Obstructive Sleep Apnea and Retinopathy in Patients with Type 2 Diabetes

A Longitudinal Study

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Abstract

Rationale: Obstructive sleep apnea (OSA) is associated with several pathophysiological deficits found in diabetic retinopathy (DR). Hence, it's plausible that OSA could play a role in the pathogenesis of sight-threatening DR (STDR).

Objectives: To assess the relationship between OSA and DR in patients with type 2 diabetes and to assess whether OSA is associated with its progression.

Methods: A longitudinal study was conducted in diabetes clinics within two U.K. hospitals. Patients known to have any respiratory disorder (including OSA) were excluded. DR was assessed using two-field 45-degree retinal images for each eye. OSA was assessed using a home-based multichannel cardiorespiratory device.

Measurements and Main Results: A total of 230 patients were included. STDR and OSA prevalence rates were 36.1% and 63.9%, respectively. STDR prevalence was higher in patients with OSA than in those without OSA (42.9% vs. 24.1%; $P = 0.004$). After adjustment for

confounders, OSA remained independently associated with STDR (odds ratio, 2.3; 95% confidence interval, 1.1–4.9; $P = 0.04$). After a median (interquartile range) follow-up of 43.0 (37.0–51.0) months, patients with OSA were more likely than patients without OSA to develop preproliferative/proliferative DR (18.4% vs. 6.1%; $P = 0.02$). After adjustment for confounders, OSA remained an independent predictor of progression to preproliferative/proliferative DR (odds ratio, 5.2; 95% CI confidence interval, 1.2–23.0; $P = 0.03$). Patients who received continuous positive airway pressure treatment were significantly less likely to develop preproliferative/proliferative DR.

Conclusions: OSA is associated with STDR in patients with type 2 diabetes. OSA is an independent predictor for the progression to preproliferative/proliferative DR. Continuous positive airway pressure treatment was associated with reduction in preproliferative/proliferative DR. Interventional studies are needed to assess the impact of OSA treatment on STDR.

Keywords: obstructive sleep apnea; diabetic retinopathy; maculopathy

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At a Glance Commentary

Scientific Knowledge on the

Subject: Obstructive sleep apnea (OSA) is known to be common in patients with type 2 diabetes. Previous studies showed a cross-sectional association between OSA and diabetes-related microvascular complications (e.g., nephropathy and neuropathy). There are no published studies assessing the relationship between OSA and diabetic retinopathy longitudinally.

What This Study Adds to the

Field: To our knowledge, this study is the first prospective examination of the impact of OSA on diabetic retinopathy. Our present study shows that OSA is independently associated with maculopathy and sight-threatening retinopathy in patients with type 2 diabetes and that OSA is associated with the development of advanced (preproliferative and proliferative) retinopathy longitudinally over approximately 4 years in patients with type 2 diabetes.

Diabetic retinopathy (DR) affects 40 to 50% of patients with diabetes, is a leading cause of blindness in the Western world, and results in significant morbidity and economic burden (1, 2). Important risk factors include age, poor glycemic control, hypertension, diabetes duration, dyslipidemia, and genetic factors (1, 3). Although the precise etiology of DR remains debated, increased inflammation, oxidative stress, and activation of multiple pathways are thought to result in functional and/or structural defects involving the microvasculature. These will increase vascular permeability (which can lead to macular edema) or cause ischemia leading to increased vascular endothelial growth factor (VEGF) levels and neovascularization (1, 4). Despite improvements in the control of metabolic and vascular risk factors, DR remains very common (5), and a significant proportion of DR cases progress to sight-threatening diabetic retinopathy (STDR) (1). Hence, improved understanding of the pathogenesis of DR is important to identify new treatment targets/strategies.

Obstructive sleep apnea (OSA) is very common in patients with type 2 diabetes (T2D) (6–10). We previously reported that OSA is associated with peripheral neuropathy, nephropathy, and estimated glomerular filtration rate decline in patients with T2D independently of obesity (10, 11). We also previously showed that OSA is independently associated with increased nitrosative and oxidative stress as well as impaired microvascular regulation in patients with T2D (10). T2D is also a risk factor for severe nocturnal hypoxemia (12). Hence, it seems reasonable to speculate that OSA could play a role in the pathogenesis of STDR, particularly because OSA is also associated with many of the pathophysiological deficits found in DR (including inflammation, oxidative stress, and increased VEGF) (13–18).

The aims of this study were therefore to determine the interrelationships of OSA and STDR in subjects with T2D and to assess whether OSA is associated with DR progression. Some of the findings reported in this paper were presented previously in the form of an abstract (19).

Methods

We conducted an observational, cross-sectional study that was converted to a longitudinal, prospective study of subjects with T2D. Patients with respiratory disease (including prediagnosed OSA), end-stage renal disease, or nondiabetic retinopathy were excluded (Figure 1). Patients were recruited consecutively from the outpatient diabetes departments of two secondary care hospitals in the United Kingdom (Birmingham Heartlands Hospital and Royal Stoke University Hospital). The project was approved by the Warwickshire Research Ethics Committee (REC number 08/H1211/145), and all patients provided written informed consent.

OSA was assessed on the basis of a single overnight home-based cardiorespiratory study using a portable multichannel device (Alice PDx; Philips Respironics, Best, the Netherlands). Sleep studies were scored in accordance with the American Academy of Sleep Medicine guidelines using the hypopnea definition of greater than or equal to 4% oxygen desaturation and greater than or equal to 30% reduction in nasal air flow signal (20). Sleep studies with less than 4 hours of

adequate recordings were repeated, and if the quality remained poor, they were excluded from analysis. All sleep studies were double scored manually, and further scoring was performed in cases of discrepancy by a consultant in sleep medicine (A.A.). An apnea–hypopnea index (AHI) greater than or equal to 5 events per hour was consistent with an OSA diagnosis (21). OSA severity was assessed on the basis of the AHI and the oxygen desaturation index (ODI) based on 4% oxygen desaturation. OSA was classified as mild, moderate, and severe on the basis of AHI greater than or equal to 5 but less than 15 events per hour, greater than or equal to 15 but less than 30 events per hour, and greater than or equal to 30 events per hour, respectively. Data regarding continuous positive airway pressure (CPAP) treatment was collected as part of routine care because all patients with moderate to severe OSA at baseline were referred to the sleep clinic in their respective National Health Service trusts for further assessment and decisions regarding treatment. CPAP was offered to all patients with moderate to severe OSA. CPAP use data were obtained from the patients' electronic records approximately 2.5 years after the OSA diagnosis and referral to the sleep clinic. CPAP use for more than 4 hours per night on 70% of days was considered to indicate compliance (22).

DR/STDR was assessed using two-field 45-degree digital retinal images for each eye in accordance with the English national screening program guidelines (Table 1) (23). The retinal images included in this study were obtained during routine care because patients with diabetes in England are invited to undergo retinal imaging as part of the national screening program once per year. All retinal images were graded at least twice, with further grading performed in cases of discrepancy by a consultant ophthalmologist. Patients with ungradable images were examined by a consultant ophthalmologist. STDR was defined as the presence of preproliferative or proliferative DR, maculopathy, or photocoagulation (Table 1) (23). Advanced DR was defined as having preproliferative (R2) or proliferative (R3) DR.

The cross-sectional baseline recruitment analysis designed to explore the relationship between OSA and STDR was conducted using data collected between 2009 and 2010. To explore the impact of

Figure 1. Flow diagram of the study. *After excluding patients with the condition at baseline to assess progression. COPD = chronic obstructive pulmonary disease; DR = diabetic retinopathy; OSA = obstructive sleep apnea; STDR = sight-threatening diabetic retinopathy.

OSA on the rate of progression of STDR, a longitudinal analysis using retinal images from one of the study centers was performed in 2014. All patients who had at least one retinal screening after the baseline visit were included in the longitudinal analysis. All images obtained between baseline and the end of follow-up were reviewed, and the

worst retinal grades prior to receiving DR treatment were included in the analysis. Progression to maculopathy was assessed by examining the progression from no maculopathy (M0) to maculopathy (M1) after excluding patients with M1 at baseline. Progression to advanced DR was examined by assessing the progression from no (R0) or

background (R1) DR to preproliferative (R2) or proliferative (R3) DR after excluding patients who had R2 or R3 at baseline. In analyzing retinal imaging grading, the worst eye grade was used.

Sleep study scorers were blinded to the patient's DR grade, and retinal graders were blinded to the patient's OSA status. All data (apart from the retinal images) were obtained during one-to-one interviews.

Data analysis was performed using IBM SPSS Statistics version 22.0 software (IBM, Armonk, NY). Data are presented as mean (SD) or median (interquartile range [IQR]), depending on data distribution. Independent continuous variables were compared using Student's *t* test or the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test. Correlations between continuous variables were performed using Pearson's or Spearman's tests. All statistical test conditions/assumptions were adhered to throughout the analysis.

To assess whether OSA and/or hypoxemia measures were independently associated with STDR, advanced DR, and maculopathy, multiple logistic regression (forced entry method) was used, in which STDR, advanced DR, and maculopathy status, respectively, were the outcome measures and OSA and other possible confounders were the covariates. To assess the predictors of DR progression, multiple logistic regression was used with progression to maculopathy and progression to advanced DR as the outcomes and OSA and other confounders as the covariates (see the RESULTS section for a full list of the covariates). To assess the relationship between OSA severity and the outcome measures in the cross-sectional and longitudinal analyses, tertiles of AHI and ODI were used in the logistic regression models.

Collinearity was considered in assessing the fit of models to data. On the basis of tolerance and the variance inflation factor tests, there was no evidence of collinearity. However, on the basis of the condition index, there was evidence of collinearity with a condition index value greater than 30, but there was no variance in proportions less than 0.5. Sequentially removing variables involved in multicollinearity had limited impact on model estimates for the main exposure. Hence, the final models presented included variables based on the known

Table 1. Disease Grading Protocol in National Guidelines on Screening for Diabetic Retinopathy

Retinopathy (R)		
Level 0	None (R0)	None
Level 1	Background (R1)	Microaneurysm(s) Retinal hemorrhage(s) $\pm$ any exudate
Level 2	Preproliferative (R2)	Venous beading Venous loop or reduplication Intraretinal microvascular abnormality Multiple deep, round, or blot hemorrhages CWS
Level 3	Proliferative (R3)	New vessels on disc New vessels elsewhere Preretinal or vitreous hemorrhage Preretinal fibrosis with or without tractional retinal detachment
Maculopathy (M)		
Level 0	M0	None
Level 1	M1	Exudate within 1 DD of the center of the fovea Circinate or group of exudates within the macula Retinal thickening within 1 DD of the center of the fovea (if stereoscopic images were available) Any microaneurysm or hemorrhage within 1 DD of the center of the fovea only if associated with a best visual acuity less than or equal to 6/12 (if no stereoscopic images were available)
Photocoagulation (P)	P1	Focal/grid to macula

Definition of abbreviations: CWS = cotton wool spots; DD = disc diameter.

outcome-related risk factors and/or possible confounders and/or variables that differed between patients with and without OSA, regardless of the presence of collinearity. A *P* value less than 0.05 was considered significant.

Results

Two hundred sixty-six patients were recruited and 36 were excluded, leaving 230 patients for baseline analysis (Figure 1). Of these 230 patients, 57.0% (*n* = 131) were men, 54.8% (*n* = 126) were white Europeans, and 45.2% (*n* = 104) were South Asians. There were no differences between those who were included and those who were excluded with regard to the prevalence of DR, maculopathy, or STDR.

OSA prevalence was 63.9% (*n* = 147). The prevalence rates of mild, moderate, and severe OSA were 37.8% (*n* = 87), 14.8%

(*n* = 34), and 11.3% (*n* = 26), respectively. STDR prevalence was 36.1% (*n* = 83), DR prevalence was 63.5% (*n* = 146) (R0, 36.5% [*n* = 84]; R1, 48.3% [*n* = 111]; R2, 6.5% [*n* = 15]; R3, 8.7% [*n* = 20]). The prevalence of advanced DR was 15.2% (*n* = 35), and the prevalence of maculopathy was 31.7% (*n* = 73).

The prevalence of OSA was higher in white Europeans. Patients with OSA (OSA+) were older and more obese and had higher systolic blood pressure than patients without OSA (OSA−) (Table 2). The use of antihypertensive agents and insulin was higher in OSA+ patients, whereas there were no differences in the use of antiplatelet or lipid-lowering therapy (Table 2).

Cross-Sectional Analysis

The prevalence rates of STDR, advanced DR (R2 or R3), and maculopathy were significantly higher in OSA+ patients than in OSA− patients (Table 3).

OSA and DR: Multivariable Analysis

To assess whether the relationship between OSA and STDR is secondary to or independent of possible confounders, logistic regression models were used (Table 4). Despite adjustment, OSA remained independently associated with STDR (Table 4). In addition to OSA (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.1–4.9; *P* = 0.035), diabetes duration (OR, 1.1; 95% CI, 1.1–1.2; *P* < 0.001), and glycated hemoglobin (HbA1c) (OR, 1.4; 95% CI, 1.0–1.7; *P* = 0.02) were also independently associated with STDR. OSA was also independently associated with maculopathy (OR, 2.6; 95% CI, 1.2–5.8; *P* = 0.01) (Table 4). For details on the relationship between OSA severity and DR, see the online supplement.

OSA and DR Progression: Longitudinal Analysis

We hypothesized that retinopathy progression from background to more advanced stages is accelerated by the presence of OSA. Therefore, to explore this construct, a longitudinal analysis was conducted in 199 of 230 patients because follow-up data were available from one site only. The average follow-up was 43.0 (37.0–51.0) months. There was no significant difference in the median (IQR) follow-up duration between OSA− patients (*n* = 71) and OSA+ patients (*n* = 122) (45.0 [37.0–51.0] mo vs. 42.5 [36.0–51.0] mo, respectively; *P* = 0.32). A summary of follow-up duration and DR progression in patients with R0 at baseline in OSA+ and OSA− patients can be found in Figure E1 in the online supplement.

When we examined the progression from R0 or R1 to advanced DR (R2 or R3), we found that we had 164 (of 199) cases available for analysis after excluding 29 patients who had advanced DR at baseline and 6 cases lost to follow-up. Of the 164 patients included in this analysis, 66 (40.2%), 60 (36.6%), 19 (11.6%), and 19 (11.6%) had no, mild, moderate, and severe OSA, respectively. For description of the baseline characteristics of this population, refer to the online supplement. The proportion of patients progressing to advanced DR was higher in OSA+ patients (18.4% [*n* = 18] vs. 6.1% [*n* = 4] for OSA+ and OSA−, respectively; *P* = 0.02), with similar trends in South Asians (14.0% [*n* = 6] vs. 8.9% [*n* = 4]; *P* = 0.45) and white

Table 2. Participant Characteristics in Relation to Obstructive Sleep Apnea Status

	Without OSA (n = 83)	With OSA (n = 147)	P Value
Male sex	41.0% (34)	66.0% (97)	<0.001
White European ethnicity	38.6% (32)	63.9% (94)	<0.001
Age, yr	54.7 (11.9)	58.7 (11.4)	0.01
Diabetes duration, yr	10.7 (7.23)	13.1 (7.8)	0.02
Body mass index, kg/m ²	31.7 (7.0)	35.8 (8.7)	<0.001
Waist circumference, cm	107.1 (15.8)	117.2 (15.9)	<0.001
Systolic blood pressure, mm Hg	125.7 (15.6)	132.6 (17.4)	0.003
Diastolic blood pressure, mm Hg	77.2 (10.2)	78.3 (10.0)	0.4
HbA1c, %	8.1 (1.5)	8.3 (1.3)	0.06
Total cholesterol, mmol/L	4.0 (1.1)	3.9 (1.0)	0.54
Triglycerides, mmol/L	1.8 (1.2)	2.1 (1.3)	0.04
Estimated GFR, ml/min/1.73 m ²	93.1 (24.7)	82.7 (27.4)	0.008
Epworth Sleepiness Scale score	6.8 (5.7)	9.1 (5.6)	0.004
Smoking (current or ex-smoker)	38.6% (32)	40.8% (60)	0.74
Alcohol (consumes alcohol)	14.5% (12)	34.7% (51)	0.001
Oral hypoglycemic agents	97.6% (81)	90.5% (133)	0.04
Thiazolidinediones	14.5% (12)	15.0% (22)	0.92
Insulin	41.0% (34)	59.9% (88)	0.006
GLP-1 analogue	7.2% (6)	13.6% (20)	0.14
Antihypertensive agents	73.5% (61)	85.7% (126)	0.02
Lipid-lowering therapy	85.5% (71)	83.7% (123)	0.71
Fibrates	4.8% (4)	4.8% (7)	0.9
Antiplatelet agents	60.2% (50)	71.4% (105)	0.08
Ischemic heart disease	16.9% (14)	21.8% (32)	0.37
Diabetic nephropathy	23.8% (19)	50.7% (71)	0.005

Definition of abbreviations: GFR = glomerular filtration rate; GLP-1 = glucagon-like peptide 1; HbA1c = glycated hemoglobin; OSA = obstructive sleep apnea. Data are presented as mean (SD) or percentage (count). Analysis was performed using the chi-square test for categorical variables, the independent *t* test for normally distributed variables, and the Mann-Whitney *U* test for nonnormally distributed variables.

Europeans (21.8% [n = 12] vs. 0.0% [n = 0]; *P* = 0.02).

Data from 129 (of 199) subjects were available to examine the progression to maculopathy (M0 to M1) after excluding 65 patients with M1 at baseline and 5 cases lost to follow-up. There was no significant difference in maculopathy progression between OSA+ and OSA− patients (20.8% [n = 15] vs. 19.3% [n = 11] for OSA+ and OSA−, respectively; *P* = 0.83).

Similarly, data from 121 patients (of 199) were available to examine the progression to STDR after exclusion of 74 patients with STDR at baseline and 4 cases lost to follow-up. The proportion of patients progressing to STDR was not statistically different between OSA+ and OSA− patients (20.6% [n = 14] vs. 13.2% [n = 7] for OSA+ and OSA−, respectively; *P* = 0.29), regardless of ethnicity (South Asians, 21.2% [n = 7] vs. 19.4% [n = 7], *P* = 0.86; white Europeans, 20.0% [n = 7] vs. 0.0% [n = 0], *P* = 0.05).

After adjustment for ethnicity, sex, diabetes duration, age at diabetes diagnosis,

systolic blood pressure, HbA1c, estimated glomerular filtration rate, body mass index (BMI), oral antihyperglycemic agents, insulin use, and number of antihypertensive medications (Nagelkerke *R*² for the model, 0.42), OSA remained an independent predictor of progression to advanced DR (OR, 5.2; 95% CI, 1.2–23.0; *P* = 0.03) (Table 5). There was also a dose–effect relationship showing that moderate to severe OSA (vs. no OSA) and tertile 3 (vs. tertile 1) of AHI and ODI were significantly associated with progression to advanced DR (Table 5).

To assess whether differences in follow-up might account for the observed relationship between OSA and progression to advanced DR, we compared the follow-up duration in patients with OSA who progressed and did not progress to advanced DR. We calculated the follow-up using two methods: (1) using the latest available retinal image or clinical data when the data were accessed in 2014, as detailed in the METHODS section; and (2) using the first mention of progression to advanced DR in

electronic records or the retinal screening images. The median (IQR) follow-up (based on first mention of advanced DR in the records) in patients with OSA who did not progress (n = 80) versus those who progressed (n = 18) to advanced DR was 44.0 (37.0–51.0) months versus 32.5 (21.8–42.3) months, respectively (*P* = 0.006). These data suggest that the follow-up duration was significantly shorter in patients with OSA who developed advanced DR than in those who did not develop advanced DR. Compared with the follow-up duration (based on the date of the last available record in 2014), we found no difference between patients with OSA who did not progress and those who progressed to advanced DR (44.0 [37.0–51.0] mo vs. 43.5 [35.5–52.5] mo, respectively; *P* = 0.9). These data suggest that our findings are not related to a longer follow-up in patients who had OSA and progressed to advanced DR. In addition, adding the follow-up duration (based on the date of the last available record in 2014) to the regression model did not change our findings (Nagelkerke *R*² remained at 0.42; OR for progression to advanced DR in patients with OSA vs. those without OSA, 5.2; 95% CI, 1.2–23.0; *P* = 0.03). Adding the follow-up duration (based on the first mention of advanced DR in the records) did not change the results either (Nagelkerke *R*² = 0.5; OR, 5.4; 95% CI, 1.1–27.4; *P* = 0.04). Hence, the length of follow-up does explain the associations between OSA and progression to advanced DR in our study.

We also assessed the impact of changes in HbA1c during the follow-up on the association between OSA and progression to advanced DR. We found that these associations were independent of changes in HbA1c during follow-up. More details are included in the online supplement.

CPAP and DR Progression

CPAP lowered the progression to advanced DR and maculopathy, but this was statistically significant only in the progression to advanced DR category (see the online supplement for details).

Discussion

To our knowledge, this is the first report of an examination of the relationship between OSA and DR longitudinally. T2D and OSA

Table 3. Relationship between Obstructive Sleep Apnea Status and Sight-Threatening Diabetic Retinopathy, Retinopathy, and Maculopathy (Unadjusted Analysis)

	Without OSA	With OSA	P Value
Total cohort	n = 83	n = 147	
Sight-threatening diabetic retinopathy*	24.1% (20)	42.9% (63)	0.004
Advanced retinopathy	7.2% (6)	19.7% (29)	0.01
Retinopathy			
R0	45.8% (38)	31.3% (46)	0.03
R1	47% (39)	49% (72)	
R2	2.4% (2)	8.8% (13)	
R3	4.8% (4)	10.9% (16)	
Maculopathy	19.3% (16)	38.8% (57)	0.002
South Asians	n = 51	n = 53	
Sight-threatening diabetic retinopathy*	27.5% (14)	35.8% (19)	0.36
Advanced retinopathy	9.8% (5)	15.1% (8)	0.42
Retinopathy			
R0	39.2% (20)	26.4% (14)	0.52
R1	51.0% (26)	58.5% (31)	
R2	3.9% (2)	7.5% (4)	
R3	5.9% (3)	7.5% (4)	
Maculopathy	21.6% (11)	34% (18)	0.16
White Europeans	n = 32	n = 94	
Sight-threatening diabetic retinopathy*	18.8% (6)	46.8% (44)	0.005
Advanced retinopathy	3.1% (1)	22.3% (21)	0.01
Retinopathy			
R0	56.3% (18)	34.0% (32)	0.04
R1	40.6% (13)	43.6% (41)	
R2	0.0% (0)	9.6% (9)	
R3	3.1% (1)	12.8% (12)	
Maculopathy	15.6% (5)	41.5% (39)	0.01

Definition of abbreviation: OSA = obstructive sleep apnea.

Data are presented as percentage (count) of the respective OSA category.

*Preproliferative or proliferative retinopathy, maculopathy, or laser treatment.

frequently coexist and can be associated with a range of metabolic and physiological perturbations that have also been implicated in the pathogenesis of DR. Our study

demonstrates that OSA (even when mild) is independently associated with STDR, maculopathy, and advanced DR in patients with T2D. We have also shown that OSA is

an independent predictor of progression to R2 or R3 over approximately 4 years and that CPAP treatment might have a beneficial impact on DR progression.

The population in our report comprises subjects attending large inner-city hospital-based diabetes clinics in which the known duration of diabetes was approximately 10 years. Many of the subjects already exhibited established diabetes complications (e.g., albuminuria, as indicated in Table 2). The participant characteristics are similar to those reported previously in a different region of the United Kingdom (24), suggesting that the present study sample was representative of the wider T2D population in secondary care. However, whether our findings are applicable to patients typically managed in primary care and those with a shorter duration of diabetes remains to be examined. The high prevalence of OSA in our sample is consistent with that in other studies of subjects with T2D (6–9). The prevalence of STDR in our cohort (36.1%) is higher than that reported in the literature (5 to 15%) (1, 25), reflecting differences in the cohorts and DR risk factors in the various studies.

OSA+ patients differed from OSA– patients in regard to multiple demographic and metabolic factors. Nevertheless, the association between OSA and advanced DR remained independent, despite adjustment for these confounders. STDR and maculopathy were also associated with mild OSA. This suggests that the adverse impact

Table 4. Association between Obstructive Sleep Apnea and Sight-Threatening Diabetic Retinopathy, Maculopathy, and Advanced Diabetic Retinopathy (R2 or R3), Based on Baseline Cross-Sectional Analysis Using Logistic Regression Models (Forced Entry Method)

Model	Nagelkerke R^2 for the Model	OR	95% CI	P Value
Sight-threatening diabetic retinopathy*				
Unadjusted: OSA	0.05	2.3	1.3–4.3	0.005
Model 1	0.32	2.3	1.1–4.9	0.04
Maculopathy				
Unadjusted: OSA	0.05	2.6	1.4–5.0	0.003
Model 1	0.28	2.7	1.2–5.9	0.01
Advanced DR (R2 or R3)				
Unadjusted: OSA	0.05	3.1	1.3–8.0	0.02
Model 1	0.32	3.0	1.0–9.3	0.06

Definition of abbreviations: BMI = body mass index; CI = confidence interval; DR = diabetic retinopathy; OR = odds ratio; OSA = obstructive sleep apnea. The ORs reported are the odds for having the outcome of interest (sight-threatening diabetic retinopathy, maculopathy, or advanced DR, depending on the model) in patients with OSA compared with patients without OSA. Model 1 is adjusted for OSA, ethnicity, age at diabetes diagnosis, diabetes duration, sex, glycated hemoglobin, BMI, systolic blood pressure, insulin use, number of antihypertensive agents, oral antihyperglycemic agents, and estimated glomerular filtration rate. Replacing BMI with waist circumference or waist-to-hip ratio does not change the results significantly. Inserting BMI and waist circumference together into the model did not have an impact on the OR.

*Preproliferative or proliferative retinopathy, maculopathy, or laser treatment.

Table 5. Longitudinal Impact of Obstructive Sleep Apnea on Progression to Advanced Diabetic Retinopathy (R2 or R3) over the Follow-up Period

	OR	95% CI	P Value
OSA vs. no OSA	5.2	1.2–23.0	0.03
Mild OSA vs. no OSA	3.7	0.7–18.0	0.11
Moderate to severe OSA vs. no OSA	14.8	2.3–94.7	0.005
AHI tertile 2 vs. tertile 1	4.0	0.8–19.8	0.09
AHI tertile 3 vs. tertile 1	7.5	1.4–41.3	0.02
ODI tertile 2 vs. tertile 1	3.9	0.8–18.8	0.09
ODI tertile 3 vs. tertile 1	6.0	1.2–31.6	0.03

Definition of abbreviations: AHI = apnea–hypopnea index; CI = confidence interval; ODI = oxygen desaturation index; OR = odds ratio; OSA = obstructive sleep apnea.

The ORs reported are the odds for progressing to advanced diabetic retinopathy in patients with OSA compared with patients without OSA, in AHI tertiles 2 and 3 compared with AHI tertile 1, and in ODI tertiles 2 and 3 compared with ODI tertile 1. The model is adjusted for ethnicity, sex, diabetes duration, age at diabetes diagnosis, systolic blood pressure, glycated hemoglobin, estimated glomerular filtration rate, body mass index, oral antihyperglycemic agents, insulin use, and number of antihypertensive medications. OSA status (yes/no), OSA status (no, mild, moderate to severe), AHI tertiles, and ODI tertiles were inserted into the model separately. The AHI tertiles were less than 4.8 events per hour, 4.8–11.89 events per hour, and greater than or equal to 11.90 events per hour for tertiles 1, 2, and 3, respectively. The ODI tertiles were less than 4.1 events per hour, 4.1–11.39 events per hour, and greater than or equal to 11.40 events per hour for ODI tertiles 1, 2, and 3, respectively. The Nagelkerke R^2 value for all three models in this table was 0.42.

of OSA in patients with T2D occurs even in patients with mild degrees of OSA, and it is possible that the impact of mild OSA is magnified in tissue that is already predisposed to damage because of chronic hyperglycemia. This is further exacerbated by the increased retinal oxygen requirements during night adaptation; hence, even mild hypoxia can result in major adverse consequences to the retina (26). In addition, there was a dose–response relationship in the association between OSA and progression to advanced DR, because this association was statistically significant mainly in patients with moderate to severe OSA and in patients with the highest AHI and ODI tertiles, suggesting potentially that OSA exacerbated retinal ischemia, which is an integral part of the development of preproliferative and proliferative DR.

There are several mechanisms that can link OSA to maculopathy and preproliferative and proliferative DR. Retinal ischemia in diabetes results in the stimulation of hypoxia-inducible factors, which are transcriptional factors that are activated under hypoxic conditions, resulting in the expression of multiple gene products, including VEGF (27). Increased VEGF leads to the development of proliferative DR, and retinal ischemia is the main stimulant of VEGF secretion, resulting in proliferative retinopathy, and as

a result, anti-VEGF is currently used in clinical practice to treat DR (1, 4). The hypoxemia associated with OSA has been shown to be associated with increased VEGF, which was lowered by CPAP treatment (28). This is particularly important because the retina is especially prone to hypoxic damage during night hours (29), which is the same time that OSA-associated hypoxemia occurs. In addition, endothelial dysfunction plays an important role in the development of DR and maculopathy. We and others have previously shown that OSA (and its associated cyclical oxygen desaturations and disruptions in sleep architecture) can lead to the activation of poly(ADP-ribose) polymerase, protein kinase C, and the polyol pathway, as well as increased advanced glycation end product production, inflammation, and oxidative and nitrosative stress, all of which can lead to endothelial dysfunction and could have contributed to the observed associations between OSA and DR in our study (10, 30, 31).

In our study, the observed cross-sectional and longitudinal associations between OSA and DR were much stronger in white Europeans than in South Asians. There might be several plausible reasons for the observed racial differences. South Asians with T2D are known to be at an increased risk of DR and STDR compared with white

Europeans with T2D (32). Hence, there are factors other than OSA that result in increased risk of DR in South Asians compared with white Europeans, making the impact of OSA on DR in South Asians smaller and hence requiring a significantly larger sample size to detect. This is supported by our analysis showing that the direction of the relationship between OSA and STDR, advanced DR, and maculopathy cross-sectionally and longitudinally is similar between South Asians and white Europeans, but the magnitude is greater in white Europeans. Another important factor is that we have previously shown in this cohort that OSA is less common and less severe in South Asians than in white Europeans with T2D (33), which might also contribute to the weaker relationship between OSA and STDR, maculopathy, and advanced DR observed in this study in South Asians than in white Europeans.

Two previous studies have shown an association between OSA and DR, but there are important differences between these studies and ours. The previous studies were cross-sectional, and unlike in our study, longitudinal analysis was not performed. In addition, the previous studies included highly selected populations, such as Japanese patients who underwent vitreous surgery (34) or only white European men (35). Our study was more comprehensive and included patients regardless of their ethnicity, sex, or severity of retinopathy. Moreover, in prior reports, the diagnosis of DR was based on case records rather than retinal images, which we used in our study (34). OSA assessment also differed between the studies; one study used pulse oximetry to diagnose OSA (34), and the other used a complex, multistep approach based on questionnaires followed by pulse oximetry in a selected subgroup (35). We performed a more in-depth assessment using a multichannel device with all the study participants. Critically, the previous studies did not adjust for important possible confounders, such as blood pressure, BMI, and medication use, or they used suboptimal measures, such as self-reported BMI (34, 35). In contrast, our extensive data ascertainment allowed us to adjust for a wide range of possible confounders.

Although OSA has been associated with several other ocular pathologies in patients without diabetes (36–40), changes similar to DR have not been described in patients with OSA without diabetes,

suggesting that the presence of hyperglycemia is mainly responsible for the development of DR but that OSA might contribute to the progression of the disease. This is supported by our data showing that the higher prevalence of DR in patients with OSA than in those without OSA in our study was driven mainly by a higher prevalence of advanced DR but that the prevalence of background DR (or early DR) was similar in patients with and without OSA, suggesting that OSA contributes to the progression rather than the development of the disease. This is biologically plausible, particularly because the intermittent hypoxia associated with OSA can result in retinal ischemia and increased VEGF production, resulting in the development of advanced DR. The lack of an effect of OSA on maculopathy development longitudinally could be due to differences in the pathogenesis between maculopathy and preproliferative/proliferative DR or to the methods used to diagnose maculopathy in this study (i.e., images) rather than to the actual measurement of macular thickness using optical coherence tomography.

Assessment of the impact of CPAP treatment on DR and DR progression was

not the focus of this study. The available observational data, however, suggest that CPAP treatment compliance might have a favorable impact on DR progression, although these patients had worse AHI. The progression to maculopathy in the CPAP-compliant group was lower than that in the noncompliant group and similar to that of patients with mild OSA. However, it is difficult to assess CPAP efficacy on the basis of observational data, owing to the small numbers of patients who were compliant. Nonetheless, these data provide further justification for future research to assess the impact of CPAP on the development and progression of DR, and they highlight the challenges of CPAP compliance among patients with T2D.

Our study has several limitations. We used home-based portable multichannel respiratory devices rather than inpatient overnight polysomnography. However, this approach is well established (41, 42). Our sample population was also drawn from hospital-based diabetes centers; hence, we cannot necessarily extend our conclusions to other patient populations. We used two-field images rather than seven-field images to assess DR, which might have resulted in missing peripheral retinal

lesions. This is unlikely to affect the results unless patients with OSA are more likely develop more peripheral lesions than patients without OSA (or vice versa), but there is no evidence to support this. The limited number of events over the follow-up period did not allow us to perform more in-depth analysis of the relationship between OSA and DR progression.

In conclusion, we have identified a relationship between OSA and STDR and maculopathy in patients with T2D. OSA was also an independent predictor for the development of advanced DR. There was a dose-response relationship between OSA severity and the development of advanced DR. CPAP treatment compliance was associated with reduction in the development of advanced DR.

Interventional studies are needed to assess the impact of OSA treatment on the development of advanced DR. ■

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