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THEORETICAL REVIEW

The link between vitamin D metabolism and sleep medicine

David E. McCarty [a,*], Andrew L. Chesson Jr. [a], Sushil K. Jain [b], Andrew A. Marino [a]

[a] Division of Sleep Medicine, Department of Neurology, Louisiana State University Health Sciences Center, P.O. Box 33932, 1501 Kings Highway, Shreveport, LA 71130, USA
[b] Department of Pediatrics, Louisiana State University Health Sciences Center, USA

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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.

* Corresponding author. Tel.: +1 318 675 8568; fax: +1 318 675 4440.
E-mail address: dmcca1@lsuhsc.edu (D.E. McCarty).

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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;