The Veterans Affairs Continuous Positive Airway Pressure Use and Diabetic Retinopathy Study

James Patrick Smith, OD, MS, FAAO,^{1*} Luke G. Cyr, OD, FAAO,¹ Laura K. Dowd, OD, FAAO,¹ Kyla S. Duchin, OD, MS, FAAO,¹ Priscilla A. Lenihan, OD, FAAO,¹ and Jennifer Sprague, OD, FAAO¹

SIGNIFICANCE: Obstructive sleep apnea has been linked to the development and progression of diabetic retinopathy. In this study, diabetic patients compliant with continuous positive airway pressure therapy (CPAP) for sleep apnea were less likely to have retinopathy, emphasizing the benefits and potential therapeutic role of CPAP in individuals with both conditions.

PURPOSE: The aim of this study was to compare the prevalence of diabetic retinopathy in type 2 diabetic patients with obstructive sleep apnea who were compliant with CPAP therapy with those who were not compliant with CPAP therapy.

METHODS: A retrospective cross-sectional review of type 2 diabetic patients using CPAP for obstructive sleep apnea was conducted. The prevalence of retinopathy was identified, and groups with and without retinopathy were compared using univariate analyses and multivariate logistic regression.

RESULTS: The prevalence of retinopathy was 19.6% (n = 321). Retinopathy was significantly less prevalent in those compliant with CPAP (odds ratio, 0.54; 95% confidence interval, 0.31 to 0.94; $P = .04$). The relationship remained statistically significant when adjusting for other factors known to impact the course of diabetic eye disease.

CONCLUSIONS: Increased CPAP compliance may mitigate the risk of developing diabetic retinopathy in type 2 diabetic patients with obstructive sleep apnea.

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Author Affiliations:

¹VA Maine Health Care System, Augusta, Maine
*enuckcha@yahoo.com

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Diabetic retinopathy is the most common microvascular complication of diabetes mellitus and the leading cause of vision loss and blindness in working-aged American adults.¹ Obstructive sleep apnea affects between 4 and 24% of the general U.S. population.^{2,3} It is associated with numerous comorbidities including cardiovascular disease, atherosclerosis, stroke, peripheral vascular disease, hypertension, and diabetes.^{4–6}

Untreated obstructive sleep apnea is a risk factor for the development and progression of diabetic retinopathy.^{7–9} It has been linked to increased hyperglycemia and insulin resistance.^{10,11} Nocturnal hypoxemia in obstructive sleep apnea also leads to oxidative stress, increased inflammation, and endothelial dysfunction.^{12–16} Body mass index, hemoglobin A_{1c}, hypertension, glomerular filtration rate, and insulin use have been identified as risk factors for diabetic retinopathy development and progression in the setting of untreated obstructive sleep apnea.^{17–20}

Continuous positive airway pressure is the first-line therapeutic intervention for moderate to severe obstructive sleep apnea.²¹ Continuous positive airway pressure use can eliminate nocturnal hypoxemia, reduce hypertension, and improve microvascular endothelial function and sympathetic autonomic regulation.^{15,22} However, compliance is a significant barrier in continuous positive airway pressure therapy, with nonadherence rates reportedly as high as 83%.²³

The association between obstructive sleep apnea and diabetes mellitus has led to the belief that continuous positive airway pressure may mitigate the risks of diabetic retinopathy. To date, there have been few studies that explore the relationship. The aim of this

study was to compare the prevalence of diabetic retinopathy in type 2 diabetic patients with obstructive sleep apnea who were compliant with continuous positive airway pressure therapy with those who were not compliant with continuous positive airway pressure therapy. Several factors that influence obstructive sleep apnea and diabetes mellitus including age, body mass index, duration of disease, hemoglobin A_{1c}, hypertension, and insulin use were considered.

METHODS

This study was a retrospective cross-sectional review of all type 2 diabetic patients being treated for obstructive sleep apnea who visited the Pulmonary and Eye Clinics at VA Maine between 2011 and 2016. Eligible subjects were seen in the respective clinics to monitor for continuous positive airway pressure compliance and diabetic retinopathy within a 12-month period. In the event multiple visits occurred during the study time frame, the most recent set of visits was used for data collection. This study was approved by the Veterans Institutional Review Board of Northern New England, a research consortium comprising VA Medical Centers from Togus (Augusta), ME; Manchester, NH; and White River Junction, VT.

Average continuous positive airway pressure wear time, percent nights worn, and treated apnea-hypopnea index was obtained from continuous positive airway pressure smart card data of diabetic subjects who visited the Pulmonary Clinic. The baseline apnea-hypopnea index was obtained by diagnostic polysomnography performed before

initiation of continuous positive airway pressure use. Successful continuous positive airway pressure compliance was defined in accordance with Centers for Medicare & Medicaid Services guidelines as an average use of at least 4 hours on at least 70% of nights.²⁴

The presence and degree of diabetic retinopathy were assessed through dilated funduscopy evaluation or nonmydriatic teleretinal image screening. For teleretinal image screening, three fundus photographs of each eye were obtained and reviewed using a validated pathway for detecting diabetic retinopathy.^{25,26} Cases of possible diabetic macular edema were subsequently seen for live examination by an eye care provider. When both eyes from a subject met the inclusion criteria, the eye with the most advanced level of retinopathy was used. Retinopathy was assigned to one of five categories based on the Early Treatment for Diabetic Retinopathy Study grading scale. The presence or absence of diabetic macular edema was also recorded.

Additional information collected was sex, age, body mass index, hemoglobin A_{1c}, duration of diabetes mellitus, duration of obstructive sleep apnea, insulin use, hypertension, hypercholesterolemia, current smoking status, and glomerular filtration rate. The findings obtained closest in time to either of the visits to the pulmonary and eye clinics were used. Hypertension was defined as either systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of antihypertensive medication. Hypercholesterolemia was defined as serum cholesterol >240 mg/dL or use of cholesterol-lowering medication.

Exclusion criteria were as follows: primary central sleep apnea, complex sleep apnea with history of adaptive servoventilation use, congestive heart failure, chronic obstructive pulmonary disease, anticoagulant use other than aspirin, and/or history of retinopathy or macular edema not due to diabetes.

Statistical Analysis

All statistical analyses were performed using Minitab 17 (Minitab, LLC, State College, PA). Descriptive statistics including mean and standard deviation for normally distributed variables, and median, first quartile, and third quartile values for nonnormally distributed variables were calculated for all quantitative data. The *z* test for proportions was conducted to test the difference in diabetic retinopathy prevalence between compliant and noncompliant continuous positive airway pressure therapy groups. Differences between diabetic retinopathy and no diabetic retinopathy groups were determined using χ^2 tests for categorical data, Student *t* tests for normally distributed continuous data, and Mann-Whitney *U* tests for nonparametric results. Multivariate logistic regression was then performed using all variables with a *P* value of less than .10 in the univariate analysis to assess for factors independently associated with diabetic retinopathy. Average continuous positive airway pressure wear time and percent nights worn were omitted from the logistic regression to avoid the possibility of collinearity with continuous positive airway pressure compliance. Level of significance was set to *P* = .05 for all statistical analyses. The prevalence of diabetic retinopathy in the United States among diabetic patients 40 years or older has been reported to be 28.5%; using 40% as a significant difference in the relative prevalence of diabetic retinopathy between the compliant and noncompliant continuous positive airway pressure therapy groups, the minimal group size to achieve a power of 0.8 was calculated to be 208 (level of significance, 0.05).²⁷

RESULTS

A total of 1771 patient charts were reviewed, with 321 meeting the inclusion criteria. Of these, 63 (19.6%) had diabetic

retinopathy (retinopathy group), and 258 (80.4%) did not have retinopathy (no retinopathy group). In the retinopathy group, 51 had mild nonproliferative disease, 7 had moderate nonproliferative disease, 2 had severe nonproliferative disease, and 3 had proliferative diabetic retinopathy. A total of nine patients had diabetic macular edema. Because of the low prevalence of more advanced stages of disease, retinopathy was grouped together for data analysis, and analysis based on disease severity was not attempted.

The descriptive characteristics and univariate statistical comparison of the retinopathy and no retinopathy groups are shown in Table 1. In the univariate analysis, continuous positive airway pressure compliance was significantly higher in the no retinopathy group than in those with retinopathy. Average wear time and glomerular filtration rate >60 ml/min were also significantly higher in the no retinopathy group, whereas hemoglobin A_{1c} level, diabetes mellitus duration, insulin use, and hypertension were significantly higher in the retinopathy group. The prevalence rates of diabetic retinopathy in the continuous positive airway pressure-compliant group and the noncompliant group were 16.1 and 26.1%, respectively. The continuous positive airway pressure-compliant group was significant less likely to have diabetic retinopathy (odds ratio, 0.54; 95% confidence interval, 0.31 to 0.94; *P* = .04). Additional information on the groups is provided in Table 2. The number of subjects in the noncompliant group was less than the size required to reach the desired power of 0.8. The resultant power of the study was 0.6.

In the multivariate logistic regression, diabetic retinopathy was assigned as the dependent variable, whereas continuous positive airway pressure compliance, body mass index, hemoglobin A_{1c}, duration of diabetes mellitus, insulin use, hypertension, current smoking status, and glomerular filtration rate >60 ml/min were identified as independent variables. After adjustment, diabetes mellitus duration, insulin use, continuous positive airway pressure compliance, and body mass index were independently correlated with the presence of retinopathy. Continuous positive airway pressure compliance and body mass index were associated with lower retinopathy prevalence, whereas diabetes mellitus duration and insulin use were associated with increased likelihood of retinopathy. Odds ratios for the statistically significant variables in the regression analysis are located in Table 3.

DISCUSSION

The results of this study show that diabetic retinopathy was significantly less prevalent in a continuous positive airway pressure-compliant group than in a group noncompliant with continuous positive airway pressure therapy. This finding was independent of other factors known to influence obstructive sleep apnea and diabetic retinopathy disease processes including obstructive sleep apnea severity and duration, diabetes mellitus duration, hemoglobin A_{1c}, and insulin use. The groups were similar in many respects including age and obstructive sleep apnea duration and severity. Diabetes mellitus duration, hemoglobin A_{1c} level, insulin use, and hypertension were significantly higher among the retinopathy group, findings that are not surprising given our understanding of risk factors for diabetic retinal disease; however, when these factors were controlled for, the relationship between continuous positive airway pressure compliance and presence of diabetic retinopathy remained.

TABLE 1. Descriptive characteristics and comparison of groups

	DR (n = 63)	No DR (n = 258)	Difference between groups	P
Age (y)*	62.6 (8.8)	62.1 (8.7)	0.5† (95% CI, −2.9 to +2.0)	.71
CPAP compliant‡	54.0 (34)	68.6 (177)	0.5§ (95% CI, 0.3 to 0.9)	.03
Nights worn (%)¶	83 (21.0–100)	91 (53.0–100)	−8.0** (95% CI, −9.0 to 0.0)	.17
Average wear time (h)¶	5.9 (3.3–7.9)	6.7 (5.0–8.0)	−0.8** (95% CI, −1.7 to −0.1)	.02
Baseline AHI¶	39 (20.5–62.7)	26 (15.0–56.0)	6.0** (95% CI, −1.5 to +15.0)	.12
Treated AHI¶	2.0 (1.0–3.4)	1.6 (0.8–3.0)	0.3** (95% CI, −0.1 to +0.8)	.12
Duration DM (y)¶	13.0 (10.0–20.0)	7.0 (4.0–11.0)	6.0** (95% CI, 5.0 to 8.0)	<.0001
Duration OSA (y)¶	5.0 (2.0–8.0)	4.0 (2.0–7.3)	1.0** (95% CI, 0.0 to 2.0)	.15
BMI (kg/m ²)¶	35.0 (31.1–39.0)	36.0 (32.6–41.0)	−1.5** (95% CI, −3.1 to +0.2)	.08
HbA _{1c} ¶	8.3 (7.1–9.4)	7.4 (6.6–8.4)	0.7** (95% CI, 0.3 to 1.2)	<.0001
Insulin‡	69.8 (44)	28.3 (73)	5.9§ (95% CI, 3.2 to 10.7)	<.0001
HTN‡	95.2 (60)	86.8 (224)	3.0§ (95% CI, 1.9 to 10.2)	.04
Hyperlipidemia‡	88.9 (56)	90.7 (234)	0.2§ (95% CI, 0.3 to +2.0)	.67
Current smoker‡	20.6 (13)	12.0 (31)	1.9§ (95% CI, 0.9 to 3.9)	.09
eGFR >60 ml/min‡	63.5 (40)	77.5 (200)	0.5§ (95% CI, 0.3 to 0.9)	.02

*Data are presented as mean (SD). †t Test. ‡Data are presented as percentage (count). §χ² Test (odds ratio). ¶Data are presented as median (interquartile range). **Mann-Whitney U test. AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; DM = diabetes mellitus; DR = diabetic retinopathy; eGFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HTN = hypertension; OSA = obstructive sleep apnea.

Several studies have shown that untreated obstructive sleep apnea is a risk factor for the development and progression of diabetic retinopathy, but the impact of continuous positive airway pressure on retinopathy has not been extensively studied.²⁸ To our knowledge, ours is the first study to focus exclusively on the relationship between continuous positive airway pressure compliance and diabetic retinopathy prevalence. Altaf et al.²⁹ followed up 230 patients longitudinally for an average of 43 months and found that obstructive sleep apnea was an independent risk factor for retinopathy progression, and those using continuous positive airway pressure were significantly less likely to progress to proliferative disease or develop maculopathy. In the Retinopathy and Concurrent Obstructive Sleep Apnea Trial (ROSA) study, the only randomized controlled trial examining continuous positive airway pressure and diabetic retinopathy, treatment for 12 months with continuous positive airway pressure failed to improve vision or retinopathy in a group of 131 subjects with macular edema. The findings led the authors to conclude that continuous positive airway pressure may be ineffective in reversing established ocular disease. Potential explanations for the absence of benefit were low continuous positive airway pressure compliance and the use of concurrent interventions for diabetic macular edema in all subjects.³⁰

The ROSA trial was done in follow-up to a prospective uncontrolled trial of subjects with diabetic macular edema who demonstrated visual acuity improvement after 6 months of highly compliant continuous positive airway pressure treatment.³¹ Because of the low number of subjects in our study with more advanced diabetic retinopathy, no conclusions may be drawn regarding the relationship between continuous positive airway pressure compliance and the different stages of disease, but the results suggest that continuous positive airway pressure may play a potential role in the prevention of diabetic retinopathy.

Continuous positive airway pressure has been shown to benefit several health factors and disease processes known to influence diabetic retinopathy, including hypertension. The greatest benefits are seen in hypertension resistant to standard therapy, in higher baseline systolic and diastolic blood pressure, and in cases of severe obstructive sleep apnea.^{32,33} In this study, hypertension was more common in the retinopathy group, but the association was not statistically significant when controlling for continuous positive airway pressure use.

Despite the strong association between obstructive sleep apnea and type 2 diabetes, studies examining the effects of continuous positive airway pressure treatment on glucose metabolism have

TABLE 2. Diabetic retinopathy and CPAP compliance

	Diabetic retinopathy	No diabetic retinopathy	Total
CPAP compliant	34	177	211
CPAP noncompliant	29	81	110
Total	63	258	321
Odds ratio (95% CI)	0.54 (0.31–0.94)		

Data represent the number of subjects in each category. CI = confidence interval; CPAP = continuous positive airway pressure; CPAP compliant = average use >4 hours on more than 70% of nights.

TABLE 3. Significant predictors of diabetic retinopathy from multivariate logistic regression

	Odds ratio (95% CI)	P
DM duration	1.12 (1.07–1.18)	<.0001
CPAP compliant	0.49 (0.26–0.94)	.03
Insulin use	4.08 (2.00–8.17)	<.0001
BMI	0.94 (0.89–0.99)	.04

BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; DM = diabetes mellitus.

yielded conflicting results. Some studies have failed to demonstrate benefit after more than 6 months of continuous positive airway pressure use, whereas others have shown improvement in as little as 1 week of treatment.^{34,35} Although differences in study design and patient populations have likely contributed to the heterogeneity in study results, insufficient nightly continuous positive airway pressure use has been cited as a possible explanation for negative findings in most reports.^{36–38} In contrast, when continuous positive airway pressure adherence is high, the impact on various glycemic factors including fasting blood glucose, mean 24-hour plasma glucose, hemoglobin A_{1c}, and insulin sensitivity has been favorable.^{39,40} These findings suggest that excellent continuous positive airway pressure adherence is required to achieve improvements in glucose metabolism in diabetic patients being treated for obstructive sleep apnea.

Although our study does not demonstrate causation, it does provide evidence that continuous positive airway pressure compliance is associated with lower prevalence of diabetic retinopathy. Given the significant burden of diabetic eye disease and the incomplete effectiveness of current interventions, the role of continuous positive airway pressure as an adjunctive treatment in the management of diabetes should not be discounted.

The study has several strengths including similarities between retinopathy and no retinopathy groups with respect to age and

obstructive sleep apnea. Except for smoking history, all data were obtained via objective measurement rather than by patient report. Limitations include the homogenous patient population, predominantly elderly men, which restricts the generalizability of the findings. The statistical power was lower than desired, thereby increasing the possibility of a type I error. Several risk factors were higher in the non-compliant group (diabetes mellitus duration, hemoglobin A_{1c}, insulin use), which may have contributed to increased retinopathy prevalence despite attempts to statistically control for these differences. A larger study composed of groups with better matched diabetic retinopathy risk profiles is recommended to confirm our findings.

CONCLUSIONS

In summary, this study found the prevalence of diabetic retinopathy to be lower in veteran patients with sleep apnea who are compliant with continuous positive airway pressure. This relationship persisted when controlling for other factors known to increase the likelihood of retinopathy including duration of diabetes mellitus and hemoglobin A_{1c}. These findings provide further evidence of the benefits of continuous positive airway pressure use in the management of obstructive sleep apnea-related comorbidities.

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