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The association of OSA with insulin resistance, inflammation and metabolic syndrome

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KEYWORDS

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Summary

Obstructive sleep apnea (OSA) shares many cardiovascular risk factors with metabolic syndrome, including obesity, hypertension, insulin resistance, and pro-inflammatory state. This study aimed to examine the possible association of OSA severity with insulin resistance, inflammation and the metabolic syndrome.

Ninety eight patients suspected for OSA (54.9 ± 13.1 years) were studied. Overnight polysomnography and blood sampling was taken for glucose, insulin, high-density lipoprotein(HDL)-cholesterol, triglycerides, high-sensitivity C-reactive protein (Hs-CRP), and serum amyloid A (S-AA). Insulin resistance was estimated by the homeostatic model assessment (HOMA). Each patient was assigned a metabolic score according to the number of discrete components of metabolic syndrome identified, and categorized by OSA severity. Nine patients had primary snoring, nine had mild, 27 moderate and 53 severe OSA. Metabolic score increased from 1.56 ± 1.01 to 2.92 ± 1.20 with OSA severity (p=0.004), and was correlated independently with apnea hypopnea index (AHI; r=0.432, p=0.001) and with body mass index (BMI; r=0.518 p=0.001). Hs-CRP increased from 3.44 ± 4.25 to 5.87 ± 4.76 mg/dL with OSA severity (p=0.066) and correlated with AHI (r=0.348; p=0.002). Insulin resistance, correlated significantly with AHI (r=0.390 p=0.021). Inflammation, insulin resistance and metabolic syndrome increase with OSA severity. The number of cardinal features of metabolic syndrome increases with an increase in OSA severity, regardless of the BMI.

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Introduction

Metabolic syndrome is a constellation of risk factors for heart disease consisting of abdominal or central obesity, hypertension, elevated triglyceride level, reduced high-density lipoprotein (HDL)-cholesterol level, and elevated fasting glucose level. These might be accompanied by a proinflammatory state and a prothrombotic predisposition. The Joint Conference of the American Heart Association/National Heart Lung Blood Institute has recognized cardio-vascular disease as a major clinical outcome of metabolic syndrome.

Obstructive sleep apnea (OSA) syndrome is a common nocturnal respiratory disorder affecting up to 5% of adults. Patients with OSA have been found to have abnormalities of each of the components of metabolic syndrome, in addition to a higher prevalence of insulin resistance than healthy persons. A growing body of evidence supports an association among OSA, metabolic syndrome and cardiovascular morbidity. However, the relative contribution of OSA per se to this association is not clear considering that obesity may account for much of the morbidity. Furthermore, the relationship of OSA with metabolic syndrome as a complete entity rather than with its individual components remains unclear.

The aim of this study, was to test the hypothesis that the severity of OSA is correlated with the severity of the sum components of metabolic syndrome.

Materials and methods

Study group

The study group consisted of 98 consecutive male patients who were referred to our sleep laboratory for whole-night polysomnography (Compumedics, E-series, Australia) because of suspected OSA. Each participant completed a detailed questionnaire on current and past medical history, atherosclerotic risk factors, and sleep quality/excessive daytime sleepiness. Patients with a history of heart failure (New York Heart Association class III–IV or ejection fraction < 35%), diabetes mellitus, chronic lung disease, inflammatory bowel disease, collagen-associated disease, other acute disease/situation, or any change in medication for a chronic disease 6 months prior to the study were excluded. The institutional Human Subjects Review Board approved the study protocol, and all patients signed an informed consent form.

Polysomnography

All participants underwent overnight polysomnography. Bedtime was between 22:00 and 24:00 h, and waking time was at 06:00 h. Sleep was staged manually using the method of Rechtschaffen and Kales. ¹⁹ Respiratory monitoring was performed with oro-nasal pressure sensors, chest and abdominal respiratory belts, and finger-pulse oximetry (Compumedics, Australia). Oxygen desaturation was measured according to minimal saturation (SaO₂ min) and time (in minutes) with oxygen saturation below 90% (SaO₂_90). Apnea was defined as a cessation in airflow of at least 10 s.

Hypopnea was defined as a decrease in the amplitude of the respiratory signal by at least 50% for a minimum of 10 s, followed by either a 4% decrease in oxygen saturation or a sign of electroencephalo-graphic arousal. The apnea hypopnea index (AHI) was calculated by dividing the total number of hypopnea and apnea events by the total hours of sleep. OSA was defined as an AHI of \geqslant 5/h. For purposes of the study, the patients were divided into three subgroups according to OSA severity, as follows: mild OSA, $5\leqslant$ AHI <15; moderate OSA, $15\leqslant$ AHI <30; severe OSA, AHI \geqslant 30. Patients with AHI <5 and snored were considered as primary snoring (PS).

Blood assays

Morning blood samples were collected after polysomnography and stored at $-80\,^{\circ}\text{C}$ until assayed. Plasma glucose and lipid levels, fibrin level, erythrocyte sedimentation rate, and cell blood count were measured with commercially available kits. Plasma insulin was determined by the INSIK-5 radioimmunoassay kit (CIS, Gif sur Yvette, France). Highsensitivity C-reactive protein (Hs-CRP) level was used as an indicator of inflammation. The homeostasis assessment model (HOMA) was used to calculate insulin resistance according to the following formula 20 : HOMA = fasting plasma insulin ($\mu\text{U/mL}$) \times fasting plasma glucose (mg/dL)/ 22.5.

Metabolic score

The number of components of metabolic syndrome present (metabolic score) was evaluated according to the diagnostic criteria of the National Cholesterol Education Program/ Adult Treatment Panel III (NCEP/ATP III)1: (1) abdominal obesity, i.e., waist circumference above 88 cm for women or 102 cm for men, or if these data were unavailable a body mass index (BMI) of 25 kg/m² or greater for women and 29 kg/m² or greater for men, based on studies showing that using BMI values yields the same prevalence of metabolic syndrome in the population as waist circumference 21 ; (2) blood pressure of 130/85 mmHg or greater or current use of antihypertensive medications, (3) fasting triglyceride level above 150 mg/dL, (4) HDL-cholesterol below 50 mg/dL for women or 40 mg/dL for men, (5) fasting blood glucose above 110 mg/dL. Each participant was assigned a metabolic score which was calculated by adding the number of positive diagnostic criteria identified (range 0–5). A score of \geqslant 3 was considered diagnostic of metabolic syndrome.¹

Statistical analysis

Univariate and multivariate analyses (ANOVA, chi-squared test and Pearson correlation) were used to investigate the association among the sleep parameters, metabolic profile, epidemiologic data, and laboratory values. The Statistical Package for the Social Sciences (SPSS-12) was used for data handling and analysis. Probability values less than 0.05 were considered statistically significant.

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Results

The background, clinical, and laboratory data for the patients are shown in Table 1.

Nine patients in the study group had mild OSA, 27 moderate OSA, and 53 severe OSA. Nine patients had an AHI of <5 and diagnosed as PS. Minimal oxygen saturation (SaO₂ min) decreased significantly with an increase in OSA severity, from 91.3 \pm 8.5% in the patients with PS to 74.9 \pm 12.3% in the patients with severe OSA, whereas oxygen saturation below 90% (SaO₂_90) increased with OSA severity, from 0 min in the PS subgroup to 88.9 \pm 105.6 min in the severe-OSA subgroup (p=0.001 for both, Table 1).

The expression of all individual components of metabolic syndrome, as well as the levels of each of the individual components, increased with an increase in OSA severity; not all the differences reached statistical significance (Table 1). The rate of central obesity increased from 67% in the PS subgroup to 91% in the severe-OSA subgroup (p=0.008), and BMI increased from 26.3 to 31.5 kg/m² (p=0.001); the rate of elevated fasting glucose increased from 0% to 34% (p=0.029), with an increase in measured levels from 89.2 to 108.7 mg/dL (NS). There was a trend toward higher levels of triglycerides, lower levels of HDL-cholesterol, and greater hypertension with OSA severity (Table 1).

The mean sum of components (metabolic score) increased significantly with OSA severity, from 1.56 ± 1.01 in the PS subgroup to 2.92 ± 1.20 in the severe-OSA subgroup (p=0.004; Table 1, Fig. 1).

On correlation analyses, increase in the metabolic score was accompanied by a significant increase in AHI and decrease in SaO_2 min (ANOVA, p=0.01; p=0.03, respectively). The metabolic score significantly correlated with AHI and SaO_2 min (r=0.432, p=0.001; r=-0.360, p=0.001; respectively), and with BMI (r=0.518; p=0.001). On multiple regression analysis, BMI and AHI significantly predicted the metabolic score (model r=0.550, p=0.003), with a clinically equal contribution for both measures (partial correlation 0.344; 0.357, respectively; Table 2). Age and oxygen saturation did not enter the model.

The calculated insulin resistance (HOMA) correlated significantly with the AHI ($r=0.390,\ p=0.021;\ Fig.\ 2$), but not with oxygen measures. Hs-CRP, as an expression of inflammation correlated with the AHI ($r=0.348,\ p=0.002;\ Fig.\ 3$) and with SaO₂ min ($r=-0.340,\ p=0.002$). However, when adjusting for BMI, the correlation with AHI was ($r=0.225\ p=0.053$), and borderline when controlling the metabolic score ($r=0.207\ p=0.07$). On multiple regression analysis metabolic score was the only parameter to

Table 1 Clinical and laboratory characteristics of patients with OSA* by severity of disease and controls.

	OSA					
	Snorers	Mild	Moderate	Severe	Р	
N	9	9	27	53		
Age (years)	48.1 ± 25.6	48.2 ± 12.9	55.7 ± 12.4	55.9 ± 13.6	0.10	
BMI (kg/m ²)	26.3 ± 5.7	24.9 ± 2.5	28.9 ± 4.5	31.5 ± 5.3	0.00	
AHI (events/h)	3.4 ± 3.2	12.0 ± 1.5	21.8 ± 4.6	57.2 ± 20.0	0.00	
SaO ₂ min (%)	91.3 ± 8.5	87.8 ± 6.9	84.4 ± 6.2	74.9 ± 12.3	0.00	
SaO ₂ _90 (min)	0	3.1 ± 5.9	23.3 ± 69.8	$\textbf{88.9} \pm \textbf{105.6}$	0.00	
Laboratory values						
Glucose (mg/dL)	88.2 ± 10.2	89.1 <u>+</u> 14.4	101.9 <u>+</u> 41.9	108.7 ± 42.6	0.33	
Triglycerides (mg/dL)	132.7 ± 76.1	178.5 ± 93.3	214.9 ± 163.8	207.3 ± 119.3	0.43	
Total chol. (mg/dL)	188.4 ± 39.5	198.4 ± 34.8	207.2 ± 39.2	192.7 ± 32.9	0.39	
HDL-chol. (mg/dL)	48.8 ± 14.4	47.13 ± 10.5	44.8 ± 8.2	43.5 ± 11.0	0.73	
Insulin (μI/mL)	24.5 <u>+</u> 11.6	27.0 ± 15.6	41.6 ± 17.3	49.6 ± 38.8	0.43	
HOMA	102.7 ± 57.1	121.6 ± 74.5	179.8 ± 152.7	239.2 ± 236.6	0.60	
S-AA (mg/dL)	7.93 ± 8.34	7.07 ± 4.86	4.37 ± 3.357	5.57 ± 3.34	0.17	
Hs-CRP (mg/dL)	3.44 ± 4.25	$\textbf{2.77} \pm \textbf{2.82}$	3.49 ± 2.83	5.87 ± 4.76	0.06	
Metabolic components an	d score					
Hypertension	1 (13%)	3 (43%)	11 (41%)	30 (58%)	0.08	
Central obesity	6 (67%)	4 (57%)	22 (82%)	48 (91%)	0.00	
Elevated glucose	0	2 (22%)	5 (18%)	18 (34%)	0.02	
High triglycerides	2 (22%)	5 (63%)	13 (48%)	34 (68%)	0.09	
Reduced HDL-chol.	0	2 (22%)	11 (39%)	25 (47%)	0.25	
Metabolic score	1.56 ± 1.01	1.78 <u>+</u> 1.48	2.21 ± 1.34	2.92 ± 1.20	0.00	
Metabolic syndrome	0	1 (11%)	6 (21%)	16 (30%)	0.03	

BMI—body mass index; AHI—apnea hypopnea index.

 SaO_2 min = minimal oxygen saturation (%); SaO_2 =90 = time (min) with oxygen saturation below 90%; HDL = high-density lipoprotein; HOMA = homeostatic model assessment; S-AA = serum aminoaminidase A; Hs-CRP = high-sensitivity C-reactive protein; metabolic score = sum of components characteristic of metabolic syndrome; metabolic syndrome = metabolic score of \geqslant 3.

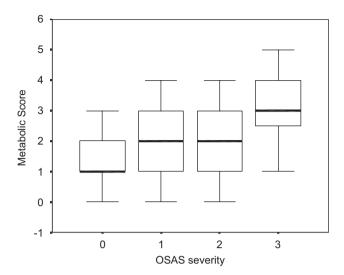


Figure 1 Increase in metabolic score by change in OSA severity (ANOVA, p=0.001). 0= controls, 1= mild OSA, 2= moderate OSA, 3= severe OSA.

Table 2 Multiple regression analysis predicting metabolic score (p = 0.003).

	β coefficient	р	Partial correlation
Constant BMI AHI	0.358 0.332	0.558 0.026 0.038	0.344 0.357

R model = 0.55; BMI—body mass index; AHI—apnea hypopnea index.

predict Hs-CRP (R model 0.386 p=0.001). Serum aminoaminidase A levels showed no significant association with any of the OSA measures, though it correlated significantly with Hs-CRP (r=0.380, p=0.001).

Discussion

Our study demonstrates that the presence of OSA was associated independently, by degree of severity, to the number of components of metabolic syndrome present, and correlated with insulin resistance and inflammatory parameters (Hs-CRP). There is a growing body of evidence supporting an association between OSA and metabolic syndrome 11-15 and, specifically, insulin resistance. 5,7–9,18,22–26 Although this association might be attributable to BMI rather than to OSA per se, the added benefit of OSA treatment by continuous positive airway pressure (CPAP) on blood pressure, 27 cardiovascular morbidity, 14 nocturnal ischemic events, ¹⁷ insulin resistance, ^{9,28} inflammatory cytokines (interleukin-6, tumor necrosis factor alpha, vascular endothelial growth factor, 29,30 and CRP, 31) indicates otherwise. The effect of OSA was further supported by the study of Harsch et al.²⁸ which showed an improvement in insulin resistance within two days of CPAP treatment, much before any change in BMI could occur.

Almost all these studies considered the variables involved in metabolic syndrome individually. Only a few investigations to date have evaluated the association of OSA with metabolic syndrome as a whole. Coughlin et al.²³ in a sample of 61 men with OSA and 43 control subjects, found that OSA was independently associated with hypertension, high fasting glucose and triglyceride levels, low HDL-cholesterol level, and a trend toward high HOMA values, with an odds ratio of 9.1 for total metabolic syndrome. However, they did

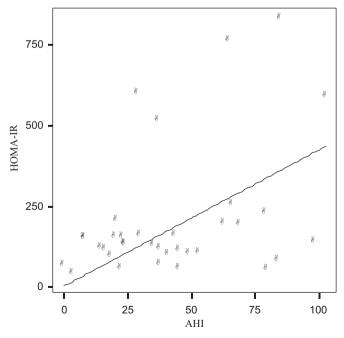


Figure 2 Increase in insulin resistance (HOMA) by increase in AHI (r = 0.390; p = 0.021). HOMA—fasting plasma insulin (μ U/mL) × fasting plasma glucose (mg/dL)/22.5.

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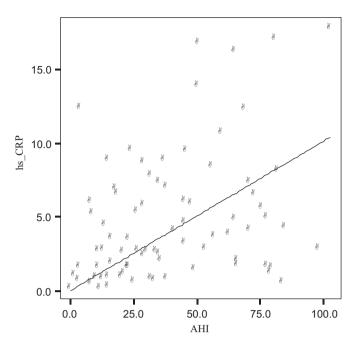


Figure 3 Increase in Hs-CRP by change in AHI (mg/dL; r = 0.348; p = 0.002).

not focus on the severity of OSA. Lam et al. 32 monitored 255 randomly selected Chinese volunteers for metabolic profile and sleep characteristics by overnight polysomnography and reported that OSA was associated with all the components of metabolic syndrome, and that metabolic syndrome was an independent predictor of OSA. The main value of the present study is our finding that with an increase in the severity of OSA, there is a significant increase in both the incidence of metabolic syndrome and the number of its components. Statistically significant differences were noted for HOMA, Hs-CRP and fasting glucose, and a trend towards an increase in hypertension and triglyceride level. These results might explain the increased incidence of stroke and fatal cardiovascular events in patients with severe OSA. 14,15 The independent contribution of the AHI to the metabolic score in our study is in agreement with the results of Marin et al. 14 showing that the increased cardiovascular morbidity in OSA supercedes the effect of BMI and age. Our finding of increased CRP with OSA severity is in agreement with previous reports. 31,33,34 However, its prediction by metabolic score and not by OSA severity has not been reported earlier. This might indicate that in the view of inflammation, studies should be adjusted for metabolic score/syndrome and not only to BMI in order to understand the isolated role of OSA.

Oxygen saturation was correlated significantly with the metabolic score, but it was not a significant predictor of the metabolic score on multivariate regression analysis. This finding is in agreement with the study of Makino et al. of 213 patients with OSA which showed that AHI, but not oxygen saturation, predicted insulin resistance. However, Ip et al. who followed 270 patients of whom 185 had OSA, reported that besides obesity, both AHI and oxygen saturation where independent determinants of insulin resistance. Punjabi et al. in a cohort of 150 patients, showed that after adjustment for BMI and AHI, for every 4% decrease in SaO_2 min, the odds of having glucose tolerance increased by

1.99. We believe that even though oxygen saturation did not enter the prediction equation in our study, hypoxia plays a significant role in the pathogenesis of OSA through oxidative stress^{35–37} and inflammatory pathways.³⁸

This study has some potential limitations. It is cross-sectional study, therefore indicates association and not causation; we used BMI and not central obesity for assessing metabolic profile and finally the groups were not BMI matched. In order to overcome the latter limitation we used logistic and partial regression analysis.

In summary, OSA per se has a significant role in the occurrence and the severity of metabolic syndrome, but its isolated contribution to inflammation should be further studied. The relative impact of the AHI on insulin resistance and metabolic score is apparently greater than that of oxygen desaturation.

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