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Key points

- Vitamin D insufficiency prevalence is increasing worldwide and presents with similar comorbidities and risk factors to OSAS.
- The nonskeletal actions of vitamin D may contribute to the development of OSAS through immune system modulation, myopathy and inflammation.
- Studies evaluating serum vitamin D concentrations in OSAS patients and the effect of CPAP treatment report contradictory results, often influenced by confounding factors, such as obesity.
- There appears to be potential for use of vitamin D supplementation in OSAS patients as a means of reducing the incidence of cardiovascular disease, a comorbidity common in both conditions.

Educational aims

- To assess the potential association between OSAS and serum levels of vitamin D.
- To discuss the pathogenetic mechanisms linking OSAS and vitamin D insufficiency.
- To illustrate the effect of CPAP treatment on vitamin D concentration in OSAS patients.

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The role of vitamin D in obstructive sleep apnoea syndrome

Obstructive sleep apnoea syndrome (OSAS) is a common disorder of multifactorial pathogenesis and is associated with obesity, diabetes and cardiovascular disease. Vitamin D is a fat-soluble vitamin with an important function in calcium absorption and homeostasis, which is also implicated in several nonskeletal conditions. The prevalence of vitamin D deficiency is increasing worldwide and is associated with similar metabolic disturbances to OSAS. Moreover, recent data suggest that in OSAS patients serum levels of vitamin D are lower compared with non-apnoeic subjects. However, the mechanisms linking vitamin D deficiency and OSAS are not completely understood and several hypotheses have been advanced. To date, a limited number of studies have assessed the association between lower serum concentrations of vitamin D and OSAS, and have reported inconsistent results. Similarly, contradictory results have been produced by studies which evaluated the effect of continuous positive airway pressure treatment on serum vitamin D levels. The aim of this review is to summarise current knowledge on the association between OSAS and vitamin D levels.

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Introduction

Obstructive sleep apnoea syndrome (OSAS) is defined by recurrent episodes of upper airway occlusion (partial or complete) leading to recurrent arterial hypoxaemia and sleep fragmentation [1]. Nowadays, it is common, with a prevalence of 10–17% among men and 3–9% among women in the developed world [2]. The pathogenesis of OSAS remains unclear and is probably multifactorial, including various mechanisms such as inflammation and oxidative stress [3]. Obesity is the most important risk factor and is reported in up to 70% of cases. Additional risk factors include older age, male sex, ethnicity and family history [4]. Of interest, OSAS seems to exhibit a seasonal predominance pattern with higher incidence and severity occurring in winter [5]. Data from the literature emphasise the association between OSAS and a number of disorders, such as cardiovascular disease, impaired glucose metabolism and other endocrinopathies, such as hypercortisolism and osteoporosis [4, 6].

Vitamin D is a fat-soluble vitamin existing in two forms: ergocalciferol, or vitamin D2, obtained through dietary sources; and cholecalciferol, or vitamin D3, produced in the skin after exposure to sunlight [7]. Serum 25-hydroxyvitamin D (abbreviated: 25(OH)D) is considered the best indicator of vitamin D status [8]. The most important function of vitamin D is regulation of bone

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Due to multiple confounding factors, vitamin D deficiency is common among sleep apnoea patients; thus, screening should be performed when clinically indicated http://ow.ly/L3ow30krmol

homeostasis [7]. However, vitamin D is implicated in several nonskeletal conditions, including cardiovascular disease, cancer, autoimmune disorders and diabetes mellitus [9]. Vitamin D receptors have been identified in several brain areas, including the hypothalamus which, among others, regulates alterations in the sleep–wake cycle [10].

OSAS and vitamin D deficiency share the same risk factors and comorbidities, particularly older age, obesity, renal failure and diabetes, while both conditions present common pathogenic features (*e.g.* inflammation) [11, 12]. However, contradictory results have been reported regarding the link between vitamin D deficiency and OSAS [13]. Thus, the aim of this review is to summarise current knowledge on the association between OSAS and vitamin D levels.

OSAS and vitamin D insufficiency

The pathogenesis of vitamin D insufficiency in OSAS is multifactorial and incompletely understood. Low serum levels of vitamin D may contribute to the development of OSAS through the following mechanism. Vitamin D receptors, located in skeletal muscles, modulate several transcription factors in muscle cells, and are implicated in muscle cell proliferation and differentiation into mature type II muscle fibres [14]. In addition, vitamin D is responsible for active calcium transportation into sarcoplasmic reticulum, thus regulating sarcomeric muscular contraction [15]. Vitamin D deficiency has been associated with proximal myopathy [16]; while in patients receiving statins, low vitamin D levels have been associated with increased incidence of statin-induced myopathy [17]. It is possible that increased parathyroid hormone levels, hypophosphataemia and decreased calcitriol levels, accompanying vitamin D deficiency, may also contribute to muscle weakness [18]. Thus, the reduced pharyngeal dilator muscle strength in vitamin D deficiency has been proposed to reduce pharyngeal patency and predispose to apnoeic events during sleep [19].

However, there are no studies evaluating the effects of vitamin D replacement therapy on pharyngeal dilator muscle strength. The results from a systematic review of 16 randomised controlled trials on the effects of treatment with vitamin D on muscle function supported a beneficial effect of vitamin D supplementation on muscle strength and function in the elderly [20]. However, a considerable number of studies included in the review failed to confirm such an effect, and there was a lack of data on possible effects in younger adults [20].

Moreover, vitamin D harbours immunomodulatory properties, which are probably similar to locally active cytokines [21]. Vitamin D metabolising enzymes and vitamin D receptors are present in various immune cells, including antigen-presenting-cells, T-cells, B-cells and monocytes [22]. Vitamin D deficiency is associated with increased autoimmunity and susceptibility to infection [23]. Calcitriol enhances the antimicrobial effects of monocytes and macrophages, which exert a pivotal role in infections such as tuberculosis [23]. Low serum 25(OH)D levels are associated with increased incidence of upper respiratory tract infections, chronic obstructive pulmonary disease (COPD), allergic asthma and allergic rhinitis [24, 25]. Recurrent infections and immune system dysregulation may promote the development of tonsillar hypertrophy and chronic rhinitis, both of which increase the risk of OSAS [26]. Furthermore, vitamin D inhibits the secretion of pro-inflammatory T-helper cell (Th)1 cytokines (interleukin (IL)-2, interferon-γ and tumour necrosis factor (TNF)-α) and promotes the production of anti-inflammatory Th2 cytokines (IL-3, IL-4, IL-5 and IL-10) [22]. The inflammatory state plays an important role in the development of cardiovascular disease in patients with OSAS [3].

Conversely, OSAS may represent a risk factor for vitamin D insufficiency. Due to excessive daytime sleepiness or obesity, OSAS patients are more likely to have limited access to outdoor activities and, hence, limited sunlight exposure, resulting in lower vitamin D synthesis [27].

Apnoea–hypopnoea index and vitamin D

The relationship between OSAS severity expressed by the apnoea–hypopnoea index (AHI) and serum concentrations of vitamin D has been the subject of numerous studies, often with contradictory results. The main results of the studies examining the relationship between serum levels of vitamin D and OSAS are presented in table 1. Several works failed to demonstrate a relationship between serum vitamin D levels and OSAS severity [28, 29]. In a cross-sectional study of 181 patients, who underwent polysomnography and were stratified according to OSAS severity [30], mean vitamin D levels were 15.5±11.6 ng·mL^{-1} (95% CI: 13–17). There was no significant difference in vitamin D levels between controls and OSAS patients (p=0.89) or among the OSAS severity groups (p=0.68) [30]. No correlation was found between vitamin D levels and AHI (p=0.35, r=–0.06), even after adjustment for sex (males: p=0.12, r=–0.18, females: p=0.59, r=–0.05) [30]. Mete *et al*. [31] compared 25(OH)D serum levels among 50 patients with mild, 50 patients with moderate, 50 patients with severe OSAS and 32 non-apnoeic controls. They found no significant difference in 25(OH)D levels between OSAS patients and controls (17.91±9.25 *versus* 19.17±7.21 µg·dL^{-1}, respectively, p=0.468) [31]. Serum 25(OH)D levels were lower in the severe OSAS group compared with the control (p=0.01),

Table 1 *Summary of studies exploring the relationship between serum levels of vitamin D and OSAS*

First author [ref.]	Comparison groups	Comments
Erden [29]	Non-OSAS controls *versus* moderate OSAS *versus* severe OSAS	Serum 25(OH)D levels were lower in both OSAS groups compared with control subjects and were negatively correlated with BMI and serum bisphenol A.
Salepci [30]	Non-OSAS controls *versus* mild OSAS *versus* moderate OSAS *versus* severe OSAS	Serum vitamin D levels were similar between patients with and without OSAS and between the various OSAS severity groups. There was no association between vitamin D levels and AHI, ODI or minimum O_2 saturation.
Mete [31]	Non-OSAS controls *versus* mild OSAS *versus* moderate OSAS *versus* severe OSAS	Serum 25(OH)D levels were similar between OSAS and controls. The severe OSAS group had lower levels of 25(OH)D compared with other groups and the number of patients with serum 25(OH)D deficiency were higher in OSAS groups than in controls.
Barceló [32]	Mild OSAS *versus* moderate OSAS *versus* severe OSAS	Serum 25(OH)D levels were lower in severe compared with mild and moderate OSAS. Increased 25(OH)D levels decreased risk for diabetes and metabolic syndrome.
Bozkurt [33]	Non-OSAS controls *versus* mild OSAS *versus* moderate OSAS *versus* severe OSAS	Serum 25(OH)D levels were decreased in OSAS patients compared with control subjects and decrement was parallel to OSAS severity. Females with severe OSAS had significantly lower 25(OH)D levels compared with non-OSAS controls.
Piovezan [34]	Non-OSAS controls *versus* mild OSAS *versus* moderate OSAS *versus* severe OSAS	Moderate/severe OSAS and objective short sleep duration were associated with increased risk of 25(OH)D deficiency.
Archontogeorgis [35]	Non-OSAS controls *versus* OSAS patients	Serum 25(OH)D levels were lower in OSAS patients and were negatively correlated with sleep stages transitions, AHI, ODI and percentage of time with an oxyhaemoglobin saturation <90%, and positively correlated with average oxyhaemoglobin saturation.
Goswami [47]	Non-OSAS controls *versus* mild OSAS *versus* moderate OSAS *versus* severe OSAS	Subjects within the lowest 25(OH)D quartile were at increased risk of severe sleep apnoea compared with the highest 25(OH)D quartile. BMI and neck circumference were independent predictors of low serum 25(OH)D levels in OSAS.
Kerley [62]	Non-OSAS controls *versus* mild OSAS *versus* moderate OSAS *versus* severe OSAS	Serum 25(OH)D levels were higher in non-OSAS subjects and decreased with OSAS severity and were inversely correlated with BMI, % body fat, ODI, AHI, time spent below 90% O_2 saturation and nocturnal heart rate.
Toujani [63]	Non-OSAS controls *versus* severe OSAS	Serum vitamin D levels were negatively correlated with nocturia severity and IL-17, and positively correlated with mean O_2 saturation and minimum O_2 saturation.

BMI: body mass index; ODI: oxygen desaturation index.

and the moderate (p=0.019), and the mild OSAS groups (p=0.001) [31]. There was no difference between the control group and the mild and moderate OSAS group (p=0.526 and p=0.607, respectively), and between the mild and moderate OSAS groups (p=0.194) [31].

A large body of evidence supports the association between OSAS severity and hypovitaminosis D [32]. Bozkurt *et al*. [33] compared serum vitamin D levels between healthy controls and OSAS patients of increasing severity. Serum 25(OH)D concentrations of OSAS patients were lower than in control subjects (17.4±6.9 *versus* 19.9±7.8 ng·mL^{-1}) and their reduction became more marked with increasing OSAS severity (18.2±6.4 for 5<AHI<15 events·h^{-1}, 17.5±7.4 for 15≤AHI<30 events·h^{-1}, and 16.3±6.9 ng·mL^{-1} for AHI≥30 events·h^{-1}, respectively; r=–0.13, p=0.097) [33]. In addition, patients with severe OSAS exhibited significantly lower 25(OH)D levels compared with controls (16.31±6.98 *versus* 19.93±7.81 ng·mL^{-1}, p<0.05) [33]. In a cross-sectional study including 657 participants, moderate and severe OSAS were associated with the risk of 25(OH)D deficiency (for moderate OSAS: OR 1.90 (95% CI: 1.21–2.98) for 25(OH)D <30 ng·mL^{-1}, p<0.01; and for severe OSAS: OR 1.64 (95% CI: 1.06–2.54) for 25(OH)D <30 ng·mL^{-1}, p=0.03) [34]. Similarly, in another study, serum 25(OH)D concentrations were decreased in 139 OSAS patients compared with

those of 30 non-apnoeic controls (17.8±7.8 *versus* 23.9±12.4 ng·mL^{-1}, p=0.019) and were negatively associated with AHI (r=–0.187, p=0.045) [35].

The correlation between OSAS severity and vitamin D status necessitates further investigation. Data from a recent meta-analysis demonstrated that OSAS patients had lower 25(OH)D serum levels compared with controls, with mean difference of –5.81 (95% CI: –10.09 to –1.53, p=0.008) [36]. However, the results should be interpreted with caution, due to the small number of studies included in the analysis [36]. Of note, some of the studies failing to demonstrate an association between OSAS severity and serum vitamin D levels reported higher mean 25(OH)D levels compared with those showing a relationship between vitamin D and AHI [32, 33]. Thus, an association between vitamin D deficiency, but not insufficiency, may be postulated among OSAS patients.

AHI is the most important prognostic factor for excessive daytime sleepiness [37]. Studies investigating the association between serum levels of vitamin D and other sleep disorders associated with hypersomnolence, such as narcolepsy, produce contradicting results. In the study by Carlander *et al*. [38], serum 25(OH)D levels were measured in 51 narcoleptic patients and 55 matched healthy controls. Patients in the narcolepsy group presented with lower 25(OH)D serum levels (p=0.0039) and had significantly greater vitamin D deficiency (p=0.0238) compared with controls [38]. Moreover, vitamin D deficiency increased the risk of being affected with narcolepsy (OR 5.34 (1.65–17.27), p=0.0051) [38].

By contrast, Dauvilliers *et al*. [39] found no difference in serum 25(OH)D levels and frequency of vitamin D deficiency between 174 type 1 narcolepsy patients and 174 healthy controls. In the narcolepsy group, no significant association was found between vitamin D deficiency, disease duration, severity and treatment [39].

In addition, there is a lack of studies evaluating the effects of vitamin D supplementation on the severity of OSAS. A double-blind, randomised, placebo-controlled trial of daily supplementation with 4000 IU vitamin D3 or placebo for 15 weeks included 19 adults with OSAS (15 under continuous positive airway pressure (CPAP) treatment and four CPAP naive), and evaluated sleepiness, quality of life, fatigue and neuropsychological function by means of questionnaires. In addition, vitamin D status and indices of inflammation, lipid profile and glycaemic indices were measured. Fatigue was significantly improved in the vitamin D group, while no differences were noted in terms of neuropsychological indices or quality of life scores [40]. A significant increase in 25(OH)D serum levels (p=0.00001) and significant decreases in low-density lipoprotein (p=0.04) and lipoprotein-associated phospholipase A2 (p=0.037), as well as trends toward decreased fasting glucose (p=0.09) and increased high-density lipoprotein (p=0.07), were observed in the supplementation group compared with the placebo group [40].

Obesity and vitamin D

A large body of evidence suggests an association between obesity and low serum vitamin D concentrations [41–43]. In healthy individuals, it has also been reported that body fat content is inversely related to serum 25(OH)D concentration [44]. In COPD and asthma patients, adiposity has been a significant predictor of low serum levels of vitamin D [45, 46]. In a study including subjects from a multicentre cohort of older males [47], individuals with lower serum 25(OH)D concentrations had greater odds of severe sleep apnoea when compared with the highest 25(OH)D quartile (OR: 1.45, 95% CI: 1.02–2.07). However, this association was no longer evident after adjustment for traditional risk factors for OSAS (adjusted OR: 1.05, 95% CI: 0.72–1.52) [47]. In logistic regression analysis, BMI (OR: 1.12, 95% CI: 0.77–1.61) and larger neck circumference (OR: 1.22, 95% CI: 0.85–1.75) were identified as major predictors of lower 25(OH)D concentrations [47].

The potential mechanisms underlying these effects may include lower dietary intake or less sunlight exposure, despite the fact that obesity produces a larger body surface area and increases cutaneous synthesis [48–50]. Subcutaneous adipose tissue presents lower expression of the enzymes responsible for vitamin D activation and a propensity towards increased catabolism [51]. Fat tissue acts as a storage site for vitamin D and oral supplementation resulted in a 57% lower increase in serum 25(OH)D concentrations in obese compared with non-obese individuals, indicating sequestration of the vitamin in adipose tissue and reduced bioavailability [43, 52]. Moreover, dilution of ingested or cutaneously synthesised vitamin D in the large fat mass of obese patients may also lead to vitamin D hypovitaminosis [53].

Adipokines have been implicated in the pathogenesis of OSAS [54]. The association between vitamin D status and serum adipokine concentrations is still to be defined. In a cross-sectional study including 426 non-diabetic participants, a direct association between vitamin D and adiponectin (β=0.02, p=0.04) was observed among lean white women and an inverse association was shown among lean African-American women (β=–0.06, p=0.01) [55]. No association was present among obese individuals [55]. A meta-analysis of observational studies and randomised controlled trials has demonstrated an inverse association between leptin levels and 25(OH)D concentration in observational studies, which was not corroborated in intervention studies with high heterogeneity [56]. Another meta-analysis that aimed to elucidate the role of vitamin D supplementation on serum adipokines failed to demonstrate a significant effect of vitamin D treatment on adiponectin and leptin levels [57].

Hypovitaminosis D persists after bariatric surgery. The cause underlying vitamin D deficiency after bariatric surgery is multifactorial. Other than poor adherence to diet and supplement recommendations, surgical procedures that include bypass of the duodenum and proximal ileum further reduce vitamin D absorption from the diet [58]. Absorption problems also occur from vomiting, reduced time available for food digestion, and bacterial overgrowth [58]. Additionally, the Roux-en-Y gastric bypass procedure circumvents the duodenum and proximal jejunum, thus bypassing the transport pathways for iron, calcium, and the fat-soluble vitamins A and D [58]. Hypovitaminosis D after weight loss surgery was correlated with increased parathormone levels and was associated with osteoporosis [58]. Several guidelines for postoperative vitamin D replacement in obese patients undergoing bariatric surgery have been proposed [58]. However, a systematic review of observational studies revealed adequate 25(OH)D levels after bariatric surgery (as evaluated at 3 months to 10 years after surgery) in only 13% of the included studies [59].

Obesity affects vitamin D status and further studies are needed to determine the complex interaction between them in OSAS patients, as well as to establish the role of supplemental vitamin D in those patients [60].

Nocturnal hypoxia and vitamin D

Chronic nocturnal intermittent hypoxia is a fundamental feature of OSAS. Fluctuations in oxyhaemoglobin saturation during sleep, caused by recurrent upper airway obstruction, mimics hypoxia-re-oxygenation or ischaemia-reperfusion injury [61]. In COPD patients, hypoxaemia ($p<0.01$) and dyspnoea ($p=0.01$) were associated with lower serum 25(OH)D levels [45]. In OSAS patients, serum levels of vitamin D have been associated with several indices of hypoxia including average and minimum oxyhaemoglobin saturation during sleep, time spent with oxyhaemoglobin saturation <90% and ODI, in some [35, 62, 63], but not in all studies [30].

In human cancer cells, vitamin D reduced protein expression of both hypoxia-inducible factor (HIF)-1α subunit and vascular endothelial growth factor (VEGF) [64]. In the study by Lu *et al*. [65], HIF-1α serum levels were increased in severe OSAS patients compared with mild and moderate OSAS and control subjects (1.17±0.15 *versus* 0.89±0.19 *versus* 0.85±0.16 ng·mL^{-1}, respectively, $p=0.025$). HIF-1α expression was positively correlated with AHI ($r=0.634$, $p<0.001$) and time spent with oxyhaemoglobin saturation <90% ($r=0.632$, $p<0.001$), and it was negatively correlated with mean ($r=-0.565$, $p<0.001$) and minimum oxyhaemoglobin saturation during sleep ($r=-0.596$, $p<0.001$) [65]. HIF-1α expression was downregulated after 2 months of CPAP therapy (1.10±0.21 before *versus* 0.78±0.32 ng·mL^{-1} after CPAP treatment, $p<0.001$) [65]. Similarly, in another study, VEGF serum levels were higher in OSAS patients compared with controls (398.4±229 *versus* 229.9±149.8 pg·mL^{-1}, respectively, $p<0.001$) [66]. VEGF levels were positively correlated with AHI ($r=0.336$, $p=0.001$) and ODI ($r=0.282$, $p=0.007$), while 6 months of CPAP therapy significantly decreased VEGF serum concentrations in OSAS patients ($p<0.001$) [66].

In vitro studies have demonstrated that vitamin D inhibits nuclear factor (NF)-κB activity by interacting with the inhibitor of κB kinase and increasing inhibitor of κB kinase alpha subunit levels [67, 68]. However, in a double-blind randomised trial including 54 overweight/obese adults, participants received a single 100000 IU bolus followed by 4000 IU daily cholecalciferol or matching placebo for 16 weeks. No difference between the groups was shown in any inflammatory marker examined or NF-κB activity ($p>0.05$) even after adjustment for various confounders, such as sun exposure, percentage of body fat and dietary vitamin D intake [69].

Thus, the association between vitamin D insufficiency and hypoxia in OSAS may be mediated by mechanisms involving HIF-1α and VEGF. Nonetheless, given that vitamin D binding protein (VDBP) changes its serum level in response to chronic hypoxia, further investigation is warranted to better understand this relationship [70].

Inflammation and vitamin D

OSAS is considered as an inflammatory disease. Intermittent hypoxia, and the accompanying apnoeic events, are associated with overexpression of inflammatory markers, increased sympathetic nervous system activation and endothelial dysfunction [3, 71, 72]. Vitamin D also interacts with the immune system, and so chronically low vitamin levels are associated with a pro-inflammatory state [13]. In a study of 90 severe OSAS patients and 30 healthy controls, serum vitamin D levels and IL-17 levels were increased in the former (7.9±2.9 *versus* 16.8±3.1 ng·mL^{-1}, respectively for vitamin D; 20.3±3.9 *versus* 10.05±3 pg·mL^{-1}, respectively for IL-17) [63]. A significant negative correlation was observed between IL-17 and vitamin D levels ($r=-0.64$, $p<0.001$) in severe OSAS patients [63]. Moreover, in healthy individuals, vitamin D supplementation (5000–10000 IU·day^{-1} over 15 weeks) produced an increase in IL-10 production by peripheral blood mononuclear cells and a reduced frequency of IL-17-producing Th17 cells [73]. IL-17 presents a synergistic action with TNF-α and IL-10 and participates in the inflammatory response in OSAS [74]. Adequate vitamin D levels, acting through multiple pathways, may attenuate this response and modulate systemic inflammation in OSAS.

CPAP treatment and vitamin D

Table 2 summarises studies examining the effect of CPAP treatment on vitamin D levels in OSAS patients. Liguori *et al*. [75] evaluated vitamin D levels in 65 compliant and 25 non-compliant OSAS patients, who underwent CPAP therapy for 7 nights. CPAP treatment significantly increased serum vitamin D concentrations in the entire OSAS population (19.21±9.45 before *versus* 21.03±9.50 ng·mL^{-1} after treatment, p<0.01). No change in serum vitamin D levels after treatment was observed in non-compliant subjects. Among compliant subjects, 7-night CPAP therapy increased serum vitamin D concentrations, compared with baseline, in male (p<0.01) but not in female (p>0.05) OSAS patients [75]. The lack of a similar response in women suggests a role for female sex hormones in vitamin D regulation. In particular, oestrogens negatively influence vitamin D homeostasis in post-menopausal women and remain unaffected by CPAP treatment [76, 77].

The same group carried out a further study looking at patients after 1 year of CPAP treatment [78]. A significant increase in vitamin D levels between baseline and the 1-year follow-up was observed in the compliant with CPAP treatment group (16.05±7.74 *versus* 25.73±12.91 ng·mL^{-1}, respectively, p<0.05) but not in the non-compliant group (16.96±8.64 ng·mL^{-1} *versus* 16.29±4.57 ng·mL^{-1}, respectively, p>0.05) [78]. Patients with good adherence to CPAP exhibited higher vitamin D levels compared with those with scarce compliance to therapy (25.73±12.91 *versus* 16.29±4.57 ng·mL^{-1}, respectively, p<0.001). Among compliant patients, a significant positive effect of CPAP therapy on serum vitamin D levels was observed in both obese (14.67±8.15 at baseline *versus* 28.61±15.11 ng·mL^{-1} after treatment, p<0.01) and non-obese (18.04±6.86 at baseline *versus* 21.59±7.51 ng·mL^{-1} after treatment, p<0.05) OSAS subjects. Interestingly, obese OSAS patients more frequently shifted from an insufficient to a sufficient vitamin D status (p<0.05) and presented higher variation in vitamin D concentrations (13.95±11.91 *versus* 3.54±5.06 ng·mL^{-1}, p<0.001), Epworth Sleepiness Scale (11.78±4.10 *versus* 8.69±1.49, p<0.05) and AHI (52.37±31.76 *versus* 34.31±8.53 events·h^{-1}, p<0.01) compared with non-obese OSAS patients [78]. Thus, obesity may mediate the influence of CPAP therapy on vitamin D levels, possibly by reducing daytime sleepiness and increasing sunlight exposure.

Theorell-Haglöw *et al*. [79] randomised 64 OSAS patients to either real or sham CPAP treatment for 12 weeks. All participants then received real CPAP therapy for an additional 12 weeks. After 12 weeks of CPAP therapy no between-group differences were observed in serum 25(OH)D levels (–0.80±5.28 *versus* 3.08±3.66 ng·mL^{-1}, p=0.42). However, after 24 weeks, irrespective of initial randomisation, 25(OH)D levels were significantly increased in patients with severe obstructive sleep apnoea (9.60 ng·mL^{-1}, CI: –1.20–20.39, p=0.045) and in patients with excessive daytime sleepiness (14.04 ng·mL^{-1}, CI: 4.86–23.23, p=0.007), indicating that CPAP treatment may have late beneficial effects on vitamin D levels. Taken together, the data suggest a positive effect of CPAP therapy on serum levels of vitamin D and factors such as duration of the intervention, sex and obesity may affect this interaction.

Future research perspectives

Vitamin D is transferred by the VDBP and exerts its numerous biological actions through the vitamin D receptor (VDR) [80]. The VDR belongs to the nuclear hormone receptor family and acts as a ligand-inducible transcription factor [80]. The VDR gene is located on chromosome 12

Table 2 *Summary of studies investigating the effect of CPAP treatment on serum levels of vitamin D in OSAS*

First author [ref.]	Comparison groups	Follow-up period	Comments
Liguori [75]	Non-OSAS controls *versus* severe OSAS responders *versus* severe OSAS non-responders	7 nights	Male, but not female, OSAS responders showed a significant increase in 25(OH)D levels. OSAS non-responders did not show modifications of serum 25(OH)D concentrations.
Liguori [78]	OSAS compliant *versus* OSAS non-compliant and obese compliant OSAS *versus* non-obese compliant OSAS	1 year	Serum 25(OH)D levels increased in OSAS compliant, but not in OSAS non-compliant patients. Obese compliant OSAS patients shifted from insufficient to sufficient vitamin D status more than the non-obese compliant OSAS patients. BMI at baseline positively correlated with serum 25(OH)D variation levels.
Theorell-Haglöw [79]	OSAS real CPAP *versus* OSAS sham CPAP	24 weeks	After 12 weeks there were no between-group differences in 25(OH)D serum levels. After 24 weeks 25(OH)D increased in patients with severe OSAS and in sleepy patients.

and a variety of polymorphisms associated with different conditions, such as diabetes, renal disease and cancer, have been described [80]. Results from a recent meta-analysis demonstrated that rs2228570, rs7975232, rs731236 and rs3782905 gene polymorphisms in VDR were associated with increased susceptibility to asthma [81]. Similarly, VDBP variants were associated with increased likelihood of asthma in a Chinese population [82]. Regarding OSAS, to date, there are no studies assessing the presence of VDR and VDBP gene polymorphisms in this patient population. Thus, future research is mandatory in order to study the biological effects of VDR and VDBP genetic variants in OSAS and their possible association with comorbidities related to the syndrome.

In addition, vitamin D supplementation has been shown to affect the course of various diseases. In asthma, vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids [83]. In COPD, vitamin D supplementation reduced osteoporotic fractures and may prevent deterioration of pulmonary function [84]. Further studies are necessary to evaluate whether prevention of vitamin D deficiency or adequate supplementation may alter the natural course of OSAS, or attenuate the associated comorbidities.

Conclusions

The association between vitamin D deficiency and OSAS is mediated by complex pathogenetic mechanisms and affected by multiple confounding factors. The fact that vitamin D deficiency appears to be common among OSAS patients suggests that screening should be performed when clinically indicated. The positive effects of vitamin D in the comorbidities associated with OSAS (*e.g.* cardiovascular disease) need to be considered, especially in the context of the relatively limited cost of vitamin D supplementation. Further research with appropriate adjustments for potential confounders is needed to fully elucidate the relationship and the mechanisms of vitamin D insufficiency in OSAS and any need for supplementation.

Self-evaluation questions

1. Regarding the role of vitamin D insufficiency in OSAS patients, which of the following is/are correct?
   a) Serum 25(OH)D is considered the best indicator of vitamin D status in OSAS patients.
   b) Vitamin D deficiency and OSAS present common risk factors and comorbidities, such as older age and obesity.
   c) There are a lack of vitamin D receptors in brain areas involved in sleep regulation.
   d) There are no common pathogenetic features between the two conditions.
2. Which of the following is/are correct regarding the mechanism by which vitamin D insufficiency enhances the development of OSAS?
   a) A decrease in pharyngeal dilator muscle strength, thus reducing pharyngeal patency and predisposing to apnoeic events during sleep.
   b) An immune system dysregulation, associated with increased incidence of upper respiratory tract infections and tonsillar hypertrophy.
   c) Promoting the secretion of pro-inflammatory cytokines.
3. Regarding the effect of obesity on serum concentrations of vitamin D, which of the following is/are correct?
   a) In healthy individuals, serum vitamin D levels are independent from obesity.
   b) Subcutaneous adipose tissue presents high expression of the enzymes responsible for vitamin D activation.
   c) Fat tissue acts as a storage site for vitamin D and it is released when serum levels decrease.
   d) Obesity may mediate the influence of CPAP therapy on vitamin D levels.
4. Regarding serum vitamin D levels in OSAS, which of the following is/are correct?
   a) Available evidence indicates increased levels after short-term CPAP therapy.
   b) Serum VDBP levels remain unchanged in response to chronic hypoxia.
   c) The association between vitamin D insufficiency and hypoxia may be mediated by mechanisms involving HIF-1α and VEGF.
   d) A positive correlation between serum vitamin D levels and inflammatory factors, such as IL-17, has been observed.

Conflict of interest

None declared.

References

1. Douglas NJ, Polo O. Pathogenesis of obstructive sleep apnoea/hypopnoea syndrome. *Lancet* 1994; 344: 653–655.
2. Peppard PE, Young T, Barnet JH, *et al.* Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177: 1006–1014.
3. Archontogeorgis K, Nena E, Papanas N, *et al.* Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. *Pulm Med* 2014; 2014: 930535.
4. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Prog Cardiovasc Dis* 2009; 51: 285–293.
5. Cassol CM, Martinez D, da Silva F, *et al.* Is sleep apnea a winter disease? meteorologic and sleep laboratory evidence collected over 1 decade. *Chest* 2012; 142: 1499–1507.
6. Pafili K, Steiropoulos P, Papanas N. The relationship between obstructive sleep apnoea and coronary heart disease. *Curr Opin Cardiol* 2015; 30: 439–446.

Suggested answers

1. b.
2. a–c.
3. d.
4. c.

7. Kulie T, Groff A, Redmer J, *et al.* Vitamin D: an evidence-based review. *J Am Board Fam Med* 2009; 22: 698–706.
8. Lips P. Worldwide status of vitamin D nutrition. *J Steroid Biochem Mol Biol* 2010; 121: 297–300.
9. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; 81: 353–373.
10. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005; 437: 1257–1263.
11. Nakashima A, Yokoyama K, Yokoo T, *et al.* Role of vitamin D in diabetes mellitus and chronic kidney disease. *World J Diabetes* 2016; 7: 89–100.
12. Evatt ML. Vitamin D associations and sleep physiology–promising rays of information. *Sleep* 2015; 38: 171–172.
13. McCarty DE, Chesson AL Jr, Jain SK, *et al.* The link between vitamin D metabolism and sleep medicine. *Sleep Med Rev* 2014; 18: 311–319.
14. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle. *J Biol Chem* 1985; 260: 8882–8891.
15. Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. *Osteoporos Int* 2002; 13: 187–194.
16. Ziambaras K, Dagogo-Jack S. Reversible muscle weakness in patients with vitamin D deficiency. *West J Med* 1997; 167: 435–439.
17. Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. *Atherosclerosis* 2011; 215: 23–29.
18. Sharma V, Borah P, Basumatary LJ, *et al.* Myopathies of endocrine disorders: a prospective clinical and biochemical study. *Ann Indian Acad Neurol* 2014; 17: 298–302.
19. Patil SP, Schneider H, Schwartz AR, *et al.* Adult obstructive sleep apnea: pathophysiology and diagnosis. *Chest* 2007; 132: 325–337.
20. Rejnmark L. Effects of vitamin D on muscle function and performance: a review of evidence from randomized controlled trials. *Ther Adv Chronic Dis* 2011; 2: 25–37.
21. Hewison M, Gacad MA, Lemire J, *et al.* Vitamin D as a cytokine and hematopoetic factor. *Rev Endocr Metab Disord* 2001; 2: 217–227.
22. Prietl B, Treiber G, Pieber TR, *et al.* Vitamin D and immune function. *Nutrients* 2013; 5: 2502–2521.
23. Aranow C. Vitamin D and the immune system. *J Investig Med* 2011; 59: 881–886.
24. Herr C, Greulich T, Koczulla RA, *et al.* The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. *Respir Res* 2011; 12: 31.
25. Lee SJ, Kang BH, Choi BS. Vitamin D serum levels in children with allergic and vasomotor rhinitis. *Korean J Pediatr* 2015; 58: 325–329.
26. Reid D, Morton R, Salkeld L, *et al.* Vitamin D and tonsil disease-preliminary observations. *Int J Pediatr Otorhinolaryngol* 2011; 75: 261–264.
27. Igelstrom H, Emtner M, Lindberg E, *et al.* Physical activity and sedentary time in persons with obstructive sleep apnea and overweight enrolled in a randomized controlled trial for enhanced physical activity and healthy eating. *Sleep Breath* 2013; 17: 1257–1266.
28. Klobucnikova K, Siarnik P, Sivakova M, *et al.* Carotid intima-media thickness is not associated with homocysteine and vitamin D levels in obstructive sleep apnea. *Scand J Clin Lab Invest* 2017; 77: 263–266.
29. Erden ES, Genc S, Motor S, *et al.* Investigation of serum bisphenol A, vitamin D, and parathyroid hormone levels in patients with obstructive sleep apnea syndrome. *Endocrine* 2014; 45: 311–318.
30. Salepci B, Caglayan B, Nahid P, *et al.* Vitamin D deficiency in patients referred for evaluation of obstructive sleep apnea. *J Clin Sleep Med* 2017; 13: 607–612.
31. Mete T, Yalcin Y, Berker D, *et al.* Obstructive sleep apnea syndrome and its association with vitamin D deficiency. *J Endocrinol Invest* 2013; 36: 681–685.
32. Barceló A, Esquinas C, Pierola J, *et al.* Vitamin D status and parathyroid hormone levels in patients with obstructive sleep apnea. *Respiration* 2013; 86: 295–301.
33. Bozkurt NC, Cakal E, Sahin M, *et al.* The relation of serum 25-hydroxyvitamin-D levels with severity of obstructive sleep apnea and glucose metabolism abnormalities. *Endocrine* 2012; 41: 518–525.
34. Piovezan RD, Hirotsu C, Feres MC, *et al.* Obstructive sleep apnea and objective short sleep duration are independently associated with the risk of serum vitamin D deficiency. *PLoS One* 2017; 12: e0180901.
35. Archontogeorgis K, Nena E, Papanas N, *et al.* Vitamin D levels in middle-aged patients with obstructive sleep apnoea syndrome. *Curr Vasc Pharmacol* 2018; 16: 289–297.
36. Upala S, Sanguankeo A. Association between 25-hydroxyvitamin D and obstructive sleep apnea: a systematic review and meta-analysis. *J Clin Sleep Med* 2015; 11: 1347.
37. Oksenberg A, Arons E, Nasser K, *et al.* Severe obstructive sleep apnea: sleepy *versus* nonsleepy patients. *Laryngoscope* 2010; 120: 643–648.
38. Carlander B, Puech-Cathala AM, Jaussent I, *et al.* Low vitamin D in narcolepsy with cataplexy. *PLoS One* 2011; 6: e20433.
39. Dauvilliers Y, Evangelista E, Lopez R, *et al.* Vitamin D deficiency in type 1 narcolepsy: a reappraisal. *Sleep Med* 2017; 29: 1–6.
40. Kerley CP, Hutchinson K, Bramham J, *et al.* Vitamin D improves selected metabolic parameters but not neuropsychological or quality of life indices in OSA: A pilot study. *J Clin Sleep Med* 2017; 13: 19–26.
41. Parikh SJ, Edelman M, Uwaifo GI, *et al.* The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 2004; 89: 1196–1199.
42. Lagunova Z, Porojnicu AC, Lindberg F, *et al.* The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Res* 2009; 29: 3713–3720.
43. Wortsman J, Matsuoka LY, Chen TC, *et al.* Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000; 72: 690–693.
44. Arunabh S, Pollack S, Yeh J, *et al.* Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab* 2003; 88: 157–161.
45. Persson LJ, Aanerud M, Hiemstra PS, *et al.* Chronic obstructive pulmonary disease is associated with low levels of vitamin D. *PLoS One* 2012; 7: e38934.
46. Vo P, Bair-Merritt M, Camargo CA. The potential role of vitamin D in the link between obesity and asthma severity/control in children. *Expert Rev Respir Med* 2015; 9: 309–325.
47. Goswami U, Ensrud KE, Paudel ML, *et al.* Vitamin D concentrations and obstructive sleep apnea in a multicenter cohort of older males. *Ann Am Thorac Soc* 2016; 13: 712–718.
48. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone level is associated with body mass index. The 5th Tromso study. *Eur J Endocrinol* 2004; 151: 167–172.
49. Kull M, Kallikorm R, Lember M. Body mass index determines sunbathing habits: implications on vitamin D levels. *Intern Med J* 2009; 39: 256–258.
50. Verbraecken J, Van de Heyning P, De Backer W, *et al.* Body surface area in normal-weight, overweight, and obese adults. A comparison study. *Metabolism* 2006; 55: 515–524.
51. Wamberg L, Christiansen T, Paulsen SK, *et al.* Expression of vitamin D-metabolizing enzymes in human adipose tissue – the effect of obesity and diet-induced weight loss. *Int J Obes (Lond)* 2013; 37: 651–657.
52. Blum M, Dolnikowski G, Seyoum E, *et al.* Vitamin D_3 in fat tissue. *Endocrine* 2008; 33: 90–94.
53. Drincic AT, Armas LA, Van Diest EE, *et al.* Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. *Obesity (Silver Spring)* 2012; 20: 1444–1448.
54. Al Mutairi S, Mojiminiyi OA, Al Alawi A, *et al.* Study of leptin and adiponectin as disease markers in subjects with obstructive sleep apnea. *Dis Markers* 2014; 2014: 706314.
55. Bidulescu A, Morris AA, Stoyanova N, *et al.* Association between Vitamin D and adiponectin and its relationship with body mass index: The META-Health Study. *Front Public Health* 2014; 2: 193.

56. Hajimohammadi M, Shab-Bidar S, Neyestani TR. Vitamin D and serum leptin: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Eur J Clin Nutr* 2017; 71: 1144–1153.
57. Dinca M, Serban MC, Sahebkar A, *et al.* Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* 2016; 107: 360–371.
58. Chakhtoura M, Rahme M, El-Hajj Fuleihan G. Vitamin D metabolism in bariatric surgery. *Endocrinol Metab Clin North Am* 2017; 46: 947–982.
59. Chakhtoura MT, Nakhoul NN, Shawwa K, *et al.* Hypovitaminosis D in bariatric surgery: a systematic review of observational studies. *Metabolism* 2016; 65: 574–585.
60. Vanlint S. Vitamin D and obesity. *Nutrients* 2013; 5: 949–956.
61. Sforza E, Roche F. Chronic intermittent hypoxia and obstructive sleep apnea: an experimental and clinical approach. *Hypoxia (Auckl)* 2016; 4: 99–108.
62. Kerley CP, Hutchinson K, Bolger K, *et al.* Serum vitamin D is significantly inversely associated with disease severity in caucasian adults with obstructive sleep apnea syndrome. *Sleep* 2016; 39: 293–300.
63. Toujani S, Kaabachi W, Mjid M, *et al.* Vitamin D deficiency and interleukin-17 relationship in severe obstructive sleep apnea–hypopnea syndrome. *Ann Thorac Med* 2017; 12: 107–113.
64. Ben-Shoshan M, Amir S, Dang DT, *et al.* 1α,25-dihydroxyvitamin D3 (Calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells. *Mol Cancer Ther* 2007; 6: 1433–1439.
65. Lu D, Li N, Yao X, *et al.* Potential inflammatory markers in obstructive sleep apnea–hypopnea syndrome. *Bosn J Basic Med Sci* 2017; 17: 47–53.
66. Archontogeorgis K, Nena E, Papanas N, *et al.* Serum levels of vascular endothelial growth factor and insulin-like growth factor binding protein-3 in obstructive sleep apnea patients: effect of continuous positive airway pressure treatment. *Open Cardiovasc Med J* 2015; 9: 133–138.
67. Cohen-Lahav M, Shany S, Tobvin D, *et al.* Vitamin D decreases NFκB activity by increasing IκBα levels. *Nephrol Dial Transplant* 2006; 21: 889–897.
68. Chen Y, Zhang J, Ge X, *et al.* Vitamin D receptor inhibits nuclear factor κB activation by interacting with IκB kinase β protein. *J Biol Chem* 2013; 288: 19450–19458.
69. Mousa A, Naderpoor N, Johnson J, *et al.* Effect of vitamin D supplementation on inflammation and nuclear factor κ-B activity in overweight/obese adults: a randomized placebo-controlled trial. *Sci Rep* 2017; 7: 15154.
70. Ahmad Y, Sharma NK, Garg I, *et al.* An insight into the changes in human plasma proteome on adaptation to hypobaric hypoxia. *PLoS One* 2013; 8: e67548.
71. Somers VK, Dyken ME, Clary MP, *et al.* Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995; 96: 1897–1904.
72. Kato M, Roberts-Thomson P, Phillips BG, *et al.* Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000; 102: 2607–2610.
73. Allen AC, Kelly S, Basdeo SA, *et al.* A pilot study of the immunological effects of high-dose vitamin D in healthy volunteers. *Mult Scler* 2012; 18: 1797–1800.
74. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med* 2009; 361: 888–898.
75. Liguori C, Romigi A, Izzi F, *et al.* Continuous positive airway pressure treatment increases serum vitamin D levels in male patients with obstructive sleep apnea. *J Clin Sleep Med* 2015; 11: 603–607.
76. Lerchbaum E. Vitamin D and menopause – a narrative review. *Maturitas* 2014; 79: 3–7.
77. Celec P, Mucska I, Ostatnikova D, *et al.* Testosterone and estradiol are not affected in male and female patients with obstructive sleep apnea treated with continuous positive airway pressure. *J Endocrinol Invest* 2014; 37: 9–12.
78. Liguori C, Izzi F, Mercuri NB, *et al.* Vitamin D status of male OSAS patients improved after long-term CPAP treatment mainly in obese subjects. *Sleep Med* 2017; 29: 81–85.
79. Theorell-Haglöw J, Hoyos CM, Phillips CL, *et al.* Changes of vitamin D levels and bone turnover markers after CPAP therapy: a randomized sham-controlled trial. *J Sleep Res* 2018; 27: e12606.
80. Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. *Clin Chim Acta* 2006; 371: 1–12.
81. Han JC, Du J, Zhang YJ, *et al.* Vitamin D receptor polymorphisms may contribute to asthma risk. *J Asthma* 2016; 53: 790–800.
82. Li F, Jiang L, Willis-Owen SA, *et al.* Vitamin D binding protein variants associate with asthma susceptibility in the Chinese Han population. *BMC Med Genet* 2011; 12: 103.
83. Jolliffe DA, Greenberg L, Hooper RL, *et al.* Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med* 2017; 5: 881–890.
84. Janssens W, Mathieu C, Boonen S, *et al.* Vitamin D deficiency and chronic obstructive pulmonary disease: a vicious circle. *Vitam Horm* 2011; 86: 379–399.