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Obstructive Sleep Apnea and Diabetes

A State of the Art Review

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e-Appendix 1.

DIABETIC COMPLICATIONS

It is well known that uncontrolled diabetes is associated with the development of microvascular complications. The presence and severity of OSA may be an additional risk factor for these complications. Intermittent hypoxemia leads to vasoconstriction and increased oxidative stress, resulting in endothelial dysfunction and microvascular impairment. [1]OSA is associated with increased endothelin-1, [2] vascular endothelial growth factor, [3] and alterations in nitric oxide synthase activity.[1] OSA-related also increase inflammatory markers and hypercoagulability likely plays a role.[1,4] Increased advanced glycation end products and alterations in protein kinase C signaling are common pathways by which OSA and hyperglycemia contribute to microvascular complications.[5,6] Lastly, hypertension and alterations in renin-angiotensin-aldosterone regulation partly mediate the relationship between OSA and diabetic kidney disease (DKD).[7]

Studies in patients with type 2 diabetes have explored the association between OSA and microvascular complications. In a meta-analysis of 7 studies, OSA was associated with a higher risk of DKD (pooled OR 1.59, 95% CI: 1.16–2.18).[8] The severity of hypoxemia was found to be related to DKD severity.[9] In addition, a cohort study with a follow up of 2.5 years revealed that patients with type 2 diabetes and OSA had a faster decline in their estimated glomerular filtration rate (eGFR) than those without OSA, with baseline nitrosative stress being an independent predictor of eGFR decline.[10]

In a systematic review of 8 studies, there was no convincing evidence that OSA was associated with diabetic retinopathy.[11] However, some evidence suggests that OSA is associated with greater severity of diabetic retinopathy, with minimum oxygen saturation level during sleep being a predictor. [11-13] Moreover, a recent longitudinal cohort study of patients with type 2 diabetes who were followed for a median of 43 months found an independent association between OSA and the risk of progression to advanced diabetic retinopathy (OR 5.2, 95% CI 1.2-23.0).[14] With regards to diabetic neuropathy, a study of 234 patients in the U.K. found that OSA was independently associated with peripheral neuropathy (OR 2.82, 95% CI 1.44-5.52).[15] A meta-analysis of 880

patients with diabetes found a significant association between OSA and neuropathy (OR 1.95, 95% CI: 1.03–3.70).[16]

Well-designed prospective studies are needed to determine if treatment of OSA can improve or delay the onset the micro and macrovascular complications in patients with type 2 diabetes and OSA.

GESTATIONAL DIABETES

During pregnancy, physical and hormonal changes such as weight gain and mucosal edema could increase susceptibility to developing OSA. AHI and snoring can increase from early to late pregnancy, especially in obese women.[17-19] Indeed, the prevalence of OSA was found to be higher in late pregnancy (2nd or 3rd trimester) compared to early pregnancy, reflecting new onset OSA in later gestation. In a study of 100 women with uncomplicated pregnancies, the prevalence of OSA (as measured by PSG) was 10.5% and 26.7% in the first and 3rd trimester, respectively.[18] A large study in 3,132 nulliparous women found a prevalence of OSA in early (6-15 weeks of gestation) and late (22-31 weeks of gestation) pregnancy to be 3.6% and 8.3%, respectively.[19] However, the nearly three quarters of these women only had mild OSA.[19] The prevalence of OSA during the 3rd trimester varies widely from 8.3% to 35%.[19-23] Such variability is likely related to different obstetric populations enrolled in these studies. Predictors of OSA in pregnancy include more advanced age, frequent snoring or snoring volume, obesity, and chronic hypertension.[21,23,24] Unfortunately, questionnaires typically used in non-pregnant population including Berlin Questionnaire and Epworth Sleepiness Scale have a poor performance in predicting OSA during pregnancy with a pooled sensitivity and specificity for Berlin questionnaire of 66% and 62%, and for the Epworth Sleepiness Scael of 44% and 62%, respectively.[25]

Gestational diabetes mellitus (GDM) is a state of abnormal glucose tolerance typically diagnosed during the 2rd or 3rd trimester, and is associated with adverse maternal and fetal outcomes. Several studies have observed an association between OSA and GDM.[26,27] A meta-analysis of 9,795 participants found that women with symptoms of OSA or a diagnosis of OSA had a 3-fold increased risk of GDM (a pooled BMI-adjusted OR of 3.06).[28] The risk, however, was much

higher in a recent large study which utilized home PSG.[19] In mid-pregnancy, increasing OSA severity was significantly associated with an increasing risk for GDM. Interestingly, the risk was seen at even an AHI of 1-5, which is below the standard threshold of OSA in non-pregnant population (adjusted ORs 4.9, 12.6, and 15.6 for AHI >0 but <5, ≥5 to <15 and ≥15, compared to AHI of 0, respectively).[19] The mechanisms underlying this association are likely similar to those linking OSA to type 2 diabetes in non-pregnant population. The prevalence of OSA in women with GDM has not been studied extensively but has been reported to be between 30-71%.[19,29,30] The large variability is likely due to different characteristics and degree of obesity in the studied populations. There was a suggestion of OSA severity correlating to glycemic control. [30] Thus far no studies have systematically explored the effect of CPAP treatment on glycemic control and pregnancy outcomes in women with GDM and OSA.

In addition to GDM, OSA during pregnancy has been linked to adverse maternal and fetal outcomes, including pre-eclampsia, emergency caesarean-section, premature delivery, low birthweight and admissions of the newborn to the intensive care unit.[31-33] Endothelial dysfunction, increased oxidative stress and sympathetic nervous system overactivity seen in OSA are likely partially responsible for this association.[34] CPAP treatment has been shown to be safe during pregnancy and was associated with a reduction in blood pressure in a small study of women with hypertension and chronic snoring.[35] Whether CPAP will affect pregnancy outcomes in women with OSA remains to be investigated.

In summary, emerging data suggest OSA may be an important risk factor for diabetic complications and may be associated with gestational diabetes. Future studies should explore a causal relationship between OSA and diabetic complications, and the impact of OSA therapy on the development/progression of these complications. Epidemiology of OSA in women with GDM needs to be further studied, including prevalence, risk factors, impact on glycemic control and maternal/fetal outcomes. Sensitive and specific screening tools for OSA in GDM women should be developed. Ultimately, well-designed clinical trials are necessary to demonstrate whether treatment of OSA improves maternofetal outcomes in GDM.

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e-Table 1: Open randomized controlled trials actively recruiting participants with sleep apnea and diabetes found on various clinical trial registries

Study Principal Investigator and Institution	Title, Trial Registration Date and Clinicaltrials.gov Identifier	Estimated Number of Participants to be Enrolled	Study Design	Intervention	Duration	Primary Outcome and Main Secondary Outcomes
Eileen R. Chasens University of Pittsburgh Pittsburgh USA	The Effect of Treatment of Obstructive Sleep Apnea on Diabetes Self-Management and Glycemic Control July 2013 NCT 01901055	210 adult participants with moderate-to-severe OSA and type 2 diabetes with HbA1c ≥6.5%	Randomized cross-over, double blind	CPAP vs. sham CPAP	3 months	Primary: HbA1c Secondary: Diabetes self-management outcomes
Naresh M. Punjabi Johns Hopkins University Baltimore, USA	Hyperglycemic Profiles in Obstructive Sleep Apnea: Effects of PAP Therapy January 2015 NCT 02454153	204 adult participants with OSA and type 2 diabetes	Randomized, Parallel group, open label	CPAP plus lifestyle/sleep education vs. lifestyle/sleep education	3 months	Primary: Glycemic variability assessed by interstitial glucose measured via continuous glucose monitoring system Secondary: Endothelial function using EndoPAT device and blood pressure
Esben Laugesen Aarhus University Aarhus, Denmark	Impact of CPAP Treatment on Arterial Stiffness in Patients With Type 2 Diabetes and Newly Diagnosed Obstructive Sleep Apnea March 2015 NCT 02482584	70 adult participants with moderate-to-severe OSA and type 2 diabetes with HbA1c ≥7.0%	Randomized, Parallel group, open-label	CPAP vs. no CPAP	3 months	Primary: Change in arterial stiffness measured by carotid-femoral pulse wave velocity Secondary: Change in insulin sensitivity by hyperinsulinemic euglycemic clamp
Daniel Cuthbertson University of Liverpool Liverpool, UK	ROMANCE: Liraglutide with or without CPAP in type 2 diabetes and OSA August 2015 ISRCTN 16250774	152 obese adult participants with moderate-to-severe symptomatic OSA and type 2 diabetes with HbA1c > 7%	Randomized, 4 parallel groups, open-label	1. Control (no intervention) 2. Liraglutide 3. CPAP 4. Liraglutide & CPAP	6 months	Primary: Change in apnea-hypopnea index Secondary: Change in HbA1c

Jonathan Jun Johns Hopkins University Baltimore, USA	Metabolic Impact of Intermittent CPAP March 2016 NCT 02824263	144 adult participants with moderate-to-severe OSA tolerating home CPAP therapy and with or without type 2 diabetes	Randomized, cross-over, open-label	Continuation of CPAP vs. CPAP withdrawal for 3 consecutive nights	3 nights of CPAP withdrawal	Primary: frequent blood sampling during sleep to measure profiles of free fatty acids, glucose, insulin and triglycerides Secondary: Endothelial function using EndoPAT device and oral glucose tolerance test
Francisco Garcia-Rio Hospital Universitario La Paz Madrid, Spain	CPAP Effect on Albuminuria in Patients with Diabetic Nephropathy and OSA May 2016 NCT 02816762	180 adult participants with untreated OSA and type 2 diabetes with diabetic nephropathy	Randomized, Parallel group, open-label	CPAP plus conventional pharmacological treatment vs. conventional pharmacologic treatment	12 months	Primary: Change in albuminuria level Secondary: HbA1c, HOMA index
Francisco Garcia-Rio Hospital Universitario La Paz Madrid, Spain	CPAP Effect on the Progression of Diabetic Retinopathy in Patients with Sleep Apnea August 2016 NCT 02874313	114 adult participants with untreated OSA and type 2 diabetes with mild non-proliferative diabetic retinopathy	Randomized, Parallel group, open-label	CPAP plus conventional pharmacologic treatment vs. conventional pharmacologic treatment	12 months	Primary: Change in retinal microaneurym or hard exudates Secondary: Central macular volume, ganglion cell layer thickness, central fovea thickness, visual acuity, level of diabetic retinopathy, HbA1c, HOMA index

The following clinical trials registries were accessed on April 20, 2017: ClinicalTrials.gov, International Standard Randomised Controlled Trial Number (ISRCTN: http://www.isrctn.com/), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) and the Chinese Clinical Trial Registry (http://www.chictr.org.cn/). Our search criteria consisted of "Diabetes" and "Apnea" or "Diabetes" and "Sleep". We only included randomized clinical trials that were actively recruiting participants as of April 20, 2017 and also provided all the information listed in the Table.