Obstructive Sleep Apnea and Atherosclerosis

Zulkifli Amin,1 Hilman Z. Amin,2 Lukman Z. Amin1

1 Department of Internal Medicine, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
2 Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

Corresponding Author:
Zulkifli Amin, MD., PhD. Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia. Jl. Salemba Raya No. 6, Jakarta 10430, Indonesia. email: pulmonologi89@yahoo.co.id.

ABSTRAK
Apnea tidur obstruktif (ATO) merupakan gangguan pernafasan saat tidur yang ditandai dengan adanya episode obstruktif saluran pernafasan total atau sebagian, yang mengakibatkan terjadinya apnea atau hipopnea. ATO dapat berperan dalam proses terjadinya aterosklerosis melalui mekanisme langsung maupun tidak langsung.

Disfungsi endotel, stimulasi saraf simpatik, dan modulasi sitokin proinflamasi yang disebabkan oleh ATO mempunyai peran yang signifikan dalam terjadinya proses aterosklerosis. Faktor-faktor resiko aterosklerosis lain seperti hipertensi dan diabetes mellitus juga berhubungan dengan ATO. Studi eksperimental dan klinis telah menunjukkan data yang mendukung adanya asosiasi antara ATO, aterosklerosis, dan faktor-faktor resiko terkait. Akan tetapi, masih terdapat inkonsistensi pada hasil data yang terkumpul hingga saat ini. Di masa yang akan datang, dibutuhkan penelitian dasar dan klinis lebih lanjut terkait hal ini.

Kata kunci: apnea tidur obstruktif, aterosklerosis.

ABSTRACT
Obstructive sleep apnea (OSA) is a sleep respiratory disorder characterized by recurrent episodes of complete or partial airway obstruction, resulting in apneas or hypopneas. OSA could contribute to atherosclerosis through direct and indirect mechanisms.

Endothelial dysfunction, sympathetic stimulation, and proinflammatory cytokine modulation caused by OSA play significant role to an atherosclerotic event. Other risk factors of atherosclerosis like hypertension and diabetes mellitus also associated with OSA. Animal and clinical studies recently showed promising data to prove association between OSA, atherosclerosis, and its risk factors. However, provided data has not showed consistent result. In the future, demand of further research both basic and clinical sciences need to be fulfilled.

Keywords: obstructive sleep apnea, atherosclerosis.

INTRODUCTION
Obstructive sleep apnea (OSA) is a sleep respiratory disorder characterized by recurrent episodes of complete or partial airway obstruction, resulting in apneas or hypopneas.1,2 This condition that associated with intermittent arterial oxygen desaturation is occurred in approximately 9-24% of the general population.3 The consequences of this condition are increased expression of systemic inflammation markers, activation of sympathetic nervous system, and endothelial dysfunction.4,5 These could be implicated and associated with pathogenesis and pathophysiology of atherosclerosis.6

Atherosclerosis has been recognized as an inflammatory disease of the arterial wall, involving innate and adaptive immunity.7 Many evidences had shown association between OSA
and atherosclerosis.\textsuperscript{8-11} The OSA syndrome is defined as more than five apneas (no breath flow for more than 10s)/hypopnea index (reduced breath flow) per hour (so called apnea/hypopnea index: AHI) in polysomnography followed by symptoms like loud snoring, breathing stoppage, nocturia, headache, excessive daytime sleepiness, deficits in memory, and attention with subsequent risk of accident by day.\textsuperscript{8} OSA could contribute to atherosclerosis through direct and indirect mechanisms. This review will briefly explain the association of OSA and atherosclerosis.

**OSA DIRECT MECHANISMS TOATHEROSCLEROSIS**

OSA could promote atherosclerosis directly through neural, vascular, mechanic, and inflammatory pathways. Through the neural pathway, it is believed that OSA could stimulate sympathetic nerves, resulting catecholamine substances release in the blood plasma and urine.\textsuperscript{4} Grassi et al\textsuperscript{12} study compared four groups of non-OSA lean group, OSA lean group, non-OSA obese group, and OSA obese group with total consisting of 86 middle-aged and normotensive subjects. After matching the age, sex, and blood pressure within all groups, in the OSA-lean group and non-OSA obese group, there were similar increased of muscle sympathetic nerve activity compared to non-OSA lean group. In the OSA obese group, further increased of sympathetic activity was found respectively. These results suggested sympathetic activation in obese patients occurring independently of OSA, but OSA has an additive sympathetic stimulation effect.\textsuperscript{12}

OSA could also contribute to the derangement of endothelial function. Oxidative stress is one of the main causes of endothelial dysfunction.\textsuperscript{13} Study from Jelic et al\textsuperscript{14} to evaluate oxidative damage from 32 OSA and 15 control subjects showed that endothelial expression of endothelial nitric oxide synthetase (eNOS) and phosphorylated eNOS decreased by 59% and 94% in untreated OSA patients. Phosphorylated eNOS is the enzyme active form for producing nitric oxide (NO) in vasculature. Whereas nitrotyrosine known as oxidative stress marker and cyclooxygenase-2 known as inflammation marker found to be 5-fold greater in OSA patients. However, when the subjects adhered to gold standard therapy of OSA that is continuous positive airway pressure (CPAP), the expression of nitrotyrosine and cyclooxygenase-2 was decreased significantly, hence restoring eNOS and phosphorylated NOS.\textsuperscript{14} Many mechanisms have been suggested for endothelial dysfunction due to OSA which are interaction on NO and reactive oxygen species (ROS) forming peroxynitrite, uncoupling of eNOS, decreased endothelial expression of eNOS, and increased levels of endogenous eNOS inhibitors.\textsuperscript{15} Diminished endothelial function is an important consequences of OSA leading to atherosclerosis formation.\textsuperscript{5,16}

Endothelial dysfunction also promotes proinflammatory mediators such as TNF-$\alpha$, IL-1, IL-8, and adhesion molecules, resulting in an environment of systemic inflammation.\textsuperscript{17} These sequence processes hence resulting in accumulating and recruiting of macrophages and fat cells that further activates lipid peroxidation and promotes endothelial cell damage and atherosclerosis.\textsuperscript{18-19}

The other OSA direct mechanism to atherosclerosis is through the mechanical pathway. OSA could result in apneas or hypopneas. The first symptom is an abrupt of inspiratory effort. In accordance to this, a sudden increase in negative intra-thoracic pressure resulting an increased in left ventricular transmural pressure (a component of ventricular afterload), left atrial wall tension, and venous return to right ventricle is occurred, hence reducing stroke volume due to impeded left ventricular filling by leftward shift of the interventricular septum. With standstill airflow, all these sequences events are causing declined of arterial oxygen and increased of carbon dioxide, resulting in mismatch of myocardial oxygen supply and demand.\textsuperscript{20-21} Imposed of oxidative stress regarding the aforementioned events could promote and predispose atherosclerosis.\textsuperscript{21-22} Moreover, even snoring has been postulated as an atherogenic factor recently.\textsuperscript{23} This could be possible because snoring vibration is transmitted through the surrounding tissues of carotid artery wall, triggering an inflammation cascade which leads to atherosclerosis.\textsuperscript{1} However, the aforementioned evidence points to an association
rather than definitive cause-effect relationships between snoring and atherosclerosis.24

**OSA INDIRECT MECHANISMS TO Atherosclerosis**

Atherosclerosis progression also could occur through OSA indirect mechanisms.1 OSA is now recognized to be an independent risk factor for daytime hypertension.25 From OSA patients, close to 35% have hypertension, whereas 30% who have OSA are undiagnosed.26-27 Wisconsin Sleep Cohort study from Peppard et al28 found a causal association between sleep disordered breathing (SDB) and hypertension events by four years later in 709 subjects. Moreover, increasing baseline AHI increased the odds of hypertension. This association was independent of age, sex, body mass index (BMI), waist and neck circumference, baseline hypertension, smoking, and alcohol use.28 Sleep Heart Health Study also supported the aforementioned study. A cross-sectional analysis revealed subjects with an AHI >30 events/hour had 1.37-fold increased odds of hypertension compared to those without OSA (AHI <1.5 per hour) after adjusting for several confounders.29 Other evidence also supported cause-effect relationship between OSA and hypertension. The trial showed ameliorative effect of hypertension of patients undergoing CPAP.30

OSA had also an independent association with insulin resistance and type 2 diabetes in many studies.31-34 Chronic intermittent hypoxia (IH) observed in OSA had been linked to the development of insulin resistance and pancreatic beta cell dysfunction.35 Studies from animal models also supported the aforementioned data.36-37 Fasting hyperglycemia, glucose intolerance, and insulin resistance in both mice with diet-induced obesity and mice with genetic obesity is exacerbated by chronic IH.36-37 In lipid metabolism, OSA animal models has shown fasting dyslipidemia in both lean and obese mice induced by chronic IH due to activation of the transcription factor sterol regulatory element-binding protein 1 and an important downstream enzyme of triglyceride and phospholipid biosynthesis, stearoyl-CoA desaturase-1.38-40 Moreover, in randomized humans study, revealed that CPAP treatment in OSA patients improved triglyceride and cholesterol levels.41 However, there are no consistent data suggesting that OSA is a major risk factor for dyslipidemia.42 Further studies need to be established to elucidate OSA association with metabolic dysregulation especially dyslipidemia.43

**CLINICAL STUDIES OF OSA AND Atherosclerosis**

Many evidence have shown significant association between OSA and atherosclerosis.6,44-45 Meta-analyses by Nadeem et al6 revealed that patients with OSA showed an increased carotid intima media thickness (CIMT) suggestive an atherosclerotic process. Total 95 studies were reviewed, with 16 studies being pooled for analyses containing 25 data sets of 1415 patients.6 Other prospective cohort study called Multi-Ethnic Study Atherosclerosis (MESA) consisted of 2603 subjects being evaluated to know the association between OSA and progression of coronary artery calcium (CAC) also support the result study aforementioned.44 The study was performed by subjects completing a sleep questionnaire and underwent coronary computed tomography (CT), and then after 8 years, the same CT examination was done again.44 This study concluded that OSA was associated with CAC score progression.
after adjustment for demographic, behaviors, ad body mass index (BMI). Although the association was not significant after adjustment for cardiovascular risk factors, it suggested the association between OSA and CAC. Parameters above mentioned like CIMT and CAC are marker for atherosclerosis formation.

**CONCLUSION**

Current evidence reveal OSA as an important cause of atherosclerosis formation. Direct and indirect mechanisms of OSA could contribute as aggravating factors of atherosclerosis. Endothelial dysfunction, sympathetic stimulation, and proinflammatory cytokine modulation caused by OSA play significant role to an atherosclerotic event. Other risk factors of atherosclerosis like hypertension and diabetes mellitus also are associated with OSA. Animal and clinical studies recently showed promising data to prove association between OSA, atherosclerosis, and its risk factors. However, provided data has not showed consistent result. In the future, demand for further research both basic and clinical sciences need to be fulfilled. Basic science research will clearly define OSA and all pathogenesis to atherosclerosis in the molecular level, whereas clinical research will help us to know the impact of OSA to atherosclerosis. Hence, early diagnosis and treatment of OSA will definitely decrease atherosclerosis morbidity and mortality.

**REFERENCES:**