

Obstructive sleep apnea and vitamin D level: Has the dust settled?

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Abstract

Obstructive sleep apnea and vitamin D deficiency are associated with multiple complications with increased morbidity and mortality. However, the relationship between these two entities remains unclear, with clinical studies demonstrating contradictory results. This narrative review aims to present the current evidence and understanding of this relationship and discuss the possible mechanisms linking these two disease entities. Finally, we summarize and propose areas of opportunity for future research.

KEYWORDS

apnea hypopnea index, cholecalciferol, continuous positive airway pressure, hypoxia, obesity, sleep disorders

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic disease, characterized by recurrent partial or complete upper airway collapse during sleep leading to intermittent hypoxia and sleep disruption.^{1,2} Abrupt oxygen desaturation during sleep leads to brief arousal from sleep in order to terminate the obstruction and restore normal breathing.³ This causes substantial sleep fragmentation and impaired sleep quality. The prevalence of OSA has been increasing over the years, especially in developed countries.^{4,5} OSA is commonly found in patients with obesity. This is believed to be due to fat

deposits in the upper airway with reduction of muscle activity in that region leading to hypopneic and apneic episodes.⁶ OSA has been demonstrated as an independent risk factor for cardiovascular diseases and is associated with increased cardiovascular morbidity and mortality.^{7,8} This might be contributed by low-grade inflammation and production of pro-inflammatory cytokines causing endothelial dysfunction.^{9–11} A recent meta-analysis demonstrated that patients with OSA have higher level of renin-angiotensin-aldosterone system hormones, blood pressure, and heart rate compared with those without OSA, which may add on to the increased cardiovascular risks among this cohort.¹²

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Although traditionally, vitamin D is thought to play its main role in calcium homeostasis and regulation, there is now increasing evidence that low vitamin D level is associated with a multitude of cardio-metabolic complications, which has sparked new interests in these extra-skeletal associations.¹³ Hypovitaminosis D is related to increased risks of cardiovascular diseases, metabolic dysfunctions, worse cardiovascular outcomes, and elevated all-cause mortality.^{14–17}

Vitamin D levels are associated with respiratory function.¹⁸ OSA and vitamin D deficiency seem to share common risk factors, such as obesity and increasing age. These two conditions have almost similar pathogenesis, such as involvement of inflammatory reactions and oxidative stress, although the exact mechanism is poorly understood. To date, studies examining the relationship between these two entities have shown contradictory results. The association is likely to be bi-directional, multi-factorial, and complex. To better comprehend the relationship between these two entities, this review aims to summarize the current evidence and to present the possible mechanisms and understanding of this association.

2 | CLINICAL STUDIES OF OSA AND VITAMIN D

2.1 | Vitamin D level in OSA

Among 139 patients with OSA, vitamin D level was significantly lower compared with 30 non-apneic cohort (17.78 ± 7.8 vs. 23.9 ± 12.4 ng/mL, $p = 0.019$). However, those with OSA were older and had significantly higher body mass index (BMI), neck, waist, and hip circumferences, which could have contributed to the lower level of vitamin D.¹⁹ Nevertheless, even among BMI-matched obese male patients, vitamin D level was still significantly lower among those with OSA compared with those without,^{20,21} suggesting a relationship between OSA and vitamin D deficiency irrespective of weight. In addition, vitamin D level was noted to have inverse correlation with sleep stage transitions, which are indicators of sleep continuity.¹⁹ Furthermore, the level was demonstrated to be inversely correlated with disease severity even after multi-variate analysis,^{20,22–27} suggesting the role of sleep fragmentation in vitamin D deficiency. This may be the reason why lower level of vitamin D is more pronounced in severe OSA compared with those without OSA.^{23,24}

Similarly, the number of patients with vitamin D deficiency was reported to be higher in the OSA group compared with those without OSA.^{24,25} Although few studies found no significant difference in vitamin D level

between these two cohorts, these studies still demonstrated that the number of patients with vitamin D deficiency, especially at a level of <10 mcg/dL, was higher in the OSA group, and more pronounced with increasing disease severity, compared with those without OSA.^{22,28,29}

2.2 | Vitamin D level in elderly

The difference in vitamin D level was not apparent among the elderly cohort. Among 72 hospitalized geriatric patients with mild dementia and confirmed OSA, vitamin D level was not significantly different compared with those without OSA ($p = 0.082$).³⁰ This could be due to less severe OSA encountered in this study. Nevertheless, the level of vitamin D was demonstrated to reduce with increasing OSA severity (mild OSA 13.5 ng/mL [8.7, 31.2]; moderate OSA 7.9 ng/mL [5.3, 22.6]).

Similarly, in a community-dwelling elderly cohort with a wide range of BMI, there was no significant difference in the prevalence of vitamin D deficiency. Besides, no association was demonstrated between vitamin D level and apnea hypopnea index (AHI).³¹ Nevertheless, those with lowest quartile of vitamin D concentrations had higher odds of severe sleep apnea. Sensitivity analysis suggested that this association was largely explained by greater BMI and larger neck circumference among men with hypovitaminosis D.³²

2.3 | Vitamin D level in metabolic syndrome

Among patients with type 2 diabetes, there was no demonstrated significant difference in vitamin D level between those with OSA and those without ($p = 0.086$).³³ However, OSA patients with metabolic syndrome had higher prevalence of vitamin D deficiency, which is most pronounced among those with severe metabolic syndrome (metabolic index >3).³⁴ They also had significantly lower vitamin D level compared with those without metabolic syndrome (18 ± 8.6 vs. 23.9 ± 14.1 ng/mL, $p = 0.012$).³⁵ Low vitamin D level was noted to be associated with increased abdominal obesity, elevated triglyceride level, and reduced HDL-cholesterol level, as well as diabetes mellitus in this cohort of patients.³⁶

2.4 | Clinical characteristics

OSA patients with vitamin D deficiency were more likely to be females, older, African Americans, with higher