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THEORETICAL REVIEW

The link between vitamin D metabolism and sleep medicine

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SUMMARY

Vitamin D is a hormone that interacts with intranuclear receptors to effect transcriptional changes in many cell types including those in gut, bone, breast, prostate, brain, skeletal muscle, and the immune system. Inadequacy of vitamin D is widely prevalent, and leads to the classic diseases of bone demineralization as well as to more recently recognized problems such as nonspecific pain and noninflammatory skeletal myopathy, which may disrupt sleep and directly cause daytime impairment. Emerging lines of evidence suggest that low vitamin D levels increase the risk for autoimmune disease, chronic rhinitis, tonsillar hypertrophy, cardiovascular disease, and diabetes. These conditions are mediated by altered immunomodulation, increased propensity to infection, and increased levels of inflammatory substances, including those that regulate sleep, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, and prostaglandin D2 (PD2). Together, the recent reports suggest a role for inadequate vitamin D in the development of symptoms of wake impairment commonly associated with sleep disorders. Persistent inadequacy of vitamin D may also increase the risk for obstructive sleep apnea via promotion of adenotonsillar hypertrophy, airway muscle myopathy, and/or chronic rhinitis. Much remains to be learned concerning the complex relationship between chronically low levels of vitamin D, normal sleep, sleep disruption, and daytime neurocognitive impairment.

Introduction: wake-impairment symptoms

Patients seeking care from a specialist in sleep medicine commonly report curtailed or disrupted sleep coupled with one or more symptoms experienced during wakefulness that the patient identifies as arising from inadequate sleep. Though excessive daytime sleepiness (EDS) is a frequently-touted daytime-impairment symptom resulting from sleep disorders, it is generally understood that curtailed or disrupted sleep may lead to a number of nonspecific complaints, involving general debility, somatic discomfort, cognitive impairment, and emotional impairment (Table 1), and that some patients have wake-impairment symptoms but deny EDS. Terms such as “daytime neurocognitive impairment” and “nonrestorative sleep” have historically been used to describe these sorts of wake-related complaints within the context of clinical management of sleep disorders. But these terms can fall short of capturing the broad spectrum of complaints that might be linked to curtailed/disrupted sleep or imply that these symptoms are inherently linked to a sleep problem (being nonspecific symptoms, other entities besides disrupted sleep might explain them). For these reasons, we will use the term *wake-impairment symptoms* (WIS) to refer to the array of different symptoms that could be interpreted by clinicians and/or patients as indicators of curtailed or disrupted sleep (Table 1).

Though clinicians are typically educated to employ diagnostic parsimony in order to identify a single etiology to explain a patient’s symptoms, in practice, multiple factors typically contribute to WIS, thus requiring a comprehensive approach [1]. Furthermore, cardiovascular morbidity constitutes one of the most serious consequences of obstructive sleep apnea, and modification of this risk constitutes a large part of the rationale to pursue treatment. It therefore follows that assessment/treatment of WIS and modification of a patient’s cardiovascular risk are among the most important responsibilities of a clinician practicing in the field of sleep medicine. This review introduces readers to evidence and analysis suggesting that chronic vitamin D inadequacy not only contributes to WIS via numerous pathways, but also may play a role in cardiovascular comorbidities associated with sleep disorders. Identification and treatment of inadequacy of vitamin D has the potential to improve the likelihood for favorable outcomes within this patient population, though more research is urgently needed.

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Abbreviations

1-25OHD	1,25 dihydroxyvitamin D (calcitriol)
25OHD	25-hydroxyvitamin D (calcidiol)
AHI	apnea/hypopnea index
CD8(α α)	cluster of differentiation (CD) 8 alpha alpha
CNS	central nervous system
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
HPA-axis	hypothalamic/pituitary/adrenal axis
IFN-γ	interferon gamma
IL	interleukin
MHC-II	major histocompatibility complex-II
MS	multiple sclerosis
NT-proANP	N-terminal pro-atrial natriuretic peptide
OSA	obstructive sleep apnea
PD2	prostaglandin D2
PTH	parathyroid hormone
RXR	retinoid X receptor
TNF-α	tumor necrosis factor alpha
VDR	vitamin D receptor
vitDd	vitamin D deficiency
Vitamin D2	ergocalciferol
Vitamin D3	cholecalciferol
WIS	wake-impairment symptoms

Biochemistry of vitamin D

Vitamin D refers to a collection of fat-soluble secosteroid hormones ingested in the diet and produced in the skin by action of ultraviolet rays in sunlight on 7-dehydrocholesterol to produce *cholecalciferol* (D3), which is the form of vitamin D found in animal products [2,3]. Vitamin D2 (ergocalciferol) is formed when the plant-product *ergosterol* is exposed to sunlight. For biological activity, both D2 and D3 must undergo two hydroxylation reactions. Hepatic hydroxylation produces 25-hydroxyvitamin D (25OHD), known as *calcidiol*, the measurement of which is commonly used to characterize functional vitamin D status. The second hydroxylation step occurs in the kidneys, yielding 1,25 dihydroxyvitamin D (1-25OHD), known as *calcitriol*. Hydroxylation is regulated by complex feedback loops involving parathyroid hormone (PTH) and by serum levels of calcium and phosphorus. 1-25OHD is also produced locally in various tissues—including smooth muscle and immune cells—to function in a paracrine or autocrine manner [4].

As is the case with other steroid hormones, vitamin D performs its biological functions by effecting transcriptional changes. 1-25OHD interacts with intranuclear vitamin D receptors (VDRs) and retinoid X receptors (RXR)—which form VDR–RXR heterodimers when in the presence of specific ligands—to ultimately bind to specific regions of DNA to function as transcription factors. In this manner, vitamin D modulates numerous metabolic processes in multiple tissues throughout the body. Pertinent to sleep, VDR–RXR has been shown to downregulate transcription of RelB, a gene encoding the protein RelB, itself a member of a family of transcription factors collectively referred to as nuclear factor κB (NFκB) [5]. NFκB plays a pivotal pro-inflammatory role, both in terms of the production of sleep-regulating substances (such as IL-1 and tumor necrosis factor alpha (TNF-α)) [6], but also in terms of the selective activation of inflammatory pathways known to occur in the setting of intermittent hypoxia, as is seen in obstructive sleep apnea [7].

Table 1
Patient-reported wake-impairment symptoms (WIS) suggesting curtailed or disrupted sleep.

Category	Symptom
General debility	Excessive daytime sleepiness
	Decreased motivation or energy
	Fatigue or malaise
Somatic discomfort	Headaches
	Gastrointestinal symptoms
Cognitive impairment	Attention impairment
	Memory impairment
	Concentration impairment
	Social or vocational dysfunction
	Poor school performance
	Proneness for accidents while driving
Emotional impairment	Mood disturbance
	Irritability
	Concerns or worries about sleep

Adapted from the International Classification of Sleep Disorders, 2nd Ed (2005) diagnostic criteria for insomnia; symptoms listed are taken as supportive evidence for daytime consequences of chronically impaired sleep.

Characterization of vitamin D status

Although the 25OHD level necessary to maintain optimal health remains unresolved, a framework for characterization of vitamin D status with respect to human disease has emerged (Table 2) [8]. Increasing evidence supports the view that essentially all diseases associated with abnormally low levels of vitamin D likely result from complex relationships between cumulative burdens of persistently low levels of 25OHD, the amount of dietary calcium intake, and/or an individual's PTH response to low 25OHD [9,10]. The dimension of time (i.e., the duration of any degree of deficiency) is one which is difficult to study, when characterizing the relationship between inadequate Vitamin D and human disease. Most research involves a point-estimation of 25OHD levels, rather than a protocol that allows the generation of a picture of the duration of exposure to such levels. For this reason, it is not known with precision how long a person must be exposed to inadequately low vitamin D, such that disease results. In addition, the methodology used for the 25OHD assay may produce erroneous results that depend upon vitamin D binding program concentration, thus increasing the degree of uncertainty when analyzing clinical research [11]. Nevertheless, despite these uncertainties, for purposes of statistically comparing different studies and evaluating proposed mechanistic pathways, it is convenient to dichotomize vitamin D levels as deficient or not deficient. Following convention, and for the purpose of this review, we accept <20 ng/mL as

Table 2
Vitamin D status classified according to circulating 25OHD concentrations in association with classical vitamin-D-related diseases and conditions.

25OHD (ng/mL)	Classical diseases/conditions
<10	Rickets, osteomalacia, myopathy, severe hyperparathyroidism, impaired immune function
10–20	Increased bone turnover, elevation in PTH, impaired muscle function/subacute myopathy
>20–30	Elevated PTH
>30–150	No generally recognized clinical changes
>150	Calcium hyperabsorption, hypercalcemia, soft tissue calcification

25OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone;

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indicative of vitamin D deficiency (vitDd) [3], the condition in which human health is jeopardized.

Epidemiology of vitamin D deficiency

The prevalence of vitDd in relation to various diseases has been described in the context of many different populations, and many risk factors have been identified including obesity, limited sunlight exposure, dark skin pigmentation, pregnancy, malabsorption syndromes, chronic use of steroids or anticonvulsants, advancing age, [2], and socioeconomic disadvantage [12]. The duration of daily sunlight exposure, work environment (indoor vs. outdoor), habits and culture regarding clothing and exposure of the skin, latitude of residence, air quality, and use of sunscreens all strongly impacted an individual's functional vitamin D synthesis [3]. Table 3 provides an overview of vitamin D levels found in different clinical populations.

Diseases classically associated with chronically low vitamin D

Rickets is the prototypical childhood syndrome of inadequate vitamin D, and involves a deforming demineralization of bones at the epiphysial growth plates. Though the images of rachitic skeletal deformity may be familiar to many clinicians, the suffering of a rachitic child may not be: myopathic symptoms of weakness, diffuse pain, and general debility are common. Although over a century old, Osler's description of the condition is still provocative for clinicians with an interest in sleep medicine:

> "First, a diffuse soreness of the body, so that the child cries when an attempt is made to move it, and prefers to keep perfectly still. This is often a marked and suggestive symptom. Secondly…nocturnal restlessness, and a tendency to throw off the bedclothes. This may be partly due to the fact that their general sensitiveness is such that even their weight may be distressing. And, thirdly, profuse sweating, particularly about the head and neck, so that in the morning the pillow is found soaked with perspiration." [13]

In adults, skeletal mineralization defects resulting in osteomalacia occur in areas of bone turnover (the epiphyseal plates have closed). Like rickets, osteomalacia is associated with diffuse bone pain resulting from hydration of the demineralized bone which stretches the periosteum to produce a nonspecific aching sensation [3]. Like rickets, osteomalacia is also associated with noninflammatory myopathy, causing skeletal-muscle weakness, and pain (see later).

Table 3
Data showing that deficiency of vitamin D has moderate to high prevalence in multiple clinically- relevant populations.

Population studied	25OHD (ng/mL)	Vitamin D deficient
Chronic, refractory musculoskeletal pain, $N = 150$ [14]	12.1 ± 5.8	93%
NHANES 2001–2004 (population based survey), $N = 13{,}369$ [98]	23.7 ± 1.0	36%
Chronic nonspecific musculoskeletal pain, $N = 276$ [15]	23.8 ± 29.1	63%
Clinically normal, $N = 202$ [15]	33.1 ± 28.4	36%
Elderly Saudi Arabian patients with traditional dress habits (only face and hands exposed), $N = 24$ [99]	3.6 ± 1.2	NR (20/24 < 5 ng/mL)
Clinically normal women, $N = 440$ [100]	17.2 ± 10.0	NR (39% < 12 ng/mL)
Clinically normal women, $N = 28$ [101]	22.0	30%
Women with a history of hip fractures, $N = 69$ [101]	17.6 ± 4.8	49%
Healthy adolescents, $N = 307$ [102]	26.2 ± 11.2 (summer) 20.2 ± 9.9 (winter)	42% (all seasons)
Nonspecific pain identified during sleep-medicine evaluation, $N = 153$ [79]	19.8 ± 11.1	54%

Mean 25OHD (in ng/mL) and prevalence of vitamin D deficiency (25OHD < 20 ng/mL) is shown. 25OHD, 25-hydroxyvitamin D; NHANES, national health and nutrition examination survey; NR, not reported.

Clinical and mechanistic basis for a link between vitamin D and sleep disorders

Pain

Diseases associated with persistently low levels of vitamin D commonly involve symptoms of somatic pain and physical discomfort, situations that naturally compound sleep disruption and WIS in patients who have this problem with or without other sleep disorders (Fig. 1).

Conversely—and of clinical utility—chronic nonspecific pain appears to be a marker for the presence of vitDd: patients who complained of refractory pain of uncertain cause had a high prevalence of vitDd [14,15]. Low levels of vitamin D were implicated in the development of statin-induced myopathic pain [16]. Individuals who developed statin-induced myalgias experienced resolution of the syndrome following treatment with vitamin D [17]. Low vitamin D was identified as a cofactor for aromatase-inhibitor associated myalgias, and vitamin D supplementation improved tolerability of the treatment agents [18].

The reports that low vitamin D caused chronic nonspecific musculoskeletal pain are significant for sleep-medicine specialists. Chronic pain is associated with poorer-quality sleep and shorter sleep duration [19]. Pain also negatively impacts mood and outlook, which may further exacerbate the subjective experience of daytime impairment, in the form of fatigue, despair, or depression [20]. Moreover, individuals with decreased total sleep time reported a higher degree of spontaneous daytime somatic pain symptoms and were more likely to report pain with a lesser degree of stimulation, compared with individuals who were not sleep-deprived, thus indicating that the relationship between pain and sleep could be bidirectional [21]. Increased pain perception associated with sleep deprivation reportedly is associated with increased IL-6 [22]—an inflammatory marker also known to be elevated in obstructive sleep apnea (OSA) [23] and in patients with low 25OHD [10]—which again raised the important point that pain, WIS, and markers of inflammation (and putatively, therefore, elevation in long-term health risks) can be driven by multiple sources.

Myopathy

Chronically low vitamin D leads to a noninflammatory skeletal myopathy, which presents with general debility, proximal motor weakness, and pain, altering body mechanics and postural stability, and increasing the likelihood for falls and injury [24]. Symptoms of mild myopathy might be variously reported by patients as fatigue, decreased exercise tolerance, decreased energy, or generalized aches, all of which could easily be dismissed as symptoms of poor sleep quality, thereby passing unrecognized as a vitamin D-related condition (Table 2). Leg extension strength in elderly patients was

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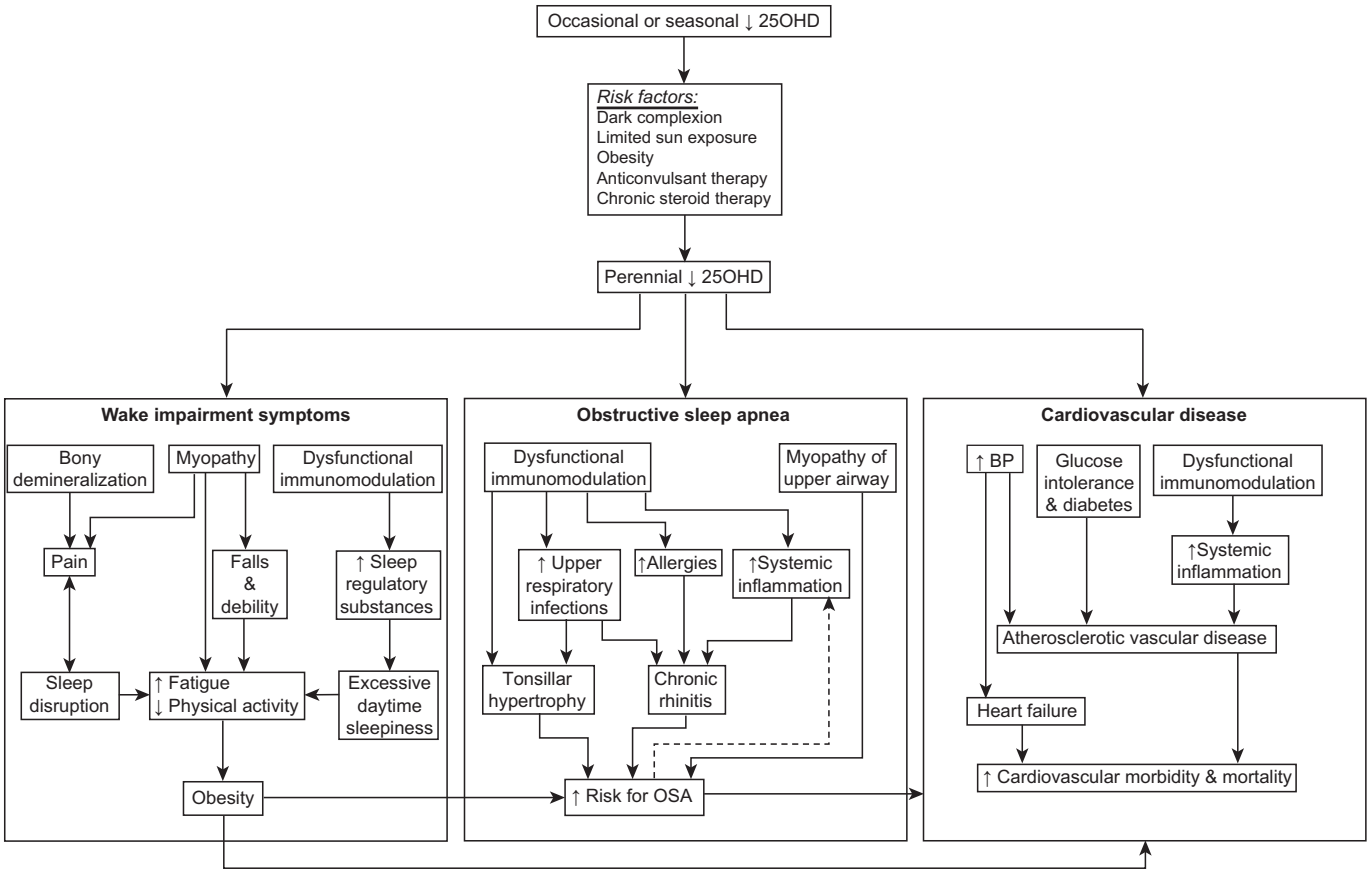

Fig. 1. Schematic of the interrelationships between vitamin D deficiency, wake-impairment symptoms, obstructive sleep apnea, and cardiovascular disease. Vitamin D deficiency, when chronic, may produce impairment across three domains that are clinically relevant to a sleep medicine clinician. Wake impairment symptoms (involving pain, daytime sleepiness, and fatigue) are a fundamental reason why many patients seek care within a sleep medicine clinic. Such physical symptoms promote alterations in behavior that can limit the propensity for physical exercise, thus promoting a more sedentary lifestyle and potentiate obesity. Vitamin D deficiency may also elevate the risk for development of obstructive sleep apnea via various mechanisms, and may increase an individual's cardiovascular risk, independent of the presence of OSA. See text for full discussion of various mechanisms. The dotted line represents the idea that obstructive sleep apnea independently increases the systemic inflammatory response. 25OHD, 25-hydroxyvitamin D; BP, blood pressure; OSA, obstructive sleep apnea.

positively associated with 25OHD levels, even at levels not commonly associated with skeletal disease, suggesting that subclinical weakness is a milder syndrome in the spectrum of myopathy [25]. The myopathy associated with chronically low vitamin D may also be profound: in one case a debilitated patient confined to a wheelchair was mobilized following identification and treatment of vitamin D deficiency [26].

Myopathy due to inadequate vitamin D can occur in the absence of elevated alkaline phosphatase, a traditional biochemical marker for increased bone turnover [27]. The noninflammatory mechanism for myopathy typically does not cause an increase in circulating muscle enzymes [28], which can lead to confusion with other lab-negative syndromes of musculoskeletal pain (such as fibromyalgia or osteoarthritis), thus delaying effective diagnosis [29]. Treatment of the underlying deficiency results in improvement of muscle strength, typically within two months [26,28].

The mechanism for myopathy in individuals with low vitamin D is incompletely understood (Fig. 2). Decreased availability of 25OHD leads to mishandling of cellular calcium transport to the sarcoplasmic reticulum [30] and mitochondria [31], and is associated with reduced actomyosin content of myofibrils [32].

Immune dysregulation

Vitamin D is essential for an appropriately responsive immune system [33–37]. Inadequate vitamin D clinically results in individuals who are more at risk for infections and inflammation involving the upper and lower airway. Understanding that much of the cardiovascular morbidity of OSA is mediated via systemic inflammation [38], and that daytime sleepiness in such patients may be mediated, in part, by inflammatory cytokines [39], the notion that low vitamin D may promote systemic inflammation is highly relevant. What follows will be a brief review of the association between vitDd and immune dysregulation in a general sense.

Tuberculosis infection [40] and reactivation [41] were more likely in patients with low vitamin D; children with rickets were more likely to suffer from pneumonia [42]. An inverse relationship was reported between latitude (a surrogate for sunlight exposure, and thus for vitamin D availability) and influenza infections [43]. Supplementation with vitamin D and calcium decreased the risk in children for subsequent upper-respiratory infection [44].

Studies in several areas suggested that vitamin D provided protection against the consequences of some autoimmune diseases [45]. Vitamin D was protective against the development of multiple sclerosis (MS) [46] and inflammatory bowel disease [47]. Treatment of MS was enhanced by the addition of vitamin D supplementation to standard therapy [48], though results are mixed [49]. Severity of rheumatoid arthritis was related to 25OHD levels [50]. Intervention trials with vitamin D in rheumatoid arthritis showed benefit in some trials, but none in others [10].

Immune dysregulation and/or propensity for infection may result in tonsillar hypertrophy, a risk factor for sleep-disordered

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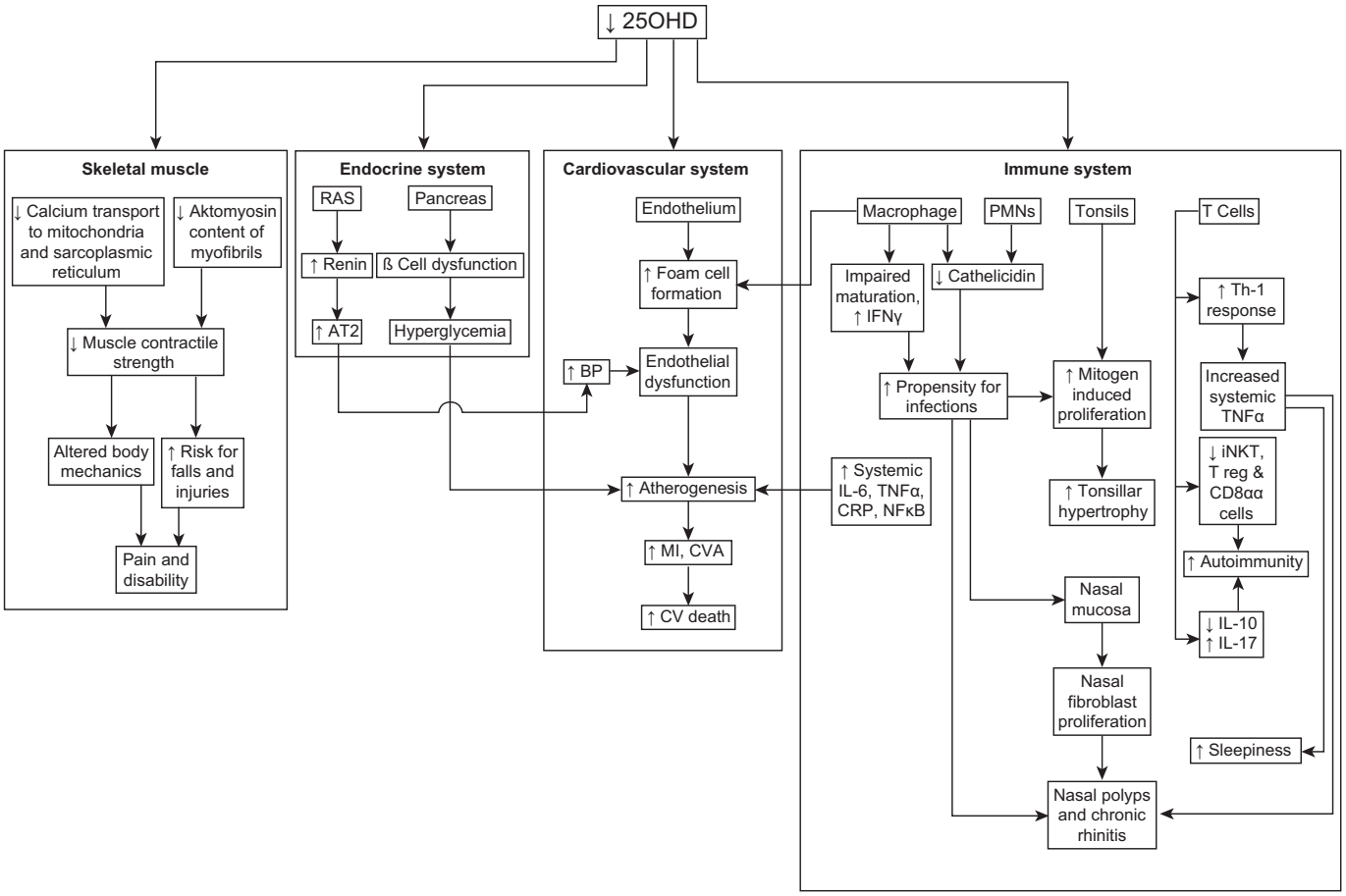

Fig. 2. Proposed mechanisms of diseases associated with vitamin D deficiency. 25OHD, 25-hydroxyvitamin D; AT2, angiotensin 2; BP, blood pressure; CD8[α α], cluster of differentiation 8 alpha alpha; CRP, C-reactive protein; CV, cardiovascular; CVA, cerebrovascular accident; IFN[γ], interferon-[γ]; IL, interleukin; iNKT, invariant natural killer T cells; MI, myocardial infarction; NF[κ]B, nuclear factor [κ]B; PMNs, polymorphonuclear cells; RAS, renin angiotensin system; TNF[α], tumor necrosis factor-[α]; T reg, regulatory T cells.

breathing. In children undergoing adenotonsillectomy, 78% had 25OHD levels <30 ng/mL and 25OHD levels were inversely correlated with tonsillar size [51].

Patients with low 25OHD have an increased risk for development of asthma [52] and allergic rhinitis [53–55]. Low 25OHD levels were documented in urban-dwelling African-American children with chronic rhinosinusitis [56], and 1-25OHD was shown to inhibit *in vitro* proliferation of nasal-polyp fibroblasts [57]. Supplementation using vitamin D showed some promise for the treatment of these chronic conditions [58].

The mechanisms by which vitamin D interacts with the immune system are many and complex (Fig. 2). A 25OHD-mediated induction in macrophage maturation and cytotoxic activity might underlie the increased risk for infection associated with chronically low vitamin D [59]. Vitamin D was shown to induce cellular production of cathelicidin, an antimicrobial peptide involved in nonspecific immunity [60]. The production of macrophage-derived IFN-γ, important for antimicrobial defense, appeared to be controlled by 25OHD [61]. Tonsillar hypertrophy may be driven by recurrent infections, or by dysregulation of tonsillar response: 1-25OHD is capable of preventing mitogen-induced proliferation of tonsillar tissue *in vitro* [62].

Chronically low vitamin D altered immunomodulation, favoring unregulated Th-1 over Th-2 immunity, an imbalance which favors a proinflammatory milieu and can promote tissue destruction and human disease [36]. This resulted in an antigenically-stimulated upregulation in multiple pro-inflammatory cytokines including TNF-α, which possibly explains the development of chronic rhinitis [53].

Essentially all cells of the immune system express the vitamin D receptor (VDR), the stimulation of which appears necessary for the production of specialized T cells important for protection against autoimmunity, including regulatory T cells (T reg), invariant natural killer T-cells (iNKT) and, in the gut, cluster of differentiation 8-alpha alpha (CD8(α α)) cells [47,63]. 1-25OHD reduced the antigen-presenting activity of macrophages by reducing the expression of surface major histocompatibility complex-II (MHC-II) molecules [10]. In healthy volunteers, high-dose vitamin D supplementation increased the anti-inflammatory cytokine IL-10, and decreased the production of T cells elaborating IL-17, a cytokine believed to play a key role in the pathogenesis of MS, type 1 diabetes, and inflammatory bowel disease [64].

Cardiovascular disease

Much attention has been paid to the notion that OSA increases the risk for adverse cardiovascular events [65,66], despite the perplexing observation that many patients with OSA are clinically asymptomatic and manifest no signs of cardiovascular disease [67]. Clearly other entities must act as cofactors to increase individual susceptibility to the development of disease. A growing body of literature supports the position that persistent inadequacy of vitamin D contributes to the burden of cardiovascular disease (Fig. 1) [68].

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Chronically low vitamin D appears to contribute directly to the development of systemic hypertension and cardiovascular disease. Ultraviolet light and oral vitamin D were shown to lower systolic and diastolic blood pressure by 6 mmHg [69,70]. An inverse correlation between 25OHD and risk for myocardial infarction was found [71]. Low vitamin D impaired insulin secretion and promoted insulin resistance [10].

Myopathy due to inadequate vitamin D may also involve myocardial tissue. Patients with severe congestive heart failure (CHF), as demonstrated by the biochemical marker N-terminal pro-atrial natriuretic peptide (NT proANP), had lower levels of 25OHD [72]. Patients with CHF who received 25OHD supplementation exhibited reduced PTH levels and a down-regulation of systemic inflammation (reduced TNF-α and increased IL-10) [73].

A recent study of adults referred for polysomnographic testing due to clinical concern for OSA provided a further clue that abnormally low levels of vitamin D were related to the development of OSA-associated cardiovascular disease [74]. In the cohort studied, indices of impaired glucose tolerance tracked 25OHD levels (lower levels correlated with worse glycemic control). In another study, oral vitamin D supplementation significantly decreased multiple markers of inflammation (TNFα, IL-6, and high sensitivity C-reactive protein (CRP)) in adults with diabetes [75].

The mechanism by which low vitamin D contributes to cardiovascular risk is complex (Fig. 2). The effects on systemic inflammation (described previously) likely figures prominently. Poor availability of 25OHD promoted an upregulation of renin, with a resulting increase in circulating angiotensin 2, leading to chronic elevation in blood pressure [76]. Atherogenesis may be accelerated due to increased foam-cell formation [77]. Myocardial cell and endothelial proliferation are also possibly regulated by vitamin D [78]. An increased propensity toward hyperglycemia and diabetes is another possible explanation [68].

Clinical and experimental evidence for a link between vitamin D and sleep disorders

Although clinical research regarding the relation between vitamin D and sleep is ongoing (Table 4), little has been published regarding direct investigations of the role of vitamin D metabolism in the presentation of WIS and sleep disorders. Nevertheless, the available reports, taken together with what is known about skeletal and nonskeletal diseases associated with vitamin D inadequacy, suggest the possibility that altered vitamin D metabolism plays an important role in the presentation and severity of sleep disorders (Fig. 1).

VitDd (25OHD $<$ 20 ng/mL) was found in over half of the subjects in a cohort admitting to the presence of nonspecific musculoskeletal pain during a comprehensive sleep-medicine specialty evaluation [79]. Surprisingly, this study occurred at a center located in the American south (latitude 32°N), an area presumed to be geographically protective against the development of deficiency, due to the short winter season.

A woman with a clinical syndrome indistinguishable from idiopathic central nervous system (CNS) hypersomnia experienced a complete resolution of her daytime hypersomnolence following treatment for severely low vitamin D (25OHD = 5.9 ng/mL) [80]. The improvement could not be explained by changes in lifestyle, sleep schedule, medications, or other identifiable factors. An alteration in systemic metabolism associated with low vitamin D levels may have directly promoted the sleepiness via a central signaling mechanism.

If low vitamin D contributes to sleepiness through such central signaling, inflammatory mediators are likely to be involved. The sleep regulating substances TNF-α and IL-1 both exhibited inverse relationships with 25OHD [81,82]. It might be argued that patients with higher degrees of systemic inflammation are likely to behave in ways that promote poor vitamin D production (avoiding sunlight, for example), but the observation that 25OHD inhibited macrophage production of TNF-α following stimulation by lipopolysaccharide suggested that the inverse relationships were actually causal rather than simple association [83].

Prostaglandin D2 (PD2), another central regulator of sleep, likely contributes to symptoms of sleepiness in OSA [39]. Vitamin D has the ability to down-regulate cyclooxygenase-2 (the rate controlling enzyme for production of PD2) in prostate tissue [84], implying that inadequate vitamin D could result in an increase in circulating PD2. Whether vitamin D status and biologically-relevant circulating levels of PD2 are correlated is presently unknown.

The evidence directly linking vitamin D status to WIS in general or to EDS specifically is scanty. 25OHD was inversely related to fatigue severity in a cohort of patients with traumatic brain injury [85], and to the severity of depression among adolescents [86].

We found a significant ($P < 0.05$) association between the symptom of sleepiness and 25OHD [87]. In a consecutive cohort of patients undergoing an initial sleep medicine evaluation, those who admitted to the presence of chronic musculoskeletal pain underwent venous blood sampling for 25OHD and completed an Epworth sleepiness scale (ESS) questionnaire. Among patients who were not vitamin D-deficient (25OHD $\geq$ 20 ng/mL), 25OHD and ESS score were inversely correlated (lower 25OHD associated with more sleepiness). Among patients with 25OHD <20 ng/mL, we

Table 4
Ongoing clinical studies exploring the link between vitamin D, wake impairment symptoms, and sleep disorders.

ClinicalTrials.gov Identifier	study title	Location	Outcomes of interest to sleep medicine clinicians
NCT01323218	Sleep apnea syndrome and vitamin D	University Hospital, Clermont-Ferrand	Effect of 400,000 IU oral vitamin D on OSA severity, inflammatory markers, and various measures of WIS
NCT00715429	Vitamin D for painful nocturnal leg cramps	University of Wisconsin, Madison	Randomized controlled study comparing effects of oral vitamin D and placebo on frequency and severity of nocturnal leg cramps in an elderly population
NCT00974922	Vitamin D deficiency in patients with hypertension	University of Connecticut Health Center	Effect of vitamin D on average blood pressure
NCT0153508	Open label trial vitamin D in children with autism	University of California, San Francisco	Effect of vitamin D on clinical global impression of improvement (CGI-I) in children with autism
NCT01385462	Factors associated with respiratory failure in obesity	University of Oxford	Measures of hormonal and nutritional status including vitamin D

IU, international units; OSA, obstructive sleep apnea; WIS, wake impairment symptoms.
Data from www.clinicaltrials.gov, accessed 30 May 2012.

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unexpectedly found that the 25OHD and ESS score were *directly* correlated in African-American but not Caucasian patients; African-American patients also had significantly lower 25OHD levels and significantly higher ESS scores. In other words, as 25OHD dropped among this group of sleepy, vitamin D-deficient African-American patients, the ESS score fell—although the subjects remained sleepy, they were incrementally less so at lower 25OHD levels. One explanation for the results was that the chronic perennial burden of abnormally low vitamin D in African-American patients provoked a different phenotype of clinical disease, possibly by giving rise to increased triggering of sympathetic nervous system or HPA-axis stress-response, acting as a countermeasure to sleepiness as 25OHD decreased still further. The underlying trigger for such a response might be increasing degrees of physical pain. Further research is needed to clarify these issues.

Given the previously mentioned associations between low vitamin D, myopathy, tonsillar hypertrophy, and rhinitis, it follows that persistently low vitamin D levels may predispose to the development of OSA (Fig. 1). If so, the heavy burden of chronically low vitamin D levels among African-American compared with Caucasian patients provides a biologically plausible mechanism for the frequent observation that OSA is more common—and is associated with greater morbidity—in African-Americans compared to Caucasians, even after adjustment for elements such as AHI, gender, habitus and age [88,89]. It also offers a novel insight to the poorly-understood observation that African-American patients have higher ESSs compared with Caucasians [90–92].

If chronically low vitamin D elevates the risk for nasal airflow limitation, the impact on sleep could be significant. An increased risk for sleep-disordered breathing is a predictable result from the nasal airflow limitation in children and adults. Children with chronic nasal airflow limitations are more likely to develop facial features associated with chronic mouth breathing, including elongated faces, high arched palate, and retro-positioned mandible [93–95], all of which would negatively impact breathing during sleep. A recent study revealed that low socioeconomic status was a risk factor for development of pediatric OSA, even after controlling for BMI and race, a result which the investigators admitted they had difficulty explaining [96]. Given the observation that poverty may constitute a risk factor for pediatric vitDd [12], the possibility of this condition functioning as a cofactor for clinical OSA disease again surfaces.

A recent epidemiological study supported the possibility of the link between OSA and abnormally low vitamin D levels [74]. In a cohort of 190 adults referred for polysomnographic testing, an inverse correlation was found between circulating 25OHD and OSA severity. Those with the most severe apnea (AHI $\geq$ 30) had significantly lower 25OHD compared to those with AHI <5. These findings were corroborated by Mete et al., who found that vitamin D deficiency (defined in this study as 25OHD $<$ 10 ng/mL) was significantly more common amongst those with OSA compared with controls, and that those with severe OSA had significantly lower 25OHD levels compared to those with moderate, mild, or no OSA [97].

Conclusion

Abnormally low levels of vitamin D are common in populations seeking care for sleep-medicine complaints, and may be causes or contributors to common sleep-disorder symptoms including chronic nonspecific pain, reduced subjective sleep quality and impaired experience of wakefulness. Evidence is mounting that persistently low vitamin D elevates the risk for cardiovascular disease, chronic systemic inflammation, and, possibly, obstructive sleep apnea. Sleep medicine specialists should be familiar with the scope of disease potentially caused by inadequacy of this essential hormone, and should be vigilant regarding detection and proper treatment. Further research will assist in determining the extent to which proper vitamin D replacement impacts the risk for—and morbidity associated with—problems typically managed by sleep-disorders specialists.

Practice points

1) Skeletal diseases associated with inadequate vitamin D include rickets and osteomalacia. These disorders are clinically characterized by a significant degree of physical pain, which is likely to have an adverse effect on sleep quality, and likely to result in symptoms of impaired wakefulness.
2) Nonskeletal diseases associated with inadequate vitamin D include myopathy, increased susceptibility to infection, an increased risk for autoimmune disease, increased susceptibility for asthma and chronic rhinitis, and cardiovascular diseases, including hypertension, increased systemic inflammation, and worsening glycemic control.
3) Vitamin D deficiency (25-hydroxyvitamin D $<$ 20 ng/mL) is common among patients complaining of nonspecific musculoskeletal pain, and among patients seen in a sleep medicine clinic who admit to chronic pain during a sleep medicine comprehensive evaluation.
4) Clinical risk factors for chronically low vitamin D include dark skin tone, obesity, limited natural sunlight exposure, pregnancy, chronic anticonvulsant use, chronic steroid use, and intestinal malabsorption syndromes.
5) Emerging data suggests that chronically low vitamin D is related to symptoms of sleepiness and other symptoms of wake impairment.
6) Chronically low vitamin D may be a cofactor for the development of OSA and OSA-associated cardiovascular disease.

Research agenda

1) Controlled studies are needed to further explore the relation between inadequate vitamin D and daytime neurocognitive impairment. Because daytime neurocognitive impairment includes symptoms that are often vague or nonspecific, the needed research will require appropriate quantification of symptomatology (such as nonspecific pain), quality of life, mood symptoms, and higher cognitive functioning.
2) The role of inadequate vitamin D in the development of obstructive sleep apnea and associated morbidity needs further elucidation in studies focused on the relationship between low vitamin D and the development of predisposing obstructive upper airway anatomy, and on determining whether vitamin D status helps explain the link between cardiovascular disease and OSA. Determining whether vitamin D status influences the development of sleep apnea in pediatric patients is a high-priority area.
3) More information is needed regarding the link between circulating 25OHD and symptoms of sleepiness. The cost/benefit of such studies is high because they can be incorporated into a sleep medicine practice while

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producing relatively little disruption. The studies should focus on the relationship between circulating 25OHD levels and subjectively reported sleepiness (such as the Epworth sleepiness scale score), objectively measured sleepiness (such as multiple sleep latency testing) and on sleep regulatory substances, with particular attention to PD2 and TNF-α. Given the possibility that chronic perennial exposure to low 25OHD may influence these relationships, the studies should allow for determination of any seasonal variation in 25OHD levels.

4) The benefits of successful vitamin D replacement with respect to symptoms of wake impairment, excessive daytime sleepiness and obstructive sleep apnea severity needs to be evaluated in carefully controlled studies.

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