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Association between obstructive sleep apnea and metabolic syndrome: a meta-analysis

Abstract

Purpose: Evidence suggests that obstructive sleep apnea (OSA) is related to metabolic syndrome; however, the relationship among metabolic syndrome parameters (blood pressure, fasting blood glucose (FBG), high density lipoprotein (HDL) and low density lipoprotein (LDL)) and OSA is unclear.

Methods: PRISMA guidelines were followed for this study. Medline, Cochrane, EMBASE and Google Scholar databases were searched until December 23, 2015, using following terms: obstructive sleep apnea, sleep apnea, OSA and metabolic syndrome.

Results: Ten studies were included in the analysis which included 2053 patients. Patients with OSA had higher systolic blood pressure (SBP) (pooled standard mean difference (SMD) = 0.56, 95% CI, 0.40 to 0.71, $P < 0.001$), lower levels of HDL (pooled SMD = -0.27, 95% CI, -0.38 to -0.16, $P < 0.001$), and higher levels LDL (pooled SMD = 0.26, 95% CI, 0.07 to 0.45, $P = 0.007$) than patients without OSA. OSA was also found to be associated with increased triglyceride levels (pooled SMD = 0.26, 95%CI, 0.07 to 0.45, $P = 0.007$) and higher FBG (pooled SMD = 0.35, 95%CI, 0.18 to 0.53, $P < 0.001$).

Conclusion: This meta-analysis found that OSA was associated with abnormal levels of multiple parameters that are markers for metabolic syndrome, and suggests that OSA broadly affects this disease. Understanding the relationships between OSA and metabolic syndrome may allow the early identification of OSA patients who may develop diseases related to metabolic syndrome such as type 2 diabetes and cardiovascular disease.

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Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete cessation of breathing during sleep, daytime sleepiness and snoring [1, 2]. It is also associated with a higher incidence of cardiovascular and cerebrovascular morbidity and mortality [3-5]. OSA is relatively common, with about 4% of men and 2% of women in western countries having the disease. Previously, it was thought that the increased cardiovascular disease in patients with OSA was related to obesity; however, OSA may be associated with a number of cardiovascular risk factors independent of obesity, such as hypertension, insulin resistance and impaired glucose tolerance [6-12].

Metabolic syndrome represents a combination of a number of metabolic abnormalities including increased blood pressure, insulin resistance, dyslipidemia and central obesity, all of which are risk factors for cardiovascular disease [13-15]. Metabolic syndrome, similar to OSA, is known to increase the risk of cardiovascular disease [16, 17]. OSA is independently associated with metabolic syndrome and about 74% to 85% of patients with OSA also have this disease [18-21]. The association between the two diseases is supported by the observation that in patients with moderate-to-severe OSA, treatment with continuous airway pressure (CPAP) lowers blood pressure and partially reverses metabolic abnormalities associated with metabolic syndrome [20].

A number of studies have investigated the coexistence of OSA and metabolic syndrome but the results have been inconsistent [2, 10, 20, 22-25]. A recent meta-analysis found OSA was associated with abnormal lipid profiles (e.g., high density lipoprotein (HDL) and low density lipoprotein (LDL) levels) [26]. Several recent meta-analyses found treatment of OSA with continuous positive airway pressure (CPAP), the primary treatment for OSA, resulted in improvement in markers of dyslipidemia, glucose metabolism and insulin resistance [20, 27, 28]. Recent re-interpretation of the data suggests that OSA may, in fact, be yet another component of metabolic syndrome [29, 30]; however, it is still unclear how different parameters (e.g., blood pressure, fasting blood glucose (FBG), HDL and LDL) associated with metabolic syndrome are related to OAS. The aim of this study was to evaluate the association of different markers of metabolic syndrome with OSA.

Methods

Search strategy

The study was performed in accordance with PRISMA guidelines. Medline, Cochrane, EMBASE, Google Scholar

databases were searched until December 23, 2015 for studies that investigated the relationship of metabolic syndrome with OSA using the following search terms: obstructive sleep apnea; sleep apnea; OSA; and, metabolic syndrome, and using the filters: English language; and, humans. Inclusion criteria were as follows: 1) prospective, retrospective and cohort studies; 2) patients with or without OSA were included, and metabolic syndrome parameters were documented; and, 3) quantitative outcome data were reported. Exclusion criteria were as follows: 1) letters, comments, editorials, case reports, proceedings and personal communications 2) patients were not divided into OSA and non-OSA groups; 3) metabolic syndrome parameters were not reported; and, 4) no quantitative outcome data were reported. The list of relevant studies was hand-searched by two independent reviewers and a third reviewer was consulted if there was uncertainty regarding eligibility.

Data extraction

The following information/ data was extracted from studies that met the following inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, the participants' age and gender, OSA criteria and individual metabolic parameters.

Quality assessment

The quality of the studies was evaluated based on their description of study participants, study attrition, measurement of prognostic factors, outcome measurements, confounding measurement and statistical analysis [31].

Statistical analysis

The relationships of OSA with individual metabolic parameters including systolic blood pressure (SBP), HDL, LDL, triglycerides (TG) and FBG were estimated by standardized difference in means (SMD) and the corresponding 95% confidence intervals (CI) for each individual study and the pooled data. If the median and interquartile range (IQR) was reported in a study, we assumed that the median of the outcome variable was equal to the mean response and width of the interquartile range was approximately 1.35 standard deviations [32]. A χ^2 -based test of homogeneity was performed and the inconsistency index (I²) and Q statistics were determined. If the I² statistic was >50%, a random-effects model was used; otherwise, a fixed-effect model was employed. Pooled effects were calculated and a 2-sided P value <0.05 was considered to

TABLE 1. Summary of basic characteristics of selected studies for meta-analysis

First author (year)	Study design	No. of patients	Group	Age (year)	BMI (kg/m ²)	Male (%)	Smoking (%)	Medical history	Criteria of Metabolic Syndrome	Metabolic Syndrome (%)
Barreiro (2013)	Prospective study	41	Mild-moderate OSA	54	30.4	76.0%	43.0%	NA	NCEP-ATPIII	43%
		75	Severe OSA		34.1	79.0%	45.0%			81%
		25	Non-OSA		30	56.0%	36.0%			32%
Agrawal (2011)	Cross-sectional study	187	OSA	46	33.5	82.0%	22.0%	NA	NCEP-ATPIII	79%
		40	Non-OSA	42	27.7	63.0%	10.0%			48%
Barcelo' (2011)	Case-control study	119	OSAS	46	28	74.0%	30.0%	HTN: 22%; DM:8%	NCEP ATP III	38%
		119	Control	45	28	73.0%	30.0%	HTN: 21%; DM:4%		19%
Basoglu (2011)	Case-control study	36	OSAS	50	33.5	64.0%	36.0%	CVD: 13.9%; Stroke:5.5%; HTN: 38.9%; DM: 19.4%	NCEP-ATPIII	47%
		34	Non-OSAS	49.7	34.5	50.0%	25.0%	CVD: 8.8%; HTN:26.5%		29%
Breuer (2012)	Prospective study	360	Proved OSA	56	32	NA	NA	DM: 22%	ATP3 update, the recent German definition of the "Metabolic Vascular Syndrome-MVS" defined by a Saxonian expert group on diabetes.	42%
		58	Excluded OSA	50	29			DM: 16%		27%
Ozol (2011)	Prospective study	27	Mild OSAHS	47.9	29.7	26.0%	NA	HTN: 22.2%; DM: 14.8%	NCEP-ATPIII	7%
		24	Moderate OSAHS	50.1	29.5	29.0%		HTN: 29.2%; DM: 12.5%		13%
		54	Severe OSAHS	55.5	31.9	30.0%		HTN: 51.9%; DM: 22.2%		37%
		20	Non-OSAHS	40.3	28.6	25.0%		HTN: 20%; DM: 10%		10%
Angelico (2010)	Cross-sectional study	54	Mild OSA	51	31.6	69.0%	NA	NA	NCEP-ATP III	44%
		51	Moderate OSA	57.4	31.2	80.0%				55%
		73	Severe OSA	53	33.2	88.0%				61%
		48	Snorers	49.8	29.2	60.0%				43%
Papanas (2010)	Prospective study	53	OSA	46.1	34.1	100.0%	NA	NA	NCEP ATP III	72%
		30	Control	45.5	29	100.0%				37%
Redline (2007)	Longitudinal cohort study	22	SDB group	13.4	NA	77.0%	NA	NA	NCEP-ATPIII	59%
		248	Non-SDB group	13.6	NA	50.0%				16%
Lam (2006)	Prospective cross-sectional study	95	OSA	45.1	27.2	67.0%	NA	NA	NCEP-ATPIII	58%
		160	Control	41.6	24	54.0%				21%

TABLE 2. Sensitivity analysis

First author (year)	Statistics with study removed				
	Points	Lower limit	Upper limit	Z-Value	P-Value
SBP					
Barreiro (2013)	0.61	0.44	0.77	7.27	<0.001
Agrawal (2011)	0.62	0.45	0.79	7.09	<0.001
Basoglu (2011)	0.53	0.37	0.69	6.43	<0.001
Papanas (2010)	0.55	0.39	0.71	6.65	<0.001
Redline (2007)	0.51	0.34	0.67	6.10	<0.001
Lam (2006)	0.53	0.34	0.72	5.53	<0.001
HDL					
Barreiro (2013)	-0.23	-0.35	-0.12	-4.14	<0.001
Agrawal (2011)	-0.30	-0.41	-0.18	-5.11	<0.001
Barcelo' (2011)	-0.31	-0.43	-0.20	-5.18	<0.001
Basoglu (2011)	-0.28	-0.39	-0.17	-4.96	<0.001
Breuer (2012)	-0.23	-0.35	-0.11	-3.85	<0.001
Ozol (2011)	-0.27	-0.38	-0.16	-4.79	<0.001
Angelico (2010)	-0.28	-0.39	-0.17	-4.79	<0.001
Papanas (2010)	-0.27	-0.38	-0.16	-4.80	<0.001
Redline (2007)	-0.27	-0.38	-0.15	-4.69	<0.001
Lam (2006)	-0.26	-0.37	-0.14	-4.22	<0.001
LDL					
Agrawal (2011)	0.26	0.04	0.47	2.32	0.020
Basoglu (2011)	0.18	0.03	0.32	2.43	0.015
Breuer (2012)	0.29	0.07	0.51	2.58	0.010
Ozol (2011)	0.27	0.06	0.48	2.54	0.011
Angelico (2010)	0.31	0.12	0.50	3.17	0.002
Papanas (2010)	0.26	0.05	0.47	2.45	0.014
Redline (2007)	0.21	0.03	0.39	2.24	0.025
Lam (2006)	0.29	0.07	0.52	2.54	0.011
TG					
Barreiro (2013)	0.39	0.16	0.62	3.30	0.001
Agrawal (2011)	0.39	0.15	0.63	3.22	0.001
Barcelo' (2011)	0.38	0.13	0.63	3.01	0.003
Basoglu (2011)	0.29	0.13	0.45	3.50	<0.001
Breuer (2012)	0.40	0.17	0.64	3.39	0.001
Ozol (2011)	0.41	0.19	0.63	3.63	<0.001
Angelico (2010)	0.40	0.17	0.64	3.42	0.001
Papanas (2010)	0.37	0.14	0.61	3.15	0.002
Redline (2007)	0.34	0.11	0.56	2.95	0.003
Lam (2006)	0.33	0.11	0.56	2.89	0.004
FBG					
Barreiro (2013)	0.35	0.16	0.55	3.59	<0.001
Agrawal (2011)	0.36	0.17	0.56	3.59	<0.001
Barcelo' (2011)	0.32	0.13	0.52	3.31	0.001
Basoglu (2011)	0.35	0.16	0.54	3.58	<0.001
Breuer (2012)	0.37	0.17	0.57	3.67	<0.001
Ozol (2011)	0.37	0.18	0.56	3.81	<0.001
Angelico (2010)	0.43	0.30	0.55	6.64	<0.001
Papanas (2010)	0.31	0.14	0.48	3.57	<0.001
Redline (2007)	0.35	0.16	0.55	3.55	<0.001
Lam (2006)	0.33	0.13	0.52	3.29	0.001

indicate statistical significance. Meta-regression was used to identify the estimated effect of the potential covariate body mass index (BMI) on each metabolic syndrome parameters. Sensitivity analysis was carried out using the leave-one-out approach. Publication bias was assessed by constructing funnel plots for primary outcome by Egger's test. The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution and one-tailed significance level $P > 0.05$ (Egger's test). In certain instances, publication bias analysis was not performed because more than 10 studies are required to detect funnel plot asymmetry [33]. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Search results

A flow diagram of study selection is shown in Figure 1. A total of 549 studies were identified in the database searches. After review by title and abstract, 529 were eliminated for not being relevant. The full texts of the remaining 20 studies were further assessed for eligibility and 10 articles were excluded, for the reasons shown in Figure 1; thus, 10 studies with a total of 2053 patients were included in the meta-analysis [2, 24, 34-41]. Two were cross-sectional studies. The others were either population-based, case control or prospective studies. In total, 1271 patients were considered to have OSA (Table 1).

The apnea hypopnea index (AHI) was calculated by dividing the total number of respiratory events by the total number of hours of sleep. Three groups were defined according to the result of AHI: non OSA (AHI <5), mild-moderate OSA (AHI ≥ 5 , <30), and severe OSA (AHI ≥ 30) (Table 1). A total of 782 patients were considered as non-OSA, 191 patients were considered as having mild to moderate OSA and 127 patients were considered as having severe OSA. The mean age of patients ranged from 13 to 57 years and the frequency of smokers was 22% to 45% in the OSA group and 10% to 36% in the control group. The use of alcohol was similar between the groups. The prevalence of metabolic syndrome was 7% to 81% in the OSA group and 10% to 48% in the non-OSA group.

Meta-analysis

Six studies provided completed information for SBP and were included in the meta-analysis. There was heterogeneity among the seven studies (Q statistic = 0.479, $I^2 = 41.03\%$); hence, a fixed-effect analysis was used. The pooled analysis indicated

that patients in non-OSA group had lower levels of SBP compared with the OSA group (pooled SMD = 0.56, 95% CI, 0.40 to 0.71, $P < 0.001$, Figure 2A).

All ten studies were included in the meta-analysis for HDL. Analysis of the data for HDLs, χ^2 -based test of homogeneity indicated there was no heterogeneity among the 10 studies (Q statistic = 14.310, $I^2 = 37.11\%$); hence, a fixed-effect model was used. The pooled analysis indicated that the non-OSA group, compared with the OSA group, had higher levels of HDL (pooled SMD = -0.27, 95%CI, -0.38 to -0.16, $P < 0.001$, Figure 2B).

Eight studies were reported LDL outcomes and were pooled for analysis. The data for LDL showed heterogeneity (Q statistics = 14.962, $I^2 = 53.22\%$); therefore, a random-effects model was used. The pooled analysis indicated that patients in non-OSA group had lower levels of LDL than the OSA group (pooled SMD = 0.26, 95%CI, 0.07 to 0.45, $P = 0.007$, Figure 2C).

All ten studies were included in the meta-analysis for TG and FBG. The data for TG and FBG showed heterogeneity; therefore, a random-effects model was used. The pooled analysis indicated that non-OSA group had lower levels of TG (pooled SMD = 0.26, 95%CI, 0.07 to 0.45, $P = 0.007$, Figure 2D) and FBG (pooled SMD = 0.35, 95%CI, 0.18 to 0.53, $P < 0.001$, Figure 2E) than the OSA group.

Meta-Regression

Meta-regression analysis indicated there was no effect of BMI on SBP ($P = 0.494$), HDL ($P = 0.746$), LDL ($P = 0.272$), TG ($P = 0.236$) and FBG ($P = 0.062$) (Figure 3A-E).

Sensitivity analysis and publication bias

Sensitivity analyses were performed using the leave-one-out approach. The direction of combined estimates did not vary markedly with the removal of the studies, indicating that the meta-analysis had good reliability and the results were not overly influenced by any one study (Table 2). Egger's test showed there was publication bias with respect to the association between OSA and HDL, TG, and FBG (Supplementary Figure 1).

Subgroup analysis by OSA severity

The association of individual metabolic parameters with OSA was further analysed in patients with mild to moderate or severe OSA. Three studies [35,38,39] provided enough data for HDL, TG and FBG evaluations between mild to moderate and severe OSA groups and were included in the analysis.

FIGURE 1. Flow diagram of study selection

Figure 4 shows patients in the mild to moderate OSA group had higher HDL and lower TG than those in the severe OSA group; however, no significant difference in FBG was observed between the mild to moderate and severe OSA groups (pooled SMD = -0.33, 95%CI, -0.71 to 0.05, $P = 0.089$) (Figure 4C)

Quality assessment

The results of quality assessment are shown in Supplemental Figure 2. Only the study by Agrawal *et al.* [34] had a high risk of bias for confounding measurement and account and analysis. Overall the results indicated that the studies were of good quality.

Discussion

This meta-analysis assessed the association of OSA with difference parameters of metabolic syndrome such as blood pressure, HDL, LDL, TG and FBG. We found that patients with OSA had higher SBP, lower HDL, higher LDL and increased TG and FBG levels. Subgroup analysis indicated that patients with mild to moderate OSA had higher HDL and lower TG levels compared with patients in the severe OSA group. Our findings indicate that OSA is associated with and may influence multiple parameters of metabolic syndrome. In addition, at least for TG and HDL, the effect of OSA on these

FIGURE 2. Meta-analysis of the associations between obstructive sleep apnea with individual metabolic parameters: (A) systolic blood pressure (SBP); (B) high density lipoprotein (HDL); (C) low density lipoprotein (LDL); (D) triglyceride (TG); and (E) fasting blood glucose (FBG) levels

characteristics is influenced by the severity of OSA, further supporting the close relationship of metabolic syndrome and OSA.

Our findings are consistent with a study by Nadeem et al. (2014) where a meta-analysis was used to evaluate the relationship of OSA with dyslipidemia [26]. Findings were pooled from 64 studies and included 18,116 patients. Similar to our results, OSA was found to be associated with high TG levels ($P=0.001$). OSA was also found to be associated with abnormal levels of HDL and LDL (P values=0.001). The authors concluded that patients with OSA have increased dyslipidemia (high total cholesterol, LDL, and TG levels, and low HDL levels). Nadeem et al. did not evaluate the relationship of OSA with blood pressure, FBG, or the impact of OSA severity on the characteristics of dyslipidemia [26]. In another meta-analysis, Nadeem et al. (2014) evaluated the

effect CPAP on dyslipidemia and found CPAP improved dyslipidemia by decreasing the levels of total cholesterol and LDL and increasing HDL levels [27]. They found no effect of CPAP on TG levels [27].

How OSA affects dyslipidemia is unclear. There is evidence that chronic intermittent hypoxia due to OSA, is independently associated with dyslipidemia possibly through the generation of stearoyl-coenzyme A desaturase-1 and reactive oxygen species, resulting in the peroxidation of lipids and sympathetic system dysfunction [42]. In addition, intermittent hypoxia associated with OSA promotes oxidative and immune-inflammatory responses [26]. In support of this idea, systemic inflammatory markers are higher in OSA patients than control subjects [43]. LDL metabolism may be altered by cytokines, specifically interleukin-1 (IL-1), resulting

FIGURE 3. Meta-regression of the effect of BMI on individual metabolic parameters: (A) systolic blood pressure (SBP); (B) high density lipoprotein (HDL); (C) low density lipoprotein (LDL); (D) triglyceride (TG); and, (E) fasting blood glucose (FBG) levels

in alteration in endothelial cell cholesterol metabolism, which may possibly result in atherosclerosis [26].

As shown in Figure 4, the mild-moderate OSA group had higher HDL, lower TG and lower FBG (although without a significant difference) than the severe OSA group. In addition to the mechanisms discussed above, it is apparent that the severity of OSA is also related to the levels of metabolic parameters. Wu *et al.* [44] reported a high prevalence of metabolic syndrome among professional drivers, especially in those with severe OSA. Overall, the severity of OSA appears to be related to the prevalence of metabolic syndrome and the levels of the individual parameters.

Several studies have found that OSA is independently associated with metabolic syndrome [2, 19, 22, 23] and abnormal TG levels [1, 27, 45]. The relationship between OSA and metabolic syndrome is also strengthened by the findings that CPAP can improve insulin resistance and glucose control in patients with OSA [46]. Two prior meta-analyses evaluated the effects of CPAP on glycemic control and insulin resistance in OSA patients [28, 47]. One study found that CPAP significantly improved insulin resistance in non-diabetic patients with moderate to severe OSA [47]; however, compared with FBG at baseline, CPAP did not change glycemic control. Another meta-analysis included five

(A) HDL

(B) TG

(C) FBG

FIGURE 4. Meta-analysis for (A) high density lipoprotein (HDL), (B) triglyceride (TG), and (C) fasting blood glucose (FBG) levels between mild-moderate and severe obstructive sleep apnea

studies (comprising 296 subjects) found that CPAP did not influence the HOMA-index or the levels of plasma insulin, adiponectin, or HbA1c. The authors concluded that OSA does not independently influence glucose metabolism. In contrast, we found that patients with OSA had higher FBG than non-OSA patients; however, it is difficult to compare our findings with these prior meta-analyses as we did not evaluate the effect CPAP therapy on the parameters associated with metabolic syndrome.

There are several limitations to our study that should be considered when interpreting the results. Although there were 2053 patients included in this study, a larger sample size may have increased the ability to detect significant associations of OSA with specific parameters associated with metabolic

syndrome. The definition of OSA varied across the studies which may have resulted in a diverse populations being compared. Additional well-designed studies are needed to further explore the relationship among OSA and the different parameters of metabolic syndrome, and the association between diastolic blood pressure and metabolic syndrome. The age distribution and alcohol use of the two groups was similar; however, in some studies there were more smokers in the OSA groups than in the control groups [34, 35, 36]. Previous studies have shown that smoking may cause endothelial dysfunction [48], which is associated with prognosis of hypertension [49]. To examine the possible effect of smoking on parameters such as blood pressure, further studies of OSA patients who do and

do not smoke are necessary. Lastly, the analysis was limited to studies published in English.

In conclusion, this meta-analysis found that OSA is independently associated with abnormal levels of multiple parameters that are markers for metabolic syndrome. Understanding the relationships between OSA and metabolic syndrome may allow the early identification of OSA patients who may develop diseases related to metabolic syndrome such as type 2 diabetes and cardiovascular disease. This could significantly impact prevention, treatment and management of patients with OSA. In addition, better knowledge of how CPAP influences different parameters associated with metabolic syndrome may help benefit patient treatment. Future studies are required to further explore the relationship of OSA, its treatment with metabolic syndrome.

Quick Look

Current knowledge

OSA is characterized by recurrent episodes of partial or complete cessation of breathing during sleep, daytime sleepiness and snoring. Metabolic syndrome represents a combination of a number of metabolic abnormalities including increased blood pressure, insulin resistance, dyslipidemia and central obesity; all of which are risk factors for cardiovascular disease. OSA is known to be independently associated with metabolic syndrome

What this paper contributes to our knowledge

Patients with OSA had higher systolic blood pressure, lower HDL, higher LDL, and increased TG and FBG levels. Subgroup analysis indicated that patients with mild to moderate OSA had higher HDL and lower TG levels compared with patients in the severe OSA group. The findings indicate that OSA is associated with metabolic syndrome and that it influences many different parameters of the disease.

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Supplemental Figures

SUPPLEMENTAL FIGURE 1. The result of publication bias analysis for the association between obstructive sleep apnea and individual metabolic parameters: (A) high density lipoprotein (HDL); (B) triglyceride (TG); and, (C) fasting blood glucose (FBG) levels

SUPPLEMENTAL FIGURE 2. Quality assessment.