Vitamin D Deficiency in Older Adults, Part I: the Prevention of Chronic Degenerative Disease and Support of Immune Health

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Accumulated research evidence suggests that vitamin D deficiency or insufficiency has profound implications for health and well-being, compromising immune responses and increasing the risk for osteoporosis, arthritis, diabetes, depression, cancer, and cardiovascular disease. Older adults, especially those who are housebound, are at increased risk for vitamin D deficiency. In addition to sun avoidance and the use of sunscreen, age, ethnicity, and obesity are risk factors for vitamin D deficiency. This article discusses the use of serum 25-hydroxyvitamin D to assess vitamin D needs and outlines current recommendations on appropriate interventions to improve vitamin D status in older adults.

Key words: *vitamin D, older adults, supplements, UVB exposure, immunity*

Introduction

Vitamin D_3 (cholecalciferol) is a fat-soluble vitamin essential for calcium, phosphate, and bone metabolism. It is synthesized on exposure of skin to ultraviolet B (UVB) radiation, either from sunshine or artificial UV light. In the absence of sufficient UV exposure, vitamin D becomes a conditionally essential nutrient—that is, it must be obtained from the diet or supplements.

The consequences of severe vitamin D deficiency for basic bone health have long been recognized and include rickets in children and osteomalacia in adults.[1] More recent evidence has established a relationship between vitamin D status and more subtle signs of musculoskeletal health: stress fractures, muscle pain and weakness, stiffness, and unsteady gait (Table 1) are all associated with vitamin D insufficiency. Better vitamin D status is associated with a reduced risk of cardiovascular disease, diabetes, and cancer (see Table 1).[2,3] Dental health[4] and pulmonary function[5] are superior in those with higher serum vitamin D levels. In older adults, the risk of admission to a long-term care facility is related to poor vitamin D status.[6] Vitamin D status is predictive of all-cause mortality, with the lowest blood levels (25-hydroxyvitamin D <45 nmol/L) increasing the risk of death by 26%.[7]

Given the potential consequences of inadequate vitamin D, it is concerning that vitamin D deficiency is much more common than previously thought, especially among older adults who are housebound.[8]

Vitamin D Synthesis and Metabolism

The angle of the sun is critical for vitamin D synthesis. At a large solar zenith angle, ozone in the upper atmosphere completely blocks UVB radiation; in Canada, skin synthesis is impossible from October through March.[9] Sunscreen (with a sun protection factor [SPF] of 15) blocks virtually all vitamin D synthesis.[10] Summer noonday sun exposure in a bathing suit without sunscreen for approximately 15 minutes produces an estimated 10,000 IU of vitamin D. Continued sun exposure does not produce toxicity since excess vitamin D is destroyed by continued UVB exposure (both previtamin D_3 and vitamin D_3 are photolyzed to several noncalcemic photoproducts), and a steady state is maintained.[9] The liver metabolizes cholecalciferol into its circulating form, 25-hydroxyvitamin D (25[OH]D), the stable vitamin D metabolite, and 25(OH)D accurately reflects vitamin D status.[11]

Cells expressing the enzyme 1-alpha-hydroxylase, primarily in the kidney, further metabolize 25(OH)D to 1,25-dihydroxyvitamin D (1,25[OH]2D). This is the active hormonal form of vitamin D, which controls the expression of more than 200 genes. In addition to its role in calcium metabolism, it activates genes controlling proliferation, differentiation, and programmed cell death (apoptosis) in a variety of cells, including epidermal, malignant tumour, and immunoregulatory cells.[12]

Vitamin D Deficiency

Adequate vitamin D is needed to maintain normal serum calcium levels. If calcium levels drop, the secretion of parathyroid hormone (PTH) occurs. This increases the activity of the enzyme 25(OH)D-1-hydroxylase in the kidney, which, in turn, increases 1,25(OH)2D production, normalizing serum calcium by increasing intestinal absorption and kidney resorption of calcium. If there is insufficient dietary calcium to maintain normal serum calcium levels, PTH mobilizes calcium from bone stores.[13] Secondary hyperparathyroidism is therefore

Table 1: Impact of Poor Vitamin D Status on Disease Risk

Disease	Reference
Musculoskeletal Health	
Rickets/osteomalacia	1
Osteoporosis	1
Osteoarthritis	24
Rheumatoid arthritis	31
Hip fractures and falls	1
Nonmusculoskeletal Associations	
Dental health, gum disease	6
Pulmonary function	5
Type 1 diabetes	3
Type 2 diabetes and glycemic control	2
Hypertension	4
Stroke	21
Seasonal affective disorder	28
Multiple sclerosis	19
Parkinson's disease	41
Breast cancer	42
Prostate cancer	43
Colorectal cancer	44

indicative of vitamin D deficiency. High bone turnover, bone loss, mineralization defects, and hip and other fractures are also caused by vitamin D deficiency.[8]

Skin pigmentation is a risk factor for vitamin D deficiency. Compared with light-skinned individuals, very dark-skinned individuals require approximately six times the sun exposure for vitamin D synthesis.[9] Genetic studies indicate that some individuals may be more susceptible to vitamin D deficiency than others. A recent study in the United Kingdom showed that a combination of low vitamin D blood levels and polymorphisms in the vitamin D receptor (VDR) gene increases the risk of breast cancer in white women.[14] Older adults are at risk of vitamin D deficiency because of age-dependent decreases in epidermal concentrations of 7-dehydrocholesterol (previtamin D_3—the precursor molecule for cholecalciferol synthesis), having 50% lower skin production compared with that of young adults.[15] Obesity is an additional risk factor for vitamin D deficiency, and an inverse relationship exists between serum 25-hydroxyvitamin D and body mass index.[16] Concentrations of 25(OH)D are associated with body composition variables, especially by body fat, independently of seasonal variability. Therefore, body adiposity should be considered when assessing vitamin D requirements in obese patients.[16]

Vitamin D and Immunity

Vitamin D status has profound implications for immunity. Innate immunity, responsible for mounting immune responses to bacteria, viruses, and other micro-organisms not previously encountered, is vitamin D dependent.[17] In the lung, epithelial cells can generate active vitamin D, which then influences the expression of genes responsible for the production of antimicrobial peptides and inflammatory cytokines by neutrophils, monocytes, and natural killer cells in response to viruses.[17] Because vitamin D deficiency suppresses these innate responses, it has been suggested that epidemic influenza could be a consequence. Although the virus exists in populations year round, influenza usually occurs in winter when vitamin D stores bottom out.[18]

Oral administration of vitamin D may suppress autoimmune diseases such as multiple sclerosis (MS), at least in animal models. Studies have shown that the risk of MS decreases as serum vitamin D increases.[19] In MS, helper T lymphocytes attack the myelin sheath of neurons, an activity that 1,25(OH)2D attenuates.

One small clinical study among individuals with MS demonstrated that high oral doses of vitamin D_3 (up to 40,000 IU/d) are safe, normalize the elevated PTH levels common in these patients, and may have had a therapeutic effect.[20] The number of gadolinium-enhancing lesions per patient with MS assessed by nuclear magnetic brain scan decreased over a 28-week period from the initial mean of 1.75 to the end-of-study mean of 0.83 ($p = .03$).[20]

Vitamin D and Chronic Disease Risk

A growing body of evidence suggests a link between low blood levels of vitamin D and cardiovascular disease. In 3,316 patients who were referred for coronary angiography, subjects with low vitamin D levels were shown to be twice as likely to have a heart attack, stroke, or other cardiovascular event during follow-up compared with those with higher vitamin D levels. In this study, low vitamin D status was predictive of future stroke in patients, who were followed up for a median of 7.7 years.[21] Low levels of 25(OH)D and 1,25(OH)2D are independently predictive for fatal strokes, suggesting that vitamin D supplementation is a promising approach in the prevention of strokes.[21]

An inverse association exists between baseline serum 25(OH)D and a future risk of glycemia and insulin resistance.[22] Vitamin D insufficiency as measured by serum 25(OH)D increases the risk of osteoporosis and hip fractures, and decreases the rate of bone loss; vitamin D repletion improves muscle performance, reducing the risk of falls and the incidence of fracture.[23] Poor vitamin D status also plays a role in the development of osteoarthritis, a leading cause of disability in older populations.[24]

Laboratory studies show that when bound to the VDR, 1,25(OH)2D exerts potent prodifferentiation, antiproliferative, antiangiogenic, and antimetastatic effects on many types of tumour cells, including prostate, colorectal, breast, and ovarian cancer cells.[25] Both normal and neoplastic breast tissues express the VDR. Several polymorphisms in the VDR gene have been identified that are associated with an increased risk of breast cancer.[14] These polymorphisms interact with low serum levels of vitamin D, increasing the risk for cancer.[26] Polymorphisms in the VDR gene also appear to affect the risk of developing melanoma, and it has been suggested that sun exposure may have an antimelanoma effect.[27]

Vitamin D deficiency may also be associated with depression. Seasonal affective disorder typically occurs when vitamin D stores are low; in one study, improving 25(OH)D levels was significantly associated with an improvement in depression scores.[28] The results of a large Dutch population–based study in older individuals showed an association between the presence and severity of depression and serum 25(OH)D and increased PTH levels.[29] Treatment with vitamin D supplements can ameliorate depression in obese and overweight adults, suggesting a causal relationship.[30]

Key Points

- Vitamin D deficiency is a risk factor for a wide range of musculoskeletal and nonskeletal conditions from osteoarthritis to diabetes, cardiovascular disease, depression, and cancer.
- Innate immunity is vitamin D dependent, and epidemic flu may be related to poor vitamin D status.
- Obesity is an independent risk factor for vitamin D deficiency.
- A lack of sun exposure and reduced skin capacity for vitamin D synthesis contribute to a higher rate of vitamin D deficiency in older populations.
- There is little evidence that intakes of supplemental vitamin D well above current recommended daily intakes are harmful.

Increasing Vitamin D Intake from Food and Supplements

Because of valid concerns about the risk of skin cancer resulting from unprotected UV exposure, increasing one's vitamin D status through food or supplements, instead of sun exposure, is generally advised. Very few foods naturally contain vitamin D. Those that do include fatty fish, liver, and egg yolks. Cod liver oil, a rich source of vitamin D, has been used in Europe to prevent rickets since the 17th century. Some foods are fortified with vitamin D, including milk products, margarine, and some cereals, but the amount of vitamin D in these foods is low. For example, 10 glasses of milk a day would be needed to meet the current daily vitamin D intake of 1,000 IU recommended for older adults by the Canadian Cancer Society.[31]

Currently, there is no consensus on vitamin D replacement regimens, nor is there an agreed-upon optimal level of serum 25(OH)D for health.[32] Consequently, there is clinical uncertainty about how to correct vitamin D deficiency. Two forms of vitamin D supplements are available—D_3 (cholecalciferol) and D_2 (ergocalciferol). Vitamin D_3 is derived from animal sources and is identical to the cholecalciferol produced in human skin, whereas D_2 is derived from fungal or plant sources. Until recently, both these forms of vitamin D supplements were considered equivalent. In clinical settings, vitamin D_2 is frequently used to treat vitamin D deficiency. However, recent studies have shown that the potency of vitamin D_2 is less than one-third that of vitamin D_3.[33] Physicians resorting to use of vitamin D_2 should be aware of its markedly lower potency and shorter duration of action relative to vitamin D_3.[33] Vitamin D_3 is the usual form found in multivitamins and health food store supplements.

Currently in Canada, the recommended supplemental intake for adults aged 50–70 is 400 IU and for those 71 years and older is 600 IU.[34] However, these recommendations have been criticized as inadequate.[35] Supplemental doses of 400–800 IU/d have not shown therapeutic benefits or significant improvements in 25-hydroxyvitamin D levels in older individuals.[36,37] Recently, normal ranges for 25(OH)D in Canada have been changed from 25–100 nmol/L to 75–250 nmol/L to reflect new research showing 75 nmol/L to be the minimum required for bone health.[4] However, for cancer prevention, desirable 25(OH)D levels are 90–120 nmol/L.[4] One estimate suggested that an intake of 1,000 IU vitamin D_3/d for all adults would bring 50% of the population up to 75 nmol/L, and that 2,000 IU/d or higher was needed to bring most individuals into the cancer-prevention range.[4] One randomized

Clinical Pearl

The stable metabolite of vitamin D in blood—25(OH)D—accurately reflects vitamin D status and should be a routine part of an annual physical examination for older adults. Test from late fall through early spring to uncover potential seasonal shortfalls.

controlled trial compared the effects of supplementing with 1,000 IU/d or 4,000 IU/d over the winter months, using a previously validated well-being questionnaire. This trial showed the 4,000 IU/d intervention to be superior.[38] Current recommendations by the Canadian Cancer Society are that all Canadian adults take 1,000 IU/d in fall and winter and that older adults take 1,000 IU/d year round.[31]

Vitamin D_3 supplements have a highly favourable safety profile. Recent data suggest that toxicity (hypercalcemia) does not occur at daily intake below 50,000 IU a day,[39] and serum levels of 25(OH)D up to 750 nmol/L.[40] A subsequent paper in this journal will discuss vitamin D deficiency in relation to musculoskeletal pain and functioning, as well as alternative approaches to optimising vitamin D supplementation in individual subjects.

Conclusion

The risk of vitamin D deficiency as measured by serum 25-hydroxyvitamin D is high in older individuals, especially if they are housebound, dark-skinned, or obese. Many skeletal and nonskeletal conditions are more prevalent among those who are vitamin D deficient, including osteoporosis, osteoarthritis, type 1 and type 2 diabetes, heart disease, stroke, and most cancers. Blood levels of 25-hydroxyvitamin D accurately reflect vitamin D status and should be checked annually to uncover vitamin D deficiency or insufficiency. Vitamin D supplements have an excellent safety profile, with vitamin D_3 being preferable to vitamin D_2, which is less than one-third as effective. The Canadian Cancer Society suggests 1000 IU vitamin D daily from supplements for older adults.

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