24. Vitamin D deficiency, sleep, sleep disruption, and daytime neurocognitive impairment

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Abstract

Vitamin D is a fat-soluble secosteroid that interacts with intranuclear vitamin D receptors (VDRs) to effect changes to DNA transcription. VDRs are located in numerous tissues of the body, including brain, components of the immune system, and skeletal muscle. Worldwide, vitamin D deficiency (VDd) is highly prevalent, with identified risk factors including dark skin pigmentation, obesity, advanced age, limited sun exposure, pregnancy, and chronic use of steroids or anticonvulsant medications. VDd causes diseases of bone demineralization known as rickets (demineralization at epiphyseal growth plates) and osteomalacia (demineralization at areas of increased bone turnover) and a painful myopathy of skeletal muscles (osteomalacic myopathy). Research on VDd and its interaction with sleep is scant, though circumstantial evidence suggests that a complex relationship is likely to exist. VDd-related pain likely promotes sleep disruption directly. VDd is associated with increases in the sleep-regulating substances TNF-α and IL-1, and possibly prostaglandin D2, suggesting that VDd may be a cofactor for the development of daytime neurocognitive impairment. VDd may also increase the risk for obstructive sleep apnea (OSA), via promotion of adenotonsillar hypertrophy, airway hypotonia, and chronic rhinitis. Further research is needed to establish the complex relationship between VDd, normal sleep, sleep disruption, and daytime neurocognitive impairment.

Keywords: vitamin D, sleep, sleepiness, obstructive sleep apnea, osteomalacia, rickets

Abbreviations

BMI	Body mass index
COX-2	Cyclooxygenase 2
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
IH	Idiopathic central nervous system insomnia
IL	Interleukin
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PD2	Prostaglandin D2
PTH	Parathyroid hormone
SRS	Sleep regulatory substance
TNF-α	Tumor necrosis factor α
VDd	Vitamin D deficiency
VDR	Vitamin D receptor

24.1 Introduction

The last decade witnessed an intense surge of interest in vitamin D, fueled by an increasing awareness of the widespread distribution of VDR in various tissues of the body, including brain, various components of natural and specific immunity, myocardium, skeletal muscle, prostate, and breast. Published studies in the past several years have yielded compelling data suggesting an inverse relationship between circulating 25-hydroxyvitamin D, natural sun exposure (or both) and risk for a diverse array of human diseases, including schizophrenia, multiple sclerosis, cardiovascular disease, and various cancers. VDd has been shown to be associated with increased risk for falls, depression, heart failure, progression of chronic obstructive pulmonary disease, and risk for childhood asthma (Holick, 2007).

It is therefore somewhat surprising that vitamin D remains essentially unexplored as a sleep medicine issue. The purpose of this chapter is to examine the existing scientific evidence that vitamin D may be related to normal sleep, sleep disorders, and daytime neurocognitive impairment, particularly EDS. To do this, we must first review the basic biochemistry of vitamin D to provide a framework for the diseases well-appreciated to result from its deficiency. Following that will be a basic review of sleep, sleepiness, and sleep disorders. This will allow an understanding of how, potentially, VDd may participate in the creation or modification of pathologies of sleep and daytime neurocognitive impairment. Suggested questions for further research will then be listed, followed last by some concluding remarks.

24.2 Basic physiology of vitamin D

'Vitamin D' refers to a collection of fat-soluble secosteroids available from select dietary sources (Table 24.1) or manufactured in the human body in a multi-step process involving multiple compounds (Table 24.2).

Upon exposure to specific wavelengths of ultraviolet light (290-315 nm), 7-dehydrocholesterol transforms to vitamin D3 (cholecalciferol), the form of vitamin D which is found in animal products and a few commercially available supplements. Vitamin D2 (ergocalciferol) is a plant-derived product, formed when ergosterol is exposed to light. Most commercially available supplements contain this form.

In order to become biologically active, vitamin D (either D3 or D2) must undergo two hydroxylation reactions. First, it is transported in the bloodstream, bound to vitamin D binding proteins. In the liver, it is hydroxylated to form 25-hydroxyvitamin D (calcidiol), the 'storage' form of the vitamin. This compound reflects overall vitamin D supply from both dietary and light-induced manufacturing sources, and is typically measured by clinicians to determine vitamin D status. The second hydroxylation step occurs in the kidneys, enzymatically controlled by 25-hydroxyvitamin D-1α-hyroxylase, producing the biologically active form of the vitamin 1,25 dihydroxyvitamin D (calcitriol), regulated via a complex series of feedback loops by PTH, serum calcium and phosphorus levels, and by calcitriol itself.

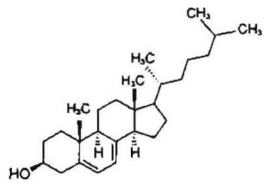
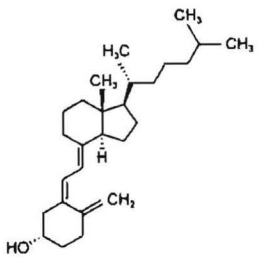
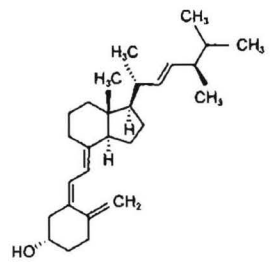
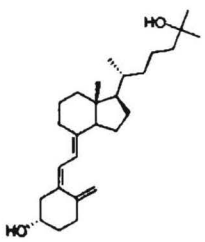
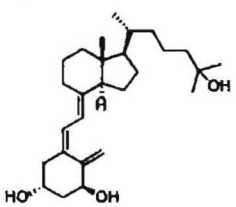
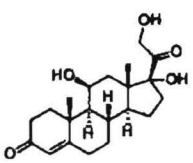
The structure of vitamin D is similar to that of steroid hormones, being 'built' as it is from the same cholesterol carbon skeleton as more 'familiar' steroid hormones, such as cortisol (Table 24.2).

Table 24.1. Dietary sources of vitamin D (adapted from Holick, 2007).

Source	Form of vitamin D	Approximate content
Sun dried shiitake mushrooms, 100g	Vitamin D2	1,600 IU
Cod liver oil, 5 cc	Vitamin D3	400-1000 IU
Wild-caught salmon, 100 g	Vitamin D3	800 IU
Canned salmon, 100 g	Vitamin D3	500 IU
Canned sardines, 100 g	Vitamin D3	300 IU
Canned mackerel, 100 g	Vitamin D3	250 IU
Farmed salmon, 100 g	Vitamin D3 or D2	200 IU
Fortified milk, 250 cc	Vitamin D3	100 IU
Fortified breakfast cereal, 1 serving	Vitamin D3	100 IU
Fresh shiitake mushrooms, 100 g	Vitamin D2	100 IU
Egg yolk	Vitamin D3 or D2	20 IU

IU = international unit.

Table 24.2. Forms of vitamin D and related compounds.

Form	Chemical structure
7-dehydrocholesterol	
cholecalciferol	
ergocalciferol	
calcidiol	
calcitriol	
cortisol	

Not surprisingly, it performs its biological functions in a 'hormone-like' way – in the nuclei of cells, effecting changes in DNA transcription. Calcitriol interacts with intranuclear VDRs and retinoid-X receptors, forming heterodimers that subsequently bind to specific regions of DNA and behave as transcription factors.

Some of the earliest understood functions of calcitriol include its actions on the gut and bone, which help maintain calcium and phosphate equilibrium. In the gut, calcitriol effects an increase in calcium absorption from the diet, by working to increase epithelial calcium channels and calcium binding proteins (calbindin 9K). In the bone, calcitriol induces the maturation of osteoclasts, which mobilize calcium and phosphorus from the bone. In the kidneys, it promotes calcium reuptake.

24.3 Diseases caused by vitamin D deficiency

In VDd, the body compensates by increasing production of PTH, promoting increased activity of renal 25-hydroxyvitamin D-1α hydroxylase, the enzyme responsible for increasing production of calcitriol. If this condition becomes chronic, the parathyroid glands may become constitutively overactive, with a resulting secondary hyperparathyroidism. As the condition continues, the calcium phosphate matrix of bone is increasingly tapped, and the bones become progressively demineralized. At some point, it is difficult for the body to maintain normal serum concentrations of calcium and phosphate, and the deficiency state becomes clinically more apparent.

The calcidiol level necessary to maintain optimum health is the subject of considerable debate. In general, PTH levels are inversely related to calcidiol (25-hydroxyvitamin D) at calcidiol levels of <75 nmol/l (Figure 24.1) (Chapuy *et al.*, 1997). For calcidiol levels >100 nmol/l, the PTH value reaches a nadir and remains flat. Intestinal calcium absorption is impaired at a level of 50 nmol/l, with a dramatic improvement in calcium absorption seen at a level of 75 nmol/l. For these reasons, most authorities set the benchmark for 'deficiency' at calcidiol levels <50 nmol/l and 'insufficiency' at <75 nmol/l (Holick, 2007). PTH levels remain normal in black individuals at lower values of calcidiol compared with Caucasians, suggesting that the definition of 'deficiency' may require adjusting for race (Wright *et al.*, 2012).

VDd has been described as a 'global pandemic'. The prevalence estimations depend heavily on the population under study, with risk factors including obesity, limited sun exposure, dark skin pigmentation, pregnancy, poverty, malabsorption syndromes (including prior gastrectomy, bariatric surgeries, and coeliac disease), chronic steroid use, chronic anticonvulsant use, and advancing age. There are several diseases known to be caused by VDd, which will be briefly reviewed in Table 24.3.

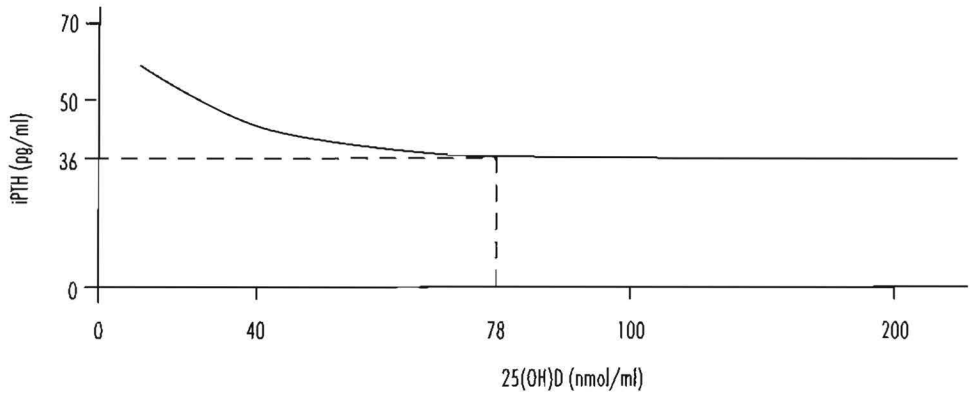


Figure 24.1. Relationship between intact parathyroid hormone (iPTH) and calcidiol (25 (OH) D) values in a population of urban dwelling adults (n=1,569). The iPTH plateau occurs at a calcidiol concentration higher than 78 nmol/l. When values are lower than 78 nmol/l, serum iPTH values begin to increase (Chapuy *et al.*, 1997).

Table 24.3. Diseases known to be associated with vitamin D deficiency.

Disease name	Pathophysiology	Clinical features	Notes
Rickets	inadequate bone mineralization at cartilage of ephiphyseal growth plates	bony pain, delayed closure of the frontal fontanelle, progressive bowing of the legs, enlargement of the costochondral junction	syndrome can also be caused by severe calcium- or phosphate deficient diets, malabsorption syndromes (e.g. celiac sprue), and renal phosphate wasting (e.g. Fanconi Syndrome)
Osteomalacia	inadequate bone mineralization at sites of newly formed osteoid in areas of bone turnover	bony pain & tenderness, muscle weakness, difficulty walking/ waddling gait; often associated with secondary hyperparathyroidism	syndrome can also be caused by renal phosphate wasting; correct diagnosis of osteomalacia is often delayed due to nonspecific symptoms
Osteomalacic myopathy	may involve defective cellular transport in skeletal muscle; hypocalcemia/hypophosphatemia may play a role	muscle pain, proximal muscle weakness, muscle wasting, difficulty walking	cofactor for development of statin-induced and aromatase-inhibitor-associated myopathy

24.3.1 Rickets

Rickets is the prototypical syndrome of childhood VDd. The classic skeletal malformations are caused by defective mineralization of the epiphyseal growth plates, and have readily-identifiable features. The 'rachitic rosary' is a description of the bulging appearance of the anterolateral costochondral junctions, draping across the thorax in a pattern similar to a necklace. The softened long bones bend with time and weight-bearing to form bowed legs in various patterns. Myopathic symptoms of weakness, diffuse pain, and general debility are common. An increase in generalized sweating, attributed to bone pain, is also noted. Individuals with rickets are understood to have an increased propensity for infectious diseases, possibly due to immune system dysregulation.

24.3.2 Osteomalacia

When bone mineralization is compromised in areas of bone turnover besides the growth plates, the term 'osteomalacia' is used. In children, osteomalacia may coexist with rickets. Adults with VDd have mineralization defects that occur exclusively in areas of bony turnover because the epiphyseal plates have closed. As with rickets, osteomalacia is associated with diffuse bone pain, likely related to increasing water content in the demineralized bone, leading to swelling, stretching the sensitive periostium (Holick, 2007). Typically, this symptom can be elicited by demonstrating marked tenderness of the tibial plateau.

24.3.3 Hypovitaminosis D myopathy

VDd can be accompanied by a painful myopathy syndrome (termed 'osteomalacic myopathy' or 'hypovitaminosis D myopathy'), with resultant proximal muscle weakness, diffuse muscle pain, and increased likelihood for falls and injury (Russell, 1994). VDd was recently identified as a cofactor for the development of statin-induced myopathic pain (Ahmed *et al.*, 2009). Many individuals who developed statin-induced myalgias experienced resolution of the syndrome upon identification and remediation of VDd. VDd is also a cofactor for aromatase-inhibitor associated myalgias, with supplementation shown to improve tolerability of these agents (Rastelli *et al.*, 2011). VDd is frequently found among patients presenting with chronic nonspecific musculoskeletal pain, patients often diagnosed as suffering from fibromyalgia or degenerative joint disease (Plotnikoff and Quigley, 2003). Furthermore, osteomalacic myopathy can occur in the absence of any elevation in serum alkaline phosphatase, the most widely-used indicator of osteomalacic bone turnover (Glerup *et al.*, 2000).

24.3.4 Secondary hyperparathyroidism

As mentioned earlier, secondary hyperparathyroidism often accompanies chronic VDd, the unregulated parathyroids mobilizing bony calcium to the point that hypercalcemia ensues. A complete review of the disease accompanying the hyperparathyroid state is beyond the scope of this chapter, but a classic medical-student mnemonic recalls the systemic nature of the disease: 'Stones, bones, groans, and moans.' Nephrolithiasis and nephrocalcinosis ('stones'), osteomalacia

and pathologic fractures ('bones'), abdominal complaints such as constipation, indigestion, and nausea ('groans'), and central nervous system complaints such as depression, lethargy, fatigue, and memory loss ('moans') are the key features of the disorder.

24.4 The biological regulation of sleep

'Sleeping' is a seemingly simple act that – when manifested in health – simply 'happens' with no requirement for effort on the part of the sleeper. In truth, the activity we universally accept as 'sleep' and the symptom we understand as 'sleepiness' result from a complex interplay of neurotransmission, metabolism, temperature, immunology, and psychology, the detailed discussion of which would fill an entire textbook and will not be attempted here. However, in order to introduce mechanisms by which VDd may contribute to sleep-related complaints, a basic discussion of some of the mechanisms of sleep is required.

The fundamental mechanism for sleep/wake regulation is best explained with the description of two independent systems (Figure 24.2) (Borbely, 1982). The first – termed 'Process S'– is best understood as a wake-driven homeostatic sleep 'pressure' which builds while the individual is awake and diminishes during sleep. There are many biological substrates mediating Process S – termed 'sleep regulatory substances' – the best-studied of which are adenosine, PD2, IL-1, and TNF-α (Opp, 2005).

While process S can be best conceived of as a 'use-dependent' phenomenon (i.e. the more time spent awake, the greater the sleep propensity), process C ('C' for 'circadian') is a phenomenon independent of prior wakefulness. Process C is driven instead by the suprachiasmatic nuclei, a

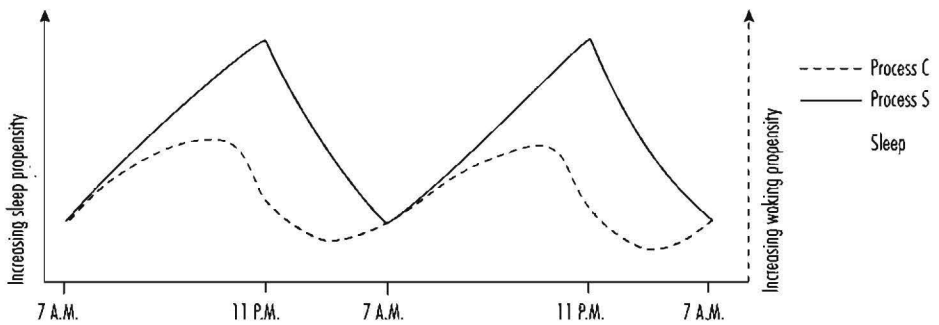


Figure 24.2. Process S and process C. Sleep propensity can be explained with a dual-process model. 'Process S' (solid line) builds during wakefulness in a use-dependent fashion ('sleep pressure'), and dissipates during sleep. The left sided y-axis shows that if process S increases, increased sleep propensity is seen. Process C is 'clock-driven,' and functions to stabilize wakefulness despite mounting homeostatic sleep pressure. Process C is most active during the second half of the waking day, and relatively quiescent during sleep. The right-sided y-axis shows that if process C increases, increased waking propensity is seen.

biological clock that achieves synchrony with the day/night variation of earth primarily via photic signaling from the retina to the hypothalamus. Process C is effected primarily via the activity of wake-promoting and wake-stabilizing neurotransmitters of the ascending reticular activating system (including hypocretin, acetylcholine, dopamine, norepinephrine, and histamine), with additional modulation from melatonin, which in humans has mild hypnotic (sleep-inducing) effects and also exerts circadian phase-dependent effects on the timing of the circadian rhythm itself.

24.4.1 Sleepiness, excessive daytime sleepiness, and daytime neurocognitive impairment

The feeling commonly described as 'sleepiness' can be functionally defined as 'having an increased propensity to fall asleep.' Though sleepiness can be a comforting feeling when it is physiologically normal (i.e. at the end of a long working day), it can be an unwelcome or even disabling symptom when it is chronic or unrelieved by the act of sleeping itself.

By far, the most common etiology for EDS is insufficient sleep, but some persons experience chronic EDS despite what would be considered adequate time spent asleep at night. A complete sleep-related history, physical exam, and polysomnography in such settings may reveal evidence for chronic sleep disruption due to specific diseases, such as OSA, restless leg syndrome or a sleep-related movement disorder such as periodic limb movements of sleep. Other individuals suffer from EDS caused by dysfunction of sleep regulation, conditions termed 'primary hypersomnia' syndromes, examples of which are narcolepsy and IH.

The term 'neurocognitive impairment' is often used to describe the myriad symptoms aside from EDS which can result from inadequate sleep. Somatic symptoms such as headaches, irritable bowel complaints, and muscle pain are all commonly associated with sleep deprivation. Mood disturbances such as anxiety or depression are also commonly reported. Sleep deprivation-induced deficits in alertness and concentration may result in an inappropriate diagnosis of attention deficit disorder (McCarty, 2010a). The nonspecificity of these symptoms represents a unique challenge to the practicing sleep medicine specialist, in that any identifiable source of sleep disruption and/or daytime neurocognitive impairment should be sought and, if possible, specifically remedied. A methodical approach to complaints of subjective sleep disturbance or daytime neurocognitive impairment may reveal more than one etiology for such symptoms, potentially increasing the likelihood of successful intervention and improved outcomes (McCarty, 2010b).

24.5 Potential mechanisms by which vitamin D deficiency may contribute to sleep/wake complaints

Though VDd has potential to interact with sleep/wake-related complaints in a number of different ways, published research on this issue is limited. Nonetheless, there are data to support a causal link between VDd and conditions generally accepted to contribute to sleep/wake complaints (Figure 24.3).

24.5.1 Vitamin D deficiency, pain, and sleep

Individuals with chronic pain have poorer quality sleep and shorter sleep duration compared with individuals who report no such symptoms (Okura *et al.*, 2008). Moreover, individuals with decreased total sleep time report a higher degree of spontaneous daytime somatic pain symptoms, and are likely to report pain with a lesser degree of stimulation, compared with individuals who are not sleep-deprived (Edwards *et al.*, 2008). Sleep deprivation-associated increases in pain perception are likely to be mediated by increases in IL-6 (Haack *et al.*, 2007). Chronic pain also negatively impacts an individual's mood and outlook, which may further increase the subjective experience of daytime impairment, in the form of fatigue, despair, or depression (Nicassio *et al.*, 2002).

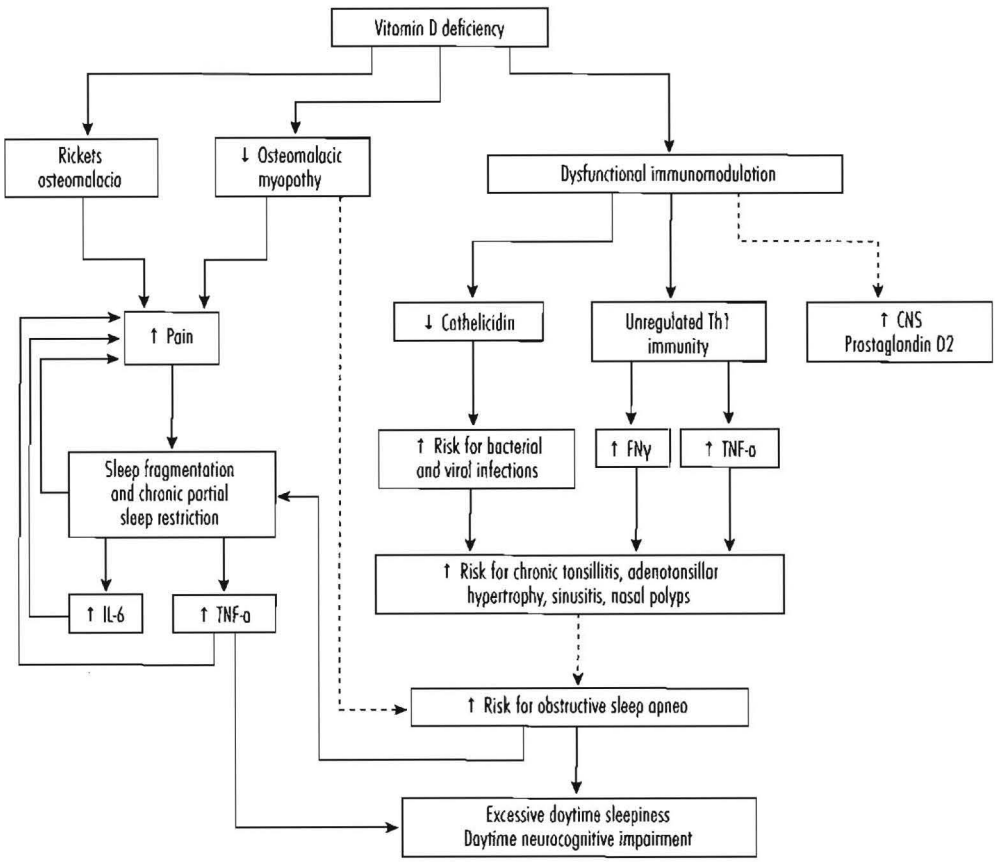


Figure 24.3. Mechanisms by which Vitamin D deficiency may interact with sleep/wake complaints. A dotted line indicates that the relationship is hypothesized, but not yet proven.
IL = interleukin; TNF-α = tumor necrosis factor α; FN = fibronectins; Th = T-cells helper

Many researchers have found that populations with nonspecific musculoskeletal pain have a high prevalence of undiagnosed VDd, suggesting that the presence of chronic nonspecific musculoskeletal pain should prompt careful consideration of possible deficiency (Holick, 2003). Similarly, among ambulatory sleep medicine specialty clinic patients endorsing chronic moderate-to-severe pain interfering with sleep or impacting daily activity, VDd (calcidiol <50 nmol/l) was found in over half (McCarty and Reddy, 2011).

A causal association between VDd and musculoskeletal pain is well-established, though many unanswered questions still exist. Some patients with documented severe VDd experience few somatic symptoms, while others may have pain that does not improve following appropriate supplementation of vitamin D, suggesting that the symptom was unrelated to the deficiency in the first place. Distinguishing *a priori* which patients will respond to supplementation is difficult.

24.5.2 Is there a link between vitamin D deficiency and obstructive sleep apnea syndrome?

OSA is term describing polysomnographic evidence of periodic obstruction of the upper airway during sleep, leading to intermittent hypoxia and/or hypercarbia affecting 2-4% of the adult population (Young *et al.*, 1993). The diagnosis of OSAS requires OSA to be associated with subjective sleep complaints or daytime neurocognitive impairment. Risk factors for the development of OSAS include obesity, large neck circumference, adenotonsillar hypertrophy, retropositioning of the mandible, low-lying or redundant soft palate, chronic nasal airflow limitation, and race – with Blacks, Hispanics, and Native Americans being higher risk, compared to Caucasians.

Daytime impairment symptoms in individuals with OSAS likely result from chronic partial sleep deprivation (frequent awakenings, difficulty returning to sleep due to sympathetic hyperstimulation) combined with the pro-inflammatory effects of intermittent hypoxia, which results in further elaboration of SRSs, particularly TNF-α and PD2 (Ryan *et al.*, 2008). However, polysomnographically-confirmed OSA has been described in individuals who fail to manifest any evidence of cardiovascular disease or daytime impairment (Pavlova *et al.*, 2008), underscoring the notion that there is variation in individual resilience against the physiologic stress of OSA, and suggesting that other elements (genetic, environmental, etc.) probably act as cofactors for the illness that results from it.

There are no published data directly addressing a possible relationship between VDd and OSAS. However, circumstantial evidence hints that such a relationship may exist, including anatomic changes to the upper airway which may result from VDd and the clustering of OSAS and VDd in similar at-risk populations. Furthermore, VDd may influence the presentation of OSA (or, for that matter, other sleep-disrupting forces) by directly stimulating the elaboration of cytokines promoting daytime neurocognitive impairment, particularly the SRSs TNF-α and PD2.

The fact that vitamin D deficiency contributes to hypotonia and myopathy of skeletal muscle is well-established (Russell, 1994). Heritable myopathies (e.g. Duchenne muscular dystrophy,

myotonic dystrophy) are known to place individuals at risk for OSAS. OSA following statin-induced myopathy (Ebben *et al.*, 2008) and steroid-induced myopathy (Yigla *et al.*, 2003) have been described. It is reasonable to speculate that VDd may elevate an individual's risk in a similar fashion, due to upper airway hypotonia combined with weakness of ventilatory skeletal muscles.

Upper airway crowding in OSAS is caused by anatomic factors besides pharyngeal hypotonia. One of the most important of these, particularly in children, is hypertrophy of the tonsils and adenoids. Evidence exists to support the idea that VDd predisposes to tonsillar enlargement. T-cell populations derived from human tonsils display decreased mitogen-induced proliferation in the presence of calcitriol, suggesting that vitamin D may offer protection from development of problematic tonsillar hypertrophy (Nunn *et al.*, 1986). If VDd contributes causally to tonsillar hypertrophy, it may also do so indirectly, via its immunologic impact on susceptibility to viral infection (Grant, 2009). Recent work complements these findings, noting low calcidiol levels in individuals who had undergone tonsillectomy for various reasons; those individuals with the greatest degrees of tonsillomegaly were most likely to have VDd (Reid *et al.*, 2011). Taken together, these data imply that VDd predisposes to adenotonsillar hypertrophy, and suggests that early identification and treatment may be of value.

The nasal airway is also an important source of upper airway resistance, and sources promoting chronic rhinitis and nasal polyposis would be expected to increase the risk for OSA. In children, chronic nasal airflow limitation can lead to obligate mouth-breathing, which can negatively impact facial skeletal development, leading to high-arched palate, bilateral maxillary posterior cross-bite and class II malocclusion, skeletal abnormalities that predispose to development of OSA.

Recent work is starting to illustrate how VDd impacts the nasal airway. There has been considerable interest recently on the impact of vitamin D on cellular and natural immunity. Vitamin D deficiency leads to altered immunomodulation, favoring unregulated Th-1 over Th-2 immunity (Kamen and Tangpricha, 2010). This results in an antigenically-stimulated upregulation in multiple pro-inflammatory cytokines (TNF-α among them), providing an explanation for the development of chronic rhinosinusitis (Abuzeid *et al.*, 2012). Epidemiologic and laboratory data are supportive of this: low calcidiol levels have been documented in urban-dwelling black children with chronic rhinosinusitis (Pinto *et al.*, 2008) and calcitriol was shown to inhibit nasal polyp fibroblast proliferation *in vitro* (Rostkowska-Nadolska *et al.*, 2009).

24.5.3 Can vitamin D deficiency independently lead to daytime neurocognitive impairment?

VDd may independently contribute to daytime neurocognitive impairment via dysfunctional immunomodulation. Recently reported was a case in which a young woman presented with symptoms highly suggestive of IH. Following identification and remediation of VDd, her EDS resolved (McCarty, 2010c). Objective measures of sleep did not explain the improvement in EDS symptoms, and it was postulated that the mechanism for improvement might involve changes in vitamin D-associated SRSs. This raises the interesting question of whether VDd could be an

independent cause of EDS, and/or behaves as a cofactor which increases the risk of developing symptoms in the setting of other sleep-disrupting forces, including OSA.

If VDd were indeed such a cofactor, one would expect (1) asymptomatic patients with OSA would have fewer risk factors for VDd compared with patients suffering from OSAS and (2) VDd and OSAS would be found in similar patients and would be associated with similar adverse health events. Though these issues have not been directly addressed in the scientific literature, circumstantial evidence implies that these relationships may exist.

The asymptomatic population studied by Pavlova *et al.* comprised physically-active adults of normal weight (BMI <30), a group with lower expected risk for VDd compared with groups considered to be high-risk for OSAS (obese patients, Blacks, Hispanics, Native Americans). Moreover, low socioeconomic status – itself a risk factor for development of VDd (Weng *et al.*, 2007) – was shown to be an unexpected risk factor for development of pediatric OSAS, even after controlling for BMI and race (Spilsbury *et al.*, 2006). In addition, mounting evidence suggests that VDd and OSAS are associated with common adverse cardiovascular outcomes. Like OSAS, VDd is linked to hypertensive disease, cardiovascular disease and the metabolic syndrome (Maki *et al.*, 2009).

If vitamin D is related to EDS, the relationship is likely to be complex. In patients with calcidiol ≥50 mmol/l, we found a statistically significant inverse trend between scores on the ESS and calcidiol levels (McCarty *et al.*, 2012). In patients with calcidiol <50 mmol/l (i.e. those with VDd), a significant *direct* relationship was seen in black patients (i.e. lower calcidiol leading to lower scores on the ESS), while a nonsignificant trend towards an inverse relationship was seen in white patients, suggesting that VDd likely provokes other changes to somehow counterbalance sleep-promoting factors in blacks, but not in whites. What these other factors might be is, at present, only the subject of speculation, but could include sympathetic stimulation due to pain or development of other disorders such as sleep apnea.

If VDd causes daytime neurocognitive impairment independently of other sleep disorders, it may do so via its effects on the immune system. The SRS TNF-α is a pro-inflammatory cytokine produced in humans mainly by macrophages, and is a part of the normal immune response to injury or infection. Sleep deprivation, acutely or chronically, can increase TNF-α levels in healthy subjects (Chennaoui *et al.*, 2011). Daytime neurocognitive impairment associated with chronic inflammatory conditions (e.g. multiple sclerosis, obstructive sleep apnea) may be mediated by TNF-α (Kos *et al.*, 2008). Moreover, many non-EDS symptoms commonly attributed to sleep loss (such as irritability, poor concentration, and enhanced sensitivity to pain) can be elicited simply by administration of TNF-α (Krueger *et al.*, 2011).

An inverse relationship between calcidiol levels and TNF-α has been shown to exist (Bellia *et al.*, 2011). In another study, two important SRSs (TNF-α and IL-1), were discovered to have an inverse relationship to circulating calcidiol levels (Khoo *et al.*, 2011). Furthermore, calcitriol was shown to inhibit macrophage production of TNF-α following stimulation by lipopolysaccharide, suggesting causality in the inverse relationship rather than mere association (Kuo *et al.*, 2010).

The SRS PD2 is derived from arachadonic acid, with the rate-limiting step being controlled by COX-2. It is proven to be a central regulator of sleep in animals and is likely to be one factor responsible for the symptoms of sleepiness in obstructive sleep apnea (Barcelo *et al.*, 2007). Vitamin D was shown to effectively down regulate the production of COX-2 in prostate tissue (Feldman *et al.*, 2007) suggesting that VDd could result in an increase in circulating PD2. At present, it is not known whether there is a correlation between vitamin D status and biologically-relevant circulating levels of PD2.

24.6 Research agenda

At present, much remains to be discovered about the role vitamin D may play in normal sleep, sleep disruption, and daytime impairment:

- Additional studies should be performed to determine if VDd directly causes daytime neurocognitive impairment. Because daytime neurocognitive impairment includes symptoms which are often vague or nonspecific, such research will require inquiry into physical symptomatology (such as nonspecific pain), quality of life, mood symptoms, and higher cognitive functioning.
- The role of VDd in the development of OSA and OSAS needs to be elucidated. Such studies should focus on the relationship between VDd and the development of predisposing obstructive upper airway anatomy, and in determining if vitamin D status helps explain the difference between asymptomatic OSA and OSAS.
- Whether VDd independently causes EDS needs to be investigated. Such studies would focus on the relationship between circulating calcidiol levels and subjectively reported sleepiness (such as the Epworth Sleepiness Scale score), objectively measured sleepiness (such as multiple sleep latency testing) and on SRSs, with particular attention to PD2 and TNF-α.
- The benefits of successful vitamin D replacement with respect to neurocognitive impairment symptoms, EDS and OSA severity needs to be evaluated.

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