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Eur Respir J 2015; 46: 1826–1829 | DOI: 10.1183/13993003.00811-2015 | Copyright ©ERS 2015

Comparison of the association with sleep apnoea of obesity *versus* insulin resistance

To the Editor:

Obesity is considered to be both a risk factor for the development of obstructive sleep apnoea (OSA), and a contributor to the abnormal sleep patterns that characterise this syndrome [1]. Obesity is also associated with insulin resistance [2]. These two phenomena may be unrelated, and represent two untoward effects of

excess adiposity. However, the situation is complicated given the apparent association between OSA and insulin resistance [3]. The current study represents an effort to clarify the complex relationships among obesity, OSA, and insulin resistance by defining the extent to which the physiological abnormalities in OSA are independently associated with obesity as compared to insulin resistance. Therefore, we evaluated the relationships of adiposity and insulin-mediated glucose uptake with sleep measurements pertaining to OSA, among overweight/obese men with untreated OSA, without other major comorbidities.

Participants were men (n=82), 30–70 years old, and overweight/obese based on body mass index (BMI; 25.0–40.0 $kg \cdot m^{-2}$). Volunteers gave informed consent, and the Stanford Institutional Review Board approved the protocol. Full-night in-laboratory polysomnograms were conducted at the Stanford Sleep Medicine Center according to standard procedures [4]. Diagnosis of OSA was made by having an apnoea–hypopnoea index (AHI) $\geqslant 5$ events$\cdot h^{-1}$ in addition to characteristic symptoms. Measures of adiposity included BMI (in $kg \cdot m^{-2}$) and waist circumference (in cm). Insulin-mediated glucose uptake was quantified by measuring steady-state plasma glucose (SSPG) concentrations during the insulin suppression test [5]. Insulin resistance was defined as a SSPG $\geqslant 8.3$ $mmol \cdot L^{-1}$, a value shown in a prospective study to predict incident diabetes mellitus type 2 [6].

Baseline characteristics of individuals grouped by OSA severity were compared by one-way ANOVA, and pairwise comparisons made using Bonferroni's adjustment. Pearson correlation coefficients were calculated between BMI or waist circumference and SSPG. Multiple regression analyses were performed to evaluate associations of individual sleep measures (dependent variables) with BMI or waist circumference and SSPG (independent variables). Sleep variables included AHI, AHI during REM (REM-AHI) and non-REM (NREM-AHI) sleep, minimum oxygen saturation, mean oxygen saturation and oxygen desaturation index (defined as the number of times per hour that oxygen saturation drops $\geqslant 3\%$ from baseline). Each sleep variable was regressed separately on BMI and SSPG jointly (model A), and on waist circumference and SSPG jointly (model B). Additional adjustments were made for age and race. Interactions between BMI and SSPG (BMI×SSPG) or waist circumference and SSPG (WC×SSPG) were not detected so the interaction terms were not included in the final models. Statistical significance was taken at $p<0.05$.

Participants were middle-aged (mean±SD age 49±10 years), overweight/obese (BMI 30.6±3.0 $kg \cdot m^{-2}$; waist circumference 106±10 cm), with elevated fasting glucose concentrations (5.7±0.5 $mmol \cdot L^{-1}$). They varied six-fold in SSPG (2.8–17.2 $mmol \cdot L^{-1}$), with 65% classified as insulin-resistant. OSA was severe on average (AHI 34.5±22.0 events$\cdot h^{-1}$), but values were distributed across all categories of OSA severity (mild, n=20 (24%); moderate, n=22 (27%); and severe, n=40 (49%)). Men with severe OSA were older than men with mild OSA (53±8 *versus* 43±9 years; $p<0.01$), but BMI, waist circumference and SSPG did not differ by OSA severity. BMI and waist circumference were highly correlated ($r=0.80$, $p<0.001$), as were correlations between BMI and SSPG ($r=0.41$, $p<0.001$), and waist circumference and SSPG ($r=0.34$, $p=0.002$).

Results of multiple regression analyses to evaluate the relationships of BMI or waist circumference and SSPG with individual sleep measures are reported in table 1. The results using model A indicate that whereas BMI was not associated with any individual sleep measures, SSPG remained an independent predictor of AHI, REM-AHI, NREM-AHI, minimum oxygen saturation and oxygen desaturation index. Similarly, results using model B demonstrate that SSPG, but not waist circumference, independently predicted all sleep measures, with the exception of mean oxygen saturation.

TABLE 1 Regression analyses of the relationships between body mass index (BMI) or waist circumference (WC) and steady-state plasma glucose (SSPG) with individual sleep measures

Sleep measures	Model A				Model B			
	BMI		SSPG		WC		SSPG	
	B	p-value	*B*	p-value	*B*	p-value	*B*	p-value
AHI	−0.04	0.70	0.34	0.002	−0.05	0.65	0.34	0.002
REM-AHI	0.01	0.93	0.39	0.001	−0.07	0.51	0.42	<0.001
NREM-AHI	0.01	0.95	0.23	0.04	0.005	0.97	0.23	0.04
Mean O_2 sat.	−0.19	0.10	−0.17	0.15	−0.175	0.13	−0.18	0.11
Min O_2 sat.	−0.22	0.052	−0.25	0.03	−0.21	0.06	−0.26	0.02
ODI	0.15	0.15	0.41	<0.001	0.14	0.19	0.42	<0.001

B: standardised regression coefficient; AHI: apnoea–hypopnoea index; REM-AHI: AHI during REM sleep; NREM-AHI: AHI during non-REM sleep; ODI: oxygen desaturation index. Dependent variables are the sleep measures shown above. Each sleep variable was regressed separately on BMI and SSPG jointly (model A), and on WC and SSPG jointly (model B). Additional adjustments were made for age and race.

Our results demonstrate that overweight/obese, nondiabetic men with untreated OSA represent a metabolically heterogeneous group. This study represents one of the largest cohort of men with OSA reported in whom direct measurements of insulin-mediated glucose disposal have been obtained, and our findings demonstrate that this basic physiological function varies six-fold in overweight/obese men with OSA. Although approximately two-thirds of the men met criteria for being insulin-resistant, one-third of this population did not, highlighting the heterogeneity in cardiometabolic risk among overweight/obese men with OSA.

The finding of greater relevance to the primary goal was that differences in degree of insulin resistance were associated with severity of OSA in untreated men with OSA, whereas differences in degree of adiposity had no appreciable independent relationship. SSPG concentrations remained significantly associated with measures of OSA severity, as well as oxygenation measures indicative of overnight hypoxaemia after adjustment for differences in BMI or waist circumference. These results are consistent with prior evidence linking OSA to alterations in glucose metabolism [3, 7, 8], and it should be emphasised that we used a direct method to quantify insulin-mediated glucose disposal, not a surrogate estimate. We are aware of another study [7], comprised of men and women, with and without OSA, in whom increasing AHI and degree of oxyhaemoglobin desaturation were associated with reductions in insulin sensitivity using the frequently sampled intravenous glucose tolerance test and minimal model analysis. We decided to only enrol men to minimise potential confounding effects of sex differences in anthropometric and polysomnographic characteristics in OSA [9], and we were able to demonstrate an independent association of insulin resistance with OSA severity without need for a control group. While the pathophysiological nature of this relationship remains uncertain, there is evidence that carotid body-mediated sympathetic activation in the setting of chronic intermittent hypoxia may contribute to metabolic abnormalities [10].

Our results also demonstrated that the inverse relationship of BMI or waist circumference with measures of oxygenation in men was no longer significant after adjustment for age, race and SSPG. These findings are contrary to data suggesting a linear relationship between excess weight and AHI in men [11], and an inverse relationship between BMI and oxygen desaturation [12, 13]. An unequivocal explanation for the differences in results is not available, but these studies differed from ours in that the BMI range was broader, individuals with comorbidities were not excluded, and the impact of insulin resistance was not assessed. It should be noted that we did not enrol lean men since the mechanism of OSA in these individuals may be attributed to factors unrelated to obesity [9].

There are several limitations to interpretation of our findings. We only enrolled 82 men, and the findings need not apply to women with OSA. BMI and waist circumference provide estimates of generalised and central obesity, but do not account for fat mass. Furthermore, inherent night-to-night sleep variability can lead to fluctuations in AHI [14], and differences in physical activity level affects insulin action. Finally, cross-sectional studies do not identify cause-and-effect relationships. Despite these caveats, our findings raise the possibility of a potential role of insulin resistance in the pathophysiology of OSA, at least in overweight/obese men. Although it is generally assumed that sleep abnormalities decrease insulin sensitivity [3], there is also evidence that insulin resistance may play a role in the pathogenesis of OSA [15]. Our findings lend additional support to that possibility. At the least, they suggest that sleep measures among overweight/obese men with untreated OSA may be more closely related to differences in insulin-mediated glucose disposal than obesity *per se*.

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Sleep apnoea severity in overweight men may be more closely related to insulin resistance than degree of obesity http://ow.ly/S1LC5

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Received: April 07 2015 | Accepted after revision: July 23 2015 | First published online: Sept 24 2015

Support statement: This research was funded by NIH grants NIDDK 5K23 DK088877, NHLBI MapGen 5U01 HL108647, and supported by an NIH/NCRR CTSA award number UL1 RR025744. This work was partially supported through a Patient-Centered Outcomes Research Institute (PCORI) Pilot Project Program Award (CE-12-11-4137) Sustainable Methods, Algorithms, and Research Tools for Delivering Optimal Care Study (C.A. Kushida). All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the PCORI, its Board of Governors or Methodology Committee. Funding information for this article has been deposited with FundRef.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

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Eur Respir J 2015; 46: 1829–1832 | DOI: 10.1183/13993003.01087-2015 | Copyright ©ERS 2015

Spontaneous pneumothorax can be associated with *TGFBR2* mutation

To the Editor:

Primary pneumothorax affects 0.01% of the population. 10% of cases have a family history of pneumothorax but in the majority, a definitive genetic diagnosis is not made. We report a 26-year-old, white British woman who presented with left apical pneumothorax (figure 1a). Previously, she had migraines, multiple stress fractures in her right foot, myopia, easy bruising, lumbar scoliosis and spontaneous dislocation of the right patella. She had no previous history of pneumothoraces or any other respiratory problems, and had never smoked.

On examination, she was hypermobile (Beighton score 7/9), and had facial milia, translucent hyperextensible skin, striae over her back, chest wall asymmetry, bilateral varicose veins and pes planus. Her uvula was bifid (figure 1b), she had a high arched palate with dental crowding and her arm span/height ratio was increased (1.14). In the ophthalmology clinic, lattice dystrophy (weakness in the peripheral retina predisposing to retinal detachment) was identified with no ocular features of Marfan syndrome. The patient's thoracic computed tomography (CT) revealed apical blebs, and her echocardiogram and CT showed aortic root dilatation (3.54 cm, Z-score >2) (figure 1c and d). Her 59-year-old mother, who had not suffered pneumothoraces, was reviewed and found to have mild features of a connective tissue disorder: skin hyperextensibility, joint hypermobility with a Beighton scale score of 5/9, a high-arched palate, mild thoracic kyphosis, easy bruising, recurrent left shoulder dislocation, hiatus hernia, stress incontinence and stress fractures of the left foot.

These findings led to the clinical diagnosis of Loeys-Dietz syndrome (LDS), an autosomal dominant disorder affecting the transforming growth factor (TGF)-β signalling pathway [1]. LDS (types I–V: Online Mendelian Inheritance in Man numbers 609192, 610168, 613795, 614816 and 615582, respectively) is