as compared to patients with mild-to-moderate OSA. We also find evidence of a threshold in increasing degree of OSA after which OSA is associated with DR/DME, suggesting that patients with severe OSA are particularly at risk of diabetic eye complications, whereas patients with mild-to-moderate OSA are not. As such, our results indicate that patients with both severe OSA and DM, although already being followed by an ophthalmologist for monitoring of DR/DME, should be identified as higher risk patients in the clinical setting. Further longitudinal studies should be conducted to explore how severe OSA in particular may be related to the development and progression of DR and DME.

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Table 1.

Summary of Cross-Sectional Studies on DR and OSA

Study	Patients	Setting	Analysis	Main Findings	
				DR	DME
Positive association between DR and OSA and/or PSG measures					
Unver et al[2] (United States)	44 DM	Outpatient retina clinic	Univariate	Significant association between DR and OSA (OR: 143.18, 95% CI: 7.41–2767.79) †	Significant association between OSA and DME (OR: 14.44, 95% CI: 2.34–147.60) †
Laaban et al[3] (France)	303 T2DM	Hospital inpatient (DM)	Univariate	Significant association between DR and OSA (OR: 0.56, 95% CI: 0.35–0.92) †	
Borel et al[4] (France)	37 T1DM	DM outpatient	Univariate	Difference in presence of DR between borderline (11.1%) and pathological (73.3%) overnight oximetry recording **	
West et al[5] (United Kingdom)	118 T2DM	1 DM outpatient and 5 primary care centers	Multivariate	Association between retinopathy scores and OSA ($R^2 = 0.19$) *	Association between DME and OSA ($R^2 = 0.30$) *
Shiba et al[6] (Japan)	219 T2DM	Hospital inpatient (eye disease)	Multivariate	NPDR versus PDR: association between PDR and OSA (OR: 1.09, 95% CI: 1.01–1.06) ** Association between PDR and minimum SpO2 (OR: 0.93; 95% CI: 0.88–0.99) **	
Kosseifi et al,[7] (United States)	98 T2DM	Outpatient sleep clinic	Univariate	Higher AHI in DR (44.2) versus no DR **	
Rudrappa et al[8] (United Kingdom)	31 T2DM	DM outpatient	Multivariate	Association between retinopathy scores and OSA * No association between PDR and OSA (OR: 12.6, 95% CI: 0.62255.76)	No association between DME and OSA (effect size not reported)
Nishimura et al,[9] (Japan)	136 T2DM	N/A	Univariate	No difference in AHI between patients with no DR (15.1 ± 13.6) and with DR (17.8 ± 15.1)	
			Multivariate	Difference in minimum SpO2 between patients with no DR (81.8 ± 7.4) and with DR (78.2 ± 9.6) **	
Manin et al,[10] (France)	67 T1DM	2 DM outpatient	Univariate	Difference in presence of DR between patients with OSA (84%) and non-OSA (42%) * No difference in presence of NPDR between patients with OSA (10%) and non-OSA (6%)	No difference in presence of DME between patients with OSA (23%) and non-OSA (8%)
Babaetal[11] (France)	60 T2DM	DM outpatient	Univariate	Difference in presence of DR between patients with OSA (55%) and non-OSA (15%) ** Difference in presence of NPDR ** and PDR ** between patients with OSA (35% and 20%) and non-OSA (7.5% and 7.5%)	Difference in presence of DME in patients with OSA (20%) and non-OSA (5%) **
No association between DR and OSA					

Study	Patients	Setting	Analysis	Main Findings	
				DR	DME
Schober et al[12] (Germany)	498 T2DM and 58 T1DM	14 primary care centers	Univariate	No difference in presence of DR between no OSA (AHI < 15; 13.9%) and moderate-to-severe OSA (AHI ≥ 15; 11.5%)	
Mason et al[13] (United Kingdom)	80 T2DM with DME	DME outpatient	Univariate	No association between DR and OSA	
Mehta et al[14] (India)	80 T2DM	Outpatient retina clinic	Multivariate	No association between DR and OSA or AHI (effect size not reported)	
Banerjee et al[15] (United Kingdom)	93 T2DM	Specialist weight management clinic	Multivariate	No association between DR and AHI (OR: 1.00, 95% CI: 0.98–1.02) or PSG measures	No association between DME and AHI (OR: 1.01, 95% CI: 0.98–1.04) Association between DME and minimum SpO2 (OR: 0.79, 95% CI: 0.65–0.95) **
Storgaard et al[16] (Denmark)	180 T2DM	DM outpatient	Univariate	No difference in DR between patients with OSA (26.4%) and non-OSA (19.4%) No difference in AHI between patients with no DR (17 ± 25) and with DR (17 ± 20)	
Zhang et al[17] (China)	233 T2DM	12 hospital inpatient (DM)	Multivariate	No association between DR and AHI or PSG measures PDR versus NPDR: no association between PDR and minimum SpO2 (OR: 0.970, 95% CI: 0.932–1.010) or other OSA parameters	

* $P < 0.01$;

** $P < 0.05$;

*** $P < 0.10$.

† P value significant but not reported.

PSG, polysomnography; SpO2, oxygen saturation; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus.

Table 2.

Summary of Patient Demographics and Comorbidities by DR Status and DME Status

	DR Status (n = 273)						DME Status (n = 317)		
	No DR	**Mild NPDR**	**Moderate NPDR**	**Severe NPDR**	**PDR**	**P†**	**No DME**	**DME**	**P‡**
Demographics									
Males	36 (37.1)	29 (40.3)	6 (42.9)	7 (63.6)	29 (36.7)	0.88	88 (39.3)	39 (41.9)	0.66
BMI, kg/m^2	37.1 [8.00]	36.7 [7.61]	36.9 [9.64]	37.5 [10.5]	36.6 [10.1]	1.00	37.5 [9.31]	36.5 [7.91]	0.60
Age, years	62.8 [11.2]	62.8 [9.07]	63.7 [9.94]	63.6 [10.0]	63.7 [11.0]	0.97	64.2 [10.4]	63.1 [10.9]	0.042 **
Hispanic	44 (45.4)	22 (30.6)	4 (28.6)	5 (45.5)	31 (39.2)	0.65	84 (37.5)	34 (36.6)	0.76
Comorbidities									
DME	4 (4.1)	19 (26.4)	8 (57.1)	8 (72.7)	50 (63.3)	0.000 *			
Diabetes duration, years	9.42 [4.22]	9.15 [4.34]	8.36 [4.05]	10.6 [4.80]	9.97 [3.56]	0.49	9.72 [4.49]	9.38 [5.28]	0.25
Age at diagnosis of diabetes	53.3 [10.1]	55.9 [9.76]	56.6 [9.56]	48.8 [12.3]	52.1 [12.2]	0.087 ***	54.3 [10.8]	54.0 [11.5]	0.83
Insulin dependence	47 (48.5)	44 (61.1)	10 (71.4)	8 (72.7)	64 (81)	0.000 *	132 [58.9]	69 [74.2]	0.094 ***
Hemoglobin A1c percentage	7.45 [1.86]	8.01 [1.53]	8.59 [1.55]	7.17 [1.88]	8.11 [1.87]	0.037 **	7.76 [1.78]	7.79 [1.75]	0.51
Smoker	55 (56.7)	32 (44.4)	11 (78.6)	6 (54.5)	38 (48.1)	0.49	111 (49.6)	52 (55.9)	0.30
Hypertension	97 (100)	72 (100)	14 (100)	11 (100)	79 (100)	N/A§	224 (100)	93 (100)	N/A§
Dyslipidemia	90 (92.8)	68 (94.4)	12 (85.7)	11 (100)	77 (97.5)	0.17	205 (92.5)	91 (97.8)	0.039 **
Carotid stenosis	5 (5.2)	3 (4.2)	1 (7.1)	2 (18.2)	11 (13.9)	0.012 **	17(7.6)	8 (8.6)	0.76
Total observations	97 (35.5)	72 (26.4)	14 (5.12)	11 (4.02)	79 (28.9)		224 (70.7)	93 (29.3)	

Data are presented as n (%) or mean [SD] unless otherwise specified.

* $P < 0.01$;

** $P < 0.05$;

*** $P < 0.10$.

† *P* values were calculated using linear-by-linear chi-square tests for all categorical variables and analysis of variance tests for all continuous variables.

‡ *P* values were calculated using Pearson chi-square tests for all categorical variables and independent samples t-tests for all continuous variables.

§ No *P* values were calculated for hypertension, as this variable is a constant.

Table 3.

Summary of Polysomnography Measures by DR Status and DME Status

	DR Status (n = 273)					DME Status (n = 317)	
	No DR	**Mild NPDR**	**Moderate NPDR**	**Severe NPDR**	**PDR**	**No DME**	**DME**
OSA[§]	92 (94.8)	67 (93.1) {0.89, 0.64}	13 (92.9) {0.67, 0.98}	11 (100.0) {0.071***, 0.11}	74 (93.7) {0.005*, 0.024**}	207 (92.4)	89 (95.7) {0.000*, 0.000*}
AHI	38.4 [30.0]	38.6 [33.2] {0.97, 0.46}	41.8 [29.4] {0.68, 0.45}	59.3 [35.0] {0.036**, 0.10}	46.0 [29.8] {0.11, 0.56}	39.1 [31.3]	46.4 [32.0] {0.063***, 0.100]
REM AHI	41.8 [23.7]	46.4 [31.0] {0.41, 0.55}	44.1 [25.8] {0.79, 0.95}	35.0 [23.4] {0.57, 0.38}	40.5 [24.1] {0.81, 0.35}	41.5 [27.1]	40.8 [22.8] {0.86, 0.77}
NREM AHI	30.0 [30.3]	29.2 [29.7] {0.88, 0.15}	31.7 [26.2] {0.86, 0.25}	50.5 [28.4] {0.11, 0.53}	35.6 [27.9] {0.35, 0.88}	29.6 [29.0]	36.0 [28.1] {0.18, 0.13}
Sleep efficiency	74.2 [13.7]	71.7 [18.8] {0.36, 0.86}	60.6 [20.6] {0.008*, 0.13}	77.7 [18.7] {0.48, 0.53}	69.4 [19.4] {0.071***, 0.77}	71.1 [17.7]	69.2 [19.2] {0.42, 0.42}
Arousal index	23.2 [22.5]	26.4 [25.5] {0.39, 0.61}	25.7 [21.8] {0.69, 0.87}	32.2 [30.8] {0.23, 0.82}	26.3 [21.4] {0.38, 0.90}	25.2 [23.6]	26.5 [21.8] {0.65, 0.96}
PLMI	3.12 [7.59]	6.46 [17.8] {0.17, 0.033**}	4.24 [13.4] {0.69, 0.33}	1.74 [5.27] {0.63, 0.86}	6.09 [19.7] {0.19, 0.28}	5.72 [15.3]	5.74 [18.2] {0.99, 0.98}
Mean event time	22.6 [6.21]	22.1 [6.08] {0.66, 0.78}	22.9 [4.36] {0.89, 0.98}	20.3 [3.53] {0.34, 0.47}	22.3 [6.76] {0.79, 0.94}	22.2 [6.27]	22.2 [5.94] {0.99, 0.88}
Minimum SpO2	76.9 [11.1]	76.2 [14.5] {0.69, 0.69}	77.9 [8.29] {0.77, 0.80}	70.6 [12.8] {0.12, 0.29}	76.4 [11.9] {0.77, 0.87}	76.2 [12.6]	76.6 [12.6] {0.77, 0.87}
ODI	20.9 [21.6]	18.0 [21.2] {0.52, 0.78}	33.5 [20.7] {0.22, 0.63}	33.8 [29.7] {0.21, 0.34}	32.7 [26.4] {0.035**, 0.086***}	24.5 [25.8]	30.4 [26.1] {0.22, 0.81}
ESS	9.84 [5.71]	10.8 [5.77] {0.35, 0.19}	12.2 [4.88] {0.34, 0.47}	10.8 [6.43] {0.68, 0.59}	9.89 [5.88] {0.96, 0.81}	9.79 [5.67]	11.03 [5.50] {0.14, 0.16}

Data are presented as n (%), mean [SD], or {unadjusted *P* value,† adjusted *P* value†,‡} unless otherwise specified.

*$P < 0.01$;

**$P < 0.05$;

**$P < 0.10$.

†Reference category for DR severity and DME: no DR and no DME, respectively.

‡*P* values are adjusted for patient sex, age, ethnicity, BMI, diabetes duration, hemoglobin A1c percentage, smoker status, hypertension, dyslipidemia, and carotid stenosis.

§*P* values are for OSA severity stratified as mild-to-moderate and severe.

ESS, Epworth Sleepiness Scale (the ESS asks patients to rate their likelihood of falling asleep [0–3] in 8 questions: a score ≥10 is considered excessive daytime sleepiness, and in combination with a diagnosis of OSA is termed OSA syndrome); NREM, nonrapid eye movement sleep; PLMI, periodic limb movement index; REM, rapid eye movement sleep; SpO2, oxygen saturation.[28] ODI, oxygen desaturation index.