Effect of Obstructive Sleep Apnea Hypopnea Syndrome on Lipid Profile: A Meta-Regression Analysis

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Background: Obstructive sleep apnea (OSA) is associated with obesity, metabolic syndrome, and dyslipidemia, which may be related to decrease androgen levels found in OSA patients. Dyslipidemia may contribute to atherosclerosis leading to increasing risk of heart disease.

Methods: Systematic review was conducted using PubMed and Cochrane library by utilizing different combinations of key words; sleep apnea, obstructive sleep apnea, serum lipids, dyslipidemia, cholesterol, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (TG). Inclusion criteria were: English articles, and studies with adult population in 2 groups of patients (patients with OSA and without OSA). A total 96 studies were reviewed for inclusion, with 25 studies pooled for analysis.

Results: Sixty-four studies were pooled for analysis; since some studies have more than one dataset, there were 107 datasets with 18,116 patients pooled for meta-analysis. All

studies measured serum lipids. Total cholesterol pooled standardized difference in means was 0.267 ($p = 0.001$). LDL cholesterol pooled standardized difference in means was 0.296 ($p = 0.001$). HDL cholesterol pooled standardized difference in means was -0.433 ($p = 0.001$). Triglyceride pooled standardized difference in means was 0.603 ($p = 0.001$). Meta-regression for age, BMI, and AHI showed that age has significant effect for TC, LDL, and HDL. BMI had significant effect for LDL and HDL, while AHI had significant effect for LDL and TG.

Conclusion: Patients with OSA appear to have increased dyslipidemia (high total cholesterol, LDL, TG, and low HDL).

Keywords: obstructive sleep apnea, dyslipidemia, cholesterol, atherosclerosis, sleep disordered breathing

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Obstructive sleep apnea (OSA) is a common disorder affecting about 4% of middle-aged males and 2% of middle-aged women in the developed world and is a significant source of morbidity and mortality.^{1,2} OSA is characterized by recurrent episodes of upper airway collapses during sleep. These recurrent episodes of upper airway collapse usually are accompanied by oxyhemoglobin desaturation and terminated by brief arousals which result in marked sleep fragmentation and chronic excessive daytime sleepiness (EDS).^{1,2}

OSA has been increasingly linked to cardiovascular and cerebrovascular disease, and many studies have shown that OSA is associated with increased cardiovascular and cerebrovascular morbidity.³⁻⁹ OSA is associated with obesity and metabolic syndrome.¹⁰ Multiple studies addressing this interesting and complex issue are available where lipid profile was measured in subjects with OSA.¹¹⁻³⁵ We performed meta-analysis (MA) and meta-regression (MR) to specifically detect if OSA adversely affects degree of dyslipidemia; elevation of total cholesterol (TC), low density lipoprotein cholesterol (LDL), triglyceride (TG), and reduces level of high density lipoprotein cholesterol (HDL).

BRIEF SUMMARY

Current Knowledge/Study Rationale: Dyslipidemia (increase in total cholesterol, LDL, and triglycerides, and decrease in HDL) and obstructive sleep apnea (OSA) are risk factors for cardiovascular and cerebrovascular disorders. This meta-regression analysis estimates the adverse effect of OSA on dyslipidemia as many studies have measured dyslipidemia in subjects with OSA.

Study Impact: Study suggests dyslipidemia may be the mechanism of atherosclerosis in subjects with OSA. It also suggests OSA as potential target for treatment to improve dyslipidemia for prevention and treatment for cardiovascular and cerebrovascular disease.

METHODS

Data Source and Study Selection

Studies for review were found searching the PubMed, Cochrane, and EMBASE databases from January 01, 1968, to November 30th, 2013. Unpublished data from scientific meetings were not searched, since most abstract do not provide detail raw data needed for meta-analysis. Searches were

Figure 1—Flow diagram for search and inclusion and exclusion of studies

conducted using the keywords; sleep apnea, obstructive sleep apnea, serum lipids, dyslipidemia, cholesterol, total cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride. Each target outcome was also searched in its abbreviated forms (Chol T, HDL, LDL, and TG) to ensure that no relevant source was left out. Additionally, each target and its abbreviated forms were searched in combination with obstructive sleep apnea. Multiple authors individually searched for and scored manuscripts for inclusion. If manuscripts scored differently by 2 authors then it was reviewed by third author to finalize its inclusion.

Studies and Endpoint Definitions

Lipid profile includes total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triglyceride (TG). Inclusion criteria defined for subsequent study selection were as follows: (1) the study must be in English, (2) studies with adult population only, (3) full-text manuscripts had to be available, (4) the study must have reported values for at least one of the outcome of interest, (5) the study must have included ≥ 2 separate groups with one being a group consisting of individuals with obstructive sleep apnea and the other consisting of individuals without obstructive sleep apnea, (6) OSA was defined as AHI ≥ 5 /h, (7) the study must have reported values in mean and standard deviation

or median with range, and (8) patient number for all groups must have been reported.

Data Extraction and Statistical Analysis

Studies identified for inclusion then underwent data extraction. Data was extracted at a study level by a single author and then reviewed by a second author to ensure no errors were made. Levels of serum lipids were extracted from studies as mean with standard deviation. For studies with data reported in median and range, mean and standard deviation were calculated utilizing methods outlined by Hozo et al.³⁶

For studies in which OSA patients were compared with more than one group of control patients (e.g., obese and lean control), each set of data in the study was included in the meta-analysis as a separate data set. For example, Barcelo et al. compared lipid profiles of obese OSA patients and non-obese OSA to healthy controls.¹¹ We used standardized differences in means method for analyzing extracted data from studies.

Study selection, data extraction, and statistical analysis were all done in accordance to previously published methodology for meta-analyses. All statistical analysis was done using Comprehensive Meta-Analysis Version 2.

Heterogeneity was assessed by calculating the Cochrane Q statistic. Additionally I^2 statistics was also calculated to assess heterogeneity. An I^2 of 25% to 49% was considered to represent a low level of heterogeneity, 50% to 60% a moderate level, and 60% to 100% a high level. Standardized differences in mean were calculated using a random effects model for all outcomes with $> 60\%$ heterogeneity ($I^2 > 60$) and fixed effect model for $I^2 < 60$. Measurement unit of lipid profile was mmol/L. If any of these values were in mg/dL they were converted into mmol/L by dividing them by their molar weight. Publication bias analysis was done using four different methods to provide robust results. The methods included funnel plot analysis, Eggers reg intercept, Duval and Tweedie trim and fill, and Kendall tau with and without continuity correction.

RESULTS

The literature was ranked according to the hierarchy of evidence of Sackett et al.³⁷ A total of 96 studies were reviewed for inclusion. Sixty-four studies (with 107 datasets) met inclusion criteria and pooled for meta-analysis including total subjects 18,116 (controls [N = 10,145] and OSA subjects [N = 7,971]) for analysis (**Figure 1**).

Total Cholesterol

A total of 63 studies with 107 datasets including 18,111 subjects were pooled for TC. Standardized differences in means ranged from -2.05 to 5.0 ; pooled mean difference was calculated to be 0.267 (lower limit [LL] 0.146 to upper limit [UL] 0.389 , p value = 0.001 ; see appendix following references, **Figure A1**).

LDL Cholesterol

For LDL, 50 studies with 82 datasets including 13,894 subjects were pooled. Standardized mean difference in LDL ranged from -1.679 to 3.243 , pooled mean difference was calculated to be 0.296 (LL 0.156 to UL 0.436 , $p = 0.001$; **Figure A2**)

Table 1—Meta Regression statistics for Lipids (TC, LDL, HDL, TG) for Age, BMI, and AHI

	Age			BMI			AHI		
	slope	intercept	p	slope	intercept	p	slope	intercept	p
TC	-0.02	1.37	0.001	-0.0052	0.23	0.12	-0.0005	0.04	0.65
LDL	0.004	0.011	0.04	0.02	0.85	0.001	0.0006	0.22	0.67
HDL	-0.01	0.39	0.001	0.02	-1.18	0.001	-0.005	-0.24	0.001
TG	-0.002	0.55	0.34	-0.002	0.51	0.51	0.007	0.18	0.001

Figure 2—Meta-regression plots for age on TC, LDL, HDL, and TG

HDL Cholesterol

For HDL, 64 studies with 107 datasets including 18,116 subjects were pooled. Standardized mean difference ranged from -17.96 to 2.364. The pooled mean difference was calculated to be -0.433 (LL -0.604 to UL -0.262, $p < 0.001$; **Figure A3**).

Triglyceride

For TG, 62 studies with 104 datasets including 17,831 subjects were pooled and analyzed. Standardized mean difference ranged from -2.476 to 15.206, pooled mean difference was calculated to be 0.603 (LL 0.431 to UL 0.775, $p < 0.001$; **Figure A4**).

Meta-Regression to evaluate the effect of Age, BMI, and AHI on Lipid Levels

Data was also analyzed by meta-regression for effect of age, BMI, and AHI on all 4 variables of interest. Results of this analysis are given in **Table 1**. Age had significant effect for TC, LDL, and HDL. BMI had significant effect for LDL and HDL,

while AHI had significant effect for HDL and TG (**Figures 2-4**). Only AHI had significant effect for TG.

Publication Bias Analysis

Publication bias analysis was done using four different methods to provide robust results. The methods included funnel plot analysis (**Figure 5**), Eggers reg intercept, Duval and Tweedie trim and fill, and Kendall tau with and without continuity correction. Overall, there was no significant publication bias in combined analysis. We also performed this analysis for individual lipid components and this analysis showed that there is low likelihood of publication bias for TC, TG, and LDL-c. HDL-c analysis showed likelihood of publication bias. We also performed precision plots (**Figure 6**).

Sensitivity Analysis

We also performed sensitivity analysis by removing one study at each step that did not change results, and it makes our results more robust (**Figures A5-A8**).

Figure 3—Meta-regression plots for BMI on TC, LDL, HDL, and TG

Figure 4—Meta-regression plots for AHI on TC, LDL, HDL, and TG

Figure 5—Publication bias estimation, Funnel plots for TC, LDL, HDL, and TG **Figure 6**—Precision plot analyses

DISCUSSION

There is strong positive associations between low-density lipoprotein (LDL) particles, which carry cholesterol, and the risk of coronary heart disease (CHD).^{38,39} Randomized trials have demonstrated that lowering LDL cholesterol with medications reduces the risk of cardiac death, nonfatal myocardial infarction (MI), ischemic stroke, and the need for revascularization procedures.⁴⁰⁻⁴²

Although a clear causal relationship of OSA and dyslipidemia is yet to be demonstrated, there is increasing evidence that chronic intermittent hypoxia, a major component of OSA, is independently associated and possibly the root cause of the dyslipidemia via the generation of stearoyl-coenzyme A desaturase-1 and reactive oxygen species, peroxidation of lipids, and sympathetic system dysfunction.⁴³ Intermittent hypoxia associated with sleep apnea promotes oxidative, and immune-inflammatory alterations.⁴⁴ Systemic inflammatory markers are higher in OSA patients than control subjects.⁴⁵ Cytokines, specifically IL-1, may alter LDL metabolism by human vascular endothelial cells and alter endothelial cell cholesterol metabolism. These changes in endothelial cell metabolism provide evidence supporting the critical role of cytokines in atherogenesis.⁴⁶

The present meta-analysis (MA) showed that there is an increase in levels of dyslipidemia in subjects with OSA including total cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride. An obvious majority of studies^{11-26,31-35} showed this effect, while few did not.^{27,30,31} Ozol et al. found less dyslipidemia in patients with moderate OSA than controls, most likely because their controls have high insulin resistance measured by HOMA and higher insulin levels than moderate OSA patients.²⁷ Moreover they found a high degree of dyslipidemia in their mild and severe OSA groups, which suggest that confounding factors may have played a role in their subjects' lipid levels (hypertension, obesity, and frequency of metabolic syndrome) in their sample. Another study which did not show significant dyslipidemia in OSA was by Salord et al. Their small sample (OSA, $n = 15$ and control $n = 12$) had unique characteristics: all controls without OSA were significantly obese (BMI 46.9) undergoing bariatric surgery.³¹ Moreover their OSA patients were being treated with CPAP, which may explain the different findings of the study.

These findings highlight the adverse role of OSA as risk factor for cardiovascular diseases. These finding also suggest that increasing dyslipidemia may also be the mechanism of atherosclerosis in patients with OSA. It provides a potential target for treatment of dyslipidemia. Conceivably there is data suggesting that treatment of OSA by CPAP improves dyslipidemia, atherosclerosis and cardiovascular disease.⁴⁷

Meta-regression Analysis for Confounding Variables

These MR plots show that dyslipidemia (HDL and TG) is correlated by severity of OSA, higher the AHI the higher the dyslipidemia. Gasa et al.¹⁹ show that level of dyslipidemia correlates well with the severity of OSA; gradual worsening with worst numbers found in severe OSA group. Their regression analysis showed beta of 0.007 for TG. Likewise, Peled et al. found dyslipidemia in their sample as follow; control < mild OSA < severe OSA < moderate OSA³⁰. Their Beta coefficient

was 0.332 for AHI, which suggests that this relationship is probably confounded by multiple factors including weight, BMI, and comorbid conditions.

These MR plots also showed the modest but significant effect of BMI on dyslipidemia (LDL and HDL). This is in agreement with many other studies. Sharma et al. showed that BMI had an independent association with OSA.

This finding of heightened dyslipidemia in patients with obstructive sleep apnea suggest that treatment of sleep apnea should improve this risk factors for heart disease directly or indirectly by affecting other confounding factors (obesity, hypertension, diabetes mellitus, and metabolic syndrome), as CPAP treatment for sleep apnea has been shown to positively affect management of these confounding variables.⁴⁸⁻⁵¹

Several limitations of this meta-analysis should be emphasized. Available literature is low level evidence. Many of the relevant studies regarding the association between OSA and level of dyslipidemia were cross-sectional in nature, so the temporal relationships between these two factors were unclear. Funnel plots suggest heterogeneity and publication bias (**Figure 5**). We could not perform the meta-regression for other confounding factors—sleepiness, presence of hypertension, or measures of visceral adipose tissue—since we have data on these variables only in few studies. These factors have been found to be associated with elevated dyslipidemia.

One weakness of our meta-analysis is that all papers written in languages other than English were excluded. Another weakness is that studies not yet published were also excluded (publication bias).

In summary, there appears to be some evidence indicating higher degree of dyslipidemia in patients with OSA, these levels may be correlated to the level of severity of disease as suggested by meta-regression plot for AHI. These findings may explain, at least in part, the mechanism for atherosclerosis leading to cardiovascular disorder in patients with OSA and the common occurrence of systemic complications among these patients. Future studies are needed to further explore the correlation between the level of dyslipidemia and severity of OSA and to determine whether levels of dyslipidemia can be modified by therapeutic interventions in these patients.

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APPENDIX

Figure A1—Total cholesterol, standardized difference in means, OSA versus controls

Figure A2—LDL cholesterol, standardized difference in means, OSA versus controls

Figure A3—HDL cholesterol, standardized difference in means, OSA versus controls

Figure A4—Triglycerides, standardized difference in means, OSA versus controls

Figure A5—TC sensitivity analysis

Figure A6—LDL sensitivity analysis

Figure A7—HDL sensitivity analysis

Figure A8—TG sensitivity analysis