Data Link Obstructive Sleep Apnea and Type 2 Diabetes

Written by **Wayne Kuznar**

Evidence supports an interaction between obstructive sleep apnea (OSA) and type 2 diabetes mellitus (T2DM). OSA is highly prevalent in persons with T2DM, with some estimates of the prevalence of moderate to severe OSA (defined as an apnea-hypopnia index [AHI] ≥5) as high as 61% [Einhorn D et al. *Endocr Pract* 2007], but the direction of causality is not yet clear.

Patrick Lévy, MD, PhD, University Joseph Fourier, Grenoble, France, gave an overview of the relationship between OSA and T2DM. In a consecutive series of 60 patients with T2DM, 77% had an AHI≥5, and adjusted HbA1C levels increased with increasing severity of OSA [Aronsohn RS et al. *Am J Respir Crit Care Med* 2010].

Data also suggest that OSA is independently associated with altered glucose metabolism to promote the development of T2DM. Adjusted odds ratios for the incidence of diabetes in moderate to severe OSA compared with no OSA range from 1.43 to 13.45 [Pamidi S, Tasali E. *Front Neurol* 2012].

Young lean men with OSA had reduced insulin sensitivity and higher total insulin secretion than controls despite similar glucose levels after an oral glucose tolerance test [Pamidi S et al. *Diabetes Care* 2012]. Increasing severity of AHI was independently associated with impaired glucose metabolism in a multicentric cohort of 1599 subjects without T2DM [Priou P et al. *Diabetes Care* 2012].

Sleep fragmentation and intermittent hypoxia can lead to insulin resistance and pancreatic β-cell dysfunction through sympathetic activation, alterations in the HPA axis (ie, increase in levels of cortisol), oxidative stress, activation of inflammatory pathways that promote the release of interleukin-6 and tumor necrosis factor-α, and adverse changes in adipokine profiles including a reduction in adiponectin.

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Intermittent hypoxia causes reduced muscle glucose utilization in the soleus muscle in lean mice [Iiyori N et al. *Am J Respir Crit Care Med* 2007] and increased β-cell proliferation and cell death presumably due to oxidative stress [Xu J et al. *Free Radic Biol Med* 2009]. An increase in free fatty acid uptake by the liver induced by intermittent hypoxia may upregulate transcriptional pathways of lipid biosynthesis through HIF-1, leading to liver insulin resistance and nonalcoholic steatohepatitis conceivably through accelerated adipose tissue lipolysis [Mirrakhimov AE, Polotsky VY. *Front Neurol* 2012].

In morbidly obese people, chronic intermittent hypoxia is an independent predictor for non-alcoholic fatty liver disease (NAFLD), hepatic fibrosis, and fibroinflammation [Aron-Wisnewsky J et al. *J Hepatol* 2012]. Chronic intermittent hypoxia was found to have differential metabolic effects in lean and obese mice, inducing NAFLD, oxidative stress, and inflammation in only the obese mice [Drager LF et al. *Obesity* 2011].

In uncontrolled studies, it has been initially evidenced that long-term continuous positive airway pressure (CPAP) reduced HbA1C levels in diabetic individuals with sleep-disordered breathing [Babu AR et al. *Arch Intern Med* 2005]. Also, a rapid improvement in insulin sensitivity in patients with OSA obtained after initiation of CPAP may reflect a reduction in sympathetic activity [Harsch IA et al. *Am J Respir Crit Care Med* 2004]. The effect was smaller in obese patients, which suggests that in obese patients, insulin sensitivity is determined more by obesity than OSA.

Anthropometric variables (weight, body mass index, subcutaneous fat, visceral fat) improved significantly in a group of OSA patients who underwent 3 months of CPAP compared with sham CPAP [Sharma SK et al. *N Engl J Med* 2011]. This may explain the overall improvement in the metabolic profile in this study where the study group was highly selected (ie, untreated moderately obese subjects presenting with dysmetabolism). So far, this paper provided the most impressive results but most randomized controlled trials did not confirm this metabolic improvement during OSA treatment [Weinstock TG et al. *Sleep* 2012; Sivam S et al. *Eur Respir J* 2012; Hoyos CM et al. *Thorax* 2012]. Pepin et

al. recently published a summary explaining the conflicting results [*Thorax* 2012]. The duration of CPAP, patient age, comorbidities, and the severity of OSA and intermittent hypoxia all appear to be critical factors in the relative success of CPAP in treating OSA.

Statin Use Improves Respiratory-Related Mortality in Patients With COPD

Written by Phil Vinall

There is mounting evidence for an association between statin use and reduced all-cause mortality among patients with chronic obstructive pulmonary disease [Lahousse L et al. *Pulm Pharmacol Ther* 2013; Young RP et al. *Eur Respir Rev* 2009; Janda S et al. *Chest* 2009; Young RP et al. *Postgrad Med J* 2009]. Robert P. Young, MD, PhD, University of Auckland, Auckland, New Zealand, presented results from an observational study indicating that this benefit is of particular significance in terms of respiratory-related mortality.

Prof. Young reported the results of a subanalysis of the data from a recent study, which reported a 30% reduction (HR, 0.69; 95% CI, 0.58 to 0.84; p<0.01) in all-cause mortality after 4 years of follow-up in COPD patients taking statins [Lawes CM et al. *Prim Care Respir J* 2012]. The study comprised 1687 patients (596 statin users; 1091 nonusers; mean age 70.6 years) who were admitted to any New Zealand public hospital during 2006 and had a discharge diagnosis of first episode of COPD. Cases of COPD were identified through national hospital codes. Medication usage was based on a national drug-dispensing database and outcomes for those patients taking statins were compared with patients not taking statins, adjusted for confounding using a propensity score approach. Cause of death was ascertained through death certificate documentation up to the end of 2012 and sub-grouped (respiratory, cardiovascular, and other deaths).

Statin users were significantly more likely to be men (58.4%) and to have a history of cardiovascular disease (58.6%) compared with non-statin users (48.5% and 25.1%, respectively; both p<0.001). Significantly more statin users were taking furosemide (which was used as a proxy for heart failure; 47.7% vs 24.5%) and significantly more had been diagnosed with diabetes (35.4% vs 11.6%; both p<0.001) than statin non-users. The proportion of deaths was similar between the two groups: 242 deaths (40.6%) in the statin group versus 429 deaths (39.3%) among those non-statin users. After adjustment for age, sex, ethnic group, history of cardiovascular disease, diabetes, and prescription for furosemide, the hazard ratio for statin users versus statin non-users for all-cause mortality was 0.69 (95% CI, 0.58 to 0.84; p<0.01).

For their follow-up analysis, Prof. Young and colleagues obtained the specific cause of death for those who died during the follow-up period of 6 years in the Lawes study [Lawes CM et al. *Prim Care Respir J* 2012]. A significant reduction was noted in respiratory death (chest infection, COPD exacerbation, pneumonia, respiratory failure) and "other deaths" with adjusted HRs of 0.55 and 0.55 respectively (95% CI, 0.43 to 0.78 and 0.35 to 0.85; p=0.0009 and p=0.008, respectively). Within the "other deaths" category there was a significant reduction in cancer deaths but no reduction in cardiovascular death.

The investigators concluded that statin therapy confers a benefit on mortality in COPD for respiratory complications leading to death. They noted that although two randomized studies of statin use in patients with COPD have shown significant improvement in exercise tolerance and quality of life [Lee T-M et al. *Am J Cardiol* 2008; McDonald VM et al. *Thorax* 2013] a reduction in mortality is even more important. The results of this study support the hypothesis that the systemic immune-modulatory effects of statins are beneficial in COPD and suggest a need for a randomized controlled trial to assess the role of adjunct statin therapy in reducing systemic and pulmonary inflammation in patients with COPD.

Addition of Spironolactone to Ambrisentan May Be a Novel Treatment Strategy to Improve Outcome in Patients With PAH

Written by Maria Vinall

Bradley Maron, MD, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA, presented the results of a retrospective study that demonstrated a trend toward additional clinical improvement when spironolactone was added to ambrisentan for the treatment of patients with pulmonary arterial hypertension (PAH).

In patients with PAH, levels of the mineralocorticoid hormone aldosterone are increased in the pulmonary arterial circulation and correlate positively with hemodynamic measures of pulmonary vascular remodeling [Maron BA et al. *Eur J Heart Fail* 2013]. In addition, results from recent basic and translational models of PAH suggest that hyperaldosteronism modulates a pulmonary vasculopathy by promoting endothelin receptor type-B (ET_B) dysfunction in pulmonary endothelial cells [Maron BA et al. *Circulation* 2012; Maron BA et al. *Am J Cardiol* 2013. In press], which is required for