Obstructive Sleep Apnea and Lipid Abnormalities

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Abstract

BACKGROUND: There has been a great interest in the interaction between obstructive sleep apnea (OSA) and metabolic dysfunction, but there is no consistent data suggesting that OSA is a risk factor for dyslipidemia.

AIM: The aim of this cross-sectional study was to evaluate the prevalence of lipid abnormalities in patients suspected of OSA, referred to our sleep laboratory for polysomnography.

MATERIAL AND METHODS: Two hundred patients referred to our hospital with suspected OSA, and all of them underwent for standard polysomnography. All patients with respiratory disturbance index (RDI) above 15 were diagnosed with OSA. In the morning after 12 hours fasting, the blood sample was collected from all patients. Blood levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL), were determined in all study patients. In the study, both OSA positive and OSA negative patients were divided according to the body mass index (BMI) in two groups. The first group with BMI ≤ 30 kg/m² and the second group with BMI > 30 kg/m².

RESULTS: OSA positive patients with BMI ≤ 30 kg/m² had statistically significant higher levels of triglycerides and total cholesterol, and statistically significant lower level of HDL compared to OSA negative patients with BMI ≤ 30. There were no statistically significant differences in age and LDL levels between these groups. OSA positive patients with BMI > 30 kg/m² had higher levels of triglycerides, total cholesterol and LDL and lower levels of HDL versus OSA negative patients with BMI > 30 kg/m², but without statistically significant differences.

CONCLUSION: OSA and obesity are potent risk factors for dyslipidemias. OSA could play a significant role in worsening of lipid metabolism in non-obese patients. But in obese patients, the extra weight makes the metabolic changes of lipid metabolism, and the role of OSA is not that very important like in non-obese patients.
Increased understanding of the independent associations between OSA, metabolic syndrome and insulin resistance is important to develop appropriate therapeutic strategies to reduce the high cardiometabolic risks in patients with OSA.

The aim of this cross-sectional study was to evaluate the prevalence of lipid abnormalities in patients suspected for OSA referred to our sleep laboratory for polysomnography.

Material and Methods

The study included 200 patients. It was conducted at University Clinic of Pulmonology and Allergy in Skopje. Inclusion criteria for patients were age from 35 to 60 years and persistence of minimum 2 of 3 clinical symptoms of OSA. The symptoms were snoring, witnessed apnea and daytime sleepiness. Exclusion criteria were previous history and treatment of diabetes and lipid abnormalities.

The study was approved by Ethical Committee of the Faculty of Medicine with No. 03-941/2, and before the study procedures, informed consent was obtained from all patients. Body mass index (BMI) was calculated, and patients were divided into two groups according to the BMI. All patients underwent polysomnography (Respironix, model Alice 5). All results from polysomnography were scored manually according to standard criteria [13]. Apnea, hypopnea and arousals were also identified according to the standard criteria and summarised in the form of a respiratory disturbance index (RDI). All patients with RDI above 15 were diagnosed with OSA.

In the morning after 12 hours fasting, a blood sample was collected from all patients. Blood levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL), were assessed. Biochemical measurements were conducted using an Architect Abbott C8000 auto analyser.

Statistical analyses were performed using Statistical software (Stat Soft). Data were expressed as mean (X) and standard deviation (SD). Comparisons between variables were made using the unpaired t test for parametric data. The multiple linear regressions were used to determine the association between OSA and metabolic parameters. Statistical significance was considered at p less than 0.05.

Results

From all study patients, 51 were female with an average age of 49 ± 9 years, and 149 were men with an average age of 47 ± 9 years. There was no significant difference in age, BMI and RDI between male and female. There was the significant difference in the occurrence of OSA in men versus women, 109 (73.2%) of males and 31 (62.8%) of females were OSA positive (p < 0.03).

According to BMI, patients in the study were divided into two groups. There were 120 non-obese patients with BMI ≤ 30 kg/m², and 80 obese patients with BMI > 30 kg/m². In a non obese group with BMI ≤ 30, 62 patients were OSA negative and 58 patients were OSA positive. In an obese group with BMI > 30, 14 patients were OSA negative, and 66 patients were OSA positive (Figure 1).

OSA patients had statistically significant higher BMI, triglycerides, total cholesterol and lower HDL when compared to OSA negative patients (Table 1). There was no statistical difference in age and LDL levels between these two groups of patients.

Table 1: Comparison between OSA positive and OSA negative patients

|          | OSA negative | OSA positive |
|----------|--------------|--------------|
|          | BMI < 30     | BMI > 30     |
|          | (76 patients)| (124 patients)|
| RDI < 15 | X             | SD            | X             | SD            |
| RDI > 15 | 5.04         | 3.81         | 43.78         | 18.71         | 0.000         |
| Ap(76)   | 47.29        | 9.73         | 48.22         | 8.49          | NS            |
| BMI (kg/m²) | 27.58       | 3.14         | 31.11         | 4.35          | 0.000         |
| TG (mg/dl) | 1.60         | 0.36         | 1.76          | 0.26          | 0.000         |
| TC (mg/dl) | 4.94         | 0.50         | 5.22          | 0.34          | 0.000         |
| HDL (mg/dl) | 1.45         | 0.23         | 1.34          | 0.23          | 0.001         |
| LDL (mg/dl) | 2.85         | 0.53         | 2.94          | 0.49          | NS            |

OSA = Obstructive sleep apnea; RDI = Respiratory disturbance index; BMI = Body mass index; TG = Triglycerides; TC = Total cholesterol; HDL= High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol.

In the study, both OSA positive and OSA negative patients were divided according to BMI in two groups, first group with BMI ≤ 30 and the second group with BMI > 30. OSA positive patients with BMI ≤ 30 had statistically significant higher levels of triglycerides and total cholesterol, and statistically significant lower level of HDL compared to OSA negative patients with BMI ≤ 30. There were no statistically significant differences in age and LDL levels between these groups (Table 2).
OSA positive patients with BMI>30 had higher triglycerides, total cholesterol and LDL and lower HDL versus OSA negative patients with BMI>30, but without statistically significant differences (Table 3.)

Table 2: Comparison between OSA positive and OSA negative patients with BMI ≤ 30

| RDI ≤ 15 (62 patients) | RDI > 15 (58 patients) | p |
|------------------------|------------------------|---|
| BMI ≤ 30               | BMI > 30               |   |
| Age (years)            | Age (years)            |   |
| 47.08                  | 47.62                  |   |
| SD                     | SD                     |   |
| 9.56                   | 8.38                   |   |
| BMI (kg/m^2)           | BMI (kg/m^2)           |   |
| 26.55                  | 27.38                  |   |
| SD                     | SD                     |   |
| 2.40                   | 2.10                   |   |
| TG (mmol/l)            | TG (mmol/l)            |   |
| 1.53                   | 1.66                   |   |
| SD                     | SD                     |   |
| 0.28                   | 0.18                   |   |
| TC (mmol/l)            | TC (mmol/l)            |   |
| 4.90                   | 5.10                   |   |
| SD                     | SD                     |   |
| 0.40                   | 0.28                   |   |
| HDL (mmol/l)           | HDL (mmol/l)           |   |
| 1.55                   | 1.35                   |   |
| SD                     | SD                     |   |
| 0.22                   | 0.19                   |   |
| LDL (mmol/l)           | LDL (mmol/l)           |   |
| 2.84                   | 5.26                   |   |
| SD                     | SD                     |   |
| 0.52                   | 0.36                   |   |
| RDI = Respiratory disturbance index; BMI = Body mass index; TG = Triglycerides; TC = Total cholesterol; HDL= High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol.

Table 3: Comparison between OSA positive and negative patients with BMI > 30

| RDI ≤ 15 (14 patients) | RDI > 15 (66 patients) | p |
|------------------------|------------------------|---|
| BMI > 30               | BMI > 30               |   |
| Age (years)            | Age (years)            |   |
| 48.21                  | 47.76                  |   |
| SD                     | SD                     |   |
| 10.76                  | 8.62                   |   |
| BMI (kg/m^2)           | BMI (kg/m^2)           |   |
| 32.14                  | 34.38                  |   |
| SD                     | SD                     |   |
| 1.59                   | 3.11                   |   |
| TG (mmol/l)            | TG (mmol/l)            |   |
| 1.85                   | 2.92                   |   |
| SD                     | SD                     |   |
| 0.49                   | 0.28                   |   |
| TC (mmol/l)            | TC (mmol/l)            |   |
| 5.12                   | 5.33                   |   |
| SD                     | SD                     |   |
| 0.53                   | 0.35                   |   |
| HDL (mmol/l)           | HDL (mmol/l)           |   |
| 1.37                   | 1.30                   |   |
| SD                     | SD                     |   |
| 0.25                   | 0.23                   |   |
| LDL (mmol/l)           | LDL (mmol/l)           |   |
| 2.94                   | 3.08                   |   |
| SD                     | SD                     |   |
| 0.60                   | 0.55                   |   |
| RDI = Respiratory disturbance index; BMI = Body mass index; TG = Triglycerides; TC = Total cholesterol; HDL= High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol.

Discussion

OSA is the potent risk factor for metabolic disorders. The mechanisms through which OSA may worsen metabolism are complex. It may trigger several pathological mediating pathways (sympathetic activation, neurohumoral changes, glucose homeostasis disruption, inflammation and oxidative stress) through chronic intermittent hypoxia (CIH), and these may ultimately cause deterioration in the metabolic function [14, 15]. According to previous studies, the prevalence of OSA is increased fourfold in patients with obesity. Obesity plays a major part in the development of the metabolic syndrome, which consists of insulin resistance, diabetes or impaired glucose tolerance, hypertension, and lipoproteinemia [16]. In this study, we have demonstrated that OSA positive patients had significantly higher level of triglycerides, total cholesterol and decreased HDL cholesterol levels versus OSA negative patients. LDL was also higher in OSA patients but with no significant value.

There were statistically significant differences in BMI between OSA positive and negative patients. So, the question is, does OSA affect lipid metabolism by itself or obesity is playing the major role in metabolic changes in these groups of patients. The relationships between OSA and various lipid parameters have not been extensively investigated like other components in the metabolic syndrome and the results have been more diverse. Studies of sleep clinic cohorts have consistently reported a higher prevalence of dyslipidemia in OSA positive subjects compared to those without OSA [17, 18].

The American Heart Health Sleep Study reported that apnea-hypopnea index (AHI) was inversely related to HDL-cholesterol levels in younger men and women, but not in older men, and triglyceride levels in younger men and women only [19]. In contrast, Lam et al. evaluated 255 patients between 30 and 60 years, and they did not find the association between OSA and HDL or TG levels, after controlling for confounding variables [20]. In our study, after dividing patients according to BMI, OSA positive patients with BMI < 30 had statistically significant higher levels of triglycerides and total cholesterol, and statistically significantly lower levels of HDL versus OSA negative patients with BMI ≤ 30. This result is corresponding with previously cited studies [6-8, 9, 17-19]. However, several studies that were searching for an association between metabolic syndrome and normal weight, over weight and obese patients, reported that prevalence of metabolic syndrome in non-obese patients (BMI 25.0-26.9 kg/m^2) is between 9.6-22.5%, depending on ethnicity and sex [21, 22]. So the possibility that OSA mechanisms are worsening lipid metabolism in a non obese group of patients is very high rather that weight gain. In obese patients, both OSA positive and OSA negative, there were no statistically significant differences in lipid blood levels. This result is corresponding with others studies. Sahin et al. in their study found out that OSA positive obese patients had statistically significant higher levels of lipids compared to OSA positive patients with normal weight. But in obese patients, both OSA positive and OSA negative, there were no statistically significant differences in blood levels of lipids [23]. Sharma et al. compared three groups of patients, 40 obese OSA positive patients, 40 obese OSA negative patients and 40 normal weight OSA negative patients and found that there was no difference in metabolic status between obese OSA positive and obese OSA negative patients [24]. Schäfer et al. found no relationship between OSA and concentration of lipoproteins in 81 male subjects [25]. Results from national surveys suggest that dyslipidemias are the most common comorbidities associated with a range of body mass indices (BMI),

Table 4: Independent predictors of OSA

| BMI = Body mass index; TC = Total cholesterol; LDL = Low-density lipoprotein cholesterol.

When all parameters were analysed with multiple linear regressions, only BMI, total cholesterol levels and LDL levels were found to be independent predictors of OSA (Table 4).

Table 4: Independent predictors of OSA

| Variable | OR       | 95%CI    | p     |
|----------|----------|----------|-------|
| BMI      | 1.6      | 1.39:1.83| 0.000 |
| TC       | 1.73     | 1.38:2.16| 0.000 |
| LDL      | 1.47     | 1.19:1.81| 0.000 |
with substantial increases found with increased body weight. It is estimated that about 68% of obese adults in the National Health and Nutrition Examination Survey population had metabolic abnormalities [26]. However, the limiting factor of this study may be not so large number of patients, particularly the small number of OSA negative patients with a BMI > 30. It should be noted that patients with previous history and treatment of diabetes and lipid disorders were excluded from the study.

In conclusion, OSA and obesity are the potent risk factor for dyslipidemias. OSA could play the significant part in worsening of lipid metabolism in non-obese patients. But in obese patients, the extra weight makes the metabolic changes of lipid metabolism, and the roll of OSA is not that very important like in non-obese patients.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230-5. https://doi.org/10.1056/NEJM199304293281074 PMid:8464434
2. Dempsey J, Veasey S, Morgan B, O’Donnell C. Pathophysiology of sleep apnea. Physiol Rev. 2010; 90: 47–112. https://doi.org/10.1152/physrev.00043.2008 PMid:20086074 PMCid:PMC970937
3. Bradley TD, Floras JS. Obstructive sleep apnea and its cardiovascular consequences. Lancet. 2009;373: 82-93. https://doi.org/10.1016/S0140-6736(08)61622-0
4. Malhotra A, Llosalzo J. Sleep and cardiovascular disease: an overview. Prog Cardiovas Dis. 2009; 51:279-351. https://doi.org/10.1016/j.pcd.2008.10.004
5. Newman AB, Nieto FJ, Guidry U, Lind BK, Redline S, Pickering TG, Quan SF; Sleep Heart Health Study Research Group. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. Am J Epidemiol. 2000; 152(5):597-619. PMid:11891626 PMCid:PMC3459210
6. Togeiro SM, Carneiro G, Ribeiro Filho FF, et al. Consequences of obstructive sleep apnea syndrome. Turk J Med Sci. 2011; 41: 443-50. https://doi.org/10.4085/1307-886X-41-3-443
7. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnea and dyslipidemia: implications for atherosclerosis. Curr Opin Endocrinol Diabetes Obes. 2010;17:161-5. Erratum in: Curr Opin Endocrinol Diabetes Obes. 2010;17:394. https://doi.org/10.1097/MED.0b013e3283373624 PMid:2125003
8. Togeiro SM, Carneiro G, Ribeiro Filho FF, et al. Consequences of Obstructive Sleep Apnea on Metabolic Profile: A Population-Based Survey. Obesity (Silver Spring). 2013;21:847-51. https://doi.org/10.1002/oby.20288 PMCid:23712988
9. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J. 2004;25:735-41. https://doi.org/10.1016/j.ehj.2004.02.021 PMid:15120883
10. Roche F, Storza E, Pichot V, Maudoux D, Garcin A, Celle S, Picard-Kosovskyy M, Gaspoz JM, Barthélémy JC. PROOF Study Group. Obstructive sleep apnoea/hypopnoea influences high-density lipoprotein cholesterol in the elderly. Sleep Med. 2009;10:882-6. https://doi.org/10.1016/j.sleep.2008.07.017 PMid:19200781
11. Tan KC, Chow WS, Lam JC, Lam B, Wong WK, Tam S, Ip MS. HDL dysfunction in obstructive sleep apnea. Atherosclerosis. 2006;184:377-82. https://doi.org/10.1016/j.atherosclerosis.2005.04.024 PMid:15975582
12. Tokuda F, Sando Y, Matsui H, Kikue H, Yokoyama T. Serum levels of adipocytokines, adiponectin and leptin, in patients with obstructive sleep apnea syndrome. Intern Med. 2008;47:1843-9. https://doi.org/10.2169/internalmedicine.47.1035 PMid:18981626
13. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012 Oct 15;8(5):957-69. PMid:23066376 PMCid:PMC3459210
14. Levy P, Bonsignore MR, Eckel J. Sleep-disordered breathing and metabolic consequences. Eur Respir J. 2009; 34: 243–260. https://doi.org/10.1183/09031936.00166808 PMid:19567607
15. McNicholas WT, Bonsignore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J. 2007; 29: 156–178. https://doi.org/10.1183/09031936.00127406 PMid:17197482
16. Ip MS, Lam KS, Ho C, Tsang KW, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. Chest. 2000; 118: 580–586. https://doi.org/10.1378/chest.118.3.580
17. Robinson GV, Pepperrell JC, Segal HC, Davies RJ, Stradling JR. Circulating cardiovascular risk factors in obstructive sleep sleep data from randomized controlled trials. Thorax. 2004; 59: 777–782. https://doi.org/10.1136/thx.2003.018739 PMid:1533385
18. Newman AB, Nieto FJ. Relation of sleep-disordered breathing to cardiovascular disease risk factors—the Sleep Heart Health Study. Am J Epidemiol. 2001; 154: 50–59. https://doi.org/10.1093/aje/154.1.50
19. Lam JC, Lam B, Lam CL et al. Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong. Respir Med. 2006; 100: 980-987. https://doi.org/10.1016/j.rmed.2005.10.003 PMid:16337115
20. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. Diabetes Care. 2004; 27: 2222-2228. https://doi.org/10.2337/diacare.27.9.2222 PMid:15333488
21. Conus F, Rabasa-Lhoret R, Peronnet F. Characteristics of metabolically obese normal-weight (MONW) subjects. Applied physiology, nutrition, and metabolism. 2007;32(1):4-12. https://doi.org/10.1139/h06-092
22. Şahin M, Berçik Inal B, Öğreden S, Yiğit O, Aralı H, Güvenen G. Metabolic profile and insulin resistance in patients with obstructive sleep apnea syndrome. Turk J Med Sci. 2011; 41: 443–54.
23. Sharma SK, Kumpawat S, Goel A, Banga A, Ramakrishnan L, Chaturvedi P. Obesity and not obstructive sleep apnea is responsible for metabolic abnormalities in a cohort with sleep-disordered breathing. Sleep Med. 2007; 8: 12–17. https://doi.org/10.1016/j.sleep.2006.06.014 PMid:17157064
24. Schäfer H, Pauleit D, Sudhop T, Gouni-Berthold I, Ewig S, Berthold HK. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. Chest. 2002; 122: 829–839. https://doi.org/10.1378/chest.122.3.829 PMid:12226021
25. Wildman RP, Mumtah N, Reynolds K, et al. The obese without cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med. 2008;168:1617–1624. https://doi.org/10.1001/archinte.168.15.1617 PMid:18695075