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Obstructive sleep apnea and dyslipidemia: evidence and underlying mechanism

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Abstract

Introduction—Over the past half century, evidence has been accumulating on the emergence of obstructive sleep apnea (OSA), the most prevalent sleep-disordered breathing, as a major risk factor for cardiovascular disease. A significant body of research has been focused on elucidating the complex interplay between OSA and cardiovascular risk factors, including dyslipidemia, obesity, hypertension, and diabetes mellitus that portend increased morbidity and mortality in susceptible individuals.

Conclusion—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. The aim of this review is to highlight the relationship between OSA and dyslipidemia in the development of atherosclerosis and present the pathophysiologic mechanisms linking its association to clinical disease. Issues relating to epidemiology, confounding factors, significant gaps in research and future directions are also discussed.

Keywords

Obstructive sleep apnea; Chronic intermittent hypoxia (CIH); Dyslipidemia; Cardiovascular risks

Introduction

Obstructive sleep apnea (OSA) is characterized by frequent arousals from sleep, chronic intermittent hypoxia (CIH), and hemodynamic changes as a result of partial or complete pharyngeal obstruction [1]. Although OSA occurs in all age groups, it is most often found among 40–60 year olds with estimated prevalence of 5–10 % in the US population [2, 3]. The condition has been associated with increased road traffic accidents [4], cardiovascular disease (CVD) [5], stroke [6], mortality [7, 8], days of work lost [9], as well as medical cost burden [10]. The public health impact of OSA is immense, particularly in its association with CVD [11] and death [12].

The authors declare that they have no conflict of interest.

Recent investigations have suggested links between OSA and CVD, and the implications for therapeutic intervention [13]. Elevations in total cholesterol, triglycerides, and corresponding reduction in HDL have been coupled to oxidative processes commonly found in OSA [14–16]. Basic and clinical data have implicated dyslipidemia in this OSA-related atherosclerosis [17, 18]. Furthermore, research has shown that the metabolic derangements in OSA mirror those in the development of atherosclerosis [19]. In this review, we discuss the relationship between OSA and dyslipidemia in the development of atherosclerosis and examine the pathophysiologic mechanisms linking its association to clinical disease. Issues relating to epidemiology, confounding factors, significant gaps in research, and future directions are also discussed.

Linking obstructive sleep apnea to dyslipidemia

Dyslipidemia, defined as abnormally elevated total cholesterol or triglycerides with or without a corresponding significantly reduced high density lipoprotein (HDL) level, is associated with progressive atherosclerosis in susceptible individuals [20]. Secondary dyslipidemia commonly coexists with positive atherosclerotic derangements, including type 2 diabetes, metabolic syndrome, obesity, coronary artery disease, and hypertension [20]. Recently, there is a rejuvenated interest on the role of OSA in the development of metabolic syndrome including dyslipidemia, a surrogate marker for atherosclerosis [21–28].

Pathophysiological mechanisms

Although the mechanisms responsible for dyslipidemia and adverse cardiovascular outcomes seen in OSA are poorly understood, it appears that CIH is a key factor linking OSA to the progression of dyslipidemia, systemic inflammation, oxidative stress, endothelial dysfunction, and atherosclerosis in both in vitro and in vivo models [29]. In a study involving adult patients with complaints of habitual snoring and without previous diagnosis of sleep-related breathing disorder that were prospectively followed for over 3 years, 85 % was diagnosed with OSA, as defined by apnea hyponea index (AHI) >5/h [30]. The overall prevalence of hypercholesterolemia, hypertriglyceridemia, and hyperuricemia was 61.1 %, 55.3 %, and 25.8%, respectively. Desaturation index, a surrogate marker for hypoxia, was found to be an independent factor contributing to hypercholesterolemia and hypertriglyceridemia [30]. In an animal model, Perry et al. was able to show that only rat exposed to CIH (over 21 days) presented with significant increase in triglyceride compared to control ($p<0.05$) and those exposed to shorter duration of intermittent hypoxia (over 4 days; $p<0.05$) [31]. As discussed below and illustrated in Fig. 1, studies have shown that CIH induced by OSA is associated with generation of sterol regulatory element binding protein-1 (SREBP-1) and stearoyl coenzyme A desaturase-1 (SCD-1), peroxidation of lipids, HDL dysfunction, increased total cholesterol level, and sympathetic dysfunction [14, 24, 32–36]. Altogether, these factors create a pro-inflammatory milieu responsible for development of dyslipidemia and propagation of atherosclerosis and CVD in OSA [29].

Effect of hypoxia on SREBP and SCD

Experiments in mice have shown that CIH results in hyperlipidemia through up-regulation of genes responsible for hepatic lipid biosynthesis [37]. In another study involving lean mice

on regular diet (chow diet), intermittent hypoxiawas associated with increased serum total cholesterol (84 to 94 mg/dl) and triglycerides (34 to 46 mg/dl) within 5 days when matched with control ($p<0.001$). Similarly, an increase in liver lipid content was noted (18.8±3.3 mg/g vs 9.6± 0.7 mg/g in control; $p<0.05$) in this study. Of note, the effect of hypoxia raised SREBP-1 level by 26.7±4.0 %; $p<0.001$ with a striking >2-fold increase in SCD-1 mRNA (and SCD-1 protein levels). These changes were absent in control mice under identical conditions [32]; however, when control mice were subjected to CIH over 12 weeks they produced similar results ($p<0.05$) without implicating SREBP-2 [37].

Putatively, CIH induces hypoxia inducible factor-1 (HIF-1) in the liver which, in turn, activates both SREBP-1 and SCD-1 [32]. In concert, SREBP-1 induces gene expression of SCD-1, independent of SREBP-2, to enhance triglyceride and phospholipid biosynthesis [32, 33]. More importantly, the degree of hyperlipidemia and changes in hepatic SCD-1 levels were directly dependent on the severity of local hypoxia [14]. Savransky et al. demonstrated both in humans and mice the pivotal role of SCD-1 in the development of dyslipidemia and atherosclerosis in OSA. It was shown that the expression of hepatic SCD-1 significantly correlated with the degree of oxyhemoglobin desaturation in patients with OSA suggesting that CIH induces SCD-1 (r00.68, $p<0.001$) [24], which may act through direct activation of SREBP-1 or via HIFs [24, 34–36].

Activation of SREBP-1 has also been suggested as a key mediator of dyslipidemia even in the absence of hypoxia [38]. It is known that a classic action of insulin is stimulation of fatty acid synthesis during a time of carbohydrate excess, an action opposed by glucagon via cyclic adenosine monophosphate. Evidently, the fatty liver that is commonly associated with obesity and insulin resistance is due to SREBP-1 which is elevated in response to high insulin levels. Available evidence suggests that this insulin action is mediated via SREBP-1 [38]. Therefore SREBP-1 also increases lipogenic gene expression and enhances fatty acid synthesis and triglyceride accumulation via other non-hypoxic activator [39, 40].

Effect of hypoxia on lipid peroxidation and HDL dysfunction

In addition to affecting the circulating levels of cholesterol, OSA may modulate the functions of lipids leading to generation of oxidized and dysfunctional lipids via oxidative stress [41, 42]. Oxidized form of low-density lipoprotein (LDL) cholesterol is much more atherogenic than the unoxidized form and individuals with OSA have been reported to exhibit lipid peroxidation with higher levels of oxidized LDL cholesterol compared with non-OSA individuals [42]. Carpagnano et al. showed that oxidative stress measured by 8-isopropstane levels, a reliable marker of lipid peroxidation formed by the effect of oxidative stress on arachidonic acid, was increased in the airway and plasma of patients with OSA and that serum level of 8-isoprostane was reduced by bi-level or continuous positive airway pressure (Bi-\CPAP) therapy [43, 44].

In another study, it was observed that increased oxidative stress in OSA is not only associated with increased lipid peroxidation but also with HDL dysfunction: OSA subjects were shown to have a greater degree of HDL dysfunction ($p<0.01$) and increased oxidized LDL levels ($p<0.05$) even though they had similar concentrations of plasma lipids and apolipoproteins compared to controls [18]. HDL isolated from subjects with OSA has

impaired ability to prevent oxidation of LDL ex vivo [18]. This HDL dysfunction is correlated with the severity of OSA in these subjects (r00.53, p<0.001) [18].

Even though the precise mechanism of HDL in mitigating atherogenesis is uncertain, several hypothesis have been suggested which include: cholesterol efflux from cells in arterial wall [45], binding of oxidant molecules as cholesteryl ester hydroperoxides which are rapidly removed by liver cell [46], destruction of lipid hydroxyperoxides that oxidize LDL phospholipids [47, 48], and more importantly, HDL inhibition of monocyte chemotactic protein (MCP-1) which along with other adhesionmolecules allow stimulated/injured endothelial cells to internalize monocytes that later transform into macrophages in the propagation of atherosclerosis [49]. These critical functions of HDL are mediated by paraoxonases (PON-1 and PON-3: enzymes synthesized by the liver but transported along with HDL in plasma) and apolipoprotein, apoA-1 [47–50], which are dysfunctional in OSA [18].

Research indicates that the protective antioxidant enzyme(PON-1) is not only diminished in OSA, but also inversely correlates with severity of OSA determined by respiratory disturbance index [51]. Evidence also suggests that these antioxidant/anti-inflammatory properties of HDL are superior to HDL concentration in terms of discriminating between those with/without coronary heart disease [52, 53]. Since atherosclerosis is in part initiated by the presence of oxidized LDL in the arterial intima, one may conclude that these antioxidant/anti-inflammatory effects of HDL may account, at least in part, for the antiatherogenic potential of HDL and possibly the role of OSA in dyslipidemia/ atherosclerosis.

Effect of hypoxia on sympathetic activity

Neurocardiogenic and neurohormonal dysregulation has been described in OSA as a consequence of hypoxia [54]. 2 Unopposed or hypersympathetic tone may have adverse effects on cholesterol metabolism [55–57]. This observation is supported by the evidence indicating that blockade of beta and alpha receptors have well-described effects on serum HDL and triglyceride levels [55–57]. Agents that block alpha-1 receptor are known to increase HDL and decrease serum triglyceride [46], while beta adrenergic blockers have the opposite effects [56, 57]. However, functional mutations of the beta-2 adrenergic receptor have no proven effect on OSA-induced lipid concentrations, perhaps implying a mechanism attributable to beta-1 receptor downstream the signal pathway [58].

Also, both noradrenaline and cortisol regulate hormone- sensitive lipoprotein and modify HDL synthesis [59, 60]. Thus, the heightened sympathetic milieu in patients with OSA is not only linked to CVD and adverse cardiovascular events [61, 62], but may play a central role in the development of dyslipidemia [53].

Evidence from clinical studies

The clinical evidence linking obstructive sleep apnea with dyslipidemia is limited. Available studies are largely cross-sectional and non-randomized trials [29]. Data compiled by Drager et al. [29] from various studies, however, shows intriguing trends and implies the following:

1. Virtually all cases without significant association had small sample size. The few studies with significant findings had large sample size and amply powered: Newman et al. (4,491 adults) and Roche et al. (846) [63, 64].
2. The few randomized studies did not show any clear evidence overall that treatment of OSA with CPAP was effective in improving dyslipidemia, besides non-examined lipids as primary outcome [29].

In 2006, Borgel et al., in a single center study of 470 patients, suggested an association of OSA with cardiovascular risk factors including dyslipidemia [61]. The 6-month study duration found: (1) the number of hypopnea or apnea (AHI) is independently associated with low HDL levels, $p<0.001$, (2) Bi-/CPAP therapy significantly increased the mean HDL serum levels by 5.8 %(p00.013) within the study period, and (3) the relation between the changes of AHI and HDL or triglyceride indicated some reversibility of dyslipidemia with Bi-/CPAP therapy. In fact, there was improvement in mean lipid/lipoprotein serum levels in all subjects with initial dyslipidemia through Bi-/CPAP therapy [61]. After adjustment for age, gender, BMI, DM, and use of lipid lowering medications, a significant improvement in lipid profiles persisted with OSA therapy [61]. These findings are consistent with observation from sleep heart health study involving 6,440 females >65 years with moderate-to- severe OSA [63].

Recently, the Sleep and Circadian Research Group conducted a randomized, placebo-controlled crossover study evaluating CPAP therapy on postprandial lipidemia over a full 24-h encompassing both sleep and wake periods among 29 patients followed over 2 months. In this study, participants were >21 years old with AHI ≥25/h of sleep ± Oxygen Desaturation Index ≥20/h measured by overnight polysomnography. Hypertriglyceridemia peaks which were found during both wakefulness (2 p.m.) and sleep (3 a.m.) were significantly reduced following CPAP treatment compared with placebo along with reduction in mean 24-h total cholesterol (95 % CI, −0.27 to −0.11; $p<0.00001$) [65]. Analysis of pooled data from two randomized controlled trials demonstrated that the group treated with therapeutic CPAP for 1 month experienced a significant decrease in serum total cholesterol, but the difference in the fall in total cholesterol between the therapeutic CPAP and the control groups failed to reach statistical significance [66].

Conclusion

Though a direct cause and effect relationship between OSA and dyslipidemia is yet to be established, there is a significant and growing body of evidence that a strong association exists. Population observations, basic science and clinical modalities have begun to unravel the complex interplay involved in the pathophysiology and mechanism of OSA-mediated dyslipidemia. Still there is need for large-scale long-term randomized clinical and translational investigations to explicate the complex relationship between OSA and dyslipidemia and define precise targets for intervention.

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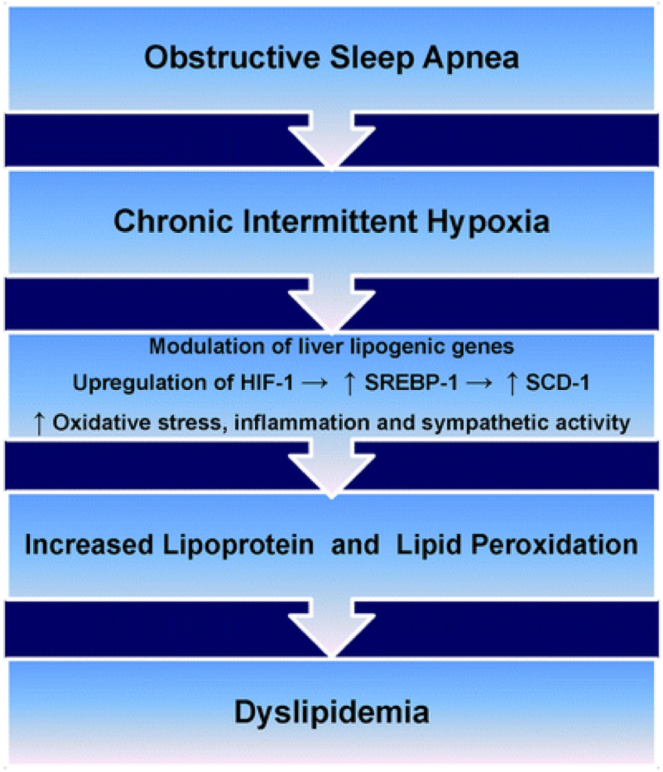

Figures.

Illustration of pathophysiological pathway by which obstructive sleep apnea via chronic intermittent hypoxia induces dyslipidemia. *HIF-1* hypoxia inducible factor 1, *SREBP-1* sterol regulatory element binding protein 1,*SCD-1* stearoyl coenzyme A desaturase 1