Review

Cardiovascular Disease Risk in Patients with Obstructive Sleep Apnea Syndrome

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Abstract

Obstructive sleep apnea syndrome is a clinical syndrome characterized by recurrent partial or total obstruction of the upper respiratory tract. The main symptoms are snoring, excessive daytime sleepiness and witnessed apnea. It is a disease that affects 3% to 7% of the middle-aged population. Studies and meta-analyzes have shown that cardiovascular diseases are more common in patients with obstructive sleep apnea syndrome. Comorbid conditions such as obesity, metabolic syndrome and smoking are higher in obstructive sleep apnea syndrome patients than in the general population. In addition, hypoxia-reperfusion injury due to intermittent oxygen desaturation occurring in obstructive sleep apnea syndrome patients, endothelial dysfunction, increased sympathetic system activity, platelet activation, monocyte increase, which play the main role in arteriosclerosis, decreased and increased low-density lipoprotein cholesterol may also be the reason for the frequent occurrence of cardiovascular diseases. The development of cardiovascular disease in obstructive sleep apnea syndrome patients is an important cause of morbidity and mortality. Evaluating white blood cell neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, hematocrit, platelet distribution width, red cell distribution width, C-reactive protein, and monocyte/high-density lipoprotein cholesterol ratio in the follow-up of obstructive sleep apnea syndrome patients may be helpful in predicting the development of cardiovascular diseases. Whether obstructive sleep apnea syndrome patients have metabolic syndrome or smoking should be questioned. Obstructive sleep apnea syndrome, obesity, smoking and depression are increasingly prevalent diseases worldwide, leading to significant mortality and morbidity. Therefore, multicentre studies involving different societies are needed.

Keywords

sleep apnea; cardiovascular disease; metabolic syndrome

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Obstructive sleep apnea syndrome (OSAS) is a disease affecting 3% to 7% of the middle aged population. OSAS is a clinical clinical syndrome with partial or total obstruction of the upper respiratory tract. The main symptoms are snoring, excessive daytime sleepiness and witnessed apnea. The gold standard for diagnosis of OSAS is overnight polysomnography (PSG). Diagnostic criteria for OSAS are the variety of symptoms. In case of PSG, the apnea hypopnea index (AHI) is > 5 or the AHI is > 15 for an asymptomatic patient [1, 2]. Recurrent nocturnal apnea episodes in OSAS patients cause sympathetic system activation, increased oxidative stress, endothelial dysfunction, sudden increase in systemic hypertension, hypoxia and hypercapnia [3]. Intermittent hypoxia episodes with intermittent hypoxia episodes, which are dormant, intermittent episodes of nocturnal hypoxemia induce the formation of oxygen radicals, which leads to low-grade inflammation [4]. Inflam-
formation is one of the main factors found in the onset and progression of atherosclerosis [5]. There is a critical aspect of inflammation in the etiopathogenesis of OSAS. Intermittent hypoxia initiates inflammation. Inflammation also activates proclamatory cytokines and adhesion molecules in OSAS. Oxidizing radicals and proteolytic enzymes accumulate leukocytes and platelets on the blood vessel walls, leading to endothelial dysfunction [6]. In structured studies, autonomic and neurohumoral abnormalities of OSAS continue during daytime; this has caused the general circadian blood pressure rhythm to deteriorate and increase the variability of short and long term blood pressure [7], where absolute blood pressure, blood pressure fluctuations are in progress and development of organ damage in preparing arterial remodelling, microvascular damage, hemodynamic imbalance, and vascular reactivity disorder. For these reasons, cardiovascular diseases (CVD) are more common in OSAS patients [8, 9].

There is endothelial dysfunction in the pathophysiology of hypertension, diabetes, coronary artery disease (CAD) and congestive heart failure. It is also seen in terms of endothelial dysfunction in OSAS patients. OSAS was found to be an independent risk factor for CVD. There is also much evidence that the incidence of cerebrovascular diseases increases in OSAS patients [10, 11].

Chronic systemic inflammation of OSAS may play an important role in the progression of CVD. The final and neutrophil/lymphocyte ratio (NLR) of white blood cells (WBC) is a good indicator of inflammation [12]. Neutrophils mediate the innate immune response that secretes mediators, and lymphocytes mediate the adaptive immune response in the inflammation mechanism [13]. In addition, OSAS has been reported to activate the platelet, which is also related to inflammation, and to collect it at the site of inflammation. Mean platelet volume (MPV) and platelet distribution width (PDW) are indicators of platelet activity and are present there with low oxygen saturation [14]. It reveals platelet/lymphocyte ratio (PLR) as a new informative marker for extremely accurate prediction of CVD [15]. Hematocrit (HTC) elevated in OSAS patients [16] as a result of secondary erythrocytosis in hypoxemic conditions. There were hypoxia in structured studies when activation of the hypothalamus-pituitary-adrenal axis erythropoiesis increased the production of systemic cortisol levels and led to an increase in HTC. In addition, red cell distribution width (RDW) OSAS, which evaluates erythrocyte variability, has an increased rate of inflammation. As a result of structured studies of WBC, lymphocyte (LYM), NLR, MPV, PDW, PLR, RDW and HTC etc., there is a negative correlation between lymphocyte ratios and severity of OSAS and hypoxemic status of low lymphocyte count. Svatikova et al. showed that NLR and atrial natriuretic peptide (ANP) are increased by hypoxia and sympathetic activation. ANP may be an indicator that is expected to reduce CVD risk with continuous positive airway pressure (CPAP) treatment [17, 18, 19].

C-reactive protein (CRP), final PLR and NLR are used as inflammatory markers and independent risk factors for atherosclerosis [20]. History of monocyte activation plays an important role in the development of CVD such as heart failure and atherosclerosis by causing chronic inflammation. There is an important formation of inflammation in CAD formation; increased inflammation in CAD such as monocytes, lymphocytes, eosinophils and neutrophils. Prentice et al. showed that patients with CAD had higher monocyte, neutrophil and eosinophil counts than those without CAD, and associated these findings with a high risk of CAD [21, 22]. The increase in neutrophils due to inflammation causes secretion of various cytokine types, proteolytic enzymes.

Monocytes account for about one-fifth of peripheral blood cells. Macrophages and monocytes are the most important cell types that cause the secretion of proinflammatory and prooxidant cytokines in the inflammation region. Monocytes are cells that have a significant effect on the development of atherosclerotic lesions [23]. Monocytes are responsible for vascular endothelial damage in the pathogenesis of atherosclerosis. Monocytes phagocytose lipids to become macrophages and secrete metalloproteinases such as elastase and collagenase, which cause atherosclerosis. The role of monocytes in atherogenesis is not limited to macrophage func-
tion within the arterial wall, and also has effects on immune stimulating agents, growth factors, cytokines, oxidized lipids, platelet-derived activation products. For these reasons, circulating monocytes and macrophages contribute to the pathogenesis and complications of CVD [24].

In the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study), it was shown that monoclonal antibodies specifically targeting interleukin-β would reduce cardiovascular events without affecting plasma low-density lipoprotein (LDL) or lipoproteins [25].

Lymphocyte count decreases in response to inflammation conditions and is associated with poor prognosis in coronary artery disease. Lymphocyte/monocyte ratio (LMR) has been proposed as a marker for different inflammation and also has prognostic and predictive value. In a study of patients with acute pulmonary embolism, low LMR was found to be an independent variable for in-hospital and short-term mortality. In another study, a significant negative correlation was found between coronary slow flow and LMR [26, 27].

In a recent study, Tamaki et al. showed that the number of monocytes in OSAS patients was higher than in the control group. Monocyte count was positively correlated with the severity of OSAS and it was emphasized that it could be used as a marker for predicting OSAS severity [28].

The association of atherosclerosis and an abnormal lipid profile is common in CAD. Triglyceride, total cholesterol and LDL levels increase with the severity of OSAS, while high-density lipoprotein (HDL) levels decrease. High LDL and low HDL concentrations are strong risk factors for CAD [29, 30].

The relationship between OSAS and dyslipidemia is due to the formation of stearoyl-coenzyme A desaturase-1 and reactive oxygen species, peroxidation of lipids and activation of the sympathetic system as a result of chronic intermittent hypoxia [31].

Low HDL cholesterol and high monocyte count seem to be indirect indicators of inflammation. HDL cholesterol consists of heterogeneous particles that can be classified by size, density, charge, shape, lipid and protein composition. In addition to cholesterol transport from HDL blood vessels to tissues, their functions including antioxidant, anti-inflammatory, antiapoptotic, antithrombotic and antiatherosclerotic effects result from these heterogeneous particles [32, 33]. Small HDL cholesterol was found to be associated with the presence and severity of atherosclerotic disease; on the contrary, large HDL cholesterol showed a negative correlation with the presence of CAD and the severity and progression of the disease [34]. HDL cholesterol has been shown to protect endothelial cells against the negative effects of LDL cholesterol and to prevent oxidation of LDL molecules. For these reasons, HDL cholesterol has been thought to have both anti-inflammatory and antioxidant effects [35, 36]. HDL cholesterol molecules prevent the migration of macrophages and allow oxidized cholesterol to flow through these cells. Recent studies also revealed that HDL has effects on monocyte activation and control of adhesion [37, 38]. In addition to anti-inflammatory and antioxidant effects of HDL molecules, vasorelaxant and endothelial nitric oxide synthase has the effect of increasing expression [39]. Monocytes show proinflammatory and prooxidant effects; however, HDL cholesterol may have a preventive effect on this process. In a study, it was stated that CPAP treatment in OSAS patients may have positive effects on dyslipidemia, atherosclerosis and CVD [40].

Monocyte/HDL cholesterol ratio (MHR) can be practical, cost-effective and highly predictive of CVD. The use of MHR as a marker has an economic advantage. It is less expensive as compared to other inflammatory markers such as interleukin-1 (IL-1), interleukin-6 (IL-6) tumor necrosis factor-α, monocyte chemoattractant protein-1, and serum amyloid A. MHR has a positive correlation with CRP in determining CVD risk. In addition to being a marker of systemic inflammation, MHR may be useful in predicting clinical outcomes in CVD associated with atherosclerotic development, progression, and inflammatory conditions [41, 42]. Studies have suggested that MHR is associated with systemic inflammation and endothelial dysfunction and may be accepted as a prognostic marker in
CVD [43, 44].

Laboratory studies revealed that HDL cholesterol levels were higher in women and MHR levels were lower in men. These findings may help explain why men are more likely to develop vascular endothelial dysfunction and atherosclerosis than women [45].

MHR is strongly associated with the severity of CVD and OSAS and can be used as a biomarker to predict CVD in patients with OSAS [36]. In a study, it was found that MHR values increased with increasing severity of OSAS [46]. In addition, it has been shown that MHRs are significantly higher in OSAS patients with CVD as compared to non-CVD patients and that MHR can be used as an independent predictor of CVD in OSAS patients. In addition, previous studies showed a significantly higher number of monocytes in patients with OSAS as compared to the control group. In the severe OSAS group, the number of monocytes was found to be higher than those with moderate and mild OSAS. These findings may explain the higher incidence of cardiovascular events in severe OSAS. There was a positive correlation between MHR and the severity of hypoxemia defined by oxygen desaturation index (ODI) [47]. MHR, AHI, rapid eye movement (REM) -AHI, non-REM-AHI and oxygen saturation have been shown to increase significantly as time increases below 90% and the minimum oxygen concentration decreases [2] independently associated with corner atherosclerosis assessed by SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score in patients with independent coronary artery disease. In addition, a positive correlation was found between CRP and MHR [48]. Recently, it has been shown that MHR is an independent variable in terms of 5-year mortality in cardiovascular events, hospitalization and ST segment elevation myocardial infarction (STEMI) [49].

All these findings show the importance of MHR in inflammation, which plays an important role in the development of cardiovascular events.

It has been shown that MHR is higher in patients with primary hypertension (PHT) than controls. In addition, in PHT group, patients with asymptomatic organ damage (AOH) had higher MHR than patients without AOH. When the newly diagnosed untreated hypertensive patients and healthy group were compared, MHR values were found to be higher than in the control group [50].

Higher MHR values have been found in patients with acute ischemic stroke (AIS) as compared to controls. High MHR levels in patients with AIS were found to be a significant independent variable of 30-day mortality [51].

In a study, it was shown that 24.3% of men and 50% of women among OSAS patients had metabolic syndrome (MS) [52]. The components of MS such as impaired glucose tolerance, central obesity, hypertension and dyslipidemia were clearly associated with CVD [53, 54]. In recent years, adipose tissue has been shown to be an endocrinologically and metabolically active organ. Adipokines are a group of specific signal molecules involved in many processes such as saturation, energy balance, inflammation, insulin resistance/sensitivity, angiogenesis, lipid metabolism and atherosclerosis [55, 56]. Subclinical chronic inflammation is a part of the insulin resistance syndrome, and chronic inflammation has been shown to have an independent association with insulin resistance. Atherosclerosis, which is one of the mortal complications of MS, is considered an inflammatory disease [57]. The activation of MS monocytes is associated with inflammation and atherosclerosis. In a study, the mean LMR was significantly lower and the CRP value was significantly higher in patients with MS as compared to patients without MS. In addition, the mean MHR value in patients with MS was reported to be significantly higher [58].

The prevalence of smoking in OSAS patients is higher than in non-OSAS patients. In addition, male OSAS patients seem to smoke more than women [59]. Smoking is known to be an important risk factor for metabolic disorders such as OSAS. Various compounds in cigarette smoke, such as volatile organic compounds, heavy metals and nicotine, increase oxidative stress and systemic inflammation, which play a role in the emergence of metabolic disorders [60]. Smoking is associated with high MHR levels and may be a useful indica-
tor of a systemic inflammatory response in smokers. Smokers with a high MHR level can be easily identified during routine complete blood count (CBC) analysis and possibly benefit from preventive treatment. Increased serum WBC, monocytes and MHR levels may be associated with inflammation in the pathophysiology of smoking. In addition, high hemoglobin and HTC values observed in smokers and dyslipidemia may be related to smoking. The relationship between smoking, systemic inflammatory response, vascular endothelial damage and atherosclerosis has been well defined both in the past and more recently [61, 62]. MHR is a simple, easy and cost-effective tool that should be used to predict the systemic inflammatory response and possible endothelial dysfunction in smokers [45].

### Conclusions

OSAS is a clinical syndrome characterized by recurrent partial or total obstruction of the upper respiratory tract. Studies and meta-analyses have shown that CVD are more common in patients with OSAS. The development of CVD in OSAS patients is an important cause of morbidity and mortality. In the follow-up of OSAS patients, WBC, NLR, PLR, LMR, HTC, PDW, RDW CRP, and MHR tests may be helpful in predicting CVD of patients. In addition, whether OSAS patients have metabolic syndrome or smoking should be questioned. OSAS, obesity, smoking and depression are increasingly prevalent diseases worldwide, leading to significant mortality and morbidity. Therefore, multicentre studies involving different societies are needed.

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