Original Article

Screening for obstructive sleep apnea in a diabetic retinopathy clinic in a tertiary care center

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Purpose: To screen for obstructive sleep apnea (OSA) in patients presenting to diabetic retinopathy (DR) clinic and to correlate its presence with the severity of DR. **Methods**: A prospective, cross-sectional study of diabetes mellitus patients in retina clinic of a tertiary care referral center, North India (January 2019–March 2020). All were subjected to STOP-Bang Questionnaire and Epworth Sleepiness Scale (ESS) score. Patients at high OSA risk (STOP-Bang score ≥5 and ESS score ≥10) were referred to Department of Otorhinolaryngology (sleep clinic) for polysomnography. Based on Apnea Hypopnea Index (AHI), OSA was graded as mild (AHI = 5–14/h), moderate (AHI = 15–30/h), and severe (AHI >30/h). Statistical analysis was done using three models of outcome measures: (1) "No DR" versus "any DR," (2) "Less severe DR" versus "More severe DR," and (3) "No diabetic macular edema (DME)" versus "DME." **Results**: Of 362 patients screened, 18 (4.97%) had OSA (11 mild, 5 moderate, and 2 severe). Though OSA did not show a significant association with various outcome measures, patients with moderate–severe OSA had higher odds in developing "any DR" (OR = 7.408; 95% CI = 0.533–102.898), "more severe DR" (OR = 1.961; 95% CI = 0.153–25.215), and "DME" (OR = 2.263; 95% CI = 0.357–14.355), on multiple logistic regression. **Conclusion**: Ours is the first screening study of OSA in DR patients in India, the diabetes capital of the world. We detected OSA in 4.97% of patients in a DR clinic, with an increased risk of "any DR," "more severe DR," and "DME" in the presence of moderate–severe OSA.

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Obstructive sleep apnea (OSA) is very frequent in type II diabetes population, reaching a prevalence of 23–86%.[1-5] It increases the risk of diabetic retinopathy (DR), and is an independent risk factor for sight-threatening diabetic retinopathy and of progression to preproliferative/proliferative DR (PDR).[1,2] However, in ophthalmic care centers, OSA remains largely undiagnosed because of multiple factors (lack of awareness, inability to report symptoms, insufficient time in the clinics, etc.). It is important to diagnose OSA in patients with DR, which is often underestimated and overlooked in patients presenting to retina care practice for the treatment of DR.

The need for systematic OSA screening in all patients with type 2 diabetes has been emphasized by the International Diabetes Federation's guidelines.[3] While patients presenting with DR are routinely screened for metabolic risk factors (anemia, hypertension, hypergylcemia, proteinuria, hyperlipidemia, obesity, smoking, nephropathy, etc.), they are not screened for OSA. Several studies (majority from the West and only a single study of 80 patients from India) have linked OSA to DR.[4-7] With India being the diabetes capital of the world, with a DR prevalence of 21.7% among the nationwide population-based cross-sectional study of diabetic patients,[7] a larger study is needed to estimate the prevalence of OSA in DR in our population.

We believe that screening for OSA in patients seeking care for DR would give an estimate of the magnitude of this problem, which is an additional, independent risk factor for the development and worsening of DR. This would provide an early diagnosis and treatment of this coexisting comorbidity, and help better in the treatment of patients with DR. Additionally, if we find the prevalence of OSA significant in this cohort, screening for OSA may become an integral part of the baseline workup of diabetic patients attending retina clinic. Hence, we conducted a screening study for OSA in patients presenting in the DR clinic of our center.

Methods

This was a prospective, cross-sectional study of patients, presenting in the retina clinic of a tertiary care center

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in North India, between January 2019 and March 2020. Patients (>18 years) of type 1 or 2 DM with DR (mild, moderate, severe nonproliferative, and proliferative) or without DR were enrolled. Patients who were critically unwell, or who were unable to fill the questionnaire, or those not willing to undergo diagnostic sleep testing, or those with retinal vascular occlusions were excluded. The Institute Ethics Committee approval was obtained (No. 11861/PG-2Trg/2018/9909, dated 08.04.2019).

The information collected from patients included demographic details and systemic risk factors (comorbidities) along with: (a) metabolic parameters; (b) clinical characteristics of OSA (age, gender, Body-Mass Index or BMI, neck circumference, smoking and alcohol status, hypertension, coronary heart disease (CHD), etc.; and (c) information from the questionnaires for OSA screening.

The screening in retina clinic had a two-step approach:

Step 1: After obtaining an informed consent, the patients were asked to fill in a questionnaire that would categorize them into a low, intermediate, or high risk of having OSA. Of the five available screening questionnaires, STOP Questionnaire (Snoring, Tiredness, Observed Apnea, High Blood Pressure), STOP-Bang Questionnaire (STOP Questionnaire plus BMI, Age, Neck Circumference, and Gender), Epworth Sleepiness Score (ESS), Berlin questionnaire, and the Wisconsin Sleep Questionnaire, we used the following two questionnaires: STOP-Bang (which has the highest sensitivity for OSA screening and validated for use in OSA) and ESS (which has a well-established sleepiness score in OSA).[8]

Step 2: Patients at high risk of OSA (STOP-Bang score of 5 or more, and ESS score of 10 or more) were referred to the department of otorhinolaryngology (sleep clinic) for polysomnography (PSG), which is the gold standard test to diagnose OSA. An Apnea Hypopnea Index >5/h was considered positive for OSA, which was further graded as mild OSA (AHI = 5–14/h), moderate OSA (AHI = 15–30 per hour), and severe OSA (AHI >30 per hour).[9]

Statistical analysis: Statistical analysis was performed using IBM, SPSS Statistics version 26 (IBM Inc.). Data is expressed as mean and standard deviation (Mean ± SD). *P* value less than 0.05 was considered statistically significant. Continuous variables were compared using *t*-test. Wherever necessary, the student *t*-test was altered to compare variances that were unequal. The independent-sample *t*-test was used to determine if a difference existed between the means of two independent groups on a continuous dependent variable. Chi-square tests were used for proportions. Univariate analysis was done to determine whether there are any statistically significant differences between the means of two or more independent groups. Based on the classification of DR, three models of the outcome variable were used for statistical purposes. It was grouped into "no DR" or "any DR" (model 1), "less severe DR" [which included "no DR" and "mild nonproliferative DR (NPDR)"] and "More severe DR" (which included "moderate NPDR," "severe NPDR," and "PDR") (model 2), and "no DME" or "DME" (model 3). After adjusting for potential confounders like age, gender, duration of diabetes, glycosylated hemoglobin (HBA1c), anemia, CHD, hypertension, dyslipidemia (LDL/HDL ratio), history of smoking/alcoholism, and presence of OSA, multivariable logistic regression was used to determine the association of these variables with the outcome measures.

Results

Of 367 patients with DM (presenting in retina clinic) screened for OSA, 24 patients were detected to have an intermediate or high risk of having OSA (ESS score ≥10) and were advised PSG. Of these, one patient declined sleep study and four were lost to follow-up. The rest 19 patients completed the sleep study, of which one was negative for OSA and 18 (4.97%) were found to have OSA.

Clinical and demographical profile

The mean age of study participants was 55.7 ± 10 (range 23–86) years. Three hundred and fifty-one (97%) patients had type 2 DM and 11 (3%) had type 1 DM. There were 234 (64.6%) males with a male to female ratio of 1.82:1. Fourteen (3.9%) patients had no DR, 15 (4.1%) had mild, 63 (17.4%) moderate, 25 (6.9%) severe NPDR, and 245 (67.7%) had PDR. Of these, 306 (84.5%) patients had DME. The mean duration of DM was 12.7 ± 6.7 (median 12) years. Three hundred and fifty-three (97.5%) patients were on oral hypoglycemic drugs and 62 (17.1%) were on insulin therapy.

Table 1 shows the patient demographics, comorbidities, biochemical profile, and OSA parameters across various outcome measures of DR.

"No DR" versus "any DR"

A longer duration of DM (*P*=0.005), high glycosylated hemoglobin or HbA1C (*P* = 0.011), and proteinuria (24 h) (*P* = 0.000) were significantly associated with the presence of "any DR" on univariate analysis. Age, gender, anemia, hypertension, CHD, lipidemic status (LDL/HDL ratio), smoking, and alcoholism were not significantly associated.

"Less severe DR" versus "More severe DR"

The presence of "more severe DR" on univariate analysis was significantly associated with a long duration of DM (*P* = 0.000), anemia (*P* = 0.013), and 24-h proteinuria (*P* = 0.000). Age, gender, glycosylated hemoglobin, hypertension, CHD, lipidemic status (LDL/HDL ratio), smoking, and alcoholism were not significantly associated with the severity of DR [Table 1].

"No DME" versus "DME present"

Diabetic macular edema was significantly associated with a long duration of DM (*P* = 0.000), anemia (*P* = 0.003), and 24-h proteinuria (*P* = 0.008). The presence of DME was not significantly associated with age, gender, glycosylated hemoglobin, hypertension, CHD, lipidemic status (LDL/HDL ratio), smoking, and alcoholism [Table 1].

OSA assessment

On STOP-Bang screening, 178 (49.2%) patients were found to have low risk (score 1–2), 170 (48%) had moderate risk (score 3–4), and 14 (3.9%) had high risk (score 5 or more) of developing OSA. On ESS, 344 (95%) had mild risk (score 1–9), 16 (4.4%) had moderate risk (score 10–12), and 2 (0.6%) had severe risk (score 13–24) of developing OSA.

On PSG, 11 (3%) patients had mild sleep apnea, 5 (1.4%) had moderate, and 2 (0.6%) had severe sleep apnea based on AHI. Table 2 summarizes the patients' demographics, clinical characteristics, and biochemical profile in relation to OSA.

Table 1: Association of patient variables (demographics, clinical, biochemical tests, and OSA) with outcome measures as "no DR" versus "any DR," Less severe DR" versus "More severe DR," and "no DME" versus "DME"

Variables	Outcome measures		*P*	Outcome measures		*P*	Outcome measures		*P*
	No DR (*n*=14)	Presence of any DR (*n*=348)		Less severe DR (*n*=29)	More severe DR (*n*=333)		No DME (*n*=56)	DME (*n*=306)	
Age (years)									
Mean+S. D.	60.3+11.23	55.7+9.8	0.153*	57.5+9.9	55.7+9.9	0.352*	55.7+10.9	55.87+9.7	0.914*
Range	45-77	23-86		42-77	23-86		23-77	23-86	
Gender									
Males (*n*=234)	8 (57.1%)	226 (64.9%)	0.576***	14 (48.3%)	220 (66.1%)	0.055**	35 (62.5%)	199 (65%)	0.715**
Females (*n*=128)	6 (42.9%)	122 (35.1%)		15 (51.7%)	113 (33.9%)		21 (37.5%)	107 (35%)	
Duration of diabetes (years)									
Mean+S. D.	6.6±6.9	12.84±6.6	0.005*	6.94±5.5	13.1±6.6	0.000*	9.3+5.9	13.2+6.7	0.000*
Median	3	12		5	12		10	12	
HbA1C (%)									
Mean+S. D.	7.5±1.2	8.5±1.9	0.011*	8.6±2.5	8.5±1.9	0.797*	8.7±2.2	8.4±1.9	0.359*
Median	7.6	8.1		7.8	8.1		8.3	8	
Anemia (*n*=249)	9 (64.3%)	240 (69%)	0.771***	14 (48.3%)	235 (70.6%)	0.013**	29 (51.8%)	220 (71.9%)	0.003**
Hypertension (*n*=232)	10 (71.4%)	222 (63.8%)	0.559**	16 (55.2%)	216 (64.9%)	0.297**	36 (64.3%)	196 (64.1%)	0.973**
Coronary heart disease (*n*=32)	2 (14.3%)	30 (8.6%)	0.356***	3 (10.3%)	29 (8.7%)	0.732***	4 (7.1%)	28 (9.2%)	0.800***
LDL/HDL ratio									
Mean±S. D.	2.01±0.94	2.3±1.02	0.240*	2.03±0.82	2.3±1.03	0.057*	2.15±0.9	2.34±1.04	0.135*
Median	1.99	2.26		2.05	2.3		2.02	2.3	
Smoking (*n*=15)	0	15	1.000***	1 (3.4%)	14 (4.2%)	1.000***	4 (7.1%)	11 (3.6%)	0.264***
Alcoholism (*n*=31)	1 (7.1%)	30 (8.6%)	1.000***	1 (3.4%)	30 (9%)	0.493***	5 (8.9%)	26 (8.5%)	1.000***
Proteinuria (24-h) (mg/day)			0.000*			0.000*			
Mean±S. D.	258.3±332.1	1044.9±3725.1		243.85±286.8	1081.6±3803.9		447.65±848.6	1118.2±3952.2	0.008*
Median	161.48	239		130	248		169.5	251	
Any OSA (*n*=18)	1 (7.1%)	17 (4.9%)	0.517***	1 (3.4%)	17 (5.1%)	1.000***	2 (3.6%)	16 (5.2%)	1.000***
Moderate-severe OSA (*n*=7)	1 (7.1%)	6 (1.7%)	0.243***	1 (3.4%)	6 (1.8%)	0.445***	2 (3.6%)	5 (1.6%)	0.296***

DR=diabetic retinopathy; SD=standard deviation; LDL=low-density lipoproteins; HDL=high-density lipoproteins; and OSA=obstructive sleep apnea. *Independent samples *t*-test; **Chi-square test; and ***Fisher's exact test

Table 2: Association of patient variables (demographics, clinical, and biochemical tests) with obstructive sleep apnea

Variables	OSA present (*n*=18)	No OSA (*n*=344)	*P*
Age (years)			
Mean±S. D.	55.83±9.7	55.84±9.9	0.998*
Range	28-69	23-86	
Gender			
Males (*n*=234)	15 (83.3%)	219 (63.7%)	0.089**
Females (*n*=128)	3 (16.7%)	125 (36.3%)	
Duration of diabetes (years)			
Mean±S. D.	11.56±4.5	12.65±6.9	0.344*
Median	10	12	
HbA1C (%)			
Mean±S. D.	8.5±1.7	8.5±1.9	0.969*
Median	8.1	8	
Anemia (*n*=249)	12 (66.7%)	237 (68.9%)	0.842**
Hypertension (*n*=232)	13 (72.2%)	219 (63.7%)	0.461**
Coronary heart disease (*n*=32)	1 (5.6%)	31 (9%)	1.000***
LDL/HDL ratio			
Mean±S. D.	2.13±0.97	2.32±1.02	0.405*
Median	1.85	2.26	
Smoking (*n*=15)	1 (5.6%)	14 (4.1%)	0.542***
Alcoholism (*n*=31)	1 (5.6%)	30 (8.7%)	1.000***
Proteinuria (24-h) (mg/day)			
Mean±S. D.	1296.7±1985.9	999.7±3723.8	0.565*
Median	465	220.8	

DR=diabetic retinopathy; SD=standard deviation; LDL=low-density lipoproteins; HDL=high-density lipoproteins; and OSA=obstructive sleep apnea. *Independent samples *t*-test; **Chi-square test; and ***Fisher's exact test

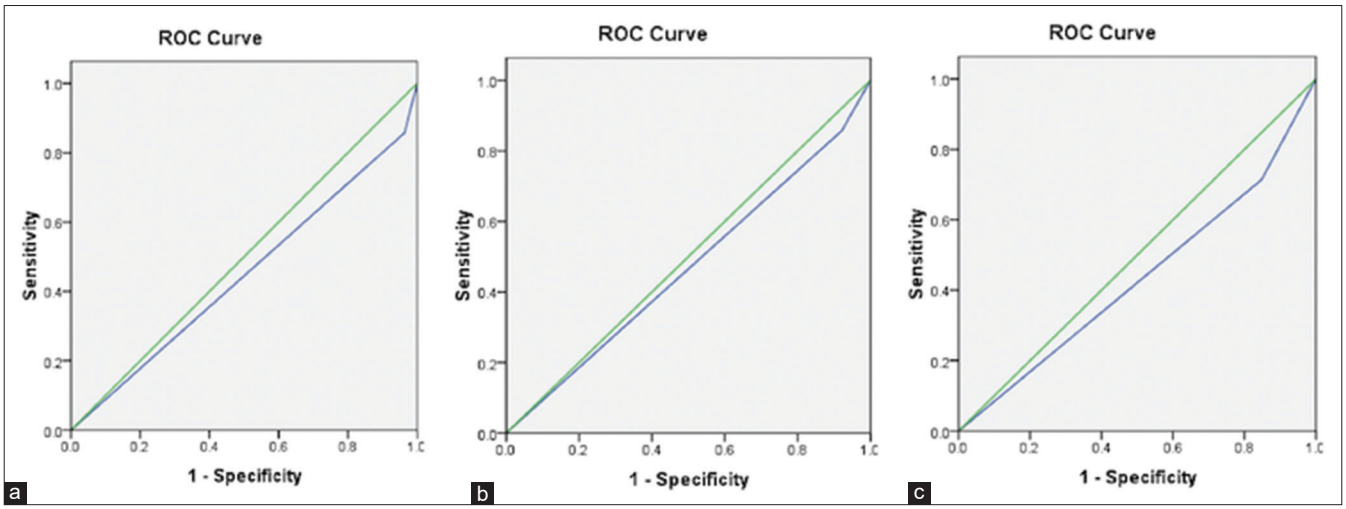

Figure 1: (a) Receiver operating characteristic (ROC) curve for prediction of "any DR" based on the presence of moderate–severe OSA, showing area under the curve (AUC) as 0.447. (b) Receiver operating characteristic (ROC) curve for prediction of "more severe DR" based on the presence of moderate–severe OSA, showing area under the curve (AUC) as 0.468. (c) Receiver operating characteristic (ROC) curve for prediction of the presence of "DME," showing area under the curve (AUC) as 0.433

Table 3 shows the multivariate odds ratio of various parameters by logistic regression analysis associated with outcome measures of "any DR," "More severe DR," and "presence of DME.

DR and OSA association

We did not find significant association of OSA (any grade) with the presence of "any DR" (*P* = 0.517), "more severe DR" (*P* = 1.000) or "DME" (*P* = 1.000) [Table 1]. The odds ratio of OSA (any grade) for determining "any DR" was 2.630 (95% CI = 0.253–27.286), for "more severe DR" was 0.784 (95% CI = 0.085–7.259), and for "DME" was 0.606 (95% CI = 0.125–2.929).

As more than half (11 out of 18) OSA patients had "mild" type of OSA, a separate analysis of "moderate-severe OSA" was done to avoid the potential bias, which also showed no significant association with presence of "any DR" (*P* = 0.243), "more severe

Table 3: Multivariate odds ratios by logistic regression analysis for various parameters associated with outcome measures of "any DR," "More severe DR," and "presence of DME"

Variables	Wald	*P*	Odds Ratio	95% Confidence interval
Presence of any DR				
Age	4.222	0.040	0.922	0.853-0.996
Gender	1.015	0.314	0.517	0.143-1.865
Duration of diabetes	10.787	0.001	1.255	1.096-1.437
HbA1C	1.637	0.201	1.289	0.874-1.903
Anemia	0.000	0.994	0.995	0.270-3.668
Hypertension	1.274	0.259	2.241	0.552-9.099
Coronary heart disease	0.082	0.774	1.320	0.198-8.807
Ratio of LDL/HDL	0.208	0.648	1.172	0.593-2.317
Proteinuria (24-h)	1.353	0.245	1.001	0.999-1.002
Smoking	0.000	0.999	0.000	0.000-
Alcoholism	0.089	0.766	1.445	0.128-16.297
OSA (moderate-severe)	2.225	0.136	7.408	0.533-102.898
Constant	0.000	0.999	4.620E7	
More severe DR				
Age	1.927	0.165	0.965	0.917-1.015
Gender	5.136	0.023	0.334	0.129-0.862
Duration of diabetes	21.130	0.000	1.237	1.130-1.354
HbA1C	0.074	0.785	1.032	0.825-1.291
Anemia	5.608	0.018	0.331	0.132-0.826
Hypertension	0.258	0.611	0.794	0.327-1.931
Coronary heart disease	0.123	0.726	1.295	0.305-5.501
Ratio of LDL/HDL	2.349	0.125	1.505	0.892-2.538
Proteinuria (24-h)	2.219	0.136	1.001	1.000-1.003
Smoking	0.427	0.513	2.252	0.197-25.695
Alcoholism	0.477	0.490	0.442	0.044-4.485
OSA (moderate-severe)	0.267	0.605	1.961	0.153-25.215
Constant	0.115	0.735	2.585	
Presence of diabetic macular edema (DME)				
Age	0.273	0.601	0.991	0.959-1.024
Gender	0.436	0.509	0.799	0.410-1.557
Duration of diabetes	15.212	0.000	1.112	1.054-1.173
HbA1C	0.106	0.744	0.975	0.835-1.137
Anemia	6.531	0.011	0.437	0.232-0.825
Hypertension	0.194	0.660	1.154	0.611-2.178
Coronary heart disease	0.464	0.496	0.671	0.213-2.112
Ratio of LDL/HDL	1.638	0.201	1.254	0.887-1.774
Proteinuria (24-hour)	2.563	0.109	1.000	1.000-1.001
Smoking	1.321	0.250	2.348	0.548-10.066
Alcoholism	0.013	0.908	0.930	0.272-3.185
OSA (moderate-severe)	0.750	0.386	2.263	0.357-14.355
Constant	0.027	0.870	0.740	

DR=diabetic retinopathy; LDL=low-density lipoproteins; HDL=high-density lipoproteins; and OSA=obstructive sleep apnea

DR" (*P* = 0.445), or "DME" (*P* = 0.296) [Table 1]. However, on multiple logistic regression [Table 3], after adjusting for confounders like age, gender, duration of diabetes, and various comorbidities, patients with "moderate–severe OSA" had higher odds in developing "any DR" (OR = 7.408; 95% CI = 0.533–102.898), "more severe DR" (OR = 1.961; 95% CI = 0.153–25.215), and "DME" (OR = 2.263; 95% CI = 0.357–14.355).

Fig. 1 shows the receiver operating characteristic curve, based on the presence of moderate–severe OSA, showing area

Table 4: Summary of studies with insignificant and significant association between DR and OSA

Author	Year	Sample size	Setting/Type	Association between DR and OSA	Main findings
Present Study	2020	351 T2DM 11 T1DM	Hospital-based cross-sectional, prospective study	insignificant	No significant association with outcome measures, but higher odds of moderate-severe OSA in developing "any DR" (OR=7.408), "more severe DR" (OR=1.961), and "DME" (OR=2.263)
Chang *et al*.[2]	2018	254 DR	Retrospective	significant	Association between DR and severe OSA (OR=2.18, *P*=0.019). Also, severe OSA and PDR (OR=2.20, *P*=0.043), and severe OSA and DME (OR=2.89, *P*=0.001)
Zhang *et al*.[26]	2016	233 T2DM	Hospital-based cross-sectional study	insignificant	Diabetic nephropathy and cardiovascular disease history were correlated significantly with OSA on univariate analysis, while all others, including DR and diabetic peripheral neuropathy, were not statistically significant in both univariate and multivariate analyses
Storgaard *et al*.[14]	2014	180T2DM	Cross-sectional study (diabetes center)	OSA and DM	Age, BMI, and HDL cholesterol levels were all significant, independent predictors of OSA The groups were not different with respect to sex, age, diabetes duration, blood pressure, diabetic complications, or medication use
Mason *et al*.[13]	2012	80 DME	Hospital-based study	significant	Individuals with CSME had a high prevalence of sleep disordered breathing
Schober *et al*.[11]	2011	498 T2DM 58 T1DM	Hospital-based prospective study.	OSA and DM	A higher prevalence for neuropathy, nephropathy, hypertension, cardiovascular disease, and heart failure in the group with an AHI ≥ 15/h
Chew *et al*.[17]	2020	92 T2DM	Hospital-based cross-sectional study	significant	Short sleep duration was associated with moderate DR while OSA-related parameters and a high risk for insomnia were associated with moderate DR, VTDR, and DME
Vié *et al*.[27]	2019	99 T2DM	Case control study	significant	Patients with DME had more severe OSA (AHI>30) than the others: 71% versus 50.8% (*P*=0.049)
Embarak *et al*.[18]	2019	110 T2DM	Cross-sectional observational study	significant	OSA was independently associated with advanced DR (OR=6.29, *P*=0.04) and maculopathy (OR=12.92, *P*<0.001) in T2DM patients Moreover, severity of OSA was directly related to DR grade
Sijapati *et al*.[19]	2019	150 T2DM	Hospital-based observational study	significant	OSA was associated with DR (OR=1.20) and DM (OR=2.05)
Baba *et al*.[24]	2016	60T2DM	Hospital-based study	significant	Patients with OSA had a higher prevalence of DR (55%) and DME (20%) compared to non-OSA group
Manin *et al*.[28]	2015	67T1DM	cross-sectional study	significant	Difference in presence of DR between patients with OSA (84%) and non-OSA (42%). No difference in presence of DME between patients with OSA (23%) and non-OSA (8%)
Nishimura *et al*.[29]	2015	136 T2DM	Hospital-based study	significant	SO2 (OR=0.89), HbA1c (OR=1.40; *P*=0.021), duration of diabetes (OR=1.23), and CVD (OR=8.96) were associated with OSA
Rudrappa *et al*.[22]	2012	31T2DM	Hospital-based study	significant	OSA associated with development and progression of DR, but independent of conventional risk factors
Shiba *et al*.[25]	2010	219 T2DM	Hospital-based study	significant	Association between PDR and OSA (OR: 1.09). Association between PDR and minimum SpO_2 (OR: 0.93)
West *et al*.[21]	2010	118T2DM	Primary care centers and outpatient	significant	Association between retinopathy scores and OSA (R^2=0.19). Association between DME and OSA (R^2=0.30)
Laaban *et al*.[12]	2009	303 T2DM	Retina clinic in hospital	significant	Significant association between OSA and DR (OR=143). Significant association between OSA and DME (OR=14.4)

T2DM (Type 2 diabetes mellitus), OSA (obstructive sleep apnoea), DME (diabetic macular edema), OR (odds ratio), and AHI (apnoea hypopnea index).
T2DM (Type 2 diabetes mellitus), OSA (obstruct ive sleep apnoea), DME (diabetic macular edema), OR (odds ratio), and AHI (apnoea hypopnea index)

under the curve (AUC) as 0.447 for prediction of "any DR," AUC as 0.468 for prediction of "more severe DR," and AUC as 0.433 for prediction of the presence of "DME."

Discussion

We detected OSA in 4.97% of patients seeking care for DR in the retina clinic. Several studies have shown an association between OSA and DR in patients with type 2 DM. However, a meta-analysis (reported in 2015) conducted to examine this association did not find convincing evidence of the association between the two.[5] This meta-analysis included 16 studies (majority of patients were type 2 DM and were from Europe) in the systematic review. Of these, only eight studies reported the effect of OSA on DR.[6,10-16] While six out of these eight reported no significant association between OSA and DR, two small studies from the United States found a significant association between OSA and DR. However, these two studies were unadjusted models for potential confounders (gender, BMI, etc.).

Another meta-analysis was done in 2017 to obtain a definitive conclusion on the controversial relationship between OSA and DR.[4] The pooled results from six eligible studies showed a significant association between OSA and an increased risk of DR, both in type 1 and 2 DM.

Of 92 participants with DM screened in Singapore, 60 (65.2%) had OSA, of which 39 (61.9%) had moderate DR.[17] The authors found associations of moderate OSA and short sleep duration, with moderate DR and vision-threatening DR. However, in a study from Egypt, OSA severity correlated with DR severity, and OSA was found to be independently associated with preproliferative and PDR and also with maculopathy.[18] Of 150 type 2 DM patients screened in Nepal (with PSG), the odds ratio of association of OSA with DR was 1.20 (95% CI: 0.67–5.89).[19] A Japanese study found chronic hypoxemia to be associated with worse PDR.[20]

We did not find any independent association of OSA (including moderate–severe OSA) with the presence or severity of DR or DME. Banerjee *et al*.[10] also found no significant association between OSA and DR. Two studies (West *et al*.[21] and Rudrappa *et al*.[22]) reported that OSA was significantly related to total DR scores. Patients with OSA, as compared to those without OSA, were reported to be more likely to progress to advanced DR.[23] Leong *et al*.[5] found some evidence of the association between OSA and advanced DR. In the first prospective, longitudinal study on the impact of OSA on DR, Altaf *et al*.[1] reported OSA to be independently associated with diabetic maculopathy and sight-threatening DR, and with development of advanced (preproliferative and proliferative) DR over a 4-year follow-up period. They reported a much stronger association between OSA and DR in white Europeans than in South Asians, probably due to many other factors increasing the risk of DR in South Asians than in white Europeans, hence, making the impact of OSA lesser on DR in the South Asians. Also, the lesser incidence and severity of OSA (as also seen in our study) in the South Asians may contribute to the weaker association between OSA and sight-threatening DR in this population as compared to white Europeans. Therefore, the authors emphasized the need for a larger sample size in our population.

Chang *et al*.[2] found that DME and severe OSA were associated. Also, there was 2–3-fold increase in the likelihood of PDR in severe OSA patients, versus all NPDR, and severe OSA predisposed the diabetic patients to an increased risk of DR, PDR, and DME. Six more studies tested the association between OSA and severity of DR. An increased prevalence of NPDR and PDR was found in patients with OSA as compared to those without OSA.[24] While Zhang *et al.* did not find a significant association, Shiba *et al.* found a significant association between OSA and DR after adjustment.[25,26]

In our study, the presence of "moderate–severe OSA" had higher odds in predicting "any DR" (OR = 7.41), "more severe DR" (OR = 1.96), and presence of "DME" (OR = 2.26). However, the presence of OSA (any grade) could predict the presence of "any DR" (OR = 2.63; 95% CI = 0.253–27.286), but not "more severe DR" (OR = 0.784; 95% CI = 0.085–7.259), or "DME" (OR = 0.606; 95% CI = 0.125–2.929).

Seven studies (five cross-sectional and two cohorts) examined the relationship between DME and OSA, with positive findings (West *et al.*)[21] or negative findings (Banerjee *et al*.[10] and Rudrappa *et al*.[22]). One cohort study found a significant association between OSA and DME (about 4- to 5-fold increase in the risk of DME in patients of OSA).[23] Chang *et al*.[2] found almost a 3-fold increase in the risk of DME in the presence of severe OSA. Hence, there is some evidence that OSA and DME may be associated, but their relationship still remains unclear.

The results of our study suggest that 14 (3.9%) patients with DR had a high risk of OSA and 170 (48%) had a moderate risk of developing OSA as per the STOP-Bang score. As per ESS, 16 (4.4%) had a moderate risk and 2 (0.6%) had a severe risk of developing OSA.

In our cohort, BMI was significantly ($P < 0.05$) higher in patients with OSA as compared to those without OSA (27.7 ± 5.6 versus 25.1 ± 3.7 kg/m^2). There is a bidirectional link between obesity, OSA, and type 2 DM, with OSA being associated with diabetes and obesity, leading to metabolic and cardiovascular complications. Banerjee *et al*.[10] investigated the potential relationship of OSA and DR among patients with severe obesity. The BMI did not differ significantly between patients with and without OSA ($P = 0.776$).

The relationship between OSA and the severity of DR has shown conflicting results. Table 4 compares various studies showing the association between OSA and DR to be insignificant[2,6,11,13,14,26] or significant.[12,17-19,21,22,24,25,27-29] This discordance of findings between studies could possibly stem from confounding factors like age, gender, obesity (BMI), duration of diabetes, level of glycaemic control (HBA1c), dyslipidemia, and presence of comorbidities. It is of utmost importance to take these factors into consideration when estimating the risk and effect size. Among these studies, only four adjusted for potential confounders; three studies found no association and one found a very strong association. In our cohort, we estimated the risk and effect size after adjusting for potential confounders and found no association between absence or presence of retinopathy. Second, several other PSG parameters need to be evaluated like mean event time, arousal index, sleep efficiency, arousal index, mean event time, and periodic limb movement index. Most studies were inconsistent with respect to these parameters and did not

evaluate whether secondary sleep measures have a role in the relationship between OSA and DR or not. Finally, some studies (Chang *et al*.,[2] Shiba *et al*.,[20] and Rudrappa *et al*.[22]) found an association between DR and markers of hypoxemia during sleep (ODI and SpO2), giving rise to the speculation that the possible relationship between OSA and DR or DME is induced by hypoxemia resulting in ischemic damage to the retina and retinal neovascularization. The conflicting findings warrant further study of ODI and its relationship to DR or DME.

Study limitations

Although our study provides a comprehensive analysis of how OSA may relate to DR, our study also has several limitations. The limitations of this study include its cross-sectional observational nature, albeit prospective; therefore, the impact of reversing retinopathy by treatment of OSA cannot be evaluated. Second, the allocation was not randomized leading to potential selection bias. Third, this study was conducted in the retina clinic. So, diabetic patients without DR coming to the retina clinic comprised of referrals from other clinics (in ophthalmology or other disciplines like endocrinology). Hence, this population does not represent the true sample population of patients with diabetes in the community. Also, more than half (11 out of 18) OSA patients had a "mild" type of OSA. This could potentially influence the results. However, this issue was addressed by considering the subgroup of "moderate–severe OSA." Finally, this study was single-centered; thus, validation in other population cohorts in the region is required. Additional PSG parameters (respiratory sleep measurements) were not evaluated, which could have further strengthened the association.

Strengths of the study

Our study is the first of its kind in two aspects. First, with our country being the diabetes capital of the world, there is no study reporting the screening of OSA in DR patients in India. Though a recent study from India reported a positive association between sleep disturbance and DR,[30] it did not screen for OSA in DR. However, second, while the majority of the studies have shown the prevalence of OSA in a population of DM, and not DR, its prevalence in DR population remains unclear. Although it is a single-center study, our hospital caters to patients from at least five states of India. Hence, it reflects a wide range of patient populations presenting to the retina clinic.

Conclusion

In conclusion, we detected OSA in 4.97% of patients in a DR clinic, with an increased risk of "any DR," "more severe DR," and "DME" in the presence of moderate–severe OSA. The STOP Bang and ESS questionnaires are known to provide an easy, reliable, and a quick screening method for OSA. In a busy DR clinic, PSG can be limited to only those patients with intermediate or low risk (based on scoring) of OSA. Though the prevalence of OSA in our DR patients is low (4.97%), their identification is important as we detected the risk of "any DR," "more severe DR," and "DME" with moderate–severe OSA. These findings indicate that patients with both DM and moderate–severe OSA should be identified as higher-risk patients in the clinical setup. Further longitudinal studies should be conducted to explore how severe OSA, in particular, may be related to the development and progression of PDR and DME. Also, it would be interesting to compare these findings with the OSA percentage in nondiabetic individuals.

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Conflicts of interest

There are no conflicts of interest.

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