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Obstructive Sleep Apnea and Dyslipidemia: Implications for Atherosclerosis

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Abstract

Purpose of review—The aim of this review is to summarize current evidence about the impact of Obstructive Sleep Apnea (OSA) and Intermittent Hypoxia (IH) on dyslipidemia and provide future perspectives in this area.

Recent findings—IH, a hallmark of OSA, induces hyperlipidemia in lean mice. Hyperlipidemia of IH occurs, at least in part, due to activation of the transcription factor sterol regulatory element-binding protein-1 (SREBP-1) and an important downstream enzyme of triglyceride and phospholipid biosynthesis, stearoyl-coenzyme A desaturase-1 (SCD-1). Furthermore, IH may regulate SREBP-1 and SCD-1 via the transcription factor hypoxia-inducible factor 1. In contrast, key genes involved in cholesterol biosynthesis, SREBP-2 and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, are unaffected by IH.

In humans, there is no definitive evidence regarding the effect of OSA on dyslipidemia. Several cross-sectional studies suggest that OSA is independently associated with increased levels of total cholesterol, LDL and triglycerides, whereas others report no such relationship. Some non-randomized and randomized studies show that OSA treatment with continuous positive airway pressure may have a beneficial effect on lipid profile.

Summary—There is increasing evidence that IH is independently associated with dyslipidemia. However, the role of OSA in causality of dyslipidemia remains to be established.

Keywords

Intermittent hypoxia; obstructive sleep apnea; dyslipidemia; atherosclerosis; cardiovascular disease

Introduction

Obstructive sleep apnea (OSA) is characterized by chronic intermittent hypoxia (IH) and frequent arousals from sleep due to the recurrent collapse of the upper airway.¹ OSA is a common disorder affecting 4–24% of men and 2–9% of women in the US.² New compelling evidence suggests that OSA is directly linked to high cardiovascular mortality and morbidity.

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^{3–5} In a prospective study from the Sleep Heart Health cohort, the investigators found that OSA causes significant increases in all-cause and cardiovascular mortality, particularly in men aged 40–70 years with severe forms of OSA.³ A Spanish observational study demonstrated that treatment of OSA with continuous positive airway pressure (CPAP) led to a significant decrease in non-fatal (myocardial infarction, stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography) and fatal (death from myocardial infarction or stroke) cardiovascular events.⁴

The mechanisms by which OSA leads to poor cardiovascular outcomes are not completely understood, but OSA has been implicated in the progression of dyslipidemia, systemic inflammation, oxidative stress, endothelial dysfunction and atherosclerosis.^{6–10} Several studies have focused on a potential independent association between OSA and dyslipidemia.^{11–12} Evidence from a murine model showed that of IH causes hyperlipidemia and upregulation of genes of lipid biosynthesis in the liver.^{13–15} The increased cardiovascular risk of OSA has been attributed, at least in part, to the lipid abnormalities induced by IH.¹⁶ The main aim of this review is to elucidate current evidence of OSA and IH in dyslipidemia.

Evidence from Clinical studies

The current clinical evidence supporting the impact of OSA on dyslipidemia is sparse. The majority of the studies are cross-sectional^{11,12,17–27} and nonrandomized^{28–33} with a small number of patients. However, the majority of the studies were not specifically designed to evaluate the lipid profile. Only a handful of studies evaluated the lipid profile pre and post treatment with CPAP.^{9,34–36} and there are no long-term studies with follow-up beyond 6 months of CPAP treatment. Finally, although the investigators usually considered changes in body weight during the trials, other important confoundings, i.e. diet, physical activity and body composition, were frequently ignored.

Table 1 summarizes the cross-sectional studies that evaluated lipid profile in patients with OSA. Overall, there is no definitive evidence regarding the effect of OSA on the lipid profile. The majority of the studies suggest that total cholesterol and LDL cholesterol are not increased in patients with OSA compared to controls. Several studies (including the larger sample size studies) showed that OSA is associated with a decrease in HDL cholesterol and an increase in triglycerides.^{12,17,24}

Data from non-randomized trials evaluating the effect of OSA treatment with CPAP in adults^{28–31, 33} or adenotonsillectomy in children³² on plasma lipids are described in Table 2. The majority of these studies demonstrated a significant decrease in total cholesterol,^{30–33} LDL cholesterol^{28–30,32–33} and triglycerides^{28,31–32} levels after treatment. In contrast, data on HDL cholesterol are varied, with investigators showing either an increase^{28–29,32} or no effect.^{30–31,33}

To the best of our knowledge, there are only 4 randomized studies^{9,34–36} that evaluated lipid profile pre- and post- CPAP treatment in adults (Table 3). Two groups of investigators examined only short-term effects of CPAP treatment (one month).^{34,36} With the exception of a clinical trial by Robinson et al.,³⁶ all studies involved a small sample size. Only Robinson et al.³⁶ found a significant decrease in total cholesterol after CPAP, whereas three other studies did not find any changes in plasma lipids in response to therapy.^{9,34–35}

Evidences from Animal models

This section describes the current evidence on lipid metabolism and mechanisms of dyslipidemia during IH in mice.

Lipid Data in animal models

Historically several different types of animal models of OSA have been developed, including spontaneous upper airway obstruction (English bulldogs), mechanical occlusion of the upper airway in small and large animals, etc. However, these models are very labor-intensive and do not allow to study a large number of animals.³⁷ A rodent model of IH has been developed to study metabolic abnormalities induced by OSA on a larger scale. Using this model, Perry et al.³⁸ demonstrated that 4 days of IH in rats did not affect plasma levels of total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride. However, animals subjected to 21 days of IH presented a significant increase in triglycerides, suggesting a time-dependent effect of hypoxia on triglycerides. Our group has shown in the mouse model that in lean C57BL/6J mice on a regular diet, IH causes increases in total cholesterol, HDL-C and triglycerides after 5 days, while an increase in LDL cholesterol became evident after 4 weeks.^{13,14}

Mechanisms of dyslipidemia induced by IH (Figure 1)

The mechanisms of dyslipidemia induced by IH are not clearly understood. Previous evidence suggests that the hypoxia-inducible factor-1 in the liver activates sterol regulatory element-binding protein-1 (SREBP-1) and stearoyl-coenzyme A desaturase-1 (SCD-1), an important gene of triglyceride and phospholipids biosynthesis controlled by SREBP-1.¹³ Others key genes involved in the cholesterol biosynthesis, including SREBP-2 and 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase, were unaffected by IH.¹³

In genetically obese *ob/ob* mice, IH (FiO₂ was cycled between 21 and 5%) for 12 weeks also induced hyperlipidemia and up-regulated the SREBP-1 pathway in the liver, whereas the SREBP-2 pathway remained intact.¹⁵ Importantly, the degree of hyperlipidemia and changes in hepatic SCD-1 levels are dependent on the severity of hypoxia: moderate IH (FiO₂ cycling between 21 and 10%) does not induce hyperlipidemia or change hepatic levels of SCD-1.¹⁴

Dyslipidemia of IH contributes to the development and progression of atherosclerosis. Savransky et al.¹⁶ studied 40 male C57BL/6J mice, 8 weeks of age, fed either a high-cholesterol diet or a regular chow diet and subjected either to IH or intermittent air (control conditions) for 12 weeks. These animals are particularly resistant to atherosclerosis. However, nine out of 10 mice simultaneously exposed to IH and a high-cholesterol diet developed atherosclerotic lesions in the aortic origin and descending aorta. In contrast, atherosclerosis was not observed in mice exposed to intermittent air and a high-cholesterol diet or in mice exposed to IH and a regular diet. Although a high-cholesterol diet resulted in significant increases in serum total and LDL cholesterol levels and a decrease in HDL cholesterol, combined exposure to IH and a high-cholesterol diet resulted in further increases in serum total cholesterol and LDL, with an additive impact on serum lipid peroxidation, and up regulation of SCD-1.

The importance of SCD-1 in dyslipidemia and atherosclerosis induced by IH has been established in the experiment showing that SCD-1 deficiency attenuated IH-induced dyslipidemia and atherosclerosis in mice.³⁹ Together, these results suggested that preexistent or coexisting dyslipidemia due to either genetic or environmental factors are necessary for expression of atherogenic properties of IH in this resistant model of atherosclerosis.

Conclusion

There is increasing evidence that IH is independently associated with dyslipidemia. However, the role of OSA in causality of dyslipidemia remains to be established. Altered lipid metabolism in OSA may be a pathway by which this condition mediates observed increases in cardiovascular risk. Thus, it is of vital importance to further our knowledge in this area, both in the clinical and experimental settings.

Investigators have focused on transcriptional pathways in the liver. However, physiological flux of lipids during IH has not yet been adequately assessed. For example, IH may delay the clearance of lipoproteins after hepatic secretion or chylomicrons after intestinal absorption. Second, hepatic synthesis of triglycerides, phospholipids, and lipoproteins may be increased by delivery of non-esterified fatty acids from the circulation.

Another potential focus of interest is to explore the potential pathways that could be involved in the pathogenesis of dyslipidemia induced by OSA/IH, such as sympathetic activity and oxidative stress. Advances in this knowledge could have potential therapeutic targets in the future. Finally, there are strong necessities of larger randomized trials that evaluate the impact of OSA treatment on lipid profile and lipid metabolism.

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Figure 1.

Putative mechanisms by which chronic intermittent hypoxia promotes dyslipidemia. HIF-1, hypoxia inducible factor 1; SREBP-1c, sterol regulatory element binding protein 1c; SCD-1, stearoyl coenzyme A desaturase 1; CE, cholesterol esters; TG, triglycerides; PL, phospholipids; FA, fatty acids.

Table 1
Cross-sectional studies involving Obstructive Sleep Apnea (OSA) and the impact on dyslipidemia.

Sample Size (OSA/controls)	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides	Author/year
104 adults (61/43)	↔	↔	↓	↑	Coughlin et al. 2004 ¹⁷
99 adults (77/22)	↔	↔	↔	↑	Czerniawska et al. 2008 ¹⁸
42 adults (30/12)	↔	↔	↔	↔	Drager et al. 2005 ¹⁹
81 adults with Metabolic Syndrome (51/30)	↔	↔	↔	↔ [*]	Drager et al. 2009 ²⁰
94 adults (42/52)	↔	NA	↔	↔	Kono et al. 2007 ²¹
60 adults (40/20)	↔	↔	↔	↑	Lefebvre et al. 2008 ²²
42 adults (21/21)	↑	↑	↔	↔	McArdle et al. 2007 ¹¹
52 adults (36/16)	↔	↔	↔	↔	Minoguchi et al. 2005 ²³
4491 adults (1988/2503)	↑ ^{**}	NA	↓	↑	Newman et al. 2001 ¹²
846 elderly (470/376)	↔	↔	↓	↑	Roche et al. 2009 ²⁴
210 adults (128/82)	↔	↔	↔	↔	Tan et al. 2006 ²⁵
68 adults (53/15)	↔	↔	↔	↔	Tokuda et al. 2008 ²⁶
99 adults with hypertension (46/53)	↑	↑	↓	↔	Tsioufis et al. 2007 ²⁷

NA: Not available

* A strong trend to increase was observed.

** In subjects <65 years

Table 2
Non-randomized studies involving interventions in Obstructive Sleep Apnea and the impact on dyslipidemia.

Sample Size	Intervention / Follow-up	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides	Author/year
22 adults	CPAP / 6 months	↔	↓	↑	↓	Chin et al. 1999 ²⁸
23 adults	CPAP / 1 month	↔	↓	↑	↔	Chin et al. 2006 ²⁹
44 adults	CPAP / 2 months	↓	↓	↔	↔	Cuhadaroglu et al. 2009 ³⁰
32 adults	CPAP / 2 months	↓ ^{**}	↔	↔	↓ ^{**}	Dorkova et al. 2007 ³¹
62 children	Adenotonsillectomy/ 6–12 months	↔ non obese ↓ obese	↓	↑	↔ non obese ↓ obese	Gozal et al. 2008 ³²
53 adults	CPAP / 6 months	↓	↓ ^{***}	↔	↔	Steiropoulos et al. 2007 ³³

* No differences in the subgroup that did not have body weight reduction.

** No differences in the noncompliant group (CPAP use <4h/night).

*** A strong trend was observed.

Randomized studies involving interventions in Obstructive Sleep Apnea and the impact on dyslipidemia.

Table 3

Sample Size CPAP/control	Intervention / Follow-up	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides	Author/y ear
24 adults (12/12)	CPAP / 4 months	↔	↔	↔	↔	Drager et al. 2007 ⁹
13 adults (cross-over)	CPAP / 1 month	↔	↔	↔	↔	Comondore et al. 2009 ³⁴
34 adults (cross-over)	CPAP / 6 weeks	↔	↔	↔	↔	Coughlin et al. 2007 ³⁵
220 adults (108/112)	CPAP / 1 month	↓	NA	NA	↔	Robinson et al. 2004 ³⁶

NA: Not available