

Obstructive Sleep Apnea Among Obese Patients With Type 2 Diabetes

GARY D. FOSTER, PHD¹
 MARK H. SANDERS, MD²
 RICHARD MILLMAN, MD³
 GARY ZAMMIT, PHD⁴
 KELLEY E. BORRADAILE, PHD¹
 ANNE B. NEWMAN, MD²
 THOMAS A. WADDEN, PHD⁵

DAVID KELLEY, MD²
 RENA R. WING, PHD³
 F. XAVIER PI SUNYER, MD⁶
 VALERIE DARCEY, MS⁵
 SAMUEL T. KUNA, MD⁵
 FOR THE SLEEP AHEAD RESEARCH
 GROUP*

OBJECTIVE — To assess the risk factors for the presence and severity of obstructive sleep apnea (OSA) among obese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Unattended polysomnography was performed in 306 participants.

RESULTS — Over 86% of participants had OSA with an apnea-hypopnea index (AHI) ≥ 5 events/h. The mean AHI was 20.5 ± 16.8 events/h. A total of 30.5% of the participants had moderate OSA ($15 \leq \text{AHI} < 30$), and 22.6% had severe OSA ($\text{AHI} \geq 30$). Waist circumference (odds ratio 1.1; 95% CI 1.0–1.1; $P = 0.03$) was significantly related to the presence of OSA. Severe OSA was most likely in individuals with a higher BMI (odds ratio 1.1; 95% CI 1.0–1.2; $P = 0.03$).

CONCLUSIONS — Physicians should be particularly cognizant of the likelihood of OSA in obese patients with type 2 diabetes, especially among individuals with higher waist circumference and BMI.

Diabetes Care 32:1017–1019, 2009

We report the prevalence of obstructive sleep apnea (OSA) and the factors that increase the risk and severity of OSA among 306 obese patients with type 2 diabetes enrolled in Sleep AHEAD, a four-site ancillary study of the Look AHEAD Trial (Action for Health in Diabetes).

RESEARCH DESIGN AND METHODS

Look AHEAD (1,2) is a 16-center trial investigating the long-term health impact of an intensive lifestyle intervention in 5,145 overweight and obese adults with type 2 diabetes. Exclusion criteria for Sleep AHEAD were previous treatment for OSA.

The protocol was approved by each site's Institutional Review Board. Participants interested in Sleep AHEAD were consented at a Look AHEAD screening visit. Efforts were made to enroll individuals with undiagnosed OSA using a symptom questionnaire (3). Because almost all of the first 80 participants had OSA upon polysomnography, the symptom screen was dropped as an eligibility criteria.

Polysomnography

A home unattended overnight polysomnogram (Compumedics, Abbotsville, Australia) was performed using techniques developed for the Sleep Heart

Health Study except that airflow was measured by nasal pressure cannula and oronasal thermistor (4). Polysomnograms were scored using recommended criteria (5). Hypopneas had to be associated with a $\geq 4\%$ oxygen desaturation (5). The overall failure rate for the home polysomnography recordings was 8%; $>90\%$ were due to equipment breakdown.

Weight, height, waist (2), and neck (6) circumferences and the Epworth Sleepiness Scale (7) were assessed within 1 week of the polysomnogram without knowledge of its results.

Statistical analysis

Participants were categorized by apnea-hypopnea index (AHI) into mild ($5-14.9$), moderate ($15-29.9$), and severe (≥ 30) OSA. Group differences were assessed using χ^2 and t tests. Variables that were correlated with AHI were included in logistic regressions to predict the presence of OSA ($\text{AHI} \geq 5$) and, after removing participants with no OSA ($n = 40$), severity of OSA. The same variables were used to predict AHI as a continuous (log-transformed) variable. Interactions were included to assess sex differences. Research site was included in all models.

RESULTS

Participant characteristics

One participant with central sleep apnea was removed from all analyses. Participant characteristics are in Table 1. A total of 60% were women. Of the females, 90% were postmenopausal. Nearly three-quarters (72.0%) had dyslipidemia, 82.6% had hypertension, and 93.4% had the metabolic syndrome.

There were no differences between individuals who were enrolled in Sleep AHEAD ($n = 305$) and those enrolled in Look AHEAD but not in Sleep AHEAD at the four Sleep AHEAD sites ($n = 1,012$) in weight, BMI, sex, race/ethnicity, or waist circumference. Sleep AHEAD participants were slightly older (61.3 ± 6.5 vs. 58.7 ± 6.9 years; $P < 0.0001$) and had lower A1C values (7.2 ± 1.1 vs. $7.4 \pm 1.2\%$; $P = 0.03$) than Look AHEAD participants who were not enrolled in Sleep AHEAD. There were small but significant differences in the frequency of snoring

From ¹Temple University, Philadelphia, Pennsylvania; ²University of Pittsburgh, Pittsburgh, Pennsylvania; ³Brown University, Providence, Rhode Island; ⁴Clinilabs, New York, New York; ⁵University of Pennsylvania, Philadelphia, Pennsylvania; and ⁶Columbia University, New York, New York.

Corresponding author: Gary D. Foster, gfooster@temple.edu.

Received 26 September 2008 and accepted 28 February 2009.

Published ahead of print at <http://care.diabetesjournals.org> on 11 March 2009. DOI: 10.2337/dc08-1776.

Clinical trial reg. no. NCT00194259, www.clinicaltrials.gov.

*A full list of the members of the Sleep AHEAD Research Group is available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc08-1776/DC1>.

© 2009 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1—Sleep AHEAD participant characteristics at baseline

	Total Sleep AHEAD participants	Sleep AHEAD participants (male)	Sleep AHEAD participants (female)	P
n	305	122	183	
Race/ethnicity (%)				<0.0001
White	73.0	90.1	61.8	
African American	19.1	6.6	27.3	
Other	7.9	3.3	10.9	
Postmenopause	90.1	N/A	90.1	n/a
Age (years)	61.3 ± 6.5	61.4 ± 7.1	61.3 ± 6.1	0.89
BMI (kg/m ²)	36.5 ± 5.8	36.1 ± 5.6	36.7 ± 5.9	0.34
Weight (kg)	101.7 ± 18.0	110.9 ± 16.5	95.6 ± 16.2	<0.0001
Height (cm)	167.0 ± 9.7	175.5 ± 7.0	161.3 ± 6.6	<0.0001
Waist circumference (cm)	115.0 ± 13.0	120.9 ± 12.1	111.0 ± 12.1	<0.0001
Neck circumference (cm)	41.1 ± 4.4	44.4 ± 3.2	39.0 ± 3.1	<0.0001
A1C	7.2 ± 1.1	7.4 ± 1.1	7.1 ± 1.0	0.03
Total sleep time (h)	6.0 ± 1.2	5.8 ± 1.3	6.1 ± 1.1	0.03
Sleep efficiency (%)	77.5 ± 11.1	77.1 ± 11.8	77.7 ± 10.6	0.69
Time in non-REM stages (h)	4.9 ± 1.0	4.9 ± 1.1	5.0 ± 1.0	0.32
Time in REM stages (h)	1.0 ± 0.5	0.9 ± 0.5	1.1 ± 0.5	0.002
Sleep time supine (h)	2.1 ± 2.0	1.9 ± 1.9	2.2 ± 2.1	0.21
Obstructive apnea index	11.1 ± 12.8	14.2 ± 15.5	9.1 ± 10.2	0.008
Central apnea index	0.4 ± 1.0	0.6 ± 1.2	0.3 ± 0.7	0.003
Hypopneas with ≥4% oxygen desaturation*				
Apnea-hypopnea index	20.5 ± 16.8	24.6 ± 18.6	17.8 ± 15.0	0.001
Hypopnea index	9.0 ± 8.1	9.8 ± 8.3	8.4 ± 8.0	0.16
Oxygen desaturation index (≥4%)†	17.6 ± 14.7	20.0 ± 15.9	15.9 ± 13.7	0.03
Participants that spent >10% of time below 90% saturation (%)	16.1	20.5	13.1	0.11
Oxygen saturation nadir	81.4 ± 8.3	81.2 ± 7.5	81.6 ± 8.8	0.65
Epworth Sleepiness Score	7.9 ± 4.6	8.0 ± 4.5	7.8 ± 4.7	0.80

Data are means ± SD. *See Ref. 5. †Based on oxygen desaturation events ≥4% (5). REM, rapid eye movement.

(3.1 ± 1.0 Sleep AHEAD; 2.8 ± 1.1 Look AHEAD, $P < 0.01$) (1 = do not snore anymore, to 4 = 6–7 nights per week) and in those already diagnosed with OSA (7.6% Sleep AHEAD; 13.4% Look AHEAD, $P < 0.01$). There were no differences in the presence or loudness of snoring or excessive daytime sleepiness. No symptoms assessed in this study predicted the presence or severity of OSA.

Sleep-disordered breathing

Only 13.4% of participants did not have OSA, whereas 33.4% had mild OSA, 30.5% moderate OSA, and 22.6% severe OSA. Similar findings were obtained in participants who did not have a previous diagnosis of OSA and had not been prescreened based on symptoms ($n = 202$). Males had a higher AHI than females. BMI, sex, and waist and neck circumference were related to AHI. Waist circumference was the only significant predictor (odds ratio [OR] 1.1; 95% CI 1.0–1.1; $P = 0.03$) of the presence of OSA (AHI ≥5). Independent of other variables, a

1-cm increase in waist circumference was associated with a 10% increase in the predicted odds of the presence of OSA (AHI ≥5).

In participants with AHI ≥5 ($n = 264$), BMI was the only significant predictor of severe OSA (OR 1.1; 95% CI 1.0–1.2; $P = 0.03$). Independent of other variables, a 1-unit increase in BMI was associated with a 10% increase in the predicted odds of severe OSA. Sex approached significance. Males were 2.2 times more likely to have severe OSA than females (OR 2.2; 95% CI 0.9–5.3; $P = 0.08$). In the full sample ($n = 305$), waist circumference was the only statistically significant predictor of continuous AHI ($\beta = 0.02$, 95% CI 0.01–0.03; $P = 0.04$). None of the interaction terms was statistically significant.

CONCLUSIONS— The most remarkable finding of this study is the exceedingly high prevalence of undiagnosed OSA (86.6%) among obese patients with type 2 diabetes. These data

were suggested by earlier studies of smaller samples and/or that used less than full polysomnography to assess AHI (8–10). Equally alarming is the unequivocally elevated mean AHI (20.5 ± 16.8) of this group and that 22.6% of participants had severe OSA. Even though obesity, age, and menopause are known risk factors for OSA (11–13), the extraordinarily high rates of undiagnosed and severe OSA in this cohort are remarkable. Given the similarities between the participants in Sleep AHEAD versus Look AHEAD (but not in Sleep AHEAD), our results do not appear to be secondary to a selection bias. Potential links between OSA and type 2 diabetes have been recently reviewed (14). Definitive conclusions about the prevalence of OSA among individuals with type 2 diabetes require a control group without diabetes.

The second major finding was that waist circumference was the only significant predictor of the presence of OSA (AHI ≥5) (15). The failure of neck circumference and BMI to contribute to the

model is likely due to the restricted upper range of these variables in this sample compared with a community sample. Having a higher BMI, however, did increase the risk of severe OSA (AHI \geq 30).

CONCLUSIONS— Physicians treating obese patients with type 2 diabetes should consider the possibility of OSA, even in the absence of symptoms, especially in individuals with higher waist circumference and BMI. The high prevalence of OSA in obese patients with type 2 diabetes represents a serious public health problem and raises the possibility that some of the morbidity and mortality associated with type 2 diabetes may be attributable to undiagnosed OSA.

Acknowledgments— This work was supported by the National Institutes of Health National Heart, Lung, and Blood Institute Grant HL070301 and National Institute of Diabetes and Digestive and Kidney Diseases grants DK60426, DK56992, and DK057135.

The authors received grant/research support from the following: Andle, Arena, Aventis, Cephalon, Elan, Epix, Evotec, Forest, GlaxoSmithKline, H. Lundbeck, King, Merck, Neurim, Neurocrine Biosciences, Neutrogen, Organon, Orphan Medical, Pfizer, Respiroics, sanofi-aventis, sanfo-synthe, Schering-Plough, Sepracor, Somaxon, Takeda Pharmaceuticals North America, Transcept, UCB Pharma, Predix, Vanda, and Whyeth-Ayerst Research. The authors received consulting fees from the following: Alexza, Arena, Aventis, Viovail, Boehringer-Ingelheim, Cephalon, Elan, Eli Lilly, Evotec, Forest, Glaxo Smith Kline, Jazz, King Pharmaceuticals, Ligand McNeil, Merck, Neurocrina Biosciences, Organon, Pfizer, Renovis, sanofi-aventis, select comfort, spracor, shire, somnus, takeda pharmaceuticals, Vels, and Wyeth. Honoraria was received from the following: Neurocrine Biosciences, King Pharmaceuticals, McNeil, sanofi-aventis, sanofi-synthelabo, Sepracor,

Takeda Pharmaceuticals, Vela Pharmaceuticals, and Wyeth-Ayerst Research. Ownership, Directorship: Clin Labs, Clinilabs IPA, and Clinilabe Physician Services. M.H.S. is a scientific consultant to Philips-Respiroics, which manufactures and distributes devices used to monitor sleep and diagnose and treat sleep disordered breathing, and is coinventor of BiPAP and has a financial interest in this brand and related technologies by Philips-Respiroics. No other potential conflicts of interest relevant to this article were reported.

References

- Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard SM, Johnson KC, Kahn SE, Knowler WC, Yankovski SZ, Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 2003;24:610–628
- Look AHEAD Research Group, Bray G, Gregg E, Haffner S, Pi-Sunyer XF, Wagenknecht LE, Walkup M, Wing R. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006;3:202–212
- Maislin G, Pack AI, Kribbs NB, Smith PL, Schwartz AR, Kline LR, Schwab RJ, Dinges DF. A survey screen for prediction of apnea. *Sleep* 1995;18:158–166
- Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study: Sleep Heart Health Research Group. *Sleep* 1998;21:759–767
- Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J Jr, Friedman L, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Loube DL, Owens J, Pancer JP, Wise M. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* 2005;28:499–521
- Calloway C, Chumlea W, Bouchard C. Circumferences. In *Anthropometric Standardization Manual*. Lohmann TG, Roche AF, Martorell R, Eds. Champaign, IL, Human Kinetics Publisher;1988:39–64
- Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep* 1992;15:376–381
- Brooks B, Cistulli PA, Borkman M, Ross G, McGhee S, Grustein RR, Sullivan CE, Yue DK. Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. *J Clin Endocrinol Metab* 1994;79:1681–1685
- Einhorn D, Stewart DA, Eрман MK, Gordon N, Philis-Tsimikas A, Casal E. Prevalence of sleep apnea in a population of adults with type 2 diabetes. *Endocr Pract* 2007;13:355–362
- West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 2006;61:945–950
- Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. *J Appl Physiol* 2005;99:1998–2007
- Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165:1217–1239
- Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, Ewy GA, Howard BV, Punjab NM. Diabetes and sleep disturbances. *Diabetes Care* 2003;26:702–712
- Shaw JE, Punjabi NM, Wilding JP, Alberti KG, Zimmet PZ. Sleep disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Task Force on Epidemiology and Prevention. *Diabetes Res Clin Pract* 2008;81:2–12
- Martinez-Rivera C, Abad J, Fiz JA, Rios J, Morera J. Usefulness of truncal obesity indices as predictive factors for obstructive sleep apnea syndrome. *Obesity (Silver Spring)* 2008;16:113–118