

Obstructive Sleep Apnea Is Independently Associated with Insulin Resistance

MARY S. M. IP, BING LAM, MATTHEW M. T. NG, WAH KIT LAM, KENNETH W. T. TSANG, and KAREN S. L. LAM

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong S.A.R., PR China

Epidemiological studies have implicated obstructive sleep apnea (OSA) as an independent comorbid factor in cardiovascular and cerebrovascular diseases. It is postulated that recurrent episodes of occlusion of upper airways during sleep result in pathophysiological changes that may predispose to vascular diseases. Insulin resistance is a known risk factor for atherosclerosis, and we postulate that OSA represents a stress that promotes insulin resistance, hence atherogenesis. This study investigated the relationship between sleep-disordered breathing and insulin resistance, indicated by fasting serum insulin level and insulin resistance index based on the homeostasis model assessment method (HOMA-IR). A total of 270 consecutive subjects (197 male) who were referred for polysomnography and who did not have known diabetes mellitus were included, and 185 were documented to have OSA defined as an apnea-hypopnea index (AHI) ≥ 5 . OSA subjects were more insulin resistant, as indicated by higher levels of fasting serum insulin ($p = 0.001$) and HOMA-IR ($p < 0.001$); they were also older and more obese. Stepwise multiple linear regression analysis showed that obesity was the major determinant of insulin resistance but sleep-disordered breathing parameters (AHI and minimum oxygen saturation) were also independent determinants of insulin resistance (fasting insulin: AHI, $p = 0.02$, minimum O_2 , $p = 0.041$; HOMA-IR: AHI, $p = 0.044$, minimum O_2 , $p = 0.022$); this association between OSA and insulin resistance was seen in both obese and nonobese subjects. Each additional apnea or hypopnea per sleep hour increased the fasting insulin level and HOMA-IR by about 0.5%. Further analysis of the relationship of insulin resistance and hypertension confirmed that insulin resistance was a significant factor for hypertension in this cohort. Our findings suggest that OSA is independently associated with insulin resistance, and its role in the atherogenic potential of sleep disordered breathing is worthy of further exploration.

Keywords: obstructive sleep apnea; independently associated; insulin resistance

Obstructive sleep apnea (OSA) is associated with increased cardiovascular and cerebrovascular morbidity (1–3). It is also recognized that many subjects with OSA have central obesity and other features of the metabolic syndrome (4–6), which is most widely accepted as being comprised of hyperinsulinemia, glucose intolerance, dyslipidemia, central obesity, and hypertension (7). These factors in the metabolic syndrome, also known as the “insulin resistance syndrome,” have been established as independent risk factors for vascular disease (7–9). Hence there is ongoing controversy regarding the causal versus comorbid relationship between OSA and cardiovascular disease.

It is postulated that the cerebral activation and increased sympathetic output related to sleep-disordered breathing may

provide a stress stimulus that triggers or aggravates some of these vascular risk factors, and thus confers independent predisposition to vascular pathogenicity. Notably, recent epidemiological studies provide strong evidence that OSA itself confers independent risks for the development of hypertension (10–12).

Insulin resistance, as indicated by an impaired biological response to insulin and hence a reduced insulin-mediated glucose disposal (13), has been implicated in the pathogenesis of the metabolic syndrome (7). Furthermore, there is evidence that insulin resistance predisposes to cardiovascular risk (7, 14–16). It is therefore important to determine if sleep apnea has any effect on insulin resistance.

Previous studies on the relationship between insulin resistance and OSA have yielded conflicting results (17–22). To test the hypothesis that sleep-disordered breathing is an independent risk factor for insulin resistance, we examined a cross-sectional cohort of subjects with a range of sleep-disordered breathing from absent to severe and analyzed the relationship between sleep-disordered breathing and insulin resistance.

METHODS

Subjects

Consecutive subjects admitted to the Sleep Laboratory at the University Department of Medicine, Queen Mary Hospital, for overnight sleep studies in March 1999 to February 2000, either as part of a community-based prevalence study (23) or because of a clinical referral for suspected sleep apnea, were recruited. Exclusion criteria were subjects with known diabetes mellitus on medications, acromegaly, chronic renal failure, on systemic steroid treatment, and on hormonal replacement therapy. A questionnaire on demographics, sleep symptoms, medical history, and medications was completed. Body habitus was measured in light clothing and bare feet using standard anthropometric methods (24). Waist and hip circumferences were measured to the nearest 0.5 cm. Waist circumference was measured midway between the lower costal margin and iliac crest, and the hip circumference as the maximal girth at the greater trochanters. On the morning after the sleep study, blood pressure was taken on waking at 7–8 A.M. in the supine position using Dinamap (Critikon Inc, Florida). Venous blood was then obtained in the fasting state for the measurement of glucose and insulin. All subjects gave written informed consent to blood taking. The study was approved by the Institutional Ethics Committee.

Polysomnogram

The polysomnography (PSG) (Alice 3 System; Healthdyne, Atlanta, GA) consisted of continuous polygraphic recording from surface leads for electroencephalography, electrooculography, electromyography, electrocardiography, thermistors for nasal and oral airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximeter for oxyhemoglobin level, tracheal microphone for snoring, and sensors for leg and sleep position. PSG records were scored manually. Sleep data were scored according to standard criteria (25). Arousals were scored according to established criteria (26). Respiratory events were scored according to AASM criteria (27): apnea was defined as complete cessation of airflow lasting 10 s or more; hypopnea was defined as either a $\geq 50\%$ reduction in airflow for 10 s or more or a less than 50% but discernible reduction in airflow accompanied either by a decrease in oxyhemoglobin saturation of $> 3\%$ or an

(Received in original form March 1, 2001; accepted in final form November 23, 2001)

Correspondence and requests for reprints should be addressed to Mary S.M. Ip, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong SAR, PR China. E-mail: msmip@hkucc.hku.hk

Am J Respir Crit Care Med Vol 165, pp 670–676, 2002

DOI: 10.1164/rccm.2103001

Internet address: www.atsjournals.org

arousal. The average number of episodes of apnea and hypopnea per hour of sleep (the apnea-hypopnea index, AHI) was calculated as the summary measurement of sleep-disordered breathing.

Plasma glucose was measured by the glucose oxidase method on a Beckman autoanalyzer (Beckman Instruments, Brea, CA). Serum insulin was determined with a microparticle enzyme immunoassay on an Abbott IMx system (Abbott, Abbott Park, IL), using a monoclonal mouse anti-human insulin antibody. Intra- and interassay coefficients of variation were < 4% (28).

The estimation of insulin resistance by the homeostasis model assessment method (HOMA-IR) as previously described (29) was calculated by the following formula: fasting serum insulin ($\mu\text{U/ml}$) \times fasting plasma glucose (mmol/L)/22.5.

Statistical Analysis

All clinical parameters were summarized by descriptive statistics. Comparisons of continuous clinical parameters between subjects with different categorization by AHI were made by Mann-Whitney test, one-way ANOVA, and Kruskal-Wallis H test, and categorical parameters were compared by Chi-square test. Spearman's rank correlation coefficient was used to examine the association of two parameters.

Severity of OSA was measured by AHI, minimum oxygen saturation (SaO_2), time duration with $\text{SaO}_2 < 90\%$, and arousal index. To determine if they were individually associated with insulin resistance independent of obesity and central obesity, stepwise multiple regression was used with either fasting insulin or HOMA-IR as the dependent variable. The corresponding set of independent variables included obesity (BMI), central obesity (either waist/hip ratio [WHR] or waist circumference), OSA (either AHI, minimum SaO_2 , time duration with $\text{SaO}_2 < 90\%$, or arousal index), sex, age, and smoking (never smoker/chronic or ex-smoker). Fasting insulin and HOMA-IR were logarithmic transformed before they were used as the dependent variable and deleted studentized residuals of all regression models were examined for the validity of model assumptions.

To determine whether a significant association of sleep parameters with insulin resistance was similar in obese and nonobese subjects, subjects were categorized into obese and nonobese groups based on the WHO recommendation for Asians, i.e., BMI < 25 and BMI \geq 25 (30). Regression analyses were then pursued with the interaction between this categorical variable and AHI, the corresponding main effects, and other identified significant confounders of insulin resistance considered as independent variables.

Apart from considering sex as a covariate in the multiple linear regression for insulin resistance, the influence of sex on the association between insulin resistance and AHI/BMI was further examined by considering their interactions (insulin levels or HOMA-IR and AHI or BMI) in the regression analysis.

The clinical importance of insulin resistance in this cohort was evaluated by performing a stepwise logistic regression of blood pressure on fasting insulin or HOMA-IR, and other confounding variables including BMI, WHR, age, smoking, and sex. Hypertension was defined as either a known history of hypertension on drug treatment or blood pressure (BP) measurements of systolic BP \geq 140 mm Hg or diastolic BP \geq 90 mm Hg.

Two-tailed p values of less than 0.05 were considered to indicate significance.

Statistical analysis was performed by SPSS for Windows software (Version 10.0.7).

RESULTS

Subjects

Table 1 summarizes the study characteristics of the 270 subjects. None of them had known diabetes mellitus on medications. Seventeen had hypertension on antihypertensive medications, and three had both hypertension and hyperlipidemia on medications.

Fasting insulin levels and HOMA-IR, unadjusted for any covariate, were significantly higher in the group with OSA, defined by AHI \geq 5 ($p < 0.001$) (Table 1). Most of the sample characteristics, including the indicators of insulin resistance

TABLE 1. COMPARISON OF SAMPLE CHARACTERISTICS IN THOSE WITH AND WITHOUT OSA*

	AHI < 5 (n = 85)	AHI \geq 5 (n = 185)	p Value
Male, no. (%) [†]	47 (55.3)	150 (81.1)	< 0.001
Smokers, no. (%) [†]	5 (5.9)	22 (11.9)	0.117
Drinkers, no. (%) [†]	5 (5.9)	12 (6.5)	0.849
AHI, no. of events/h	2.0 (1.0, 3.9)	21.9 (12.2, 43.8)	< 0.001
Min O ₂ , %	90.0 (85.9, 93.0)	76.0 (69.0, 81.0)	< 0.001
SaO ₂ < 90%, min	0.0 (0.0, 1.5)	27.0 (7.0, 85.5)	< 0.001
Arousal index	14.2 (8.4, 20.5)	20.7 (12.1, 31.6)	< 0.001
Age, yr	42.0 (37.0, 46.0)	45.0 (39.5, 52.0)	< 0.001
Body mass index, kg/m ²	24.4 (21.8, 26.6)	27.8 (24.8, 30.7)	< 0.001
Neck circumference, cm	36.0 (32.6, 38.0)	39.0 (37.0, 41.5)	< 0.001
Waist circumference, cm	84.3 (75.6, 89.4)	95.0 (88.0, 102.0)	< 0.001
Hip circumference, cm	96.8 (93.9, 99.9)	101.3 (96.0, 107.0)	< 0.001
Waist/hip ratio	0.86 (0.82, 0.91)	0.93 (0.89, 0.97)	< 0.001
Insulin, $\mu\text{U/ml}$	5.4 (3.5, 8.9)	7.8 (5.2, 11.7)	0.001
Glucose, mmol/L	5.1 (4.7, 5.6)	5.3 (5.0, 5.7)	0.001
HOMA-IR	1.3 (0.8, 2.1)	1.8 (1.2, 3.0)	< 0.001
Systolic BP, mm Hg	123.0 (115.0, 131.0)	128.5 (120.0, 139.0)	0.003
Diastolic BP, mm Hg	71.0 (62.0, 79.0)	78.5 (70.0, 85.8)	< 0.001

Definition of abbreviations: AHI = apnea-hypopnea index; BP = blood pressure; HOMA-IR = homeostasis model assessment for estimating insulin resistance; OSA = obstructive sleep apnea.

* All parameters stated by median (interquartile range) unless otherwise stated. Comparison by Mann-Whitney test.

[†] Comparison by Chi-square test.

and its major determinants, obesity, central obesity, and male sex, were significantly different over the range of AHI stratum, with an apparent increase with increasing severity of sleep-disordered breathing (Table 2).

The relationship between AHI and fasting insulin or HOMA-IR was nonlinear (Figure 1). The fasting insulin and HOMA-IR values from one patient were found to be outlying from other observations, and data from this one subject have been removed before proceeding to regression analysis.

In the regression models using fasting insulin level as the dependent variable, significant predictors were BMI, age, AHI, and minimum oxygen saturation (Table 3). In the models using HOMA-IR as the dependent variable, significant predictors were similarly BMI, AHI, and minimum oxygen saturation when WHR was the parameter for central obesity, whereas AHI was no longer significant when waist circumference was used as the parameter for central obesity (Table 4).

The β coefficients of AHI for insulin level and HOMA-IR were 0.005 (Tables 3 and 4). Because logarithmic transformation of insulin/HOMA-IR values have been used, a one unit increase in AHI would result in a 0.5% increase in fasting insulin levels or HOMA-IR values.

In the analysis for a differential effect of the association between OSA and insulin resistance in obese and nonobese subjects, the interaction term for obesity and AHI was not significant (Table 5), suggesting that the association was similar in both obese and nonobese subjects.

Analysis for influence of sex on the association between insulin resistance and AHI/BMI did not reveal any substantial effect of sex on the identified associations ($p > 0.15$ for all interaction terms).

In this cohort, hypertensive subjects had significantly higher insulin and HOMA-IR values compared with normotensive subjects (insulin: 15.1 ± 31.8 versus 7.7 ± 8.1 $\mu\text{U/ml}$, $p < 0.001$; HOMA-IR: 3.9 ± 7.7 versus 1.8 ± 2 , $p < 0.001$). Multiple logistic regression showed that insulin resistance was a significant independent determinant of blood pressure status (Table 6).

TABLE 2. SAMPLE CHARACTERISTICS ACCORDING TO AHI CATEGORIES*

	AHI Stratum				p Value
	Group I < 5	Group II ≥ 5 to < 15	Group III ≥ 15 to < 30	Group IV ≥ 30	
No., %	85 (31.5)	59 (21.9)	48 (17.8)	78 (28.9)	
Male, no. (%) [†]	47 (55.3)	42 (71.2)	38 (79.0)	70 (89.7)	< 0.001
Smokers, no. (%) [†]	5 (5.9)	3 (5.1)	7 (14.6)	12 (15.4)	0.010
Drinkers, no. (%) [†]	5 (5.9)	1 (1.7)	3 (6.3)	8 (10.3)	0.236
AHI, no. of events/h [‡]	2.3 (1.6)	9.3 (2.8)	20.6 (4.4)	50.2 (13.7)	< 0.001
Min O ₂ , % [‡]	88.3 (10.7)	82.1 (5.9)	75.7 (8.9)	63.6 (15.1)	< 0.001
Sa _{O₂} < 90%, min [‡]	3.4 (14.8)	16.5 (55.1)	27.7 (38.3)	121.4 (90.1)	< 0.001
Arousal index [‡]	15.0 (9.2)	18.3 (12.4)	18.1 (9.9)	31.5 (19.6)	< 0.001
Age, yr [‡]	42.2 (7.9)	46.3 (9.2)	47.2 (11.2)	46.6 (12.0)	0.004
Body mass index, kg/m ²	24.4 (3.5)	26.9 (4.1)	28.4 (4.6)	29.5 (4.8)	< 0.001
Neck circumference, cm	35.7 (3.4)	37.6 (3.8)	39.3 (3.1)	40.7 (3.7)	< 0.001
Waist circumference, cm	83.3 (10.1)	89.6 (10.1)	95.2 (9.6)	99.5 (11.9)	< 0.001
Hip circumference, cm [‡]	96.5 (7.0)	99.8 (8.1)	101.6 (7.9)	105.6 (9.4)	< 0.001
Waist/hip ratio	0.86 (0.07)	0.90 (0.06)	0.94 (0.06)	0.94 (0.07)	< 0.001
Glucose, mmol/L	5.3 (1.4)	5.3 (0.8)	5.4 (0.7)	5.6 (0.7)	0.166
Insulin, μU/ml [‡]	6.8 (4.2)	9.0 (12.7)	9.1 (6.7)	15.6 (34.3)	< 0.001
HOMA-IR [‡]	1.6 (1.1)	2.2 (3.1)	2.3 (2.0)	4.0 (8.4)	< 0.001
Systolic BP, mm Hg	123.1 (13.9)	127.4 (17.5)	127.3 (13.5)	130.8 (14.0)	0.023
Diastolic BP, mm Hg	70.6 (10.8)	74.8 (14.3)	78.8 (13.3)	78.8 (12.1)	< 0.001

Definition of abbreviations: AHI = apnea-hypopnea index; BP = blood pressure; HOMA-IR = homeostasis model assessment for estimating insulin resistance.

* All parameters stated by mean (SD) unless otherwise indicated. All tested by one-way ANOVA.

[†] Tested by Chi-square test.

[‡] Tested by Kruskal-Wallis H test.

DISCUSSION

The findings of this study suggested that sleep-disordered breathing has an independent adverse effect on insulin resistance. Results demonstrated that obesity was the major determinant of insulin resistance in this cohort, but despite controlling for obesity and other important confounding factors of insulin resistance, AHI and/or minimum oxygen saturation were significant determinants of fasting insulin level and HOMA-IR.

The relationship of insulin resistance and other metabolic variates is one of a complex interactive regulation. It is established that central obesity leads to insulin resistance via increased lipolysis and fatty acid availability (31, 32). Furthermore, it has been hypothesized that a stress reaction activating

the hypothalamic-pituitary-adrenal axis leading to release of cortisol and other hormones may be a trigger for mechanisms generating insulin resistance and preferential abdominal fat accumulation (33) and may thus contribute to insulin resistance.

In the context of subjects with OSA, the strong association of sleep-disordered breathing and atherosclerotic vascular diseases has long been observed (1-3). Many subjects with OSA are known to have coexisting risk factors for cardiovascular and cerebrovascular diseases, in particular the factors that comprise the metabolic syndrome of central obesity, hypertension, dyslipidemia, and insulin resistance or glucose intolerance. However, OSA itself is characterized by increased nocturnal sympathetic output (34) and other pathophysiologi-

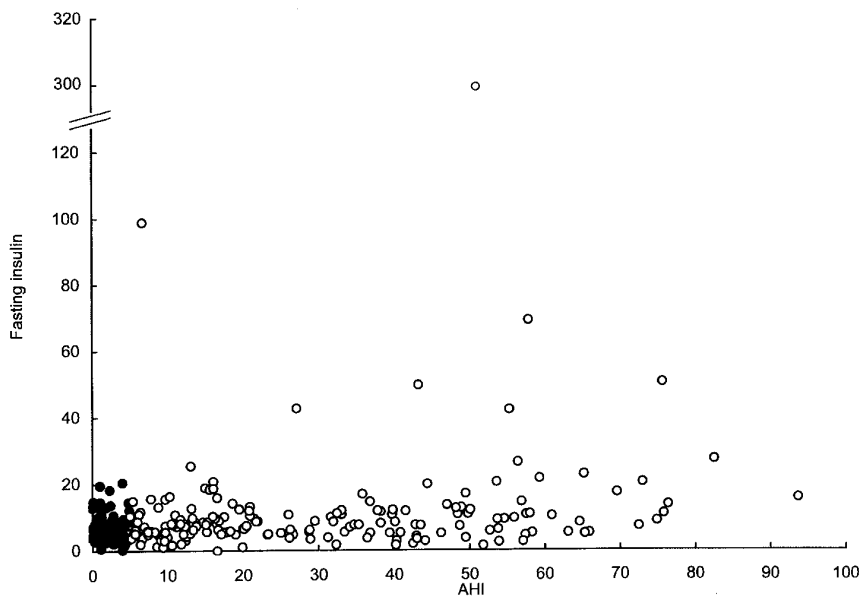


Figure 1. Scatter plot of apnea-hypopnea index (AHI) and corresponding fasting insulin levels (μU/ml). Number of subjects = 270. ● AHI < 5; ○ AHI ≥ 5.

TABLE 3. STEPWISE MULTIPLE LINEAR REGRESSION MODELS FOR FASTING INSULIN

	BMI + Waist/Hip Ratio*			BMI + Waist*	
	Estimate ± SE	p Value		Estimate ± SE	p Value
R ² = 22.6%			R ² = 22.6%		
BMI, kg/m ²	0.060 ± 0.010	< 0.001	BMI, kg/m ²	0.060 ± 0.010	< 0.001
AHI, event/h	0.005 ± 0.002	0.020	AHI, event/h	0.005 ± 0.002	0.020
Age, yr	-0.009 ± 0.004	0.020	Age, yr	-0.009 ± 0.004	0.020
R ² = 22.2%			R ² = 22.2%		
BMI, kg/m ²	0.061 ± 0.009	< 0.001	BMI, kg/m ²	0.061 ± 0.009	< 0.001
Min Sa _O ₂	-0.007 ± 0.003	0.041	Min Sa _O ₂	-0.007 ± 0.003	0.041
Age, yr	-0.009 ± 0.004	0.019	Age, yr	-0.009 ± 0.004	0.019

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index.
 * Other independent variables: AHI, time with oxygen saturation < 90%, minimum oxygen saturation (Min Sa_O₂), arousal index, age, sex, and smoking.

cal mechanisms that may provide an independent predisposition to the generation of atherosclerosis, either directly or through aggravation of some of the risk factors such as hypertension (35, 36). Sympathetic activation also raises circulating free fatty acid via stimulation of lipolysis and promotes insulin resistance (37). Furthermore, these risk factors may also interact and develop a vicious cycle culminating in increased vascular risks. There is now substantial epidemiological evidence to support the finding that OSA has an independent adverse effect on hypertension (10–12).

The association between OSA and insulin resistance remains controversial. Previous studies have used different methodological approaches and target populations, and results have been conflicting. Our study has the strength of having a relatively large sample size with good representation of both subjects with and without OSA. Furthermore, the documentation of sleep-disordered breathing was based on full in-laboratory polysomnograms.

In the evaluation of insulin sensitivity (or its corollary, insulin resistance), the gold standard is the euglycemic clamp method (38). However, this method is invasive and labor intensive, thus hindering its application as a research tool when investigating a large number of subjects. Instead, we have used the absolute fasting insulin level as well as the computer-solved index, HOMA-IR. The fasting insulin levels in an individual is determined by both insulin secretion and insulin resistance, although the former is usually stable in nondiabetic subjects. It has been shown to be a useful guide to insulin resistance in normoglycemic individuals, although less so in subjects with established diabetes mellitus (13). The HOMA of insulin sensitivity was proposed as a simple and inexpensive alternative to more sophisticated techniques (29). The method derives an estimation of insulin sensitivity from mathematical modeling of fasting blood glucose and insulin concentrations and

has been compared with several other methods of measuring insulin sensitivity, including different glucose clamp techniques and intravenous glucose tolerance tests (39–41). Results have indicated the close correlation between the degree of insulin resistance estimated by HOMA and these methods. Recently, HOMA has been validated against the gold standard method of euglycemic clamp in 115 subjects, and there was a strong correlation between clamp-measured total glucose disposal and HOMA-estimated insulin sensitivity, with a correlation coefficient of -0.820 (39). Furthermore, this close correlation did not show any substantial difference between men and women, young and older subjects, nonobese and obese subjects, nondiabetic and diabetic subjects, and normotensive and hypertensive subjects (39). Due to its simplicity, HOMA has been used in large clinical or epidemiological studies (41–44).

In a previous study that utilized the euglycemic clamp to investigate insulin resistance in a group of 50 healthy subjects of whom one-third had an AHI ≥ 10 on a sleep study with a portable device MESAM-IV, no correlation was identified between insulin resistance and sleep-disordered breathing after adjusting for BMI (18). The conclusion was that insulin resistance preceded rather than followed sleep-disordered breathing. However, the small number of subjects with sleep apnea in the cohort and the use of limited polysomnographic assessment could limit the ability to detect any independent effect of sleep-disordered breathing on insulin resistance.

On the other hand, in a study involving 261 men in which the relative contributions of body weight and sleep apnea to blood pressure, fasting insulin, and fasting glucose were examined, there was evidence for an independent association between sleep apnea and fasting insulin levels in those with a BMI > 29 (17).

More recently, a study on cytokines, insulin resistance, and visceral obesity in OSA indicated that mean plasma insulin

TABLE 4. STEPWISE MULTIPLE LINEAR REGRESSION MODELS FOR HOMA-IR

	BMI + Waist/Hip Ratio*			BMI + Waist*	
	Estimate ± SE	p Value		Estimate ± SE	p Value
R ² = 24.5%			R ² = 24.4%		
BMI, kg/m ²	0.071 ± 0.010	< 0.001	BMI, kg/m ²	0.047 ± 0.017	0.005
AHI, event/h	0.005 ± 0.002	0.044	Waist, cm	0.014 ± 0.006	0.028
R ² = 24.5%			R ² = 24.5%		
BMI, kg/m ²	0.070 ± 0.010	< 0.001	BMI, kg/m ²	0.070 ± 0.010	< 0.001
Min Sa _O ₂	-0.008 ± 0.004	0.022	Min Sa _O ₂	-0.008 ± 0.004	0.022

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index.
 * Other independent variables: AHI, time with oxygen saturation < 90%, minimum oxygen saturation (Min Sa_O₂), arousal index, age, sex, and smoking.

TABLE 5. REGRESSION ANALYSIS OF FASTING INSULIN LEVELS AND HOMA-IR TO DETERMINE WHETHER THE EFFECTS OF AHI ON OBESE AND NONOBESE PATIENTS WERE SIMILAR

Independent Variable	Estimate	Standard Error	p Value
Fasting insulin levels			
Body mass index			
< 25	-0.41	0.12	0.001
≥ 25	0		
AHI	0.008	0.002	0.001
Age	-0.009	0.004	0.019
AHI × BMI interaction	0.0002	0.004	0.962
HOMA-IR			
Body mass index			
< 25	-0.56	0.12	< 0.001
≥ 25	0		
AHI	0.007	0.003	0.011
AHI × BMI interaction	0.004	0.005	0.403

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; HOMA-IR = homeostasis model assessment for estimating insulin resistance.

levels in 14 obese subjects with OSA were significantly higher than BMI-matched controls with no OSA, suggesting that sleep-disordered breathing was an independent risk factor for hyperinsulinemia (22). The same group of workers also studied women with polycystic ovary syndrome compared with premenopausal controls, and insulin resistance was shown to have a stronger association with sleep-disordered breathing than with BMI or testosterone, supporting a close independent link between insulin resistance and OSA in these subjects (45).

The association of diabetes mellitus and OSA has been evaluated in a sample of 116 age-stratified men with hypertension selected from subjects in a population-based study in Sweden. It was shown that although obesity was the main risk factor for diabetes mellitus, coexistent severe OSA may add to the risk independently (46).

Studies looking at the effect of treatment of OSA on insulin resistance also showed conflicting results. In a study that compared fasting insulin levels in 15 subjects with OSA with body habitus-matched controls, before and after 3 mo of continuous positive airway pressure (CPAP) treatment in the OSA group, no difference was detected in either comparison (20). Similarly, in a recent report on leptin and visceral fat in OSA, no significant change was seen in insulin levels in 12 subjects treated with CPAP (47). However, in another study, CPAP treatment of 10 subjects with diabetes and OSA resulted in a

reduction of fasting insulin despite maintenance of BMI (19). The independent effect of OSA on insulin resistance, if any, is anticipated to be of modest magnitude only, and may not be easy to detect. The compliance of the use of CPAP in these studies was probably based on self-reporting, which made it difficult to evaluate the "true effectiveness" of CPAP. Furthermore, OSA is a chronic disorder and metabolic changes such as fat redistribution to visceral component may have occurred (47), rendering treatment of OSA, especially in the short term, apparently ineffective in modifying insulin sensitivity.

The major confounding factor in analysis of insulin resistance in OSA is obesity. Measures of obesity including BMI, waist circumference, and WHR have been demonstrated to correlate closely with insulin resistance, and central or abdominal obesity has been shown to be more predictive of insulin resistance than general obesity (48, 49). The regression models indicated that insulin resistance in this cohort was highly dependent on BMI. Nevertheless, AHI and minimum oxygen saturation emerged consistently as independent determinants of insulin resistance, although their effects were much smaller than that of obesity. In the HOMA regression models in which waist circumference was considered, only BMI, waist circumference, and minimum oxygen saturation were significant determinants of insulin resistance and not AHI. It is known that waist circumference is closely correlated with AHI and this may render it very difficult to see any effect of AHI on insulin resistance (50).

In this cohort, age was also noted to have a negative correlation with fasting insulin levels, which would not be expected of a general population in which age per se marginally increases insulin resistance. However, insulin levels are also affected by insulin secretion and the reduction with age may be more obvious in those with increased demand on β -cell reserve such as these subjects with OSA. This may explain the inverse relationship seen between age and insulin level but not HOMA-IR, which is a more reliable index of insulin resistance.

In a previous study, it has been reported that the effect of OSA on insulin resistance was seen only in obese subjects but not in nonobese subjects with OSA (17). In our subjects, there was no significant effect of interaction between AHI and BMI, suggesting that this association between sleep-disordered breathing and insulin resistance was present in both obese and nonobese subjects.

Premenopausal women are more insulin sensitive than men because women have less visceral fat despite a higher total body fat mass, whereas postmenopausal women have insulin sensitivity similar to men (51). Sex has been considered as one of the covariates, and no independent effect on insulin resistance was seen. There was also no evidence of a different susceptibility to insulin resistance in males and females with the same degree of obesity and sleep-disordered breathing, although the sample sizes of the two sexes may not be large enough to exclude this definitively.

Although our findings support an independent association between sleep-disordered breathing and insulin resistance, the clinical relevance of this modest magnitude of increased insulin resistance due to OSA is difficult to define. Because insulin resistance is a known risk factor for hypertension, we analyzed the relationship between blood pressure and insulin resistance in this cohort. Results showed that insulin resistance was an independent determinant of hypertension despite controlling for major confounding variables of obesity and age. No direct quantitative interpretation can be given to these findings, but it would be reasonable to surmise that severe OSA with a very high AHI or very low minimum oxygen saturation would not be devoid of adverse clinical relevance.

TABLE 6. STEPWISE MULTIPLE LOGISTIC REGRESSION MODELS FOR HYPERTENSION*

Independent Variable	Systolic BP \geq 140 mm Hg or Diastolic BP \geq 90 mm Hg or the Use of Antihypertensive Medication	
	Odds Ratio	95% CI
Model with insulin		
BMI	1.11	1.04-1.18
Insulin	1.04	1.00-1.08
Age	1.03	1.00-1.06
Model with HOMA-IR		
BMI	1.09	1.02-1.17
HOMA-IR	1.21	1.02-1.44
Age	1.03	1.00-1.06

Definition of abbreviations: BMI = body mass index; BP = blood pressure; CI = confidence interval; HOMA-IR = homeostasis model assessment for estimating insulin resistance.

* Parameters entered into model: insulin/HOMA-IR, BMI, waist/hip ratio, age, sex, and smoking.

Hence, our results suggest that sleep-disordered breathing is independently associated with insulin resistance. The role of increased insulin resistance as one of the intermediary mechanisms by which sleep apnea predisposes to vascular pathogenicity is worthy of further exploration.

Acknowledgment: The authors gratefully acknowledge Dr. Daniel Fong, senior medical statistician of the Clinical Trials Center, The University of Hong Kong, for his expert statistical advice. We also thank Ms. Audrey Ip and Ms. Rosa Wong for technical assistance and Ms. Wendy Mok for assistance in statistical analysis.

References

- Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkilä K, Sarna S. Snoring as a risk factor for ischaemic heart disease and stroke in men. *Br Med J* 1987;294:16–19.
- Hung J, Whitford EG, Parsons RW, Hilman DR. Association of sleep apnea with myocardial infarction in men. *Lancet* 1990;336:261–264.
- Fletcher EC. Obstructive sleep apnoea and cardiovascular morbidity. *Monaldi Arch Chest Dis* 1996;51:77–80.
- Levinson PD, McGarvey ST, Carlisle CC, Eveloff SE, Herbert PN, Millman RP. Adiposity and cardiovascular risk factors in men with obstructive sleep apnea. *Chest* 1993;103:1336–1342.
- Grunstein RR, Wilcox I, Yang TS, Gould Y, Hedner J. Snoring and sleep apnea in men: association with central obesity and hypertension. *Int J Obes* 1993;17:533–540.
- Wilcox I, McNamara SG, Collins FL, Grunstein RR, Sullivan CE. "Syndrome Z": the interaction of sleep apnea, vascular risk factors, and heart disease. *Thorax* 1998;53:S25–S28.
- Reaven G. Role of insulin resistance in human disease. Banting Lecture. *Diabetes* 1988;37:1595–1607.
- Kannel WN. Some lessons in cardiovascular epidemiology from Framingham. *Am J Cardiol* 1976;37:269–282.
- Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Interventional Trial (MRFIT). *JAMA* 1986;256:2823–2828.
- Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378–1384.
- Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *Br Med J* 2000;320:479–482.
- Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA* 2000;283:1829–1836.
- American Diabetes Association. Consensus Development Conference on Insulin Resistance. *Diabetes Care* 1998;21:1–5.
- Haffner SM, Miettinen H. Insulin resistance implications for type II diabetes mellitus and coronary heart disease. *Am J Med* 1997;103:152–162.
- Laakso M, Sarlund H, Salonen ZR, Suhonen M, Pyorala K, Salonen JT, Karhapää P. Asymptomatic atherosclerosis and insulin resistance. *Arterioscler Thromb* 1991;11:1068–1076.
- Bressler B, Bailey S, Matsuda M, Fronzo RM. Insulin resistance and coronary artery disease. *Diabetologia* 1996;39:1345–1360.
- Strohl KP, Novak RD, Singer W, Cahan C, Boehm KD, Denko CW, Hoffstein VS. Insulin levels, blood pressure and sleep apnea. *Sleep* 1994;17:614–618.
- Stoohs RA, Facchini F, Guilleminault C. Insulin resistance and sleep-disordered breathing in healthy humans. *Am J Respir Crit Care Med* 1996;154:170–174.
- Brooks B, Cistulli PA, Borkman M, Ross G, McGhee S, Grunstein 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 Endo Metab* 1994;79:1681–1685.
- Davies RJO, Turner R, Crosby J, Stradling JR. Plasma insulin and lipid levels in untreated obstructive sleep apnoea and snoring; their comparison with matched controls and response to treatment. *J Sleep Res* 1994;3:180–185.
- Tiihonen M, Partinen M, Narvanen S. The severity of obstructive sleep apnoea is associated with insulin resistance. *J Sleep Res* 1993;2:56–61.
- Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endo Metab* 2000;85:1151–1158.
- Ip MSM, Lam B, Lauder IJ, Chung KF, Tsang KW, Mok YW, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest* 2000;119:62–69.
- Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign IL: Human Kinetics Books; 1988. p. 39–54.
- Rechtschaffen A, Kales AA, editors. A manual of standardized terminology, techniques and scoring for sleep stages of human subjects. Washington, D.C.: Government Printing Office. NIH Publication No. 204, 1968.
- American Sleep Disorders Association. EEG arousals: scoring rules and examples; ASDA report. *Sleep* 1992;15:173–184.
- The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;22:667–689.
- Lam KSL, Tiu SC, Tsang MW, Ip TP, Tam SCF. Acarbose in NIDDM patients with poor control on conventional oral agents. *Diabetes Care* 1998;21:1154–1158.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419.
- International Diabetes Institute, World Health Organisation. The Asia-Pacific perspective: redefining obesity and its treatment. Melbourne, Australia: Health Communications Australia Pty Ltd; 2000. p. 15–21.
- Rebrin K, Steil GM, Mittelman S, Bergman RN. Causal linkage between insulin suppression of lipolysis and suppression of liver glucose output. *J Clin Invest* 1996;98:741–749.
- Hertz R, Magenhem J, Berman I, Bar-Tana J. Fatty acyl-CoA thioesters are ligands of hepatic nuclear factor-4 α . *Nature* 1998;392:512–516.
- Rosmond R, Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. *J Clin Endo Metab* 1998;83:1853–1859.
- Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96:1897–1904.
- Dean RT, Wilcox I. Possible atherogenic effects of hypoxia during obstructive sleep apnea. *Sleep* 1993;16:S15–S22.
- Hedner JA, Wilcox I, Sullivan CE. Speculations on the interaction between vascular disease and obstructive sleep apnea. In: Saunders N, Sullivan C, editors. Sleep and breathing, 2nd edition. New York: Marcel Dekker; 1994. p. 823–846.
- Björntorp P. Metabolic implications of body fat distribution. *Diabetes Care* 1991;14:1132–1143.
- De Fronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;237:E214–E223.
- Bonora E, Targher G, Alberiche M, Bonadonna RC. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. *Diabetes Care* 2000;23:57–63.
- Galvin P, Ward G, Walters J, Pestell R, Koschmann M, Vaag A, Martin I, Best JD, Alford F. A simple method for quantitation of insulin sensitivity and insulin release from an intravenous glucose tolerance test. *Diabet Med* 1992;9:921–928.
- Anderson RL, Hamman RF, Savage PJ, Saad MF, Laws A, Kades WW, Sands RE, Cefalu W, for the insulin resistance atherosclerosis study. Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests: the insulin resistance atherosclerosis study. *Am J Epidemiol* 1995;142:724–732.
- Haffner SM, Gonzales C, Miettinen H, Kennedy E, Stern MP. A prospective analysis of the HOMA model: the Mexico City Diabetes Study. *Diabetes Care* 1996;19:1138–1141.
- Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. *Diabetes Care* 1997;20:1087–1092.
- Lansang MC, Williams GH, Carroll JS. Correlation between the glucose clamp technique and the homeostasis model assessment in hypertension. *Am J Hypertens* 2000;14:51–53.
- Vgontzas AN, Legro VS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endo Metab* 2001;86:517–520.
- Elmasry A, Lindberg E, Berne C, Janson C, Gislason T, Awad Tageldin M, Boman G. Sleep-disordered breathing and glucose metabolism in hypertensive men: a population-based study. *J Intern Med* 2001;249:153–161.
- Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mish-

- ima M, Nakamura T, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome. *Circulation* 1999;100:706-712.
48. Yamashita S, Nakamura T, Shimomura I, Nishida M, Yoshida S, Kotani K, Kameda-Takemura K, Tokunaga K, Matsuzawa Y. Insulin resistance and body fat distribution. *Diabetes Care* 1996;19:287-291.
49. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes* 1998;47:699-713.
50. Grunstein RR, Wilcox I, Yang TS, Gould Y, Hedner JA. Snoring and sleep apnea in men: association with central obesity and hypertension. *Int J Obes* 1993;17:533-540.
51. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes* 1998;47:699-713.