Not enough vitamin D

Health consequences for Canadians

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ABSTRACT

OBJECTIVE To review the evidence on vitamin D (VTD) insufficiency and deficiency from a Canadian perspective and to highlight some of the known and evolving implications of insufficiency or deficiency for health.

QUALITY OF EVIDENCE PubMed was searched for articles on VTD insufficiency or deficiency and the role they play in various diseases and conditions. Level I and II evidence indicates that lack of VTD has a major role in short- and long-latency diseases.

MAIN MESSAGE The long winters in Canada and lack of exposure to the sun contribute to lower levels of VTD among Canadians in late winter and spring. Currently recommended levels of fortification and supplementation are likely not high enough to restore adequate levels of VTD in the body. Repletion and maintenance therapy might be needed.

CONCLUSION Many Canadians are at risk of VTD insufficiency or deficiency. Assessment of VTD status is important because optimal levels of VTD have been determined for various conditions. Low levels of VTD have negative implications for bone health and the health of other cell types.

RÉSUMÉ

OBJECTIF Faire le point sur les données concernant l'insuffisance/la déficience en vitamine D (VTD) d'un point de vue canadien et rappeler certaines des conséquences connues ou présentement à l'étude de ce problème pour la santé.

QUALITÉ DES PREUVES On a consulté PubMed à la recherche d'articles sur l'insuffisance ou la déficience en VTD et sur leur rôle dans diverses maladies ou conditions. Des preuves de niveaux I et II indiquent qu'un manque de VTD joue un rôle important dans des maladies d'apparition rapide ou lente.

PRINCIPAL MESSAGE Les longs hivers canadiens et le manque d'exposition au soleil contribuent à abaisser les niveaux de VTD chez les Canadiens en fin d'hiver et au printemps. Il est probable que les niveaux d'aliments enrichis ou de suppléments actuellement recommandés ne soient pas suffisants pour assurer des niveaux adéquats de VTD dans l'organisme. Il pourrait être nécessaire de restaurer et de maintenir les réserves.

CONCLUSION Plusieurs Canadiens sont à risque d'insuffisance ou de déficience en VTD. L'évaluation du bilan de la VTD est important parce que des niveaux optimaux de VTD ont été établis pour diverses conditions. Les bas niveaux de VTD ont des effets négatifs sur la santé de l'os et sur celle d'autres types de cellules.

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This article reviews the guidelines for adequate intake of vitamin D (VTD), some of the basic physiology of VTD, and the relevance of the VTD receptor in some disease states. The definition of VTD status, and the prevalence, etiology, and treatment of inadequate status for various diseases will be discussed.

Quality of evidence

MEDLINE was searched using the words "vitamin D" and "vitamin D receptor" combined with "insufficiency," "deficiency," "osteoporosis," "neuromuscular function," "falls," "cardiovascular disease," "autoimmune disease," "diabetes," "cancer," and "treatment." Articles containing levels I, II, and III evidence were found. Original studies reviewed in this paper are listed in **Table 1**.[1-53]

Past and current (1997) guidelines for adequate intake of vitamin D (VTD) are shown in **Table 2**.[54-57] Some have recommended that new guidelines for breastfed infants and people with osteoporosis are needed. New guidelines might be forthcoming after review of new data relating to our understanding of VTD and its role in chronic diseases with long latency periods.[58]

Background

Vitamin D, a steroid hormone produced in the skin, has specific regulatory or functional effects on other parts of the body. Vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (25[OH]D) and further hydroxylated in the kidney to 1,25-dihydroxyvitamin D. Hydroxylation in the kidney is regulated closely by parathyroid hormone (PTH), hypocalcemia, and hypophosphatemia and is inhibited by 1,25-dihydroxyvitamin D.[59] As well, 1,25-dihydroxyvitamin D (produced locally within cells) regulates gene transcription through nuclear high-affinity VTD receptors.[60] These receptors are found in the classic target organs: gut, bone, kidney, and parathyroid[61] and many other tissues as well, such as brain, breast, colon, heart, pancreas, prostate, skin, and immune system. Vitamin D regulates cell growth and maturation, inhibits renin production, stimulates insulin secretion, and modulates the function of activated T- and B-lymphocytes and macrophages[62,63] (**Table 3**,[1,2,4,33,59,62,64-82] **Figure 1**).

Assessing VTD status

The major circulating metabolite of VTD is serum 25(OH)D, which has a half-life of between 10 and 19 days.[5] It is the best indicator of VTD status and reflects levels from dietary intake and synthesis in the skin.[83] Levels <25 nmol/L are generally considered deficient; levels <80 nmol/L are considered insufficient.[84] There is some concern about the reliability and consistency of serum 25(OH)D laboratory results,[85] although there has been some improvement in the quality of tests in the past few years. The 2 main assays commercially available are listed in **Table 4**.[86,87] Liquid chromatography, which is the criterion standard, is not readily available.

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Prevalence of VTD insufficiency or deficiency

Globally, VTD insufficiency or deficiency has been noted in many countries, from high school students in Iran[7] to healthy western Canadians.[8] Substantial seasonal variability has been noted in both Canada and Australia above and below the 37th parallel, respectively, with up to 97% of Canadians having inadequate levels of VTD at some time during the winter or spring.[8,9]

Mothers and infants among native Canadian Cree in Manitoba have been found to be severely deficient in VTD, even in midsummer.[10] In Inuvik, 48% of Inuit mothers were found to be deficient in VTD despite supplementation.[11] Seasonal variations were found in a Canadian study of healthy women in Toronto, Ont, and supplementation with 400 IU of VTD did not prevent insufficiency in the winter.[12] A study in Edmonton, Alta, showed that children and adolescents had low levels of VTD.[13,88]

Three studies in the United States, Finland, and Israel found that inpatients had insufficient or deficient levels of VTD.[14-16] Only 30% of patients in 3 Canadian long-term care facilities got adequate amounts of VTD through diet alone.[17] Long-term care residents in Toronto had VTD deficiency that increased from 9% in the fall to 18% in the spring.[18] Not only are inpatients at risk, but internal medical residents who work long hours indoors are also.[19] A global study of VTD in postmenopausal women with osteoporosis showed that levels were deficient in 28.4% of them. There was no significant difference in levels among community-dwelling people and nursing-home patients. Deficiency increases with age; about 50% of those aged 70 and 80% of those aged 90 are deficient.[89] In a study of North American postmenopausal women, all taking an agent to treat or prevent osteoporosis and 59% taking ≥400 IU of VTD daily, 18% had levels below 50 nmol/L, and 52% had levels below 75 nmol/L. Despite supplementation, about 50% of women have suboptimal VTD levels.[20] A systematic review of 30 articles written in the past 10 years on VTD inadequacy in menopausal women supports these findings.[21]

Etiology of VTD deficiency and insufficiency

The risk factors that contribute to low levels of VTD are numerous and are summarized in **Table 5**.[10,22-24,90-110]

Classic effects of VTD insufficiency or deficiency on disease

Vitamin D deficiency causes rickets in children and osteomalacia in adults. Rickets cases are still being reported in Canada.[25,111] Osteomalacia also still occurs, but its symptoms are much less specific and

Table 1. Articles reviewed, number of subjects, design, outcomes, and comments

STUDY	N	DESIGN	OUTCOME	COMMENTS
Krejs et al[1]	10	Intestinal perfusion study before and after administration of VTD	Calcium and magnesium absorption increased 2%-300% from baseline	None
Zittermann et al[2]	68: 34 controls, 34 patients with congestive heart failure	Case-control study	With lower VTD levels ($P<.001$), PTH levels ($P<.001$) and inflammatory markers ($P<.001$) were raised	Lower VTD levels were seen in patients with more severe congestive heart failure
Latham et al[3]	2496	Systematic review	NS reduction in falls among patients receiving VTD	None
Chui et al[4]	126	Univariate and multivariate regression analysis	Positive correlation of VTD levels with insulin sensitivity ($P<.0001$); negative effect on beta cell function ($P<.0045$)	Subjects with VTD deficiency are at higher risk of insulin resistance
Barger-Lux et al[5]	116	Open-label treatment groups: 1000 IU VTD3, 10 000 IU VTD3, 50 000 IU VTD3	Raised 25(OH)D levels by 29 nmol/L, 146 nmol/L, and 643 nmol/L, respectively	8 weeks before steady state achieved
Chapuy et al[6]	1569	Population prevalence study (cross-sectional study) of VTD and PTH levels	Parathyroid secretion initiated when serum 25(OH)D falls below 78 nmol/L	14% of the population had wintertime levels <30 nmol/L
Moussavi et al[7]	318	Population prevalence study (cross-sectional study) of VTD deficiency in Iran	46.2% had levels <50 nmol/L (72.1% of women and 18.3% of men)	95% of women had levels <80 nmol/L
Rucker et al[8]	188	Population prevalence study (cross-sectional study) of VTD and PTH levels in western Canada	97% of subjects had levels <80 nmol/L at some time during the year; levels were lower during fall, winter, and spring than during summer	34% had levels <40 nmol/L sometime during the year; levels were taken 4 times yearly
Pasco et al[9]	3280	Cross-sectional study of seasonal periodicity of serum VTD, PTH, and fractures in Australia	In winter, VTD levels were lower ($P<.001$) and falls were more likely to result in fractures ($P<.001$)	VTD levels of <28 nmol/L were found in 14% of subjects in winter
Lebrun et al[10]	160	Cross-sectional study in Manitoba	43% of children and 76% of mothers had levels <25 nmol/L	70% of mothers drank no milk; 24% were intolerant of milk
Waiters et al[11]	121: 22 whites, 51 Inuit, 37 Native Canadians*	Cross-sectional study of mothers and newborns in Inuvik	Average 25(OH)D levels at time of delivery were 50.1 nmol/L in Natives and 59.8 nmol/L in non-Natives	Plasma levels of 25(OH)D in newborns averaged only 67% of levels in mothers
Vieth et al[12]	796	Cross-sectional study in Toronto, Ont, of women aged 18-35 y	21% of women reporting no consumption of VTD, 26% of women reporting <200 IU, and 20% reporting >200 IU of VTD were deficient (<40 nmol/L) during winter months	Recommended intake is too low to prevent VTD insufficiency and deficiency; deficiency could be determined only by laboratory tests, not by dietary history
Roth et al[13]	90	Cross-sectional study in children presenting to a emergency department in Edmonton, Alta	34% of patients had VTD levels <40 nmol/L, 6% had levels <25 nmol/L (deficiency)	Levels taken at end of winter
Thomas et al[14]	290	Cross-sectional study in consecutive medical inpatients	57% considered deficient in VTD (<37.5 nmol/L); 22% severely deficient (<20 nmol/L)	37% of patients who consumed more than the recommended intake of VTD were deficient
Kauppinen-Makelin et al[15]	205: 106 inpatients, 99 outpatients	Cross-sectional study in consecutive medical inpatients and outpatients	70% of female and 61% of male inpatients had levels <37.5 nmol/L, and 44% of female and 37% of male outpatients had levels <37.5 nmol/L	Inpatients were more deficient in VTD than outpatients

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STUDY	N	DESIGN	OUTCOME	COMMENTS
Hochwald et al[16]	296	Cross-sectional study of consecutive medical inpatients in Israel	26.27% of inpatients had levels <37.5 nmol/L	Even in a sunny country, >25% of patients were deficient in VTD
Lee et al[17]	53	Analysis of dietary intake in Canadian long-term care	70% of nursing-home patients consumed inadequate amounts of VTD through diet alone	Supplementation is necessary in these settings
Liu et al[18]	155	Cross-sectional study in Toronto; prevalence and seasonal variation in long-term care	9% of subjects had VTD levels <25 nmol/L in September; 18% had similar levels after the winter	<25 nmol/L is considered high risk for osteomalacia
Haney et al[19]	35	Cross-sectional study in internal medicine residents	74% had VTD levels <50 nmol/L in spring compared with 26% in fall	69% of residents took in <400 IU/d of VTD
Holick et al[20]	1536	Cross-sectional study of postmenopausal women in North America	Serum VTD was <50 nmol/L in 18%, <62.5 nmol/L in 36%, and <75 nmol/L in 52% of women	>50% of women taking osteoporosis therapy had inadequate VTD levels
Gaugris et al[21]	11 023	Systematic review of VTD status in postmenopausal women with osteoporosis	50%-70% of women with a fracture had VTD levels <37.5 nmol/L	High prevalence of low VTD levels in women with a history of fractures
Matsuoka et al[22]	40	Randomized controlled trial	VTD levels lower in sunscreen users (40.2 nmol/L) than controls (91.3 nmol/L) ($P<.001$)	Lower 25(OH)D levels suggest lower VTD stores
Lo et al[23]	14: 7 healthy, 7 with fat malabsorption	Controlled trial. Intestinal absorption study before and after VTD radiolabeled	Absorption reduced from 60% in normal subjects to <18% (pancreatitis) in study subjects, 0% in those with bilary obstruction, and <50% in those with celiac disease	Various conditions involving malabsorption result in VTD insufficiency or deficiency
Jones et al[24]	209	Double-blind, placebo-controlled study	19% reduction in absorption of VTD in treated group	Unlikely to have substantial reduction with cutaneous production of VTD
Binet and Kooh[25]	17	Case review in Toronto	Native people* and immigrants at risk of VTD deficiency	Rickets is still a public health issue
Bischoff-Ferrari et al[26]	19 114: 9294 in hip and other fracture trial, 9820 in non-vertebral fracture trials	Meta-analysis of randomized controlled trials of fracture prevention	RR 0.74 (95% CI 0.61-0.88); reduced hip fracture by 26%; RR 0.77 (95% CI 0.68-0.89); reduced nonvertebral fracture by 23%	700-800 IU/d of VTD reduces risk of hip and nonvertebral fractures; 400 IU/d does not
Dawson-Hughes et al[27]	389	Randomized, double-blind, placebo-controlled study	Prevalence of fractures in placebo group was 10% compared with 4% in treatment group ($P=.02$)	500 mg of calcium and 700 IU of VTD reduced incidence of nonvertebral fractures
Chapuy et al[28]	583	Multicentre, randomized, double-masked, placebo-controlled confirmatory study	Prevalence of fractures in placebo group was 11.1% compared with 6.9% in treatment group ($P=.07$, NS)	1200 mg of calcium and 800 IU of VTD reduced incidence of nonvertebral fractures
Porthouse et al[29]	3314	Randomized controlled trial of primary prevention	No evidence that calcium and VTD reduced fractures in community-dwelling older women	Only 63% of subjects were taking the supplements at 12 mo (poor compliance); no baseline or follow-up VTD levels taken
Grant et al[30]	5292	Randomized, placebo-controlled trial of secondary fracture prevention	No evidence for secondary prevention of fractures with use of VTD or combined VTD and calcium; baseline 25(OH)D level rose from 38 to 62.25 nmol/L in treatment group	Only 60% had compliance rates of >80% of tablets taken; only 60 patients had baseline and follow-up 25(OH)D levels taken

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STUDY	N	DESIGN	OUTCOME	COMMENTS
Dhesi et al[31]	139	Randomized, double-blind, placebo-controlled study	With treatment, significant change in choice reaction time ($P<.01$), postural sway ($P<.02$), and aggregate functional performance time ($P<.05$)	NS difference in falls; small trial
Bischoff-Ferrari et al[32]	1237, 5 trials reviewed	Meta-analysis of double-blind, randomized controlled trials	VTD reduced risk of falling by 22%	Number needed to treat was 15 to prevent 1 fall
Bischoff-Ferrari et al[33]	4100	Cross-sectional, population-based survey	2.5-m walk test ($P=.001$ for trend) and sit-to-stand test ($P=.017$ for trend); comparison of highest to lowest quartile 25(OH)D levels	In ambulatory patients, active or inactive concentrations of 40-94 nmol/L of 25(OH)D resulted in better lower-extremity musculoskeletal function
Sato et al[34]	96	Randomized placebo-controlled trial	1000 IU of VTD2 resulted in 59% reduction in falls ($P=.049$) in patients with long-standing stroke	VTD levels were deficient with 25(OH)D levels <25 nmol/L
Al Faraj and Al Mutairi[35]	341	Cross-sectional interventional study	299 (83% of total) with 25(OH)D levels <22.5 nmol/L and idiopathic back pain had a 100% improvement in symptoms when treated with 5000-10 000 IU of VTD until 25(OH)D levels were normal	In 299 patients, VTD levels were clearly deficient; very high doses were used for repletion therapy with no side effects
Al-Allaf et al[36]	87	Case-control study	25(HO)D levels <20 nmol/L were more common in fibromyalgia patients than in controls ($P=.015$)	Unclear whether low VTD levels are causative in fibromyalgia or result from the disease
Plotnikoff and Quigley[37]	150	Cross-sectional population study	93% of patients with persistent nonspecific musculoskeletal pain had 25(OH)D levels <30 nmol/L	Osteomalacia is a known cause of nonspecific musculoskeletal pain
Hyppönen et al[38]	10 821	Study of children given 2000 IU of VTD supplements	Regular supplementation resulted in a 78% reduction in risk of developing type 1 diabetes later in life	A subset receiving supplementation with >2000 IU of VTD had an 86% RR[39]
Pfiefer et al[40]	148	Randomized placebo-controlled trial of blood-pressure therapy supplementing with VTD	800 IU of VTD supplementation decreased systolic hypertension by 9.3% ($P<.01$)	Short-term study (8 weeks). No statistical benefit on diastolic blood pressure
Van den Berghe et al[41]	124	Randomized controlled trial; comparison of 200 and 500 IU of VTD	C-reactive protein levels fell significantly in the group taking the higher dose ($P<.05$)	25(HO)D levels were deficient and did not normalize with 200 IU of VTD
Forman et al[42]	216 313	Summary of 3 large prospective cohort studies	Higher VTD intake was not associated with lower risk of incident hypertension	Patients followed up for 8 years
Garland et al[43]	Unstated	Summary of 63 epidemiologic studies: 30 of colon cancer, 13 of breast cancer, 26 of prostate cancer, and 7 of ovarian cancer	25(OH)D levels <75 nmol/L double the risk of those with levels >75 nmol/L; women in lowest quartile of VTD intake had 5 times the risk of developing breast cancer than those in highest quartile. In a study on prostate cancer (19 000 men), incidence was 70% higher among those with 25(OH)D levels <40 nmol/L than among those with levels >40 nmol/L	No studies showed an increase in cancer rates with VTD, but some showed no effect

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STUDY	N	DESIGN	OUTCOME	COMMENTS
Munger et al[44]	187 563	Summary of 2 prospective cohort studies	Supplementation with ≥400 IU of VTD resulted in a 41% decrease in incidence of multiple sclerosis	Dietary intake of VTD resulted in a lower reduction of 33%
Merlino et al[45]	29 368	Prospective cohort study	Supplementation with ≥400 IU of VTD resulted in a 36% decrease in incidence of rheumatoid arthritis	Dietary intake resulted in a slightly lower reduction of 28%
Berwick et al[46]	528	Population-based study of cutaneous melanoma	Intermittent sun exposure was associated with increased survival in melanoma patients	Antiproliferative effect of VTD
Kennedy et al[47]	966	Cohort case-control study	Painful sunburn early in life increased melanoma, squamous cell carcinoma, and especially actinic keratosis	Lifelong moderate sun exposure decreased risk of melanoma
Linday et al[48]	94	Case-control study	Supplement with ~700 IU of VTD significantly decreased upper respiratory tract infections over time ($P<.042$)	Decreased need for antibiotics in control group; compliance was only 70%
Wayse et al[49]	150	Case-control study	Low VTD levels were associated with increased risk of severe acute lower respiratory infection: 25(OH)D <22.5 nmol/L ($P<.001$)	Despite abundant sunlight, 25(OH)D levels were deficient
Krall et al[50]	145	Randomized controlled trial using calcium and VTD supplements	13% of patients taking supplements lost teeth compared with 27% of patients not taking supplements	VTD was not independently related to risk of losing teeth
Vieth et al[51]	64	Randomized comparison control study; 4000 IU of VTD compared with 600 IU (current recommended intake); based on 1-tail Mann-Whitney well-being score, ($P=.034$)	No side effects of high dose of VTD other than improved mood	6-mo trials
Vieth et al[52]	61	Randomized comparison control study; 1000 vs 4000 IU of VTD supplementation for 3 mo	Average 25(OH)D levels were 68.7 nmol/L and 96.4 nmol/L, respectively, after 3 mo	NS changes in serum calcium and urinary calcium excretion in patients taking high doses
Aloia et al[53]	208	Randomized controlled trial in 50- to 70-year-old African-American women	Only 60% of women treated with 2000 IU of VTD daily achieved normal 25(OH)D levels after a year	87% compliance for 1 y

25(OH)D—25-hydroxyvitamin D, CI—confidence interval, IU—international units, NS—nonsignificant, PTH—parathyroid hormone, RR—risk reduction, VTD—vitamin D.
*Native is used to refer to the indigenous and aboriginal inhabitants of Canada and their descendants.

are easily missed.[112] Vitamin D is used to treat osteoporosis, but studies using calcium and 400 IU of VTD showed little effect on fractures. Most but not all studies using calcium and 700 to 800 IU of VTD did show a reduction in fractures.[26-28,113] No benefit was seen from 1000 mg of calcium and 800 IU of VTD in a primary prevention trial[29] and a secondary prevention trial.[30,114] Compliance was poor in both studies, and only 63% of patients were still taking treatment after 12 months in the former study, and only 1.1% of patients had baseline VTD levels taken in the latter study.

Supplementing with 400 IU of VTD for 8 weeks raised the measured 25(OH)D level by a mere 11 nmol/L in healthy men.[5] To date, no studies have ensured that all subjects in treatment groups consistently had VTD levels >78 nmol/L. There is still great controversy over the benefit of VTD in fracture control.

Table 2. Canadian recommendations for adequate intake of vitamin D: *1975 to 2007.*

AGE	1975-1983 IU	1990 IU	1997 IU	1997-2007 IU
0-12 mo	100	200	200	400*
1-50 y	100	200	200	200
51-70 y	100	200	400	800†
≥71 y	100	200	600	800†

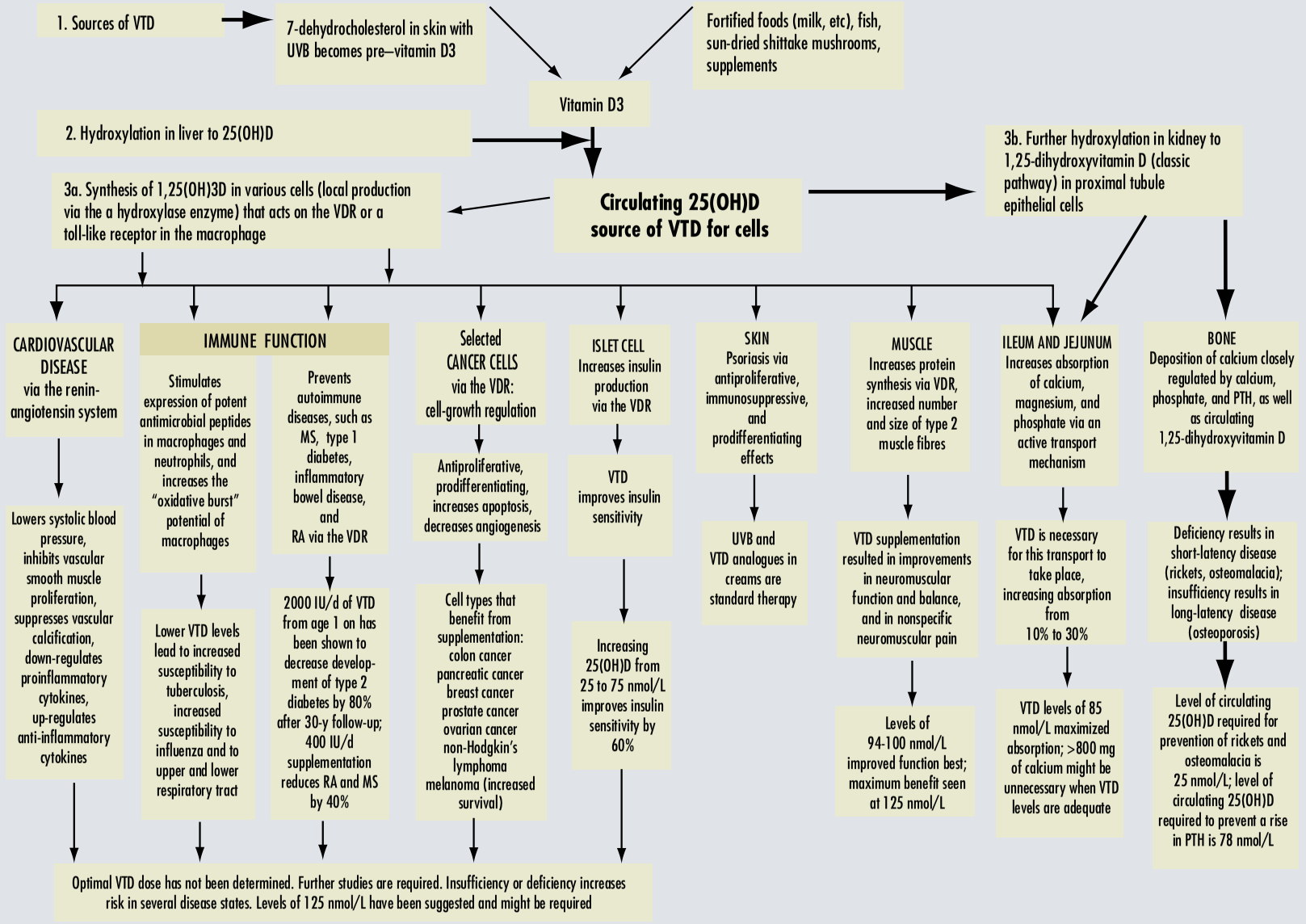
Data derived from Committee for the Revision of Dietary Standards in Canada,[54,55] Scientific Review Committee,[56] and Institute of Medicine.[57]
*Recommended by the Canadian Paediatric Society.
†Recommended by the Canadian Osteoporosis Society for patients at risk of osteoporosis.

Table 3. Studies of functions of vitamin D

ORGAN OR SYSTEM	EFFECT OF SUFFICIENT VITAMIN D	EFFECT OF INSUFFICIENT OR DEFICIENT LEVELS OF VITAMIN D	OPTIMAL VITAMIN D INTAKE FOR HEALTH
Jejunum and ileum	Increases absorption of calcium and magnesium to 30%[1]	Absorption of calcium and magnesium reduced to 10%	85 nmol/L allows maximum absorption[64,65]; with adequate VTD levels, >800 mg of calcium might be unnecessary[66]
Bone	Maintains calcium and phosphate homeostasis and is required for proper mineralization[59]	Rickets or osteomalacia;[62] short-latency disease	Rickets and osteomalacia are prevented when VTD levels are >25 nmol/L[67]
Parathyroid	Regulates calcium and phosphate levels, controls conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D[59]	Parathyroid hormone excretion increases as levels of VTD decrease resulting in secondary hyperparathyroidism, which in turn results in resorption of calcium from bone and exacerbates osteoporosis	Parathyroid hormone levels are dramatically suppressed when VTD levels are maintained at >50 nmol/L[67]; levels begin to rise when 25-hydroxyvitamin D levels fall <78 nmol/L
Cardiovascular system via VDR	Inhibition of vascular smooth-muscle proliferation; suppression of vascular calcification; down-regulation of pro-inflammatory cytokines; up-regulation of anti-inflammatory cytokines. VTD acts as a negative endocrine regulator of the renin-angiotensin system[68]	Might contribute to congestive heart failure[2,69]; deficiency results in loss of calciotropic effect in long-latency disease	Currently unknown, but 2000-4000 IU of vitamin D3 are being suggested[70]
Muscle via VDR	Modulates calcium transport, protein synthesis, and kinetics of muscle contraction[71]	Muscle weakness, limb pain, and impaired physical function[72]; loss of calciotropic effect	Maximum neuromuscular performance achieved with VTD levels of 125 nmol/L[33]
Skin via VDR	Production of calcitrol that regulates cellular function in keratocytes	Antiproliferative, immunosuppressive, and prodifferentiating effects	VTD analogues are used for psoriasis[73]
Islet cells via VDR	Improvement in insulin sensitivity[4]	Negative effect on beta cell function with reduced insulin secretion; loss of immune modulatory effect	Raising VTD levels from 25 to 75 nmol/L improves sensitivity by 60%; optimal level has not been determined
Certain cancer cell types mediated via VDR	Suppressed growth and increased apoptosis[74,75]; stabilized chromosomal structure and prevented DNA breakdown[76]	Loss of antiproliferative effect	Optimal level undetermined
Immune system modulator	Stimulated expression of potent anti-microbial peptides, increased "oxidative burst" potential of macrophages[77]	Increased susceptibility to influenza[77] and tuberculosis[78]	Optimal level undetermined; summer levels of 125 nmol/L likely required[77]
Innate immune function	Increased production of cathelicidins effective against *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida*	Decreased wound barrier function	Optimal dose undetermined[79-82]

VTD—vitamin D, VDR—vitamin D receptor.

Figure 1. Physiologic actions and potential benefits of vitamin D: *References are listed in Tables 1,3, and 7.*



MS—multiple sclerosis, PHT—parathyroid hormone, RA—rheumatoid arthritis, UVB—ultraviolet B, VDR—vitamin D receptor, VTD— vitamin D, 25(OH)D— 25-hydroxycholecalciferol.

Table 4. Assessment of vitamin D levels

ASSAY	MEASUREMENT	COMMENTS
Radioimmunoassay	Uses antibodies that recognize both 25(OH)D3 and 25(OH)D2	Most commonly used assay; coefficient of variability in assay is 12%-18% in normal range of VTD (85-147.5 nmol/L) and 10%-25% in lower range of VTD (20-62.5 nmol/L)[86]
Competitive binding protein assay	Reagent separates VTD from binding proteins	Often yields values about 30% higher (nonspecific) but might not detect 25(OH)D2[87]

25(OH)D3—25-hydroxyvitamin D3, 25(OH)D2—25-hydroxyvitamin D2, VTD—vitamin D.

Table 5. Risk factors for low serum vitamin D levels

RISK FACTORS	REASON
Inadequate exposure to the sun	
• Skin type	- Dark skin requires up to 5 times the length of exposure because of melanin content
• Season, latitude, angle of the sun	- People living at latitudes higher than the 37th parallel cannot get adequate amounts of UVB from the sun during winter months
• Use of sunscreen[22,90]	- Continuous use of sunscreen with greater than factor 8 UVB protection[22]; controversial because of risk of skin cancer, but UVB decreases risk of internal cancer
• Time of day	- Ultraviolet B is at its maximum from 10:00 AM to 2:00 PM[91]; exposure to 1 minimal erythemal dose* in a swimsuit can provide the equivalent of 10 000 IU of VTD[92]
• Covering the skin	For various religious or cultural reasons
Inadequate dietary intake	Limited intake of foods rich in VTD, such as oily fish and fish-liver oil, low intake of fortified foods or no use of supplements; strict vegans and non-milk drinkers are at higher risk[93]
Obesity	Irreversible sequestration of VTD in the fat pool, especially if body mass index is >30 and person does little outdoor activity[94]
Exclusive breastfeeding	Breast milk is low in VTD[10,95]; supplementing with 4000 IU of VTD has been shown to achieve adequate levels in both mother and child[96]
Pregnancy	Adequate maternal VTD levels are required to ensure fetal bone health and general health of mother and child[97-100]
Age	
• Decreased production of VTD through the skin	- A 70-year-old person's skin can synthesize only 25% as much VTD as a young person's[101-102]; conversion of 7-dehydrocholesterol in aging skin is considerably lessened[103]
• Age-related lactose intolerance	- Reduced intake of fortified milk
• Immobility	- More time housebound or in hospital; many are institutionalized
• Aging kidneys	- Decreased renal conversion of VTD
Comorbid conditions	Malabsorption syndromes, such as Crohn disease, Whipple disease, cystic fibrosis, and sprue, as well as severe liver disease[23]
Drug interactions	
• Drugs that impair VTD activation or increase its clearance	- Phenytoin, carbamazepine, rifampin, cimetidine, thiazides[104-106]; lithium raises parathyroid hormone levels and lowers levels of the active hormone 1,25-dihydroxyvitamin D[107]
• Drugs that impair VTD absorption	- Mineral oil laxatives or fat substitutes, such as Olestra[24]; obesity management medications, such as orlistat[108]; or bile-acid sequestrants, such as cholestyramine and colestipol[109]
Variations in metabolism of VTD	Some Indo-Asians have increased 24-hydroxylase activity that results in low serum levels of 25-hydroxyvitamin D[110]

IU—international units, UVB—ultraviolet B, VTD—vitamin D.
*The amount of sunlight to which a person can be exposed before the skin begins to turn slightly red. Minimal erythemal dose varies from person to person depending on skin type.

Effects of insufficiency or deficiency on other disease states

Neuromuscular effects. Vitamin D acts on the VTD receptor in skeletal muscle cells by binding to the nuclear receptor and also to a cell membrane receptor, which results in numerous physiologic actions.[71] Severe VTD deficiency is associated with muscle weakness, limb pain, and impaired physical function.[3,31,115] A meta-analysis looking at ambulatory and institutionalized older patients found a reduction in falls of more than 20% with use of VTD. This effect was independent of calcium supplementation.[32] In the most current multidose study of institutionalized older patients, supplementation with 800 IU of VTD resulted in a 72% reduction in falls.[116] Another review found no such association.[3] There is also evidence that idiopathic low back pain in patients with VTD deficiency markedly improves when VTD levels are restored.[35] Low levels of VTD are also common in patients with fibromyalgia and chronic refractory nonspecific musculoskeletal pain.[36,37,117]

Type 1 and 2 diabetes. A prospective study (begun in 1966) using 2000 IU of VTD in children resulted in an 80% reduction in development of type 1 diabetes during the next 30 years.[38] Studies using 400 IU of VTD early in life did not show a protective effect, and higher doses are being suggested.[39,118] Increasing VTD levels from 25 to 75 nmol/L results in a 60% improvement in insulin sensitivity.[4,119] Low VTD levels were also shown to have a negative effect on beta cell function.[120] The improvement in insulin sensitivity was greater with VTD than improvement seen with either troglitzone (54%) or metformin (13%).[4,121]

Multiple sclerosis and rheumatoid arthritis. Living at higher than 37° latitude increases the risk of developing multiple sclerosis by >100%. Taking a multivitamin with 400 IU of VTD reduces the risk by 40%.[44,122] Women taking a multivitamin with 400 IU of VTD reduced their risk of developing rheumatoid arthritis by 40%.[45,122]

Cardiovascular disease. Increased VTD levels suppress renin expression and renin levels and thus result in down-regulation of the renin-angiotensin system in animals.[123] Several mechanisms have been suggested for VTD's protective role in cardiovascular disease.[68]

Supplementation with calcium and VTD results in a substantial 9.3% decrease in systolic blood pressure and a 5.4% decrease in heart rate.[40] Supplementing with VTD substantially reduces C-reactive protein levels in critically ill patients.[41] Low VTD levels might contribute to congestive heart failure.[2] In 3 large prospective cohort studies, however, higher intake of VTD was not associated with lower risk of hypertension.[42] Clinical trials are needed to evaluate whether the morbidity and mortality associated with cardiovascular disease are reduced by optimal intake of oral VTD.

Cancer. Evidence from 63 observational studies indicates that inadequate VTD levels are a risk factor for certain types of cancer, such as breast, colon, ovarian, and prostate cancer.[43,124,125] Vitamin D and VTD analogues can induce cell death in some cancer cell lines.[74,75] Exposure to the sun might increase risk of skin cancer, but VTD has been shown to suppress growth and increase apoptosis in melanoma cells.[126] The risks and benefits of sun exposure are a topic of hot debate at this time.[46,127,128]

Psoriasis. Vitamin D analogues are used for psoriasis along with ultraviolet-B light. Treatment is successful because of the antiproliferative, immunosuppressive, and prodifferentiating effects of VTD.[73,129]

Sources of VTD

The best way to increase VTD levels is to expose the skin to the sun. This has never been known to cause toxicity because of self-regulatory factors in the skin. Other sources of VTD are listed in **Table 6**.[47,91,130,131]

Table 6. Sources of vitamin D

SOURCE	RISKS AND BENEFITS
Sun	Exposure has never been known to cause toxicity; however, risk of skin cancer increases with exposure[47]
Oily fish or fish oils	High levels of vitamin A in fish oils (cod, halibut); sometimes high levels of mercury and other toxins (dioxins) are found in fish[130,131]
Fortified foods, such as milk, soya milk, or rice milk (in some countries); cereal; orange juice	Lactose intolerance limits consumption of milk for some people; celiac disease limits consumption of cereal for some people
Shittake mushrooms (sun-dried)[91]	Beneficial for those on a strict vegan diet
Supplements	Inexpensive (<5¢/d for 2000 international units of vitamin D3); vitamin D2 is ergocalciferol; vitamin D3 is cholecalciferol, which is 1.7 times as potent as ergocalciferol

Treatment of VTD insufficiency and deficiency

The beneficial effects of VTD on various diseases are listed in **Table 7**.[4,35,38,44,45,48-50,73,77,78,98,111,112,117,132-145] The question is, how can one vitamin influence so many disorders in a positive way? Just as abnormal levels of thyroid hormone can affect many cell systems, abnormal levels of VTD, a hormone, appear to affect many cell systems. Our understanding of the non-bone effects has greatly increased in the last 10 years.

To maintain a healthy blood level of 25(OH)D (80 to 100 nmol/L), most healthy patients require at least 1000

Table 7. Benefits of vitamin D for various diseases, dosages, and comments

DISEASE	DOSE OF VITAMIN D USED OR CHANGE IN LEVEL OF VITAMIN D	RISK REDUCTION OR IMPROVEMENT	COMMENTS
Rickets[111]	Requires repletion therapy when diagnosed; usually prevented with VTD levels >25 nmol/L	Complete resolution of symptoms and signs (except in cases of vitamin D resistance[132])	Adequate intake of calcium also needed
Osteomalacia[112]	800 IU required; patients might need up to 2200 IU for up to a year	Resolution of symptoms, including bone pain, especially in pelvis, lumbar spine, and ribs	
Psoriasis	Topical VTD creams	Plaque thickness and redness markedly improved by UVB and VTD analogues	First-line therapy worldwide[73]
Multiple sclerosis[44]	400 IU/d	40% risk reduction	
Rheumatoid arthritis[45]	400 IU/d	40% risk reduction	
Type 1 diabetes[38]	2000 IU/d	80% risk reduction	
Type 2 diabetes[4]	VTD level raised from 25 to 75 nmol/L	63% improvement in insulin sensitivity	
Gestational diabetes and hypertension during pregnancy[98]	Individualized dosing to restore levels to >80 nmol/L	Marked improvement in insulin sensitivity and insulin production	
Birth weight[133]	For each IU/d of VTD intake, birth weight increased	Birth weight increased by 11 g/IU of VTD	
Osteogenesis imperfecta	6-8 IU/kg daily	Correction of deficiency status	Recommendation of the Kennedy Krieger Osteogenesis Imperfecta Clinic
Polycystic ovary disease[134]	50 000 IU of VTD weekly or biweekly	Normalized menstrual cycles in >50% of patients	Very small study
Premenstrual syndrome[135]	700 IU/d	40% reduction in risk of having symptoms	Increased dietary calcium is known to decrease symptoms[135]
Colon cancer[136-138]	To achieve levels of 65-100 nmol/L	40%-80% risk reduction with supplement; rectal cancer reduced by 48%; exposure to sunlight reduced risk by 38%[137]	Increased dietary calcium is known to decrease risk, but benefit for >700 mg/d is minimal[139]
Cancer of the prostate[140]	Serum level of 25(OH)D ≥40-<60 nmol/L	50% risk reduction[125]	1 study suggests >80 nmol/L might increase risk[141]
Cancer of the pancreas[142]	300-450 IU/d compared with 150 IU/d	43% risk reduction 22% risk reduction	Higher doses gave no further protection[142]
Cancer of the breast	>50 nmol/L compared with 50 nmol/L	50%-70% risk reduction[143]	Sun exposure reduces mortality[144]
Cancer of the ovary[144,145]	Exposure to sunlight	16% risk reduction; risk is 5 times higher among those living farther north in the United States	Despite these studies, more information is needed
Upper respiratory tract infections[48]	600-700 IU given as cod-liver oil	50% risk reduction	Also given selenium and omega-3 fatty acids
Lower respiratory tract infections[49]	Children with levels <25 nmol/L	11 times more likely to be infected	
Seasonal influenza[77]	Levels as high as 125 nmol/L have been suggested	Immune function improved in various immune cells	Clinical trials needed
Mycobacterium tuberculosis[78]	To restore levels to normal physiologic levels, >100 nmol/L are suggested	Increased production of macrophages' antimicrobial peptide cathelicidin kills *Mycobacterium tuberculosis*	Clinical trials needed
Idiopathic back pain[35]	Restoring levels from <25->80 nmol/L	100% of deficient patients had pain resolve using 5000 IU/d of VTD	340 patients (85%) had deficient levels of 25(OH)D
Nonspecific chronic musculoskeletal pain[117]	Restoring levels from 21 nmol/L to normal levels	67% of patients had complete resolution of symptoms	Diagnosis prior to VTD deficiency was somatization
Reduced tooth loss in the elderly	400-600 IU of VTD and 1000 mg of calcium	50% improvement in tooth retention over 2 y	Effect of VTD not assessed independently[50]

25(OH)D—25-hydroxyergocalciferol, IU—international units, UVB—ultraviolet B, VTD—vitamin D.

Table 8. Source and dose of vitamin D, side effects, and potential toxicity: *Reported side effects of vitamin D include nausea, vomiting, headache, metallic taste, vascular or nephrocalcinosis, and pancreatitis. Reported contraindications to vitamin D include hypercalcemia in sarcoidosis; metastatic bone disease[148]; other granulomatous diseases, such as tuberculosis and Crohn disease (active phase) that have disordered vitamin D metabolism in activated macrophages[149]; and Williams syndrome[150] (infantile hypercalcemia).*

SOURCE AND DOSE OF VITAMIN D*	SIDE EFFECT OR TOXICITY	COMMENTS
Maximum sun exposure	No known vitamin D toxicity, but too much exposure to UVB (burns) results in increased risk of skin cancer	10 000 IU (oral equivalent easily achieved with full-body exposure and results in levels of 148-163 nmol/L); in lifeguards exposed to the sun, kidney stones are more common[151]
About 10 to 15 min of sun exposure of hands and arms midday when sun is overhead needed to achieve daily requirement (about 400 IU)	No known side effects; too much exposure to UVB (burns) results in increased risk of skin cancer	Dark skin requires 4 times as much sun exposure to get the same dose
Use of 2000 IU in African Americans (after 1 y)	No known side effects	Failed to achieve a level of 80 nmol/L in 40% of patients[53]
Use of 4000 IU for 6 mo	Improved mood the only side effect noted	Average level of 25-hydroxyvitamin D was 110 nmol/L,[51] a level seen with adequate sun exposure; no increase in serum calcium noted
4000 IU for 3 mo	No notable side effects[52]	
Use of vitamin D2 (synthetic analogue)	Several metabolites with unknown side effects	Toxicity reported using higher levels[152,153]

UVB—ultraviolet B.
*Vitamin D3 unless specified.

IU of VTD each day if they do not get exposure to the sun.[63,146] Topping up to adequate levels quickly is the goal. Recommended repletion therapy consists of 50 000 IU of vitamin D2 weekly for 8 weeks or 2000 IU of vitamin D3 daily for 8 weeks.[147] Doses of 4000 IU of vitamin D3 have been used safely for several months, and there is evidence that doses up to 2000 IU/d can be considered safely (**Table 8**[51-53,148-153]).[52]

Conclusion

Low levels of VTD are considered a major public health problem in Canada, especially during the winter. Those with risk factors should be screened for low 25(OH)D levels and repletion therapy instituted if needed. Researchers have estimated that the oral dose of vitamin D3 to attain and maintain 25(OH)D levels >80 nmol/L is 2200 IU/d if baseline levels are 20 to 40 nmol/L, 1800 IU/d if levels are 40 to 60 nmol/L, and 1160 IU/d if levels are between 60 and 80 nmol/L.[64]

We need to ensure that patients have healthy blood levels of 25(OH)D to prevent levels of parathyroid hormone from rising and to maximize absorption of calcium, magnesium, and phosphate. Positive effects on bone are marginal at best unless patients consume at least 800 IU/d of VTD. The emerging and exciting role of the VTD receptor and the actions of VTD in maintaining health in other cell types have become more apparent during the last decade.

Competing interests
None declared

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EDITOR'S KEY POINTS

- Inadequate levels of vitamin D (VTD) have classically been associated with bone disorders, such as rickets, osteomalacia, and osteoporosis.
- New research has demonstrated that VTD receptors are present throughout the body and that VTD has much broader effects than previously believed.
- Current recommendations for VTD supplementation might be inadequate to ensure appropriate blood levels of VTD.

POINTS DE REPÈRE DU RÉDACTEUR

- Les niveaux inadéquats de vitamine D (VTD) ont généralement été associés à des anomalies osseuses comme le rachitisme, l'ostéomalacie et l'ostéoporose.
- Les études récentes ont montré qu'il y a des récepteurs de VTD un peu partout dans l'organisme et que la VTD a des effets beaucoup plus étendus qu'on ne le croyait auparavant.
- Les recommandations actuelles sur les suppléments de VTD pourraient donc ne pas assurer des niveaux sanguins adéquats de VTD.

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