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Protection of Endothelium critical in the management of Obstructive Sleep Apnea Syndrome

Research Article

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Obstructive Sleep Apnea Hypoapnea Syndrome (OSAHS) is a systemic disease often involving the eyes. Given that coagulation and fibrinolysis are central to its pathogenesis, the ocular manifestations should be related, resulting from the ongoing pathogenesis involving hemostatic alterations, inflammation, oxidative stress and endothelial dysfunction. The pathogenesis of ocular manifestations should be evaluated from a focused view through the 'Hemostasis" lens. OSAHS affects approximately 1 in 15 Americans or 6.62% of the United States Population and interestingly, a significant majority (1 in 50 individuals) do not even realize that they suffer from it. These growing numbers either manifest as significant morbidity and mortalityin the hospitals ordrowsy driving on roads accounting to100,000 car accidents, 40,000 injuries and 1,550 deaths annually, as per National Highway Traffic Safety Administration. Untreated patients may succumb to potential consequences including excessive daytime sleepiness, loss of productivity, metabolic dysfunction and an increased risk of cardiovascular, ocular and cerebrovascular diseases. Even children are affected, as nearly 263,000 children undergo tonsillectomies, mostly due to sleep apnea.A recent study reported that intermittent hypoxia and sleep fragmentation due to obstructive sleep apnea may contribute to oxidative tissue damage and apoptotic neuronal death, intracellular edema in the brainresulting in cortical thinness and enlarged hippocampal volume in adolescent children with obstructive sleep apnea [1]. According to the National Commission on Sleep Disorders Research, approximately 38,000 deaths annually are related to cardiovascular problems connected to sleep apnea. Given that OSAHS is a systemic disease, it may result in cardiovascular and neurovascular [2], neuropsychiatric, metabolic and endocrine disorders [3]. Frost and Sullivan calculated that the annual economic burden of undiagnosed sleep apnea among US adults is approximately $149.6 Billion. The estimated costs include $86.9 Billion in lost productivity, $26.2 Billion in motor vehicular accidents and $6.5 Billion in workplace accidents (www. frost.com). Despite significant research,the pathogenesis of OSAHS is not completely understood. Albeit endothelium is by far the largest endocrine, paracrine and autocrine gland ever known to man, oxidative stress, inflammation and endothelial dysfunction play a central role in the pathophysiology of OSAHS and deserve absolute attention and consideration in its effective management.

Ocular manifestations of OSAS may result from mechanical, and vascular events of the syndrome [4]. A recent study evaluated the effect of OSAS on the ocular surface and conjunctival cytology and the relationship between the findings and disease severity and concluded that in addition to decreased tear production and Tear Break Up Time (TBUT), cytological changes including squamous metaplasia were detected between patients with OSAS and the control group [5]. Mechanical and vascular events due to sleep apnea may lead to other ocular complications such as Floppy Eyelid Syndrome, papilledema leading to permanent vision loss, Non-arteritic anterior ischemic optic neuropathy (NAION), central serous retinopathy, retinal vein occlusion and glaucoma [4, 6], palpebral hypermobility syndrome [7], keratoconus [8] and other ocular surface abnormalities [9].

OSAHS results in hypercoagulable state which may result in increased risk of vascular events [10, 11]. Several studies report increased fibrinogen, other prothrombotic factorsand endothelial dysfunction [12]. Tissue plasminogen activator (tPA) is released by thrombin, proinflammatory cytokines, and Vascular Endothelial Growth Factor (VEGF) from the storage granules in the endothelium [13]. Markers of systemic inflammation [14], thrombin [15, 16] and Vascular Endothelial Growth Factor (VEGF) levels are reported to be increased in OSA, contributing to high tPA levels. Although, the levels of tPA were reported to be variable ranging from, no difference in tPA levels [17] and activity [18, 19], higher tPA levels [20], and lower tPA activity [18], but that they were consistently reported in Obstructive Sleep Apnea. It would be interesting to study the net increase in the circulatory levels of tPA over time in patients with OSA, and its seepage and entry into the aqueous humor of the eye and its potential fibrinolytic effects on the corneal endothelial glycocalyx. The glycocalyx is connected to the endothelium via proteoglycans and glycoproteins [21]. The glycocalyx composed of a mixture of proteoglycans, glycosaminoglycans and glycoproteins, is reported to be a central regulator of vascular function and is known to participate

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in many vascular processes, including but not limited to vascular permeability, inflammation, thrombosis, mechanotransduction and cytokine signaling [22]. The glycocalyx is seen in all blood vessels , ranging from small capillaries [23] to large arteries and veins [24]. The endothelial glycocalyx is reported to be a possible therapeutic target in cardiovascular diseases [25]. The human corneal endothelial cells are arrested in G1 phase in vivo and do not normally replicate to replace dead or injured cells. This lack of cell division results in a physiological reduction of cell density of about 0.3-0.5% per year [26]. It would be interesting to see alterations of cell density due to effects of tPA, oxidative stress and endothelial dysfunction in patients with sleep apnea.

Recent articles have addressed the effects of OSAHS on Corneal Morphological Characteristics and Thickness Alterations. Bojarun et al reportedthat the severity of hypoxemia and the increase in Apnea Hypopnea Index (AHI) in patients with OSAHS reduces Central Corneal Thickness (CCT) and Endothelial Cell Density (ECD) when compared to the controls [27]. Koseuglu et al [28] and Ekinci et al [29] also concluded that CCT is significantly lower in patients with OSAHS when compared with control groups. However, Chalkiadaki et al concluded from their study that low percentage of REM sleep, usually found in patients with OSAHS may cause an increase in corneal thickness [30]. Hypoxia is reported to induce stromal acidosis and may be a cause of corneal thinning [31]. These contrasting resultswarrant future controlled studies to confirm the relationship between REM sleep and CCT and determine its clinical significance.

Given that the pathophysiology of OSAHS is incompletely understood, the role of coagulation and fibrinolysis in OSAHS should be carefully evaluated. The central mechanism involving procoagulation, inflammation, cytokines and endothelial dysfunction should be explored further. Endothelin-1 is also overexpressed by the endothelial cells in OSA which may cause increased expression of von Willebrand Factor (vWF) and tissue factor (TF) [32, 33]. Beyond hemostasis, the role of vWF in innate immunity has recently been reported, demonstrating that vWF binding to macrophages (either THP-1-derived or blood-borne monocyte-derived) inducing p38MAP signaling, forcing a change in gene expression, with 1334 genes displaying modified expression and upregulating proinflammatory cytokines and chemokines and increasing production of tumor necrosis factor, interleukin (IL)-6, IL-1β, chemokine C-C ligand (CCL)-2, CCL-3, and CCL-4 [34]. Lower levels of vWF were reported to be associated with lower risk of cardiovascular disease [35]. The effects of increased levels of tPA in patients with OSA on the corneal endothelial glycocalyx disruption may have a probable answer as a causefor alterations of Central Corneal Thickness(CCT) in these patients and warrant future studies. Further studies focused on corneal endothelial glycocalyx disruption, protection and regeneration, designed to address coagulation and fibrinolysis in patients with OSAHS may hold the key to better understanding of the pathogenesis and its effective management. Better understanding of the potential role of coagulation and fibrinolysis in OSAHS, effective pharmacological intervention to manage endothelial dysfunction in addition to CPAP may be necessary to realistically control, the heavy disease burden of cardiovascular, cerebrovascular, metabolic and ocular diseases.

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