SLEEP-DISORDERED BREATHING AND DIABETIC RETINOPATHY

By Regina Patrick, RPSGT

Retinopathy is disease of or damage to the retina. Injury to the retinal blood vessels, decreased retinal blood flow or abnormal growth of retinal blood vessels are features of retinopathy that can cause vision loss. Sleep-related disordered breathing may contribute to the development of retinopathy. Some researchers have reported vascular changes in the retinas of people with obstructive sleep apnea (OSA).[1-5] The association between retinopathy and OSA may be especially problematic for people with diabetes since diabetes itself is a risk factor for retinopathy. Approximately 80% of people who have had type 2 diabetes for 20 to 25 years develop retinopathy.[6] Diabetes is the leading cause of new cases of blindness among adults 20 to 74 years old.[7] Some research now indicates that presence of OSA in people with diabetes may hasten the progression of retinopathy.

Diabetes is an endocrine disorder in which the hormone insulin is produced in insufficient amounts or the body's cells do not respond to (i.e., resist) the effects of insulin. Insulin plays a role in removing excessive levels of glucose from the blood. Two forms of diabetes exist: type 1 and type 2. In type 1 diabetes, a person does not produce sufficient amounts of insulin and must depend on an exogenous source of insulin to live. Type 1 diabetes is often called "insulin-dependent diabetes." In type 2 diabetes, a person is resistant to the effects of insulin (although insulin levels may be normal) or insulin levels are reduced; however, the person's blood glucose level can often be maintained with dietary changes and/or medication. Type 2 diabetes is often called "non–insulin-dependent diabetes." Both forms of diabetes are associated with pathological changes in the small blood vessels of the eye, kidney, and small arteries throughout the body.

Improper utilization or production of insulin impairs many metabolic functions such as fluid balance and the metabolism of proteins, fats, and carbohydrates. As a result, a person with untreated diabetes may experience excessive thirst, diuresis (i.e., frequent urination), polyuria (i.e., excretion of a large amount of urine), dehydration, excessive hunger with weight loss, or ketoacidosis (i.e., the accumulation of ketone bodies, which are acidic molecules formed as a byproduct of faulty glucose metabolism).

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Diabetic retinopathy can be nonproliferative or proliferative. In nonproliferative diabetic retinopathy, retinal blood vessels leak plasma or fatty substances. This decreases or blocks blood flow within the retina. The retinal blood vessels may also develop microaneurysms (i.e., a balloon-like outpouching of a vessel) that can burst and leak blood within the retina. Some people with nonproliferative retinopathy experience no symptoms, but others may experience symptoms such as central vision loss and decreased night vision. In proliferative diabetic retinopathy, new vessels begin to grow (i.e., neovascularization) into other areas of the eye such as the vitreous humor or the optic disc. (The vitreous humor is a semisolid substance that fills the posterior portion of the eye between the lens and retina; the optic disc is the portion of the eye where the fibers from the retinal cells converge and extend out of the eye to form the optic nerve.) New blood vessels that grow into the vitreous humor can rupture and cause sudden vision loss. Scar tissue may form in the retina as the tissue attempts to heal the damage caused by ruptured blood vessels. However, scar tissue can pull retinal tissue away from its supportive underlying tissue – a process called retinal detachment – and contribute to vision loss. Scar tissue that forms on the macula – a specialized area on the retina that is responsible for central vision – can cause problems with central vision such as seeing an "inky" spot in the center of one's vision.

Japanese researcher Tomoaki Shiba[8] and colleagues recently found that sleep-related disordered breathing (SDB) may be a risk factor for neovascularization in people with diabetes. In the study, Shiba compared the prevalence of SDB in diabetic patients who had neovascularization with its prevalence in diabetic patients who did not have neovascularization. All patients were monitored by pulse oximetry to determine the number of desaturations per hour of sleep (i.e., the oxygen desaturation index [ODI]). If the patient's ODI was greater than 5 desaturations per hour, the patient was diagnosed as having SDB.

Shiba noted SDB in 62 percent of the patients with neovascularization, compared to 46 percent of the patients without neovascularization. There were a significantly greater number of desaturations in the neovascularization group (12.6 desaturations) in comparison to the non-neovascularization group (6.6 desaturations). Statistical analysis indicated that ODI was one risk factor for neovascularization in diabetic patients.

Other researchers have similarly noted that sleep-related disordered breathing – in particular OSA – appears to play a role in the development of retinopathy in people with diabetes. For example, Semaan Kosseifi[5] and colleagues investigated the correlations between various features of OSA (e.g., oxygen desaturation) and diabetes (e.g., retinopathy) in veterans

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who had well-controlled type 2 diabetes. Kosseifi found a significant positive correlation between retinopathy and the number of apneas or hypopneas per hour of sleep (i.e., the prevalence of retinopathy increased with the number of apneas and hypopneas), and found a significant, inverse relationship between oxygen desaturation and retinopathy (i.e., the lower a person's oxygen desaturation during the night, the greater the risk of retinopathy). Sophie West[9] and colleagues assessed retinopathy and maculopathy (i.e., injury or damage to the macula) in type 2 diabetic men with and without OSA. West found that retinopathy and maculopathy were significantly worse in diabetic men with OSA; that OSA was a significant independent predictor of retinopathy; and that OSA was the only independent significant predictor of maculopathy. Yaprak Unver[10] and colleagues found that diabetic patients with OSA typically had three or more infarcts (i.e., areas of dead tissue resulting from low blood flow) in the retina of each eye, whereas diabetic patients without OSA rarely had infarcts in the retina. Based on this finding, Unver suggests that OSA may contribute to a more aggressive course of retinopathy in a person with diabetes.

OSA may contribute to retinopathy through the hemodynamic and physiological changes that occur during an episode. In OSA, upper airway tissues such as the tonsils, tongue, and adenoids block (i.e., obstruct) the airway during sleep. The upper airway muscles, which would normally keep the airway open during sleep, relax excessively during sleep in people with OSA and allow the upper airway tissues to collapse into and obstruct the airway. During the obstruction, a person continues to make respiratory movements but little or no air enters the lungs. The lack of airflow (i.e., lack of breathing) is apnea. The blood oxygen consequently falls. When the blood oxygen falls to a certain point, the person arouses briefly to take some deep breaths to restore the blood oxygen level. Once it is restored, the person falls promptly back to sleep. However, sleep allows the upper airway muscles to relax again, setting the stage for another episode of OSA.

Hemodynamic changes during an OSA episode involve sudden decreases and increases in blood flow and blood pressure. During the apnea phase, blood flow and blood pressure decreases; during the arousal phase, blood flow and blood pressure suddenly increases. The frequent changes in blood flow and blood pressure during an OSA episode may damage fragile small blood vessels in the retina or cause them to break and leak blood.

Hypoxemia (i.e., low blood oxygen level) and hypercapnia (i.e., high blood carbon dioxide level) are physiological effects of OSA that can affect the function of blood vessels. During the apnea phase of an OSA episode, hypoxemia and hypercapnia occur. Hypoxemia induces vasodilation (i.e., opening) of the central retinal artery. Vasodilation of this artery can compress the central retinal vein since the two vessels travel closely side by side through the center of the optic nerve. Compression of the retinal vein can decrease the outflow of blood from the retina and damage the retina. Hypercapnia appears to induce neovascularization and vascular degeneration; however, scientists currently can not explain how hypercapnia induces neovascularization.[11]

Treating OSA reduces the risk of cardiovascular disease (e.g., stroke, heart attack) and may improve glucose control in some diabetics. With this in mind, scientists have begun investigating the impact of OSA treatment on retinopathy. In a recent study, Rebecca Mason[12] and colleagues recorded the visual acuity of 28 diabetic patients with macular edema (i.e., swelling of the macula due to the retention of fluid) and OSA. All patients were treated by continuous positive airway pressure (CPAP), which involves blowing a continual flow of pressurized air into the airway through a nasal or or nasal mask to prevent upper airway collapse. The patients were grouped as high treatment compliance (i.e., the CPAP mask was used 2.5 hours or more night) or low treatment compliance (i.e., the CPAP mask was used less than 2.5 hours per night). At the end of 6 months, the high treatment compliance group had improved visual acuity. However, there was no significant improvement in macular edema. Because not many studies exist focusing on the effect of OSA treatment on retinopathy, future studies may more clearly show whether OSA treatment improves retinopathy.

Although many studies indicate a relationship between OSA and retinopathy, whether mild SDB contributes to retinopathy is unclear. To investigate this, researchers Lori Boland[13] and colleagues calculated the average number of apneas and hypopneas per hour of sleep in a group of middle-aged and elderly subjects who were assessed for retinopathy. Boland noted that the prevalence of retinopathy was slightly higher in people with a high number of apneas and hypopneas. However, after adjusting for age, body-mass index, hypertension, diabetes, and other factors, statistical analyses indicated that retinopathy was not associated with SDB. Boland therefore concluded there is no relation between SDB and retinopathy, but encourages more research to determine if the findings of other researchers will be consistent or inconsistent with her findings.

Because of the apparent relation between OSA and diabetes, some researchers suggest that physicians should screen diabetic patients for OSA if they have symptoms such as snoring, fragmented sleep, daytime somnolence, and hypertension,[5,10] or if they have an accelerated course of retinopathy.[10] Future studies may more clearly reveal the extent that treating OSA or other sleep-related disordered breathing can slow or reverse the progression of retinopathy. If future studies prove that treating OSA or SDB can improve retinopathy, then identifying and treating OSA or SDB early may spare a diabetic person's vision or delay the progression of retinopathy.

REFERENCES:

1. Chou KT, Huang CC, Tsai DC, et al. Sleep apnea and risk of retinal vein occlusion: A nationwide population-based study of Taiwanese. *American Journal of Ophthalmology*. Jul 2012;154(1):200-205 e201.

2. Glacet-Bernard A, Leroux les Jardins G, Lasry S, et al. Obstructive sleep apnea among patients with retinal vein occlusion. *Archives of Ophthalmology*. Dec 2010;128(12):1533-1538.

3. Kanai H, Shiba T, Hori Y, et al. Prevalence of sleep-disordered breathing in patients with retinal vein occlusion. *Nihon Ganka Gakkai Zasshi*. Feb 2012;116(2):81-85 [article in Japanese].

4. Mojon DS, Hedges TR 3rd, Ehrenberg B, et al. Association between sleep apnea syndrome and nonarteritic anterior ischemic optic neuropathy. *Archivies of Ophthalmology*. May 2002;120(5):601-605.

5. Kosseifi S, Bailey B, Price R, et al. The association between obstructive sleep apnea syndrome and microvascular complications in well-controlled diabetic patients. *Military Medicine*. Nov 2010;175(11):913-916.

6. *Professional Guide to Diseases*. 5th ed. Springhouse, PA: Springhouse Corporation 1995.

7. National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics, 2011. Feb 2011; NIH Publication No. 11-3892. Available at. Accessed 1-1-2013, 2013.

8. Shiba T, Takahashi M, Hori Y, et al. Relationship between sleep-disordered breathing and iris and/or angle neovascularization in proliferative diabetic retinopathy cases. *American Journal of Ophthalmology*. Apr 2011;151(4):604-609.

9. West SD, Groves DC, Lipinski HJ, et al. The prevalence of retinopathy in men with Type 2 diabetes and obstructive sleep apnoea. *Diabetic Medicine*. Apr 2010;27(4):423-430.

10. Unver YB, Yavuz GSA, Stafford CA, Sinclair SH. A putative relation between obstructive sleep apnea and diabetic macular edema associated with optic nerve fiber layer infarcts. *Open Sleep Journal*. 2009;2:11-19.

11. Leduc M, Kermorvant-Duchemin E, Checchin D, et al. Hypercapnia- and trans-arachidonic acid-induced retinal microvascular degeneration: Implications in the genesis of retinopathy of prematurity. *Seminars in Perinatology*. Jun 2006;30(3):129-138.

12. Mason RH, Kiire CA, Groves DC, et al. Visual improvement following continuous positive airway pressure therapy in diabetic subjects with clinically significant macular oedema and obstructive sleep apnoea: Proof of principle study. *Respiration*. 2012;84(4):275-282.

13. Boland LL, Shahar E, Wong TY, et al. Sleep-disordered breathing is not associated with the presence of retinal microvascular abnormalities: The Sleep Heart Health Study. *Sleep*. May 1 2004;27(3):467-473. ❖