

Does Low Vitamin D Status Contribute to “Age-Related” Morbidity?

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ABSTRACT: It is increasingly appreciated that vitamin D plays important physiological roles beyond the musculoskeletal system. As such, it is plausible that endemic vitamin D deficiency contributes to much nonskeletal morbidity that adversely affects quality of life with advancing age among older adults. This overview will explore the evidence for, and potential involvement of, vitamin D deficiency in nonbone conditions that are currently accepted as “age-related” morbidity among older adults.

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INTRODUCTION

ADVANCING AGE IS ASSOCIATED with a decline in function of multiple organ systems leading to a high prevalence of classical “geriatric” syndromes in older adults. Examples of these morbidities include osteoporosis and fracture, falls, dementia, urinary incontinence, malnutrition, and sensory impairment.⁽¹⁾ These and other chronic conditions currently account for 80% of all medical care expenditures.⁽²⁾ Importantly, the number of older adults is rapidly increasing, and it is estimated that the number of older Americans will grow by almost 60% from 2000 to 2020 from 35 to 55 million.⁽³⁾ This demographic imperative requires study and implementation of measures to reduce the personal and societal burden of these “age-related” chronic diseases.

In this regard, it has been proposed that the development of morbidities with advancing age can be postponed (i.e., that what is widely accepted as “age-related” morbidities are not solely dependent on chronologic age).⁽⁴⁾ This premise, often referred to as the compression of morbidity hypothesis, suggests that effective preventive strategies will minimize and compress morbidity into a short period toward the end of life.⁽⁵⁾ Such “rectangularization” of the survival curve would, ideally, minimize lifetime disability and potentially reduce personal burden and health care expense.^(4,5) To this end, it has recently been stated that “Increasing our understanding of the aging process and applying available interventions will greatly enhance healthy aging.”⁽⁶⁾ Given that vitamin D deficiency is epidemic among older adults,^(7,8) is it plausible that low vitamin D status contributes to the development of what is currently accepted as “age-related” morbidities? If so, would optimization of vitamin D status be one of the aforementioned

interventions to prolong active life, compress morbidity, and reduce health care expenses?

DISCUSSION

The autocrine/paracrine importance of vitamin D is becoming increasingly widely recognized.^(9,10) Thus, it is logical that endemic low vitamin D status could adversely impact function of multiple organ systems. For example, it is widely known that vitamin D deficiency is associated with increased osteoporotic fracture risk,^(11,12) but less well appreciated is that low vitamin D status is associated with other common geriatric syndromes including sarcopenia, falls, urinary incontinence, respiratory disease, and sensory/neurologic impairment. The evidence, albeit limited, to support this contention follows.

Because vitamin D receptors are present in human muscle tissue,⁽¹³⁾ a direct effect of vitamin D on muscle physiology is probable.⁽¹⁴⁾ Additional effects of vitamin D on muscle function, potentially mediated through effects on intracellular calcium homeostasis,⁽¹⁵⁾ are probable. Thus, it is not surprising that vitamin D deficiency has long been clinically associated with impaired muscle strength^(16–19) and also is associated with loss of muscle mass.⁽²⁰⁾ Because muscle weakness is a major risk factor for falls,⁽²¹⁾ it should be expected that low vitamin D status would be associated with an increased falls risk; this observation has been reported in a recent longitudinal study.⁽²²⁾ Moreover, a recent meta-analysis confirmed that vitamin D treatment reduces falls risk by ~20% in older adults.⁽²³⁾ It is likely that a substantial portion of the antifracture efficacy of vitamin D reflects improved muscle performance and lower risk from falls.

Thus, there is a substantial body of data documenting clinically important effects of vitamin D deficiency on lower extremity muscle function in older adults. Given that vitamin D is important for optimal leg muscle function and that many common geriatric syndromes may be related to muscle weakness, it is plausible that vitamin D deficiency

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could be a unifying causal factor contributing to the observed concomitant occurrence⁽²⁴⁾ of “age-related” morbidities.

One such syndrome could be bladder dysfunction in that bladder musculature possesses vitamin D receptors and responds to vitamin D analogs.^(25,26) Urinary continence obviously requires coordinated muscle function with relaxation of the bladder detrusor allowing the bladder to fill, followed by detrusor contraction with concomitant sphincter relaxation at a time controlled by the individual. However, overactive bladder (the symptom complex of urinary frequency and urgency with or without incontinence)⁽²⁷⁾ becomes extremely common with advancing age. A recent survey found urinary incontinence to occur in 45% of older women, increasing to 55% among those >80 yr of age.⁽²⁸⁾ Urinary incontinence is associated with reduced quality of life, including an increased risk for falls, fractures, depression, and nursing home admission.^(29,30) Despite the plausible association of low vitamin D status with bladder dysfunction, only a single study has investigated this relationship. Specifically, a longitudinal study, in which 5816 community-dwelling women >40 yr of age completed a postal survey, found that a higher dietary vitamin D intake was associated ($p < 0.01$) with lower risk of the onset of overactive bladder. These authors appropriately concluded “The potential role of vitamin D in the function of the detrusor muscle needs to be considered.”⁽³¹⁾

An additional common morbidity of advancing age is swallowing impairment (dysphagia), which occurs in from 10% to 40% of those >50 yr of age⁽³²⁾ and has important consequences such as undernutrition, sarcopenia, and aspiration pneumonia. Although it has classically been felt that the dysphagia increase with advancing age reflects neurologic disease, recent work documents that normal healthy older adults swallow more slowly and generate lower tongue pressures than do younger adults.^(33,34) As such, muscle weakness could contribute to swallowing difficulties with advancing age. Moreover, it is intuitively apparent that swallowing is a complex process requiring coordinated muscle function. Thus, low vitamin D status with impaired muscle performance could be associated with dysphagia. However, to this point in time, no evaluation of this possibility has been performed.

Additionally, nonmuscular effects of low vitamin D status could contribute to morbidities associated with aging. One such example may be pulmonary function, for which two commonly measured parameters, forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁), both decline with advancing age. This deterioration of function may contribute to increased risk of pneumonia, which becomes an increasingly common cause of death with advancing age. Interestingly, a recent cross-sectional study of pulmonary function found that older individuals with the highest 25(OH)D level had greater FVC and FEV₁ values.⁽³⁵⁾ This association is biologically plausible⁽³⁶⁾ because vitamin D modulates fibroblast proliferation and collagen synthesis. As lung tissue, like bone, undergoes repair and remodeling throughout life, vitamin D deficiency might impair this repair process.⁽³⁵⁾ Additionally, an effect on declining pulmonary function with age could potentially be

immune mediated, because inflammatory mediators are believed to play a major role in causing lung damage leading to chronic obstructive pulmonary disease.⁽³⁷⁾ Vitamin D's immune-modulating effects⁽³⁸⁾ could conceivably reduce lung inflammation and thereby retard the decline observed with advancing age.

Finally, it is plausible that low vitamin D status contributes to the development of sensory and cognitive deterioration with age. For example, low vitamin D status has recently been associated with increased risk for the presence of early age-related macular degeneration,⁽³⁹⁾ the most common cause of legal blindness among white Americans.⁽⁴⁰⁾ Because inflammation/immune complex disease may be associated with the development of macular degeneration,⁽⁴¹⁾ a role of vitamin D in its pathogenesis is possible. In addition to a potential role in “age-related” visual impairment, vitamin D inadequacy might be involved in dementia. Specifically, severe vitamin D deficiency has been reported in women with Alzheimer's disease at the time of their nursing home admission.⁽⁴²⁾ Moreover, circulating 25(OH)D concentration has recently been positively correlated with mini-mental status examination results of older adults.⁽⁴³⁾ Cognitive decline is an extremely common and important “age-related” morbidity whose incidence increases markedly with advancing age such that the annual incidence exceeds 8% for those >85 yr of age.⁽⁴⁴⁾ It has been estimated that >2% of the U.S. population will be affected by Alzheimer's disease in 2040.⁽⁴⁵⁾ Much like osteoporosis, the pathogenesis of cognitive decline may be a lifelong process that manifests in later life, thus making prevention efforts essential. In this regard, it is feasible that vitamin D might be important for normal neural function⁽⁴⁶⁾ because vitamin D₃ 25-hydroxylase and 25-hydroxyvitamin D₃-1 α -hydroxylase are present in brain tissue.⁽⁴⁷⁾ Potential mechanisms of a vitamin D effect on neural function could potentially include 1,25(OH)₂D-mediated increases in choline acetyltransferase (documented in rats)⁽⁴⁸⁾ and/or increased nerve growth factor synthesis.^(49,50) Moreover, it is plausible that vitamin D enhances neuroprotection from ischemic or toxic insults,^(51,52) potentially through induction of calcium binding proteins in the brain.⁽⁵³⁾

In summary, it is attractive to speculate that low vitamin D status contributes to the development of multiple common geriatric syndromes that are often simply thought of as being related to advancing age including, but not necessarily limited to, osteoporosis, falls, dysphagia, urinary incontinence, macular degeneration, and cognitive decline. Biologically plausible mechanisms can be hypothesized to explain these observed relationships. However, it must be stressed that data supporting the associations reported here are very preliminary and require further study. Moreover, observations of relationships between syndromes of aging and vitamin D status certainly do not establish that vitamin D deficiency causes, or contributes to, development of these syndromes. However, given the increase in number of older adults projected for the immediate future, further evaluation of the possibility that vitamin D may prevent and/or be an effective therapy for what are currently accepted as “age-related” morbidities is clearly indicated.

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